


CARDIOTHORACIC ANESTHESIOLOGY:

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High-Dose Insulin Therapy Attenuates Systemic Inflammatory Response in Coronary Artery Bypass Grafting Patients

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Background. Cardiac surgery with cardiopulmonary bypass (CPB) induces an acute phase reaction that is implicated in the pathogenesis of several postoperative complications. Studies have shown that proinflammatory cytokines are increased by acute hyperglycemia. Recent evidence suggests that insulin has antiinflammatory properties. Therefore, we hypothesized that high-dose insulin therapy would attenuate the systemic inflammatory response to cardiopulmonary bypass and surgery in coronary artery bypass patients while maintaining normoglycemia.

Methods. A total of 52 patients who presented for elective coronary artery bypass were randomized to receive intraoperative intravenous insulin infusion, titrated to maintain blood glucose concentrations less than 180 mg/dL (group I, n = 25), or receive intraoperative fixed high dose of intravenous insulin infusion (5 mU/kg/min) with dextrose 20% infused separately to main-

tain a blood glucose level between 70 and 110 mg/dL (group II, n = 27). Blood samples were collected at different time points to determine tumor necrosis factor α (TNF α), interleukin 6 and 8 (IL6 and IL8), and complement factor 3 and 4 (C3 and C4).

Results. Patients in both groups had similar preoperative characteristics. Patients in the high-dose insulin group had higher blood insulin concentrations and tighter blood glucose control. There were lower levels of IL6 (150 pg/dL vs 245 pg/dL, $p = 0.03$), IL-8 (49 pg/dL vs 74 pg/dL, $p = 0.05$), and TNF α (2.2 pg/dL vs 3.0 pg/dL, $p = 0.04$) in group II in the early postoperative period.

Conclusions. High-dose insulin therapy blunts the early postoperative surge in inflammatory response to CPB as reflected by decreased levels of IL6, IL8, and TNF α .

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Organ dysfunction after cardiac surgery is attributed in part to the systemic inflammatory response caused by high levels of cytokines released after surgical trauma and when blood is exposed to artificial surfaces during cardiopulmonary bypass (CPB) [1].

Furthermore, acute hyperglycemia frequently develops in patients undergoing coronary artery bypass grafting (CABG), usually after CPB [2], and it has been demonstrated in both rats and humans that proinflammatory cytokine concentrations are increased by acute hyperglycemia [3]. Prevention of the inflammatory response after cardiac surgery has been attempted using different strategies such as methylprednisolone, aprotinin, leukocyte depletion, and heparin-bonded circuitry, all with muted success or nondesired side effects [4].

Recent evidence from animal studies suggests that insulin has antiinflammatory properties [5]. Most of the previous studies on insulin therapy in cardiac surgery patients focused on its metabolic effects (ie, increasing glycogen content, decreasing free fatty acid levels, etc) [6] with inconsistent support of its beneficial effects. The results of these studies were difficult to evaluate due to inadequate study design, differences in protocols and inclusion criteria, lack of randomization, the time point of insulin application, and the primary endpoints assessed [7]. Interestingly, there was a trend toward more beneficial effects when glucose and insulin were given in high dosages [6]. We have previously described an insulin clamp technique, which demonstrated that high-dose insulin therapy is safe and effective in maintaining perioperative normoglycemia in CABG patients [8].

The objective of this study was to investigate the role of high-dose insulin therapy using the insulin clamp technique in elective CABG, and we hypothesized that intraoperative implementation of high-dose insulin therapy

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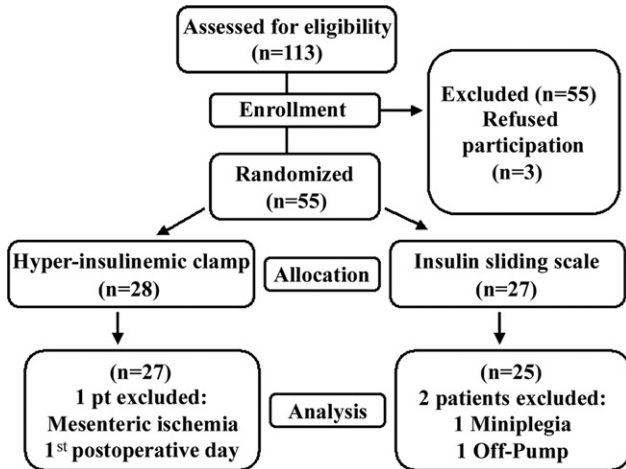


Fig 1. Patients' distribution flow chart.

used for tight glycemic control may have additional benefit of reducing the systemic inflammatory response to surgery and CPB.

Material and Methods

Study Design and Patient Enrollment

After obtaining approval from the Research Ethics Committee in our institution, an informed consent was obtained from all participants and the study was conducted according to the Declaration of Helsinki. All patients referred for elective CABG between June 2005 and July 2006 were assessed for eligibility. Among 113 patients assessed, 58 patients were excluded due to the presence of one or more of the exclusion criteria, which included the following: (1) emergency CABG; (2) redo CABG; (3) combined CABG and any other cardiac procedure; (4) preoperative use of steroids or nonsteroidal antiinflammatory drugs; and (5) any deviation from the protocol. The other 55 patients were randomized using computerized randomization tables (with blinded envelopes opened sequentially by study personnel after participants signed the patient consent form) into group I (the standard of care), and group II (the high-dose insulin therapy) (Fig 1).

Treatment Protocols

The study included both diabetic and nondiabetic patients. Administration of oral hypoglycemic agents in diabetic patients was discontinued 24 hours prior to surgery. Diabetic patients on insulin had their daily dose of insulin held the evening before surgery and a standard subcutaneous insulin sliding scale was started. Intraoperatively, group I received the standard of care using an intravenous insulin infusion titrated to maintain blood glucose level less than 180 mg/dL (<10 mmol/L) (Table 1). Blood glucose levels were checked every 30 minutes with the Accu-chek glucose monitor (Roche Diagnostics, Switzerland). As previously described [8], group II received a fixed dose of intravenous insulin infusion at 5 mU/kg/

minute. Dextrose 20% infused separately at a rate adjusted to maintain a BG of 70 to 110 mg/dL (4 to 6 mmol/L). Additional boluses of insulin were given if the blood glucose remains greater than 110 mg/dL (>6 mmol/L) with incremental 2 units of insulin for each 36 mg/dL (2 mmol/L) increase in blood glucose. Arterial blood glucose was measured every 5 to 10 minutes throughout the procedure. In both groups the protocol was started immediately on arrival to the operating room and stopped just before being transferred to the intensive care unit (ICU). Potassium intravenous boluses of 20 mEq were given to maintain potassium within the normal range. All patients had the same protocol for blood glucose management postoperatively, which consisted of continuous insulin infusion that is titrated to achieve a blood glucose level between 108 and 144 mg/dL (6 to 8 mmol/L).

Anesthetic Management

Preoperative sedation with 1 to 3 mg of lorazepam (by mouth) and oxygen was administered to patients on call to the operating room. All patients received prophylactic perioperative antibiotics (cefazolin 2 g preincision and 2 g post-CPB, or vancomycin 1 g preincision and 500 mg post-CPB if allergic to penicillin). The same anesthesiologist administered standardized total intravenous anesthesia using sufentanil, midazolam, and pancuronium. Immediately prior to CPB, heparin 400 IU/Kg was administered intravenously followed by additional doses, if necessary, to maintain an activating clotting time greater than 500 seconds. Protamine was administered as 1 mg/100 IU of the heparin dose after complete separation from CPB.

Surgical Procedure

All patients had CABG by the same surgeon with the use of CPB, which was conducted with a roller pump, and a membrane oxygenator. Temperature was allowed to drift with active rewarming at the end of CPB. Cardioplegia solution was free of glucose and consisted of high-dose (100 mEq/L) and low-dose (40 mEq/L) potassium used at the discretion of the cardiac surgeon. A single-clamp technique was used and cardioplegia was given in an antegrade fashion with blood in a ratio of 1:4. After rewarming and suturing of all anastomoses prior to the

Table 1. Intraoperative Intravenous Insulin Sliding Scale for the Standard Group

• If baseline blood glucose level > 180 mg/dL, start with a bolus of 2 units followed by insulin infusion at 2 units/hour.	
• Repeat blood glucose measurement every 30 minutes.	
• If blood glucose	Action
> 180 mg/dL	Increase infusion by 2 units/hour
> 108 and < 180 mg/dL	Maintain current infusion rate
< 108 mg/dL	Stop insulin infusion
< 72 mg/dL	Stop insulin infusion and administer 25 mL of Dextrose 50%

Maximum insulin infusion = 20 unit.

removal of the aortic cross-clamp “a hot shot” of 1 L of warm cardioplegia was administered.

Inflammatory Markers and Sampling Protocol

Inflammatory markers were studied including interleukin 6 and 8 (IL-6 and 8), tumor necrosis factor α (TNF α), and complement factor 3 and 4 (C3 and C4). These markers were collected preoperatively (on arrival to the operating room) and 0, 6, 24, and 48 hours postoperatively. Additionally, the levels of IL-6, IL8, and TNF α were measured intraoperatively at the following time points: prior to pericardiectomy (prior to heparin administration), before starting CPB and immediately after separation from CPB.

Low Systemic Vascular Resistance (SVR) State and Troponin Level

Given the limitations of the clinical criteria to define systemic inflammatory response syndrome (SIRS) in cardiac surgery patients, we used the indexed systemic vascular resistance (SVR_i) described by Kristof and colleagues [9] calculated by the following formula: SVR_i = (mean arterial pressure – central venous pressure) \times 80/cardiac index. These parameters were obtained preoperatively as well as 0, 4, 8, 12, and 16 hours postoper-

atively. A low SVR state was defined as SVR_i less 1,800 dyne/sec/cm⁵/m² at two consecutive hours. The duration and the total amount of vasopressor agents used in those patients to maintain a mean blood pressure greater than 60 mm Hg were collected. The temperature and white blood cell count (WBC) were measured at 0, 6, 24, and 48 hours corresponding to the same time points at which the samples for the inflammatory markers were collected. Troponin level was measured 4 hours postoperatively as an indicator of myocardial injury.

Statistical Analysis

The study was designed to compare the difference in the peak level of antiinflammatory markers as a primary outcome variable. The number of patients needed was calculated based on means and standard deviations obtained from other studies that measured antiinflammatory markers in cardiac surgery. In order to achieve a power level of 80%, with an alpha error of 5% and beta error of 20%, the number needed was 28 patients in each arm. Statistical analysis was performed using NCSS statistical software (2004) (NCSS, Kaysville, Utah). Continuous variables were compared using either the two-sample *t* test or the Wilcoxon rank sum test as appropriate by the distribution of data. Categorical variables were

Table 2. Demographic and Intraoperative Characteristics

Characteristics	Standard (n = 25) n (%)	High-Dose Insulin (n = 27) n (%)	<i>p</i> Value
Age (years)	67 \pm 2 ^a	62 \pm 2 ^a	0.09
Female	8 (32%)	7 (26%)	0.63
Diabetes mellitus	10 (40%)	11 (41%)	0.96
Hypertension	22 (88%)	21 (78%)	0.33
Hypercholesterolemia	21 (84%)	20 (74%)	0.38
Smoker	9 (36%)	11 (41%)	0.85
NYHA class:			
I	2 (8%)	0 (0%)	
II	7 (28%)	6 (22%)	0.19
III	15 (60%)	16 (59%)	
IV	1 (4%)	5 (19%)	
Ejection fraction	0.55 (0.50 – 0.60) ^b	0.55 (0.40 – 0.60) ^b	0.56
Left main disease	6 (24%)	7 (26%)	0.87
Myocardial infarction:			
Recent	3 (12%)	4 (15%)	0.77
Old	4 (16%)	5 (19%)	0.81
Atrial fibrillation	2 (8%)	1 (4%)	0.51
Peripheral vascular disease	1 (4%)	2 (7%)	0.60
Stroke	1 (4%)	0 (0%)	0.29
Asthma	2 (8%)	0 (0%)	0.13
Chronic obstructive pulmonary disease	2 (8%)	2 (7%)	0.94
Peptic ulcer disease	2 (8%)	3 (11%)	0.70
CPB time (minutes)	89 \pm 4 ^a	79 \pm 5 ^a	0.10
Aortic cross clamp time (minutes)	74 \pm 4 ^a	67 \pm 4 ^a	0.20
Number of grafts	3.5 \pm 0.2 ^a	3.1 \pm 0.2 ^a	0.10

^a Mean \pm standard error or the mean. ^b Median (95% confidence limits).

CPB = cardiopulmonary bypass; NYHA = New York Heart Association.

compared using the χ^2 test or Fisher exact test depending on the number of items in each group. Statistical significance for grouped data over time was ascertained using two-way analysis of variance. The statistical analysis was done using the “per-protocol” method and statistical significance was deemed present when p was less than 0.05.

Results

Demographic and Intraoperative Characteristics

Among 113 patients assessed for eligibility, 58 patients were excluded from the study; 3 patients refused, 4 patients were planned to be done off-pump, 19 redo cases, 25 combined procedures including CABG with aortic valve replacement, mitral valve replacement or repair, tricuspid valve repair, and ascending aortic replacement, 2 patients on steroids, and 5 patients on nonsteroidal antiinflammatory drugs. Of the remaining 55 patients enrolled in the study, 27 patients were randomized to the control group (standard; group I) and 28 patients to the high-dose insulin therapy group (clamp; group II). Two patients were excluded from the standard group intraoperatively; the first patient was done off-CPB due to calcification of the ascending aorta and in the second patient a nonstandard cardioplegia (miniplegia) was used. One patient was excluded from the clamp group postoperatively when he developed extensive mesenteric ischemia, which would have biased the level of inflammatory markers. Demographic data are shown in Table 2. The prevalence of diabetes mellitus was 40% (10 of 25) in the standard group and 41% (11 of 27) in the high-dose insulin group. There was 1 insulin-dependent diabetic patient in the standard group and 2 in the high-dose insulin group.

Intraoperative Blood Glucose and Insulin Level

The median average blood glucose level intraoperatively was 124 mg/dL (95% confidence limits [CL] = 108 and 137 [6.8 mmol/L {6 to 7.6}]) in the standard group, while it was 88 mg/dL (95% CL = 81 and 92 [4.8 mmol/L {4.5–5.1}]) in the clamp group ($p < 0.01$). Also, the standard group had lower median average intraoperative blood insulin level than the clamp group (90 μ mol/L [95% CL = 44 and 143] vs 3,720 μ mol/L [95% CL = 2,871 and 4,016], consequently $p < 0.01$). Both groups had similar blood levels of glucose and insulin on arrival to the operating room. However, the clamp group had significantly lower blood glucose levels and higher blood insulin levels (Fig 2) at all time points intraoperatively. The potassium measurements were similar between the two groups intraoperatively (5.3 ± 0.5 in the standard group vs 4.7 ± 0.5 in the clamp group). However, our threshold to replace potassium postoperatively in the first 24 hours was higher in the clamp group (<3.3 mmol/L) compared with the standard group (<4.0 mmol/L) due to the tendency of the potassium levels to increase spontaneously in the clamp group postoperatively.

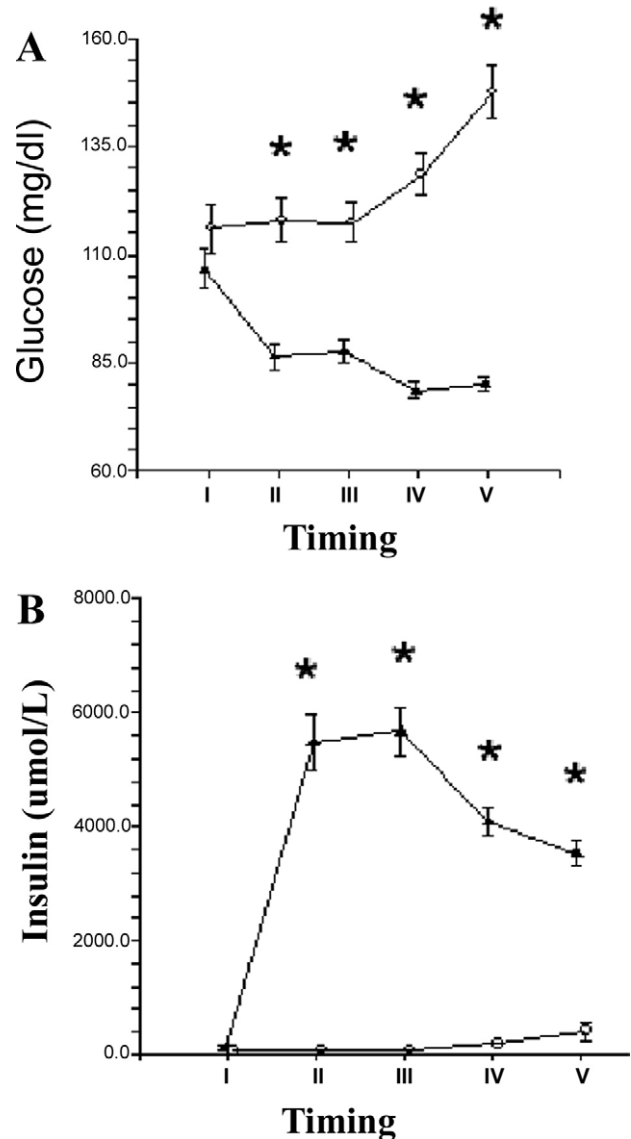


Fig 2. Intraoperative blood glucose and insulin levels. (A) Intraoperative blood glucose level. (B) Intraoperative blood insulin level. (* $p < 0.01$; black triangles represent the high-dose insulin group; white circles represent the standard group; Timing: I = immediately preoperatively, II = before pericardiotomy [heparin administration], III = immediately before CPB, IV = immediately after CPB, V = immediately postoperatively.)

Inflammatory Markers

There was no significant elevation of IL-6, IL-8, or TNF α in either group intraoperatively but started to rise significantly after separation from CPB. The peak level of IL-6 and IL-8 was reached 6 hours postoperatively while the peak level of TNF α was immediate postoperatively (Fig 3). In the clamp group there was significant reduction of the median peak level of IL-6 (150 pg/dL [95% CL = 127 and 340] vs 245 pg/dL [95% CL = 157 and 470], $p = 0.03$), IL-8 (49 pg/dL [95% CL = 33 and 63] vs 74 pg/dL [95% CL = 43 and 116], $p = 0.05$), and TNF α (2.2 pg/dL [95% CL = 1.9 and 3.7] vs 3.0 pg/dL [95% CL = 2.2 and 5.0], $p = 0.04$).

The levels of these markers decreased back close to their baseline level 24 to 48 hours postoperatively. Due to the exclusions made after the randomization, the actual power of the study for the peak level of inflammatory

markers compared was 77.8%, 76%, and 76.4% for IL-6, IL-8, and TNF α , respectively. There were no differences in the lowest C3 (standard C3 = 0.65 ± 0.04 , clamp C3 = 0.63 ± 0.04 , $p = 0.72$) and C4 levels (standard C4 = 0.12 [95% CL = 0.11 and 0.15], clamp C4 = 0.13 [95% CL = 0.11 and 0.18], $p = 0.37$) between the two groups. There was no difference in the postoperative temperature or WBC between the two groups at all time points.

Low SVR State and Troponin Level

Calculated SVR_i, as indicated in the method section above, was used to study the SVR status postoperatively. The lowest SVR status occurred 4 hours postoperatively with a median SVR_i = 1,901 dyne/sec/cm⁵/m² (95% CL = 1,506 and 2,171) in the standard group compared with 1,976 dyne/sec/cm⁵/m² (95% CL = 1,725 and 2,163) in the clamp group ($p = 0.72$). There was a tendency toward lower SVR status in the standard group at 8 and 12 hours postoperatively but it did not reach statistical significance. In the standard group, 10 out of 25 patients (40%) had low SVR state (SVR_i < 1,800) but it occurred in only 5 out of 27 patients (19%) in the clamp group ($p = 0.08$). Troponin I concentrations were measured in the arterial blood 4 hours postoperatively and were found to be significantly higher in the standard group at 7.5 ng/L (95% CL = 4.09 and 16.7 ng/L) compared with the high-dose insulin group at 4.3 ng/L (95% CL = 3.0 and 6.0 ng/L) ($p = 0.05$).

Postoperative Vasopressors Requirement

Norepinephrine was the only vasopressor agent used in all the study patients. Nineteen patients (76%) in the standard group required vasopressor support postoperatively, which was required for greater than 8 hours in 14 patients (56%). In the clamp group, 16 patients (59%) required postoperative vasopressor support and it was required greater than 8 hours in 11 patients (41%). Median duration of vasopressor support was equal to 9 hours (95% CL = 3 and 13) in the standard group compared with 7 hours (95% CL = 0 and 12) in the clamp group ($p = 0.46$). The mean total amount of vasopressor agent used was 28 μ g/minute (95% CL = 7 and 69) in the standard group compared with 21 μ g/minute (95% CL = 0 and 65) in the clamp group ($p = 0.51$).

Postoperative Complications

The incidence of postoperative complications was low and was similar between the two groups (Table 3). No patient in either group developed hypoglycemia intraoperatively or postoperatively.

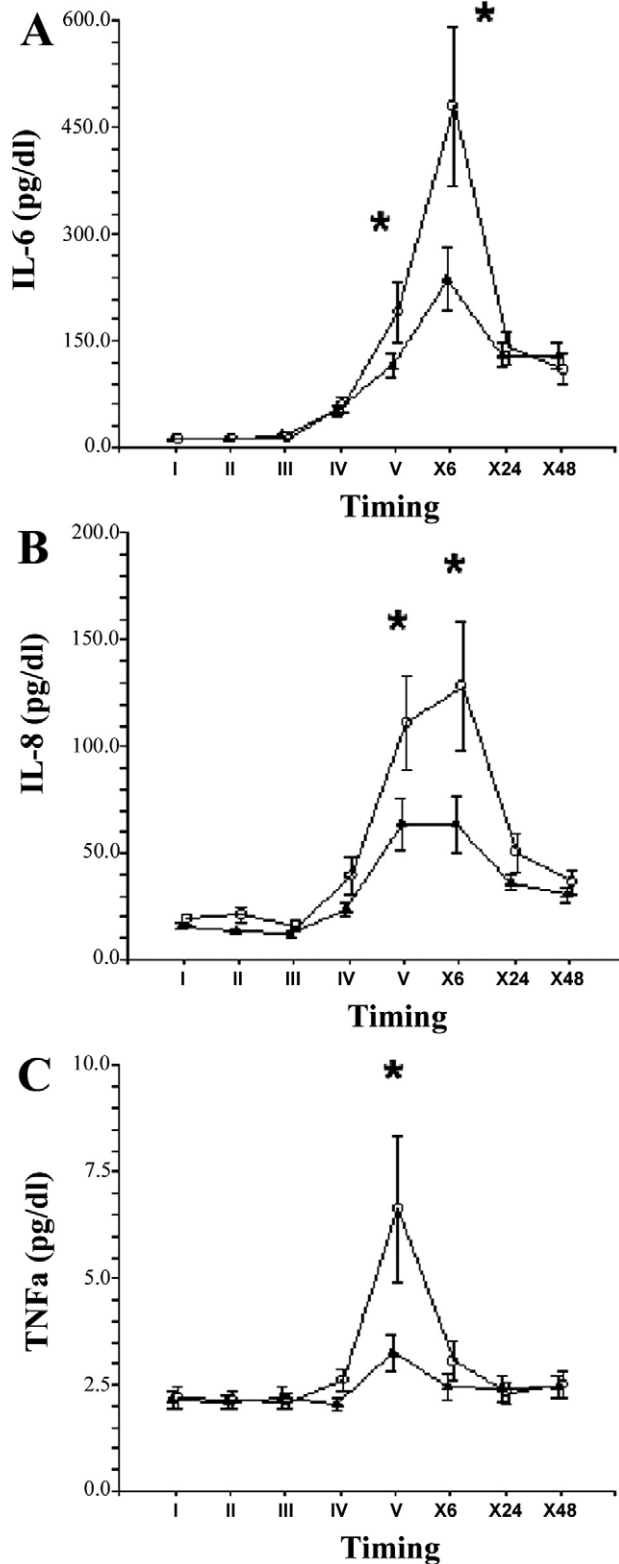


Fig 3. Perioperative level of (A) interleukin (IL)-6, (B) IL-8, and (C) tumor necrosis factor alpha (TNF α). (* $p < 0.05$, black triangles represent the high-dose insulin group; white circles represent the standard group; Timing: I = immediately preoperatively, II = before pericardiotomy (heparin administration), III = immediately before cardiopulmonary bypass (CPB), IV = immediately after CPB, V = immediately postoperatively; X6-X24-X48 = 6-24-48 hours postoperative, consequently.)

Table 3. Postoperative Complications

Characteristics	Standard (n = 25) n (%)	High-Dose Insulin (n = 27) n (%)	p Value
Perioperative myocardial infarction	1 (4%)	0 (0%)	0.30
Atrial fibrillation	4 (16%)	7 (26%)	0.38
Stroke	0 (0%)	0 (0%)	
Confusion	3 (12%)	1 (4%)	0.29
Acute renal failure	0 (0%)	0 (0%)	
Superficial wound infection	1 (4%)	1 (4%)	0.99
Gastrointestinal bleeding	0 (0%)	0 (0%)	
Length of intubation (hours)	16 ± 1 ^a	14 ± 1 ^a	0.41
Length of ICU stay (hours)	41 ± 7 ^a	40 ± 7 ^a	0.88
Length of hospital stay (days)	7 ± 1 ^a	8 ± 1 ^a	0.32
In-hospital mortality	0 (0%)	0 (0%)	

^a Mean ± standard error of the mean.

ICU = Intensive care unit.

Comment

Cardiac surgery, with or without CPB, is known to trigger a systemic inflammatory response of varying intensity leading clinically to a postperfusion syndrome characterized by fever, fluid accumulation in the interstitium, and low systemic vascular resistance [10, 11]. Proinflammatory cytokines are felt to be responsible for this response triggered by surgical trauma and CPB.

In our study we demonstrated that the use of the insulin clamp technique, which titrates glucose infusion to high fixed doses of insulin to maintain tight glucose control, reduces the systemic inflammatory response measured biochemically when compared with standard glucose control with insulin titrated to normoglycemic levels in both diabetic and nondiabetic patients. Although different glycemic ranges were achieved in the two groups, both ranges are considered normoglycemic ranges (100 to 150 mg/dL [5.6 to 8.3 mmol/L]) according to Portland protocol [12]. The antiinflammatory effect could have resulted from the high doses of insulin infusion in the clamp group or the tighter glycemic control achieved in the same group, or both. The separation of the two effects, although important, may be difficult but warrant further studies.

Rationale for Using Fixed High-Dose Insulin Therapy in Cardiac Surgery Patients

Doenst and colleagues [13] provided evidence that hyperglycemia is an independent predictor of perioperative morbidity and mortality in both diabetic and nondiabetic patients. Tight glycemic control in diabetic CABG patients improves perioperative outcomes, enhances survival, and decreases the incidence of ischemic events and wound complications, as illustrated in many studies [12, 14, 15].

The major concerns involving insulin therapy is the presence of insulin resistance (after ischemia and especially after cardiac surgery [16]), which is present in both diabetic and nondiabetic patients. Such insulin resistance may explain why protocols supplying low doses of insulin have failed to demonstrate significant beneficial effects [17]. It is not yet clear whether such whole-body insulin resistance translates to the heart. It is no secret that large amounts of insulin can be administered after cardiac surgery without significantly causing hypoglycemia [18] and studies using high doses demonstrated impressive reductions in mortality [19]. Additionally, the use of protocol titrating insulin infusions to maintain normoglycemia (like glucose-insulin-potassium [GIK] cocktail infusion) may cause severe disturbances in glucose homeostasis oscillating between hyperglycemia and hypoglycemia. Therefore, the use of a fixed high dose of insulin to maintain glucose homeostasis is a convincing concept. In our protocol, we implemented a new strategy of insulin therapy that is different from GIK solution (which titrates insulin infusion to the blood glucose level) by fixing the insulin infusion at a high concentration, while infusing dextrose to maintain a very tight glycemic control (known as insulin clamp), to stress the importance of hyperinsulinemia while maintaining normoglycemia. The study by Van den Berghe and colleagues [20] showed that in order for tight glucose control to be effective it has to be achieved for at least 5 days. We showed in this study that some beneficial effects could be achieved if the high-dose insulin infusion is started early intraoperatively. Whether it is the high-dose insulin that made the early difference or it is the prophylactic use intraoperatively before the damage is inflicted versus the therapeutic dose, as in the Van den Berge and colleagues study, will be an important question yet to be investigated. Gandhi and colleagues [21], from the Mayo Clinic College of Medicine, showed that intensive intraoperative insulin therapy is ineffective in reducing postoperative death and morbidity and it may even be harmful. However, the authors admitted that normoglycemia was not achieved intraoperatively. Additionally, the total amount of insulin infusion was not high and was even lower than the amount given postoperatively in the ICU in the same study. Our study focuses attention on the systemic effect of high-dose insulin infusion in addition to its effect in maintaining normoglycemia. We also considered measuring the blood insulin level rather than the amount of infused insulin to control for the naturally produced insulin.

Mechanism of Action of Insulin in Cardiac Surgery Patients

Insulin was initially used as a polarizing agent to promote electrical stability in the form of GIK solution [22]. The mechanistic focus shifted over the years toward insulin-induced changes in metabolism, but there is convincing evidence that the beneficial effects of insulin in cardiac surgery are multifactorial [6] and go far beyond simple metabolic benefits [23]. Yet, the exact underlying mechanisms remain unknown. We demonstrated in our

study that high-dose insulin therapy has an antiinflammatory effect post-CABG that may contribute to the beneficial effects of insulin therapy mentioned above. These antiinflammatory properties were demonstrated previously on animal studies and in trauma patients [5]. Visser and colleagues [24] showed that GIK applied as a hyperinsulinemic-normoglycemic clamp reduces postoperative C-reactive protein levels, but no difference was shown in the level of other inflammatory markers such as IL-6, IL-8, and TNF α , which was likely due to their sampling protocol that did not include the time at which these inflammatory cytokines reach their peak; 0 to 6 hours postoperatively, as we have shown in our study and supported by other studies as well [25]. Based on these findings we think that high-dose insulin therapy protocols have to start as early as possible preoperatively or immediately intraoperatively.

Significance of Increased Levels of Inflammatory Markers Post-CABG

Increased levels of proinflammatory cytokines have generally been associated with negative outcomes after cardiac surgery. Recent data allow us to better understand these effects. The IL-6 plays an important role during the acute-phase response. It stimulates the release of immune-competent proteins from the liver (like C-reactive protein) and together with TNF- α and IL-1 causes activation of T cells. The IL-8 is a proinflammatory cytokine released by cells, which has an important influence on the chemotactile activation of T cells and the endothelial barrier function of the endothelium, and has been recognized as a relevant mediator of organ dysfunction based on its major role of recruitment and activation of leukocytes seen in adult respiratory distress syndrome [26]. Interleukin-8 also seems to participate in myocardial ischemic injury. Indeed, a monoclonal antibody directed against IL-8 reduces myocardial ischemia-reperfusion injury [27] and the levels of IL-8 correlate positively with the levels of cardiac troponin I, suggesting a role for IL-8 in myocardial injury after cardiac surgery [28]. The TNF- α and IL-1 β synergistically depress human myocardial contractile function [29].

Study Limitations

Our study is a biochemical study and was not powered to detect clinical differences. We also included a relatively healthy cohort with a low-risk profile and we demonstrated a trend toward improved clinical markers of SIRS (ie, higher SVR status and lower vasopressor requirement). However, our study demonstrates a point of principle and a large clinical outcome trial is needed to confirm the clinical outcome of this novel therapy, which may even be more evident in high-risk groups (ie, patients with chronic renal failure, congestive heart failure, etc). We did not study the insulin resistance in our patients; therefore, whether diabetic patients would have different response to insulin than nondiabetics in terms of suppression of inflammatory response would need further study. The use of high-dose insulin therapy in our study was associated with a tighter control of blood

glucose level. Whether the antiinflammatory effect is related to one or both of these effects is not known yet and it may be very difficult to separate these effects.

Conclusion

High-dose insulin therapy blunts early postoperative surge in inflammatory response to surgery CPB as reflected by decreased levels of IL6, IL8, and TNF α . Early institution of this high-dose regimen intraoperatively is essential to achieve its antiinflammatory effect. Whether the high-dose insulin therapy has a direct antiinflammatory effect or an indirect effect through its tight glycemic control is still to be elucidated.

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INVITED COMMENTARY

Although it is well recognized that hypoglycemic and hyperglycemic conditions during cardiopulmonary bypass (CPB) can lead to untoward clinical outcomes, normoglycemia in this particular setting may still need to be better defined. In the current randomized study involving 52 patients undergoing coronary artery bypass grafting (CABG), Albacker and colleagues [1] demonstrated that maintaining a high blood insulin level perioperatively while maintaining the lower limit of normoglycemia could result in a reduced production of pro-inflammatory cytokines after CPB. Echoing with their previous observation [2], such treatment is associated with better myocardial protection as reflected by the lower postoperative release of cardiac troponin I.

Compared with the widely used glucose-insulin-potassium solution, which sometimes leads to hyperglycemia during CPB, the “insulin clamp” technique advocated by Albacker and colleagues [1] seems unique in that high-dose insulin can be safely delivered while maintaining normoglycemia. In addition, the authors are to be commended for demonstrating that high-dose insulin therapy may provide additional anti-inflammatory benefits independent of (or in combination with) tightly controlling blood glucose levels before, during, and after CPB. These observations are of interest and importance, but they do not eliminate the need for further investigation.

A potentially important concern of the current study, as acknowledged by the authors, is the lack of a proper measurement of insulin resistance, which is known to be positively linked with the release of pro-inflammatory

cytokines. Without thorough intergroup analysis of this particular issue, it is difficult to reach a solid conclusion. The heterogeneity among the patients recruited (ie, the presence or absence of diabetes mellitus and the mixed diabetic types of patients) can lead to different insulin resistance statuses. For instance, unlike the chronic insulin resistance typically seen in diabetic patients, acute insulin resistance in nondiabetic subjects, which occurs only during CPB, may not be predictive of poor outcomes after cardiac operations. Moreover, it has been revealed that diabetic myocardial metabolism carries some special characteristics. Hence, the clinical significance of high-dose insulin therapy for different patient subgroups can only be proven when the underlying mechanisms are completely understood.

Regarding myocardial injury after cardiac surgery, it has been proposed that pro-inflammatory cytokines such as interleukin (IL)-6 and IL-8 do not exert equally important effects. The current study would have provided more meaningful insights into the mechanisms involved if the authors had been able to simultaneously investigate some anti-inflammatory mediators, such as IL-10. In fact, careful evaluation of the anti-inflammatory profiles can always supply much food for thought. We and other investigators have noted that the release of IL-10 during CABG is often proportional to the levels of IL-8. Therefore, to focus all of one’s attention on *Yin* and ignore *Yang*, or vice versa, may well turn out not to be the best approach to take [3]. At the end of the day, maintaining a balance between the pro-inflammatory and anti-