The Heart Surgery Forum #2010-1017
13 (5), 2010 [Epub October 2010]
doi: 10.1532/HSF98.20101017

Online address: http://cardenjennings.metapress.com

Impacts of Intensive Insulin Therapy in Patients Undergoing Heart Valve Replacement

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ABSTRACT

Background and Aims: Cardiac surgery with cardioplegic cardiac arrest and cardiopulmonary bypass (CPB) is associated with severe stress response, systemic inflammatory response, and injury. This study was designed to investigate the effects of intensive insulin therapy on patients undergoing valve replacement with CPB.

Methods: One hundred nondiabetic inpatients undergoing valve replacement were randomly assigned to a control group or an intensive insulin therapy (IT) group. Plasma cytokine and cardiac troponin I (cTnI) levels were monitored perioperatively.

Results: Compared with the control group, the IT group had smaller increases in plasma concentrations of tumor necrosis factor α, interleukin 1β (IL-1β), IL-6, and cTnI, and had a more pronounced increase in IL-10 levels after the initiation of CPB. After surgery, the required inotropes were reduced in the IT group. In the IT group, the time of artificial ventilation and the postoperative length of stay in the hospital were markedly shortened; however, there were no significant differences between the IT and control groups in mortality and the rate of nosocomial infections of deep sternal wounds.

Conclusions: IT can significantly attenuate the systemic inflammatory response and improve a damaged cardiac function, but it does not reduce the in-hospital mortality rate.

INTRODUCTION

Among patients undergoing cardiac surgery, cardiopulmonary bypass (CPB) and the trauma of the cardiac surgery itself, in conjunction with ischemia-reperfusion, postoperative pain, dysphoria, and ventilator placement, typically provoke a systemic inflammatory response and may cause detrimental stress responses. At the same time, disturbances of general metabolism and endocrine functions, including abnormal glucose tolerance and hyperglycemia stress, may occur [Rassias 2006]. Hyperglycemia may also induce cell injuries and hydroelectric disturbance via increasing concentrations of proinflammatory cytokines, hyperpermeability, and weakened immunity, making such patients more susceptible to various infections [Shilling 2008]. These results will affect the prognosis of the cardiac operation [Golden 1999; Doenst 2005].

The magnitude and duration of the systemic inflammatory response determine the development and degree of tissue damage, multiple organ failure, or even death [Tracey 1987; Wang 1999]. The pathophysiological cascade is mediated by proinflammatory cytokines, such as interleukin 1β (IL-1β), IL-6, or tumor necrosis factor (TNF), which are balanced by anti-inflammatory cytokines such as IL-2, IL-4, or IL-10 [Jeschke 2004]. Despite recent advances in the understanding of the molecular cascade of the systemic inflammatory response and hyperglycemia, the defined levels for glucose control are still evolving. Recent research has indicated that intensive insulin therapy (IT) may markedly improve the prognosis and reduce the morbidity and mortality of patients with serious illnesses [van den Berghe 2001, 2006], such as diabetes [Furnary 2006], who undergo cardiac surgery. Data are scarce, however, regarding how IT affects the prognosis of nondiabetic patients undergoing cardiac surgery with CPB in the context of mixed surgical/medical intensive care unit (ICU) conditions. Therefore, we designed a randomized clinically controlled trial aimed at examining the influence of IT on the systemic inflammatory response, the recovery of cardiac function, and the prognosis of nondiabetic patients undergoing valve replacement with CPB.

MATERIALS AND METHODS

Patients

The study was approved by our institutional research ethics committee. Anonymous acquisition and publication of patient data were in accordance with the Declaration of Helsinki. One hundred patients who underwent heart valve

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Received January 27, 2010; accepted March 29, 2010.

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Table 1. Baseline and Operative Characteristics of Inpatient Populations*

Characteristic	Control Group (n = 50)	IT Group (n = 50)
Male-female ratio	1:1.17	1:1.08
Age, y	44.0 ± 11.5	43.3 ± 11.7
Body weight, kg	59.9 ± 10.3	60.5 ± 11.3
Blood glucose level, mmol/L	77.5 ± 2.6	78.4 ± 3.8
TNF-α, pg/mL	31.9 ± 2.5	32.3 ± 3.2
IL-1β, pg/mL	6.3 ± 1.2	6.2 ± 1.5
IL-6, pg/mL	18.9 ± 3.7	21.2 ± 2.5
IL-10, pg/mL	34.5 ± 4.2	35.1 ± 3.2
Preoperative EF, %	53.6 ± 8.8	54.9 ± 6.9
Type of operation, n (%)		
MVR	23 (46.00)	24 (48.00)
AVR	10 (20.00)	11 (22.00)
MVR/AVR	17 (34.00)	15 (30.00)
Bypass time, min	103.5 ± 34.9	100.5 ± 48.6
Cross-clamp time, min	60.4 ± 26.5	59.9 ± 33.2

*Data are presented as the mean ± SD where indicated. IT indicates intensive insulin therapy; TNF-α, tumor necrosis factor α; IL-1β, interleukin 1β; EF, ejection fraction; MVR, mitral valve replacement; AVR, aortic valve replacement.

replacement with CPB from September 2005 to April 2007 were enrolled in this prospective, randomized single-center study. None of the patients had a history of diabetes mellitus. Preoperatively, all patients received detailed information on the proposed insulin therapy and provided written consent. All patients referred to a single surgeon for valve replacement were assessed for eligibility. The 100 patients were randomized with computerized randomization tables. Study personnel opened the blinded envelopes sequentially after the participants had signed the patient consent form, and patients were assigned to receive either routine therapy (control group, n = 50) or IT (n = 50). Table 1 summarizes the patient characteristics. No significant differences between the 2 groups were noted for age, sex, body weight, or any other operative procedure (Table 1). Exclusion criteria included preoperative liver or kidney disease or dysfunction, preoperative coagulation disorder, palliative operation, or a second operation.

Blood Glucose Control

Patients in the control group received standard institutional operative and postoperative care, but not control for blood glucose. In the IT group, blood glucose levels were approximately 70 to 110 mg/dL during and after the surgery according to the Portland Protocol [Furnary 2006], with some modifications. For the IT group, glycemic control was instituted immediately after induction of anesthesia. In brief, (1) 0.3 to 0.4 U/kg insulin per hour was continuously infused intravenously after anesthesia was induced preoperatively; (2) the insulin dosage was changed to 10 U/h when the thoracic cavity was open; (3) the insulin dosage was further adjusted to 1 to 1.5 U/kg per hour when CPB commenced. Blood glucose was tested every 15 minutes. Subsequent insulin delivery was modified as follows: Six units of insulin was added when the blood glucose reading was 150 to 160 mg/dL. Similarly, we added 8 U at readings of 160 to 170 mg/dL, 12 U at 170 to 180 mg/dL, and 16 U at ≥180 mg/dL. We subtracted 8 U at 60 to 70 mg/dL and 16 U at 50 to 60 mg/dL. There was no insulin input at blood glucose concentrations ≤50 mg/dL, but 50 mL of 20% glucose was administered intravenously instead. (4) Insulin administration was terminated when the body temperature began to recover. (5) Postoperative blood glucose levels were measured every 60 minutes, and an insulin infusion was started if the blood glucose level exceeded 110 mg/dL. The infusion was adjusted to maintain the level at a value between 70 and 110 mg/dL in accordance with the Portland Protocol.

Measurement of Insulin, IL-1β, IL-6, TNF-α, IL-10, and Cardiac Troponin I

Blood samples were collected from each patient into heparinized tubes at 7 time points: after anesthesia induction (T1), at the initiation of CPB (T2), after the termination of CPB (T3), at 6 hours after CPB (T4), at 12 hours after CPB (T5), at 24 hours after CPB (T6), and at 48 hours after CPB (T7). Plasma insulin levels were measured in all patients of the 2 groups with an insulin kit (R&D Systems, Abingdon, UK). As described in our previous study [Gu 2008a], plasma IL-1, IL-6, IL-10, TNF-α, and cardiac troponin I (cTnI) levels were measured with commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems). All ELISA protocols were carried out according to kit guidelines. Measurements were corrected according to the following formula (with the hematocrit as an example): Corrected Value = Measured Value × (1 – Hematocrit of Sample)/(1 – Hematocrit before Anesthesia).

Western Blot Analysis

As documented in our previous study [Gu 2008b], peripheral blood mononuclear cells (PBMC) were isolated from blood samples obtained from each patient at 7 time points. PBMC lysates were prepared by adding 1 mL boiling lysis buffer (1% sodium dodecyl sulfate [SDS]), 1 mmol/L sodium orthovanadate, and 10 mmol/L Tris (pH 7.4) to the PBMC pellet. The protein concentration was quantitated with the BCA Protein Assay Kit (Pierce/Thermo Scientific, Rockford, IL, USA). Sixty micrograms of total cell lysate were electrophoresed on 12% SDS gels for nuclear factor κBp65 (NF-Bp65) and/or 15% SDS gels for IκB. Proteins were separated by SDS/polyacrylamide gel electrophoresis and transferred onto polyvinylidene difluoride (Bio-Rad Laboratories, Hercules, CA, USA) by the semi-dry electrophoretic transfer technique, blocked with 5% skim milk, and incubated at 4°C overnight with polyclonal anti-IκB antibody (Sigma-Aldrich, St. Louis, MO, USA) or a monoclonal anti–NF-κBp65 antibody (Sigma-Aldrich). The membranes were washed and then

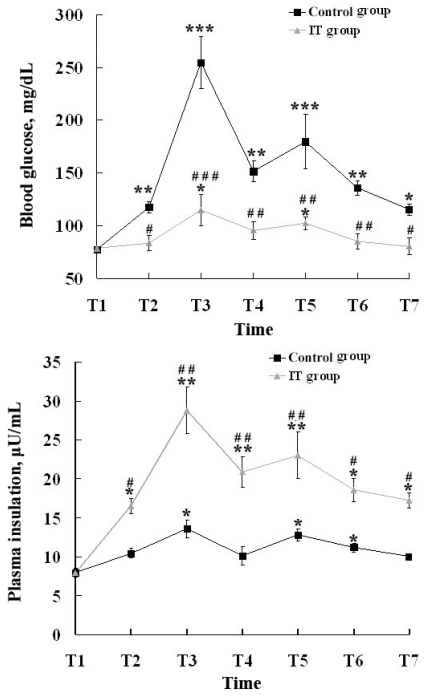

Figure 1. Changes in blood glucose (top) and plasma insulin (bottom) levels in the perioperative period. *P < .05, **P < .01, and ***P < .001, compared with baseline levels. #P < .05, ##P < .01, and ###P < .001, compared with the control group. Data are presented as the mean ± SD. Sample-collection times: before anesthesia induction (T1), at the initiation of cardiopulmonary bypass (CPB) (T2), after the termination of CPB (T3), at 6 hours after CPB (T4), at 12 hours after CPB (T5), at 24 hours after CPB (T6), and at 48 hours after CPB (T7). IT indicates intensive insulin therapy.

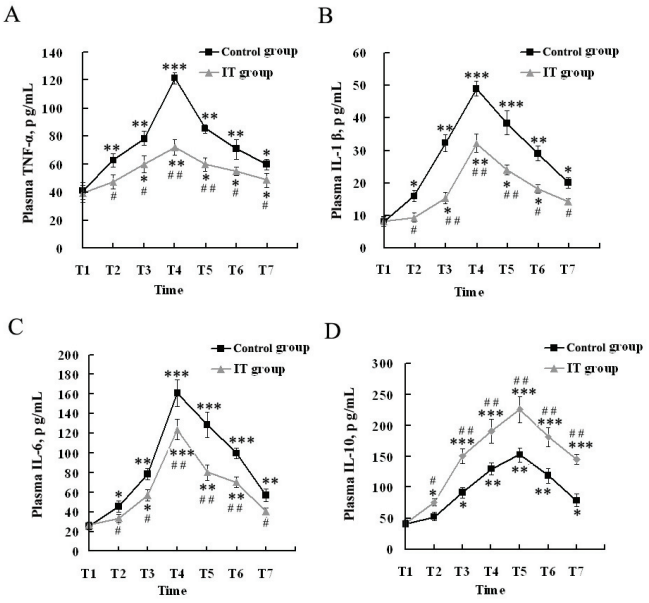

Figure 2. Pre- and postoperative interleukin levels. *P < .05, **P < .01, and ***P < .001, compared with baseline levels. #P < .05, and ##P < .01, compared with the control group. Data are presented as the mean ± SD. In both groups, tumor necrosis factor α (TNF-α) (A), interleukin 1β (IL-1β) (B), IL-6 (C), and IL-10 (D) levels were higher than baseline levels. Levels did not normalize within the study period. IL-1β, IL-6, and TNF-α levels were higher in the control group than in the intensive insulin therapy (IT) group; however, IL-10 levels were higher in the IT group. Sample-collection times: before anesthesia induction (T1), at the initiation of cardiopulmonary bypass (CPB) (T2), after the termination of CPB (T3), at 6 hours after CPB (T4), at 12 hours after CPB (T5), at 24 hours after CPB (T6), and at 48 hours after CPB (T7).

incubated for 1 hour at room temperature with the secondary antibody. An immunodetection kit was used for fluorescence detection (Pierce/Thermo Scientific).

Clinical Data

Cardiac index (CI) measurements were made via a Swan-Ganz thermodilution catheter and were obtained at T1, T3, T4, T5, T6, and T7. Moreover, the first postoperative 48-hour quantitative measurements of inotropes were evaluated by calculating an inotropic score according to the following formula [Lazar 2004]: ([Dopamine + Dobutamine] × 1) + (Milrinone × 15) + ([Epinephrine + Norepinephrine + Isoproterenol] × 100). The time on a ventilator, the length of the ICU stay, the length of the hospital stay, the nosocomial infection rate, mortality, and the rate of hypoglycemic events were recorded concurrently.

Statistical Analysis

All data are presented as the mean ± SD. Statistical analyses were performed with SPSS software (version 11.0; SPSS, Chicago, IL, USA). Patient demographics and surgical characteristics were analyzed with the Student t test for continuous, normally distributed variables, and the χ^2 test was used for the analysis of categorical variables. Laboratory data were analyzed with 2-way repeated-measures analysis of variance with the Greenhouse-Geisser correction (the Mauchly test demonstrated that sphericity assumptions were not met). This analysis was followed by the Mann-Whitney U test of the groups if the analysis of variance detected a significant difference. A P value <.05 was considered statistically significant.

RESULTS

Changes in Blood Glucose and Insulin Levels

Following CPB, a biphasic response was observed for blood glucose levels in the control group (Figure 1). The first phase consisted of a 1.5-fold increase in blood glucose levels at the initiation of CPB and a 2.9-fold increase at the end of CPB, compared with the preoperative baseline level. The blood glucose level transiently decreased to 1.7-fold greater than the baseline level by 6 hours after CPB. The second phase of the increase in blood glucose levels occurred by 12 hours after CPB. The blood glucose level then recovered continuously, but it did not reach the preoperative level by 48 hours after CPB. Blood glucose levels were relatively controlled in the IT group at values between 70 and

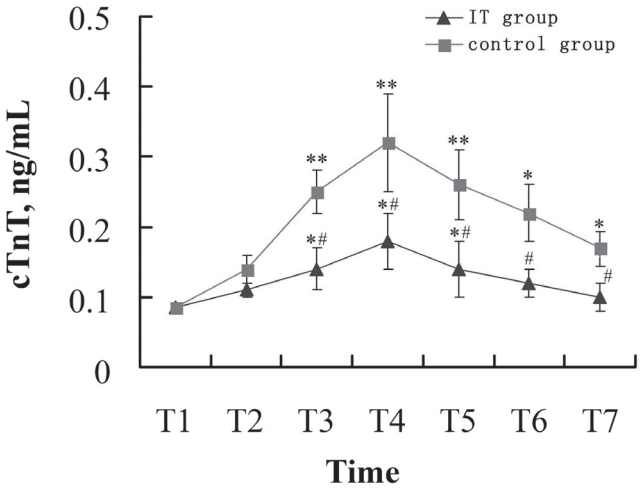

Figure 3. Changes in blood cardiac troponin I (cTnI) levels. *P < .05, and **P < .01, compared with baseline levels. #P < .05, compared with the control group. Data are presented as the mean ± SD. Sample-collection times: before anesthesia induction (T1), at the initiation of cardiopulmonary bypass (CPB) (T2), after the termination of CPB (T3), at 6 hours after CPB (T4), at 12 hours after CPB (T5), at 24 hours after CPB (T6), and at 48 hours after CPB (T7).

110 mg/dL. Blood glucose levels were significantly higher in the control group than in the IT group after the initiation of CPB (P < .01; Figure 1, top).

Plasma insulin levels in the 2 groups showed similar biphasic responses. After an initial increase at the termination of CPB (3.6-fold for the IT group and 1.7-fold for the control group), plasma insulin levels declined transiently in both groups 3 hours later, but the second phase of the increase at 12 hours was not as marked as the first phase. Plasma insulin levels were significantly lower in the control group than in the IT group at each time point after the initiation of CPB (P < .05, or P < .01; Figure 1, bottom).

Changes in Plasma Cytokine Levels

Proinflammatory cytokines TNF-α, IL-1β, and IL-6 showed a monophasic response in the 2 groups (Figures 2A, 2B, and 2C). Samples from the control group showed 3.1-fold, 6.4-fold, and 6.1-fold increases for TNF-α, IL-1β, and IL-6, respectively at 6 hours after CPB. Decreases were then observed to 48 hours after CPB, although levels did not return to the preoperative levels (Figures 2A, 2B, and 2C). The levels remained significantly higher in the control group than in the IT group after the initiation of CPB (P < .01 for all; Figures 2A, 2B, and 2C). Levels of the anti-inflammatory cytokine IL-10 were elevated immediately after the initiation of CPB and reached a peak at 12 hours after CPB. IL-10 levels then dropped but failed to reach the preoperative level by 48 hours after CPB in either group. IL-10 levels were significantly higher in the IT group than in the control group after the termination of CPB (P < .01; Figure 2D).

Changes in Plasma cTnI Levels

Figure 3 presents the measurements of serum cTnI levels in samples collected from the 2 patient groups at the 7 time points. The preoperative plasma cTnI levels in the 2 groups were similar. After the initiation of CPB, cTnI levels increased significantly in both groups. The degree of the cTnI increase was significantly higher in the control group after the termination of CPB (P < .05).

Clinical Outcomes

CI values in both groups decreased until postoperative hour 12; the CI then increased in both groups (IT group, P = .0009; control group, P = .042). CI values were significantly higher in the IT group than in the control group at T5 (P = .016) and T6 (P = .024) (Table 2).

After surgery, 21 patients in the control group and 17 patients in the IT group used either dopamine at >5 μg/kg per minute or epinephrine. A statistical analysis did not reveal a significant difference (P = .251), but when inotropic drug use was evaluated with the inotrope score method used by Shore and colleagues [2001], a significant difference was found between the 2 groups. The scores for the IT group were much lower than the corresponding scores of the control group at the same time points (P < .05 for all; Table 3).

Tight glycemic control with insulin in the IT group reduced ventilator times markedly, as well as the lengths of stay in the ICU and the hospital after surgery (P < .05 for all; Table 4). There was no significant difference between the

Table 2. Cardiac Index in the Study Population following Surgery*

Time Point	Control Group (n = 50), L/min per m^2	IT Group (n = 50), L/min per m^2	P
T3	1.9 ± 0.2	2.1 ± 0.4	NS
T4	2.3 ± 0.3	2.5 ± 0.2	NS
T5	2.5 ± 0.2	3.3 ± 0.2	.016
T6	2.7 ± 1.0	3.3 ± 0.3	.024
T7	3.1 ± 0.6	3.2 ± 1.0	NS

*Data are presented as the mean ± SD. The data for the 2 groups were analyzed by 2-way analysis of variance. IT indicates intensive insulin therapy; NS, not statistically significant; T3, after the termination of cardiopulmonary bypass (CPB); T4, 6 hours after CPB; T5, 12 hours after CPB; T6, 24 hours after CPB; T7, 48 hours after CPB.

Table 3. Inotropic Scores of the Patient Population following Surgery*

Time Point	Control Group (n = 50)	IT Group (n = 50)	*P*
T2	5.2 ± 3.6	4.2 ± 2.5	.011
T3	6.1 ± 3.5	4.6 ± 2.9	.012
T4	6.5 ± 3.6	4.8 ± 3.1	.004
T5	6.6 ± 3.5	5.0 ± 3.3	.005
T6	6.7 ± 2.8	4.9 ± 3.1	.002
T7	4.8 ± 3.1	3.9 ± 3.0	.017

*Data are presented as the mean ± SD. The data for the 2 groups were analyzed by 2-way analysis of variance. IT indicates intensive insulin therapy; T2, at the initiation of cardiopulmonary bypass (CPB); T3, after the termination of CPB; T4, 6 hours after CPB; T5, 12 hours after CPB; T6, 24 hours after CPB; T7, 48 hours after CPB.

Table 4. Postoperative Characteristics of the Patient Population*

Variable	Control Group (n = 50)	IT Group (n = 50)	*P*
Ventilation time, h	14.5 ± 4.8	10.2 ± 4.1	.021†
ICU stay, h	59.0 ± 5.5	46.7 ± 5.9	.011†
Postoperative hospital stay, d	10.9 ± 5.2	8.2 ± 4.3	.031†
Nosocomial wound infection, cases (%)	4 (8.00)	1 (2.00)	NS‡
Hospital deaths, n (%)	3 (6.00)	2 (4.00)	NS‡
Hypoglycemic events, n (%)	1 (2.00)	3 (6.00)	NS‡

*Data are presented as the mean ± SD. IT indicates intensive insulin therapy; ICU, intensive care unit; NS, not statistically significant.
†Student *t* test, or the Mann-Whitney *U* test when variances were not homogeneous.
‡χ^2 Test.

control and IT groups in mortality and in the rate of nosocomial infections of deep sternal wounds ($P > .05$; Table 4).

DISCUSSION

Many studies have confirmed that IT improves the prognosis of severe chronic diseases, especially cardiovascular disease [Lazar 2004; Taylor 2005]; however, reports pertaining to the impact of IT on nondiabetic patients undergoing valvular replacement are still lacking. In an effort to further clarify the best practice for managing this subgroup of patients, this study investigated the effects of IT on hyperglycemia, the inflammatory response, cardiac protection, and prognosis in nondiabetic patients undergoing heart valve replacement.

Among patients undergoing cardiac surgery with CPB, the trauma of the surgery itself may elicit a severe stress response that is accompanied by unsteadiness of artificial circulation, postoperative pain, and fever. These responses lead to disturbances in general metabolism and endocrine function, such as glucose intolerance and hyperglycemia [Rassias 2006]. Furnary and Wu [2006] indicated that prolonged hyperglycemia (>110 mg/dL) after open cardiac surgery was an independent risk factor for high mortality, infection of deep lesions, and longer hospitalizations. The application of IT, however, reduced the occurrence of these events, thereby ameliorating the prognosis of cardiac surgery in patients with diabetes [Furnary 2006]. A randomized controlled study performed by van den Berghe and colleagues [2001] revealed that if blood glucose is maintained at ≤110 mg/dL after administration of exogenous insulin, the morbidity and mortality of complications of patients in surgical ICU wards may decrease drastically, and the postsurgery times of mechanical ventilation and ICU stay may also decrease. Further evidence has suggested that a blood glucose concentration maintained at ≤110 mg/dL via IT improves the prognosis of coronary artery bypass grafting and decreases the incidence of re-ischemic events [Aebert 2000]. Our study found that when glucose was reasonably controlled in the IT group according to the criteria of van den Berghe et al in mixed surgical/medical ICU conditions, blood glucose levels were significantly higher in the control group after the initiation of CPB. Furthermore, use of IT with a large dose without obvious adverse effects and without modifying other therapy plans was found to attenuate the inflammation response considerably and to shorten ventilator times and the lengths of stay in the ICU and/or hospital.

CPB and the surgery itself cause a systemic inflammatory response [Asahara 1999; Ha 2002]. This inflammatory reaction and injury may contribute to the development of postoperative complications. Our study has shown that TNF-α, IL-1β, IL-6, and IL-10 levels were significantly increased in both the control and IT groups following the initiation of CPB; however, the levels of proinflammatory cytokines were

significantly lower in the IT group after the initiation of CPB, whereas those for the anti-inflammatory cytokines were significantly higher in the IT group after the termination of CPB. The mechanism may be as follows: First, hyperglycemia may promote the development of oxidative stress, whereas control of blood glucose could reduce oxidative stress [Tripathy 2003]. In addition, insulin may modify the metabolism of free fatty acids, thereby weakening proinflammatory effects to reduce the release of inflammatory mediators [Dandona 2002]. Therefore, IT may reduce proinflammatory mediators by reducing blood glucose and by decreasing the release of proinflammatory mediators [Koh 1998].

The intraoperative net troponin release is closely associated with ischemia time, which reflects the delayed recovery of left ventricular function and oxidative metabolism. Consequently, measurements of the net troponin release may be used as an indicator of the myocardial injury sustained during cardiac surgery with CPB [Collard 2001]. In our study, postoperative cTnI levels and the inotrope scores in the control group were significantly higher than those in the IT group. This finding implies that the myocardium injury in the IT group would be much less than in the control group, possibly indicating that the technique we used can alleviate myocardial injury in patients during heart valve replacement.

Although the application of cardioplegia is an effective strategy for myocardial protection, it does not completely eradicate myocardial ischemia—reperfusion and inflammatory injuries that contribute to the observed decrease in cardiac function. Reversible ischemia is largely characterized by a failure to resynthesize energy-rich phosphates (adenosine triphosphate) and to induce a proinflammatory state that promotes myocardial damage by reactive oxygen species generated during reperfusion [Das 2006a]. IT may attenuate the inflammation that occurs during cardiac surgery with CPB, although it could significantly improve the use of glucose and energy synthesis [Das 2006b]. This consideration underscores why IT could rescue myocardial injury occurring in patients during heart valve replacement.

A meta-analysis of 13,567 patients from 26 trials published in *CMAJ* by Griesdale et al [2008] has shown that IT does not decrease the overall mortality and significantly increases the risk for hypoglycemia with IT among critically ill patients. The study showed, however, that IT might be beneficial to patients admitted to a surgical ICU. Our study showed similar results, in that IT was able to attenuate the inflammatory response and alleviate myocardial injury in patients during heart valve replacement. There were no significant differences between the IT group and the control group, however, in the risk for hypoglycemia, the rate of nosocomial infections of deep sternal wounds, and hospital mortality. Even so, further studies are needed to specify the influence of IT on the rates of nosocomial infections and mortality.

In conclusion, IT applied from the commencement of surgery may control stress hyperglycemia, attenuate the systemic inflammatory response caused by the surgery and CPB, and help in protecting cardiac function. It does not, however, improve the rates of nosocomial infections and mortality in nondiabetic patients undergoing cardiac valvular replacement.

ACKNOWLEDGMENTS

This work was supported by grants from the National High Technology Research and Development Program of China (2006AA02A138), the National Natural Science Foundation of China (no. 30600137), and the Shaanxi Province of China (no. 2008DA07).

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