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Relationship between Nadir Hematocrit during Cardiopulmonary Bypass and Postoperative Hyperglycemia in Nondiabetic Patients

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ABSTRACT

Background: Hyperglycemia is common after cardiac surgery in both diabetic and nondiabetic patients and is associated with increased morbidity and mortality. Association between nadir hematocrit levels on cardiopulmonary bypass (CPB) and postoperative hyperglycemia is not clear. This study was carried out to determine the relationship between nadir hematocrit during CPB and postoperative hyperglycemia in nondiabetic patients.

Methods: Records of 200 nondiabetic patients undergoing coronary artery bypass grafting operation were retrospectively reviewed. In the first analysis, patients were divided into two subgroups according to the presence or absence of hyperglycemia. Further analysis was made after dividing the patients into 3 subgroups according to nadir hematocrit levels on CPB (less than 20%; 20% to 25%; greater than or equal to 25%).

Results: Compared to patients without hyperglycemia, patients with postoperative hyperglycemia had significantly lower preoperative hematocrit levels (p = 0.004) and were associated with lower nadir hematocrit levels during CPB (p= 0.002). Peak intensive care unit blood glucose levels and number of blood transfusions were significantly higher in patients with nadir hematocrit levels less than 20. ($p<0.001$ and $p<0.001$ respectively). Logistic regression analysis demonstrated that nadir hematocrit levels less than 20% (OR 2.9, p=0.009) and allogenic blood transfusion (OR 1.5, p=0.003) were independently associated with postoperative hyperglycemia.

Conclusions: Nadir hematocrit levels on CPB less than 20% and allogenic blood transfusions were independently associated with postoperative hyperglycemia in nondiabetic patients. Patients with a nadir hematocrit levels less than 20 % during CPB should be closely monitored for hyperglycemia in the perioperative period.

INTRODUCTION

Hyperglycemia is common after cardiac surgery in both diabetic and nondiabetic patients [Estrada 2003; Furnary 2003]. Hyperglycemia has been shown to be an independent risk factor for postoperative morbidity, mortality, and prolonged hospital stays after cardiac surgery both in patients with and without diabetes mellitus [van den Berghe 2006; McAlister 2003; Ouattara 2005; Doenst 2005]. Thus, the identification of factors associated with postoperative hyperglycemia are crucial for prevention of hyperglycemia, and predicting postoperative hyperglycemia may have potentially important clinical implications.

Preoperative patient characteristics, acute stress due to surgery, and perioperative events are associated with hyperglycemia after cardiac surgery [Garg 2013]. Major surgical trauma stimulates cortisol, catecolamines, and glucagon secretion and leads to tissue insulin resistance and hyperglycemia [Thorell 1999; McLaughlin 2003]. Cardiopulmonary bypass (CPB) has been shown to exacerbate inflammatory response, insulin resistance, and hyperglycemia induced by surgical stress. The use of CPB during coronary artery bypass grafting (CABG) surgery has been reported to be the foremost cause of perioperative hyperglycemia after cardiac surgery [Anderson 2005; Rassias 2002].

The nadir hematocrit levels on CPB is a known risk factor for morbidity and mortality in patients undergoing cardiac surgery [Ranucci 2006; Karkouti 2005a; Habib 2005]. Nadir hematocrit during CPB has been associated with renal [Karkouti 2005; Habib 2005; Swaminathan 2003] and neurologic injury [Karkouti 2005b], low cardiac output syndrome, need for intraaortic balloon pump support, and return to bypass after attempted separation [DeFoe 2001]. However, to the best of our knowledge, none of these studies evaluated the relationship between nadir hematocrit levels on CPB and postoperative hyperglycemia in nondiabetic patients.

The relationship between nadir hematocrit levels on CPB and postoperative hyperglycemia remains unclear. This study was carried out to determine the relationship between nadir hematocrit during CPB and postoperative hyperglycemia in nondiabetic patients. To the best of our knowledge the present study is the first to examine the association between nadir hematocrit during CPB and postoperative hyperglycemia.

MATERIALS AND METHODS

Study Population

The present study was approved by the local ethics committee and complies with the requirements of the Declaration of Helsinki. We retrospectively reviewed the clinical records of patients who underwent elective first-time on-pump

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CABG surgery in our hospital between 2011and 2014 for coronary artery disease.

The exclusion criteria were as follows: (1) patients who received glucogenic drugs in the perioperative period; (2) obesity; (3) patients with diabetes mellitus; (4) patients with other endocrinological disorders; (5) patients with elevated levels of HbA1C (6) emergent surgery; (7) redo-CABG; (8) off-pump CABG; (9) chronic kidney and hepatic diseases; (10) chronic heart failure; (11) reduced myocardial function; (12) severe systemic illness; (13) malignant tumors; (14) acute or chronic infections; (15) postoperative myocardial infarction (MI); (16) patients with perioperative hemodynamic instability. All patients underwent surgery after an overnight fast of at least 8 hours. The nadir hematocrit level on bypass was defined as the lowest hematocrit level throughout the CPB.

Anesthesia

The following premedication was administered: 10 mg diazepam, p.o. was given to all patients on the night prior to operation and 0.1 mg/kg morphine HCl was administered i.m. half an hour before the operation. Anesthesia was induced with intravenous fentanyl 5μg/kg to 10μg/kg, midazolam 0.1 mg/kg, rocuronium bromide 0.6-0.8 mg/kg; was maintained with fentanyl 1μg/kg/h to 2μg/kg/h, rocuronium bromide 0.3 mg/kg/hour; and was supported with inhalation of 1% to 2% sevoflurane.

Management of Cardiopulmonary Bypass

All procedures were performed with median sternotomy. Standard non-pulsatile CPB with a roller pump (stroker) and a membrane oxygenator was used. The extracorporeal system was primed with ringer lactate. CPB was established between the ascending aorta and right atrium using dual-stage venous cannula. Prior to the cannulation, 300-400 U/kg heparin sulphate was administered to every patient in order to maintain ACT values above 480 seconds. During CPB, nonpulsatile pumpflow was kept at 2.2 L/m^2/min to 2.5 L/m^2/min. Cold blood cardioplegia was used in all patients. Core temperature was cooled to 28°C. Alpha-stat strategy was used for pH management, and all patients were kept at normocapnic levels ($PaCO_2$ = 35 mmHg to 45 mmHg). Concentrated erythrocyte suspensions were added to pump prime volume if required to keep the hematocrit levels above 20% during CPB. Mean arterial pressure during CPB was stabilized between 50 mmHg and 70 mmHg.

Blood Glucose Levels

In all patients, blood glucose levels were measured by an automated analyzer (Radiometer ABL-90 FLEX) every two hours during the first 24 hours after admission to the postoperative intensive care unit (ICU). When clinically indicated, additional blood samples were taken. From ICU charts, peak glucose levels were identified for each patient. Hyperglycemia was managed with intravenous insulin infusion. Hyperglycemia was defined as blood glucose level ≥200 mg/dL.

Statistical Analysis

Statistical analysis was conducted using SPSS for Windows version 17 (SPSS, Chicago, IL, USA). All variables were investigated using visual (histograms, probability plots) and analytic methods (Kolmogorov-Smirnov test) to determine whether or not they were normally distributed. Continuous variables were reported as means and standard deviation for normally distributed variables, and as medians and interquartile range (IQR) for the non-normally distributed variables. Categorical variables were presented using numbers and percentages.

In the first analysis, patients were divided into two subgroups according to the presence or absence of postoperative hyperglycemia. Comparison between the two groups was performed using the χ^2 test for qualitative variables, independent *t* test for normally distributed continuous variables, and Mann-Whitney *U* test for non-normally distributed continuous variables. Further analysis was performed to analyze the influence of nadir hematocrit levels on postoperative hyperglycemia. For this purpose, patients were divided into 3 subgroups according to their nadir hematocrit levels on bypass: less than 20% (hematocrit 1); 20% to 25% (hematocrit 2); greater than or equal to 25% (hematocrit 3). The differences between hematocrit groups were analyzed with the χ^2 test for qualitative variables. Hematocrit groups were compared by one-way analysis of variance

Table 1. Differences in Clinical and Biochemical Characteristics of the Patients According to Presence or Absence of Hyperglycemia in the Postoperative Period*

	Patients with hyperglycemia (n = 100)	Patients with normoglycemia (n = 100)	*P*
Age, median, y (IQR)	59.4 (51-72)	59 (50.2-68)	.39
Male sex, n (%)	62	71	.11
BMI, kg/m^2	23.9 ± 3.3	24.7 ± 2.7	.7
HT, n (%)	65	70	.31
HL, n (%)	46	38	.25
Smoking, n (%)	52	56	.33
COPD, n (%)	32	38	.2
Anastomoses	3.47 ± 1.07	3.6 ± 1.1	.23
Preoperative Hct, median (IQR)	37 (34-40.9)	39.6 (35.8-42.9)	.004
Preoperative blood glucose, median (IQR)	95 (88-102)	97 (88-101.7)	.92
CPB time, min	107.4 ± 29.3	113.2 ± 29.7	.16
Cross-clamp time, min	70.6 ± 24.8	77.1 ± 24.8	.06
Lowest Hct on bypass, %, median (IQR)	20.6 (18-23)	22.3 (20-24.7)	.002
Peak ICU glucose, median (IQR)	211 (208-220)	163.5 (155-172)	<.001
Number of transfusions	2.1 ± 1.2	1.6 ± 1.1	.02

*Data are presented as the mean ± SD where indicated. BMI indicates body mass index; HT, hypertension; HL, hyperlipidemia; COPD, chronic obstructive pulmonary disease; Hct, hematocrit levels; CPB, cardiopulmonary bypass.

(ANOVA) test for normally distributed continuous variables and by Kruskal-Wallis test for non-normally distributed continuous variables. When a significant difference between groups was observed using one-way ANOVA test, posthoc TUKEY HSD test was used to determine the differences between the groups. When a significant difference between groups was observed using Kruskal-Wallis test, Mann-Whitney *U* test was used to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. Spearman correlation test was used to assess the relationship between postoperative hyperglycemia and clinical variables. Logistic regression analysis was used to evaluate the associations between postoperative hyperglycemia and nadir hematocrit levels. *P* values <.05 were considered statistically significant.

RESULTS

Two-hundred patients were enrolled in this study (133 males; median age 60 years, IQR 51-70 years).

Relationship between Postoperative Hyperglycemia and Clinical Variables

Clinical and biochemical characteristics of the patients without postoperative hyperglycemia (n = 100;

Table 2. Relationship between Nadir Hematocrit during Bypass and Clinical Variables*

	<20 (n = 64)	20-25 (n = 93)	≥25 (n = 43)	*P*†	*P* ‡
Age, median, y (IQR)	63 (53-71.7)	60 (50-72)	57 (47-63)	.08	
Male sex, n (%)	33 (51.6)	62 (66.7)	38 (88.4)	<.001	<20 versus 20-25: <.001
					<20 versus ≥25: <.001
					20-25 versus ≥25: <.001
BMI, kg/m²	23.7 ± 2.8	24.3 ± 3.2	25.3 ± 2.9	.03	<20 versus 20-25: .45
					<20 versus ≥25: .02
					20-25 versus ≥25: .18
Anastomoses	3.44 ±1.04	3.65 ± 1.09	3.56 ± 1.1	.9	
Preoperative Hct, median (IQR)	36.9 (33.2-40.85)	37 (34.9-42.6)	40 (39-44)	<.001	<20 versus 20-25: .02
					<20 versus ≥25: <.001
					20-25 versus ≥25: .002
Preoperative blood glucose, median (IQR)	93.5 (88-103.25)	98 (88-101)	94 (88-103)	.94	
Anastomoses	3.44 ± 1.04	3.65 ± 1.09	3.56 ± 1.1	.5	
CPB time, min	109.9 ± 31.3	111.1 ± 29.8	109.3 ± 27	.94	
Cross-clamp time, min	69.9 ± 23.3	77.2 ± 25.9	72.4 ± 24.8	.18	
Lowest Hct on bypass, %, median (IQR)	17 (16-18)	22 (21-23)	26.5 (25-28)	<.001	<20 versus 20-25: <.001
					<20 versus ≥25: <.001
					20-25 versus ≥25: <.001
Peak ICU glucose, median (IQR)	211.5 (180.2-223)	176 (159-209.5)	172 (158-207)	<.001	<20 versus 20-25: <.001
					<20 versus ≥25: <.001
					20-25 versus ≥25: .6
Number of transfusions	3.1± 0.7	1.6 ± 0.6	0.3 ± 0.4	<.001	<20 versus 20-25: <.001
					<20 versus ≥25: <.001
					20-25 versus ≥25: <.001

*Data are presented as the mean ± SD where indicated. <20 indicates patients with hematocrit levels less than 20%; 20-25, patients with hematocrit levels 20% to 25%; ≥25, patients with hematocrit levels greater than or equal to 25%; BMI, body mass index; Hct, hematocrit levels; CPB, cardiopulmonary bypass.

†*P* values between group comparisons.

‡*P* values for pairwise comparisons.

71 males, median age [IQR] 59 [50.2-68]) and patients who had postoperative hyperglycemia (n = 100; 62 males, median age [IQR] 59.4 [51-72]) are presented in Table 1.

Patients with postoperative hyperglycemia had significantly lower preoperative hematocrit levels than patients without postoperative hyperglycemia (37 [34-40.9] versus 39.6 [35.8-42.9], P = .004). Compared to patients without postoperative hyperglycemia, patients who had postoperative hyperglycemia were associated with lower nadir hematocrit levels during CPB (22.3 [20-24.7] versus 20.6 [18-23], P = .002). There were no statistically significant differences in other clinical characteristics between the two groups.

Relationship between Nadir Hematocrit Levels during CPB and Postoperative Hyperglycemia

Patients were divided into three subgroups according to their nadir hematocrit levels during CPB: <20%; 20% to 25%; ≥25% (Table 2). The relationship between nadir hematocrit levels during CPB and postoperative hyperglycemia is presented in Table 2. There were no significant differences between groups in preoperative blood glucose levels, number of anastomoses, CPB time, and cross-clamp time. Peak ICU blood glucose levels and number of blood transfusions were significantly higher in patients with nadir hematocrit levels less than 20 compared to other hematocrit subgroups (P < .001 and P < .001 respectively). Patients with nadir hematocrit levels <20 had a significantly greater percentage of males compared to other hematocrit groups (P < .001). Patients with nadir hematocrit levels ≥25 had significantly higher BMI values compared to patients with nadir hematocrit levels <20 (P = .02). Preoperative hematocrit values were significantly lower in patients with nadir hematocrit levels <20 compared to other hematocrit groups (P = .02 and P < .001 respectively).

Multivariate Analysis

The correlation between peak ICU glucose and evaluated parameters is shown in Table 3. Peak ICU blood glucose levels showed a weak negative correlation with preoperative hematocrit levels (rho = -0.24, P < .001). There was a moderate negative correlation between peak ICU blood glucose levels and nadir hematocrit levels during CPB (rho = - 0.39, P < .001). Also, there was a moderate positive correlation between peak ICU blood glucose levels and number of transfusions (rho = 0.38; P < .001). Results of logistic regression analysis are presented in Table 4. Logistic regression analysis demonstrated that nadir hematocrit levels less than 20% (OR 2.9, 95% CI 1.3-6.5, P = .009) and allogenic blood transfusion (OR 1.5, 95% CI 1.15-1.8, P = .003) were independently associated with postoperative hyperglycemia. Preoperative hematocrit levels, nadir hematocrit levels 20% to 25%, and nadir hematocrit levels equal to or greater than 25% were not associated with postoperative hyperglycemia.

Table 3. Correlation between Peak ICU Blood Glucose Levels and Other Clinical Parameters

	rho	P
Preoperative glucose	-0.15	.12
Preoperative Hct	-0.31	.001
Minimum Hct	-0.45	<.001
BMI	-0.04	.64
CPB time	0.11	.24
Cross-clamp time	0.11	.28
Number of anastomosis	0.15	.13
Number of transfusions	0.38	<.001

rho indicates Spearman correlation coefficient; Hct, hematocrit levels; BMI, body mass index; CPB, cardiopulmonary bypass.

DISCUSSION

In the present study, we have found that nadir hematocrit levels less than 20% during CPB and allogenic blood transfusions were independently associated with postoperative hyperglycemia in nondiabetic patients. We also demonstrated that peak ICU blood glucose levels were significantly higher in patients with nadir hematocrit levels less than 20% compared to patients with nadir hematocrit levels greater than 20%. To the best of our knowledge, this is the first study to examine the association between nadir hematocrit levels during CPB and postoperative hyperglycemia in nondiabetic patients undergoing CABG. Although the specific mechanisms have not been clearly identified, several mechanisms may be responsible for postoperative hyperglycemia in patients with nadir hematocrit levels less than 20 during CPB. Postoperative hyperglycemia develops due to an increase in insulin resistance, overproduction of glucose, and inflammatory response induced by surgical stress [Fahy 2009; Collier 2008; Sakharova 2007; Langouche 2007; van den Berghe 2003]. The degree of insulin resistance has been related to the magnitude and endurance of surgical stress [Sicardi Salomón 2006]. It is demonstrated that onset of CPB further increases postoperative glycemia and insulin consumption in both diabetic and nondiabetic patients [Anderson 2005; Knapik 2009] and decreases glucose uptake by 25% to 30% [Kuntschen 1985]. There may be several

Table 4. Logistic Regression Analysis

	OR	95% CI	P
Preoperative Hct	0.93	0.001-1	.051
Nadir Hct <20%	2.9	1.3-6.5	.009
Nadir Hct 20% to 25%	1.2	0.6-2.5	.061
Nadir Hct 25%	0.82	0.4-1.7	.62
Allogenic blood transfusion	1.5	1.15-1.8	.003

Hct indicates hematocrit levels; OR, odds ratio; CI, confidence interval.

factors responsible for the marked insulin resistance during CPB. The most likely factor would be elevated plasma levels of the counter-regulatory hormones cortisol, catecholamines, and glucagon. Heparin can also contribute to insulin resistance through stimulating lipoprotein lipase activity and the release of FFA [Boden 1997; Grossman 1955]. CPB during cardiac surgery induces a systemic inflammatory response and promotes the release of different cytokines, particularly TNF-α, IL-1, and IL-6 [Brix-Christensen 2001; Wan 1999; Schwartz 1998]. Inflammatory cytokines, especially TNF-α, has been demonstrated to cause insulin resistance in both liver and skeletal muscle [Collier 2008]. Low hematocrit levels during CPB is one of the major determinants of allogenic blood transfusions [Ranucci 2006; Habib 2005; Engoren 2002; Kuduvalli 2005; Koch 2006; Speiss 2002]. Systemic inflammatory response is aggravated and circulating inflammatory mediators are markedly increased by allogenic blood transfusions in addition to an ongoing systemic inflammatory response induced by cardiac surgery [Fransen 1999]. One of the mechanisms responsible for hyperglycemia in patients with nadir hematocrit levels less than 20 may be exacerbated systemic inflammatory response and subsequent increase in insulin resistance after CPB due to increased blood transfusions.

Excessive hemodilution and the resulting anemia during CPB may impair tissue oxygen delivery. The primary purpose of blood transfusion is to increase the oxygen transport capacity of the blood and improve tissue oxygenation. It has been demonstrated that transfusion of allogenic blood does not improve, and may lead to further deterioration of the ischemic organ injury [Vincent 2007; van Bommel 2001; Tsai 2004]. Changes in shape, rigidity, depletion of 2,3-diphosphoglycerate (2,3 DPG), and nitric oxide scavenging during storage of red blood cells are suggested to result in impaired perfusion and oxygen delivery [Ho 2003]. Another mechanism may be the desaturation and arterial hypoxemia as a result of excessive hemodilution and subsequent increase in sympathetic autonomous response, which in turn further increases the release of cortisol, catecholamines, and glucagon, and inhibits insulin secretion. Stimulation of hepatic glycogenolysis and inhibition of glucose clearance due to elevated circulating levels of catecholamines and low insulin levels result in hyperglycemia [Baum 1980].

In our study, we observed that preoperative hematocrit levels were lower in patients with hyperglycemia. Compared with men, women had preoperative lower hematocrit levels, with a resultant increase in blood transfusions. This could be due to the fact that the degree of hemodilutional anemia that is observed on CPB is related to the patients' preoperative hematocrit levels and body surface area. Women have lower body surface area and preoperative values of HCT, which results in a severe hemodilution [Ranucci 2006; Karkouti 2005; Habib 2005].

This study has several limitations. A major limitation of our study is its retrospective design. Whether hyperglycemia was due to impaired tissue oxygen delivery or exacerbated systemic inflammatory response and subsequent increase in insulin resistance after CPB due to increased blood transfusions cannot be determined from this study. This study was not designed to determine the mechanisms for increased hyperglycemia incidence.

CONCLUSION

In summary, the results of our study suggest that nadir hematocrit levels on CPB less than 20% may be associated with increased incidence of postoperative hyperglycemia in nondiabetic patients undergoing cardiac surgery. We also demonstrated that peak ICU blood glucose levels were significantly higher in patients with nadir hematocrit levels less than 20% compared to patients with hematocrit levels over 20%. Patients with nadir hematocrit levels less than 20% during CPB should be closely monitored for hyperglycemia in the perioperative period.

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