Chinese Journal of Physiology 56(2): 101-109, 2013
DOI: 10.4077/CJP.2013.BAA078

Comparison of the Effect of Intensive versus Conventional Insulinotherapy in Patients with Cardiac Surgery after Cardiopulmonary Bypass

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Abstract

Hyperglycemia occurs commonly in clinically ill patients. Insulin therapy and glycemic control have been recommended for patients with septic shock. The present study investigated the effect of intensive (INIT) versus conventional insulinotherapy (COIT) in cardiac surgery patients who received cardiopulmonary bypass (CPB). In this quasi-experimental study, a total of 50 patients undergoing coronary artery bypass grafting (CABG) were recruited into the INIT and COIT groups. Study measures included serum glucose levels, cardiac output, cytokines, C-reactive protein (CRP), duration of mechanical ventilation and length of stay in the intensive care unit (ICU), and ICU mortality rate. In the INIT group, mean blood glucose level during the first two postoperative days was significantly lower than that in the COIT group. Cardiac output was significantly greater at the second postoperative days in the INIT patients than those in the COIT group. There were no differences in cytokines, CRP levels and the outcome data between two groups. Intensive insulinotherapy reduced the blood glucose and led to improve cardiac output after CABG in comparison with conventional insulinotherapy.

Key Words: cardiac surgery patients, cardiopulmonary bypass, intensive insulinotherapy

Introduction

Hyperglycemia has been observed in critically ill patients and is associated with high mortality rates (20, 24). Intensive insulin therapy and glycemic control have been recommended for patients with severe sepsis (28, 29). Hyperglycemia is one of the independent factors that worsen the prognosis in patients with both acute coronary syndromes and those undergoing coronary artery surgeries. In addition, diabetes increases the risk of cardiac surgery nearly twofold (11). Prolonged hyperglycemia causes higher morbidity, more frequent infections, hemodynamic impairment and longer and more expensive hospital stays (13). The increase in blood glucose level has been considered a response to stress. Stress-induced increases in blood glucose may in turn stimulate the production of insulin, cortisol and other hormones that work to reduce inflammation and organ injury (24). Insulin resistance may also be a contributing factor, since it has been demonstrated in more than 80% of critically ill patients (26).

Knapik and colleagues (19) have reported that cardiopulmonary bypass increases postoperative

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Received: October 13, 2011; Revised: February 9, 2012; Accepted: April 20, 2012.
 ISSN : 0304-4920. http://www.cps.org.tw

glucose and insulin consumption in both diabetic and nondiabetic patients. Hyperglycemia enhances the production of interleukin (IL)-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α) and C-reactive protein, thus, creating inflammatory responses (7). Pro-inflammatory cytokines are involved in the pathophysiology of loss in vascular tone, capillary fluid leakage and leukocyte extravasation leading to organ dysfunction after cardiopulmonary bypass (22). In critically ill patients in a surgical intensive care unit (ICU), maintenance of blood glucose levels between 80 and 110 mg/dl resulted in a 42% reduction in mortality compared with conventional treatment aiming at blood glucose levels between 180 and 200 mg/dl. In addition, patients with difficult glycemic control (postoperative blood glucose levels >200 mg/dl despite aggressive insulin treatment) have more serious postoperative complications resulting in higher mortality (2.5% versus 0.4%; $P = 0.02$) (28).

In an experimental study using a conscious rat model (6), we used various doses of lipopolysaccharide (LPS) that produce septic shock. Insulin infusion at doses of 0.5, 1 and 5 μU/kg/min was given 5 min before LPS. Plasma glucose was clamped at 90-100 mg/dl. Insulin produced dose-dependent effects attenuating the LPS-induced increases in plasma nitric oxide (NO) metabolites and hydroxyl radical. In addition, insulin diminished the systemic hypotension and acute lung injury (ALI) caused by endotoxin. These studies provide evidence that insulin exerts an anti-inflammatory effect. Several studies further showed beneficial effects of an intravenous infusion of glucose, insulin and potassium (GIK). GIK regimen improves myocardial functions during sepsis and septic shock by enhancing cardiac output, stroke volume, arterial pressure and oxygen consumption (3, 14).

The interaction and association among glucose, insulin and various diseases are subjects of interest. Hyperglycemia has not been well controlled in ICU (15). The optimal blood glucose range is controversial. Insulin infusion should be used to control hyperglycemia in the majority of critically ill patients in the ICU setting (25). Although strong evidence is lacking, lower glucose targets may be appropriate in selected patients. Use of insulin infusion protocols with demonstrated safety and efficacy, resulting in low rates of occurrence of hypoglycemia, is highly recommended by the American Association of Clinical Endocrinologists and American Diabetes Association consensus statement (25).

The aim of the present study was to compare the effects of intensive insulinotherapy (INIT) versus conventional insulinotherapy (COIT) in cardiac surgery patients who received cardiopulmonary bypass.

Materials and Methods

Participants

Fifty patients undergoing cardiac surgery with cardiopulmonary bypass were included in this study. To avoid the Hawthrone effect, Group 1 (COIT) was enrolled before recruitment of Group 2 (INIT) patients. Patients or next-of-kin received informed consent. Inclusion criteria were subjects scheduled for elective coronary artery bypass grafting surgery without any known immune or hypothalamic-pituitary-adrenal axis dysfunctions. Patients with a history of myocardial infarction during the six weeks before surgery were excluded. Exclusion also included patients with emergency surgery, previous heart surgery, valve combined coronary artery bypass grafting (CABG) and valve surgery, and left ventricular ejection fraction less than 0.30. Other exclusion criteria were: exogenous hormone therapy, chronic renal failure (creatinine >2.0 mg/dl), history of malignancy, signs of acute infection or inflammation, malnutrition and diabetes mellitus type I. The INIT group received the Yale insulin infusion protocol (15) after CABG to maintain a blood glucose level between 90-119 mg/dl (INIT group, n = 20); the COIT group received a conventional insulin sliding scale after CABG to maintain a blood glucose level between 180-200 mg/dl (COIT group, n = 30).

Anesthesia

Patients received intramuscular injection of flunitrazepam, morphine and atropine for premedication. The anesthetic technique was standardized and consisted of 5 μg/kg fentanyl, 0.3 mg/kg diazepam and 0.1 mg/kg pancuronium to perform intubation. Fentanyl at 7-10 μg/kg dosage was administered before sternotomy. Anaesthesia was maintained using continuous infusion of sufentanil (0.1 mg/kg/h) and midazolam (0.03 mg/kg/h). Repetitive doses of pancuronium (0.03 mg/kg) were given on an hourly basis to maintain adequate neuromuscular blockade.

Cardiopulmonary Bypass (CPB) Technique

The CPB comprises a roller pump (Sarns Inc., Ann Arbor, MI, USA), membrane oxygenator (Hiltie 7000; Medos, Medizintechunk, AG, Stolberg, Germany), cardiotomy reservoir (Medos, Medizintechunk, AG, Stolberg, Germany) and a tubing set (Hym) including an arterial filter (Gish Biomedical, Santa Ana, CA, USA). Standard cannulation of the ascending aorta and the right atrium was performed. After starting the CPB at a flow rate of 2-4 l/min/m^2, the body was cooled to 32°C - 34°C in all patients. For cardioplegia, 1,000 to 1,500 ml of ice-cold cardioplegia (Hospira Inc, Chicago, IL, USA) was used.

Mannitol (3 ml/kg), $NaHCO_3$ (5 ml/kg) and heparin (5,000 IU) were added.

Study Protocol

The working group for the present study included two cardiovascular surgeons and cardiovascular intensive care unit (CVSI) nurses with cardiovascular expertise. Patients in the COIT group received a conventional insulin sliding scale (Table 1) after surgery to maintain a blood glucose level between 180-200 mg/dl. In the INIT group, the Yale insulin infusion protocol (15) (Table 2) was used after CABG to maintain a blood glucose level between 90-119 mg/dl. Before this investigation, nurses involved in this study received an explanation of the Yale insulin infusion protocol and training with the study procedures and clinical practice for initiating an insulin infusion and blood glucose monitoring. When the patient was transferred to ward, insulin infusion protocol was discontinued.

Data collections included mean blood glucose levels after surgery admission at CVSI and 1 and 2 postoperative days, and cardiac output, cardiac index of preoperative and 1 and 2 postoperative days. Cytokines (IL-6 and IL-10) were determined before CPB, at the end of CPB, 6 and 12 h after CPB. C-reactive protein and white blood cells were examined at preoperative and 1 and 2 postoperative days. Duration of mechanical ventilation, duration of ICU stay, duration of postoperative hospital stay and complications, ICU mortality rate were recorded.

Measurements of Cytokine and CRP

Blood was withdrawn from the radial catheter and collected in plastic tubes containing plastic pearls and allowed to clot at room temperature. Following centrifugation, serum samples were stored in polypropylene tubes at -70°C until use. Serum concentrations of IL-6 and IL-10 were measured using quantitative sandwich enzyme immunoassay techniques. Results were presented as picograms per milliliter (pg/ml). Commerical kits for IL-6 (Pierece Endogen, Rockford, IL, USA) and IL-10 (RayBio, Norcross, CA, USA) were used. All data represent the means from duplicate measurements. The sensitivity was 6 pg/ml and 2.5 pg/ml for IL-6 and IL-10, respectively. The interassay coefficient of variation for IL-6 and IL-10 was less than 10%. Normal values (measured in 6 healthy volunteers) were below 6 pg/ml for IL-6 and 2.5 pg/ml for IL-10. CRP was assayed with image immunochemistry system and calibrator 5 plus by rate nephelometry (Beckman Coulter, Mountain View, CA, USA). All laboratory testing performed by personnel was blinded to patient information and study objectives.

Table 1. Conventional insulin sliding scale

Blood Glucose (mg/dl)	Insulin Infusion Rate (Unit/h)
<150	0
150-199	1
200-249	2
250-299	4
300-349	6
350-399	8
>400	Inform Doctor

Postoperative Assessment of Cardiac Functions

Serial cardiac outputs measurements were obtained immediately on the preoperative day and 1 and 2 postoperative days in the CVSI with pulmonary artery thermodilution. Duration and cumulative dose of postoperative inotropic use (within total 3 postoperative days) were collected. Inotropic support, defined as epinephrine infusions at any dose or dopamine infusions, was initiated to maintain a cardiac index ≥2 l/min/m^2 and a mean arterial pressure (MAP) ≥60 mmHg.

Demographic and Medical Variables

Demographic and medical data were collected, including gender, age, body mass index (BMI), diabetes mellitus (DM) history, left ventricle ejection fraction (LVEF), cardiopulmonary bypass time, Acute Physiology and Chronic Health Evaluation II (APACHE II), force expiratory volume/forced vital capacity (FEV1/FVC) and complications.

Definition of Outcome Measures

Tracheal extubation was performed when hemodynamic were stable and the rectal temperature was 36°C, and there was adequate spontaneous breathing (PaO_2 >80 mmHg with FiO_2 0.3, breathing frequency <15/min). Duration of mechanical ventilation was defined as the time from CVSI admission to endotracheal extubation. Epinephrine or dopamine was given when MAP was <60 mmHg and cardiac index was <2.0 l/min/m^2. Despite administration of IV fluid (crystalloid, 25% albumin, 10% hydroxyethyl starch) to reach pulmonary capillary wedge pressure (or central venous pressure) >16 mmHg, inotropic support (epinephrine or dopamine) (μg/kg/min) were recorded throughout the first three postoperative days. The criteria for discharge from the CVSI were endotracheal extubation and stable hemodynamic conditions. Patients were discharged if they were on

Table 2. Yale insulin infusion protocol (15)

■ **Initiating an Insulin Infusion**

1. INSULIN INFUSION: Mix 1 unit Regular Human Insulin per 1 ml 0.9% NaCl. Administer *via* infusion pump (in increments of 0.5 unit/h)
2. PRIMING: Flush 50 ml of infusion through all IV tubing before infusion begins (to saturate the insulin binding sites in the tubing)
3. THRESHOLD: IV insulin is indicated in any critically ill patient with persistent BG ≥ 140 mg/dl; *consider* use if BG ≥ 110 mg/dl.
4. TARGET BLOOD GLUCOSE (BG) LEVELS: **90-119 mg/dl**
5. BOLUS & INITIAL INSULIN INFUSION RATE: If initial BG ≥ 150 mg/dl, divide by 70, then round to nearest 0.5 units for bolus AND initial drip rate. If initial BG < 150 mg/dl, divide by 70 for initial drip rate only (*i.e.*, NO bolus)
   Examples: (1) Initial BG = 335 mg/dl: 335 ÷ 70 = 4.78, round ↑ to 5: 5 units IV bolus + start infusion @ 5 units/h. (2) Initial BG = 148 mg/dl: 148 ÷ 70 = 2.11, round ↓ to 2: start drip @ 2 units/h (NO bolus)

■ **Blood Glucose (BG) Monitoring**

1. Check BG hourly until stable (3 consecutive values within target range). In hypotensive patients, capillary blood glucose (*i.e.*, fingersticks) may be inaccurate and obtaining blood sample from an indwelling vascular catheter may be preferable.
2. Then check BG q 2 h; once stable × 12-24 h. BG checks can then be spaced to q 4 h IF:
   (1) no significant change in clinical condition AND (2) no significant change in nutritional intake.
3. If any of the following occur, consider the temporary resumption of hourly BG monitoring, until BG is again stable (2-3 consecutive BG values within target range):
   (1) any change in insulin infusion rate (*i.e.*, BG out of target range)
   (2) significant changes in clinical condition
   (3) initiation or cessation of pressor or steroid therapy
   (4) initiation or cessation of renal replacement therapy (dialysis, CVVH, *etc*.)
   (5) initiation, cessation, or rate change of nutritional support (TPN, PPN, tube feedings, *etc*.)

■ **Step 1 Determine the rate of change**

BG 70-89 mg/dl	BG 90-119 mg/dl	BG 120-179 mg/dl	BG ≥ 180 mg/dl	Instructions
		BG ↑ by > 40 mg/dl/h	BG ↑	↑ Infusion by "2Δ"
	BG ↑ by > 20 mg/dl/h	BG ↑ by 1-40 mg/dl/h or BG Unchanged	BG Unchanged or BG ↓ by 1-40 mg/dl/h	↑ Infusion by "Δ"
BG ↑	BG ↑ by -20 mg/dl/h, BG Unchanged or BG ↓ by 1-20 mg/dl/h	BG ↓ by 1-40 mg/dl/h	BG ↓ by 41-80 mg/dl/h	No infusion change
BG Unchanged Or BG ↓ by 1-20 mg/dl/h	BG ↓ by 21-40 mg/dl/h	BG ↓ by 41-80 mg/dl/h	BG ↓ by 81-120 mg/dl/h	Infusion by "Δ"
BG ↓ by > 20 mg/dl/h DC insulin infusion	BG↓ by > 40 mg/dl/h	BG ↓ by > 80 mg/dl/h	BG ↓ by > 120 mg/dl/h	Hold X 30 min then ↓ Infusion by "2Δ"

■ **Step 2 Changes infusion rate ("Δ") are determined by the current rate**

Current Rate (units/h)	Δ = Rate Change (units/h)	2Δ = 2 X Rate Change (units/h)
< 3	0.5	1
3-6	1	2
6.5-9.5	1.5	3
10-14.5	2	4
15-19.5	3	6
20-24.5	4	8
≥ 25	≥ 5	10 (Inform Doctor)

oral medication only, were able to walk stairs and showed no signs of significant pericardial or pleural effusions. Duration of postoperative hospital stay was defined as the time from CVSI to discharge.

Data Analysis

Data are presented as means ± standard error of mean (SEM) or as percentages as appropriate. Statistical analysis was performed with SPSS software (SPSS Inc, Chicago, IL, USA). Mann-Whitney U test was used to test the difference between the INIT and the COIT groups regarding demographic and medical

variables of patients, appropriate perioperative data, inotropic support, duration of mechanical ventilation, length of ICU stay, duration of postoperative hospital stay and to account for pre-CPB and post-CPB cytokines, paired *t*-test was used. To illustrate the individual blood glucose levels of the two groups, cardiac output, cardiac index, white blood cell count and CRP change in the measurement period using repeated measures ANOVA with Greenhouse Geisser correction within groups was used. A nonparametric analysis for blood sugar, cardiac output, cardiac index, white blood cell count and CRP of the first three postoperative days was conducted by Mann-Whitney U test to compare the differences between means in the INIT group *vs*. the COIT group. Statistical significance was defined as a value of $P < 0.05$.

Results

Demographic and Medical Data

Demographic and medical data are shown in Table 3. Patients in both groups had similar preoperative characteristics. In the present study, the INIT group had a significantly less total dose of inotropic support (epinephrine or dopamine) during the first three postoperative days than in the COIT group (77.5 μg/kg/min versus 170.1 μg/kg/min). Patient outcome data indicated that there were no significant differences between the two groups in terms of duration from the termination of extubation, as well as the length of postoperative ICU stay. The incidence of postoperative complications was low and was similar between the two groups. Four patients suffered from postoperative complications, one patient in the INIT group developed pleural effusion and three patients in the COIT group manifested pleural effusion, cardiogenic shock and reoperation related to sternal wound oozing. No ICU mortality occurred and all patients survived in CVSI.

Differences in Blood Sugar Levels

Both groups had similar blood levels of glucose before CABG. In the fifty patients after CABG admission at CVSI, the mean blood sugar level greater than 110 mg/dl was 98%. The mean blood sugar was 175 mg/dl and 199.9 mg/dl in the INIT and COIT groups at admission in CVSI, respectively ($P = 0.17$). The prevelance hyperglycemia (>200 mg/dl) in nondiabetes mellitus *vs*. diabetes mellitus patients after CPB was 30.6% and 61.5%, respectively. In the INIT group, the mean morning blood glucose during the first two postoperative days was significantly lower than that in the COIT group (Fig. 1). In the INIT group, blood sugar in non-DM patients (n = 13)

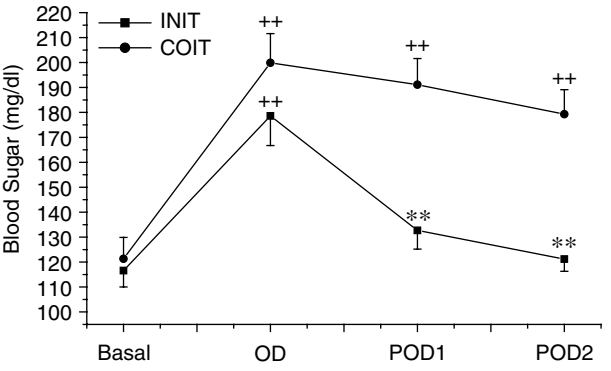

Fig. 1. Comparison of blood glucose levels during postoperative days. Values are means ± SEM; INIT, intensive insulinotherapy group; COIT, conventional insulinotherapy group. OD, operative day; POD1, the first day after surgery; POD2, the second day after surgery. Comparison of the difference versus the basal value (repeated measures ANOVA, $^{++}P < 0.01$). Significantly different between the INIT and the COIT groups ($^{**}P < 0.01$). In the INIT group, the mean morning blood glucose during the first two postoperative days was significantly lower than that in the COIT group.

reached the target blood sugar control (90-119 mg/dl) within 8 h, the efficacy of the blood sugar control was 69.2%. In DM patients in the INIT group (n = 7), blood sugar levels reached the same target blood sugar control within 18 h, and the efficacy of the blood sugar control was 57.1%. There were no difficulties in hyperglycemic control (postoperative blood glucose >200 mg/dl) and severe hypoglycemia occurred (defined as a blood glucose <40 mg/dl) during the CVSI in both groups.

Differences in Cardiac Output

Both groups had increased mean cardiac output on the preceding surgery days ($P < 0.05$). The mean cardiac output was significantly greater at the second postoperative days in the patients of the INIT group than those in the COIT group ($P < 0.05$, Fig. 2).

Changes of Levels of Plasma Cytokines, CRP and WBC

IL-6 and IL-10 levels were elevated significantly after separation from CPB within groups ($P < 0.05$). Patient treated with INIT had lesser tendency for intense inflammatory response with lower levels of IL-6 and higher levels of IL-10 after separation from CPB than the COIT patients, but there were no significant differences between the groups (Table 4). CRP and WBC increased to high levels after CPB on the preceding days, but there were no significant differences between the groups (Table 5).

Table 3. Demographics, medical variables and operative data

	INIT (n = 20)	COIT (n = 30)	*P* Value
Age (yr)	62.3 ± 2.5	64.4 ± 2.0	0.57
Male Sex, n (%)	17 (85)	24 (80)	0.46
BMI (kg/m^2)	24.9 ± 1.2	25.6 ± 0.7	0.71
DM	7 (35)	6 (20)	0.17
LVEF	51.0 ± 3.3	52.6 ± 2.2	0.34
FEV1/FVC	73.3 ± 2.2	73.7 ± 1.5	0.89
APACHE II			
Admission ICU	23.9 ± 0.9	23.4 ± 0.7	0.7
1 Day ICU	14.8 ± 1.3	16.5 ± 0.7	0.11
2 Day ICU	11.9 ± 0.8	11.0 ± 0.6	0.24
Cardiopulmonary Bypass Time (min)	134.9 ± 8.1	147.7 ± 8.5	0.20
Inotropic Support (μg/kg/min)[a]	77.5 ± 25.0	170.1 ± 37.1	0.01
Duration of Mechanical Ventilation (h)	39.5 ± 16.2	33.9 ± 7.0	0.72
Duration of ICU Stay (days)	3.8 ± 0.7	4.3 ± 1.0	0.89
Duration of Postoperative Hospital Stay	14.6 ± 3.2	10.3 ± 2.0	0.45
Duration of Hospital Stay	25.8 ± 4.0	22.7 ± 1.9	0.85
Complications (%)	1 (5.3)	3 (10)	0.41

Values are expressed as numbers (%), or means ± SEM. INIT, intensive insulinotherapy group; COIT, conventional insulinotherapy group. BMI, body mass index; DM, diabetes mellitus; LVEF, left ejection fraction; FEV1/FVC, force expiratory volume/forced vital capacity; APACHE II, Acute Physiology and Chronic Health Evaluation II. [a]Data collected during the first three postoperative days. [b]Data collected during postoperative day. Comparison of the differences between the INIT *vs*. COIT groups. $P < 0.05$, significant difference.

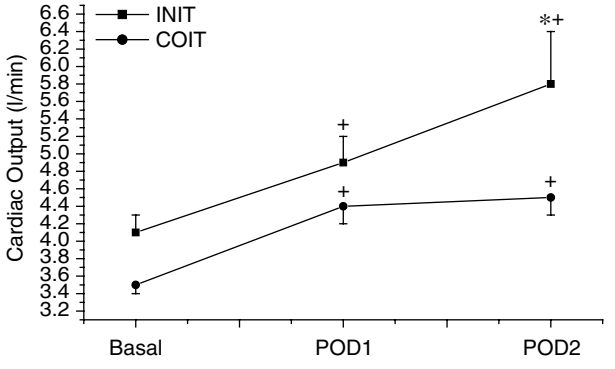

Fig. 2. Comparison of cardiac output during postoperative days. Abbreviations used are as in legend to Fig. 1. Comparison of the difference versus the baseline value (repeated measures ANOVA, $^+P < 0.05$). Significantly different between the INIT and COIT groups ($^*P < 0.05$). The mean cardiac output was significantly greater at the second postoperative days in the patients treated with INIT group than those treated with COIT group ($^*P < 0.05$, one-tailed).

Discussion

Knapik and colleagues (19) have reported cardiopulmonary bypass increases postoperative glucose and insulin consumption in both diabetic and nondiabetic patients. In our study, the prevalence of diabetes mellitus in the fifty patients studied with CABG was 26%. The mean blood sugar level in the fifty patients after CABG in CVSI greater than 110 mg/dl was 98%. The prevalence of hyperglycemia (> 200 mg/dl) in non-diabetes mellitus *vs*. diabetes mellitus patients after CPB was 30.6% and 61.5%, respectively. The mean morning blood glucose in the INIT group during the first two postoperative days was significantly lower than in the COIT group. The occurrence of hypoglycemia is problematic because low blood glucose can lead to seizures, brain damage, depression and cardiac arrhythmias (10, 21). A retrospective cohort study in more than 5,000 medical and surgical critically ill patients found that a blood glucose < 40 mg/dl was an independent risk factor for death after adjustment for severity of illness, age, mechanical ventilation, renal failure, sepsis and diabetes (adjusted odds ratio 2.28, 95% CI, 1.41-3.70) (21). The hypoglycemic effect on mortality is uncertain, since various randomized trials have reported increased mortality, no effects on mortality, or decreased mortality.

Hyperglycemia increases circulating free fatty acids (FFAs), which are toxic to the myocardium and induce arrhythmias. In addition, high blood glucose levels cause osmotic diuresis, and the resulting volume depletion may further compromise myocardial functions (7). Furnary and colleagues (12) presented a study of insulin management in patients who had undergone CABG. During a 15-year period, their

Table 4. Cytokines data

		Before CPB	End CPB	6 h after CPB	12 h after CPB
IL-6	INIT	0.3 ± 0.2	59.6 ± 18.2**	112.6 ± 31.9**	89.0 ± 23.8**
	COIT	0.2 ± 0.2	109.9 ± 29.6**	260.4 ± 61.8**	134.5 ± 31.2**
IL-10	INIT	13.2 ± 6.3	161.9 ± 30.9**	60.2 ± 14.8**	83.1 ± 16.3**
	COIT	2.9 ± 0.7	105.2 ± 23.6**	49.5 ± 9.5**	62.7 ± 8.0**

Values are means ± SEM. INIT (n = 20) and COIT (n = 30). CPB, cardiopulmonary bypass; IL-6, interleukin 6; IL-10, interleukin 10. Comparison of the differences between the INIT *vs*. COIT groups. Comparison of the differences within groups *vs.* values before CPB (repeated measures ANOVA, $^{**}P < 0.01$). There was no significant difference between groups ($P > 0.05$).

Table 5. WBC and CRP data

		Before Operation	POD1	POD2
WBC (cells/mm^3)	INIT	7,410.7 ± 610.6**	9,503.7 ± 816.3**	12,725.0 ± 885.9**
	COIT	7,506.7 ± 449.0**	9,531.7 ± 568.9**	11,150.0 ± 659.8**
CRP (mg/dl)	INIT	1.7 ± 1.0**	4.9 ± 0.4*	13.9 ± 1.5**
	COIT	0.7 ± 0.2**	6.0 ± 0.1**	15.1 ± 1.0**

Values are means ± SEM. INIT (n = 20) and COIT (n = 30). WBC, white blood count; CRP, C-reactive protein. POD1, the first day after surgery; POD2, the second day after surgery. Comparison of the differences between the INIT *vs*. COIT groups. Comparison of the differences within groups *vs.* value before operation (repeated measures ANOVA, $^{*}P < 0.05$, $^{**}P < 0.01$). There was no significant difference between groups ($P > 0.05$).

management of glucose levels was to change blood glucose from 200 mg/dl to 100 mg/dl by continuous intravenous insulin infusion for cardiac surgery patients during the study interval. The mortality related to cardiovascular diseases was significantly decreased as a consequence of glucose and insulin management. In our study, we demonstrated that INIT according to the Yale insulin infusion protocol (15) after CABG to maintain a blood glucose level between 90-119 mg/dl, the INIT group had a significantly lower total dose of inotropic support (epinephrine or dopamine) during the first three postoperative days than the COIT group. The mean cardiac output and cardiac index were significantly greater at the second postoperative days in INIT patients than those in the COIT group.

Pro-inflammatory cytokines such as TNF-α and IL-6 are released in response to cardiac surgery and have been suggested to play an important role in the pathogenesis of myocardial dysfunction in ischemia-reperfusion injury (31). Our study showed that the levels of IL-6 increased after CPB. During CPB and cardioplegic arrest, the heart is essentially undergoing an ischemia/reperfusion injury. Complement has been implicated as one of the initiators of this phenomenon. However, other inflammatory cytokines, including TNF-α and IL-6, may also play a role. IL-6 levels may be correlated with the severity of tissue damage induced by surgery and the inflammatory response to CPB (31). Elevated IL-6 production has also been associated with poor outcome (31). It has been demonstrated by Biffl *et al*. (1) that IL-6 inhibited neutrophil apoptosis *in vitro*. They have also proposed that circulating IL-6 in critically ill patients may limit neutrophil apoptosis and prolong its toxic effects. Anti-inflammatory cytokines such as IL-10 may significantly abrogate these complications. In our study, IL-10 was peaked from the beginning of reperfusion and remained at a high level during the 12 h period after CPB. It has been demonstrated that IL-10 mediates inhibition of oxygen free radicals generation in macrophages in response to lipopolysaccharide through IκB-α degradation (8). There is evidence that glucose can stimulate the production of pro-inflammatory cytokines, such as TNF-α and IL-6, with no effects on the anti-inflammatory cytokine IL-10 (32). Recent evidence from animal studies has suggested that insulin exerts anti-inflammatory properties (6). The effects of glycemic control on the immunologic response have not been examined extensively in clinical studies. Hoedemaekers and colleagues (16) provided evidence that the protective effect of intensive insulin therapy in patients after cardiac surgery with cardiopulmonary bypass is not related to changes in the cytokine balance from a pro-inflammatory to an anti-inflammatory pattern. In the present study, the INIT group had a lesser tendency for intense inflammatory

response with lower levels of IL-6 and higher levels of IL-10 after separation from CPB than the COIT group. However, the extent of increase was not statistically significant. It is possible that the small sample size is not enough to assess IL-6 and IL-10 differences between the INIT and COIT groups. The separation of the two effects, although important, is difficult to explain. Further studies are required to define the mechanism.

CRP is a risk marker and plays a role in the pathogenesis of inflammation and atherosclerosis. It is synthesized and secreted mainly by hepatocytes in response to IL-6 and either IL-1 or TNF-α (23). CRP activates complement, increases phagocytic activity of neutrophils, increases respiratory burst of neutrophils, and induces expression of adhesion molecules, synthesis of tissue factors and cytokines from monocytes and platelet aggregation (18, 27). In our study, CRP increased to high levels after CPB on the preceding surgery days, but there were no significant differences in both groups.

In myocardial dysfunction and ischemia/reperfusion heart injury, hyperglycemia was shown to precede contractile insufficiency and exaggerate the decrease in cardiac output (4, 9, 30). The results of these studies support our findings that hyperglycemia enhances the impairment of cardiac output. Our data further reveals that myocardial dysfunction can be reversed by insulin administration. Evidence suggests that cardiomyocytes might also produce endothelin-1 (ET-1), which might directly impair myocyte contractility by increasing intracellular calcium levels. Because hyperglycemia is a potent stimulus for ET-1 production, several studies have proved that hyperglycemia directly impaired cardiomyocyte survival through the production of ET-1 (4, 9, 30). On the other hand, recent studies focusing on mitochondrial functions pointed towards an important role of abnormalities in cardiac mitochondria. The results showed that abnormalities in cardiomyocyte mitochondrial energetics appeared to contribute significantly to the development of cardiac dysfunction in diabetes (2, 5, 17). Taking together, evidences support that hyperglycemia impairs cardiac function, and insulin is beneficial.

In conclusion, our data showed that cardiopulmonary bypass increased postoperative glucose in both diabetic and nondiabetic patients. Intensive insulinotherapy resulted in improvement of cardiac output after CABG as compared to conventional insulinotherapy.

Acknowledgments

The present study was supported by grants from the Taipei Veteran General Hospital (VGH95A-134). The authors are grateful to the cardiovascular physicians, pumpists of heart lung machines and nurses of CVSI for their assistance in data collection.

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