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The Role of Hyperglycemia in the Perioperative Period in Carrying out Aortocoronary Shunting

ABSTRACT

In this article we presented pathophysiological features of hyperglycemia and its negative effects on the cardiovascular system, the ways to achieve optimal perioperative glycemic control, as well as the results of studies aimed to determine the optimal level of blood glucose for preventing postoperative complications and achieving optimal clinical results.

Keywords: diabetes mellitus, hyperglycemia, coronary artery bypass grafting.

The prevalence of diabetes mellitus (DM) in patients with coronary artery disease contributes to their increasing among the candidates for myocardial revascularization. According to various authors, from 30 to 40% diabetic patients in need for surgical treatment coronary artery disease (13). However, the results of the study suggest that the results of coronary artery bypass grafting (CABG) in patients with DM, in General, worse than in other groups of patients without diabetes (3,8). Revealed that among patients with diabetes has increased postoperative mortality increase in the frequency of the number of postoperative complications (infectious, neurological, renal) (19, 25, 28), which in turn significantly increases their hospital stay, and, consequently, the cost of their medical care (9). Recently, control of blood glucose levels during CABG surgery and other cardiac surgery becomes the object of intense study. According to most researchers, hyperglycemia that arises in the postoperative period is associated with increased mortality and morbidity in the postoperative period. The undeniable fact is recognized the need for careful monitoring of intraoperative blood glucose levels in order to correct the violation and prevent the adverse effects of hyperglycemia on the cardiovascular system.

Influence of hyperglycemia on the cardiovascular system.

To understand and assess the negative influence hyperglycemia the cardiovascular system is necessary to allocate some points. The energy substrate for no ischemic myocardium is free fatty acids. During ischemia metabolism of fatty acids is disturbed and increased theirs concentration, which adversely affects the myocardium in the form of increased oxygen demand, reduced contractility and occurrence of arrhythmias, and also increase the concentration of

oxygen free radicals, which in turn leads to endothelial dysfunction (26). Elevated levels of free fatty acids, also impairs the metabolism of glucose, which is the main substrate myocardial energy during episodes of ischemia. The transition from the oxidative metabolism of fatty acid oxidation of carbohydrates is a defensive reaction, as it allows more efficient use of myocardial oxygen under conditions of ischemia to produce ATP necessary for the normal functioning of the transport system channels of the cell membrane and prevent cell death. In diabetic patients disturbed glucose transport into the myocardium. Accordingly, the disadvantage is realized in ischemia substrate for ATP generation and increased levels of serum glucose [34]. Hyperglycemia leads to the formation of glycosylation end products and their receptors on cell membranes. Receptors glycosylation end products cause amplification of the inflammatory response by activating three proinflammatory transcription factors (nuclear factor-activating protein-1, epidermal growth factor receptors, which under normal conditions is suppressed endogenous insulin [38]. Hyperglycemia directly influences the processes responsible for changes in endothelial function, inflammation, and development oxidative stress in due to the alteration of the polyol pathway glucose`s metabolism and increase synthesis diacylglycerol, which activates protein kinase C [14]. Endothelial dysfunction is associated with reduced nitric oxide activity and increased production of superoxide radicals. These changes are characteristic of diabetic changes in the internal mammary artery, as well as conduits for autovenous [22]. Ultimately, a result of vascular oxidative stress, inflammatory response is amplified, which contributes to thrombosis, plaque rupture, and inhibition of platelet function [29]. Accordingly, the above listed pathological reactions in patients with diabetes help to reduce permeability conduits return ischemic events and the need for repeat revascularization of the myocardium. Insulin levels the activating effect of hyperglycemia on the processes of vascular oxidative stress by increasing myocardial glucose uptake, reduces the inflammatory response and reduces the activity of cell apoptosis. Insulin is a catalyst myocardial glucose metabolism by stimulating glucose transport process in myocytes, thereby reducing the release of free fatty acids, and indirectly through activation of pyruvate dehydrogenase enhances aerobic metabolism. Also, insulin acts as an anti-inflammatory agent inhibiting proinflammatory transcription factors, nuclear factor kappa B, early growth response factor-1 activating protein-1 and reduces the activity of inflammatory mediators such as - IL-6, tumor necrosis factor - alpha, intercellular adhesion molecule 1 and E-selectin [16, 20]. Under the action of insulin leads to regulation of nitrogen metabolism, namely system «L-Arginine / Nitric Oxide," which leads to vasodilation, improvement of vascular endothelial functions and platelet function by inhibiting platelet

aggregation inhibitor, increased synthesis of prostacyclin. Also, a suppression of apoptosis of cells by increasing levels of nitric oxide [12]. Clinical studies have shown that insulin lowers the level of free fatty acids after bypass surgery improve aerobic metabolism when added in cardioplegic solution reduces the concentration of active oxygen species, adhesion molecules, and C - reactive protein [32, 35].

Hyperglycemia as a risk factor for developing complications in the perioperative period of aortocoronary shunting.

Several studies have demonstrated that hyperglycemia is the reason for the increase in morbidity and mortality in all patients undergoing CABG, without dependence from presence of diabetes. Thus, Donts T. et al. in the analysis of clinical outcomes patients undergoing 6280 cardiac surgery found that patients with high peak levels of blood glucose (360 mg /dL) during coronary artery bypass surgery had the highest rates of morbidity and mortality independently of the presence of diabetes [5]. Fish L. et al. found the following pattern - with an increase in blood glucose levels in the postoperative period (more than 250 mg/dL) in 10 times increased risk of various complications [10]. Similar conclusions were reached in other studies [15, 36]. Henderson et al., concluded that in patients with impaired fasting glucose annual mortality rate doubles after suffering a coronary artery bypass grafting [11]. Thus, these studies convincingly show that, regardless of the presence of diabetes, with an increase in blood glucose levels in the perioperative period of CABG associated increase in morbidity and mortality.

Glycemic control during perioperative period.

Glycemic control in the cardiac surgical patient is best achieved with strategies that are instituted in the preoperative period. All patients should have a hemoglobin A1c (HbA1c) drawn prior to surgery. The HbA1c is an indication of glycemic control in the 6–8 weeks prior to surgery. Adequate glycemic control is associated with an HbA1c < 7% [37]. In general, oral hyperglycemic medication should not be taken in the 12 hours prior to surgery. Patients who are taking insulin and who are admitted on the day of surgery should continue their basal insulin dose and hold their nutritional insulin. Intravenous insulin is the preferred method of insulin delivery to achieve rapid and effective glycemic control in hospitalized patients who are hyperglycemic prior to surgery [11]. During surgery, it is important to realize that insulin resistance increases but then rapidly decreases in the postoperative period. This results in an intraoperative rise in insulin requirements followed by a rapid fall in the immediate postoperative period. This is due to hypothermia, the increased glucose load associated with cardioplegia delivery, the glucose used to prime the cardiopulmonary bypass circuit, and the need for

inotropic support. Following discontinuation of cardiopulmonary bypass, when these factors are no longer present, insulin requirements decrease rapidly and if unrecognized, severe hypoglycemia can result (27). Therefore, it is necessary to check glucose levels prior to leaving the operating room and make the appropriate reduction in insulin delivery. Glucose levels should be monitored every 30–60 minutes in the operating room, and as often as every 15 minutes during periods of rapid fluctuation, such as during cardioplegic infusions and systemic cooling and rewarding. In the ICU, all patients should have serum glucose values ≤180 mg/dL as recommended by the STS guidelines (23). Patients who require ≥3 days in the ICU because of ventilatory dependency, the need for inotropes, intraaortic balloon pump or left ventricular assist device support, antiarrhythmics, dialysis, or continuous venovenous hemofiltration should receive continuous insulin infusions to keep blood glucose <150 mg/dL regardless of their diabetic status.

The following are the current recommendations of the Society of Thoracic Surgery regarding blood glucose management during adult cardiac surgery [23].

(I) All patients with diabetes undergoing cardiac surgical procedures should receive an insulin infusion in the operating room and for at least 24 hours postoperatively to maintain serum glucose levels <180 mg/dL (Class I; Level of Evidence B).

(II) An HbA1c level should be obtained prior to surgery in patients with diabetes, and those patients at risk for postoperative hyperglycemia to characterize the level of postoperative glycemic control (Class I; Level of Evidence C).

(III) Glucose levels >180 mg/dL that occur in patients without diabetes only during cardiopulmonary bypass may be treated initially with a single intermittent dose of i.v. insulin as long as the levels remain <180 mg/dL. However, in those patients with persistently elevated glucose (>180 mg/dL) after cardiopulmonary bypass, a continuous insulin drip should be instituted (Class I; Level of Evidence B).

(IV) Patients with and without diabetes with persistently elevated serum glucose (>180 mg/dL) should receive i.v. insulin infusions to maintain serum glucose <180 mg/dL for the duration of their ICU care (Class I; Level of Evidence A).

(V) All patients who require ≥3 days in the ICU because of ventilatory dependency requiring the need for inotropes, intraaortic balloon pump or left ventricular assist support, antiarrhythmics, dialysis, or continuous venovenous hemofiltration should have a continuous insulin infusion to keep blood glucose ≤150 mg/dL, irregardless of their diabetic status (Class I; Level of Evidence B).

In order to avoid wide fluctuations in glucose levels, it is imperative that they be frequently monitored in the ICU. (Fig.1). The common practice of obtaining hourly glucose values until stable targeted blood glucose levels have been achieved [33]. Most patients have either an arterial or central venous monitoring line that allows for painless blood sampling. When there is anticipation of an inotrope or a dextrose solution causing rapid hyperglycemia, glucose values may be obtained every 30 minutes so that the target glucose level can be maintained.

Unfortunately, the accuracy of most hand-held glucose meters is far from optimal [7]. There is an accepted variance between meter readings and central laboratory results (allowed to be up to 20% by FDA regulations), which can potentially lead to inappropriate therapy [17]. Many patient factors are known to affect the accuracy of the POC testing including pH changes, oxygenation status, and low hematocrit [17]. Given these factors, all patients in the ICU have blood glucose levels determined by the central laboratory every 2 to 4 hours in the early postoperative period, and twice daily for up to 2 days. All glucose levels <70 mg/dL or >300 mg/dL are verified with blood samples sent to the central laboratory (Figure 1).

Transitioning the patient to SC insulin therapy is the most difficult of all the perioperative stages in terms of reliably maintaining adequate glycemic control (25):

(1) A stable intravenous insulin infusion rate is maintained for at least 4 hours in the fasting state.

(2) The patient is extubated and is off pressor agents.

(3) The patient is ready to receive oral, enteral, or parenteral nutrition.

According to clinical guidelines Society of Thoracic Surgeons and the American Association of Clinical Endocrinology for the period of diabetic patients in the ward must be committed to maintaining optimal blood glucose:

— (1) A target blood glucose level <180 mg/dL should be achieved in the postprandial state.

— (2) A target blood glucose level between 100 and 140mg/dL should be achieved in the fasting and premeal states after transfer to the floor. The more effective way to achieve control of blood glucose levels is a combination of basal insulin "by the hour" and bolus insulin short-acting. Titration is carried out based on the diet and blood plasma glucose levels of the patient.

— (3) It is necessary to inform the patient that if you can not eat a meal injection of short-acting insulin should be skipped. However, injection of long-acting insulin preparations skip forbidden irrespective of the glucose concentration (even when normal) or skipping meals.

Often the main goal of restarting home oral agents is to ensure tolerability and safety in a patient who has achieved good control in the hospital postoperatively, is medically stable, and is

expected to require at least another day in hospital. Sulfonylureas (glipizide, glyburide, and glimepiride) and short-acting insulin secretagogues (repaglinide, nateglinide) should be started slowly and based on the patient's appetite. Metformin should not be restarted until the patient is documented to have normal renal function. Based on the data presented, it is now accepted that glycemic control improves short- and long-term outcomes in CABG patients with diabetes mellitus and those nondiabetics who exhibit perioperative hyperglycemia. However, the optimal target for serum glucose levels in the perioperative period is unknown. All studies have shown that maintaining serum glucose levels <180 mg/dL reduces morbidity and mortality, the effects of more aggressive control on clinical outcomes are less clearly defined. In order to determine the effects of more aggressive glycemic con- trol in diabetic patients during CABG surgery, Lazar and coworkers prospectively randomized patients to either an aggressive (90–120 mg/dL) or moderate (120–180 mg/dL) protocol [114]. There was no difference in the incidence of a 30-day mortality, myocardial infarction, neurological events, deep sternal infections, or atrial fibrillation between the groups. These results are consistent with those of Bhamidipati and coworkers who showed that moderate glycemic control (120–179 mg/dL) in diabetic CABG patients were associated with the least amount of morbidity and mortality [2]. The American College of Physicians now recommends achieving a more moderate glucose level of 140–200 mg/dL in surgical and medical intensive care unit patients [31].

Conclusions

Hyperglycemia which occurs during CABG and cardiac surgery increases perioperative morbidity and mortality and results in decreased long-term survival and recurrent ischemic events. Maintaining serum glucose ≤180 mg/dL with continuous insulin infusions in patients with and without diabetes mellitus reduces morbidity and mortality, lowers the incidence of sternal wound infections, reduces hospital length of stay, and enhances long-term survival. Patients who require >3 days of ventilatory support or develop sepsis or multiorgan failure should have serum glucose levels <150mg/dL. More aggressive glycemic con- trol (80–120 mg/dL) in the absence of these complications appears to offer no benefits and does not improve clinical outcomes.

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BOSTON MEDICAL

120–180 mg/dL insulin infusion guideline

*** not to be used in patients in acute diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome ***

Goal: the goal is to maintain whole blood glucose level and/or finger sticks between 120 and 180 mg/dL.
Revised 03/10

	Below desired range		Desired range	Above desired range					
Glucose level	<80 mg/dL	80–119 mg/dL	120–180 mg/dL * see example end of page	181–220 mg/dL	221–250 mg/dL	251–300 mg/dL	301–350 mg/dL	>351–400 mg/dL	>400 mg/dL
Infusion rate of ≤1 unit/hour	D/C infusion: give 25 cc of D50 IVP	Decrease infusion by 0.5 unit/hour	Once in range, if glucose↓ over 2 consecutive checks, ↓ infusion by 0.5 unit/hr.*	↑infusion by 1 unit/hr.	Give 2 units insulin IVP and ↑infusion by 1 unit/hr.	Give 3 units insulin IVP and ↑infusion by 1 unit/hr.	Give 4 units insulin IVP and ↑infusion by 1 unit/hr.	Give 5 units insulin IVP and ↑infusion by 1 unit/hr.	Call MD
Infusion rate of 2–5 units/hr	Call MD √glucose level in 30 min. if >120 mg/dL, restart at 1/2 pervious rate	Decrease infusion by 1 unit/hour	Once in range, if glucose↓ over 2 consecutive checks, ↓ infusion by 0.5 unit/hr.*	↑infusion by 1 unit/hr.	Give 2 units insulin IVP and ↑infusion by 1 unit/hr.	Give 3 units insulin IVP and ↑infusion by 1 unit/hr.	Give 6 units insulin IVP and ↑infusion by 1 unit/hr.	Give 8 units insulin IVP and ↑infusion by 1 unit/hr.	
Infusion rate of 6–10 units/hr	Resume q 1 hr fingersticks until stable. restart drip as above any time glucose is >120	Decrease infusion by 2 units/hour	Once in range, if glucose↓ over 2 consecutive checks, ↓ infusion by 1 unit/hr.*	↑infusion by 1.5 unit/hr.	Give 2 units insulin IVP and ↑infusion by 2 units/hr.	Give 3 units insulin IVP and ↑infusion by 2 units/hr.	Give 6 units insulin IVP and ↑infusion by 2 units/hr.	Give 8 units insulin IVP and ↑infusion by 2 units/hr.	
Infusion rate of 11–16 units/hr		Decrease infusion by 3 units/hour	Once in range, if glucose↓ over 2 consecutive checks, ↓ infusion by 2 unit/hr.*	↑infusion by 2 unit/hr.	Give 2 units insulin IVP and ↑infusion by 3 units/hr.	Give 3 units insulin IVP and ↑infusion by 3 units/hr.	Give 6 units insulin IVP and ↑infusion by 3 units/hr.	Give 8 units insulin IVP and ↑infusion by 3 units/hr.	
Infusion rate of >16 units/hr				Call MD					

Monitoring: Check glucose q1h until stable (blood glucose remins in desired range for 3 consecutive measurements) then reduce checks to q2h. Blood sugars should be checked at least every 2 hours while a patient is on an insulin infusion.

* "Once in range" example:

Glucose	190	140 (in range now)	130 (drop number 1)	120 (drop number 2)	130
Units/hr	4	4	4	↓3.5	3.5

FIGURE 1: Continuous insulin infusion protocol.

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