Revista Mexicana de Anestesiología

REVIEW
Vol. 31. No. 4 October-December 2008
pp 298-310

The strict glycemic control and cardioprotection

Pastor Luna-Ortiz, MD;* Roxana Carbó, PhD;** Eduardo Rojas, MD;***
Alfredo de Micheli, MD;* Gustavo Pastelín, MD;* Martín Martínez, PhD.**

* Department of Pharmacology.
** Department of Physiology.
*** Department of Anesthesiology.

Instituto Nacional de Cardiología «Ignacio Chávez» México, D.F.

Reprints requests:
Martín Martínez-Rosas
Departamento de Fisiología
Instituto Nacional de Cardiología
Juan Badiano Núm. 1
Col. Sección 16
México, D.F.
CP 14080
E-mail: martin5163@yahoo.com

Received for publication: 28-11-08
Accepted for publication: 15-12-08

SUMMARY

Glucose homeostasis is seriously altered during stress periods such as sepsis, trauma and surgery. Blood glucose levels rise up in critically ill patients or during the perioperative period, without distinction between normal or diabetic patients. This condition has been called stress hyperglycemia, and for many years it has been considered an adaptive and beneficial response from the organism. However, new evidences have emerged showing that this condition increases morbidity and mortality in patients undergoing cardiac surgery and specially in those patients with extracorporeal circulation. In this review, it was analyzed the results of different studies of association between stress hyperglycemia and adverse outcomes of critically ill patients, those patients exposed to extensive surgery, especially cardiac surgery, as well as trauma patients. Here, the benefits of strict glycemic control (glucose levels between 80-110 mg/dL), using intensive insulin therapy in this group of patients are described. Additionally, the probable mechanisms of deleterious effects of the acute or chronical hyperglycemia and the most used protocols in the glycemic management are described. It is commented the experience obtained at the Instituto Nacional de Cardiología «Ignacio Chávez» in the management of patients at the surgery peri- and post-operative periods.

Key words: Hyperglycemia, cardioprotection, diabetes, insulin.

RESUMEN

La homeostasis de la glucosa se afecta importantemente en los períodos de estrés como en el caso de sepsis, trauma y cirugía. Los niveles de glucosa en sangre se elevan en el paciente críticamente enfermo o durante el perioperatorio, independientemente si es diabético o no. Esta condición ha sido llamada hiperglucemia del estrés y durante mucho tiempo se consideró como una respuesta adaptativa y benéfica, sin embargo, recientemente se ha generado evidencia de que aumenta la morbimortalidad en particular en los pacientes sometidos a cirugía cardíaca con circulación extracorpórea. En este trabajo se analizan los resultados de diversos estudios de asociación entre la hiperglucemia del estrés y los desenlaces adversos de pacientes críticamente enfermos, en los sometidos a cirugía mayor, en particular en cirugía cardíaca, y en los politraumatizados. Se describen los beneficios del control estricto de la glucemia (el mantenimiento de los niveles de glucosa en un rango de 80-110 mg/dL), utilizando la terapia intensiva con insulina en estos pacientes. Se describen también los posibles mecanismos de los efectos deletéreos de la hiperglucemia aguda y crónica y se presentan los protocolos más utilizados en el manejo de la glucemia. Se comenta además, la experiencia obtenida en el Instituto Nacional de Cardiología «Ignacio Chávez» en el manejo perioperatorio y postoperatorio de pacientes sometidos a cirugía cardíaca.

Palabras clave: *Hiperglucemia, cardioprotección, diabetes, insulina.*

INTRODUCTION

The glucose levels increase during stress periods as in the case of sepsis, trauma and surgery[1]. For a long time the stress hyperglycemia had been considered as an adaptive and benign action; however, in recent years evidence has been generated regarding that stress hyperglycemia is a detrimental condition in critically ill patients and those subjected to a major surgery or polytraumatized patients. The surgery stress-induced hyperglycemic response increases due to anesthetic effects and preoperative emotional stress[1]. These conditions, as a whole, produce an increased glucose production or release, a decrease in the insulin secretion, resistance to this hormone and an increase in the renal glucose reabsorption. The preoperative hyperglycemia degree depends on the type, severity and extension of the surgical trauma to tissues[1]. During the surgery, the glycemic levels could reach levels over 270 mg/dL in non-diabetic subjects and higher than 370 mg/dL in diabetic patients[2]. Apparently, patients suffering from cardiovascular disease are more sensible to the increase in blood glucose. Mortality in cardiac surgery is significantly correlated to blood glucose levels, being the lowest mortality when blood glucose level is lower than 150 mg/dL[3] and this risk increases by 17%[4] per each 18 mg/dL of increase in the glucose over 110 mg/dL. Recently, the insulin therapy has been used to maintain the blood glucose levels between 80-110 mg/dL as a part of the intensive cares in order to improve survival and reduce the morbidity of critically ill, high risk, trauma or extensive surgery patients[5-12]. However, the strict glucose control (stabilization and maintenance of glycemia as close to normal as possible) has become a controversial subject since some recent studies reported greater mortality in those patients who have received intensive insulin therapy (IIT) to control blood glucose levels[13,14].

This review compares the literature reports in which hyperglycemia is correlated to the results of survival and morbidity of critically ill patients, the patients underwent different kind of surgery and, in particular, to those subjected to cardiac surgery, emphasizing cardioprotection. The possible cytotoxic mechanisms of hyperglycemia are analyzed in a general manner, and most used protocols for blood glucose management are provided. Besides, it should be mentioned the experience acquired in the National Institute of Cardiology "Ignacio Chávez" on the preoperative and postoperative management of patients that underwent cardiac surgery.

THE FIRST STUDY OF THE STRICT GLUCOSE CONTROL

In a study referred as a classic published in 1993, there was provided the first evidence that the strict glucose control in humans reduces the risk of diabetic complications on a long term[12]. This multicenter, randomized and prospective study known by its acronym in abbreviations in English as DCCT (Diabetes Control and Complications Trial), was performed on 1441 patients with type I diabetes who were chosen randomly to receive conventional therapy (CT) or IIT. The two groups were formed: one of 715 patients with mild retinopathy and the another one of 726 patients without retinopathy at the beginning of the study. Patients of two groups were represented in the two treatments in order to establish if IIT can prevent the retinopathy or affect the mild progression of retinopathy. The effects on renal, neurological, cardiovascular and neuropsychological parameters and any adverse effect also were studied.

The patients in the CT group were injected with insulin (an insulin mixture of fast and intermediate action) one or twice per day and the urine or blood glucose was monitored; usually no daily adjustments on the insulin doses were performed. The patients received information about their diets and exercise and were examined every 3 months. The objectives of the CT were: 1) absence of symptoms of hyperglycemia; 2) absence of ketonuria; 3) preservation of normal growth, development and ideal corporal weight; and 4) absence of recurrent or severe hypoglycemia. IIT group received insulin ≥ 3 times daily by injection or external pump. Adjustments in dose were made based on monitoring blood glucose (≥ 4 times per day), food intake and exercise. Patients in this group were examined every month and were contacted frequently by phone to review and adjust their insulin regime. The objectives of the IIT included preprandial blood glucose levels from 70 to 120 mg/dL, postprandial blood glucose levels <180 mg/dL and levels > 65 mg/dL measured at 3 am once a week to monitor the level of hypoglycemia; moreover values of glycated hemoglobin (HbA1c) <6.05% were recollected. Currently this work is considered as a reference for establishing the normal levels of HbA1c in patients with type 1 diabetes. This molecule is formed in proportion to the level of glucose within the erythrocyte.

The importance of having controlled HbA1c levels in patients with either type of diabetes is that they are highly related to the incidence and/or progression of diabetic retinopathy, the incidence of urine protein, the incidence loss of touch sensations and loss of temperature[15]. Patients were followed for an average period of 6.5 years (limits between 3 and 9 years) and 99% of them had completed the study up to that point. The DCCT study has been maintained up to

now a day. The results obtained in this first report were that the patients in the IIT group had average blood glucose levels of 155 ± 30 mg/dL, compared with 231 ± 55 mg/dL of CT group ($p < 0.0001$). The average values of HbA1c during the study were significantly lower in IIT group than CT group (≈7 *vs* ≈9%, $p < 0.0001$)

The DCCT conclusively demonstrated that in patients with type 1 diabetes the IIT slows onset (primary prevention) and slows the progression (secondary prevention) of retinopathy associated with diabetes and it decreases other complications associated with microvasculature such as nephropathy and neuropathy.

IMPACT OF THE STRICT BLOOD GLUCOSE CONTROL WITH IIT DURING THE CRITICAL DISEASE

The beneficial results of the DCCT study proved the effects of IIT in other patients, particularly those in critical condition; also a clear association between hyperglycemia and increased risk for morbidity and mortality was found. Well controlled randomized studies are required to establish this causal relationship between hyperglycemia and the risk of morbidity and mortality in the severely ill patients. The first of these studies[5] was performed in Leuven, Belgium by Van den Berghe et al. and published in 2001. This study included adult patients receiving mechanical ventilation, admitted to the Intensive Care Unit (ICU) after extensive and complicated surgery or trauma, or after medical complications resulting from major surgical procedures. Van den Berghe involved 1548 patients of the ICU, where 63% of them were cardiac surgery patients at high risk. They maintained glucose levels between 80-110 mg/dL using a continuous intravenous infusion of insulin. The mean was 103 mg/dL (normoglycemia) and in patients treated with CT was 153 mg/dL. Hospital mortality decreased by 34%[5] and there was a reduction of 40-50% in major comorbidities when the patients were treated with IT. This groundbreaking study, although was harshly criticized, promoted the development of protocols for glucose management in the ICU around the world.

The Leuven's study showed that the IIT not only reduced mortality but prevented several complications associated with critical state of the patient such as the development of polyneuropathy, and critical illness, as sepsis, anaemia, acute kidney failure and hyperbilirubinemia. Patients were also less dependent on mechanical ventilation and intensive care. On the other hand, IIT protected the peripheral and central nervous system from secondary damages and improved long-term rehabilitation of patients with isolated brain injury[6]. The therapy was also associated with a substantial saving of costs[7]. A 4 years follow-up of cardiac surgery patients (63% of the study population) showed that IIT also improved long term outcome, as the benefit of survival was maintained without the need for additional medical care[8].

Another recent, small (n = 61), prospective, randomized, well controlled study[9] included a population predominantly of general surgery patients. We tried to achieve glucose levels of 80-120 mg/dL by IIT to observe whether hyperglycemia in glucose intolerant patients without diabetes may increase the number of infections in the ICU. The study was conducted in adult patients presenting hyperglycemia ≥ 140 mg/dL, they were randomized to receive CT (180-220 mg/dL) and IIT (80-120 mg/dL) during their stay in the ICU. The results were: average daily levels of 125 ± 36 mg/dL with IIT compared with 179 ± 61 mg/dL in the standard glycemic control group.

We found a significant decrease in the incidence of total nosocomial infections ($p < 0.05$) predominantly in non-diabetic surgical patients in ICU. Another observational study conducted in a heterogeneous population of medical-surgical patients (n = 1,600), published in 2004, assessed the impact of a strict protocol to maintain glucose in the ICU[10]. In this case, insulin was administered by intravenous (IV) route only if glucose levels were above 200 mg/dL on two successive measurements to try to maintain glucose below 140 mg/dL. Mean glucose levels of 131 mg/dL were reached in the protocol period, compared with 152 mg/dL in the baseline period. Compared with the historical control group, hospital mortality decreased from 20.9 to 14.8%. Other parameters that decreased were: stay in the ICU, incidence of newly developed renal damage and the number of patients requiring transfusion of red blood cells. The implementation of this protocol also resulted in a substantial saving of money[11]. All these results were indicating the importance of strictly controlling the blood glucose levels in order to obtain favourable results, which led to the conduction of an increased number of assays in critically ill patients. Polytraumatized patients who are in the ICU are a typical example of critically ill patients and it has been found that high levels of blood glucose predict mortality and stay in the ICU in addition to determining the time of hospitalization. This relationship also occurres in the morbidity of infection and prolonged need of mechanical ventilation[16-19]. Levels of hyperglycemia have a high predictive value for mortality of patients with severe brain damage. It has been found a significant relationship among high blood glucose levels and deterioration of neurological status, the decrease in pupillary reactivity, increased intracranial hypertension and a longer stay in hospital[20,21]. In patients who have suffered a cerebrovascular accident, hyperglycemia predicts increased risk of death and poor functional recovery in survivors[22]. It has also described a strong link between high blood glucose levels and risk for polyneuro-

pathic disease during sepsis and systemic inflammatory response syndrome[23].

HYPERGLYCEMIA AND THE PATIENT UNDERGOING CARDIAC SURGERY

Cardiac surgery, along with the effect of anesthetics and perioperative anxiety status, releases regulatory hormones that alter the metabolism of carbohydrates, producing an increase in glycogenolysis, increased glyconeogenesis, insulin resistance and decreased secretion of this hormone (24,25) (Figure 1).

The surgical stress response makes difficult to maintain normoglycemia during surgery, in addition aggressive administration of insulin has the risk of producing hypoglycemia in the postoperative period when there is no stress[2]. To achieve the most benefit, it is required to maintain strict glucose control for at least three days; it has been shown that the impact of this strategy depends on the time required for the application[26].

In order to assess the risk for death or congestive heart failure after a myocardial infarction in non-diabetics and diabetics patients, articles published from 1966 to October 1998 were analyzed in a review published in the journal *Lancet* in 2000[27]. Researchers identified fifteen studies that reported either the hospital mortality or congestive-heart failure rate in relation to the stress hyperglycemia at the time of admission. In summary, the findings were: patients without diabetes who had serum glucose levels of 110-144 mg/dL had a death risk (95% CI 2.9-5.4) 3.9 times higher than patients without diabetes at lower levels of blood glucose. Glucose concentrations of 144-180 mg/dL at the time of admission were associated with an increased risk of congestive heart failure or cardiogenic shock. In patients with diabetes who had serum glucose between 180-198 mg/dL, the death risk increased but moderately (relative risk of 1.7). The authors concluded that stress hyperglycemia with myocardial infarction is associated with a higher risk of hospital death in both diabetic both non-diabetic patients. It was considered that diabetes mellitus (DM) is a predictor of increased mortality in patients suffering from cardiovascular disease. Even in non-diabetic patients they have a high risk of congestive heart failure or cardiogenic shock with stress hyperglycemia[27].

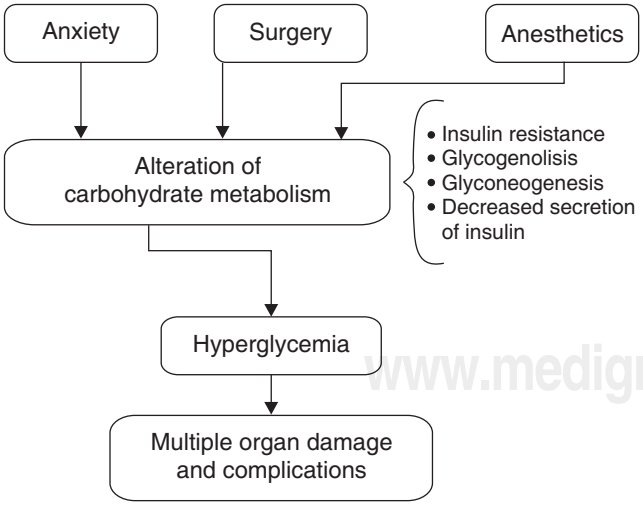

Figure 1. Effects that induce perioperative hyperglycemia.

In a recent study in patients with coronary artery disease (CAD)[28], it was determined the degree to which the blood glucose level is predictive of mortality in glucose intolerant non-diabetic, non-diabetic and diabetic patients. The importance of this study was to assess the risk of mortality when the fasting blood glucose (GluA) is below the threshold of diabetes (126 mg/dL).

In total, 1612 patients were included with CAD, who underwent percutaneous coronary intervention (PCI) and who had previously determined level GluA or a diagnosis of DM. Patients were grouped as DM, non-DM with blood glucose ≥ 126 mg/dL, non-DM with blood glucose 110-125 mg/dL and normal glucose < 110 mg/dL. Survival was determined at 2.8 ± 1.2 years. The results showed a higher mortality rate in patients with diabetes (44/394, 11.2%, p < 0.0001), followed by the non-diabetic patients with glucose ≥ 126 mg/dL (27/283, 9.5%, p <0.001) and the group without DM with blood glucose 110-125 mg/dL (20/305, 6.6%, P <0.04). Only 12/630 patients died in group with normal glucose, i.e. 1.9%. This group of researchers concluded that the prognosis depends on the GluA abnormalities in patients with CAD undergoing PCI; additionally they concluded that, despite the bypass, the mortality risk associated with even slight elevations in GluA is substantial, by emphasizing the importance of early detection and treatment of risk associated with hyperglycemia. Should be noted that, in this work, the authors propose the level of 109 mg/dL as the best cut-off point to consider an increased risk. It is generally considered that the increase in GluA is predictive of hospitalization in patients with heart failure and is a factor increasing cardiovascular events compared with chronic hyperglycemia[29,30].

Intraoperative hyperglycemia appears to contribute as an independent risk factor determining adverse outcomes after cardiac surgery. The degree of association between intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients was estimated in a retrospective study conducted at the Mayo Clinic in 2005[31]. The average intraoperative glycemia was considered as the independent variable and the variable to be determined was the

combination of death and/or any of the following events: infections (of the sternal wound, urinary tract infection and sepsis), neurological complications (cerebral vascular events, coma, delirium), renal (acute kidney failure), heart (atrial fibrillation of new onset, AV block, cardiac arrest) and pulmonary (prolonged pulmonary ventilation, pneumonia), which were developed in the following 30 days after cardiac surgery. The results showed that of 409 patients involved, who have predominantly any of the endpoints to be evaluated were first the male and elderly individuals followed by those with DM, subsequently those underwent coronary artery bypass, and finally who underwent insulin during surgery. The conclusion of this study was that intraoperative hyperglycemia is an independent risk factor for complications and death after cardiac surgery.

DIABETES MELLITUS AND CARDIOVASCULAR RISK

It is known for decades that DM is an important risk factor for cardiovascular disease. It has been reported that prolonged insulin resistance and increased blood glucose can cause left ventricular hypertrophy[32], and high levels of HbA1c are associated with increased risk for myocardial infarction, angina, ischemic heart disease and cardiac death[33]. It was reported that a 1% increase in the HbA1c level is associated with a 14% increase in risk of myocardial infarction mortality and also with a 37% risk of microvascular complications[34]. Approximately 30% of patients undergoing coronary artery surgery suffer from DM, resulting in a 3.7% mortality at 30 days[35]. Patients with DM undergoing surgery have a greater risk of developing nosocomial infections of any kind when the blood glucose concentrations are above 198 mg/dL[36]. It has been reported that the frequency of surgical wound infections is related to blood glucose level, increasing from 1.3% in patients with glucose of 99-144 mg/dL to 6.7% in those with blood glucose greater than 252 mg/dL[37]. In patients of the ICU, hyperglycemia accentuates the catabolic loss of protein and it is suggested that this might alter the process of wound healing[38]. On the other hand, in patients with diabetes who have more than 4 hours of acute hyperglycemia, there is platelet activation, endothelial dysfunction and capillary leak, this situation might explain the increased frequency of the non-flow phenomenon after heart attack in these patients[39]. In general, diabetic patients have increased morbidity and mortality during cardiac surgery[40,41] and there is evidence that these patients improve in these when its blood glucose is between the normal[42,3]. These results support the hypothesis that hyperglycemia is a risk factor *per se* regardless of the degenerative processes associated with this disease.

POSSIBLE MECHANISMS OF THE DELETERIOUS EFFECTS OF HYPERGLYCEMIA

Many studies of the cytotoxic effects of hyperglycemia have been conducted in animal models and in vitro assays. Although it is not possible to extrapolate these results directly to human, this explains to some extent the mechanisms of the deleterious effects of both acute and chronic hyperglycemia. Hyperglycemia causes damage through various biochemical processes such as an increased glucose metabolism by sorbitol pathway resulting in the formation of polyols, an increase in the de *novo* synthesis of diacylglycerol (DAG) which activates the protein kinase C (PKC), an enzyme that phosphorylates several functional proteins, there is also a rise flow in the hexosamine formation, an augmentation of reactive oxygen species (ROS) and finally the non-enzymatic glycosylation of proteins with the consequent formation of advanced glycosylation end products (Figure 2).

A) *Sorbitol pathway*: In non-diabetic persons, the excess glucose is metabolized by glycolytic pathway and the pentaphosphates. In diabetic patients, these two pathways are saturated and excess glucose is metabolized by polyol pathway (pathway of sorbitol), where two enzymes are involve: aldolase reductase and sorbitol dehydrogenase, transforming glucose to sorbitol. The excess of intracellular sorbitol increases osmotic pressure, intracellular edema and hypoxia. The abundance of sorbitol is associated with cataracts, retinopathy, and diabetic neuropathy[43].

B) DAG: The formation of DAG is favored by glycolysis and the pathway of polyols, the primary activator of PKC, and involved in the secretion of growth factors such as tumor growth factor-beta (TGF-β) producing synthesis of extracellular matrix (ECM). The PK decreases the production of nitric oxide and increases the synthesis of endothelin 1[44]. It also induces a greater expression of plasminogen activator factor 1 and plasminogen 1[45].

C) Hexosamine pathway: Some of the effects of high glucose may be mediated by other metabolic pathway, the hexosamine pathway, in which fructose-6-phosphate is converted to glucosamine-6-phosphate, and then loses its amino group to become into glutamate(46). This study has demonstrated that glucosamine is a structural analogue of glucose and it increases the production of TGF-β and fibronectin.

D) *Increase in the production of ROS*: ROS produce an increase in the synthesis of various molecules involved in the remodeling of ECM and cell proliferation in the kidney[47,48]. Finally, it has been shown that ROS produces an increase in the TGF-β expression and activity accordingly to an increase in the production of MEC[49].

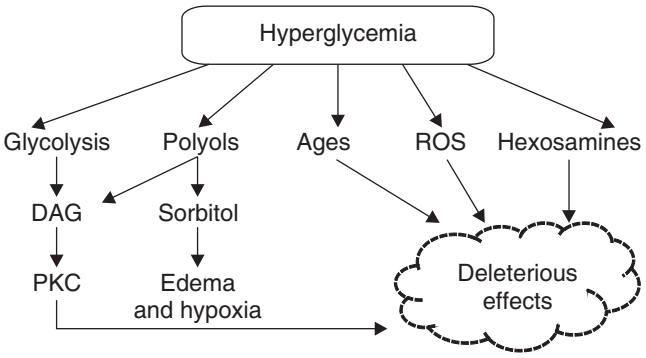

Figure 2. Signaling pathways that lead to deleterius effects of hyperglycemia.

E) *Non-enzymatic glycosylation pathway of proteins*: The non-enzymatic glycosylation of proteins is an irreversible reaction in which glucose binds to the epsilon-amino groups of lysine of an already formed protein, denaturalizing this protein and causing functional changes. These chronically events are called advanced glycosylation end products (AGES). The AGES act through their receptors (RAGES) producing fibronectin and collagen type IV. Glycosylated hemoglobin is an example of this alteration, and its determination is useful to assess glycemic control of diabetic patient[43]. AGES are highly related to the development of long-term complications of diabetes[50] and serum levels are recognized as a marker for monitoring treatment of patients with diabetes, especially those with kidney damage and/or vascular complications. However, the use of measurements of AGES levels in the clinic is limited by the lack of fast and simple analytical procedures endotheliome. It has been reported that in the high concentration of glucose inhibits the replication of endothelial cells in culture[51] and endothelial activation is associated with the expression of several adhesion molecules, including E and P selectins and intracellular- (I-CAM) and vascular adhesion molecules (V-CAM) on the cell surface[51]. Langouche et al.[52] investigated the local activation of endothelium and its relation to the IIT, finding that insulin decreases the levels of selectin E and circulating adhesion molecules, a mechanism that helps to protect the vascular endothelium of the lesion and prevent organ dysfunction.

On the other hand, hyperglycemia increases the hexokinase activity, an enzyme responsible for phosphorylation of glucose, the first step of glycolysis. This event stimulates the production of growth factors involved in the proliferation of fibroblasts and vascular smooth muscle cells[53].

It is known that increased concentration of glucose causes an increase in blood viscosity in the DM. This impairs the mechanisms of autoregulation of blood flow by alterations in the autonomic nervous system. Furthermore, these hemodynamic changes produce degeneration of pericytes and capillary and venular dilation, leading to an increased permeability of blood vessels with departure of plasma and proteins causing endothelial injury. By reducing the blood flow, erythrocytes tend to cluster reaching obstructing traffic. It has been reported that in diabetes, erythrocyte loses the physiological ability of deformation because its membrane is made rigid by the non-enzymatic glycosylation previously described. Increased blood viscosity is exacerbated by an increase in fibrinogen and globulins, which leads to a prothrombotic state. The increase of Von Willebrand factor and an decreased fibrinolytic activity also contributes to this situation[43]. Moreover, acute hyperglycemia produces in rats a low activity of tissue plasminogen activator and high levels of plasminogen activator inhibitor[54]. Hyperglycemia also decreases the half-life of fibrinogen and platelet aggregation and increases levels of fibrinopeptide A and factor VII; all these phenomena suggest increased activation of prothrombotic factors[55,56]. These changes deserve to be taken into account when patients with hyperglycemia are subject to surgery, as this condition is a risk factor for cardiovascular and cerebrovascular.

On the other hand, high levels of glucose produce increased markers of vascular inflammation. High levels of C-reactive protein, interleukin 6 and tumor necrosis factor alpha have been reported in studies performed in vitro and in vivo[57,58]. Also the high glucose is associated with an increase in the generation of reactive oxygen species (ROS) which can induce tissue injury[59].

Moreover, Turina et al.[60] suggested that hyperglycemia produces the following effects on the immune system: 1) decrease in adhesion and migration of leukocytes; 2) decrease in the complement fixation; 3) decreased phagocytosis; 4) decreased production superoxide radicals; 5) reduced production of cytokines and reduced apoptosis; and 5) it is altered microvascular response. All these effects may be responsible for increased infection and dysfunction of various organs in diabetic patients. Recent studies in humans[61] suggest that the acute increase in glucose levels can have a most powerful impact on oxidative stress than chronic sustained hyperglycemia.

POSSIBLE MECHANISMS OF TOXICITY IN MYOCARDIAL

When the diabetes progresses, the excessive availability of lipids and fatty acids and the uptake thereof may exceed the heart's capacity to use these substrates, which could result in lipid accumulation within the cardiomyocyte. It has been

shown previously that the progression of diabetes is associated with a dramatic decrease of expression of PPAR-g (peroxisome proliferator-activated receptor-gamma). It produces insulin resistance with accumulation of lipids in the cardiomyocyte causing a phenomenon known as lipotoxicity. This lipotoxicity accumulates (ROS), induced nitric oxide and apoptosis, leading to cardiac dysfunction[62]. While the accumulation of lipids is deleterious, the excessive accumulation of metabolites of glucose is associated with several pathologies and is called glycotoxicity. Excessive intake of glucose induces insulin resistance in multiple organs such as skeletal muscle, liver and adipose tissue. One hypothesis is that through the hexosamine pathway, important pathway in the deleterious role of hyperglycemia, insulin resistance to glucose is increased; this is induced also by fats. The increase in this pathway in turn causes an increase in the glycosylation of proteins involved in insulin transduction signal. This is the case of insulin receptor substrates (IRS-1 and IRS-2), which would alter the activation of phosphatidylinositol-3-kinase (PI3-kinase) and and decrease the activation of Akt kinases[63].

Chronic hyperglycemia is associated with the formation of AGES and the generation of ROS; moreover the excessive generation of free radicals can affect the homeostasis of calcium channels, the mitochondrial function and the activation of DNA transcription factors and initiate apoptosis[64].

In addition to the participation of the mechanisms previously described, several physiological studies have shown that hyperglycemia may have direct deleterious effects on ischemic myocardium through several mechanisms. High levels of glucose in patients with acute coronary syndromes are associated with high concentrations of free fatty acids, insulin resistance and alterations in myocardial glucose use, thus increasing oxygen consumption and therefore ischemia[65]. In turn, the high concentrations of free fatty acids increase the incidence of malignant ventricular arrhythmias[66]. Kersten et al. have shown a decrease in collateral circulation and increased infarct size during severe hyperglycemia[67,68]. Animal studies show that high glucose may abolish the ischemic preconditioning and promote apoptosis[68]. Hyperglycemia is also associated with elevated blood pressure and ST-segment elevation in rats; these anomalies are corrected by reversing hyperglycemia[69]. Marfella et al.[70] have reported the same hemodynamic and electrocardiographic effects in healthy humans, as well as increased circulating catecholamines during hyperglycemia artificially induced in these volunteers (glucose > 270 mg/dL). In diabetic patients, postprandial hyperglycemia is associated with myocardial perfusion defects due to microvascular dysfunction; this condition lowers the glycemic control[71,72].

One of the main causes of the hyperglycemia complications is caused by increased levels of ROS. The electron transport chain of mitochondria is the site of production of these radicals during hyperglycemia[73]. The high concentration of glucose causes an increase in the mitochondrial metabolism altering respiratory chain and causing hyperpolarization of these organelles and the overproduction of ROS[74]. Elevated levels of the ROS open mitochondrial membrane transition pore and cause cell death by apoptosis[75,76]. Hyperglycemia increases the production of ROS through the hexosamine pathway, causing resistance to insulin. This is due to those molecules involving in receiving the signal from the cascade of second messengers of this molecule are glycosylated[77,78].

In ventricular myocytes incubated in a high glucose concentration medium, production of ROS and the concentration of proinflammatory cytokines were increased dramatically and the number of myocytes was increased with apoptosis and necrosis[79]. Recent evidence suggests that increased production of ROS caused by hyperglycemia produces phosphorylation of insulin receptors, which alters the ability of binding to PI3-kinase and activate it, thereby reducing the activation of AKt kinases generating insulin resistance when the cascade thereof is blocked.

Taking this evidence, it is very likely that hyperglycemia is the main mechanism responsible for the increase in ischemia-reperfusion injury in animals treated with high concentrations of glucose.

In this regard, Verma[80] demonstrated that cellular injury is higher in human ventricular cells when they are subjected to conditions of hyperglycemia. When energy substrates are administrated in combination with insulin and glucose for the heart, beneficial additive effect is achieved along with glucose control [81,82].

This is evidenced by the use of the glucose-insulin-potassium (GIK) infusion is associated with improved outcomes after cardiac surgery[83,84]. Strict blood glucose control in hospitalized patients dates back nearly 50 years with the work by Sodi-Pallares[85]. The strategy of combining the administration of GIK with continuous infusion of insulin (glucose clamp) in patients undergoing cardiac surgery has shown to have a low frequency of atrial fibrillation, less use of inotropic agents, reduced need for pacemaker, shorter stay in intensive care, fewer myocardial ischemic events, and fewer cases of kidney failure, wound infection and postoperative death[86,87].

Insulin administered at the GIK solution to restore normoglycemia may be cardioprotective, as anti-inflammatory, vasodilatory and antiapoptotic effects have been described[88]. Several mechanisms have been proposed to explain how GIK solution may be cardioprotective. Opie[89] has suggested two main mechanisms: decrease in the concentration of free fatty acids (by decreased lipolysis) and

increase in glycolysis. Although free fatty acids are the dominant substrate for the myocardial cells under aerobic conditions, under conditions of ischemia occurs a shift in metabolism towards consumption of glucose and long chain free fatty acids can have deleterious effects. The metabolism of fatty acids can produce lactate and hydrogen ions, leading to cellular acidosis; and as they are responsible for the reduction of myocardial contractility, also they can cause diastolic dysfunction and decrease the threshold of the myocardium as regards arrhythmias[89]. The GIK solution increases availability and facilitates glucose uptake in cardiomyocytes; on the other hand, insulin has anti-inflammatory and antioxidant effects[88] and vasodilator effect by releasing nitric oxide[90,91]. Insulin also inhibits platelet aggregation and has profibrinolitic effects[92]; the cardioprotective mechanism of insulin is complex. The possible protective mechanisms of insulin are listed in Table I[92]. In experimental studies it has been observed that GIK can reverse the damage caused by hypoxia on vascular contraction through the mechanism of nitric oxide, where it was observed that GIK expanded coronary arteries and allowed a best infusion during an infarction[93].

In summary, we believe that the effects of GIK are beneficial at the level of metabolic support for the heart in case of suffering, but perhaps it is more difficult to have a fine glycemic control compared to IIT, since glucose is administered in addition to the existing in the body, and response times are difficult to control. Perform a blood glucose measure before the beginning of venoclysis with GIK would be beneficial.

PROTOCOLS FOR HYPERGLYCEMIA MANAGEMENT

It has published a great variety of protocols on the use of insulin to treat perioperative hyperglycemia[3,5,94-96] and it is possible that different institutions require protocols based on the type of patient, availability of personnel and physical plant. In general, the insulin infusion is appropriate for the type 1 diabetics patients hospitalized for acute illness, when it can not be administered orally at least 24 h before surgery or in case of patients who will undergo general anesthesia for more than 2 h. Although there are significant differences in insulin requirements in different patients, insulin IV is more predictable than insulin SC.

Diabetic patients undergoing coronary bypass surgery with extracorporeal circulation (ECC) require special mention. Hypothermia that occurs during this process may produce insulin resistance and is very likely to need higher doses of insulin. During warming, insulin resistance is reduced and it is need to adjust dosages. Historically, the insulin infusion protocols were based on the glucose blood concentration in patient and the infusion rate was changing with fixed increments for all patients[97]. In clinical practice this type of protocols rarely work because they do not take into account the differences in insulin sensitivity in patients. A young woman with type 1 DM prepared for a surgical procedure requires fewer changes in insulin dose as compared to a patient of 60 years with type 2 DM undergone cardiac surgery with ECC. It has been observed that although the blood glucose is within normal level, it is required to adjust insulin infusion in order to prevent hypoglycemia. For example, if glucose is lowered from 200 to 130 mg/dL for an hour is needed to decrease the infusion in order to prevent hypoglycaemia <60 mg/dL in the next hour. The ideal insulin infusion protocols are based not only on the current glucose level but also on the insulin sensitivity and speed with which the change was made. The ideal protocol for the use of IV insulin should be easy, effective, safe, and applicable throughout the hospital. The goals of glucose control should be (in mg/dL): Perioperative 110-140, surgical 110-140, medical ICU 140-180, pregnancy > 100. There are several published protocols, some examples are: Van der Berghe[5], Portland[3], Markovitz[94], Yale[95], GRIP[96]. Several of them have been developed to achieve strict glucose control, including computer-controlled algorithms[96], these algorithms are comparable to those performed manually in predetermined tables. The risk of hypoglycemia is the greatest barrier to the implementation of these protocols within the perioperative period and the risk/benefit ratio is an issue that is still discussing.

IIT AND THE RISK OF HYPOGLYCEMIA

Severe hypoglycemia (<40 mg/dL) and prolonged it can cause convulsions, coma and irreversible brain damage, as well as and cardiac arrhythmias. The risk of hypoglycemia is a potential danger when insulin infusion is administrated in the perioperative infusion although early symptoms of hypoglycemia is easily recognized[98]. This risk increases from 0.8 to 5.1% in the surgical intensive care[5] and from 3.1 to 18.7% in the intensive medical therapy[99]. Patients in medical intensive care represent a population of patients with more pronounced pathology than those of surgical therapy. In particular, patients with sepsis have a higher risk of hypoglycemia 11.9% (2.9% for CT and 19% for IIT) versus 3.9% in patients without sepsis (1.2% and 6.8% with TC IIT)[100]. The strongest argument of this work is that IIT can cause severe hypoglycemia. In that sense, it has been reported that serum glucose levels below 100 mg/dL are deleterious and this situation is considered as the transition point from 100 to 109 mg/dL.

Despite the evidence in favours of the IIT, it is still not accepted as a convincing strategy to be used in intensive

Table I. Effects of the insulin.[92]

Reduces production of free radicals
Attenuates the inflammatory action of glucose
Decreases the production of inhibitory migration factor of macrophages
Reduces the harmful actions of tumor necrosis factor
Inhibits the production of non-esterified free fatty acids
Potentiates the possible release of nitric oxide synthase
Decreases the production of protein p-47, wich is a key protein in the NADP oxidase
Anti-apoptotic effect by activating the fosfatidol-3-kinase AKT pathway
Decreases the concentration of cytokines, the 1-protein of monocytes chemical-attractants and the plasminogen activating factor, especially noticed in patients with exogenous obesity
In experimental models it has been observed that the peptide stimulates d-6-desaturasa and d-5-desaturasa, which are essential in the formation of prostaglandin E2 and its precursors, antiplatelet, powerful vessel dilator and suppress the formation of tumor necrosis factor and interleukin 2
Neuroprotective effect against cerebral ischemia and spinal cord, together with insulin, growth factor and activation of NF-κB y Janus Kinase 8JAK

care units. Recently some studies were interrupted by the events of hypoglycemia (glucose less than 40 mg/dL). It is true that the IIT allows a stricter hyperglycemia control but presents the risk of hypoglycemia.

IMPORTANCE OF ACHIEVING NORMOGLYCEMIA

In clinical studies on the effect of IIT is impossible to separate completely the impact of the insulin infusion versus the blood glucose control; however it seems that both have beneficial effects. In this regard, in a study in a rabbit with prolonged critical condition [101], it is evaluated the relative impact of maintaining normoglycemia versus the effects of insulin are not related to glycemia. In this work, the blood glucose was manipulated independently of insulin levels; additionally the impact of both conditions on mortality, myocardial contractility and on endothelial function in isolated aortic rings, liver and kidney, and in the leukocyte function was observed. The results showed that glycemic control had a greater impact on the survival of animals than insulin *per se*, whereas the insulin level does not contribute to survival. Clinical data are consistent with these experimental observations, however, the relative beneficial effect of both compounds is still to be determined.

EXPERIENCE IN THE DEPARTMENT OF ANESTHESIOLOGY ON STRICT GLYCEMIC CONTROL

The Department of Anesthesiology, National Institute of Cardiology "Ignacio Chávez", began the study of the importance of perioperative glycemic control in diabetic and nondiabetic patients with a work published in 1985[102]. In this study, the perioperative management of diabetic patients in cardiac surgery is investigated.

In total, 24 diabetic patients were included and divided into 5 groups: one group was administered with 10 to 50 units bolus insulin depending on its blood sugar. For the remaining 4 groups, a continuous pump infusion at doses of 2.5, 5.0, 7.5, and 10.0 units/hour was administrated, respectively. A group of 10 non-diabetic patients who had been monitored for the level of glycemia was included. In groups of insulin infusion was found that the 5 units/hour dose was the best for controlling blood glucose with figures similar to those of non-diabetic patients and a lower morbidity in both groups. This pioneering work showed that by strictly controlling blood glucose using insulin infusion, better results in patients undergoing cardiac surgery are obtained. In another study conducted in 1996, 20 non-diabetic patients with ischemic heart disease undergoing coronary bypass with extracorporeal circulation were included and divided into two groups[103]. The 10 patients of group I received GIK solution (10% glucose, insulin 20 units, 60 meq KCl; 1000 mL) at a 16 mL/min rate. Group II did not receive GIK. In both groups, all the hemodynamic parameters derived from pulmonary artery catheter (Swanger-Ganz), arterial line and central venous pressure were studied. It was found that these parameters were best in the GIK group as compared to the control group, these parameters were: cardiac index, left ventricular work index and the stroke volume, among other measured parameters. It was concluded that the use of GIK solution produces better hemodynamic results in patients undergoing coronary bypass with extracorporeal circulation.

In a review published in 2006[104] about the GIK and the cardioprotective effects of insulin emphasizes the effects of insulin on coronary blood flow and treatment of hyperglycemia with this solution.

A study on the hyperglycemia control using GIK solution in 40 non-diabetic patients undergoing cardiac surgery[105] with extracorporeal circulation and divided into 4 groups was recently published in 2008. All patients received 10% glucose; differences were in the insulin and K doses, as well as in the infusion rate.

It was found that with GIK solution with 40 units of insulin to 50 mL / hour, there is a better control of hyperglycemia in the GIK than 20 units of insulin.A better hyperglycemia control in the GIK was observed using GIK solution with 40 units insulin at 50 mL/hour as compared to 20 units insulin.

Some of the mechanisms described so far on the deleterious effects of hyperglycemia especially in patients undergoing cardiac surgery are shown in this review. The large number of evidence on that normoglycemia prevents adverse outcomes and provides cardioprotección, leads us to propose the strict blood glucose control as part of standard perioperative care in order to reduce infections, reduce the length of stay in ICU. On the other hand, all previously described benefits produce best outcomes y prevent possible future damage.

REFERENCES

1. Schricker T, Lattermann R, Schreiber M. The hyperglycemic response to surgery: Pathophysiology, clinical implications and modification by the anaesthetic technique. Clin Intens Care 1998;9:118-128.
2. Chaney MA, Nikolov MP, Blakeman BP. Attempting to maintain normoglycemia during cardiopulmonary bypass with insulin may initiate postoperative hypoglycemia. Anesth Analg 1999;89: 1091-1095.
3. Furnary A, Gao G, Grunkeimer GL. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003;125:1007-1021.
4. McAlister FA, Man J, Bistritz L. Diabetes and coronary artery bypass surgery: An examination of perioperative glycemic control and outcomes. Diabetes Care 2003;26:1518-1524.
5. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-1367.
6. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology 2005;64:1348-1353.
7. Van den Berghe G, Wouters PJ, Kesteloot K, Hilleman DE. Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. Crit Care Med 2006;34:612-616.
8. Ingels C, Debaveye Y, Milants I, Buelens E, Peeraer A, Devriendt Y, Vanhoutte T, Van Damme A, Schetz M, Wouters PJ, Van den Berghe G. Strict blood glucose control with insulin during intensive care after cardiac surgery: impact on 4-years survival, dependency on medical care and quality of life. Eur Heart J 2006;27:2716-2724.
9. Grey NJ, Perdrizet GA. Reduction of nosocomial infections in the surgical intensive-care unit by strict glycemic control. Endocr Pract 2004;10:46-52.
10. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 2004;79:992-1000.
11. Krinsley JS, Jones RL. Cost analysis of intensive glycemic control in critically ill adult patients. Chest 2006;129:644-650.
12. The Diabetes Control and Complications Trial Research group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986.
13. Van den Berghe G. Does tight blood glucose control during cardiac surgery improve patient outcome?. Ann Intern Med 2007;146:307-308.
14. Gandhi G, Nuttall G, Abel M, Mullany C, Schaff H, O'Brien P, Johnson M, Williams A, Cutshall S, Mundy L, Rizza R, McMahon M. Intensive intra-operative insulin therapy versus conventional glucose management during cardiac surgery. Ann Intern Med 2007;146:233-243.
15. Klein R, Klein BEK, Moss SE. Relation of glycemic control to diabetic microvascular complications in diabetes mellitus. Ann Int Med 1996;127:90-96.
16. Yendamuri S, Fulda GJ, Tinkoff GH. Admission hyperglycemia as a prognostic indicator in trauma. J Trauma 2003;55:33-38.
17. Laird AM, Miller PR, Kilgo PD, Meredith JW, Chang MC. Relationship of early hyperglycemia to mortality in trauma patients. J Trauma 2004;56:1058-1062.
18. Bochicchio GV, Sung J, Joshi M, Bochicchio K, Johnson SB, Meyer W, Scalea TM. Persistent hyperglycemia is predictive of outcome of critically ill trauma patients. J Trauma 2005;58:921-924.
19. Sung J, Bochicchio GV, Joshi M, Bochicchio K, Tracy K, Scalea TM. Admission hyperglycemia is predictive of outcome in critically ill trauma patients. J Trauma 2005;59:80-83.
20. Rovlias A, Kotsou S. The influence of hyperglycemia on neurological outcome in patients with severe head injury. Neurosurgery 2000;46:335-342.
21. Jeremitsky E, Omert LA, Dunham M, Wilberger J, Rodriguez A. The impact of hyperglycemia on patients with severe brain injury. J Trauma 2005;58:47-50.
22. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. Stroke 2001;32:2426-2432.
23. Bolton CF. Sepsis and the systemic inflammatory response syndrome: neuromuscular manifestations Crit Care Med 1996;24:1408-1416.
24. Soop M, Nygren J, Thorell A, Ljungqvist O. Stress-induced insulin resistance: recent developments. Curr Opin Nutr Care 2007;10:181-186.
25. Anderson R, Brismar K, Barr G, Ivert T. Effects of cardiopulmonary bypass on glucose homeostasis after coronary bypass surgery. Eur J Cardiothorac Surg 2005;28:425-430.
26. Van den Berghe G, Wilmer A, Milants I, Wouters PJ, Bouckaert B, Bryninckx F. Intensive insulin therapy in mixed medical/sur-

gical intensive care units: benefit versus harm. Diabetes 2006;55:3151-3159.
27. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000;355:773-778.
28. Muhlestein JB, Anderson JL, Horne BD, Lavasani F, Allen Maycock CA, Bair TL, Pearson RR, Carlquist JF. Intermountain Heart Collaborative Study Group. Effect of fasting glucose levels on mortality rate in patients with and without diabetes mellitus and coronary artery disease undergoing percutaneous coronary intervention. Am Heart J 2003;146:351-358.
29. Held C, Gerstein HC, Yusuf S, Zhao F, Hilbrich L, Anderson C. Glucose levels predict hospitalization for congestive heart failure in patients at high cardiovascular risk. Circulation 2007;115:1371-1375.
30. Gerstein HC, Capes SE. Dysglycemia: a key cardiovascular risk factor. Semin Vasc Med 2002;2:165-174.
31. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, Williams BA, Schrader LM, Rizza RA, McMahon MM. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. Mayo Clin Proc 2005;80:862-866.
32. Sharma N, Okere IC, Duda MK, Chess DJ, O'Shea KM, Stanley WC. Potential impact of carbohydrate and fat intake on pathological left ventricular hypertrophy. Cardiovasc Res 2007;73:257-268.
33. Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simon-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545-2559.
34. Vega CP. Higher risk for mortality with intensive diabetes treatment—Now What? A best evidence review. N Engl J Med 2008;358:2545-2559.
35. Cosgrove DM, Loop FD, Lytle BW. Determinants of 10-year survival after primary myocardial revascularization. Ann Surg 1985;202:480-490.
36. Pomposelli J, Baxter J, Babineau T. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. J Parent Enter Nutr 1998;22:77-81.
37. Zerr K, Furnary A, Grunkemeier G. Glucose control lowers the risk of wound infection in diabetes after open heart operations. Ann Thorac Surg 1997;63:356-361.
38. McMurphy JF. Wound healing with diabetes mellitus. Surg Clin North Am 1984;64:769-778.
39. Iwakura K, Ito H, Ikushima M. Association between hyperglycemia and the no-reflow phenomenon in patients with acute myocardial infarction. J Am Coll Cardiol 2003;41:1-7.
40. Szabó Z, Hakanson E, Svedjeholm R. Early postoperative outcome and medium-term survival in 540 diabetic and 2,239 nondiabetic patients undergoing coronary artery bypass grafting. Ann Thorac Surg 2002;74:712-719.
41. Carson JL, Scholz PM, Chen YA. Diabetes mellitus increases short-term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. J Am Coll Cardiol 2002;40:418-423.
42. Lazar HL, Chipkin SR, Fitzgerald CA. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation 2004;109:1497-1502.
43. Pereira E. Nuevas perspectiva en oftalmología: Retinopatía diabética. Barcelona. Editorial Glosa 2005.
44. Ishii H, Jirousek MR, Koya D, Takagi C, Xia P, Clermont A, Bursell SE, Kern TS, Ballas LM, Heath WF, Stramm LE, Feener EP, King GL. Amelioration of vascular dysfunctions in diabetic rats by an oral PKC beta inhibitor. Science 1996;272:728-731.
45. Feener, Xia P, Inoguchi T, Shiba T, Kunisaki M, King GL. Role of protein kinase C in glucose- and angiotensin II-induced plasminogen activator inhibitor expression. Contrib Nephrol 1996;118:180-7.
46. Kolm-Litty SU, Nerlich A, Lehmann R, Schleider ED. High glucose-induced transforming growth factor beta 1 production is mediated by the hexosamine pathway in porcine glomerular mesangial cells. J Clin Invest 1998;101:160-169.
47. Scharschmidt LA, Dunn MJ. Prostaglandin synthesis by rat glomerular mesangial cells in culture. Effects of angiotensin II and arginine vasopressin. J Clin Invest 1983;71:1756-1764.
48. Trachtman H, Futterweit S, Singhal P. Nitric oxide modulates the synthesis of extracellular matrix proteins in cultures rat mesangial cells. Biochem Biophys Res Commun 1995;207:120-125.
49. Iglesias-de la Cruz MC, Ruiz-Torres MP, Alcamí J, Díez-Marqués ML, Ortega-Velázquez R, Chen S, Rodríguez-Puyol M, Ziyadeh FN, Rodríguez-Puyol D. Hydrogen peroxide increases intracellular matrix mRNA through TGF-beta in human mesangial cells. Kidney Int 2001;59:87-95.
50. Brownlee M, Cerami A, Vlassara H. Advanced products of nonenzymatic glycosylation and the pathogenesis of diabetic vascular disease. Diabetes Metab Rev 1988;4:437-451.
51. Stout RW. Glucose inhibits replication of cultured human endothelial cells. Diabetologia 1982;2:436-439.
52. Langouche L, Vanhorebeek I, Vlasselaers D. Intensive insulin therapy protects the endothelium of critically ill patients. J Clin Invest 2005;115:2277-2286.
53. McClain DR, Crook ED. Hexosamines and insulin resistance. Diabetes 1996;45:1.003-1.009.
54. Pandolfi A, Giaccari A, Cilli C, Alberta MM, Morviducci L, De Filippis EA, Buongiorno A, Pellegrini G, Capani F, Consoli A. Acute hyperglycemia and acute hyperinsulinemia decrease plasma fibrinolytic activity and increase plasminogen activator inhibitor type 1 in the rat. Acta Diabetol 2001;38:71-76.
55. Ceriello A, Giacomello R, Stel G, Motz E, Taboga C, Tonutti L, Pirisi M, Falleti E, Bartoli E. Hyperglycemia-induced thrombin formation in diabetes: the possible role of oxidative stress. Diabetes 1995;44:924-928.
56. Sakamoto T, Ogawa H, Kawano H, Hirai N, Miyamoto S, Takazoe K, Soejima H, Kugiyama K, Yoshimura M, Yasue H. Rapid change of platelet aggregability in acute hyperglycemia: detection by a novel laser-light scattering method. Trhomb Haemost 2000;83:475-479.
57. Morohoshi M, Fujisawa K, Uchimura I, Numano F. Glucose-dependent interleukin 6 and tumor necrosis factor production by human peripheral blood monocytes *in vitro*. Diabetes 1996;45: 954-959.
58. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002;106:2067-2072.
59. Mohanty P, Hamouda W, Garg R, Aljada A, Ghanim H, Dandona P. Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. J Clin Endocrinol Metab 2000;85:2970-2973.
60. Turina M, Gry DE, Polk HC. Acute hyperglycemia and the innate immune system: clinical, cellular, and molecular aspects. Crit Care Med 2005;33:1624-1633.
61. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295:1681-1687.
62. Young ME, McNulty P, Taegtmeyer H. Adaptation and maladaptation of the heart in diabetics: part II. Circulation 2002;105:1861-1871.
63. Valverde AM, Benito M. The brown adipose cell: a unique model for understanding the molecular mechanism of insulin resistance. Mini Rev Med Chem 2005;5:269-78.

64. Alonso E. Metabolic syndrome and cardiac arrest. Act Med Colomb 2005;30:154-163.
65. Tansey MJ, Opie LH. Relation between plasma free fatty acids and arrhythmias within the first twelve hours of acute myocardial infarction. Lancet 1983;2:419-422.
66. Oliver MF. Metabolic causes and prevention of ventricular fibrillation during acute coronary syndromes. Am J Med 2002;112: 305-311.
67. Kersten JR, Toller WG, Tessmer JP, Pagel PS, Warltier DC. Hyperglycemia reduces coronary collateral blood flow through a nitric oxide-mediated mechanism. Am J Physiol Heart Circ Physiol 2001;281:H2097-H2104.
68. Kersten JR, Schmeling TJ, Orth KG, Pagel PS, Warltier DC. Acute hyperglycemia abolishes ischemic preconditioning *in vivo*. Am J Physiol 1998;275:H721-H725.
69. D'Amico M, Marfella R, Nappo F, Di Filippo C, De Angelis L, Berrino L, Rossi F, Giugliano D. High glucose induces ventricular instability and increases vasomotor tone in rats. Diabetologia 2001;44:464-470.
70. Marfella R, Nappo F, De Angelis L, Sniscalchi M, Rossi F, Giugliano D. The effect of acute hyperglycaemia on QTc duration in healthy man. Diabetologia 2000;43:571-575.
71. Scognamiglio R, Negut C, De Kreutzenberg SV, Tiengo A, Avogaro A. Postprandial myocardial perfusion in healthy subjects and in type 2 diabetic patients. Circulation 2005;112:179-184.
72. Scognamiglio R, Negut C, de Kreutzengerg SV, Tiengo A, Avogaro A. Effects of different insulin regimes on postprandial myocardial perfusion defects in type 2 diabetic patients. Diabetes Care 2006;29:95-100.
73. Shiojima I, Yefremashvili M, Luo Z, Kureishi Y, Takahashi A, Tao J. Akt signaling mediates postnatal heart growth in response to insulin and nutritional status. J Biol Chem 2002;277:37670-37677.
74. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813-820.
75. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature 2000;404:787-790.
76. Lemasters JJ, Nieminen AL, Qian T, Trost LC, Elmore SP, Nishimura Y. The mitochondrial permeability transition in cell death: a common mechanism in necrosis, apoptosis and autophagy. Biochim Biophys Acta 1998;1366:177-196.
77. Zorov DB, Filburn CR, Klotz LO, Zweier JL, Sollott SJ. Reactive oxygen species (ROS)-induced ROS release: a new phenomenon accompanying induction of the mitochondrial permeability transition in cardiac myocytes. J Exp Med 2000;192:1001-1014.
78. Haber CA, Lam TK, Yu Z, Gupta N, Goh T, Gogdanovic E, Giacca A, Fantus IG. N-acetylcysteine and taurine prevent hyperglycemia-induced insulin resistance *in vivo*: possible role of oxidative stress. Am J Physiol Endocrinol Metab 2003;285:E744-E753.
79. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 2006;113:1888-1904.
80. Verma S, Maitland A, Weisel RD, Li SH, Fedak PW, Pomroy NC, Mickle DA, Li RK, Ko L, Rao V. Hyperglycemia exaggerates ischemia-reperfusion-induced cardiomyocyte injury: reversal with endothelin antagonism. J Thorac Cardiovasc Surg 2002;123:1120-1124.
81. Taegtmeyer H, de Villalobos D. Metabolic support for the postischemic heart. Lancet 1995;345:1552-1555.
82. Szabó Z, Arnqvist H, Hakanson E. Effects of high-dose glucose-insulin-potassium on myocardial metabolism after coronary surgery in patients with type II diabetes. Clin Sci 2001;101:37-43.
83. Bothe W, Olschewski M, Beyersdorf F. Glucose-insulin-potassium in cardiac surgery: A meta-analysis. Ann Thorac Surg 2004;78:1650-1657.
84. Quinn DW, Pagano D, Bonser RS. Improved myocardial protection during coronary artery surgery with glucose-insulin-potassium: A randomized controlled trial. J Thorac Cardiovasc Surg 2006;131:34-42.
85. Sodi-Pallares D, Testelli M, Fishleder F, Bisteni A, Medrano GA, Friedland C, de Micheli A. Effects of intravenous infusion of a potassium-insulin-glucose solution on the electrocardiographic signs of myocardial infarction. Am J Cardiol 1962;9:166-181.
86. Pomposelli JJ, Baxter JK 3rd, Babineau TJ. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. J Parenter Enteral Nutr 1998;22:77-81.
87. Bruemmer-Smith S, Avidan MS, Harris B. Glucose, insulin and potassium for heart protection during cardiac surgery. Br J Anaesth 2002;88:489-495.
88. Koskentari JK, Kaukoranta PK, Rimpiläine J, Vainionpää PP, Ohtonen PP, Surcel HM, Juvonen T, Ala-Kokko TI. Anti-inflammatory effect of high-dose insulin treatment after urgent coronary revascularization surgery. Acta Anaesthesiol Scand 2006;50:962-969.
89. Opie LH. The glucose hypothesis: relation to acute myocardial ischaemia. J Mol Cell Cardiol 1970;1:107-114.
90. Rojas E, Luna P, Serrano X, Fernández B, de Micheli A. Glucose-Insulin-Potassium solution (GIK): Insulin's cardio protective effects. Arch Cardiol Mex 2006;76:144-151.
91. Ma H, Zhang HF, Yu L, Zhang QJ, Li J, Huo JH, Li X, Guo WY, Wang HC, Gao F. Vasculoprotective effect of insulin in the ischemic/reperfused canine heart: role of Akt-stimulated NO production. Cardiovas Res 2006;69:57-67.
92. Khaury W, Klausner JM, Ben-Abraham R, Szold O. Glucose control by insulin for critically ill surgical patients. J Trauma 2004;57:1132-1134.
93. Nava P, Carbó R, Guarner V. Coronary and femoral arterial contraction with high glucose, insulin, and glucose-insulin-potassium solution: effects of hypoxia. Heart & Vessels 2002;16:57-63.
94. Markovitz LJ, Wiechmann RJ, Harris N, Hayden V, Cooper J, Johnson G, Harelstad R, Calkins L, Braithwaite SS. Description and evaluation of a glycemic management protocol for patients with diabetes undergoing heart surgery. Endocr Pract 2002;8:10-18.
95. Goldberg PA, Siegel MD, Sherwin RS, Halickman JI, Lee M, Bailey VA, Lee SL, Dziura JD, Inzucchi SE. Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit Diabetes Care 2004;27:461-467.
96. Vogelzang M, Loef BG, Regtien JG, van der Horst IC, van Assen H, Zijlstra F, Nijsten MW. Computer-assisted glucose control in critically ill patients. Intensive Care Med 2008;34: 1421-1427.
97. Hirsch IB, Paauw DSs, Brunzell J. Inpatient management of adults with diabetes. Diabetes Care 1995;18:870-878.
98. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M. Attempting to maintain normoglycemia during cardiopulmonary bypass with insulin may initiate postoperative hypoglycemia. Anesth Analg 1999;89:1091-1095.
99. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R. Intensive insulin therapy in the medical ICU. N Engl J Med 2006;354:449-461.
100. Van Cromphaut SJ, Vanhorebeek I, Van den Berghe G. Glucose metabolism and insulin resistance in sepsis. Curr Pharm Des 2008;14:1887-1899.

101. Ellger B, Debaveye Y, Vanhorebeek I, Langouche L, Giulietti A, Van Etten, Herijgers P, Mathieu C, Van den Berghe G. Survival benefits of intensive insulin therapy in critical illness: impact of maintaining normoglycemia *versus* glycemia-independent actions of insulin. Diabetes 2006;55:1096-1105.
102. Olguín R, Medina H, Luna P, Paratz M, Posadas C. Perioperative handling of diabetic patients in cardiac surgery with extracorporeal circulation. Arch Cardiol Mex 1985;55:389-394.
103. Molina FJ, Luna P, Lesprón MC, González O, Ruíz A, Romero J, Fernández B, Bernal ML, Álvarez H. Glucose-Insulin-Potassium in coronary revascularization. Rev Mex Anest 1996;19: 122-127.
104. Rojas E, Luna P, Serrano X, Fernández B, de Micheli A. Glucose-Insulin-Potassium solution (GIK): Insulin's cardio protective effects. Arch Cardiol Mex 2006;76:S4,144-151.
105. Rojas E, Sánchez S, Delfín R, Luna P, Molina FJ, Sanchez-Miranda G, De Micheli A, Lesprón MC, Fernández B. Hyperglycemia control with control with Glucose-Insulin-Potassium solution in diabetic patients undergoing cardiac surgery. Arch Cardiol Mex 2008;78:171-177.