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Original Article

Anti-inflammatory Effects of Perioperative Intensive Insulin Therapy During Cardiac Surgery with Cardiopulmonary Bypass

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Abstract

Purpose. Recent studies have reported that controlling blood glucose with insulin can suppress systemic inflammation. In the present study, we evaluated how perioperative intensive insulin therapy (IIT) influences the inflammatory response in an artificial pancreas during cardiac surgery with cardiopulmonary bypass.

Methods. We randomly divided the patients undergoing cardiac surgery with cardiopulmonary bypass into two groups: an IIT group ($n = 13$) and a conventional treatment (CT) group ($n = 12$). For the IIT group, blood glucose control was initiated with an artificial pancreas at initiation of surgery. Blood glucose was maintained at 100 mg/dl until 24 h postoperatively. Blood samples were collected to determine changes in serum cytokine levels over time.

Results. Patients' characteristics did not differ significantly between groups. Blood glucose levels were significantly higher in the CT group after surgery. Serum levels of tumor necrosis factor-α, interleukin-6, and high-mobility group box 1 were higher in the CT group than in the IIT group.

Conclusions. Use of IIT in the artificial pancreas during the perioperative period significantly decreased the inflammatory response. Moreover, we did not find evidence of hypoglycemia in those treated with IIT. This suggests that use of IIT in an artificial pancreas can be safe and effective for critically ill patients.

Key words Intensive insulin therapy · Cytokine · Inflammation · Cardiovascular surgery · General anesthesia

Introduction

Surgical procedures exert considerable physical stress on patients during the perioperative period. The immune system responds to this threat by producing cytokines and other inflammatory mediators.[1] However, an excessive inflammatory response is detrimental to the body, causing problems such as organ failure.[2]

Recent studies have demonstrated that hyperglycemia exacerbates the inflammatory response. Van den Berghe et al.[3] reported that, although conventional treatment involves maintaining blood glucose levels between 180 and 200 mg/dl, subsequent organ failure could be ameliorated, and survival rates improved, by maintaining blood glucose levels between 80 and 110 mg/dl. We have also reported that hyperglycemia exacerbates systemic inflammation and major organ failure in animals.[4,5] However, intensive insulin therapy (IIT) has been associated with hypoglycemic attacks.[6,7]

Insulin therapy to control blood glucose typically consists of a single insulin administration; however, this conventional method may not lower blood glucose to the target level, or conversely, can produce hypoglycemia when the insulin takes effect.[6,7] An artificial pancreas has recently been developed that stabilizes glucose levels by continuously administering insulin and monitoring blood glucose. This device is currently used in clinical practice.[8]

In the present study, we assessed the possibility of circumventing hypoglycemia, the number one problem in IIT, and attenuating the perioperative inflammatory response by using an artificial pancreas.

Materials and Methods

We initiated the present study after obtaining approval from the Ethics Committee of the Oita University Faculty of Medicine. Informed consent was received from patients

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Table 1. Patients' characteristics

	IIT (n = 13)	CT (n = 12)
Age (years)	66.4 ± 5.4	65.5 ± 13.0
Body weight (kg)	57.3 ± 16.7	57.0 ± 11.9
Duration of surgery (h)	4.37 ± 0.61	4.48 ± 0.38
Duration of extracorporeal circulation (min)	133.6 ± 40.0	107.5 ± 25.6
Duration of aortic cross-clamping (min)	115.7 ± 36.2	91.3 ± 22.8
Duration of anesthesia (h)	6.10 ± 0.85	6.49 ± 0.83
Amount of blood loss (g)	171.9 ± 55.4	260.0 ± 150.0
Preoperative cardiac index (l/min/mm^2)	2.53 ± 0.52	2.68 ± 0.71
Fasting blood glucose level (mg/dl)	91.4 ± 7.9	92.0 ± 7.9
Blood glucose level on the morning of surgery (mg/dl)	92.4 ± 18.0	100.9 ± 10.2

CT, conventional treatment; IIT, intensive insulin therapy

before initiation of the study. The subjects consisted of 25 surgery patients scheduled to undergo cardiac surgery with cardiopulmonary bypass at Oita University Hospital during the 6-month examination period. Selection criteria included age 20–89 years, body mass index (BMI) between 18 and 35, and an American Society of Anesthesiologists (ASA) physical status (PS) of 1–3. Exclusion criteria included diabetes, abnormal glucose tolerance, or severely reduced cardiac function.

Patients were randomly divided into two groups before cardiac surgery: (1) the conventional treatment (CT) group, in which insulin administration was initiated when the blood glucose level was >200 mg/dl, adjusting the dose as appropriate based on sliding-scale insulin (n = 12); and (2) the IIT group, in which insulin management was carried out immediately after anesthesia to maintain a blood glucose level of 100 mg/dl with an artificial pancreas (STG-22; Nikkiso Eiko, Tokyo, Japan) (n = 13). Patients' characteristics are shown in Table 1.

In the IIT group, a 20-gauge intravenous catheter (Insyte; Becton Dickinson Infusion Therapy System, Sandy, UT, USA) was placed into a forearm vein immediately after initiating anesthesia and was connected to the artificial pancreas. The artificial pancreas maintains target blood glucose levels by continuously collecting blood samples (2 ml/h) from the intravenous catheter and successively measuring blood glucose levels with an oxygen membrane electrode. Based on these values, computer-controlled injections of insulin or glucose were administered using a closed-loop blood glucose control system. Blood glucose was intermittently (at least once every 2 h) measured through an indwelling radial artery catheter in all cases. The blood glucose levels were determined immediately after sample collection with an ABL3 acid–base laboratory analyzer (Radiometer Medical, Brønshøj, Denmark).

The patients were treated and maintained with propofol, vecuronium, and fentanyl. The anesthesiologist was solely responsible for varying the levels of each drug. After completion of surgery, the patient was quickly brought to the intensive care unit (ICU) to receive standard postoperative care. During this time, blood glucose was managed with the artificial pancreas in the IIT group.

Blood samples were collected preoperatively, immediately after detachment from cardiopulmonary bypass (CPB), immediately after ICU entry, 1 day postoperatively, and 2 days postoperatively. Blood serum was separated with a centrifuge and preserved at –80°C until assays were performed.

Measurement of Cytokine and High-Mobility Group Box 1 Secretion

Cytokine and high-mobility group box 1 (HMGB1) secretion were determined with serum samples by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (HMGB1 [measurement range: 0–80 ng/ml], Shino-Test, Tokyo, Japan; interleukin [IL]-6 [measurement range: 0–2000 pg/ml] and tumor necrosis factor [TNF]-α [measurement range: 0–100 pg/ml], Invitrogen, Carlsbad, CA, USA). All samples and standards were measured in duplicate. Absorbance at 450 nm was determined with an automated plate reader (Bio-Rad Laboratories, Hercules, CA, USA).

Statistical Analysis

All data were expressed as the mean ± standard deviation. Data were analyzed by the nonparametric test (Mann–Whitney U-test) for single comparisons. $P < 0.05$ was considered to be statistically significant.

Results

Evaluation of Blood Glucose Level Using an Artificial Pancreas

We determined the correlation between blood glucose levels determined simultaneously by the artificial pan-

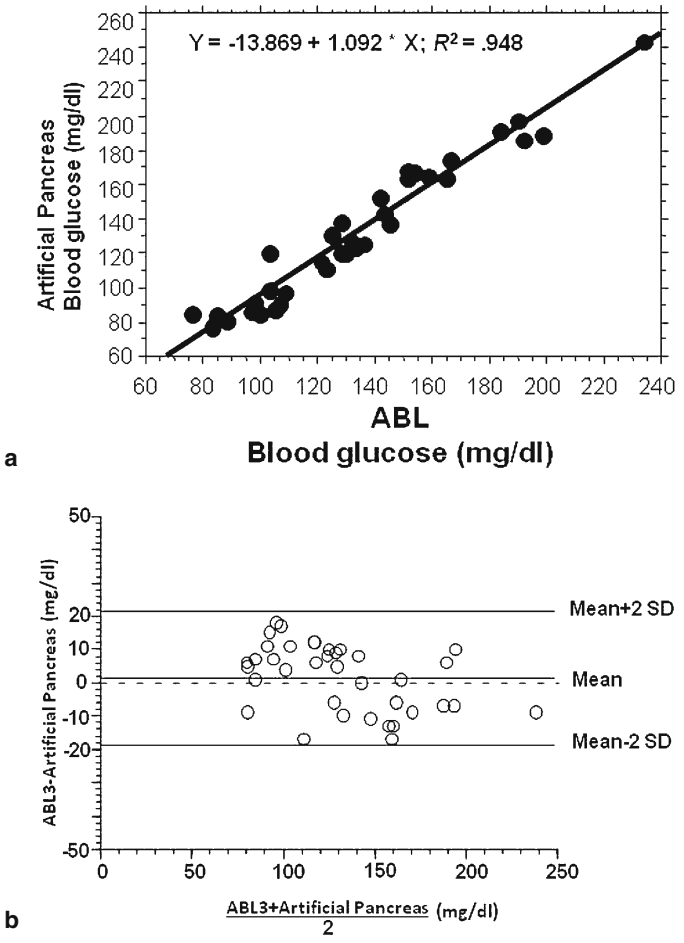

Fig. 1a,b. Evaluation of blood glucose measurements with an artificial pancreas device. **a** Correlation between the blood glucose level determined by an ABL3 acid–base laboratory analyzer and that determined by the artificial pancreas. **b** Difference between the blood glucose level determined by ABL3 and that determined by the artificial pancreas. *SD*, standard deviation

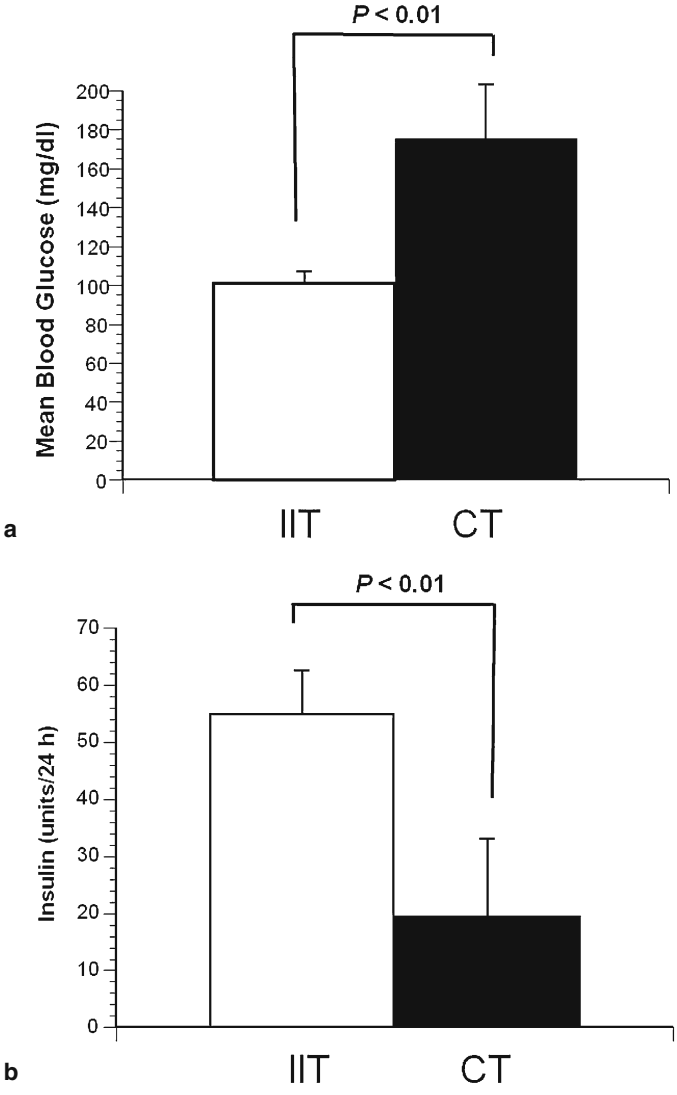

Fig. 2a,b. Amount of insulin used and the mean blood glucose level during the perioperative period. **a** Mean blood glucose level during the study period. **b** Total amount of insulin used during the study period. Data are expressed as the mean ± SD. conventional treatment (*CT*) group, $n = 12$; intensive insulin therapy (*IIT*) group, $n = 13$

creas and ABL3, which is the standard for measuring blood glucose levels. As shown in Fig. 1a, the blood glucose levels determined by ABL3 and the artificial pancreas were strongly correlated ($r^2 = 0.948$), with nearly identical values (Fig. 1b).

Patients' Characteristics

No significant differences in height, body weight, age, preoperative blood glucose level, or cardiac function were observed between treatment groups. In addition, no differences were observed in the duration of surgery, extracorporeal circulation, anesthesia, or blood loss between the two groups (Table 1). In the conventional therapy group, blood glucose was intermittently measured through an indwelling radial artery catheter. If a subject had a blood glucose level >200 mg/dl, we administered insulin and checked serum glucose levels regularly. The blood glucose levels during the study were approximately 160 mg/dl. For those in the IIT group, we performed real-time monitoring of blood glucose levels. Insulin was continuously administered to the IIT group in order to maintain blood glucose levels of approximately 100 mg/dl. The mean blood glucose of the IIT group was significantly lower than that of the CT group ($P < 0.01$) (Fig. 2a). In addition, the amount of insulin used was significantly higher in the IIT group than in the CT group ($P < 0.01$) (Fig. 2b).

Changes in Perioperative Cytokine Levels

We measured the serum levels of TNF-α, IL-6, and HMGB1. The preoperative values did not differ significantly between groups. The TNF-α levels peaked immediately after CPB detachment in the CT group and were significantly higher compared with the IIT group ($P < 0.05$), declining thereafter in both groups (Fig. 3a). Similarly, IL-6 was elevated immediately after CPB detachment, and was significantly higher in the CT group than in the IIT group ($P < 0.05$) (Fig. 3b). HMGB1 demonstrated the highest values immediately after CPB detachment, but the difference between treatment groups at this time point was not significant. However, the HMGB1 levels decreased more rapidly in the IIT group, and were significantly lower on the first and second postoperative days compared with the CT group (Fig. 3c; $P < 0.05$).

Discussion

In the present study, we demonstrated that IIT with an artificial pancreas during cardiac surgery with cardiopulmonary bypass exerted anti-inflammatory effects without inducing hypoglycemia. Stressors associated with surgery trigger an inflammatory response, which serves an important role in the healing process; however, an excessive response can lead to organ failure.[1,2] Inflammatory cytokines (e.g., TNF-α and IL-6) and HMGB1 are associated with the aggravation of organ failure.[9,10] The present study also showed increased serum levels of TNF-α, IL-6, and HMGB1 as part of the body's defensive reaction during cardiac surgery with cardiopulmonary bypass. However, IIT with an artificial pancreas effectively reduced the levels of these inflammatory mediators. These findings suggest that IIT with an artificial pancreas may affect the body's defense against stressors, and decrease the stress level following invasive surgery.

Recent studies have reported that hyperglycemia exacerbates the inflammatory response and aggravates organ failure.[11] However, IIT can ameliorate organ failure and improve survival rates by maintaining blood glucose levels within a more narrow range than those achieved by conventional methods.[3] We also reported that systemic inflammatory response syndrome and organ failure are exacerbated by hyperglycemia, but can be reduced by blood glucose control with insulin.[4,5] In the present study, the serum cytokine levels were lower in patients receiving IIT with an artificial pancreas than in patients receiving conventional blood glucose management. Thus, IIT during the perioperative period may attenuate the inflammatory response.

A recent study demonstrated that hyperglycemia commonly occurs during major vascular surgery.[12] Fur-

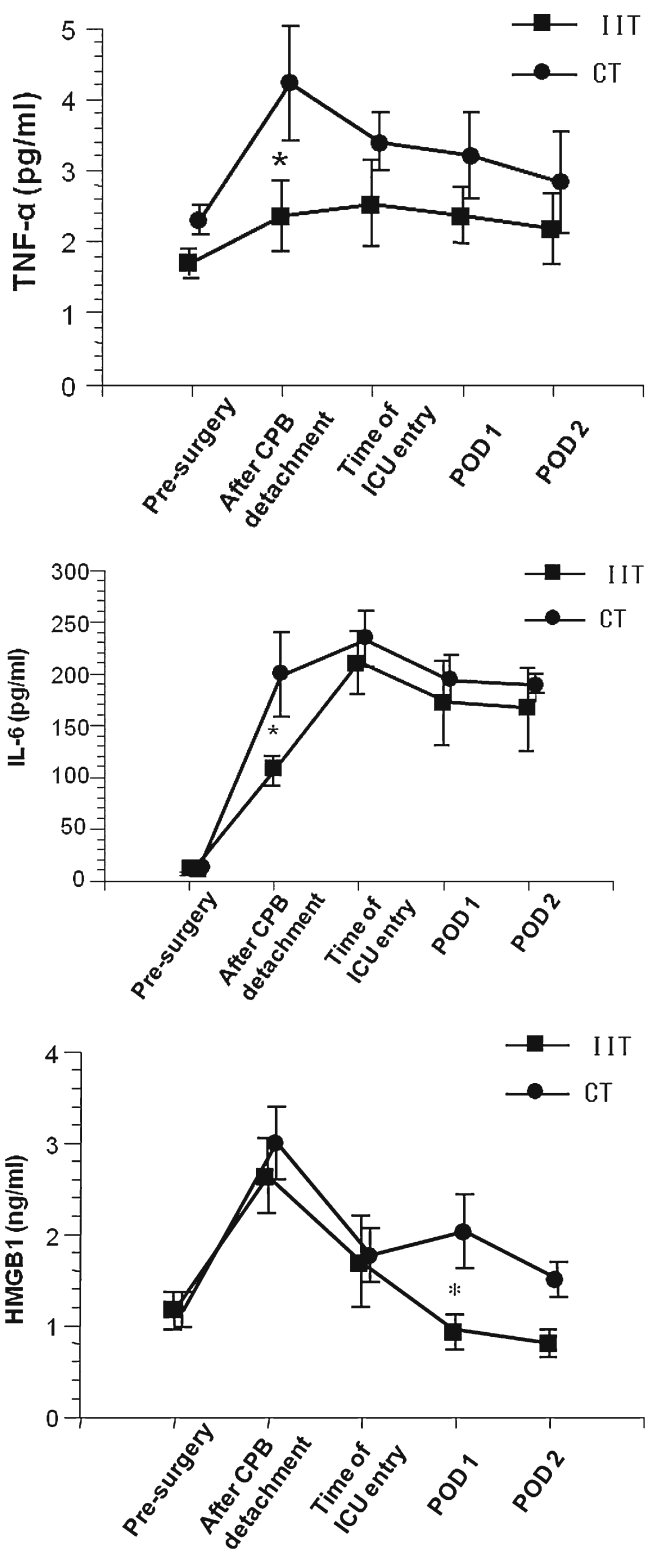

Fig. 3a–c. Serum levels of cytokines and high-mobility group box 1 (*HMGB1*) during the perioperative period. Time-dependent changes in serum levels of **a** tumor necrosis factor-α (*TNF-α*), **b** Interleukin-6 (*IL-6*), and **c** HMGB1. Data are expressed as the mean ± SD. conventional treatment (*CT*) group, $n = 12$; intensive insulin therapy (*IIT*) group, $n = 13$. *$P < 0.05$. *CPB*, cardiopulmonary bypass; *ICU*, intensive care unit; *POD*, postoperative day

thermore, Kawahito et al.[13] reported that insulin secretion may be decreased in response to hypothermia and cardioplegia. In the present study, blood glucose levels increased during cardiovascular surgery in the CT group. This effect was largely circumvented by administering insulin via the artificial pancreas. Based on this finding, we concluded that continuous insulin administration is important for controlling blood glucose levels during cardiovascular surgery.

Some studies have indicated that IIT using an artificial pancreas has beneficial effects during perioperative management. Indeed, surgical site infections are reduced in pancreatectomized and hepatectomized patients.[14,15] Furthermore, increases in the cytokine levels are associated with surgical site infection.[16] In this study, we demonstrated that IIT using an artificial pancreas significantly reduced serum cytokine levels. This may, in turn, reduce surgical site infections.

On the other hand, hypoglycemic attacks during IIT are not uncommon.[6,7] Hypoglycemic attacks are serious complications that can lead to death if left untreated.[6,7] Conventional treatment may deliver excessive or insufficient glucose, thus making it difficult to maintain blood glucose within the target range. In the present study, an artificial pancreas was able to achieve strict blood glucose control without causing hypoglycemic attacks by measuring blood glucose continuously and administering insulin and glucose as needed.[8] Yamashita et al.[17] reported the blood glucose levels of artificial pancreas and ABL analyzer to be closely correlated. We also demonstrated that the blood glucose levels measured by the artificial pancreas correlated strongly with the blood glucose values obtained by ABL3, confirming the reliability of artificial pancreas glucose measurements. As such, the use of the artificial pancreas allowed us to maintain blood glucose levels within a narrower range. Hanazaki et al.[18] reported that maintenance of a narrow range of serum glucose levels with IIT via an artificial pancreas prevents hypoglycemia. In addition, glycemic control was maintained at 150 mg/dl, which is in the lower ranges of the Surviving Sepsis Campaign Guidelines 2008. We showed that maintaining glucose levels by IIT with an artificial pancreas increased the safety of cardiac surgery.

This study has a number of limitations worth noting. First, because this clinical study was conducted at a single facility, the number of subjects was small. Second, this study assessed only the short-term effects of IIT, and did not evaluate the long-term prognosis. Finally, we did not investigate the effects of IIT on organ function (e.g., cardiac function). Large-scale multicenter collaborative studies will be needed to address these issues.

In the present study we were able to carry out IIT safely during cardiac surgery with cardiopulmonary bypass by using an artificial pancreas during the perioperative period. Further, IIT demonstrated anti-inflammatory effects. Intensive insulin therapy with an artificial pancreas during the perioperative period has the potential to become an effective method for perioperative blood glucose management, thus leading to a decrease in the number of perioperative and postoperative complications.

Conflict of Interest Statement. The authors have no conflicts of interest to report. The work has not received any financial assistance from any institution.

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