The 44th Annual Meeting of the Japanese Society for Artificial Organs Luncheon Seminar

Current Status of ICU-based Glycemic Control and Outlook for the Artificial Pancreas

- Glycemic Control Using the Artificial Pancreas: Latest Findings -

Chair

Dr. Michio Ogawa

Director of Kumamoto Rosai Hospital
(former Vice President of Kumamoto University)

Speaker

Dr. Kazuhiro Hanazaki

Professor of the Department of Surgery 1,
Kochi Medical School, Kochi University

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Greeting from the Chairman

Today, Professor Hanazaki will present a lecture entitled, "Current Status of Intensive Care Unit (ICU)-based Glycemic Control and Outlook for the Artificial Pancreas." In addition to his outstanding surgeon's career, Professor Hanazaki has focused on research in intra- and post-operative glucose metabolism and glycemic control for total pancreatectomy and hepatectomy patients. Professor Hanazaki graduated from Niigata University in 1984, and was appointed as Assistant Professor of the First Department of Surgery of Shinshu University and Chief of Surgery-I of Shinonoi General Hospital. In 2006, he was appointed as Professor and Chairman of the Department of Surgery at Kochi Medical School. He has specialized in hepato-biliary-pancreatic surgery and has been conducting research projects using the artificial pancreas including clinical applications.

Michio Ogawa

Artificial Pancreas: Background and Research Motivation

During 2001, I was a research associate under Professor Brunicardi, Chairman of Department of Surgery, Baylor College of Medicine, Houston, Texas. At that time, Dr. Brunicardi advised me to initiate a new research project for the development of an artificial pancreas. For scientific guidance, he introduced me to Professor Yukihiko Nosé, a world renowned leader in the field of artificial organs research. Under Professor Nosé's guidance, I adopted the bedside-type artificial endocrine pancreas, Nikkiso STG-22, which instrumented a superior glucose sensor compared to conventional devices, and I started to learn the basic structure and operational procedures of the system. An artificial pancreas STG-22 is composed of a glucose sensor, which performs glucose detection/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 predefined prior to the system initiation. It is important to recognize that the STG-22's glucose sensor, which withdraws the blood from the patient at a rate of 2ml/hour, is capable of continuously measuring the blood glucose level with its glucose sensor, and automatically infuses insulin or glucose to adjust the blood glucose level of the patient in accordance with a target glucose value, which is adopting what we call "closed loop system".

International Joint Research Program in U.S.

At Baylor College of Medicine, I was engaged in an international joint research program initiated in 2001 as a principal investigator for the

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Figure 1

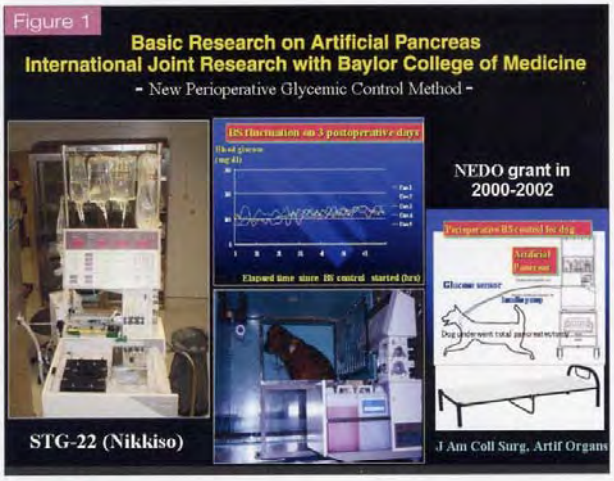


Figure 2a

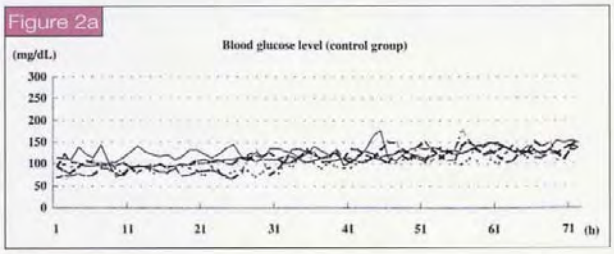
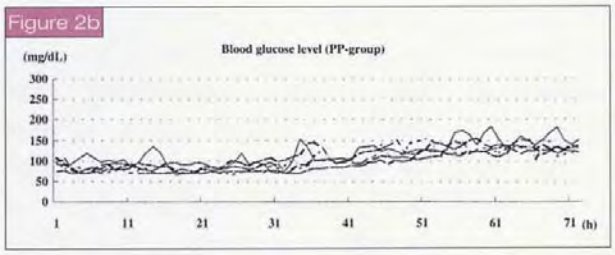


Figure 2b



development of artificial pancreas. This program was supported by the Japanese government agency, NEDO (New Energy and Industrial Technology Development Organization, Japan). For evaluating device safety and feasibility, I used a total pancreatectomy canine model.

All of the animals underwent total pancreatectomy. The Nikkiso STG-22 was installed during surgery and continuously managed the blood glucose level intra- and post-operatively for 3 days after surgery in the animal ICU (Figure 1). This study was designed to confirm the safety and feasibility of blood glucose stabilization using the STG-22 and to observe other physiological parameters.

Since the initial three days after surgery required both post-oral diet uptake and intravenous fluid injection, we also monitored the influence of dietary uptake during the course of the study. We set the target blood glucose level at 100 mg/dL, and could maintain a stable blood glucose level during the entire experimental period. This series of animal studies ended uneventfully and successfully. These positive results encouraged me and pointed to a promising glucose management tool for various clinical applications in the future. In my clinical experience, the intraoperative and acute post-operative blood glucose level, particularly after total pancreatectomy, can fluctuate widely between hyper and hypoglycemia states. Therefore it is often difficult to gain stable glucose control even though medical caregivers carefully examine the patient's blood glucose level and administer insulin accordingly. I was very surprised by this result of the artificial pancreas, even though it was from animals.

Figure 2a shows blood glucose levels in experimental dogs controlled by the STG-22 artificial pancreas performing sole insulin administration for 3-days after surgery. Blood glucose levels for the animals that underwent total pancreatectomy remained around 100 mg/dL. Figure 2b shows the blood glucose levels administered with pancreatic polypeptide. Dr. Brunicardi hypothesized that the administration of pancreatic polypeptide would be beneficial in stabilizing the blood glucose level and reducing the amount of insulin administered. As he speculated, the use of pancreatic polypeptide could reduce the insulin requirements for the initial 2-days after surgery and achieved relatively stable blood glucose control (these results were published in 2005[1]). This research data significantly contributed to establish a basic method for glycemic control using the artificial pancreas in animals with total pancreatectomy, which mimics the most severe diabetic condition. It proved the effectiveness of the infusion of pancreatic polypeptide in reducing the insulin requirements and also in stabilizing of the blood glucose level.

Artificial Pancreas Clinical Trials: Pilot Studies at Kochi University

These successful research results motivated us to move forward into the clinical arena. It is our goal to improve the clinical results for severe surgical patients. In 2006, my clinical team at Kochi University initiated a clinical trial to eval-

Figure 3

Control of Diabetes Seen in Surgical and Emergency Settings

1. Pancreatogenic DM induced by pancreatectomy
2. Surgical and emergency control of DM patients
3. Post-operative surgical DM
4. Unstable glycemic control of patients with infections
5. Glycemic control of critically ill patients in ICU

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uate the efficacy of the artificial pancreas for post-operative patients.

Need of Critical Glycemic Control for Better Clinical Outcome

Figure 3 summarizes typical clinical scenarios presenting hyper glycemic/diabetic conditions requiring intensive glucose control. Clinically, we often face difficulties in achieving proper glucose control after surgery in patients with pancreatectomy. As is generally known, any kind of surgical intervention may cause hyperglycemia, and deterioration of glycemic control increases the risk of post-operative infections. Also, critically ill patients in the Intensive Care Unit (ICU) develop immunological impairment and those patient groups with a high risk of infections under unstable glycemic condition should have immediate and precise management; yet manual administration of insulin or continuous IV insulin injection is not satisfactory for severely diabetic patients.

The report published by Van den Berghe and associates demonstrated that intensive insulin therapy maintaining blood sugar level between 80-110 mg/dL could reduce the hospital mortality rate from 20.2% to 10.6% in critically ill patients[2]. Another publication reinforced the importance of intensive insulin therapy to improve hepatic function after severe trauma[3].

In addition, there are several papers demonstrating the effectiveness of critical post-operative glycemic control for the purpose of preventing infection. It is widely recognized that appropriate glycemic control in diabetic patients is very important for the control of perioperative infections[4]; that there is a significant correlation between HbA1c levels and SSI (surgical site infections)[5]. During the first 2 post-operative days, it is favorable to maintain the glucose level less than 200 mg/dL to prevent SSI[6]. According to these evidence-based clinical results, pre-and post operative intensive glycemic control is the most crucial factor to reduce the infection and mortality rates of critically ill patients (Figure 4).

Figure 4

Importance of Glycemic Control in Surgical and Emergency Settings.
Stable glycemic control enables:

1. Reduction of infections
2. Prevention of development to severer infections
3. Reduction of mortality rate in critically ill patients

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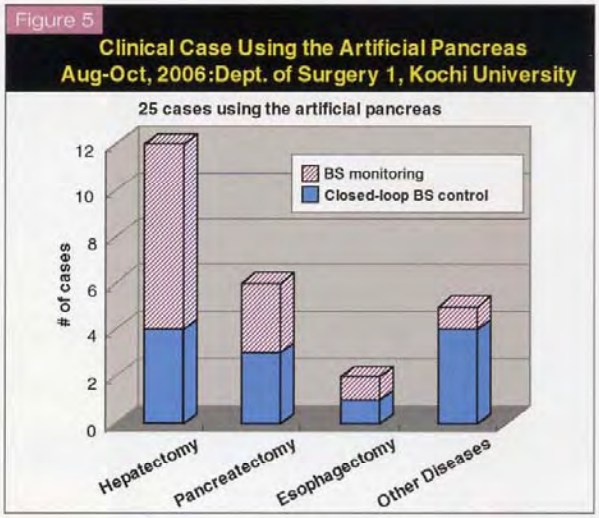
Figure 5



Clinical Experience with Artificial Pancreas

Two Nikkiso STG-22 artificial pancreas systems were clinically used at Kochi University for intra- and post-operative glucose control applications. With the aid of anesthesiologists, continuous glucose monitoring and closed-loop intensive glucose control were conducted for patients who had underwent highly invasive surgeries such as pancreatectomy, hepatectomy and esophagectomy, throughout surgery and during their ICU stay.

We conducted a total of 25 artificial pancreas clinical studies including 12 hepatectomies, 6 of pancreatectomies, 2 esophagectomies, and 5 miscellaneous cases (Figure 5). In Figure 5, the blue bar graph indicates the "Closed" group treated by the artificial pancreas through closed-loop circuit, and the red bar graph indicates the "Monitor" group, continuously monitored by the artificial pancreas and treated by sliding scale insulin infusion procedures if needed.

In order to familiarize ourselves with device operation, we initially used the STG-22 only for glucose monitoring purposes, with insulin sliding scale administration, and not for glucose control application. Once the standard operational procedure was established, we used the STG-22 for closed-loop intensive glucose control application.

Placement of the Artificial Pancreas

STG-22 artificial pancreas systems are assembled in a preparation room next to the operating room prior to surgery. The target glucose level is individually customized to meet each patient's requirements and pre-operative baseline laboratory data. The anesthesiologist inserts a specialty catheter into a peripheral vein for monitoring the blood glucose level. Since this catheter provides for blood sample withdrawal, the connection between the catheter and sampling tubing must be secure and stable, otherwise the measured glucose value will be unreliable. The venous puncture site of the monitoring and sampling catheter must be closely monitored to avoid line occlusion, due to clogging, and leakage to maintain accurate glucose measurement.

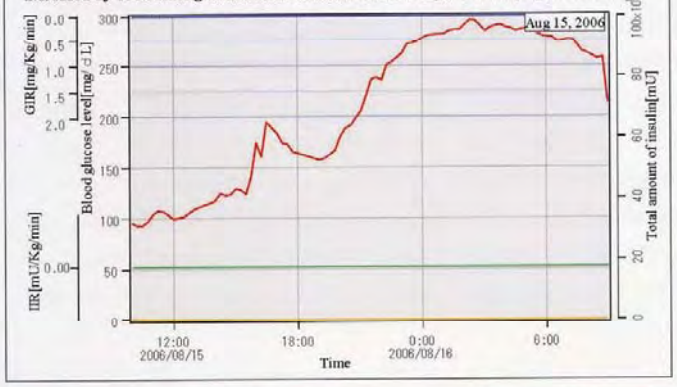
In order to detect catheter problems, I suggest using an adherent, transparent protective film over the venous puncture site for easy visualization. In summary, in order to achieve accurate glucose measurement and intensive glucose control, the sample catheter must be monitored for proper positioning, connection failure, line clogging, and/or blood leakage from the puncture site. During operations, the surgeon can be informed glucose levels with reference to the glucose value displayed on the monitoring screen.

Since the infusion lines require a relatively large venous catheter for insulin and glucose injection, central veins such as the jugular vein are used. In our institution, the pre-operative set-up of the artificial pancreas is performed by a surgeon experienced in using the artificial pancreas, and further intra-operative management is handled by the anesthesiologist in conjunction with the surgeon. The surgeon and the anesthesiologist also conduct a joint regime of glucose control during a patient's stay in ICU.

Figure 6

Hepatic and Pancreatic Cancers: Left Hepatic Lobectomy (Glycemic Monitoring Only)

Suregry-induced increase of blood glucose in a non-DM patient. The level further increased by TPN. Sliding scale insulin infusion was not helpful in reducing the level.



Utilization of STG-22 Artificial Pancreas only for Blood Glucose Monitoring

As previously mentioned, in order to establish a standard operational procedure and training of individuals involved in this program, we initially used the STG-22 as a continuous glucose monitoring tool instead of intensive glucose control purpose.

Today, I'd like to present one of my clinical experiences with a patient who underwent left hepatic lobectomy due to hepatocellular carcinoma. This patient was nondiabetic, yet blood glucose level gradually increased during surgery and plateaued. However, the blood glucose level again started to increase just before the end of the surgery. It temporarily decreased but elevated again (Figure 6). Therefore, we performed sliding-scale insulin infusion. Despite the sliding-scale insulin management, the blood glucose level remained at an extremely high level. There was no explicit effect of the sliding-scale, and the blood glucose level gradually decreased by the morning.

Such major traumatic surgeries frequently cause "surgical diabetes", and sliding-scale insulin administration is not adequate to control the blood glucose level.

Media Released News: Patient Death due to Insufficient Blood Glucose Testing

On October 4, 2006, an article on a malpractice report was published in the Daily Yomiuri newspaper. According to the article, a male cancer patient underwent esophagealectomy surgery died 11 days after surgery due to hyperglycemia caused by improper glucose management. He was a mildly diabetic patient and needed total esophageal resection surgery. After surgery, he received TPN (total parenteral nutrition) therapy, which may result in a certain degree of hyperglycemia. An in-depth analysis was not described in the article, but the patient developed a serious infection and went into a deep coma, then a medical caregiver noticed hyperglycemia. His hyperglycemia was immediately treated but was ineffective, and he died on the 11th postoperative day. The hospital was a 500-bed teaching hospital for educating residents accredited by the Japan Diabetes Society. The lesson to be learned from this article is that a human error with regard to glycemic control may occur even at a specialized hospital for diabetes treatment". I wondered how an artificial pancreas might deliver clinical benefit to patients with a risk of diabetes. This tragedy might not have happened if they had had an artificial pancreas.

At Kochi University, we have had two cases of surgery for esophageal cancer using the STG-22 artificial pancreas. In one case, the blood glucose level continued to rise from the beginning of surgery, hence sliding-scale insulin administration was applied. When the glucose level exceeded 250 mg/dL, we switched to the closed-loop method with the artificial pancreas system to stabilize the glucose level (Figure 7). We set the target glucose level at 100 mg/dL, and the actual level remained between 100-150 mg/dL, which was an acceptable range. The intra- and post-operative stage was uneventful, and this patient was successfully discharged from the hospital without any major complications. Since we have not yet performed randomized control clinical trials comparing two groups using the artificial pancreas or insulin sliding-scale method, we cannot conclude the efficacy of the STG-22 artificial pancreas at this time. However, it is a fact that we were able to control the blood glucose level very easily and safely with the use of the artificial pancreas. At least, I would say that this device can provide peace of mind for physicians in ICU blood glucose control and management. Furthermore, it should be much safer for patients suffering from severe hyperglycemia

Figure 7

Esophageal Cancer: Thoracic Esophagectomy

Intraoperative hyperglycemia in a non-DM patient. Switched to closed-loop control.

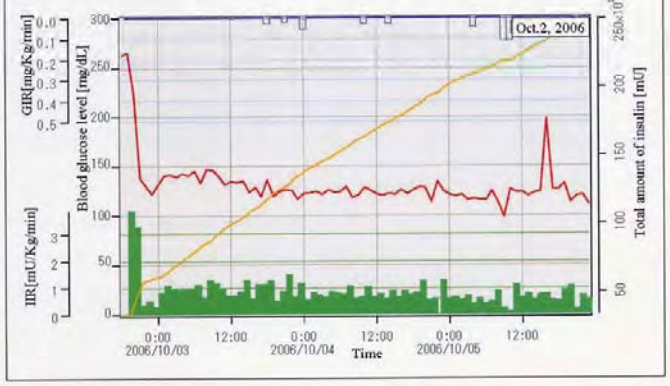


Figure 8

Invasive Pancreatic Cancer:Distal Pancreatectomy+Left Nephrectomy+Jejunectomy

DM: closed loop control enables more stable glycemic control

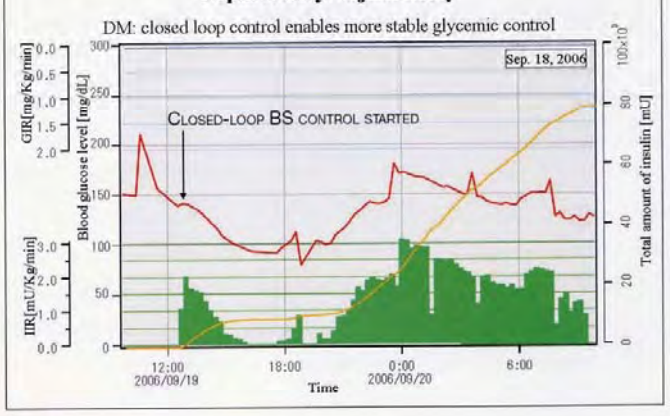
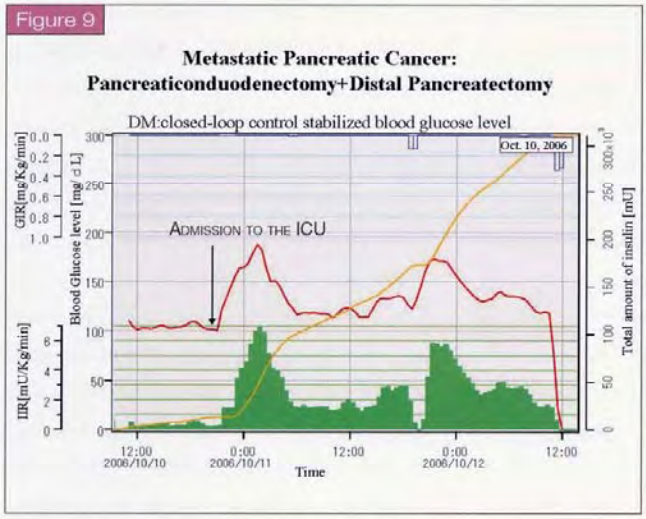


Figure 9



and may improve wound healing and decrease mortality rates.

Case Reports in Use of the Artificial Pancreas

< Case 1 >

Case 1 was an invasive pancreatic cancer patient who underwent a distal pancreatectomy. Since infiltration to the kidney and jejunum was observed, we performed a combined resection of the left kidney and the jejunum. Since this patient was diabetic, the blood glucose level began to rise. However, by switching to the STG-22 closed-loop system, it remained below 200 mg/dL with ease (Figure 8). Not only in partial pancreatectomy cases but also in distal pancreatectomy with extended concomitant surgical procedures such as the jejunum and kidney resection, the STG-22 provided stable glycemic control during the perioperative period. The post-operative clinical course was uneventful.

< Case 2 >

This case involved a metastatic cancer in the pancreatic head and tail, and we performed pancreaticoduodenectomy and distal pancreatectomy (Figure 9). Since the patient was diabetic, we adopted the STG-22 closed-loop system from the beginning of the surgery. During the surgery, blood glucose level was quite stable around 100 mg/dL. However, it suddenly increased immediately after admission to the ICU. The STG-22 quickly captured the elevation of glucose level and automatically infused necessary insulin through the closed-loop circuit. Eventually, the blood glucose level was well maintained with a large dose of insulin. It is important to remember that sampling line failure (i.e. occlusion, leakage, disconnection, etc) will cause measurement error. Particularly, low blood glucose level is caused by these blood sampling failures. Therefore, when a low glucose level is measured, which might happen 3-4 times a day, I double check the glucose level with another measuring device. Even if you need to reconfirm blood glucose level a couple of times a day, the STG-22 is still a user friendly and useful device for stable glucose management.

Based on my experience of 25 clinical cases utilizing the STG-22 artificial pancreas, I conclude: 1) surgical diabetes occurs from the early stage of the surgery, regardless of the presence of pre-operative diabetes, and once a patient is exposed to a major surgical procedure and the blood glucose level is elevated over 250-300 mg/dL, and 2) the sliding-scale insulin administration method is not effective enough to demonstrate stable glucose control depending on the degree of surgical invasion. I am now confident that the STG-22 artificial pancreas can enable stable and easy perioperative glucose management for severely diabetic patients.

Clinical Assessment of the Artificial Pancreas: Testimonial from key personnel

In my series of clinical studies, key medical personnel who used the STG-22, assessed and gave their impression in the clinical application of the artificial pancreas.

An anesthesiologist who was responsible for intra- and post-operative patient management commented that: "Glycemic control during anesthesia became much easier. Particularly it was very convenient in monitoring various diabetic patients."

The physician in charge of the ICU commented: "Glycemic control in ICU patients with infections is no longer a burden."

Also, ICU nurses said: "Because the patient's blood glucose level is always displayed on the monitor, we feel much more confident and assured in taking care of patients." From the ICU nurses point of view, real-time monitoring of the blood glucose trend was very useful for detecting an early-phase physiological abnormality. In case of an abnormal blood glucose reading on the monitor display, the nursing staff had a safe margin of time to measure the blood glucose level with another analysis device for confirmation.

Another staff member operating the artificial pancreas said that "Some learning curve will be needed to familiarize the operational procedures, but it will be a useful system." Surgeons in other departments of our hospital have requested use of the artificial pancreas for their cases.

Towards A Next-Generation Artificial Pancreas

Drug therapy for diabetes is advantageous for ease of use and cost effectiveness, but it is not always possible to gain stable glycemic control. In contrast, pancreas transplantation is physiologic and enables stable glycemic control. However, it is expensive and the lack of donors is still a remaining issue. Also patients must be on chronic immunosuppressive therapy. An artificial pancreas system, such as the bedside-type STG-22, can achieve stable glucose control and does not require organ donors; yet it is expensive, large, difficult to operate, and usable for only a short period of time. They may require replacement of enzyme membrane for a long term use of more than one day, which is time consuming and increases treatment costs.

Surgical and emergency applications demand the capability for quick and easy system initiation. Also, compact design is essential in OR(operating room) and ICU settings which are equipment-crowded already. The device should be inexpensive to penetrate the market for

applying this technology to 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 device improvements are underway.

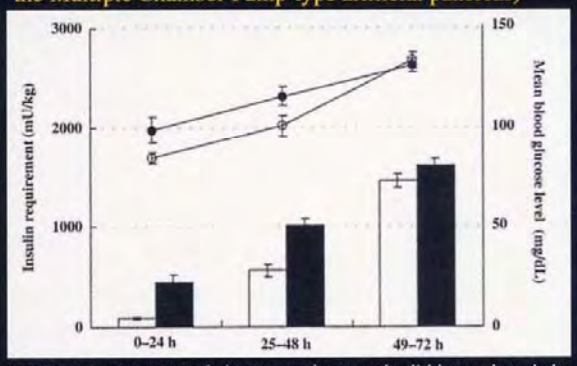
Development of the Multiple Chamber Pump-type Artificial Pancreas

The majority of pancreatic hormone-secreting cells are insulin-secreting cells; the remaining 15-20% are glucagon-secreting cells, 3-10% are somatostatin-secreting cells, and 1% are pancreatic polypeptide-secreting cells. Although pancreatic polypeptide-secreting cells are a minority in these cell groups, they have an important role.[7] In fact, the concentration ratio of pancreatic hormones to insulin in the peripheral veins is 5.8 for C-peptide, 0.75 for glucagons, and 0.59 for pancreatic polypeptide.[8]

We have reported that the amount of insulin infusion can be reduced when pancreatic polypeptide is administered in combination with insulin (Figure 10).[1] In addition to insulin reduction, this report also suggests further insight for more stable glycemic control in insulin and pancreatic polypeptide combination therapy, compared to sole insulin administration. We are seeking a way to utilize this theory with the development of the Multiple Chamber Pump-type artificial pancreas.[9] We believe that a more physiological artificial pancreas will be possible by using "cocktail administration" of pancreatic polypeptide, C-peptide, and insulin all together. In order to achieve this goal, the appropriate mixture of the necessary pancreatic hormones could be infused by the Multiple Chamber Pump or New Injection Pack-type artificial pancreas. We call it a "Mixed Juice of Pancreatic Hormones," of which a mixture of hormones will contribute to more stable glycemic control.

Figure 10

Use of pancreatic polypeptide can reduce insulin infection (Results leading to the development of the Multiple Chamber Pump-type artificial pancreas)



Insulin requirement of the control group (solid boxes) and the pancreatic polypeptide (PP) group(open boxes), and mean blood glucose level of the control group(solid circle) and the PP-group(open circle). The insulin requirement for the 0 to 24-h and 25- to 48-h period of the PP group was less than that of the control group(*P<0.05).

Outlook for the Artificial Pancreas

There are several unsolved problems and challenges in the study of the artificial pancreas. Currently, the artificial pancreas is primarily utilized for glucose clamp testing in internal medicine, rather than therapeutic/controlling application. Because a majority of the research interest and efforts have focused on device miniaturization over the past several decades, people have not focused attention on the practical clinical applications even though such a device is clinically needed.

Recently, several clinical studies have demonstrated the effects of intensive glycemic control in reducing the mortality rate of post-operative or emergency patients.[2),3)] This evidence was derived from conventional glucose management regimens without an artificial pancreas. I believe that it is necessary to establish a more accurate glycemic control method, and extensive EBM experience in glycemic control using the artificial pancreas is becoming more and more important .

Future advancement of the artificial pancreas requires a prospective randomized clinical study to be conducted comparing the artificial pancreas with the current sliding-scale insulin infusion method.[10] Second, I would like to conduct clinical research on the use of the next-generation artificial pancreas for dissemination of this technology, especially in the fields of surgery, emergency medicine, intensive care, and anesthesiology. At present, there is no doubt that the United States is the largest market for artificial pancreas technology. Therefore, it is my dream to promote artificial pancreas research and clinical activities in the United States, including the Multiple Chamber Pump-type systems we invented.

In my view, the role of the artificial pancreas is vast and brings a huge clinical benefit in enhanced glycemic control that has the potential to reduce infection rates and decrease mortality in surgical and ICU patients in the future.

Summary

Along with the global increase in diabetes, it is expected that glycemic control in surgical and emergency settings will become more and more important. Artificial pancreas systems are not solely intended for glucose clamp studies; rather they should be used for intensive glycemic control. We believe that aggressive and tight glycemic control using the artificial pancreas, will contribute to prevent infections and improve clinical outcomes in surgical and emergency patients.

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