Intraoperative hyperglycemic stress response and tissue perfusion in cardiac surgery

Aslı Demir[1], EDA BALCI[1], Hülya Yiğit Özay[1], and MELİKE BAHÇECİTAPAR[2]

[1]Ankara City Hospital Anesthesiology Department
[2]Hacettepe Universitesi

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Abstract

Background and aim of the study Approximately 30% of patients undergoing cardiac surgery have a history of diabetes and 60-80% of patients without diabetes have stress hyperglycemia. We examined patients undergoing cardiac surgery to determine the presence of stress hyperglycemia and its relationship to tissue perfusion. Methods Hemodynamic parameters, central venous oxygen saturation, lactate,oxygen delivery and consumption, oxygen extraction rate were analyzed at four intraoperative time points. Results The stress-induced hyperglycemic response during cardiac surgery was more severe in patients without diabetes. When focusing on the oxygen extraction rate in terms of tissue oxygenation, diabetic patients had 1.22 times higher and significant oxygen extraction rate than non-diabetic patients. Conclusions Although lactate values were slightly higher and central venous oxygen saturation were slightly lower in the diabetic group, considering the fact that oxygen extraction rate reflects the total outcome of small changes in all these parameters, we can emphasize the conclusion that diabetic patients undergoing cardiac surgery have greater tissue oxygen demand/supply imbalance compared to non-diabetic patients. In our study, this tissue oxygenation defect in diabetic patients was not found to be directly correlated with blood glucose levels. Perhaps, even if the disease is under control, the negative effects of diabetes on all systems have accumulated and led to such a result.

Introduction

The term stress hyperglycemia describes transient increases in blood sugar in patients without a history of diabetes mellitus (DM) that occur during acute illness or stress. Hyperglycemia seen in cardiac surgery patients is important in terms of its severity and its relationship with postoperative complications.[1-3] Intraoperative hyperglycemia has been associated with increased morbidity in diabetic patients.[4] Mortality has also increased in diabetic and non-diabetic hyperglycemic patients who underwent cardiac surgery with cardiopulmonary bypass (CPB).[5] Approximately 30% of patients undergoing cardiac surgery have a history of DM and approximately 60-80% of patients without DM have stress hyperglycemia, which is defined as blood glucose value above 140 mg / dL.[6-8] It is thought that certain disorders in glucose metabolism such as increased levels of insulin resistance, cortisol, adrenocorticotropic hormone (ACTH), growth hormone (GH), epinephrine and norepinephrine during cardiac surgery and CPB in patients with and without DM contribute to hyperglycemia.[9]

The key determinants to maintain of tissue perfusion and cellular integrity are adequacy of macrocirculation and delivery of oxygen at values exceeding the current rate of consumption.[10]Oxygen extraction rate (O_2ER) is the ratio of the body's oxygen consumption (VO_2) to systemic oxygen delivery (VO_2 / DO_2), which is a practical way to describe the adequacy of systemic oxygen delivery.[11]

To our knowledge, there are no previous studies focusing on tissue perfusion-related outcomes with the degree of hyperglycemia that may occur in cardiac surgery patients with and without a history of DM.

We hypothesized that stress hyperglycemia may be correlated (or associated) with reduced tissue perfusion during cardiac surgery, therefore, we closely examined a series of consecutive cases undergoing cardiac surgery to determine the presence of stress hyperglycemia and its relationship to tissue perfusion. Primary outcome measures were associated with stress hyperglycemia and tissue perfusion parameters in non-diabetic patients undergoing cardiac surgery and patients with non-insulin-dependent diabetes mellitus (NIDDM). Data may be relevant for tailored intervention and proper management.

Material and Methods

This was a observational longitudinal study and was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee for Clinical Research at local hospital (11.01.2019, 29620911-929-67). Ninety consecutive adult patients of the American Society of Anesthesiologists (ASA) Class II-III who underwent elective cardiac surgery with CPB over a 2-months period were included in this study. Patients undergoing emergency or re-do surgery, off-pump surgeries, transplant surgeries, vascular surgery were excluded from the study. Patients with insulin dependent diabetes mellitus (IDDM), those with a history of ejection fraction under 40% or pulmonary, renal or hepatic failure, those with hematologic disorder, those under 18 years old or those using alcohol, or any medication suppressing stress response as corticosteroids, vitamin C, or n-acetylcysteine, were not included the study. Since IDDM has a different pathogenesis, it was excluded from the study, considering that it may interact more negatively with tissue perfusion parameters. NIDDM patients discontinued their oral antidiabetic medications 24-hour before surgery. So the aim of this study is to evaluate the degree of stress response and related tissue oxygenation parameters in NIDDM patients whose documented preoperative normoglycemia with oral antidiabetic drug use and patients without DM.

Pulse oximetry, five channel electrocardiography, invasive blood pressure monitoring, bispectral index monitoring (BIS, Covidien, MN, ABD) and invasive internally calibrated pulse wave analysis (ProAQT; Pulsion Medical Systems, Feldkirchen, Germany; PPV_{ProAQT}, CO_{ProAQT}) were performed. As baseline measurement, patients received an initial hemodynamic assessment based on stroke volume, cardiac output (CO), and mean arterial pressure. DO_2 (CO x arterial content of O_2), VO_2 (CO x [arterial-venous content of O_2]), and O_2ER calculations were performed with these calculated CO values by pulse wave analysis. However, when the CPB was initiated, pump flow was used as CO value due to inaccurate pulse wave analysis measurements during CPB.

Patients with no history of DM prior to surgery, may exhibit transient elevation of blood glucose >180 mg/dL during cardaiac surgery and cardiopulmonary bypass, they may have insulin resistance. We treated with a single or intermittent dose of intravenous insulin to maintain glucose [?] 180 mg/dL at these patients. After a single dose insulin push therapy, blood glucose levels were re-evaluated and intravenous insulin regimen was started when necessary as recommended by Duggan et al.[12] An endocrinology consultation was obtained in the postoperative period in case DM was detected in some of these patients. In patients with NIDDM, the bolus dose calculated with the formula (blood glucose value - 100/40) was applied when blood glucose was above 180 mg/dl. Then blood glucose value/100 units/hour infusion dose was started.[12] Blood glucose levels were monitored with half an hour intervals.

Following adequate activated clotting time (>480 sec), cannulation were performed and CPB was initiated. CPB was performed in moderate hypothermia (28-31°C). Hemoglobin concentrations were kept above 7.5 g/dl during operation.

Blood samples were collected from the radial artery and internal jugular vein. Although jugular venous ($ScvO_2$) and mixed venous oxygen saturation values differ slightly, it is acceptable to use $ScvO_2$ instead of mixed venous oxygen saturation.[13] Blood glucose and gas analysis were performed at four time points: after the induction of anesthesia before the surgery as baseline values (T1), at the 5-10^{th}minute of CPB (T2), at the 30-40^{th} minute of CPB (T3), and while the sternum was closing (T4). At these four time points, hemodynamic parameters, central venous oxygen saturation ($ScvO_2$), lactate level, oxygen delivery (DO_2), oxygen consumption (VO_2), oxygen extraction rate (O_2ER), mean arterial pressure (MAP) and urine output

values were recorded.

Statistical analysis

All statistical analyses were performed using IBM SPSS 22.0 for Windows. Kolmogrov-Smirnov and Shapiro Wilk tests were used for evaluating whether the observations are from the normal distribution. In describing the features of data, number of cases (n) and their proportions (%) for categorical variables, median and range for non-normally distributed continous variables and mean and standard deviation for normally distributed continous variables were calculated. Pearson chi-square or Fisher Exact test was used to compare NoDM and NIDDM groups according to categorical variables. The Mann-Whitney U test or two sample t-test were used to compare NoDM and NIDDM groups for continous data obtained from basic features of patients such as age, weight and height. According to the other continous variables, these two tests were also used for the comparison of NoDM and NIDDM groups at each time point. Additionally, the longitudinal data sets in this study were analyzed by a linear regression model with Generalized Estimating Equations (GEE) method which can be applied for normally or non-normally distributed measurements of same patients over time. In GEE analyses, working correlation matrix was assumed to be unstructured. The results of GEE method are corresponding to overall comparison of two groups over all four time points. A p-value$<$0.05 for two-sided tests was considered statistically significant.

Results

A total of 90 patients who underwent cardiac surgery at the Cardiothoracic Surgery operating room in tertiary city hospital were included in the study. Seven patients were not analyzed due to lost of follow-up. NIDDM was detected in 19 of 83 patients included and determined as group NIDDM, the remaining non-diabetic 64 patients were determined as group NoDM. In only 5 patients in the non-diabetic patient group, blood glucose levels did not exceed 140 during the operation, so the rate of stress hyperglycemia was 78%. In the NIDDM group, blood glucose levels were high from the beginning.

Pre-operative and intra-operative demographic and clinical characteristics of the study population are summarized in Table 1. There were no statistically significant difference in the age, gender, comorbidities, duration of CPB, and aortic clamping between groups (Table 1).

The characteristics of hemodynamic and tissue oxygenation parameters during surgery of groups were shown in Table 2. The glucose values were significantly different between groups. There was a statistically significant effect of DM on blood glucose values (p$<$.001) as expected. NIDDM patients had 1.67 times higher blood glucose values than those with NoDM, (p$<$0.05) [95% CI: 1.47, 1.91]. In general, time has a positive and statistically significant effect on blood glucose levels (p$<$.001). As time progresses, blood sugar increases 1.18 times (p$<$0.05) [95% CI: 1.17, 1.20]. When the change in the blood glucose values of the patients in the NIDDM and NoDM groups is examined, the blood glucose levels of the patients with NIDDM increase 0.879 times as time progresses, while the patients with NoDM increase 1/0.879=1.14 times as time progresses (Figure 1). Hypoglycemic attack was not observed in any patient.

The O_2ER values were significantly different between groups when repeated measurements were analyzed together with GEE method (p=0.004) (Figure 2). There is a statistically significant difference between the groups at the 4^{th} time point (p=0.022). Patients in the NIDDM group had higher O_2ER values than patients in the NoDM group at time points 1, 2, and 4. NIDDM patients had 1.22 times higher O_2ER values than those with NoDM, and this result was statistically significant [95% CI: 1.06-1.40]. There was no statistically significant effect of time on O_2ER values (p=0.746).

There was no statistically significant effect of blood glucose values on O_2ER (p=0.549), and also no statistically significant effect of O_2ER values on blood glucose was found (p=0.578).

There was no statistically difference at lactate level, DO_2, VO_2, SVR, $ScvO_2$, Hb, MAP, HR, temperature, and urine output values between groups.

Intraoperative inotropic medications, blood product transfusion rates, postoperative complications, and mortality data were not statistically different as shown in Table 3.

Discussion

This study hypothesized that stress hyperglycemia associates with tissue perfusion. This stress response may cause reduced tissue perfusion parameters and may differ in non-diabetic patients and in patients with non-insulin-dependent diabetes mellitus undergoing cardiac surgery. The stress-induced hyperglycemic response during cardiac surgery was more severe in noDM patients than in patients with NIDDM (1.14 & 0.879). When focusing on the O_2ER parameter in terms of tissue oxygenation, NIDDM patients had 1.22 times higher and significant O_2ER values than NoDM patients. However, blood glucose values and O_2ER parameters had no effect on each other, and/or no correlation was found between them.

Hyperglycemia is common in cardiac surgery and seen as high as 60-80% of patients.[8,14] Hyperglycemia occurs as a result of decreased insulin production caused by pancreatic β cell insufficiency, or insulin resistance. In the absence of autoimmune diabetes, transient disturbances in pancreatic cell secretion during CPB were found to be associated with hypothermia.[15] However, the causes of insulin resistance are the secretion of catecholamines and cortisone against effects such as systemic inflammatory response syndrome, hemodilution, systemic heparinization together with CPB (surgical stress).[5] The severity of the hyperglycemic response increases with the intensity of the stress, so in cardiac surgery, inflammation initially caused by anesthesia and surgery peaks together with CPB and hypothermia.[16] In our study, blood glucose in the NoDM group which stress hyperglycemia ratio was found 78% reached its highest values at T2 and T3 periods, that is, when the effects of CPB and hypothermia effects were strongest. In the NIDDM group, blood glucose levels were above 140mg/dl from the beginning, and also peaked during T2 and T3 periods, similar to the NoDM group. In accordance with our clinical protocol, if blood glucose rises above 180mg/dl in the intraoperative period, continuous insulin infusion is started. A randomized controlled study of 400 diabetic and non-diabetic surgical patients comparing the two groups who received a continuous infusion of insulin to keep the intraoperative glucose level between 80-100 mg/dL and the glucose target kept below 200 mg/dL did not report any improvement in clinical outcome or complications.[17] In a meta-analysis including the results of 706 cardiac surgery patients, it was reported that strict intraoperative glycemic control decreased infection rate but not mortality compared to conventional therapy.[18] In another coronary surgery patient group, when a blood glucose target of 90-120 mg / dL and 121-180 mg/dL was achieved, no difference was observed in deep sternum wound infection, pneumonia, perioperative renal failure, or mortality.[19] Similarly, other studies targeting the same glucose values did not report any difference between the groups in terms of perioperative complications, length of stay in hospital, and mortality.[20,21] Although our study population is smaller compared to these studies, we would like to state that in our results, no difference was observed between non-diabetic and NIDDM cardiac surgery patients in terms of postoperative complications and mortality. As the surgery progressed, the rate of increase in blood glucose observed in the NoDM group was higher than in the NIDDM group. Although the mechanism is not fully known, all these studies show that NIDDM provides a tolerance to stress-induced hyperglycemia, and an approach that does not require tighter control can be preferred for glycemic control with NIDDM.[22]

In general, global body oxygen delivery in anesthesia practice is mathematically formulated by DO_2, that is the product of cardiac output and arterial oxygen content. Although medical physiological facts often do not agree with this simple mathematical calculation, interpretation can be made about tissue oxygenation by evaluating many other parameters such as O_2ER, $ScvO_2$, lactate, systemic vascular resistance (SVR) and hemoglobin. It has been stated that global tissue hypoperfusion detected with SvO_2 and lactate is common in non-diabetic coronary artery surgery patients, in addition high blood glucose level is not suitable for use as a perioperative marker for global tissue hypoperfusion.[23] On the other hand, in another study, it was suggested that patients with diabetes mellitus who underwent cardiac surgery had impairments in cerebral oxygen saturation, possibly due to microcirculatory disorders, and SvO_2 measurement did not reflect this deficiency.[24] It is known that hyperlactatemia seen in cardiac surgery does not always indicate an anaerobic condition and/or a lack of tissue oxygen delivery, a condition called type B hyperlactatemia.[25,26] Conversely,

it has been suggested that reduced increase in lactate levels in the presence of hyperglycemia may be a result of decreased activation of the glycolytic pathway in patients with diabetes mellitus compared to patients with NoDM.[27] In our study, the lactate values were around 2-3 mmol/L in both groups, which was quite acceptable during cardiac surgery and the $ScvO_2$ value was around 70% and there was no clinical significance between the groups. No difference was found between non-diabetic and NIDDM patients in terms of other parameters such as hemoglobin, MAP, SVR and blood product transfusion, but a significant difference emerged when the O_2ER parameter was examined. Accordingly, O_2ER values in both groups were above the normal value of 25%, and in addition, NIDDM patients had significantly higher O_2ER values. The situations encountered with high O_2ER are as follows: inadequate oxygen delivery such as hypoxia, anemia, circulatory failure; increased oxygen consumption such as increased muscle activity, exercise, shivering, seizures, and inflammation; increased metabolic rate such as hyperthermia, hyperthyroidism, catecholamine excess and massive injury; abnormal circulation, such as cyanotic shunt, arterio-venous malformation. In our study, the reason for the relatively high O_2ER from the beginning of the operation in anesthetized patients may be because of inflammation, and/or increased catecholamine due to the fear of surgery, as the surgery progresses, many other factors such as hemoglobin decrease due to hemodilution, hypothermia, nonpulsatile flow come into play and the severity of inflammation increases. The critical DO_2 in humans is the maximum O_2ER (O_2ER 0.6-0.8) at 4ml kg^{-1} min^{-1}, and at this stage VO_2 is said to be supply dependent. If DO_2 continues to fall further below its critical value, anaerobic metabolism and type A hyperlactataemia occur due to the imbalance between ATP supply and demand. Although lactate values were slightly higher and $ScvO_2$ values were slightly lower in the NIDDM group in our study, considering the fact that O_2ER reflects the total outcome of small changes in all these parameters, we can emphasize the conclusion that NIDDM patients undergoing cardiac surgery have greater tissue oxygen demand/supply imbalance compared to NoDM patients. In our study, this tissue oxygenation defect in NIDDM patients was not found to be directly correlated with blood glucose levels. Perhaps, even if the disease is under control, the negative effects of diabetes on all systems have accumulated and led to such a result. Studies with more patients will shed light on the subject.

Limitations of this study; while this theoretical understanding underpins the physiology of oxygen in the critically ill patient, empirical evidence to support them is limited and the concepts remain controversial. Even if global oxygen supply and consumption appears to be normal, it does not exclude the presence of pathological oxygen supply/demand at the regional or local level. The small number of our patients is another limitation as noted earlier. And it would be more valuable if we had chance to measure cortisol levels to determine catabolic stress.

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Declaration of conflicting interests

The authors declare that there is no conlict of interest.

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Table 1: Demographic and clinical characteristics of the study population

Variables	Group NoDM (n=64)	Group NIDDM (n=19)	p-value
Age (years) (Median (Range))	58 (60)	62 (30)	0.244¥
Male Gender (n/%)	47 (73.4)	15 (78.9)	0.769
Weight (kg) (Median (Range))	78 (49)	74 (50)	0.218¥
Height (cm) (Median (Range))	170 (45)	165 (28)	0.213¥
Body Mass Index (Median (Range))	0.28 (0.15)	0.26 (0.14)	0.481¥
Hypertension (n/%)	23(35.9)	12(63.2)	0.065
Chronic obstructive pulmonary disease (n/%)	5(7.8)	1(5.3)	1.000
Cerebrovascular accident (n/%)	2(3.1)	1(5.3)	0.547
Operation duration (hours) (Median (Range))	5.0 (5.5)	5.0 (5.0)	0.161¥
CPB duration (min) (Median (Range))	107 (202)	96 (209)	0.209¥
Cross clamping duration (min) (Median (Range))	69.5 (165)	57 (164)	0.257¥

: Chi-square test

¥: Mann-Whitney-U test

CPB: Cardiopulmonary bypass

Table 2: Intraoperative datas during time points

Variables	Group NoDM (n=64)	Group NIDDM (n=19)	p-value	p-value
Glucose T1	101.5 (128)	153 (167)	<.001*¥	<.001*
T2	127.5 (127)	170 (159)	<.001*¥	
T3	165 (182)	193 (115)	0.015*¥	
T4	171 (186)	182 (104)	0.599¥	
Lactate T1	0.90 (2.3)	0.90 (1.5)	0.568¥	0.426
T2	2.30 (4.7)	3.10 (6.4)	0.271¥	
T3	2.40 (6.3)	2.70 (7.1)	0.660¥	
T4	2.75 (6.8)	2.70 (7.2)	0.425¥	
DO_2 T1	915.19 (1954.69)	798.15 (1562.92)	0.229¥	0.609
T2	525.26 (388.80)	473.34 (266.80)	0.095¥	
T3	497.00 (492.10)	450.00 (303.53)	0.237¥	
T4	729.5 (1315.14)	647.28 (718.03)	0.186¥	
VO_2 T1	256.72 (537.03)	243.92 (444.26)	0.803¥	0.575
T2	166.13 (206.28)	179.22 (179.11)	0.862¥	
T3	136.27 (204.55)	118.21 (219.17)	0.061¥	
T4	204.40 (455.19)	211.88 (599.82)	0.786¥	
O_2ER T1	0.28 (0.32)	0.31 (0.27)	0.201¥	0.004*
T2	0.31 (0.49)	0.33 (0.26)	0.091¥	
T3	0.29 (0.53)	0.28 (0.28)	0.343¥	
T4	0.28 (0.42)	0.32 (0.41)	0.022*¥	
SVR T1	1295 (2430)	1270 (1280)	0.978¥	0.378
T4	820 (1460)	940 (1090)	0.165¥	
$ScvO_2$ T1	0.73 (0.36)	0.71 (0.29)	0.198¥	0.080
T2	0.76 (0.53)	0.74 (0.30)	0.266¥	
T3	0.73 (0.61)	0.76 (0.47)	0.305¥	
T4	0.71 (0.37)	0.69 (0.40)	0.037*¥	
Hemoglobin T1	13.70 (8.5)	13 (4.6)	0.132¥	0.063
T2	8.55 (5.9)	7.5 (5.1)	0.059¥	
T3	8.45 (6.1)	8.1 (3.7)	0.248¥	
T4	8.75 (5.9)	8.2 (3.5)	0.235¥	
MAP T1	76.33 (53.0)	81 (44)	0.380¥	0.606
T2	62 (50)	63 (40)	0.438¥	
T3	70 (40)	76 (33)	0.368¥	
T4	68.67 (42)	73 (33)	0.213¥	
Heart rate T1	68.33±14.07	69.68±9.76	0.696ᵛ	0.624
T4	85.84±13.88	86.11±14.86	0.944ᵛ	
Temperature T1	36.5 (2.1)	36.4 (1.8)	0.069*¥	0.720
T2	32.0 (6.7)	32.0 (4.0)	0.982¥	
T3	30.0 (5.0)	31.0 (3.0)	0.152¥	
T4	37.0 (4.7)	36.8 (2.8)	0.713¥	
Urine output (cumulative) T1	50 (350)	20 (500)	0.660¥	0.753
T2	200 (880)	150 (970)	0.836¥	
T3	500 (1800)	400 (1050)	0.295¥	
T4	1050 (2750)	700 (1850)	0.109¥	

Values are presented as median (range) or mean±standard deviation

DO_2: Oxygen delivery, VO_2: Oxygen consumption, O_2ER: Oxygen extraction rate, SVR: Systemic vascular

rezistance, $ScvO_2$: Central venous oxygen saturation, MAP: Mean arterial pressure

¥: Mann-Whitney-U test

: GEE method

ᵛ: Independent two-sample test

*: p <0.05

Table 3: Intraoperative and postoperative variables of the study population

Variables	Grup NoDM (n=64)	Grup NIDDM (n=19)	p-value
Intraoperative transfusion n(%)	9 (14.1)	3 (15.8)	1.000
Intraoperative inotropic infusions n(%)			-
Dopamine	4 (6.3)	3 (15.8)	
Dobutamine	4 (6.3)	0 (0.0)	
Noradrenaline	2 (3.1)	0 (0.0)	
Major adverse cardiac events n(%)	6 (9.4)	2 (10.5)	1.000
Cerebrovascular accident n(%)	1 (1.6)	1(5.3)	1.000
Tamponade n(%)	1 (1.6)	1 (5.3)	0.408
Respiratory complications n(%)	0 (0.0)	0 (0.0)	-
Renal complications	0 (0.0)	0 (0.0)	-
Sternal wound infection	0 (0.0)	0 (0.0)	-
Mortality	0 (0.0)	0 (0.0)	-

-: Chi-square assumptions are not met.

Figure Legends

Figure 1: Blood glucose levels during four intraoperative time points.

Figure 2: The O_2ERs during four intraoperative time points

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