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Glycemic Control in Cardiac Surgery

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1. Introduction

In cardiac surgery, hyperglycemia is a common occurrence in patients with and without diabetes (1,2). For many years, stress-induced hyperglycemia was considered an adaptive and beneficial response of the organism. However, both human and animal studies suggest that it is not a benign condition and, in contrast, it is associated with a high risk of morbidity and mortality. Stress hyperglycemia is defined as an elevation of plasma glucose levels (above 126 mg/dl in fasting condition or 200 mg/dl at any time) in critically ill or hospitalized patients, with or without history of diabetes (3). More specifically, elevated values of blood glucose in presence of normal levels of glycosylated hemoglobin (HbA1c), regardless of diabetes status, may be considered a stress response; this kind of hyperglycemia is developed during any physiological reaction to a situation of high metabolic demand or injury, in which diverse mechanisms become active for maintaining homeostasis, for example: major burns, severe trauma, hemorrhage, septicemia, and major surgery, in which it is very common for blood sugar to reach levels up to 370 mg/dl (4). It was the French physiologist Claude Bernard who first described this phenomenon in dogs subjected to hemorrhagic shock in 1885 (5); since then, this finding has been extensively studied, especially in recent decades because of it´s impact on outcomes of critically ill patients.

Hyperglycemia is a well recognized condition that increases the overall hospital morbidity and mortality of any patient admitted for any reason. In addition, it also increases the rate of complications in diabetic and non-diabetic patients undergoing major surgeries; besides this condition is associated with a longer hospital-stay and higher costs (1). Considering the strong association between hyperglycemia and general morbidity and mortality in surgery, there has been great interest for developing protocols to control blood-glucose levels during the perioperative period in order to prevent hyperglycemia, to achieve euglycemia and to reduce episodes of hypoglycemia, aiming the improvement of patient outcomes. In particular, the glycemic control in cardiac surgery has become a very important matter in

the full standard care as a mean of reducing infections and further complications, and in consequence, the patient's improvement.

This chapter reviews the mechanisms of stress hyperglycemia, the evidence of the association between hyperglycemia and adverse outcomes in surgical patients particularly in cardiac surgery. Besides, it offers a general overview about discordant reports found in the literature on the strict glycemic control during the peri-operative period of a cardiac surgery. In addition to, it also recommends common approaches to control the glycemia in surgical intensive care unit (ICU) and post-surgical cardiovascular patients based on the best performed randomized controlled trials.

2. Mechanisms of stress hyperglycemia

Stress Hyperglycemia, also called stress-induced diabetes, diabetes (6), is a multifact metabolic disorder that is characterized by the presence of hyperglycemia with hyperinsulinemia, peripheral resistance to insulin and an over-production of glucose by different mechanisms that result in incremented glycogenolysis and increased gluconeogenesis. Figure 1 shows how endogenous and exogenous predisposing factors may trigger the development of stress hyperglycemia, particularly during a cardiac surgery. The most important trigger is the surgical stress itself that conduces to a catabolic state that results in high levels of blood-glucose; the appearance of stress-hormones and a diminished peripheral response to insulin, cause hyperglycemia, and raises even more previous glycemia breeding an abnormal immune response (3, 6-9.). Stress hyperglycemia is caused mainly by the effects of counter-regulatory hormones (catecholamines, growth hormone, and cortisol) and by depletion of the functional reserve of the beta-cells in the Langerhans islets of the pancreas (7). During perioperative period of major surgeries, the counter-regulatory hormones and the inflammatory response induced by surgical stress are the most important triggers of hyperglycemia (10). The degree of insulin resistance has been related to the magnitude and endurance of surgical stress. In addition, it has been reported that in the perioperative period, increased glucose reabsorption or decreased renal glucose clearance may enhance this phenomena that contribute to hyperglycemia (11).

Predisposing factors

Although stress hyperglycemia is mainly caused by six events: severe trauma, bleeding, hypothermia, septicemia, severe burns and great-magnitude surgeries, there are several factors that may contribute to this alteration, which could and should be explored in the preoperative examinations (Table 1). All of these predisposing factors can be divided in endogenous and exogenous factors.

a. Endogenous factors

The first and most important predisposing factor for developing stress hyperglycemia is to be previously diagnosed with Diabetes Mellitus; in this case glucose blood-levels after cardiac surgery may reach even 20 mmol/l (370mg/dl) or more, compared with non-diabetic patients which might reach 15 mmol/l (270 mg/ml) (12-14). With a previous diagnosis of diabetes, it is not just more likely to develop stress hyperglycemia, but this one is more severe.

Other endogenous factor is acute pain which inhibits the suppression of endogenous glucose by insulin; in addition, it releases diverse acute-stress hormones that contribute hyperglycemia, such as cortisol, glucagon, growth hormone, etc. (15). It has been impossible

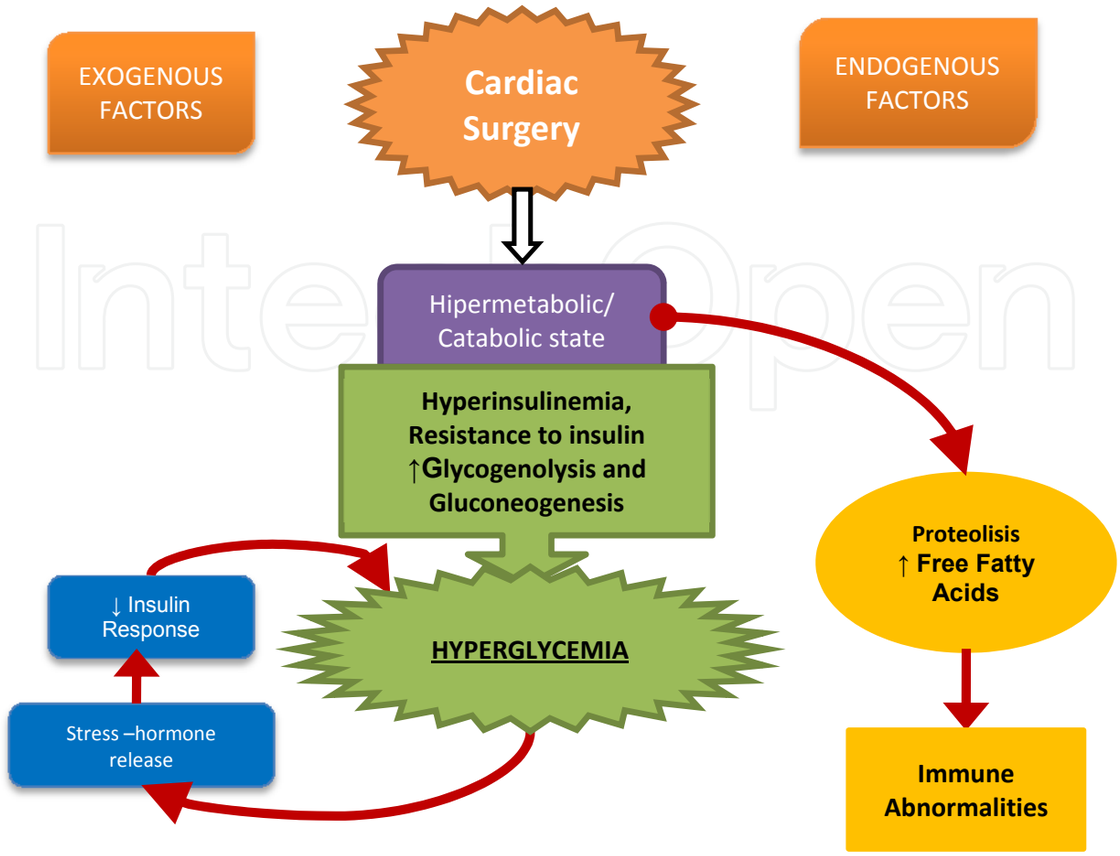

Fig. 1. It is showed how endogenous and exogenous predisposing factors may trigger the developing of stress hyperglycemia, adding cardiac surgery's aggression. Physiological-stress triggers a catabolic state that results in stress hyperglycemia; the appearance of stress-released hormones and a diminished peripheral response to insulin augment glycemia, and condition the release of proteins and free fatty acids that in addition to hyperglycemia entail an abnormal immune response.

to quantify the real affection caused by pain in the glucose-metabolism, but the tendency of an aggressive-pain management might be helpful for decreasing the peripheral resistance to insulin (16).

Elderly patients represent an important group that undergoes cardiac surgeries; it is well known that insulin secretion is diminished in this group of age. This is reinforced by different studies; the comparison between patients over 60 years versus younger people shows incidence-reduction of hyperglycemia up to 38% in young adults (17). So, elderliness is a very important factor for elevated blood glucose levels (18).

b. Exogenous factors

Hypothermia, especially present in coronary bypass surgery due to cardioplegic solutions, provokes hyperglycemia by inhibiting the negative-feedback of the insulin response (19). Also, desaturation and arterial hypoxemia, increase a sympathetic autonomous response that favors glucagon release by an alpha-receptor action (20).

Many drugs commonly used with inpatient care might modify glucose metabolism. Some of them are well known as 'diabetogenic' medications such as glucocorticoids and opiates;

Action	Factor
Insulin deficiency (relative or absolute)/Insulin resistance	Diabetes mellitus
Higher counterregulatory hormone levels	Acute Pain Elevated Acute Physiology and Chronic Health Evaluation (APACHE) score
Insulin Peripheral resistance	Catecholamine-Infusion Glucocorticoid treatment Overweight Septicemia/Sepsis/Septic Shock Uremia Bed rest Fasting
Insulin impaired secretion	Elderly Hypothermia Hypoxemia

Modified from ref. 29: McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin* 2001; 17: 107-24.

Table 1. Predisposing factors for developing stress hyperglycemia

others are used for treating hypertension such as calcium channel blockers, clortalidone, and prazosin. Every synthetic catecholamine or catecholamine-agonist or blocker (such as epinephrine, norepinephrine, salbutamol, metoprolol, propanolol) and tricyclic anti-depressants, might elevate glucose levels. Particularly, catecholamine-infusion during cardiac surgery contributes greatly to this metabolic state during surgery, as well as in the early postoperative period; it might also overlap and/or worsen stress response. Even alcohol and salicylates raise glycemia. All volatile anesthetic agents, including halothane, enflurane, and isoflurane, inhibit the insulin response to glucose in a dose dependent manner in vitro (21). The hyperglycemic response during inhaled anesthesia with isoflurane is a consequence of both impaired glucose clearance and increased glucose production (22,23).

Other factor that contributes to augment glycemia is bed resting. This condition reduces the sensitivity of the skeletal muscle to insulin, and in consequence increases fasting plasma insulin concentration as well as oral glucose challenge; insulin clamp studies showed no insulin secretion deficiency during repose. This response is mainly because of proteolysis that reduces total muscle mass and decreases the total number of transporters (24).

Other exogenous factor is the preoperative fasting. Fasting is a routinely action taken before undergoing a programmed cardiac surgery; fasting before surgery diminishes the glycogen reserve, induces protein breakdown (that releases alanine) and might disrupt insulin action and the stress responsiveness (25).

An underappreciated cause of hyperglycemia in critically ill patients is the provision of dextrose in excessive of amounts that can be easily oxidized or stored. In addition to hyperglycemia, other complications may result from the administration of dextrose over the rate of 4 mg/kg/min, inducing lipogenesis and increased carbon dioxide production (26).

The role of the glucose transporters

Stress-induced diabetes seems to be supported mainly by peripheral resistance to insulin, i.e. the inability of skeletal muscles and adipocytes to uptake glucose. This condition appears because of the affection of the glucose transporter type 4, called GLUT4 which is dependent of insulin. This very important hexose-transporter is located in skeletal-muscle, cardiac muscle and adipocytes (27). This protein is member of a family of transmembranal proteins that are responsible for uptaking glucose in different cells which depend of insulin for their action. These transporters are responsible of plenty of physiological phenomena that maintain glucose homeostasis (28,29). The physiological stress inhibits -by different mechanisms- the insulin's action on the GLUT4, mainly by impairing the phosphorylation of several molecules of the intracellular signaling pathway of insulin (30); the result is a decreased function of the transporter and therefore, a diminution of insulin-mediated glucose uptake. Additionally, the transporters GLUT1 (present in endothelial and non-skeletal muscle cells) and GLUT3 (present in neurons) are affected –as well as GLUT4 -by diverse cytokines such as IL-1, IL-6 and C-Reactive Protein which are augmented in surgical stress (29, 31,32).

Non-glucosydic substrates used during stress hyperglycemia

The carbohydrate metabolism during periods of stress uses different non-glucosydic substrates for gluconeogenesis such as glycerol, alanine, pyruvate and lactate. The last two mentioned molecules are generated when aerobic glucolysis and Kreb's cycle is impaired (23). In particular, lactate is produced because of inhibition of the pyruvate-dehydrogenase enzyme, mainly by IL-1, IL-6 and Tumoral Necrosis Factor-alpha (TNF-α) (33,34). The aminoacids alanine and glutamine are substrate for gluconeogenesis of critical illness. They are derived from proteolysis of skeletal muscle (33). The alanine is converted to glucose via Cori´s cycle (29). Glycerol is a product of lypolisis, and might be elevated because of the action of several counter-regulatory hormones (29), glycerol is used as a substrate of 20% of hepatic-derived glucose (29).

The role of the counterregulatory hormones

Hyperglycemia severity is directly correlated with the intensity of the inflammatory response (6). It is well known that inflammation produces an endocrine response that releases the so called "stress hormones" that raise glucose plasma levels. A wide variety of both hormones and cytokines affect glucose homeostasis by different pathways, including the promotion of gluconeogenesis or provoking insulin resistance; when hypoglycemia becomes present (less than 70 mg/dl, 3.9 mmol/l) there is a correlation with the initial threshold for releasing counterregulatory hormones and cytokines (35,36).

In healthy people, when gluconeogenesis is augmented, glucagon production is inhibited and insulin is released to the circulation; in the post-operated patient, there is an inflammatory response in which endogenous –or exogenous- cytokines and cathecolamines may interfere with this negative-feedback system and allow a hyperglycemic state by augmenting hepatic gluconeogenesis and glycogenolysis (34).

Although adrenaline, noradrenaline and cortisol are the best-studied hormones in the metabolic response to trauma, the most important stress hormone in postsurgical stress is the Growth Hormone (37). In other hand, adrenaline and noradrenalin are cathecolamines that greatly impair carbohydrates' metabolism. Adrenaline has shown to increase hepatic gluconeogenesis (29, 38), favors glycogenolysis in skeletal muscle and impairs glucose

uptake in peripheral tissues, and via the β-3 adrenergic receptor, elevates free fatty acids (FFAs) in plasma (39). Likewise, noradrenaline may promote gluconeogenesis because its lipolytical effects and the marked glycerol supply to the liver (40). The glucogenolytic state mediated by these cathecolamines lasts no more than 36 hours (29). Additionally, cortisol is a major insulin counterregulatory hormone, which stimulates hepatic glucose production and enhances renal glucose production through glyconeogenesis, favors the presence of FFAs in plasma (34,41).

Growth Hormone is a very well known "diabetogenic" hormone and is the most important counterregulatory hormone present in surgical stress. It inhibits the insulin signaling cascade and it has been demonstrated in experimental animals to reduce the number of insulin receptors, as well as it reduces the phosphorylation on tyrosine residues triggered by insulin (42). Growth hormone also raises FFAs into plasma, and greatly affects the GLUT-1 and GLUT-4 activity (43). The Insulin-like Growth Factor (IGF-1 and -2) characterizes hepatic resistance to insulin's action, it has been proved that it keeps a direct association with mortality (44). There is not a clear relationship between every individual hormonal response that may result in a common phenomenon: hyperglycemia. More research is needed for augmenting our knowledge about hormonal regulation of this phenomenon, and also for understanding the role and importance of each one of these endocrine signals. Figure 2 shows how stress hormones might disrupt glucose metabolism by causing resistance to insulin's action and starting the usage of non-glucosydic substrates that contribute to raise glycemia.

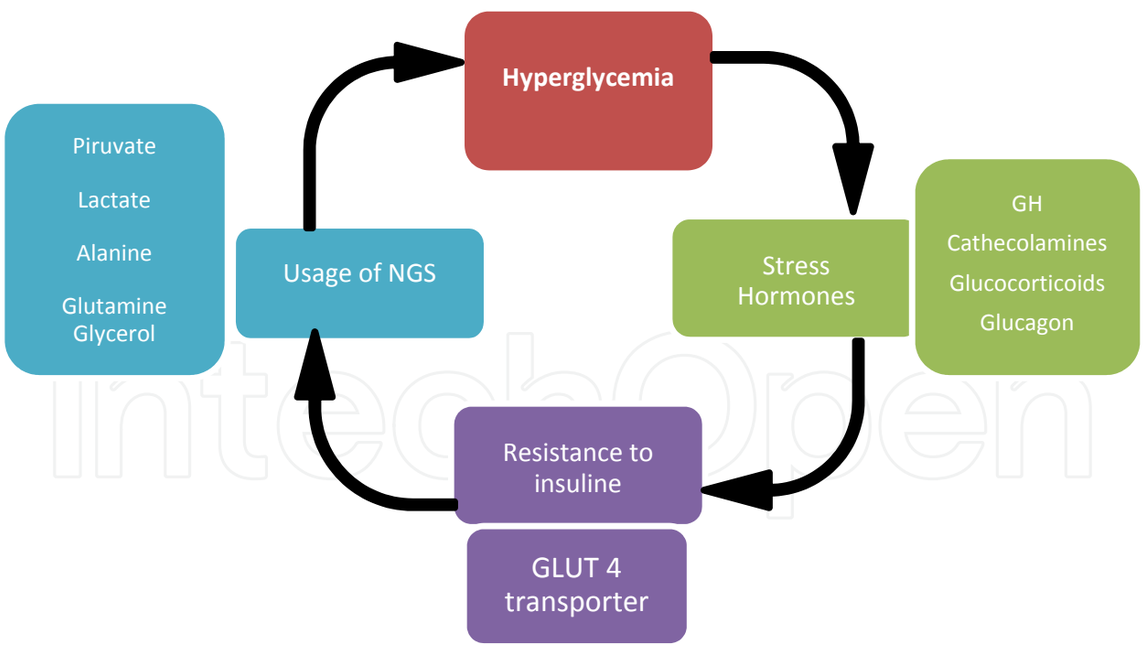

Fig. 2. The release of stress hormones produces gluconeogenesis and peripheral resistance to insulin. Stress hormones might disrupt glucose metabolism by causing resistance to insulin's action in the GLUT-4 transporter and originates the usage of non-glucosydic substrates, that contribute to raise glycemia. GH: Growth Hormone. NGS: non glucosydic substrates.

The role of the inflammatory response

Surgical stress establishes an acute inflammatory response that promotes the release of different cytokines –specifically TNF-α, IL-1, IL6- from mononuclear cells, this contributes to insulin resistance (29) and raising glucose levels in blood; at the same time, induces the production of diverse pro-inflammatory and mitogen cytokines like the nuclear factor kappa-B (NF-kB), the Early Growth Response-1 gene, the Plasminogen Activator Inhibitor-1 (PAI-1), Intracellular Adhesion Molecule-1 (iCAM-1), Monocyte Chemotactic Protein-1 (MCP-1) and matrix metalloproteinases-1, -2 and -9.

The mechanism whereby TNF-α mediates stress hyperglycemia has been well studied. This cytokine causes insulin resistance in both liver and skeletal muscle (6) most likely through the modification of signaling properties of insulin receptor substrates. In particular, endotoxin derived from cell wall of Gram-negative bacterial is also a potent stimulant of secondary production of TNF-α and various proximate interleukins, mainly IL-1 and -6 which disrupt both the insulin post-receptor signaling and the phosphorylation of molecules associated to the tyrosine-kinase receptor that lastly affects GLUT's activity, and glucose uptake (32, 45).

The Nuclear Factor kappa-B (NF-kB) is a pleiotropic transcription factor that is present in almost all cell types and is involved in many biological processes such as inflammation, immunity, cell differentiation, growth and apoptosis, and carcinogenesis. The early growth respone-1 gene is a nuclear protein that functions as a transcriptional regulator that favors cell differentiation and mitogenesis. The intracellular Adhesion Molecule-1 (iCAM-1) favors leucocyte adhesion, and metalloproteinases help in extracellular matrix remodeling (46-48). Hyperglycemia affects immune cellular responsiveness by reducing neutrophyle activation, chemotactism, fagocytosis, and diminishing bactericidal activity of the reactive oxygen species (ROS). Humoral-cell response is affected by immunoglobulin glycosylation and altered synthesis of IL-6 and TNF-α (6,9). As mentioned, hyperglycemia has been associated to an altered immune response, an enhanced proinflammatory response, endothelial dysfunction, a hypercogulability state as well as neural damage with an augmented oxidative stress and secondary release of ROS from leucocytes (8,49).

All conditions above mentioned make up a not favorable setting for the surgical patient and represent a challenge to reach out a condition of stable normoglycemia. Figure 3 shows the relationship in between the abnormal glucose usage and how does physiological stress modifies the carbohydrate metabolism, leading to a deleterious non-homeostatic condition.

3. The stress hyperglycemia and adverse outcomes in surgical patients

The hyperglycemic response to acute stress induced by surgery was initially considered a beneficial-adaptive response, being the raised blood glucose a ready "source of fuel" for several tissues including the neural and cardiac-muscle cells. However, retrospective studies in patients undergoing cardiac surgery have suggested that perioperative hyperglycemia was associated with an increased risk of post-operative infections and an increased mortality (50-52). Furthermore, these studies suggested that control of blood glucose reduced these complications. The severity of hyperglycemia depends on many factors as showed in Table 1. There are different mechanisms in which a variety of risk factors affect the glucose metabolism and insulin responsiveness (53). Specifically, on surgery-invasiveness: the more invasive the surgery, the more intense the hyperglycemia (11, 54). Stress hyperglycemia has many deleterious effects, including vasodilatation, impaired

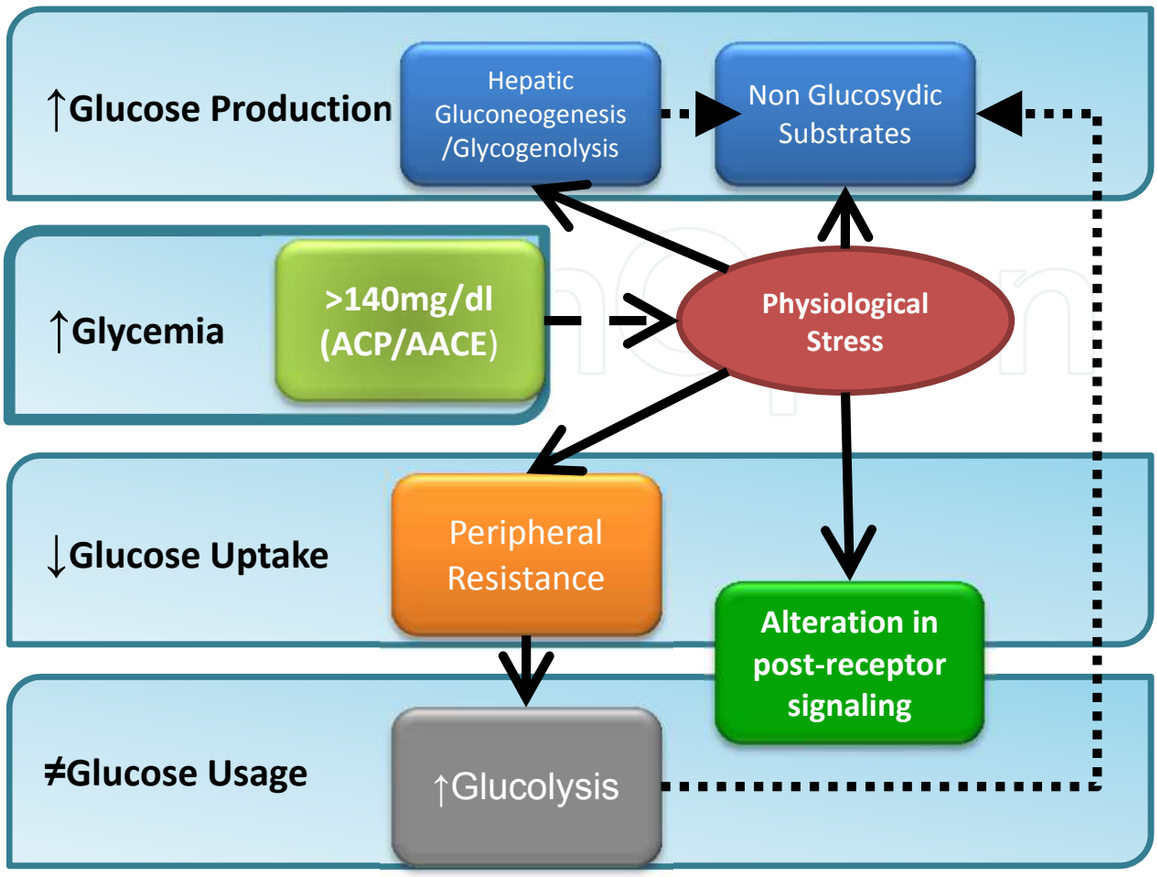

Fig. 3. The relationship between the abnormal glucose usage and physiological stress is exposed. Stress modifies the carbohydrate metabolism, the augmented glucose production and a diminished glucose uptake raises blood glucose levels, as well as the glucose intracellular metabolism is deviated.

reactive endothelial nitric oxide generation, decreased complement function, increased expression of leukocyte and endothelial adhesion molecules, increased cytokine levels, and impaired neutrophyle chemotaxis and phagocytosis, leading to increased inflammatory state and infection-vulnerability, and multiorgan system dysfunction (55). Others effects of excessive glucose levels include the impairment in hepatic functions, abolishment of ischemic preconditioning, and protein glycosylation (56).

Cardiac Surgery has been traditionally considered a highly-invasive procedure (57, 58) and taking in account that the hyperglycemic response is increased by anesthetics and the preoperative emotional stress (59), this major surgery, induces the release of several counter-regulatory hormones and deeply modifies the metabolism of carbohydrates, causing increased hepatic gluconeogenesis, insulin resistance in various peripheral tissues, and the relative insulin production deficiency (60,61). This insulin resistance has been related to an increased risk of postoperative complications in cardiac surgery, regardless of the patient´s diabetic status (62).

These metabolic and physiological responses to surgical stress often cause maintaining euglycemia during a cardiac surgery, to become a very difficult goal. Nevertheless, the reports about association of hyperglycemia and adverse outcomes in cardiac surgery make

the glycemic control, something indispensable. Cardiac surgery mortality, tightly correlated to glucose blood levels, becomes significant lower when glycemia reaches less than 150 mg/dl (63) and it raises to even 17% with every 1 mmole/l (18 mg/dl) over 6.8 mmole/l (110 mg/dl) (61,64). Hyperglycemia during cardiac procedures and pulmonary bypass is severe, particularly in diabetic patients - who comprise a significant percentage of the patient population that undergo cardiac surgery. As it was commented, this impairment in glucose metabolism is related considerably to the metabolic response to surgical trauma, but it is associated mostly to specific aspects of cardiopulmonary bypass, such as heparinization, hypothermia, and rewarming (65, 66).
Independently of controversy about the reports on tight control of glycemia during perioperative period, is well known than poor perioperative glycemic control is associated with an increased morbidity and mortality.

4. Approaches on glycemic control during the perioperative period in cardiac surgery

In 2001, van den Berghe and coworkers (67) published a "landmark study" named "The Leuven Intensive Insulin Therapy Trial". In this study, they demonstrated that in critically-ill patients –the majority of them undergoing cardiac surgery- the Tight Glycemic Control (TGC) (blood glucose between 80-110 mg/dl) using intensive insulin therapy (IIT), improved the general clinical outcome (significant reduction in mortality; 42%) (67). After this study was published, TGC became rapidly adopted as the reference standard of care in surgical ICUs throughout the world (63, 68). The publication of new randomized controlled trials has diminished the initial enthusiasm on TGC because it has also been linked with increased morbidity and mortality. In last decade, there have been reports about the IIT has led to an increased iatrogenic rate of hypoglycemia episodes, emerging as an important risk factor for mortality exceeding, in some cases, the mortality-risk associated with hyperglycemia. In fact, even moderate and short hypoglycemia events in the ICU can produce permanent brain damage (69). After van den Berghe's work, two multicenter-randomized European studies were prematurely discontinued due to an alarmingly high rate of hypoglycemia in the TGC arm, showing no mortality benefits (70, 71). Two additional single centers, randomized studies showed a trend towards a higher mortality in the TGC arm (72, 73). TGC is strongly associated with an even sixfold-increase in episodes of severe hypoglycemia (glucose levels < 2.2 mmole/l, 40 mg/dl) (20) and, as mentioned before, this state can have dramatically adverse effects such as coma or even death (74). The recent NICE-SUGAR study showed that an intensive glucose control increased mortality among ICU adults, and that an 81-108 mg/dl target was too ambitious and potentially dangerous (12).
On the other hand, glucose variability has emerged as another important factor associated with mortality (75). Glucose profiles from patients are characterized by important fluctuations, even during continuous intravenous insulin infusion. However, many of the reported trials have evaluated the effects of IIT based on the absolute glucose levels, although clinical effects of IIT should be interpreted using temporal courses (76, 77). From this point of view, we should consider simultaneously the combined and independent clinical impact of glycemia's sudden fluctuations, glycemia temporal trends, and glycemia variability during hospitalization. In this way of thought, in a study including over 7,000 critically ill patients was demonstrated that the standard deviation of glucose concentration is a significant independent predictor of ICU and hospital mortality (78). Recently, it has

been reported a relationship between ICU mortality and glucose variability in a cohort of 5,728 patients managed with IIT (79).

Although there is agreement that both hyperglycemia and hypoglycemia are deleterious, and that we should consider the fluctuations in blood glucose levels, there is no a consensus on the target glucose values to enhance desirable clinical outcomes. In this regard, relatively recent guidelines have been published from different international study-groups, like the American College of Physicians (ACP), American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE) and the European Society of Cardiology (ESC) (80,81). The next section is related with recommendations about management of hyperglycemia in both patients with and without diabetes undergoing cardiac surgical, and the procedures that should be taken into account during the perioperative period, obtained from the Society of Thoracic Surgeons (STS) Practice Guideline series (81), which is derived in turns from evidence-based recommendations. We consider these guidelines as the most important work on the glucose management in cardiac surgery and we mention several paragraphs textually.

In summary, these useful guidelines offer some central ideas about the management of glycemia during cardiac surgery. The first of them is about detrimental effects of hyperglycemia in perioperative period, and they highlight that poor perioperative glycemic control is associated with increased morbidity and mortality, quoting the guidelines: "Collectively, these studies strongly suggest that increased fasting glucose levels during and immediately after cardiac surgery, are predictive of increased perioperative morbidity and mortality in patients with and without diabetes" (81). In this regard, the following central idea is about the beneficial effects of glycemic control on clinical outcomes during cardiac surgery, and afterwards, it recommends - after a review of the most important randomized trials - a glycemic control <180 mg/dl, mainly in patients with diabetes during cardiac surgery.

In the following paragraph, guidelines are focused about glycemic control in patients without diabetes during cardiac surgery, and they point –after analyzing several randomized trials of good quality- that "intraoperative glycemic control using intravenous insulin infusions is not necessary in cardiac surgery patients without diabetes, as well as glucose values remain < 180 mg/dl. This previous conclusion was obtained from the comparison between groups with TGC using IIT and without insulin finding no difference in the primary outcome, which consisted of the composite incidence of death, sternal wound infections, prolonged ventilation, cardiac arrhythmias, strokes, and renal failure within 30 days of surgery (82). There was also no difference in ICU or hospital stay between the groups. There was a tendency for more deaths (p=0.06) and strokes (p=0.02) in the IIT".

In the next section, the guidelines point to management of hyperglycemia using insulin protocols in the perioperative period considering that intravenous insulin therapy is the preferred method of insulin delivery during this period. It is used an evidence-based recommendations, depending on the procedure it is classified as beneficial, useful and effective (table 3; ref. 81). The recommendations class I are based on when glycemic control is best achieved with continuous insulin infusions rather than intermittent subcutaneous insulin injections or intermittent intravenous insulin boluses (level of evidence A). In addition, 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 (level of evidence=B; table 3).

Following the recommendations of the guidelines, the next part refers to the perioperative management and assessment for patients with diabetes. The next recommendations are classified after an exhaustive analysis of several trials with this kind of patients. Thus, we

Action	Factor
Lypolisis	Adrenaline Noradrenaline Growth Hormone
Enhanced Gluconeogenesis	Glucagon Glucocorticoids Growth Hormone
Supression of Insulin Secretion	Adrenaline Glucocorticoids (Cortisol)
Glucogenolysis	Adrenaline Glucagon
Peripheral Insulin Resistance	Tumoral Necrosis Factor alpha Adrenaline Glucocorticoids (Cortisol) Growth Hormone
Hepatic Insulin Impairment	Tumoral Necrosis Factor alpha

Modified from ref. 29: McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin* 2001; 17: 107-24.

Table 2. Major actions of counterregulatory hormones and cytokines in stress hyperglycemia

Class I: Conditions for which there is evidence for and/or general agreement that the procedure is beneficial, useful, and effective.
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIA: Weight of evidence/opinion is in favor of usefulness/efficacy
Class IIB: Usefulness/efficacy is less well-established by evidence/opinion
Class III: Conditions for which there is evidence or general agreement that the procedure/treatment is not useful/effective, or both, and in some cases may be harmful
Level of Evidence – A: Data derived from multiple randomized clinical trials
Level of Evidence – B: Data derived from a single randomized trial or nonrandomized studies
Level of Evidence – C: Only consensus opinion of experts, case studies, or standard- of-care

Modified from ref. 81: Lazar. *Ann Thorac Surg* 2009; 87: 663-669.

Table 3. Classification system used for evidence based recommendations from society of thoracic surgeons practice guidelines

have summarized the experience of these trials. Class I: a) "patients taking insulin should hold their nutritional insulin after dinner the evening prior to surgery (level of evidence=B). b) Scheduled insulin therapy, using a combination of long-acting and short-acting subcutaneous insulin, or an insulin infusion protocol, should be initiated to achieve glycemic control for in-hospital patients awaiting surgery (level of evidence=C; table 3). c) All oral hypoglycemic agents and noninsulin diabetes medications should be held for 24

hours prior to surgery (level of evidence=C). d) The hemoglobin A1c (HbA1c) level should be obtained prior to surgery in patients with diabetes or those patients at risk for postoperative hyperglycemia to characterize the level of preoperative glycemic control" (level of evidence=C; table 3). Class IIA. Prior to surgery, it is reasonable to maintain blood glucose concentration ≤ 180 mg/dl (level of evidence=C; table 3). Efforts should be made to optimize glucose control prior to surgery, because poor preoperative glycemic control has been associated with increased mortality, including a higher incidence of deep sternal wound infections and prolonged postoperative length of stay. In general, all oral diabetes medications should be withheld within 24 hours prior to surgery, especially sulfonylureas (eg, glipizide) and glinides (eg, nateglinide or repaglinide). These drugs can induce hypoglycemia in the absence of food. Patients who are taking insulin and who are admitted on the day of surgery should be instructed to continue their basal insulin dose (eg, glargina, determir or NPH) and hold their nutritional insulin (eg, lispro, aspart, glulisine, or regular) unless instructed otherwise by their primary physician. The NPH insulin may be reduced by one half or one third of the dose prior to surgery to avoid hypoglycemia.

"To achieve rapid control in hospitalized patient with hyperglycemia (glucose > 180 mg/dl for more than 12 hours before surgery), insulin therapy -either with intravenous variable-rate continuous infusion or subcutaneous basal plus rapid-acting insulin- should be used depending on the availability of either therapy. For the hyperglycemic patient in the preoperative area, on the day of surgery, IV insulin therapy is an effective way to achieve immediate control. Patients with a known history of diabetes (either type 1 or type 2) can be started immediately on IV therapy in the preoperative area. All preoperative medications should be reviewed to determine the potential for insulin resistance. These include steroids, protease inhibitors, and anti-psychotic drugs. Finally, patients with renal insufficiency should be identified, because insulin clearance is impaired and the risk for hypoglycemia is increased".

Next section is the "intraoperative control recommendations". Above recommendations are classified upon the level of evidence and quality of trials. Class I. a) Glucose levels > 180 mg/dl that occur in patients without diabetes only during cardiopulmonary bypass may be treated initially with a single or intermittent dose of IV insulin as long as levels remain ≤ 180 mg/dl. However, in those patients with persistently elevated serum glucose (> 180 mg/dl) after cardiopulmonary bypass, a continuous insulin drip should be instituted, and an endocrinology consult should be obtained (level of evidence = B; table 3). b) If an intravenous insulin infusion is initiated in the preoperative period, it should be continued throughout the intraoperative and early postoperative period according to institutional protocols to maintain serum glucose ≤ 180 mg/dl (level of evidence = C; table 3).

Concerning glycemic control in the ICU, guidelines recommend the following procedures: Recommendation Class I. a) Patients with and without diabetes with persistently elevated serum glucose (> 180 mg/dl) should receive IV insulin infusion to maintain serum glucose < 180 mg/dl for the duration of their ICU care (level of evidence = A; table 3). b) All patients who require ≥ 3 days in the ICU because of ventilatory dependency or requiring the need for inotropes, intra-aortic balloon pump, or left ventricular assist device support, anti-arrhythmics, dialysis, or continuous veno-venous hemofiltration should have a continuous insulin infusion to keep blood glucose ≤ 150 mg/dl, regardless of diabetic status (level of evidence =B; table 3). b) Before intravenous insulin infusions are discontinued, patients should be transitioned to a subcutaneous insulin schedule using institutional protocols (level of evidence=B; table 3).

Finally, the Glycemic control in the stepdown units and on the floor recommendations is the last part of the guidelines. Class I. a) A target blood glucose level < 180 mg/dl should be achieved in the peak postprandial state (level of evidence = B; table 3). b) A target blood glucose level ≤ 110 mg/dl should be achieved in the fasting and pre-meal states after transfer to the floor (level of evidence = C; table 3). c) Oral hypoglycemic medications should be re-started in patients who have achieved target blood glucose levels if there are no contraindications. Insulin dosages should be reduced accordingly (level of evidence = C; table 3). d) According to the AACE, a reasonable goal for a noncritically ill patient on a regular hospital ward is < 110 mg/dl and< 180 mg/dl postprandial or randomly (83). The best method to realize this control is with scheduled subcutaneous basal and, or bolus insulin therapy, such as glargine or determir (basal) and lispro, aspart, or glulisine (bolus). Patients with type 2 diabetes who have used oral diabetes medications preoperatively can be restarted on those medications once they have reached their targeted glucose goals and are eating a regular diet. Metformin should not be restarted until stable renal function has been documented. In relation to preparation for hospital discharge, the guidelines recommend that prior to discharge, all patients with diabetes and those who have started a new glycemic control regimen, should receive in-patient education regarding glucose monitoring, medication administration (including subcutaneous insulin injection if necessary), nutrition, and lifestyle modification (level of evidence = C, table 3). Upon discharge, changes in therapy for glycemic control should be communicated to primary care physicians, and follow up appointments should be arranged with an endocrinologist when appropriate (level of evidence = C, table 3). All patients with hyperglycemia after cardiac surgery should be assessed by an inpatient diabetes team to decide on a glycemic control program after discharge.

The conditions that are important to consider are, in summary: avoidance of deep hypothermia, excessive blood losses, a prolonged preoperative fasting period and prolonged immobilization, because all these conditions augment perioperative insulin resistance. In addition, considering that most anesthetic agents cause hyperglycemia, the choice of anesthetic agent will be influenced by the severity of systemic diseases, such as coronary artery disease, nephropathy (with the concomitant risk of hyper/hypokalemia and other hidroelectrolytic disorders), and hypertension, and the choice of neuromuscular blocking agent will be affected by renal function.

5. Conclusion

Although reports differ, and not enough data are available to allow specifying optimal treatment goals or the best approach to perioperative management of glycemia, it is clear that surgical outcomes are improved in patients who are maintained in good metabolic control. Physicians must be cognizant of patients´ preoperative control, in diabetic patients, their relative need for insulin, and any factors that may be likely to increase insulin requirements. The guidelines presented here represent just an approximate approach based in evidence with different qualities. So, the administration of adequate glucose in conjunction with the judicious use of insulin will prevent hypoglycemia. However, diabetic ketoacidosis or hyperosmolar states, which may result from inadequate dosing of insulin, are not so easily managed. The key to success of any perioperative management plan is frequent monitoring of glucose, electrolyte, and fluid levels, and acid-base status. Prevention of surgical complications as a result of hyperglycemia is possible with

meticulous perioperative glucose management. Finally, we need further research to be done to provide definitive answers on the benefits of tight glycemic control for cardiac surgery patients.

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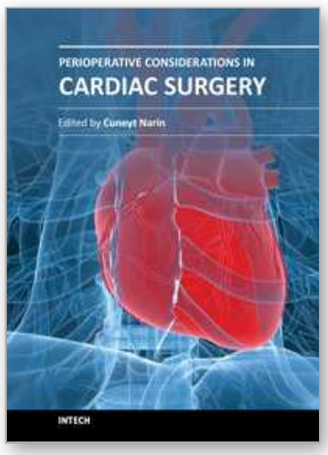

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This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

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