REVIEW

Intensive insulin therapy during cardiovascular surgery

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Abstract : Recent evidence in the fields of surgery, emergency and critical care medicine indicates that strict glycemic control results in lower mortality. Hyperglycemia occurs frequently in patients with and without diabetes during cardiovascular surgery, especially during cardiopulmonary bypass. However, strict glucose control is difficult to achieve during cardiovascular procedures. To establish effective intensive insulin therapy during cardiovascular surgery, we conduct continuous blood glucose monitoring and employ automatic control by using an artificial endocrine pancreas (the STG®-22, Nikkiso, Tokyo, Japan). In this review, we will outline the present status and problems of conventional glycemic control for perioperative cardiovascular surgery and introduce the new perioperative blood glucose management method that we are testing now. We will also discuss the importance of perioperative glycemic control for cardiovascular surgery as well as future prospects. J. Med. Invest. 57 : 191-204, August, 2010

Keywords **:** *intensive insulin therapy, cardiovascular surgery, cardiopulmonary bypass, artificial endocrine pancreas, diabetes*

INTRODUCTION

Hyperglycemia can worsen a number of perioperative problems, including cardiac, neurologic, and infectious complications (1). Hyperglycemia occurs frequently in patients with and without diabetes during cardiovascular surgery, especially during cardiopulmonary bypass. In a study by Van den Berghe and colleagues (2), intensive insulin therapy after surgery reduced morbidity and mortality in critically ill patients, most of whom underwent cardiac surgery. High-risk cardiac patients were found to derive the greatest benefit from intensive insulin therapy. However, strict glucose control is difficult to achieve during cardiovascular procedures requiring cardiopulmonary bypass because of the stress

of surgery, including anesthesia, cardioplegia, and inotropic support (3-5). Optimal glucose control is unlikely when glucose concentrations are measured only episodically.

In the first half of this review, we will present problems associated with glucose toxicity, role of insulin, and literature review of large randomized studies regarding intensive insulin therapy in the field of cardiovascular surgery. In the latter half, our clinical trial to evaluate the efficacy of the artificial endocrine pancreas during cardiovascular surgery will be presented and discussed.

GLUCOSE TOXICITY AND THE ROLE OF INSULIN

Glucose Toxicity

Glucose toxicity, in its narrow sense, refers to a clinical condition where control of diabetes is particularly poor, since hyperglycemia itself reduces the insulin secretion capacity of pancreatic β-cells,

and the induced insulin resistance leads to further hyperglycemia. This vicious circle finally leads to the total incapacity of β-cells to secrete insulin (6, 7). On the other hand, glucose toxicity in its wide sense refers to various complications due to diabetes. As for the cytotoxic mechanism due to hyperglycemia, the four contributing metabolic pathways are known as :

1. The polyol pathway
2. The hexosamine pathway
3. The advanced glycosylation end product (AGE)-producing pathway and
4. The diacyl glycerol (DAG)-producing pathway.

Recent fundamental research findings suggest that oxidative stress greatly influences the molecular mechanism of the reduction of insulin biosynthesis and secretion, which constitutes the main etiology of this glucose toxicity (1). Figure 1 shows the mechanism for the increase of oxidative stress in diabetes. There are two pathways known as the glycation reaction and the mitochondreal electron transfer system. In the glycation reaction, a Shiff base is formed of glucose and protein followed by an Amadoric compound, after which AGE and reactive oxygen species (ROS) are produced as metabolites, leading to an increase in oxidative stress (8). In the mitochondreal electron transfer system, ATP and ROS are produced through the TCA cycle, which also leads to oxidative stress increase. Figure 2 illustrates the molecular mechanism of the reduction in insulin secretion caused by the increase in oxidative stress. When ROS increases due to chronic hyperglycemia, and oxidative stress increases, PDX-1 (pancreatic duodenal homeobox-1) activity decreases in pancreatic β-cells, and, as a result, glucokinase activity and insulin biosynthesis decrease, followed by a decrease in insulin secretion. MafA is a recently isolated β-cell specific transcription factor which functions as a potent activator of insulin gene transcription. It was shown recently that
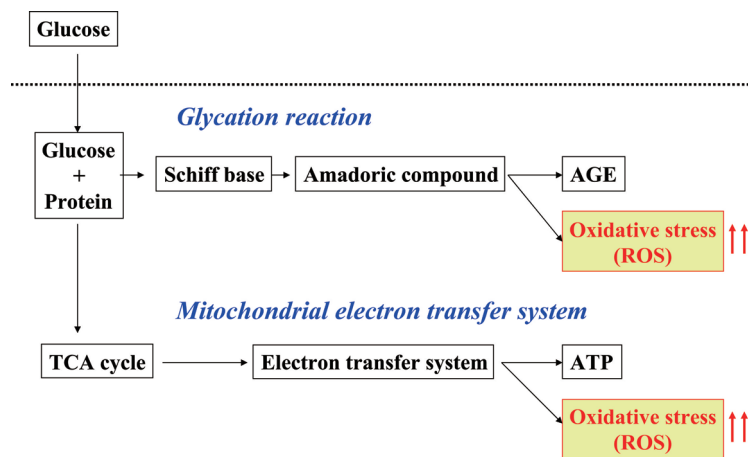
Figure 1.   Increase in oxidative stress in the diabetic state
Acceleration of glycation response and the intramitochondrial electron transfer system was detected in the diabetic state, causing oxidative stress as the responses accelerate. AGE : advanced glycosylation end products ; ROS : reactive oxygen species ; TCA cycle : tricarboxilic acid cycle ; ATP : adenosine tri-phosphate
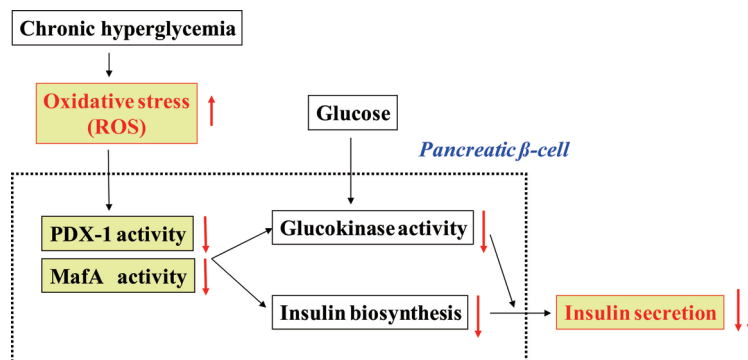
Figure 2.   The mechanism of insulin secretion reduction due to glucose toxicity
DNA binding activities of PDX-1 and MafA decrease as a result of oxidative stress caused by hyperglycemia, while insulin biosynthesis and secretion also decrease. ROS : reactive oxygen species ; PDX-1 : pancreatic duodenal homeobox-1

expression and/or DNA binding activities of MafA, together with PDX-1, are reduced after chronic exposure to a high glucose concentration (9).

Diabetic complications

These mechanisms cause complications in diabetes, which are divided into chronic and acute complications based on the disease course (Table 1). Chronic complications are further divided into microvascular diseases, which are specific, to and common in diabetes, and macrovascular diseases, which are not specific but frequent and thus important for prognosis. Chronic hyperglycemia can induce microvascular complications such as retinopathy, neuropathy or nephropathy (10). It can also induce macrovascular complications partially, such as aortic sclerosis, stroke, myocardial infarction, angina pectoris, and obstructive peripheral vascular disease. Acute complications include diabetic coma and acute infection. Especially, acute infection is the biggest problem in surgery patients.

The two major problems associated with acute hyperglycemia are infection and cardiovascular disorders. The causes of infection are :
1. Diminished leukocyte chemotaxis,
2. Diminished granular phagocytic activity, and
3. Diminished intracellular bactericidal capacity (11, 12).
Cardiovascular disorders, on the other hand, are caused by :
1. Impaired myocardial protection by hyperglycemia due to changes in cardiomyocyte cell communication
2. Diminished control function of coronary circulation in the ischemic region
3. Impaired myocardial protection resulting from ischemic preconditioning and anesthetic preconditioning. Inhibition of mitochondrial K_{ATP} channel activation is thought to be another cause of this impairment (13-15).

Effects of insulin

In addition to reducing blood glucose levels, the insulin used in intensive insulin therapy has itself a vulnerary effect and provides myocardial protection. The basic vulnerary effects of insulin are anti-inflammatory and antioxidant (16). In fact, it is claimed that intensive use of insulin for an injury can reduce mortality due to multiple organ failure associated with sepsis. Insulin is thought to exert its constant growth promotion and wound healing effects because it is closely related to growth factors with vulnerary effects such as the insulin-like growth factor (IGF) (17). Also, insulin maintains the constant state of vascular endothelial cells through nitric oxide (NO) synthase activation, while it also diminishes oxidative stress and cytokine production. On the other hand, glucose insulin (GI) and glucose insulin potassium (GIK) therapies are representative of the myocardial protective effect of insulin (18).

LITERATURE REVIEW OF INTENSIVE INSULIN THERAPY

Effects of glucose management in ICU

Intensive insulin therapy is used for critically ill patients, and its specific aims are multiple organ protection and the prevention and treatment of infection (2, 19-24). Intensive insulin administration normalizes blood glucose levels and maintains normal levels. Originally, the target for this method was a blood glucose level of 80-110 mg/dl (2), but later many modified versions were introduced that aimed for a blood glucose level upper limit of around 140 to 180 mg/dl (22-24). The greatest reduction in mortality resulting from this therapy involves death due to multiple-organ failure with a proven septic focus.

The first paper deals with the effects of glucose

Table 1 :   Types of diabetic complications

Chronic complications 　· Microvascular diseases : retinopathy, neuropathy, nephropathy 　· Macrovascular diseases : aortic sclerosis, stroke, myocardial infarction, angina pectoris, obstructive peripheral vascular disease, etc. 　· Others : cataract, dermatopathy, hypertension, osteopenia, osteomalacia, arthropathy, soft tissue fibromatosis, etc.
Acute complications 　· Diabetic coma : ketoacidotic coma, non-ketotic hyperosmolar coma, lactic acidosis 　· Acute infection : bacterial, mycotic, viral, etc.

management in the intensive care unit (ICU). Van den Berghe and co-workers (2) in Belgium published the paper "Intensive Insulin Therapy in Critically Ill Patients" in the New England Journal of Medicine in 2001. Patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg/dl) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg/dl and maintenance of glucose at a level between 180 and 200 mg/dl). With a total of 1,548 patients enrolled, intensive insulin therapy reduced mortality during intensive care from 8.0% with conventional treatment to 4.6%. The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in ICU for more than five days (20.2% with conventional treatment, as compared with 10.6% with intensive insulin therapy). Figure 3 represents Kaplan-Meier curves showing cumulative survival of patients who received intensive insulin treatment or conventional treatment in ICU. Figure 3A shows the survival rate in ICU, and Figure 3B the in-hospital survival rate. Later, the same authors published many study reports which had a major impact, so that intensive insulin therapy rapidly found acceptance worldwide (19-21).

Surviving Sepsis Campaign guidelines

In association with the Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock were published in Critical Care Medicine in 2004 (25). With these guidelines, the survival rate improved with a blood glucose level of 80-110 mg/dl, but a target blood glucose level of 150 mg/dl was recommended because of the risk of hypoglycemia. It was shown that blood glucose value management is more important than managing the total amount of insulin, while frequent blood glucose measurements are essential. A revised edition of the guidelines was published in 2008 (26), but the recommended target blood glucose value remained 150 mg/dl or less.

Prospective randomized controlled studies of glycemic control

Several large-scale multicenter studies of glycemic control have been performed, and three of the most well-known are the VISEP Trial (27), the Glucontrol Study (28), and the NICE-SUGAR study (29). The VISEP Trial was started as a 2-year study of insulin therapy or other effects of severe sepsis involving 17 German institutions. The study started with 600 patients in 2003, but was discontinued in 2005 when the number had dropped to 537. The reason for the dropout was frequent hypoglycemia.

The Glucontrol Multi-Center Study was a large study, which started with 3,500 patients in 21 European institutions in 2004. The aim of this study was to compare results for two groups with target blood glucose values of 80-110 and 140-180, but this was
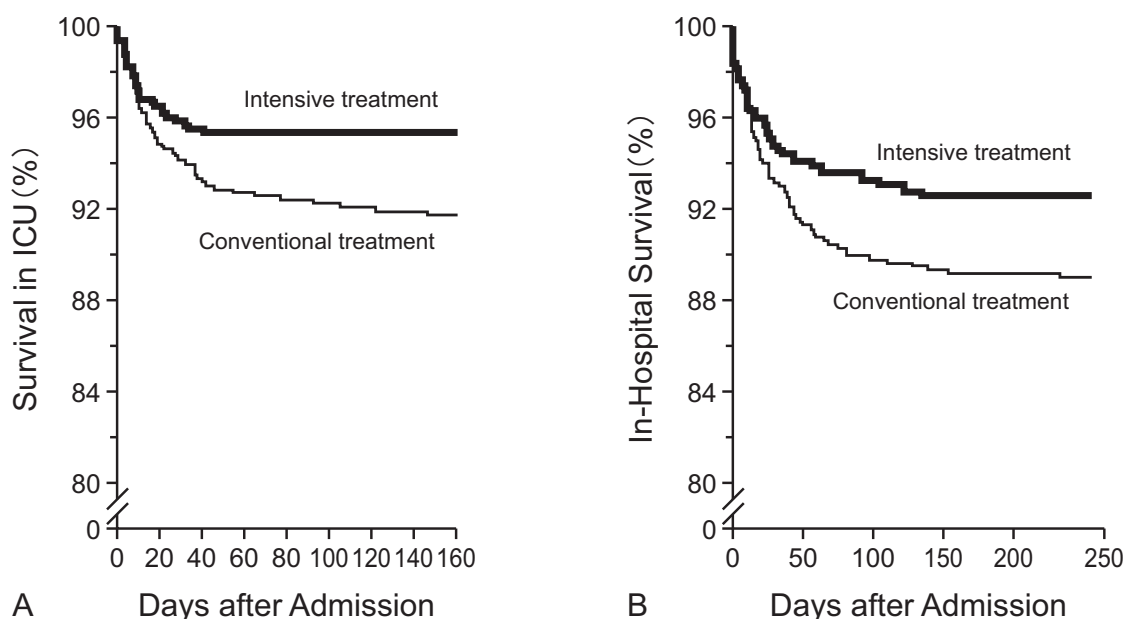

Figure 3.   Kaplan-Meier curves showing cumulative survival of patients who received intensive insulin treatment or conventional treatment in the intensive care unit.
(from Ref. 2 Van den Verghe G, et al. N Eng J Med 345, 1359-1367, 2001)

also discontinued suddenly with only 1,101 cases remaining. For this study, too, the reason for cancellation was a very high incidence of hypoglycemia.

The results of the subsequent NICE-SUGAR study, which compared target blood glucose values of 81-108 and 144-180 in two groups and was performed in Oceania and North America attracted the most interest. Results were presented recently, but were contrary to expectations. We will discuss the details later. In a large study, we found that "tight glycemic control with the aid of a manual easily leads to hypoglycemia".

Recent reports on intensive insulin therapy

Some recent negative reports about intensive insulin therapy have led to a reconsideration of intensive insulin therapy (29-31). One study which used a meta-analysis to examine mortality among critically ill patients was published in JAMA of August, 2008 (30). No differences in in-hospital mortality rates were observed between the conventional and intensive therapy groups. Few patients in the intensive therapy group suffered from sepsis, but hypoglycemic incidence was very high (13.7% vs. 2.5%), thus warranting further attention.

The results of the previously mentioned NICE-SUGAR study were presented in the March issue of the New England Journal of Medicine (29). Contrary to everyone's expectations, the mortality for the intensive therapy group after 90 days (target blood sugar value : 81-108 mg/dl) was higher (27.5% vs 24.9%) than that for the conventional therapy group (target blood sugar value : 144-180 mg/dl). Do these findings mean that intensive insulin therapy should be discarded entirely? Although this is probably not the case, it is clear that there is an urgent need for the establishment of a new blood glucose control method that does not cause hypoglycemia.

Intensive insulin therapy during cardiovascular surgery

Next, we will briefly introduce the main publications on intensive insulin therapy during cardiovascular surgery. In the field of cardiovascular surgery, the importance of controlling postoperative blood glucose values at 200 mg/dl or less has been recognized since the late 1990s (32, 33). After that, many reports regarding usefulness of intensive insulin therapy during cardiovascular surgery were published (34-37). In a study by Van den Berghe and colleagues, intensive insulin therapy after surgery reduced morbidity and death in critically ill patients, most of whom had undergone cardiac surgery.

Furnary et al. (32) reported in 1999 that sternal infection decreased by 58% when they controlled postoperative blood glucose values at 150-200 mg/dl in coronary artery bypass patients. Similarly, when they closely controlled blood glucose values in coronary artery bypass patients from the intraoperative stage (before median sternotomy) for three days postoperatively, not only sternal infection but also mortality reportedly decreased by 57%. They therefore emphasized the significance of glycemic control during and after surgery (34).

As for glycemic control during cardiopulmonary bypass, one study analyzed 1,579 adult patients with diabetes who underwent cardiovascular surgery in 2005 (38). For patients whose blood glucose level during cardiopulmonary bypass was more than 360 mg/dl, the mortality increased from 1.7% to 6%. That is why hyperglycemia of more than 300 mg/dl should be avoided, even temporarily, if the patients have diabetes. Cases with blood glucose levels exceeding 300 mg/dl may be considered rare occurrences, but as I will show later, there were a great many cases with blood glucose levels of more than 300 mg/dl during cardiopulmonary bypass when we used continuous monitoring.

These background findings resulted in a review that was published in 2006, which could be considered guidelines for cardiopulmonary bypass (39). This review covers eight risk factors of adult cardiopulmonary bypass as evidence for the guidelines. In addition to neuropathy, hemodilution, and inflammatory reaction, glycemic control is mentioned as very important evidence. The review emphasizes the importance of maintaining blood glucose levels within the normal range for all patients, including those with no diagnosis of diabetes and those undergoing cardiopulmonary bypass, during the entire perioperative period classified as Class I, Level B.

CURRENT INTRAOPERATIVE BLOOD GLUCOSE MANAGEMENT

Intraoperative glycemic control at Tokushima University Hospital

For a clear understanding of the present conditions of perioperative glycemic control at our hospital, here is a brief retrospective presentation of intraoperative glycemic control policies for major surgery and changes in real blood glucose values

during 2007. This review covers 74 hepatectomies, 12 pancreatico duodenectomies, 24 esophagectomies and 35 cardiovascular surgeries with cardiopulmonary bypass. Table 2 shows intraoperative blood glucose levels and insulin consumption divided into groups according to presence or absence of diabetes and the operative method. The conventional glycemic control policy resulted in target blood glucose values maintained at around 150-200 but frequently cases were not managed within the target range. Especially during cardiovascular surgery, hyperglycemic states with blood glucose values of 400 mg/dl or more often occurred during extracorporeal circulation, even in cases without diabetes, and blood glucose control was often difficult.

The next year, from January 2008, we tried intensive insulin therapy for stricter glycemic control by using manual insulin injection according to a sliding scale. Table 3 shows intraoperative glycemic control from January to the end of May 2008. Glucose and insulin were administered positively and the targeted intraoperative blood glucose value was between 100 and 150 mg/dl. Use of insulin was higher than in 2007, and slightly lower blood glucose values were maintained, but remained unsatisfactory. Intraoperative glycemic control was also difficult especially for cardiovascular surgery.

The challenge

The challenge we faced was how to achieve strict intraoperative glycemic control without hypoglycemic risk when blood glucose values vary widely. We had to choose between two methods. One was a stricter protocol of glycemic control. For this, we shortened the time between blood sugar measurements and made the insulin dose more precise. However, this increased the work load of the anesthesiologist. The other method was to entrust the work to a computer and a machine, which allows for continuous blood glucose monitoring and an automatic control system. We firmly opted for the second method.

Table 2 : Intraoperative glycemic control situation of Tokushima University Hospital from January to December in 2007 (Retrospective study)

Target BS : 150-200 mg/dl

[Median (Max-Min)]
[Mean± SD]

		BS (mg/dl)	Insulin (U)
Hepatectomies (n=74)	DM (-) n=57 DM (+) n=17	175 (72-309) 218 (84-449)	1.5± 3.6 9.3± 12.5
Pancreatico duodenectomies (n=12)	DM (-) n=7 DM (+) n=5	162 (105-270) 172 (79-261)	4.7± 10.0 3.9± 4.4
Esophagectomies (n=24)	DM (-) n=22 DM (+) n=2	120 (90-165) 163 (107-210)	0 0
Cardiovascular surgeries with cardiopulmonary bypass (n=35)	DM (-) n=29 DM (+) n=6	179 (74-454) 204 (95-361)	1.4± 3.6 4.8± 6.9

BS : Blood sugar, DM : Diabetes mellitus

Table 3 : Intraoperative glycemic control situation of Tokushima University Hospital from January to May in 2008 (Prospective study)

Target BS : 100-150 mg/dl

[Median (Max-Min)]
[Mean± SD]

	BS (mg/dl)	Insulin (U)
Hepatectomies (n=18, DM 2 cases)	174 (85-317)	2.2± 4.5
Pancreatico duodenectomies (n=6, DM 1 case)	162 (92-251)	1.7± 4.1
Esophagectomies (n=8, DM 0 case)	114 (88-160)	0
Cardiovascular surgeries with cardiopulmonary bypass (n=11, DM 3 cases)	169 (72-341)	7.2± 7.1

BS : Blood sugar, DM : Diabetes mellitus

CONTINUOUS BLOOD GLUCOSE MONI-TORING AND CONTROL SYSTEM

Artificial endocrine pancreas

In December 2007, our clinical team at Tokushima University initiated a clinical trial to evaluate the efficacy of the artificial pancreas for intra-operative patients. Two Nikkiso STG®-22 artificial pancreas systems (Figure 4) were put into clinical use at Tokushima University for intra- and post-operative glucose control. In order to familiarize ourselves with the device we first used the STG®-22 only for glucose monitoring purposes combined with insulin administration according to a sliding scale, and not for glucose control. Once the standard operational procedure was established, we used the STG®-22 for closed-loop intensive glucose control.

The STG®-22 from Nikkiso in Tokyo is an original artificial endocrine pancreas with a closed-loop glycemic control system that provides continuous blood glucose monitoring through a glucose sensor electrode and automatically administers subsequent insulin and glucose infusions to maintain appropriate blood glucose levels (40, 41).

The applications for this device are :
1. Emergency treatment during hyperglycemia (that is, diabetic coma)
2. Diagnosis of insulin resistance and the secretional capacity of patients with diabetes
3. Glycemic control during surgery, trauma and delivery (including patients without diabetes).

This device is designed to simulate the pancreatic function by means of mechanical engineering (Figure 4). The glucose infusion pump is equivalent to the glucagon secretion mechanism in the α-cells of the pancreas, the glucose reservoir to the α-granules, the glucosensor to the cell membrane, the battery to the mitochondria, the computer to the nucleus, the insulin reservoir to the β-granules of the β-cells of the pancreas, an the insulin infusion pump to the insulin secretion mechanism.

The artificial pancreas STG®-22 is composed of a glucose sensor, which performs glucose detection and monitoring, and pumps for infusing the appropriate amount of insulin or glucose. The insulin and glucose pumps are computer-regulated based on a targeted blood glucose value determined before operation of the system is started. It is important to recognize that the STG®-22's glucose sensor, which withdraws the blood from the patient at a rate of 2 ml per hour, is capable of continuously measuring the blood glucose level with its glucose sensor, and
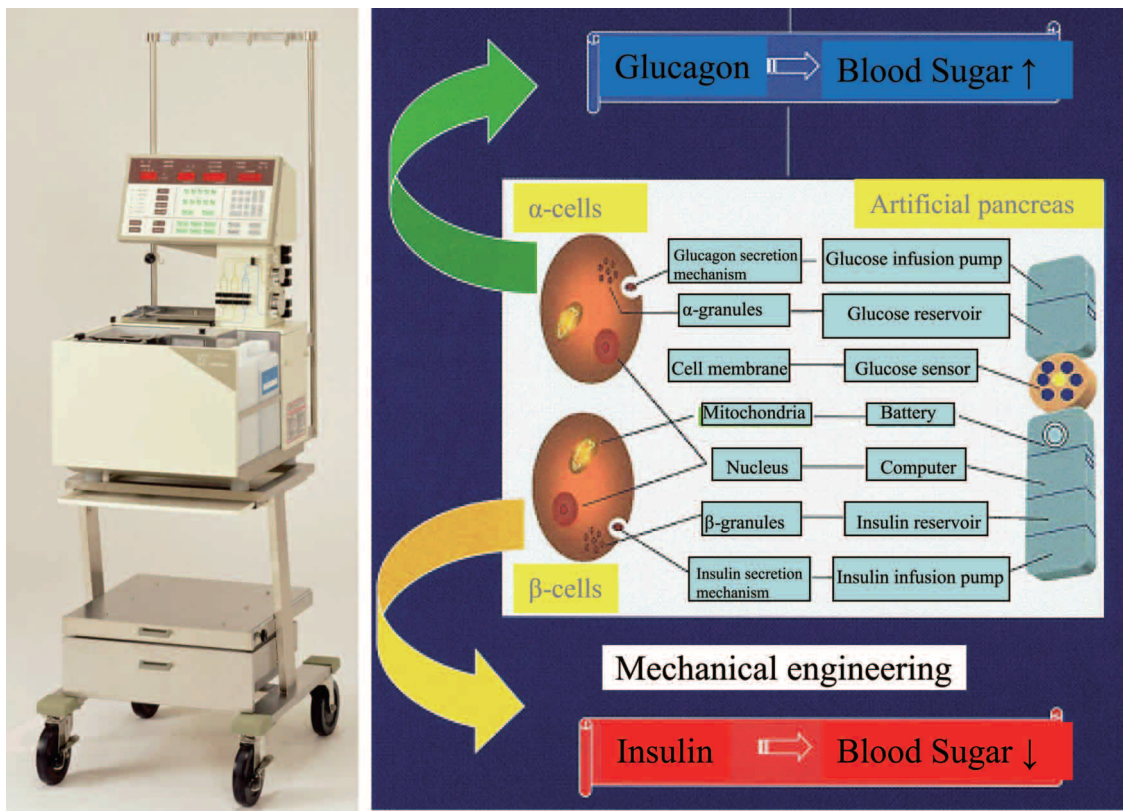

Figure 4.   Concept of artificial endocrine pancreas

automatically infuses insulin or glucose to adjust the blood glucose level of the patients in accordance with the target glucose value, which is an adaptation of what we call the "closed loop system". This device provides continuous blood glucose monitoring by means of dual lumen catheter blood sampling, a high-quality roller pump and a glucose sensor electrodes with glucose oxidase membrane. The measured blood glucose level is then inputted into a computer, and the infusion rate of insulin or glucose is determined with an algorithm.

Accuracy of a continuous blood glucose monitoring

Yamashita et al. have published several papers regarding the reliability and accuracy of the STG®-22 for continuous blood glucose monitoring (42, 43). Figure 5A shows data obtained during surgery, and Figure 5B shows the data after surgery. Blood glucose measured continuously with the STG®-22 correlated strongly with measurements obtained intermittently with a conventional laboratory glucometer.

Two types of continuous glucose monitoring systems are currently in use : a continuous subcutaneous glucose monitor and a continuous blood glucose monitor. The continuous subcutaneous glucose monitoring system might be less invasive than a continuous blood glucose monitoring system. However, the precision of both these types of continuous glucose monitors is controversial. It has been reported that a continuous subcutaneous glucose monitor had a larger error (44). STG®-22 is currently the only continuous blood glucose monitoring device in the world, it might be a useful option for intensive insulin therapy.
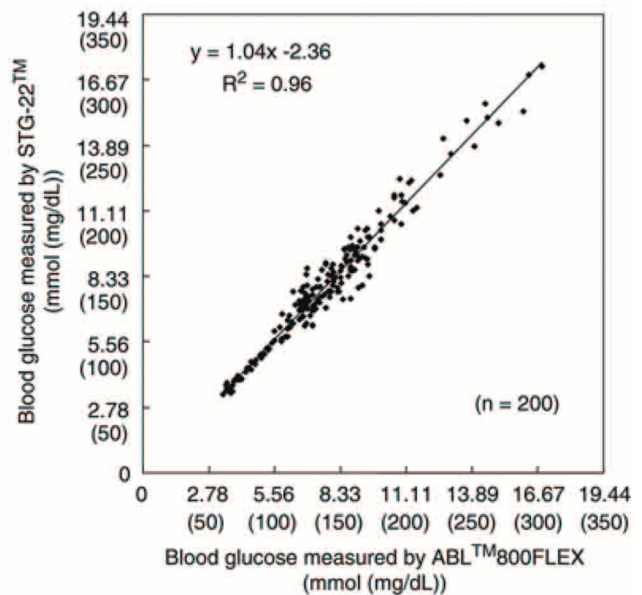
INTENSIVE INSULIN THERAPY DURING CARDIOVASCULAR SURGERY

Continuous blood glucose monitoring during off-pump coronary artery bypass grafts

To establish an intensive insulin therapy during cardiovascular surgery, we first employed continuous monitoring of blood glucose values while using off-pump coronary artery bypass grafts (OPCAB) and during cardiovascular surgery with a cardiopulmonary bypass, and looked for any changes in intraoperative blood glucose values. Figure 6 shows continuous blood glucose monitoring during OPCAB. Effective continuous blood glucose monitoring was possible, but in all cases few changes in intraoperative blood glucose levels were observed during OPCAB surgery.
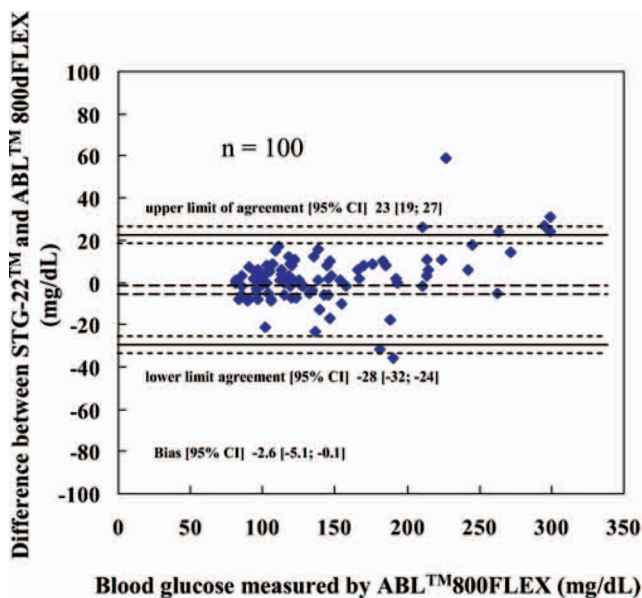
A

B

Figure 5.   Accuracy of a continuous blood glucose monitoring
(A : from Ref. 42 Yamashita K, et al. Anesth Analg 106 : 160-163, 2008, B : from Ref. 43 Yamashita K, et al. Acta Anaesthsiol Scand 53 : 66-71, 2009)
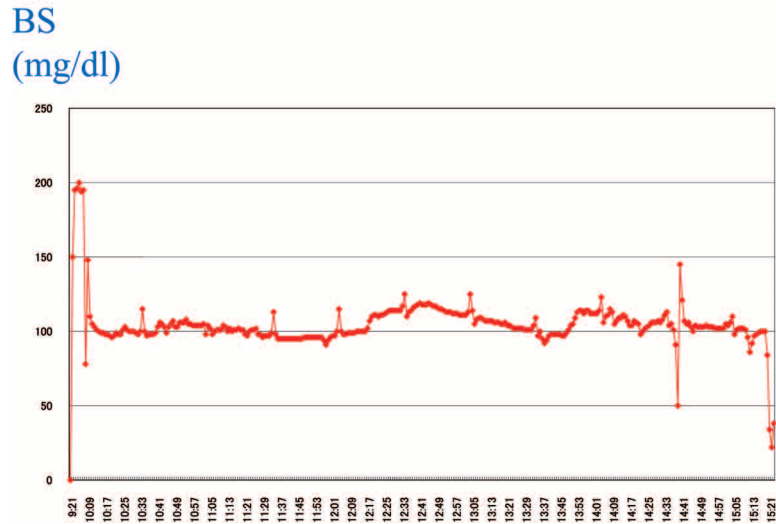
Figure 6.   Continuous blood glucose monitoring during off-pump coronary artery bypass grafts
BS ; blood sugar

Continuous blood glucose monitoring during cardiovascular surgery with cardiopulmonary bypass

Next, we tried continuous blood glucose monitoring during cardiovascular surgery with cardiopulmonary bypass. However, we encountered a major problem here because not enough blood was obtained for monitoring. This necessitated intraoperative suspension of continuous blood glucose monitoring in three of the first five cases. Blood sampling via the venous side of the cardiopulmonary bypass circuit was tried in the subsequent cases, which enabled us to obtain sufficient quantities of blood.

Figure 7 is one typical case of continuous blood glucose monitoring during cardiovascular surgery

with cardiopulmonary bypass. We found that significant hyperglycemia occurred during cardiopulmonary bypass after initiation of cardiopulmonary bypass using an aortic clamp, the blood glucose level increased markedly to around 300 mg/dl. After the aortic de-clamp and termination of the extracorporeal circulation, blood glucose showed a tendency to decrease, but hyperglycemia of around 200 mg/dl persisted in many cases.

Why does hyperglycemia occur during cardiovascular surgery (especially during cardiopulmonary bypass) ?

One of the main reasons for the occurrence of hyperglycemia during cardiovascular surgery (especially during cardiopulmonary bypass) is suppression
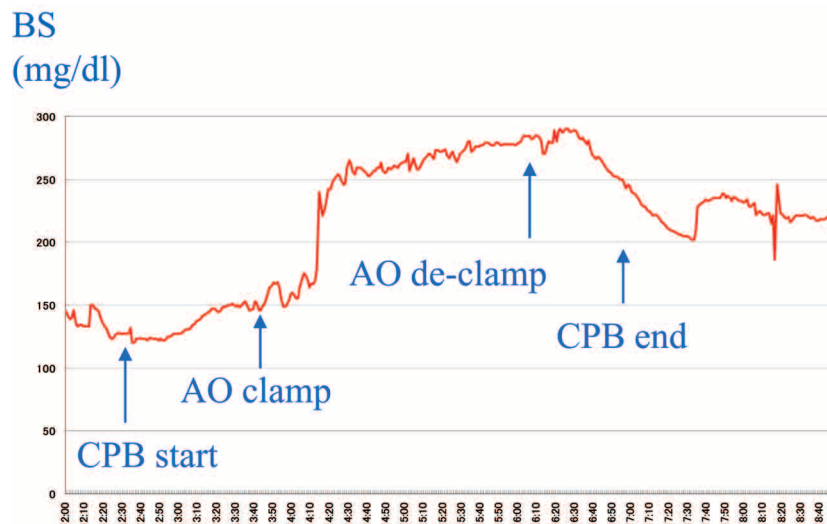

Figure 7.   Continuous blood glucose monitoring during cardiovascular surgery with cardiopulmonary bypass
BS ; blood sugar : CPB ; cardiopulmonary bypass : AO ; Aorta

of insulin secretion. This is caused by a reduction in the pancreatic blood flow, the inhibition of β-cell activity of the pancreas due to hypothermia, and the increased secretion of insulin counter-regulatory hormones. Other reasons are intracellular disorder of glucose use due to peripheral circulatory failure and inhibition of the glycolytic pathway enzyme due to hypothermia.

We do not use it in this hospital, the effect of cardioplegia and priming solution including glucose may be thought.

The causes of insufficiency of blood drawn during cardiopulmonary bypass are due to hypothermia, peripheral circulatory failure (low perfusion), vasoconstriction and posture (especially with arms elevated or bent). This problem was solved by sampling blood via the venous side of the cardiopulmonary circuit, thus rendering continuous blood glucose monitoring stable and reliable even during cardiovascular surgery with cardiopulmonary bypass.

Intensive insulin therapy during cardiovascular surgery using the artificial endocrine pancreas

Figure 8 shows one case of intensive insulin therapy during cardiovascular surgery using the artificial endocrine pancreas. The blood glucose level suddenly started to increase after the initiation of cardiopulmonary bypass, but only to a maximum of 150 mg/dl, and the level was controlled by appropriate insulin administration. After termination of the cardiopulmonary bypass, the blood glucose level began to decrease, but hypoglycemia was avoided by means of appropriate glucose administration.

PROBLEMS AND PROSPECTS

Problems

Some of the questions associated with intensive insulin therapy are :
What is the optimal glycemic control target?
Which patients are indicated?
In this connection, glycemic control policy may be determined depending on patients, clinical conditions, and particular operative procedures. Other questions are :
Is the mean blood glucose value important? Is it important to reduce variability of blood glucose concentration (45, 46)? An artificial pancreas system, such as the bedside-type STG®-22, can help achieve stable glucose control (47-50), but it is large and expensive, difficult to operate, and can be used for only a short period of time.

Merits and demerits of the representative perioperative blood glucose management procedures

The merits of the conventional sliding scale method are few hypoglycemic attacks, a small work load because of few blood glucose measurements, and low cost. On the other hand, a disadvantage is that close glycemic control is difficult. An advantage of open-loop intensive insulin therapy is that it allows for close glycemic control, but drawbacks are the possibility of hypoglycemic attack, a heavier work load due to frequent blood glucose measurements, and an increase in incident development.

The merits of closed-loop intensive insulin therapy using the artificial endocrine pancreas are that
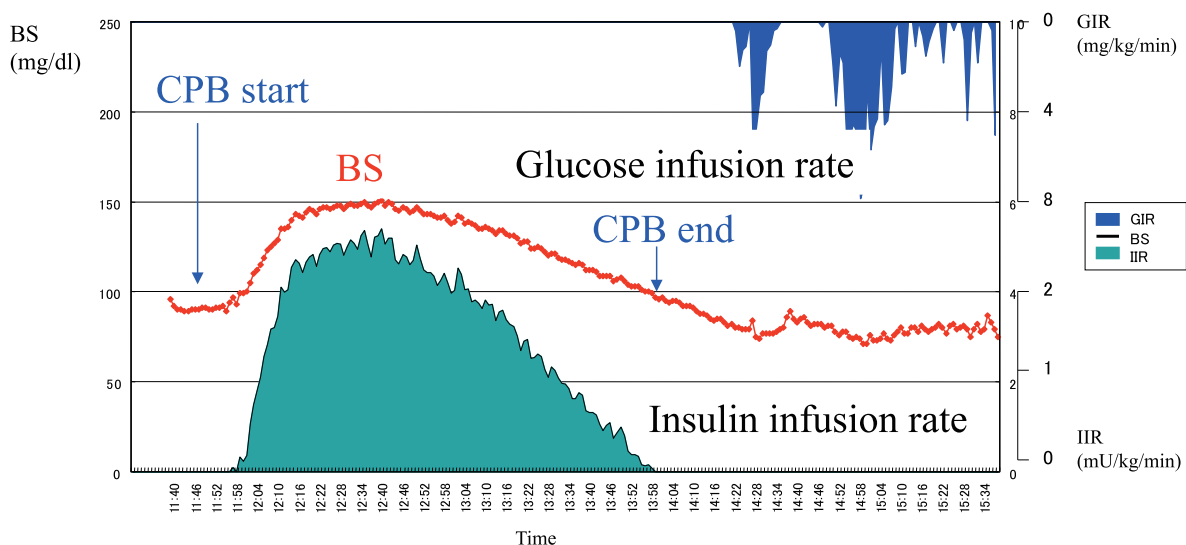

Figure 8.   Intensive insulin therapy during cardiovascular surgery using the artificial endocrine pancreas
BS ; blood sugar : CPB ; cardiopulmonary bypass : GIR ; glucose infusion rate : IIR ; insulin infusion rate

strict glycemic control is possible, an absence of hypoglycemic attacks, a reduced work load in spite of frequent blood glucose measurements, and a reduction in incidents. On the other hand, the demerits are high cost, problems associated with an insufficient quantity of blood obtained for monitoring, the need for much preparation time, and difficulty of operation.

Next-generation artificial endocrine pancreas

It is hoped that development of the next-generation artificial pancreas will overcome the demerits of the current models. The development concept targets treatment where the device can be used in an operating room or the ICU during an acute phase. Surgical and emergency applications demand quick and easy system initiation. Moreover, compact design is essential for operating room and intensive care unit settings which are already crowded with equipment. The device should also be inexpensive so that this technology can be used for many patients.

Ideally, the next generation artificial pancreas should be equipped with a disposable and modular tubing circuit with an auto-priming function, automatic calibration with quick response in sensor set-up, and a compact structure. These improvements are now being developed (Figure 9). It is expected that such an improved model will be authorized soon, and we also hope to be able to use it soon.

Prospects

It seems that distinct operative methods for example, glycemic control made to order for individual patients, will become important in the future. Also, establishment of a simpler and easier to use perioperative blood glucose control method is urgently needed. We want to make every effort to use strict intraoperative glycemic control which can lead to improvement in long-term prognosis for cardiovascular surgery patients. In addition, large-scale multi-center studies in the field of internal medicine such as ACCORD and ADVANCE were reported (51, 52). Lowering of HbA1c from less than 6.5 with the traditional approach to less than 5.8 is feasible, but development of hypoglycemia is a problem, making support of at-home management important. By changing these preoperative care policies, perioperative glycemic control may benefit in the future (53).

As for the artificial pancreas, it seems that we can look forward to a small and light simple low-cost model with a continuous subcutaneous glucose sensor using near-infrared light (54). Eventually, we may see the development of a portable closed-loop artificial pancreas for at-home management support.

CONCLUSIONS

In conclusion, strict perioperative glycemic control is effective for the protection of many organs and a reduced incidence of infection so that it is believed that it can lead to improved prognosis for surgery. It is thought that the main benefit of intensive insulin therapy can be realized in cardiovascular surgery (especially during cardiopulmonary bypass). However, strict perioperative glycemic control is difficult due to the need for intermittent blood glucose measurements and the manual administration of insulin. Intensive insulin therapy during cardiovascular surgery may thus be provided by the use of the artificial pancreas.

Figure 9.   Next-generation artificial endocrine pancreas

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