Glucose metabolism in cardiovascular surgery

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ABSTRACT

During the past few years, it has become evident that metabolic control is a major determinant of postoperative outcomes, not only for diabetic patients but for all patients undergoing surgery.

In cardiac and vascular surgery, myocardial ischemia is a common challenge and the management of hyperglycemia should be part of the strategy aimed at optimizing cardiac protection during these types of surgery, since performed in high risk patients.

Little informations are available on the relation between glucose substrate and the type of anesthesia and few studies have been performed on glucose metabolism in the perioperative risk assessment as well as on intraoperative and post surgical management of hyperglycemia in patients submitted to cardiac and vascular surgery. Evidence exists that even slight increased in glycemia are detrimental for patients (diabetic and non) elective for cardiac and vascular surgery, though the precise details of the timing of insulin therapy, the desired target serum glucose level, and the duration of therapy are so far to be completely elucidated. Anesthestiologists can therefore affect outcome by simply preserving a normal blood glucose concentration initiating in the operating room. The challenge to optimize glucose control should begin during preoperative evaluation.

Keywords: *glucose, perioperative, insulin, cardiac surgery, vascular surgery.*

INTRODUCTION

Patients with diabetes mellitus run a greater risk of complications when subjected to surgery (1, 2) and diabetes is a common coexisting disease in patients submitted to vascular surgery (3).

Metabolic control is a major determinant of postoperative outcomes, not only for diabetic patients but for all patients undergoing surgery (4). In cardiac and vascular surgery myocardial ischemia is a common challenge and the management of hyperglycemia should be part of the strategy aimed at optimizing cardiac protection during these types of surgery.

Little information is available on the relationship between glucose substrate and the type of anesthesia and few studies were performed on glucose metabolism in the perioperative risk assessment as well as on intraoperative and post surgical management of hyperglycemia in patients submitted to cardiac and vascular surgery.

Glucose metabolism in ischaemic myocardium

Heart metabolism is predominantly aerobic, with the majority of energy supplied by oxidative phosphorylation. In physiologic conditions, oxidation of free fatty acid (FFA) supports 60 % of the total energy demand, ketone bodies 27 %, and lactate 12 % while glucose participates for less than 1 % (5).

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During mild or moderate ischaemic conditions, when oxygen availability is reduced, glycolysis may become the main source for the ATP needed to maintain the ionic gradients through membranes and glucose uptake is then improved.

Deleterious effects of hyperglycemia on the heart

Hyperglycemia harms the heart in several ways:

a) *hypovolemia*. Hyperglycemia may promote osmotic diuresis, leading to a reduced circulating volume and decreased end-diastolic and stroke volumes (6), though the importance of such a mechanism has not been completely elucidated.

b) *inflammation*. Hyperglycemia per se induces a pro-inflammatory state, involving both cellular and oxidative stress. At the cellular level, glucose is known to increase pro-inflammatory transcriptor factors (such as intranuclear NFkB binding, activator protein-1 and early growth response-1) that are conversely suppressed by insulin (7).

c) *pro-coagulation*. Acute glycemic variations are associated with a prothrombotic status related to several alterations of the haemostatic pathway, including lengthening of fibrinogen half- life, increased number of pro-thrombin fragments, factor VII, and an enhanced platelet aggregation. Accordingly, glucose and hyperglycemia, even if transient, may promote atherosclerotic plaque rupture and the resulting vessel occlusion, presumably via an inflammatory phenomenon (8, 9).

d) *modulation of nitric oxide metabolism*. Hyperglycemia inhibits the activity of endothelial nitric oxide synthase activity via the hexosamine pathway, thus promoting endothelial activation, increased microvascular permeability, capillary leakage, leukocyte adhesion and aggregation together with intravascular coagulation and thrombosis (7, 10-12).

e) *modulation of oxidative stress*. In the presence of high glucose concentrations, several steps of the glycolytic pathways can induce the release of toxic derivatives, including polyols derived from glucose, hexosamines from fructose-6-phosphate, advanced glycation products, and activators of the protein kinase C pathway from glyceraldehyde-3-phosphate.

Glucose substrate and the anesthetic technique

Little information is available on the relationship between glucose metabolism and anesthetic technique, mainly deduced from studies in animal models.

The fasting procedure before cardiac elective operation, at least 12 hours, results in low insulin levels (removing insulin-inhibition of lipoprotein lipase), increased FFA concentration and decreased glucose concentration. General anesthesia results in higher blood glucose concentration than does local or epidural anesthesia (12). Many anesthetics differently affect plasma glucose and insulin levels, with minor effects on plasma FFA. In animal models pentobarbital and sufentanil-propofol are without effect on plasma glucose concentration while volatile anesthetics result in hyperglycemia, and that (which) can be explained, at least partly, by impaired glucose-induced insulin release (13). Propofol, at anesthetic concentrations, was able to prevent the endothelial dysfunction induced by glucose overload in bovine aortic cells mainly by the inhibition of cellular glucose uptake (18). A progressive increase in glucose, as a function of time, was described during remifentanil infusion in patient undergoing gynecologic videolaparoscopy (14).

Moreover, other drugs frequently used during vascular and cardiac surgery, apart from anesthetics, can affect glucose metabolism during operation (15). Heparin (frequently used during cardiac surgery operations) can

induce a several-fold increase in plasma FFA levels by inducing the release of hepatic and endothelial-bound lipoprotein lipase (16). Catecholamines, both endogenous and exogenous inhibit insulin secretion and activate lipolysis in adipose tissue with increased plasma FFA (17, 18).

Therefore each surgical/anesthesia team should assess the metabolic profile associated with its perioperative protocols, especially in cardiac and vascular surgery.

Operative (stress)-induced changes on glucose metabolism

Surgical stress induces a series of metabolic reactions. From a metabolic point of view, the most prominent changes involve the release of cytokines and stress hormones which rapidly induce catabolism. A crucial phenomenon typically linked with stress-induced modifications in glucose metabolism is the development of insulin resistance.

These metabolic changes negatively affect the postoperative course, either by hampering recover of normal function, or by increasing the metabolic stress and the consequent risk for complications (especially infections). The likelihood of improved recovery would increase if metabolism could be controlled, either by avoiding or reducing the stress reactions induced by the surgical procedure or by counteracting the metabolic stress that typically occurs after surgery.

Evidence exists on the relationship between intraoperative glucose values and prognosis for cardiac surgery. High glucose level achieved during cardiopulmonary bypass proved to be an independent predictor of mortality in both diabetic (odds ratio, 1.20; confidence interval, 1.08-1.32) and nondiabetic (odds ratio, 1.12; confidence interval, 1.06-1.19; per millimole per liter increase in glucose) patients (19) and it was also an independent predictor of all major adverse events in both patient groups (odds ratio, 1.06; confidence interval, 1.03-1.09). It was not closely related to cardiopulmonary bypass (r = 0.3) or aortic crossclamp times (r = 0.4). In a restrospective study Gandhi et al. (17) reported that intraoperative hyperglycemia occurred most likely in older diabetic males undergoing coronary artery bypass grafting (CABG). It resulted to be an independent risk factor for complications (atrial fibrillation, prolonged mechanical ventilation, delirium and urinary tract infection) and death after cardiac surgery. In 2005, Ouattara et al. (20) presented the results of a prospective observational study on intraoperative blood glucose control (BGC) in 200 diabetic patients undergoing cardiac surgery. A poor intraoperative glycemic control, despite insulin therapy, was significantly more frequent in patients who suffered from severe in-hospital morbidity. All in-hospital morbidities (including cardiovascular, neurologic, respiratory, and renal morbidities), excepting for infectious complications, were significantly more frequent in patients with poorer intraoperative glycemic control.

Intraoperative Glucose Control

Gandhi et al. (21) conducted a prospective randomized study to investigate whether a rigorous intraoperative glycemic control reduces death and morbidity in cardiac surgery patients with and without diabetes. Cardiac surgical patients were randomly assigned to tight glycemic control (blood glucose concentration 80–100 mg/dl) during surgery or usual intraoperative care (use of insulin only when blood glucose concentration reached 200 mg/dl or more). Both groups underwent tight glucose control postoperatively. Intensive insulin therapy during cardiac surgery did not significantly reduce perioperative mortality, morbidity (including deep incisional surgical site infection at the sternum), or length of stay in

ICU or hospital. As well, an increased incidence for stroke was observed in the group undergoingintensive treatment. These findings should be considered with caution because of the small sample size of patients included in the study and because discordant results exist (21).

In a large cohort of diabetic patients undergoing CABG, Furnary et al. (22) observed that mortality was significantly lower (2.5% vs 5.3%) in patients receiving endovenous continuous insulin (with continuous infusio) when compared to subcutaneous insulin. Furthermore, they found that continuous insulin infusion was independently protective against death. Accordingly to these authors, the protective effect of continuous insulin infusion may stem from the effective metabolism of exceeding glucose that improves production adenosine triphosphate in myocytes.

In the Portland Diabetic Project (a prospective, non-randomized, observational study of 5,510 consecutive diabetic cardiac surgery patients (23), hyperglycemia in the first 3 postoperative days, resulted as independent predictor of mortality, deep sternal wound infection and increased length of stay. Conversely, continuous insulin infusion, aimed to achieve predetermined target glucose levels, was shown to independently reduce the risks of death and deep sternal wound infection by 60% and 77%, respectively. In another retrospective study conducted in 91 consecutive diabetic patients (24) submitted to infrainguinal bypass surgery, a poor perioperative glycemic control (evaluated by the Area Under the Curve method) was associated with unfavorable outcome (death, major amputation or graft occlusion at 90 days).

In both non-diabetic and diabetic patientsundergoing to cardiothoracic surgery, postoperative hyperglycemia was associated with a higher incidence of site surgical infections (25).

Perioperative hyperglycemia wss was associated with increased resource utilization (longer postoperative stay and increased hospitalization costs (26) both in diabetic and non-diabetic patients undergoing CABG.

Literature data so far available strongly support the opinion that perioperative hyperglycemia, both in diabetic and in non-diabetic patients, is associated with increased mortality and with an higher rate of complications in patients undergoing cardiac and vascular surgery. Unfortunately we have no evidence about the best intraoperative glucose target and the best therapeutic regimen, since randomized trials on these topics are so far not available and hypoglycemia could be harmful.

Post operative Glucose Control

Glucose metabolism impairment after surgery is also not specific of patients with diabetes mellitus and in cardiac surgery postoperative hyperglycemia is associated with poor outcome. In a recent study by Ascione et al. (27) the effect of different degrees of BGC on clinical outcomes after cardiac surgery was investigated in a large cohort of adult patients (8727 patients). On the basis of the highest blood glucose level recorded over the first 60 hours postoperatively patients were classified as follows: good (< 200 mg/dL), moderate (200 to 250 mg/dL), or poor (> 250 mg/dL) BGC. Most patients resulted to have a good BGC (85%), whereas poor BGC was observed only in the 4%. The subgroup of patients with inadequate BGC were more likely to have an higher incidence of advanced New York Heart Association class, congestive heart failure, hypertension, renal dysfunction, and ejection fraction < 50%. Diabetic patients exhibited a poor BGC in more than half cases (52%), and a good BGC only in 8%. Interestingly, it was observed that inadequate BGC, but not diabetes mellitus

itself, was associated with in-hospital mortality. Moreover, inadequate BGC also was associated with postoperative myocardial infarction and with pulmonary and renal complications in patients without known diabetes mellitus. This investigation underlines the clinical and prognostic importance of glucose control in the post CABG period in both diabetic and not diabetic patients. Similarly, Ramos et al. (28) confirmed that postoperative hyperglycemia, independently of diabetic status is associated with an increased risk of postoperative infections and length of hospitalization in patients submitted to general and vascular surgery.

In the recent prospective, randomized trial by Saager et al. (29), the Authors aimed at determining which method (a standard insulin protocol vs a computer-guided glucose management system) performed better in a small group of diabetic patients scheduled for cardiac surgery. Patients were randomized to have their glucose controlled after induction of anesthesia and were treated throughtout operation and for the first 9 hours in the ICU. The computer-guided glucose management system managed to achieve tighter BGC than a standard paper-based protocol but in both subgroups few patients showed a satisfactory BGC, underlying the challenges in achieving normoglycemia during coronary surgery.

What about hypoglycemia?
The main concern against a tighter glucose control is represented by hypoglycemia (30) which is more dreadful in patients under anesthesia or sedation than in patients who might manifest symptoms. Hence, cardiopulmonary bypass leads to contro-regulatory hormone activation, exacerbating insulin resistance, which is further enhanced by hypothermia and hypoperfusion of peripheral muscles (31).

Data on this topic are not univocal. Chaney et al. (32) reported that 40% of patients

in the "tight control" group required treatment for postoperative hypoglycemia. On the other hand several studies using a modified insulin clamp technique and various modifications of insulin infusion regimens reveal the safe and effective use of this treatment in cardiac surgical patients (33-36).

Glucose for preoperative risk stratification in cardiac and vascular surgery
Patients scheduled for major vascular surgery as well as for cardiac surgery are screened for cardiac risk factors using standardized risk indexes, including diabetes mellitus but recent studies documented that even patients with impaired glucose metabolism have a mortality rate comparable with that of diabetics.

In a large cohort of patients undergoing CABG (37), it was observed that patients with undiagnosed diabetes (5.2% of the overall population) showed the highest mortality, probably because they had not been appropriately treated as known diabetes. The Authors emphasize the importance of fasting glucose measurements in clinical practice to stratifies cardiac risk of vascular patients. Recently Feringa et al. (38), investigated, in vascular surgical patients, whether impaired glucose regulation and elevated glycated haemoglobin (HbA 1c) levels are associated with increased cardiac ischemic events. The Authors documented that impaired glucose regulation is common in vascular surgery patients (28%) and most importantly, both impaired glucose regulation and elevated HbA1c were associated with an increased incidence of perioperative myocardial ischemia, perioperative troponin T release, and 30-day and long-term cardiac events, independent of age, gender and clinical risk factors. This study stresses the value of glucose and HbA1c in defining perioperative and long-term risk in vascular surgery patients though, the management of these patients remains a challenge.

On the clinical ground:
- Intraoperative and postoperative hyperglycemia are predictors of poor outcome, independently of diabetic status, in patients undergoing cardiac and vascular surgery
- In spite of multiple blood-glucose control protocols (39-44), there is a paucity of clinical evidence on the effect of stress-induced hyperglycemia control in diabetic and non-diabetic patients undergoing cardiac and vascular surgery.
- Benefits of insulin therapy have not been confirmed in all critical care settings (4,45). Evidence on the efficacy of insulin therapy in patients undergoing cardiac surgery is rather poor whereas no information is available for vascular patients.
- Hypoglycemia is a major problem, even if its clinical significance in surgical patients is not clear and controversial opinions exis (46).
- Since no randomized trial is so far available on the optimal glucose target and the best glycemic regimen in vascular patients such research has to be encouraged.

Even in the critically ill, the optimal glucose target is far to be clearly identified. In fact the results of the NICE-SUGAR study (47), documented that tight intensive glucose control (81 to 108 mg/dl) increased hypoglycemia and mortality among adults in the general ICU.
In a recent meta-analysis (48), including 26 trials, intensive insulin therapy significantly increased the risk of hypoglycemia and conferred no overall mortality benefit among critically ill patients, though this therapy may be beneficial to patients admitted to a surgical ICU. Moreover, the Authors underlined that discrepancies between trials may be due to several factors (apart from glucose target values) such as patients' selection (medical vs surgical), and nutrition (parenteral vs enteral).

CONCLUSIONS

Evidence exists that even slight increased in glycemia are detrimental for diabetic and non-diabetic patients undergoing cardiac and vascular surgery, though the precise details of the timing of insulin therapy, the desired target serum glucose level, and the duration of therapy are unknown.
The challenge to optimize glucose control should begin during preoperative evaluation and should take in account the risks of intraoperative and postoperative hypoglycaemia.

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