Case Report

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Effect of different perioperative glycemic protocols in nondiabetic patients undergoing open heart surgery: a comparative study

Abstract

Introduction: Hyperglycemia during cardiac surgery is common due to stress response and cardiopulmonary bypass. Increased blood glucose is associated with poor outcomes, more complications and increased mortality in diabetic as well as nondiabetic patients due to negative effect on endothelial function, myocardium and inflammatory response. Perioperative blood glucose control and correct target value in cardiac surgery patients remain an ongoing controversy. This study was conducted to observe the effect of two different glycemic protocols in non-diabetic patients undergoing on pump cardiac surgery.

Materials and methods: A total of 102 non diabetic patients were randomly distributed into two groups: Group A, Group B. After induction a continuous insulin infusion at the rate of 0.1 unit/kg/hr was started in both groups when blood glucose level (BGL) was >140mg/dl in Group A and >180mg/dl in Group B. The infusion rate was adjusted to maintain BGL at 120-140mg/dl in Group A and 160-180mg/dl in Group B. BGL was measured at different points of time. Perioperative effects, requirement of cardiac drugs, insulin used and infection related complications were assessed.

Results: Finally data of 100 patients were analyzed. Rate of deep sternal wound infection [Group A:B= 3(6.12%):4(7.84%)] and other infection related complications were similar in both the groups ($p>0.05$). Length of ICU stay was significantly longer in Group B than Group A ($p=0.013$).

Conclusion: Perioperative infection rate in nondiabetic cardiac patients is not higher when Target blood glucose level is 160-180mg/dl as compared to120-140mg/dl. Though length of ICU stay is less in lower blood glucose group; perioperative morbidities and 30 day mortality is similar in both blood glucose range.

Keywords: nondiabetic, hyperglycemia, cardiac surgery, deep sternal wound infection

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Introduction

Perioperative hyperglycemia is a risk factor for morbidity and mortality. Hyperglycemia during cardiac surgery is associated with poor outcomes, more complications and increased mortality, not only in diabetic patients but also in patients who are not previously diagnosed as diabetics. In long back, it has been established that hyperglycemia is an independent risk factor for postoperative surgical wound infection.[1-3]

Stress response and cardiopulmonary bypass can induce profound hyperglycemia in cardiac surgery which provokes numerous deleterious effects on myocardium subjected to ischemia–reperfusion process. Myocardial infarct size is strongly correlated with blood glucose concentration.[4] Hyperglycemia causes impaired glucose transport into the myocardium, leads to the formation of advanced glycation end products (AGE) and its cell surface receptor (RAGE).[5] RAGE increases the inflammatory response by activating three key pro-inflammatory transcription factors which are normally suppressed by insulin: NFKB (nuclear factor), AP-1 (activated protein), and EGR-1 (early growth response).[6,7] Moreover, high blood glucose concentration abolishes ischemic preconditioning[4] and amplifies reperfusion injuries.[8] Because hyperglycemia provokes coronary endothelial dysfunction,[9,10] it may further increase the incidence of myocardial ischemic events. Hyperglycemia also directly affects pathways responsible for changes in endothelial function, inflammation and oxidative stress by altering the polyol pathway and increasing the synthesis of diacylglycerol which activates protein kinase-C.[11,12] The beneficial effects of glycemic control may be also related to the metabolic effects of insulin, including a decrease in concentration of free fatty acids and the scavenging of free radicals.[13]

Perioperative blood glucose control in cardiac surgery patients remains an ongoing controversy. Clinical trials have shown a reduction in morbidity with a lesser impact on mortality using tight blood glucose control.[14] Though previously it was thought that tight glycemic control during cardiac surgery is associated with decreased infection rates and improved survival,[15-18] benefit of tight blood glucose control have shown a negative impact on mortality due to hypoglycemia and contribute to the body of evidence disputing the need for tight blood glucose control.[19] Due to such conflicting results of these recent trials, the target blood glucose range for cardiac surgery patients is still not clearly defined. It is still a question whether rigorous perioperative glycemic control reduces death and morbidity in cardiac surgery patients. We shall compare the perioperative outcomes of two different glycemic protocols in non-diabetic patients undergoing on pump cardiac surgery.

Material and methods

After obtaining the institutional ethics committee approval and written informed consent from all patients, the study was conducted.

Inclusion criteria:

Non diabetic patient with NYHA functional status < IV of either sex, aged between 25-60 years scheduled for elective open heart surgery under cardiopulmonary bypass were included in this study.

Exclusion criteria:

Patients with Parsonnet score >10, on chronic steroid therapy, with history of diabetes mellitus, epilepsy, pregnant mother, hematological disease, impired hepatic, renal function and aortic cross clamp time more than 2 h were excluded from the study.

In the preanesthetic check-up, all patients were explained the procedure. All patients were instructed to follow the fasting guideline.

Angiotensin-converting enzyme inhibitor was suspended the day before surgery.

Calcium-channel antagonists and β-adrenergic blockers were continued till the morning of surgery. Patients of both the groups were premedicated with lorazepam 1 mg, ranitidine 150 mg, and metoclopramide 10 mg orally, the night before surgery. Patients were wheeled into operating room and standard ASA monitors (pulse oxymeter, NIBP till the IBP was done, ECG) were attached.

Lactated Ringers' solution was started through an intravenous line with 18 G intravenous (iv) cannula at the anterior aspect of right dorsum or forearm. All patients received piperacillin and tazobactum intravenously (iv) (4.5 gm). Arterial cannulation was established in the left radial artery under local anaesthesia.

Induction of Anaesthesia was done by IV inj of midazolam (0.01 mg/kg), fentanyl (2-3µg/kg) and sleep dose of thiopentone sodium till loss of eyelash reflex. Neuromuscular blockade was achieved by 1 mg/kg of rocuronium to facilitate rapid endotracheal intubation and intraoperative relaxation was maintained with rocuronium.

The lungs were ventilated with nitrous oxide in oxygen (50: 50). End-tidal CO2 was maintained between 35 and 40 mmHg throughout. Anaesthesia was maintained with isoflurane at 0.8 –1.0 minimal alveolar concentration. Pulmonary artery catheterization and central venous cannulation were performed thereafter and surgery was started. All the drugs were repeated as bolus, before incision, before sternotomy and every 30 minutes interval. Baseline ABG and pre-heparin activated clotting time (ACT) were checked.

In both groups blood glucose level was checked preoperatively and was evaluated after skin incision, after sternotomy, after cross clamp application, after cross clamp release and after return from CBP. Insulin infusion was started if any reading showed more value than the predetermined target blood glucose level. After starting of insulin infusion, blood glucose was checked at 30 minutes interval to maintain the target blood glucose range. ABG was done hourly to check acid base imbalance and electrolytes mainly K+ level and corrected accordingly. Urine output was also monitored.

Patients of Group A received insulin infusion at the rate of 0.1unit/kg/hr when blood glucose level >140mg/dl and the dose of insulin infusion was adjusted to maintain the blood glucose level 120-140mg/dl. Group B received insulin infusion at the rate of 0.1unit/kg/hr while blood glucose level >180mg/dl and the dose of insulin infusion adjusted to maintain the blood glucose level 160-180mg/dl after induction of anaesthesia. All patients received the routine drugs of GA along with vasoactive drugs if required. All the drugs were diluted/ dissolved in normal saline. The CPB circuit was primed with priming fluid Ringers' Injection and sodium bicarbonate, mannitol, and heparin. No dextrose containing fluid was used in the study. If any of the blood glucose value becomes <70 mg/dl, 25% dextrose solution was administered to the patient immediately. If two blood glucose reading >200 mg/dl even after increasing the dose of insulin infusion, it was considered as poor control. If consecutive three blood glucose level comes >200 mg/dl without responding to increasing insulin dose, it was considered as insulin resistance. Those patients were excluded from the study.

Heparin (400 units/kg) was administered before aortic purse string to achieve an ACT of > 480s before commencement of cardiopulmonary bypass. Hematocrit was maintained at 25% during CPB. Mild to moderate hypothermia was initiated. Myocardial protection was achieved by antegrade cold cardioplegia (at 4°C, St. Thomas' solution-based crystalloid-blood cardioplegic solution PLEGIOCARD as 1:4 ratio) after aortic cross clamp and the cardioplagia was repeated every 20 minutes. The cardiac repair or valve replacement was carried out under CPB with mild hypothermia using standard extracorporeal techniques. Nitroglycerine infusion 0.5µg/kg/min, adrenaline 0.05µg/kg/min and dopamine 5µg/kg/min were started at the onset of rewarming as per the institutional protocol. Infusion of milrinone, noradrenaline and amiodarone was also initiated according to the need to maintain mean arterial pressure >70mmHg, pulmonary artery pressure below 30mmHg and normal sinus rhythm. All the patients were rewarmed to 37°C. Serum potassium levels were optimized to 4-4.5 mEq/L throughout surgery.

Ventricular fibrillation (VF) or ventricular tachycardia (VT) was treated with inj Xylocard (1.5mg/kg), $MgSO_4$ (2gm), amiodarone (3mg/kg) as appropriate and in cases refractory to medical management internal defibrillation with 20-50 J was administered. Protamine sulphate 1.3 times the heparin dose was given to reverse the effect of heparin and return the activated clotting time to within 20% of the preoperative value.

At the end of surgery, patients were shifted to the intensive care unit (ICU). In the post operative period, blood glucose was evaluated hourly for first 6 hours and then 2 hourly for next 18 hours. The adverse events like cardiac morbidity, new onset arrhythmia, hypoglycaemia, electrolyte imbalance, bleeding, infections, acute renal failure was noted and managed accordingly.

Statistics

For the purpose of sample size calculation, the frequency of infection in the study group was considered as the primary outcome measure. It was estimated that 49 subjects would be required per group in order to detect a reduction of one third in the frequency of infection assuming that the rate in the control group would be 36% on the basis of earlier study.[8] This sample size was provided with 80% power and at 5% probability of type I error. Considering 10% drop out, we had included 110 patients (55 patients in each group) in this study. Statistical Analysis was done using standard statistical software Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001] and Graph Pad Prism version 5. Haemodynamic parameters and other variables normally distributed values were analysed by Student's unpaired t test. Mann-Whitney U test was used for variables which were not normally distributed. Categorical variables were compared between groups by Fischer's exact test. All analysis was two-tailed and a p-value <0.05 was considered as statistically significant.

Results

The study was conducted in 102 patients 51 in each group according to a computer generated randomization chart. Two patients

in Group A were excluded because of aortic cross clamp time more than 2 hours. So, data of remaining 100 patients were finally analyzed [Group A (n=49), Group B (n=51)].

Postoperative infection rate in terms of deep sternal wound infection, UTI, sepsis, RTI, culture positive ETT tip, arterial catheter, CV catheter, pulmonary artery catheter, urinary catheter and positive sternal wound swab are found to be similar in both the groups ($p>0.05$) (Table 1). In the intraoperative period blood glucose level was estimated after skin incision, after sternotomy, after CPB on, after Axcl on and off, after weaning of CPB. After skin incision blood glucose level was similar in both the groups ($p=0.544$). However, it was significantly high ($p<0.05$) in Group B throughout the intraoperative period to maintain the target glucose level as per protocol (Figure 1).

Table 1 Postoperative infections in between two groups

Infections	Group A (n=49)	Group B (n=51)	*p* value*
Deep sternal wound infection	3(6.12%)	4(7.84%)	1.000
UTI	1(2.04%)	2(3.92%)	1.000
Sepsis	2(4.08%)	3(5.88%)	1.000
RTI	5(10.20%)	5(9.80%)	1.000
Culture positive ETT tip	2(4.08%)	0(0.00%)	0.238
Culture positive arterial catheter tip	1(2.04%)	1(1.96%)	1.000
Culture positive central venous catheter tip	1(2.04%)	2(3.92%)	1.000
Culture positive pulmonary artery catheter tip	1(2.04%)	1(1.96%)	1.000
Culture positive sterna wound swab	3(6.12%)	4(7.84%)	1.000
Culture positive urinary catheter tip	1(2.04%)	2(3.92%)	1.000

Values represent numerically and in percentage. *$p<0.05$ is statistically significant. UTI, Urinary tract infection; RTI, Respiratory tract infection; ETT, Endotracheal tube

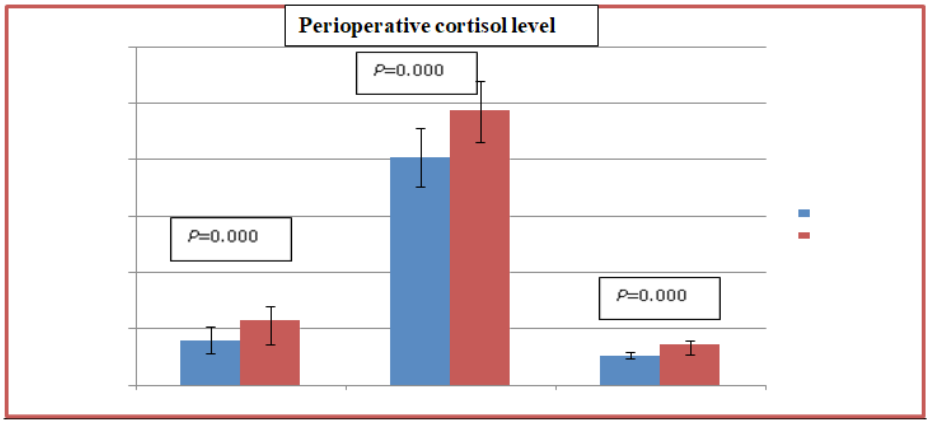

Figure 1 Perioperative cortisol level.

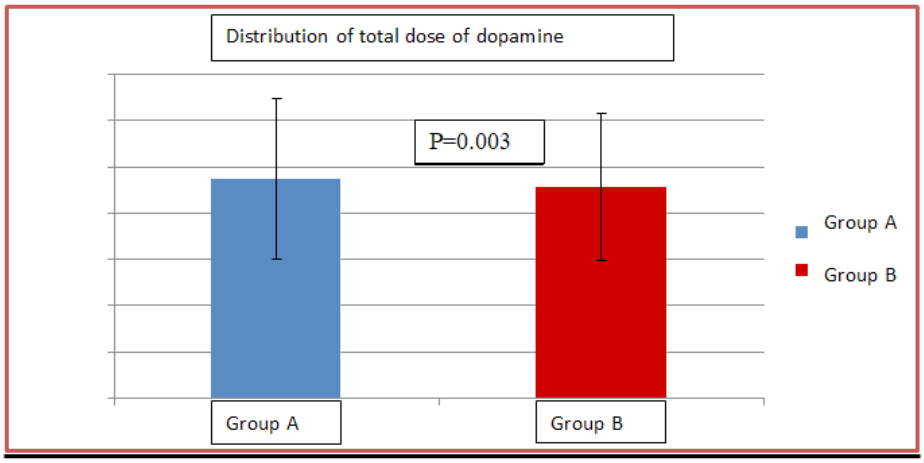

Figure 2 Distribution of total dose of dopamine.

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Total requirement of insulin was significantly high in Group A (p=0.000) as compared to Group B to maintain predetermined blood glucose level (Table 2). However, the incidence of hypoglycemia was not significant in between the groups. Only 2 patients (4.08%) in Group A and 1 patient (1.96%) in Group B suffered from hypoglycemia in the postoperative period which is neither statistically (p=0.614) nor clinically significant.

Requirement of dopamine and other cardiac drugs are found to be similar (p>0.05) in both the groups as shown in Table 3.

Length of ICU stay was significantly longer in Group B as compared to Group A (p=0.013) though duration of surgery and time for extubation were similar in both the groups (p>0.05) (Table 4). Patient profile (age, weight, height, sex, BSA) was comparable between the groups (Table 5).

Table 2 Requirement of Insulin

Total requirement of insulin (unit)	Group A (n=49) (Mean ± SD)	Group B (n=51) (Mean ± SD)	*p* value*	t-value
	100.14±13.46	83.47±10.81	0.000	6.844

Values represent mean±SD. *p<0.05 is statistically significant. SD, Standard deviation

Table 3 Comparison of cardiac drugs requirement

	Group A (n=49) (Mean ± SD)	Group B (n=51) (Mean ± SD)	*p* value*	t-value
Total Dopamine (mg)	236.69±86.83	220.12±72.45	0.302	1.04
Total adrenaline(mg)	2.57±2.25	3.59±3.41	0.082	1.758
Total NTG(mg)	25.29±10.50	29.8±14.47	0.079	1.778

Values represent mean±SD. *p<0.05 is statistically significant. NTG, Nitroglycerin; SD, Standard deviation

Table 4 Comparison of perioperative events

	Group A(n=49) (Rank Sum)	Group B(n=51) (Rank sum)	*p* value*	U	Z
Duration of surgery(hour)	2456.00	2594.00	0.899	1231.00	-0.128
Time for extubation(hour)	2569.00	2480.00	0.899	1154.500	0.655
Length of ICU stay (day)	2114.500	2935.500	***0.013***	889.5	-2482

Values represent in sum. *p<0.05 is statistically significant. ICU, Intensive care unit

Table 5 Patient profile of two groups

	Group A (n=49) (Mean ± SD)	Group B (n=51) (Mean ± SD)	*p* value*	t-value
Age (year)	39.51±8.92	36.51±8.82	0.059	1.911
Body weight (Kg)	59.10±7.71	58.25±7.47	0.578	0.558
Sex (Male :Female)#	27:22	29:22	1.000	_
BSA (m^2)	1.61±0.123	1.61±0.117	0.947	-0.067
Height (cm)	159.45±6.46	161.69±6.47	0.087	-1.730

Values represent mean±SD except sex. *p<0.05 is statistically significant. BSA, Body surface area; SD, Standard deviation

Discussion

Post sternotomy mediastinitis and deep sternal wound infection in cardiac surgery patients increases operative mortality two to threefold due to hyperglycemia.[20] Despite recent advances in the prevention of the long-term sequelae of hyperglycemia,[21] the reduction of acute infectious problems related to surgical trauma has been elusive. Perioperative hyperglycemia has been established as an independent risk factor for postoperative surgical wound infection. The surgical stress response and concomitant inflammation augment perioperative blood glucose concentrations.[22] "Stress hyperglycemia" is exacerbated by factors specific to cardiopulmonary bypass including heparin administration, hypothermia and administration of glucose-containing cardioplegic solutions.[23-25] Other factors include increased renal absorption of glucose, increased substrate availability in the form of lactate and decreased exogenous insulin activity.[26] Perioperative hyperglycemia itself induces inflammation and expression of proinflammatory cytokines.[27]

We have selected continuous insulin infusion (CII) rather than intermittent bolus dose.

CII provides better control of perioperative blood-glucose level in patients than does conventional intermittent injection of insulin. In 2006 Li JY and coworkers[28] reported the advantages of continuous infusion as they found that on the 1st and 2nd postoperative days, the mean value for the CII group was significantly lower than that for

the glucometer guided injection of insulin (GGI) group. Use of the strategy of continuous infusion of insulin, in our study translated into faster attainment of adequate glucose control in both the groups.

In our study in Group A the requirement of total insulin was much higher (100.14±13.46 unit) as compared to Group B (83.47±10.81 unit) (p=0.000). This is because of relatively strict target blood glucose control (120-140mg/dl) in Group A than Group B (160-180mg/dl). Preoperative creatinine level was measured to rule out renal dysfunction as it is important to identify all patients with abnormal renal function since the risk for hypoglycemia is increased in all these patients.[29-31] Lazar et al.[32] in 2011 stated fewer episodes of hypoglycemia and no major differences in adverse events in diabetic cardiac surgery patients with a blood glucose goal of 120- 180 mg/dl compared to 90-120 mg/dl. The results of the present study is also consistent with the result of a randomised controlled trial by Desai et al.[33]56 (2012) who reported that liberal glycemic control (121-180 mg/dl) in coronary artery bypass graft patients was associated with less hypoglycemia and was not inferior compared to strict glycemic control.

In this present study total requirement of cardiac drugs were similar in both groups (p>0.05).

In a retrospective review conducted by McAlister and coworkers[34] it has been demonstrated that an increase of 1 mmol/l (or 18 mg/dl) of glucose on the 1st postoperative day was associated with a 17% increase in the risk of adverse outcomes in terms of infection rate. Furnary and colleagues[35] found a significant impact on the risk of postoperative deep sternal wound infection.

Our study reported that there is no added benefit when blood glucose level is maintained in the range of 120-140mg/dl as compared to conventional blood glucose level (160-180mg/dl). In this study the difference in incidence of other infections like UTI (p=1.000), RTI (p=1.000), other catheter site infections (p>0.05), sepsis (p=1.000) were not found to be significant in two glycemic groups.

Perioperative electrolytes are comparable in between groups and the incidence of perioperative arrhythmias in terms of atrial fibrillation, ventricular tachycardia, ectopic beats were also similar in patients of Group A and Group B [VT (p=0.264), AF (p=0.438), Ectopic beats (p=0.715)]. Postoperative electrolytes Na+ (p=0.434), K+ (p=0.371), Ca++ (p=0.803) were similar in both the groups.

This study shows that two different glycemic protocol has no added advantage over other on time for extubation (p=0.899) and 30 days mortality (p=1.000) after open heart surgery. However the ICU stay was significantly less in Group A (p=0.013) as found previously in many studies.

Limitations of our study

One of the most important limitations of our study is that we could not measure the plasma concentration of insulin. Thereby patients may suffer from hyperinsulinemic normoglycemia which has adverse effect on neurocognitive function and can cause perioperative delirium. If measured, it might have also corrected the possibility of inter-individual variability. We could not achieve a continuous monitoring of blood glucose level in the perioperative period; rather we have measured glucose level only in certain points of time. Thereby we do not know whether the smooth targeted blood glucose levels in two groups were maintained or not as we are totally unaware of peaks and troughs of blood glucose levels if any, in perioperative period. If measured, it would also help to comment on infection rates between the groups perfectly. We could not measure other stress factors which might have influence on blood glucose level.

Conclusion

Perioperative infection rate along with perioperative morbidities and 30 day mortality in non diabetic patients undergoing open heart surgery under cardiopulmonary bypass with targeted blood glucose level 120-140mg/dl is same with target level 160-180mg/dl though requirement of total dose of dopamine and length of ICU stay and cortisol level were less in those patients with target blood glucose level of 120-140mg/dl.

References

1. Gadaleta D, Risucci DA, Nelson RL, et al. Effects of morbid obesity and diabetes mellitus on risk of coronary artery bypass grafting. *American Journal of Cardiology.* 1992;70:1613–1614.
2. Grossi EA, Esposito R, Harris LJ, et al. Sternal wound infections and use of internal mammary artery grafts. *Journal of Thoracic & Cardiovascular Surgery.* 1991;102(3):342–346.
3. Lilienfeld DE, Vlahov D, Tenney JH. Obesity and diabetes as risk factors for postoperative wound infections after cardiac surgery. *American Journal of Infection Control.* 1988;16(1):3–6.
4. Kersten JR, Toller WG, Gross ER. Diabetes abolishes ischemic preconditioning: Role of glucose, insulin and osmolality. *Am J Physiol.* 2000;278:1218–1224.
5. AM Schmidt, SD Yan, J L Wautier. Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. *Circulation Research.* 1999;84(5):489–497.
6. H Vlassara. Recent progress in advanced glycation end products and diabetic complications. *Diabetes.* 1997;46: S19–S25.
7. P Dandena, A Algada, P Mohauty, et al. Insulin inhibits intranuclear nuclear factor kappa B and simulates 1 kappa B in mononuclear cells in obese subjects: evidence for anti–inflammatory effect. *The Journal of Clinical Endocrinology and Metabolism.* 2001;86:3257–3265.
8. Verma S, Maitland A, Weisel RD, et al. Hyperglycemia exaggerates ischemia–reperfusion–induced cardiomyocyte injury: Reversal with endothelin antagonism. *J Thorac Cardiovasc Surg.* 2002;123(6):1120–1124.
9. Koltai MZ, Hadhazy P, Posa I, et al. Characteristics of coronary endothelial dysfunction in experimental diabetes. *Cardiovasc Res.* 1997;34:157–163.
10. Gross ER, LaDisa JF, Weihrauch D, et al. Reactive oxygen species modulate coronary wall shear stress and endothelial function during hyperglycemia. *Am J Physiol.* 2003; 284:1552–1559.
11. B Guerci, P B¨ohme, A Kearney–Schwartz, et al. Endothelial dysfunction and type 2 diabetes. Part 2: altered endothelial function and the effects of treatments in type 2 diabetes mellitus. *Diabetes and Metabolism.* 2001;27:436–447.
12. JY Park, N Takahara, A Gabriele, et al. Induction of endothelin–1 expression by glucose an effect of protein kinase C activation. *Diabetes.* 2000;49(7):1239–1248.
13. Hess ML, Okabe E, Poland J. Glucose, insulin, potassium protection during the course of hypothermic global ischemia and reperfusion: A new proposed mechanism by the scavenging of free radicals. *J Cardiovasc Pharmacol.* 1983;5(1):35–43.
14. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006;354(5):449–461.

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15. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac *Cardiovasc Surg.* 2003;125:1007–1021.

16. Ouattara A, Lecomte P, Le Manach Y, et al. Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. Anesthesiology. 2005;103(4):687–694.

17. Gandhi GY, Nuttall GA, Abel MD, et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. *Mayo Clin Proc.* 2005;80(7):862–866.

18. Doenst T, Wijeysundera D, Karkouti K. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg.* 2005;130(4):1144.

19. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360(12):1283–1297.

20. Zerr KJ, Furnary AP, Grunkemeier GL, et al. Glucose control lowers the risk of wound infection in diabetics after open heart operations. *Annals of Thoracic Surgery.* 1997;63(2):356–361.

21. Anonymous. The effect of intensive treatment of diabetes on the development and progression of long–term complications in insulin–dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *New England Journal of Medicine.* 1993;329(14):977–986.

22. Thorell A, Nygren J, Ljungqvist O. Insulin resistance: A marker of surgical stress. *Curr Opin Clin Nutr Metab Care.* 1999;2(1):69–78.

23. Lee KU, Lee HK, Koh CS. Artificial induction of intravascular lipolysis by lipid–heparin infusion leads to insulin resistance in man. *Diabetologia.* 1988;31:285–290.

24. Lehot JJ, Piriz H, Villard J, et al. Glucose homeostasis. Comparison between hypothermic and normothermic cardiopulmonary bypass. *Chest.* 1992;102(1):106–111.

25. Werb MR, Zinman B, Teasdale SJ, et al. Hormonal and metabolic responses during coronary artery bypass surgery: Role of infused glucose. *J Clin Endocrinol Metab.* 1989;69(5):1010–1018.

26. Carvalho G, Moore A, Qizilbash B, et al. Maintenance of normoglycemia during cardiac surgery. *Anesth Analg.* 2004;99(2):319–324.

27. Lefèbvre PJ, Scheen AJ. The postprandial state and risk of cardiovascular disease. *Diabet Med.* 1998; 15(suppl 4):S63–S68.

28. Li JY, Sun S, Wu SJ. Continuous Insulin Infusion Improves Postoperative Glucose Control in Patients with Diabetes Mellitus Undergoing Coronary Artery Bypass Surgery. *Tex Heart Inst J.* 2006;33(4):445–451.

29. P. Varghese, V. Gleason, R. Sorokin, C. Senholzi, S. Jabbour, and J. E. Gottlieb.Hypoglycemia in hospitalized patients treated with antihyperglycemic agents. Journal of Hospital Medicine.2007; 2**:** 234–240.

30. M. Kosiborod, S. E. Inzucchi, A. Goyal et al., "Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. The Journal of the American Medical Association2009; 301:1556–64.

31. D. J. Rubin, D. Rybin, G. Doror et al. Weight–based, insulin dose–related hypoglycemia in hospitalized patients with diabetes. Diabetes Care.2011; 34**:**1723–8.

32. Lazar HL, McDonnell M, Chipkin SR et al. Effects of aggressive versus moderate glycemic control on clinical outcomes in diabetic coronary artery bypass graft patients. Ann Surg. 2011; 254:458–63.

33. Desai SP, Henry LL, Holmes SD et al. Strict versus liberal range for perioperative glucose in patients undergoing coronary artery bypass grafting: a prospective randomized controlled trial. J Cardiovasc Surg. 2012;14:318–25

34. McAlister FA, Man J, Bistritz L, Amad H, Tandon P. Diabetes and coronary artery bypass surgery: an examination of perioperative glycemic control and outcomes. Diabetes Care 2003;26:1518–24

35. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg. 1999;67:352–62