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Perioperative glycemic control in patients undergoing cardiac surgery

Dariusz Bednarski[1], Łukasz J. Krzych[2,3]

[1]Department of Anesthesiology and Intensive Care, School of Medicine, Medical University of Silesia, Katowice, Poland
[2]Department of Cardiac Anesthesiology and Intensive Care, Silesian Center for Heart Diseases, Zabrze, Poland
[3]Department of Acute Medicine, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland

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Abstract

Diabetes mellitus (DM) is one of the most common chronic diseases, affecting globally about 537 million adults. Cardiovascular disease remains the leading cause of death and medical emergencies in the DM patient population. As a result, about 40% of patients with DM undergo cardiac surgery, mainly in the coronary arteries. Uncontrolled hyperglycemia, especially the prolonged condition, is an independent factor in postoperative mortality and the cause of many serious complications, such as surgical wound infection, sepsis, renal failure or cerebral or cardiovascular incidents. Adequate glycemic control in the perioperative period is the most important way to prevent the above complications. The issue has remained an important topic of many observational and experimental studies for years. This paper summarizes the current knowledge with regard to strategies of hyperglycemic control in patients undergoing cardiac surgery.

Key words: diabetes, glycemia, insulin therapy, perioperative medicine, cardiac surgery.

Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases and globally currently affects approximately 537 million adults. This number is estimated to increase to nearly 643 million before 2030 [1]. DM is a leading cause of impaired vision, kidney failure, acute coronary conditions, strokes and lower limb amputations [1]. According to World Health Organization (WHO) data, it was the direct cause of 1.5 million deaths in 2019, 48% of which involved patients before the age of 70. Cardiovascular disease is the leading cause of death and medical emergencies in the DM patient population [2]. As a result, about 40% of patients undergo cardiac surgery, mainly coronary artery bypass grafting (CABG) [3]. DM is an independent factor in postoperative mortality and a cause of many complications, such as surgical wound infection, sepsis, renal failure, stroke or postoperative myocardial infarction [3–5]. This paper summarizes the current knowledge with regard to glycemic maintenance strategies in a group of patients undergoing cardiac surgery, primarily in the coronary arteries.

Diabetes and its clinical implications

Hyperglycemia is a condition of elevated blood glucose levels inappropriate to the body's metabolic demand and consumption at the cellular level. When analyzing a patient's glycemic values, it is necessary to take into account not only numerical, individual values, but the entire well-being of the body, on a personalized assessment basis. This determines what glycemic norms will be adopted, and in what time frame, as other values will be expected in ambulatory patients in good general condition, and completely different in intensive care settings. Hyperglycemia can be caused by conditions such as impaired or complete lack of insulin production, cellular insulin resistance, decreased glucose catabolism or glucose overproduction. Endothelial cells are particularly susceptible to the toxic effects of hyperglycemia in the form of oxidative stress [6]. This explains the spectrum of DM complications, which mainly involve the macro- and microcirculation, resulting in impaired renal function, coronary circulation, wound healing and the risk of acute brain injury, among others.

One of the major problems in cardiac surgery patients with DM is sternal wound infection (SWI). Sternal wound infection can be limited to the superficial layers of the skin or subcutaneous tissue, causing superficial sternal wound infection (SSWI), but it can also penetrate deep into the mediastinum and lead to the spread of infection within the bones and internal organs (DSWI, deep sternal wound

Address for correspondence: Dariusz Bednarski, Department of Anesthesiology and Intensive Care, School of Medicine, Medical University of Silesia, Katowice, Poland, e-mail: dariuszbednarski92@gmail.com
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infection) [7]. SSWI complicates between 0.5 and 8% of procedures, with mortality rates of up to 9% [8]. The diagnosis is based on the presence of clinical symptoms, such as redness and swelling of the skin, wound exudate, fever, and instability of the sternum. In most cases, intravenous antibiotic therapy and wound care are sufficient forms of treatment [8]. DSWI affects between 1% and 5% of cardiac surgery patients and contributes to prolonged hospitalization, the need for reoperation and an increased mortality rate of up to 47%. The diagnosis of DSWI according to Centers for Disease Control and Prevention (CDC) criteria is based on the finding of at least one of three criteria: (1) isolation of a pathogenic microorganism from tissue or fluid from the mediastinum, (2) intraoperatively visible signs of mediastinitis, (3) presence of chest pain, fever > 38°C, sternal instability, and purulent mediastinal discharge, or culture of a pathogenic microorganism from the blood/mediastinal area. DM is one of the main predisposing factors for SWI. Others cited include obesity, chronic obstructive pulmonary disease, female gender, recent myocardial infarction, resternotomy, and coronary artery bypass grafting with internal thoracic artery [7–10]. Ding *et al.* [11] detected a lower risk of DSWI among patients with DM with unilateral bypass with a single internal thoracic artery (SITA), compared with bilateral internal thoracic artery (BITA). In 2022, the results of a post-hoc analysis from the Arterial Revascularization Trial (ART) on a group of 3020 patients were published, confirming that patients with DM after CABG with multiple arterial grafting (MAG) had a higher incidence of DSWI than patients with single arterial grafting (SAG) (7.9% vs. 4.8%). The highest incidence of DSWI was observed in the group of patients treated with insulin. However, despite the higher risk of DSWI in the MAG group, these patients showed a significantly lower mortality rate compared to SAG patients at 10-year follow-up [12].

Acute kidney injury (AKI) is defined according to the 2012 Kidney Disease Improving Global Outcomes (KDIGO) criteria as an increase in serum creatinine of ≥ 0.3 mg/dl (26.5 µmol/l) within 48 hours or ≥ 1.5-fold in the past 7 days, or diuresis < 0.5 ml/kg/h for 6 hours [13]. DM is an independent risk factor for the development of AKI, which affects up to 30% of cardiac surgery patients, of which about 1–2% require renal replacement therapy (RRT) [14–16]. Patients following CABG complicated by AKI have a higher risk of death and prolonged minimum intensive care unit (ICU) stay, duration of mechanical ventilation and infection [15, 17, 18]. Risk factors also include nicotinism, hypertension, mechanical ventilation, blood transfusion, and elevated creatinine in the preoperative period [19, 20]. Less understood but important risk factors include malnutrition. Gucu *et al.* [21] found that a low prognostic nutritional index was associated with a significantly higher incidence of AKI, suggesting that patients with DM should not make significant dietary restrictions at the expense of glycemic control and that the first-line approach would be to optimize pharmacotherapy. Patients with the above risk factors require close surveillance for renal complications in the postoperative period. Wang *et al.* [18] analyzed three groups of patients: with no history of DM (no-DM), DM treated with oral hypoglycemic drugs (DM-oral) and DM treated with insulin (DM-insulin) in terms of the risk and severity of AKI (defined according to AKIN – Acute Kidney Injury Network criteria). In the DM-oral group relative to no-DM, AKI was statistically significantly more frequent, while there was no difference between the groups in the different stages of AKI according to the AKIN scale. In contrast, the DM-insulin group had both a higher rate and more severe AKI compared to the no-DM group. In this study, patients were not divided by DM type. The results of a more severe course of AKI in the DM-insulin group may be due to the presence of patients with type 1 DM, and thus typically longer-lasting disease, which has a greater predisposition to renal impairment than type 2 DM [22]. Patients with type 2 DM in the insulin-treated group also included those who were unable to control their glycemia with oral hypoglycemic medications, and were therefore at risk of prolonged hyperglycemic conditions.

Various strategies have been proposed for the prevention of AKI used in patients undergoing surgery, including cardiac surgery, also in those with DM. Such approaches as the use of the antioxidants acetylcysteine, erythropoietin, vitamins C and E, or drugs to increase renal flow can be mentioned among them. None of these have withstood the test of time. The only proven method of importance remains adequate hydration of the patient, appropriate for the degree of renal and cardiovascular capacity in the preoperative period, which can be a problem in patients with uncompensated diabetes due to the presence of polyuria [22] In an analysis of 83 publications, Gillies *et al.* [23] found that the use of fenoldopam in the preoperative period reduces the risk of AKI, but without affecting the need for RRT or in-hospital mortality. Therefore, no binding therapeutic recommendations can be made on this basis.

Type 1 neurological damage in the form of stroke or transient ischemic attack (TIA) affects between 1 and 6% of patients undergoing cardiac surgery. The highest risk is for aortic and mitral valve surgery [24]. In a large study of 16,184 patients, Bucerius *et al.* [25] analyzed stroke risk factors. Patients with a history of DM accounted for as many as 40.9% of stroke patients diagnosed in the postoperative period. In a study of 872,936 patients from the STS Adult Cardiac Surgery Database, MacKay *et al.* [26] demonstrated that careful monitoring by intraoperative transesophageal echocardiography (TEE) in valve and aortic (proximal part and arch) surgery can significantly minimize the risk of stroke, as well as 30-day mortality and the need for reoperation. Manipulations within the aorta during its cannulation and clipping are an independent risk factor for ischemic stroke [27, 28]. The use of TEE allows for better control of the aortic cannulation site, and also protects against air embolism by enabling better control of cardiac venting before exiting the extracorporeal circulation. Despite the proven advantages of using TEE [26–29], recommendations from the American Heart Association (AHA) and the American College of Cardiology (ACC) lack a requirement for the routine use of TEE in cardiac surgery, which may critically affect the ability to identify embolic material intraoperatively.

Atrial fibrillation is among the most common causes of stroke in the postoperative period. Atrial fibrillation (AF) is one of the most common cardiac complications following cardiac surgery. Its incidence ranges from 10% to 60% [26]. Many risk factors for AF have been identified, ranging from non-modifiable ones such as age, gender, and race, to modifiable risks associated with, for example, obesity and nicotinism. Most chronic cardiovascular, respiratory, and urinary diseases also increase the risk of AF. Hyperglycemia remains one of the independent risk factors [30–32]. Postoperative AF increases the risk of in-hospital death, stroke, prolonged mechanical ventilation, sepsis, postoperative bleeding, renal failure and other severe complications prolonging the time and cost of hospitalization [32–34]. Although β-blockers and amiodarone [35, 36] show the greatest efficacy in the pharmacological prevention of postoperative AF, there are no official regimens for the use of the above drugs for its prevention.

Postoperative delirium affects between 2% and 70% of patients undergoing cardiac surgery and is the most common type 2 postoperative neurological complication according to the ACC/AHA classification. Delirium contributes to prolonged ICU hospitalization and total hospitalization time, increased risk of infection, prolonged duration of mechanical ventilation and higher long-term mortality rates. A study by Krzych *et al.* [37] in a group of 5781 patients indicated that diabetes is a significant risk factor for postoperative delirium. The above observation was also confirmed in a meta-analysis by Chen *et al.* [38], where 8 studies on the effect of diabetes on postoperative delirium were analyzed (including the study by Krzych *et al.*). In addition to diabetes, independent risk factors for delirium may independently include age > 65 years, significant carotid artery stenosis, history of cerebral ischemia, duration of extracorporeal circulation, decreased left ventricular ejection fraction, and need for blood product transfusion [37, 38]. In preventing and reducing the effects of delirium, increasing attention is being paid to non-pharmacological methods, such as ensuring that the patient is in a quiet, comfortable environment, promoting sleep, eliminating distractors from the environment, ensuring contact with the family, engaging in reorientation talk (where he/she is, why, what his/her situation is), as well as early motor mobilization, and adequate hydration and nutrition [39]. These methods fit perfectly into the concept of a holistic approach to improving treatment outcomes according to ERAS (enhanced recovery after surgery) recommendations. Pharmacological treatment, outside of situations of extreme agitation of the patients, in which they are a danger to themselves and those around them, has no proven clear efficacy in terms of prevention and reduction of the duration of delirium.

Patients with DM have up to 6 times greater risk of developing sepsis [40]. Until recently, the burden of DM was considered to be an independent factor increasing mortality in the course of sepsis [41, 42]. However, a meta-analysis by Jiang *et al.* [43] showed that a history of DM alone does not affect higher mortality compared to patients without DM. In contrast, increased mortality was proven in a group of patients with hyperglycemia on admission, regardless of a history of DM. This effect is presumed to be related to impaired immune system function, particularly in neutrophil functioning. In addition, patients with hyperglycemia experience endothelial dysfunction, which also plays a key role in immune system activation [44]. The use of insulin shows a protective effect, not only by restoring proper glycemia, but also by having a direct anti-inflammatory role [45]. A large cohort study showed that patients with DM were more likely to develop AKI in the course of sepsis than patients without DM (13% vs. 7%), while acute respiratory failure was observed less frequently (9% vs. 14%). There was no difference in other complications, such as circulatory failure, liver failure, hematological and metabolic disorders [46].

Glycated hemoglobin standards

Glycated hemoglobin (HbA_{1C}) is formed by glycation of globin. The HbA_{1c} concentration provides an estimate of a patient's average glycemia over the past 90 days [47]. Since 2010, the American Diabetes Association (ADA) has introduced the possibility of diagnosing DM with an HbA_{1C} result > 6.5%. The HbA_{1c} value is affected not only by blood glucose levels, but also by anemia, pregnancy, significant hypertriglyceridemia, cirrhosis, erythropoietin use, and dialysis therapy, among others. According to the Society of Thoracic Surgeons (STS), it is recommended that every patient with diabetes mellitus, on admission, have their HbA_{1C} determined [48]. The STS recommends that the cutoff point for effectively controlled preoperative glycemia is HbA_{1C} < 7%. The question of the value of preoperative HbA_{1C} and its impact on mortality and complications in cardiac surgery patients is not clear. In a meta-analysis of 19 studies, Wang *et al.* [47] studied the effect of HbA_{1C} control on mortality in patients after cardiac surgery (mainly CABG). Two standards of HbA_{1C}, ≤ 6.5% and ≤ 7.0% (analyzed separately), were used as the cutoff point. There was no difference in mortality between patients with low HbA_{1C}, either ≤ 6.5% or ≤ 7.0%, compared to those with HbA_{1C} > 6.5% and > 7.0%. On the other hand, in a prospective study by Halkos *et al.* [49], HbA_{1C} > 8.6% was associated with a 4-fold increase in mortality. It was observed that the effect of preoperative HbA_{1C} as an independent predictor of mortality was more significant in the group of patients without a history of diabetes [50]. Numerous publications have confirmed the impact of elevated HbA_{1C}, most often defined as a value > 7%, on the increased risk of postoperative infection, in terms of both complications typical of cardiac surgery, such as SWI, and respiratory and urinary tract infections [49, 51, 52]. In contrast, in a meta-analysis of 4 studies, Wang *et al.* [47] found no difference between groups with high and low HbA_{1C} in terms of the incidence of sepsis. In addition, HbA_{1C} > 7% was associated with an increased risk of myocardial infarction, renal failure, and prolonged hospitalization [47]. The study by Kotfis *et al.* [53] demonstrated that HbA_{1C} > 6.5% was an independent factor that increased the risk of postoperative delirium.

Glycemic maintenance strategy

Guidelines for perioperative glycemic maintenance are varied, and large randomized trials reserved for the cardiac surgery patient group are lacking. Recommendations are mostly extrapolated from observations in the general population of surgical or critically ill patients. The most recent recommendations from the Society of Thoracic Surgeons (STS) of the US on glycemic maintenance strategies date back to 2009 [48].

Preoperative period

The preoperative period is a key moment in the surgical treatment, allowing for clinical evaluation of patients, selection of the appropriate mode of surgery, and optimization of metabolic compensation. Proper preparation of a patient with diabetes for surgery begins even before admission to the cardiac surgery unit. There is increasing advocacy for the implementation of ERAS recommendations [54]. It is necessary to optimize not only pharmacological treatment, but also the often overlooked non-pharmacological preparation, consisting of changing the patient's diet, motivating weight loss if obesity is present, and increasing physical activity to achieve a decrease in insulin resistance. In addition, care should be taken to control risk factors, e.g. hypertension and hypercholesterolemia. Among patients with diabetes, this is also the time to modify the form of pharmacotherapy. According to STS guidelines, patients taking oral hypoglycemic drugs should discontinue them 24 hours before surgery. On the other hand, patients taking insulin with a meal should take the last dose with their evening food the day before surgery [48]. The standard recommendation is to defer elective surgery if one of the following criteria is met: HbA_{1C} > 8.5%, daily glycemic profile with sustained glycemia > 250 mg/dl, glucosuria with acetonuria [55]. In a group of 7310 patients Lauruschkat *et al.* [56] observed that 29.6% of patients admitted for CABG surgery had undiagnosed diabetes. Hyperglycemia (≥ 126 mg/dl as fasting blood glucose or ≥ 200 mg/dl as casual blood glucose) in patients without a history of diabetes is associated with higher mortality rates, longer hospitalization times, and more frequent need for ICU admission than in patients with diabetes [57]. Given that most cardiac surgery patients have risk factors for diabetes, measurement of fasting blood glucose should be included in the panel of baseline tests when each patient is admitted to the department. Impaired fasting glucose (IFG), which is a fasting blood glucose level of 100–125 mg/dl, is also a risk factor for postoperative complications and an increased risk of death [58]. According to the STS, it is recommended that intravenous insulin therapy be implemented in the preoperative period, using a continuous infusion technique when blood glucose is > 180 mg/dl [48]. Furnary *et al.* [59, 60] found that the use of continuous insulin infusion, compared to subcutaneous injections, allowed a statistically significant reduction in DSWI incidents and in-hospital mortality. An important observation is that the majority of cardiac surgery patients, either due to their underlying disease or cardiovascular risk factors, are taking statin drugs on a permanent basis. Although statins have a well-established role in the prevention of cardiovascular incidents, it should be kept in mind that their use is associated with an increase in insulin resistance [61, 62]. This phenomenon was also confirmed in a group of patients undergoing cardiac surgery. In a study by Sato *et al.* [63], patients taking statins in the preoperative period were characterized by higher values of mean glucose and its greater variability in the postoperative period. Insulin sensitivity in this group of patients was about 20% lower. There are no official recommendations on the principles of statin use among patients with metabolically unstable diabetes in the preoperative period. Given the beneficial pleiotropic effect of this group of drugs on patients with cardiovascular disease [64], the benefits of continued therapy appear to outweigh the potential risks associated with inadequate glycemic control. Among patients with DM, there is no consensus on the use of high-carbohydrate oral fluids 2 hours before surgery (according to the ERAS protocol). Concerns are related to the occurrence of hyperglycemia and increased risk of aspiration during intubation [65]. Some studies have confirmed higher intraoperative glycemia after high-carbohydrate fluid administration among patients with DM compared to patients without DM [66, 67]. In contrast, its use has not been shown to be associated with more frequent complications (pneumonia, wound infection, increased length of hospital stay, mortality) [68].

The first important data on the relevance of intravenous glycemic control came from the study by van den Berghe *et al.* [69] in a critically ill population, in which, in a group of 1,548 patients, tight glycemic control (80–110 mg/dl) versus liberal control (180–200 mg/dl) was associated with reduced mortality, shorter total hospitalization, shorter duration of mechanical ventilation and reduced need for renal replacement therapy (RRT). These observations were negated when the results of the randomized NICE-SUGAR study of 6104 patients were published in 2009, which introduced new insights into glycemic norms among patients treated in the ICU [70]. It showed that the previously favored strict glycemic control (81–108 mg/dl) was associated with increased mortality compared to the liberal model (~180 mg/dl). This discrepancy has highlighted the need for a scientific discussion on the topic of adequate glycemic control, which has been ongoing for many years and has resulted in a number of interesting scientific studies, including in the population of patients undergoing cardiac surgery. Desai *et al.* [71] compared two glucose maintenance models – liberal (121–180 mg/dl) and restrictive (90–120 mg/dl) – in a group of 189 patients. The liberal group had statistically significantly fewer hypoglycemic incidents (< 60 mg/dl), but there was no difference in severe hypoglycemia (< 40 mg/dl) or other endpoints (AKI, DSWI, pneumonia, duration of hospitalization, AF, death within 30 days) [71]. Pezzella *et al.* [72] evaluated long-term mortality during a forty-month follow-up period in the same group of patients. There was no significant difference in prognosis between the groups of patients. Preoperative glycemic control and avoidance of hyperglycemia (> 200 mg/dl) reduce postoperative complications and shorten the length of stay in the ICU [73].

Perioperative period

According to STS recommendations, the glycemic value measured intraoperatively should not exceed 180 mg/dl [48]. The Society for Ambulatory Anesthesia Consensus Statement recommends maintaining intraoperative blood glucose between 100 and 180 mg/dl [74]. If the values are higher, continuous intravenous insulin therapy should be introduced and continued in the postoperative period for a minimum of 24 hours [48]. Intraoperative glycemic control should be performed at intervals of 30 minutes to 60 minutes [48]. It is recommended that each center should have a standard for the use of insulin therapy, which consists of appropriate calculation of insulin doses, depending on glycemic values. It has been proven that the use of such regimens allows for better control and less fluctuation in glucose levels [75]. One of the algorithms for applying insulin therapy is presented below: the Yale Infusion Insulin Protocol [76]. Hazar *et al.* [76] analyzed two models of glycemic maintenance – liberal (120–180 mg/dl) and restrictive (90–119 mg/dl) – during the intraoperative period and for 18 hours after CABG surgery. The study included only patients with a history of DM [77]. As in the study by Desai *et al.* [71], which looked at the preoperative period, statistically significantly fewer hypoglycemic incidents were recorded in the liberal strategy, but with no effect on other major endpoints (30-day mortality, myocardial infarction, neurological incidents, DSWI, AF) [77]. Bhamidipati *et al.* [78] in a retrospective study, analyzed, in a large group of 4658 patients, three models for maintaining glycemia in the postoperative period: restrictive (≤ 126 mg/dl), moderate (127–179 mg/dl), and liberal (≥ 180 mg/dl) strategies. The lowest mortality was observed in the moderate model along with the lowest rates of sepsis, prolonged mechanical ventilation and AKI. The aforementioned complications were most common in the restrictive group [78]. In a meta-analysis of five randomized trials on the effect of insulin therapy in cardiac surgery, a favorable effect of an intensive intraoperative insulin therapy strategy on reducing the incidence of postoperative infections was demonstrated, but with no effect on reducing mortality, cardiac complications or hypoglycemic incidents [79]. Not all studies support the above observations. In a meta-analysis, Hui *et al.* [80] found no difference between the restrictive strategy (< 120 mg/dl) and the liberal strategy (< 200 mg/dl) in terms of mortality, ICU length of stay, SWI, and cardiovascular complications. Goldberg *et al.* [81] in a study in a group of 5050 patients undergoing CABG, found no correlation between hyperglycemia and the risk of death among patients with DM. However, they found a significant difference in this regard among patients without a history of DM. Similar results were obtained in the GLUCO-CABG Trial, where, also in a group of post-CABG patients, they found no significant difference in mortality and postoperative complications (SWI, pneumonia, sepsis, respiratory failure, AKI, cardiovascular incidents) between the restrictive group with glycemia (100–140 mg/dl) and the liberal group (141–180 mg/dl). On the other hand, the restrictive strategy was proven to have a benefit in reducing postoperative complications in a group of patients without a history of DM [82]. These findings may be related to poorer tolerance of stress hyperglycemia in normoglycemic patients. Patients with stress hyperglycemia, without a history of DM, may benefit from a strategy of strict glycemic control (< 140 mg/dl) in reducing in-hospital mortality and severe complications. In a randomized study by Bláha *et al.* [83] involving 2686 patients, the investigation included the optimal timing of the inclusion of intensive insulin therapy (intraoperative vs. postoperative period) to maintain glycemia (80–150 mg/dl). Among patients without DM, a reduction in major postoperative complications (with the exception of respiratory failure) was noted in the group with intraoperative insulin therapy (PERI), with the greatest statistical significance in neurological complications and infections. Patients with DM in the PERI group benefited in terms of reduced rates of cardiac incidents and reduced total hospitalization time [84]. Despite somewhat divergent findings regarding perioperative glycemic maintenance strategies, the liberal model (120–180 mg/dl) remains the preferred option [48]. This model clearly reduces the risk of potentially fatal and irreversible consequences of severe neurohypoglycemia, which is an independent factor that worsens prognosis [85], while protecting against complications associated with a persistent hyperglycemic condition.

Insulin dosing algorithm according to the Yale Infusion Insulin Protocol for a glycemic target of 140–180 mg/dl:

Infusion of 50 units of human short-acting insulin in 50 ml of NaCl 0.9%.

1. Start insulin therapy when blood glucose (BG) >180 mg/dl.
2. When BG 181–299 mg/dl, start continuous insulin infusion at rate: current glycemia/100. When BG ≥ 300 provide insulin bolus: current glycemia/100 and start continuous insulin infusion at rate: current glycemia/100.
3. Monitor glycemia every 1 hour (until stabilization is achieved in 3 measurements, then every 2–4 hours).
4. Based on the variation of glycemia in control measurements, modify insulin infusion according to the Table I.

Example: First measurement of patient's glycemia – 350 g/dl, administer bolus: 350/100 = 3.5 ml and start insulin infusion at a flow rate of 350/100 = 3.5 ml/h. Then after 1 hour measure glycemia, glycemia: 340 mg/dl. Change in glycemia 350–340 = 10 mg/dl. We read from table b, the current glycemic value, column BG > 200, then in this column we find the range for a decrease in BG of 10 mg/dl, then the type of change, in this case increasing the infusion

Table I. Change of blood glucose according to the Yale Infusion Insulin Protocol

A

BG 75–99 mg/dl	BG 100–139 mg/dl	BG 140–199 mg/dl	BG > 200 mg/dl	Type of change
		BG↑ > 50 mg/dl/h	BG↑	Infusion↑ 2Δ
	BG↑ > 25 mg/dl/h	BG↑ 1–50 mg/dl/h or NC	BG NC or ↓ 1–25 mg/dl/h	Infusion↑ Δ
BG↑	BG↑ 1–25 mg/dl/h or NC or BG 1–25 mg/dl/h ↓	BG↓ 1–50 mg/dl/h	BG↓ 26–75 mg/dl/h	NC
BG NC or BG 1–25 mg/dl/h ↓	BG↓ 26–50 mg/dl/h	BG↓ 51–75 mg/dl/h	BG↓ 76–100 mg/dl/h	Infusion↓ Δ
BG↓ > 25 mg/dl/h		BG↓ > 75 mg/dl/h	BG↓ > 100 mg/dl/h	Infusion↓ 2Δ

B

Current flow ml/h	Δ
< 3.0	0.5
3.0–6.0	1
6.5–9.5	1.5
10–14.5	2
15–19.5	3
20–24.5	4
≥ 25	≥ 5

BG – blood glucose, NC – no change.

by one Δ value (delta). The current flow rate is 3.5 mg/dl, so the delta value is 1. We increase the flow rate from 3.5 ml/h to 4.5 ml/h.

Variability of glycemia

When treating disorders of glucose metabolism, one cannot focus only on the laboratory norms within which glycemia should be maintained; an equally important factor is its variability over time. Glycemic variability (GV, glucose/glycemic variability) can be determined in various ways, including standard deviation (SD), coefficient of variation (CV), or more elaborate mathematical formulas, such as mean amplitude of glycemic excursions (MAGE), which measures the arithmetic mean of the difference between the highest and lowest consecutive measurements, continuous overlapping net glycemic action (CONGA), which counts the SD of the difference between current measurements and those measured several hours earlier, and mean absolute glucose (MAG), which sums the absolute differences between consecutive readings divided by the time between the first and last glucose measurements [86]. Continuous glucose monitoring (CGM) systems, which measure glucose concentrations in tissue fluid at intervals of several minutes, play a very important role in determining GV, providing more realistic monitoring of daily glycemic variability [87]. The multitude of formulas for determining GV can make it difficult to make comparisons of results between studies.

The large amplitude of glycemic changes exacerbates mechanisms related to free radical release, contributing to oxidative stress, macro- and microvascular complications, and impaired immunity [88]. GV analysis is not only a matter of measuring absolute glycemic values in the short term, but also the possibility of assessing long-term variability through HbA_{1C} analysis. In a meta-analysis by Besch *et al.* [89] it was proven that increased HbA1c variability in the group of patients with DM1 and DM2 was associated with a higher incidence of AKI, retinopathy and cardiovascular incidents; in addition, an increase in mortality was observed in the group of patients with type 2 DM. Many publications have succeeded in proving the adverse effect of glycemic variability on the prognosis of patients treated in the ICU [90, 91]. The study by Kapłan *et al.* [92] showed that the use of adrenaline and steroid therapy increased GV in critically ill patients, while an increase in GV correlated with an increase in mortality. The number of papers on the importance of GV in the cardiac surgery patient population is limited and focused mainly on subjects with ischemic heart disease. Predisposing factors for high perioperative GV have been shown to include elevated preoperative HbA_{1C} (≥ 6.5%), type 1 DM, and emergency surgery [93, 94]. In a retrospective analysis, Bansal *et al.* [95] identified increased GV as an independent risk factor for postoperative AKI and prolonged ICU stay. The effect on the development of postoperative AKI was also confirmed in a study by Nam *et al.* [96]. Sustained high GV was also associated with the risk of postoperative delirium among patients with aortic dissection. Sato *et al.* [97] reported that higher glycemic variability, as measured by continuous measurement in the postoperative period, increased the risk of SWI and AF. However, a major limitation of the study was the small study group of 76 patients [98]. In a meta-analysis of 22 publications, Liang *et al.* [99] found that in a group of patients with type 2 DM, a reduction in GV was associated with a decrease in insulin resistance and a decrease in the thickness of the intima-media complex of the carotid arteries. A higher rate of vascular complications, such as stroke and myocardial infarction (MI), as well as an increase in mortality, was observed in the group of patients with higher GV who underwent transcatheter aortic valve implantation (TAVI) [99].

Conclusions

Although the pernicious impact of hyperglycemia, most often in the course of DM, on the occurrence of perioperative complications is well known and documented, there is still a lack of comprehensive guidelines on the appropriate strategy for maintaining glycemia in the preparation for surgery and the perioperative period in cardiac surgery patients, taking into account baseline disease compensation, the burden of other chronic diseases, the additional impact of perioperative stress or fluctuations in glucose levels over time. The nature of the procedure and the pathophysiology of the condition that is the indication for surgery are also important. Most of the publications presented in this article concern the largest group of cardiac surgery patients, namely those with coronary artery disease undergoing CABG. These observations should not be uncritically transferred to other groups of patients, such as those with congenital heart disease. The lack of updated recommendations is a concern. The STS guidelines for the perioperative management of patients with DM are still the leading recommendations worldwide, even though they date back 13 years.

In the preoperative period, the focus should be on glycemic control, both in the form of daily profile and HbA_{1C}, and optimization of individual cardiovascular risk factors. It is advisable to postpone elective surgery in a situation of metabolic disequilibrium. If hyperglycemia > 180 mg/dl occurs, an intravenous insulin delivery route should be chosen. If it was started in the preoperative period, it should be continued uninterrupted in the intraoperative window and for a minimum of the first 24 hours after surgery, taking into account the influence of additional hyperglycemic factors, such as parenteral nutrition or intravenous steroid therapy. It is recommended that each center have an established algorithm for insulin use and glycemic control to ensure a more stable course of treatment.

Summarizing the set of scientific data presented, the liberal model is currently recommended. It represents a compromise between the adverse effects of both hyper- and hypoglycemia. However, determining the boundary between these strategies still requires further research. Phrases such as liberal or restrictive control, on the other hand, are still ambiguous, as they are sometimes defined differently in scientific designs (different glycemic thresholds), and the timing of the intervention (insulin therapy) and the prospective follow-up itself (prognosis analysis) vary. It is also noted that high variability of glycemia, both in the short and long term, is associated with increased mortality and postoperative complications. In the postoperative period, one should also focus on factors that may exacerbate hyperglycemia that were not present before surgery, such as inadequate pain control. Efforts should be made to mobilize the patient as soon as possible and to introduce oral nutrition to improve glucose metabolism.

Nevertheless, data on the effect of DM treatment on postoperative complications and prognosis of strictly cardiac surgery patients are still lacking. This prompts further research that may influence clinical practice.

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