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Research Article / Araştırma

# Intraoperative Hyperglycemic Stress Response and Oxygen Extraction Ratio in Cardiac Surgery

## *Kardiyak Cerrahide İntraoperatif Hiperglisemik Stres Yanıtı ve Oksijen Ekstraksiyon Oranı*

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## ABSTRACT

**Objectives:** Approximately 30% of patients undergoing cardiac surgery have a history of diabetes mellitus (DM) and approximately 60–80% of patients without DM have stress hyperglycemia, and this may be correlated with reduced tissue perfusion during cardiac surgery. We aimed to evaluate the effect of stress hyperglycemia on oxygen extraction ratio ($O_2ER$) in non-diabetic (NoDM) and non-insulin-dependent diabetic patients (NIDDM).

**Methods:** In this observational longitudinal study, cardiac surgery patients were grouped as NoDM and NIDDM. For both groups, blood glucose and lactate levels, and hemodynamic measurements (arterial pressures, heart rate, oxygen delivery and consumption, $O_2ER$, and systemic vascular resistance) were performed at four intraoperative time points.

**Results:** A total of 83 consecutive adult patients were analyzed. In NoDM group, the rate of stress hyperglycemia was 78%. There was significant difference between the groups at the end of operation time point in terms of $O_2ER$. NIDDM patients had 1.22 times higher $O_2ER$ values than those with NoDM.

**Conclusion:** Stress-induced hyperglycemic response during cardiac surgery was more severe in NoDM patients than in patients with NIDDM. In terms of the $O_2ER$ parameter that reflects tissue oxygenation, NIDDM patients had significantly higher $O_2ER$ values than NoDM patients. When taken into account, $O_2ER$ reflects the total outcome of small changes on microcirculation, we can highlight the conclusion that NIDDM patients undergoing cardiac surgery have greater tissue oxygen demand/supply imbalance compared to NoDM patients.

**Keywords:** Cardiac surgery, diabetes mellitus, oxygen extraction ratio, stress hyperglycemia, tissue perfusion

## ÖZ

**Amaç:** Kalp cerrahisi geçiren hastaların yaklaşık %30'unda diabetes mellitus (DM) öyküsü ve DM olmayan hastaların yaklaşık %60-80'inde stres hiperglisemisi vardır. Bu da kalp cerrahisi sırasında azalmış doku perfüzyonu ile ilişkilendirilebilir. Bu çalışmada, diyabetik olmayan (NoDM) ve insüline bağımlı olmayan diyabetik hastalarda (NIDDM) stres hiperglisemisinin oksijen ekstraksiyon oranı ($O_2ER$) üzerindeki etkisinin değerlendirilmesi amaçlanmıştır.

**Yöntem:** Bu gözlemsel çalışmada, kalp cerrahisi hastaları NoDM ve NIDDM olarak gruplandırıldı. Her iki grup için; kan şekeri, laktat seviyeleri ve hemodinamik ölçümler (arteryel basınçlar, kalp hızı, oksijen iletimi ve tüketimi, $O_2ER$, sistemik vasküler direnç) dört intraoperatif zaman noktasında yapıldı.

**Bulgular:** Çalışmada 83 yetişkin hasta analiz edildi. NoDM grubunda stres hiperglisemi oranı %78 idi. $O_2ER$ açısından operasyon bitiş zamanı noktasında gruplar arasında anlamlı fark vardı. NIDDM hastaları, NoDM'li hastalardan 1,22 kat daha yüksek $O_2ER$ değerlerine sahipti.

**Sonuç:** Kardiyak cerrahi sırasında strese bağlı hiperglisemik yanıt, NoDM hastalarında NIDDM hastalarına göre daha şiddetliydi. Doku oksijenasyonunu yansıtan $O_2ER$ parametresi açısından, NIDDM hastaları, NoDM hastalarına göre anlamlı olarak daha yüksek $O_2ER$ değerlerine sahipti. $O_2ER$, mikrosirkülasyon üzerindeki küçük değişikliklerin toplam sonucunu yansıttığından, kalp cerrahisi geçiren NIDDM hastalarının NoDM hastalarına kıyasla daha fazla doku oksijen talebi/sunumu dengesizliğine sahip olduğu sonucuna varılabilir.

**Anahtar sözcükler:** Kardiyak cerrahi, diabetes mellitus, oksijen ekstraksiyon oranı, stres hiperglisemisi, doku perfüzyonu

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## 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 post-operative 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 $dL^{-1}$.[6–8] It is thought that certain disorders in glucose metabolism such as increased levels of insulin resistance, cortisol, adrenocorticotropic hormone, growth hormone, 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 ratio ($O_2ER$) 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]

We hypothesized that stress hyperglycemia may be associated with increased $O_2ER$ during cardiac surgery; therefore, we examined patients undergoing cardiac surgery to determine the presence of stress hyperglycemia and its relationship to tissue perfusion.

## 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 (January 11, 2019, 29620911-929-67). Ninety consecutive adult patients of the American Society of Anesthesiologists Class II-III who underwent elective cardiac surgery with CPB over a 2-month period were included in this study. Patients undergoing emergency or re-do surgery, off-pump surgeries, transplant surgeries, and vascular surgery were excluded from the study. Patients with insulin-dependent DM (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-h before surgery. Hence, NIDDM patients whose documented pre-operative normoglycemia with oral antidiabetic drug use and patients without DM were included in this study.

Pulse oximetry, five channel electrocardiography, invasive blood pressure monitoring, bispectral index monitoring (BIS™, Covidien, MN, and ABD), and invasive pulse wave analysis (ProAQT; Pulsion Medical Systems, Feldkirchen, Germany; PPVProAQT, COProAQT) 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. When the CPB was initiated, pump flow was determined as CO.

In the event of elevation of blood glucose >180 mg $dL^{-1}$ in patients with no history of DM, a single or intermittent dose of intravenous insulin were used to maintain glucose ≤180 mg $dL^{-1}$. After a single dose insulin therapy, blood glucose levels were re-evaluated and intravenous insulin regimen was started when necessary as recommended by Duggan et al.[12] In patients with NIDDM, the bolus dose calculated with the formula (blood glucose value – 100/40) then (blood glucose value/100 units/hour) infusion dose was applied when blood glucose was above 180 mg $dL^{-1}$.[12] Blood glucose levels were monitored with half an hour intervals.

Following adequate activated clotting time (>480 s), cannulation was performed and CPB was initiated. CPB was performed in moderate hypothermia (28–31°C). Hemoglobin concentrations were kept above 7.5 g $dL^{-1}$ 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 4 time points: after the induction of anesthesia before the surgery as baseline values (T1), at the 5–10$^{th}$ min of CPB (T2), at the 30–40$^{th}$ min of CPB (T3), and while the sternum was closing (T4). At these 4 time points, hemodynamic parameters, central venous oxygen saturation ($ScvO_2$), systemic vascular resistance (SVR), lactate level, $DO_2$, $VO_2$, $O_2ER$, mean arterial pressure (MAP), hemoglobin, and urine output were recorded.

**Table 1.** Demographic and clinical characteristics of the study population

| Variables | Group NoDM (n=64) | Group NIDDM (n=19) | p |
|---|---|---|---|
| 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; NoDM: Non-diabetic; NIDDM: Non-insulin-dependent diabetic patients; CPB: Cardiopulmonary bypass.

## 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. In addition, 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. p<0.05 for two-sided tests was considered statistically significant.

## Results

A total of 90 patients who underwent cardiac surgery 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 five patients in NoDM group, blood glucose levels did not exceed 140 mg

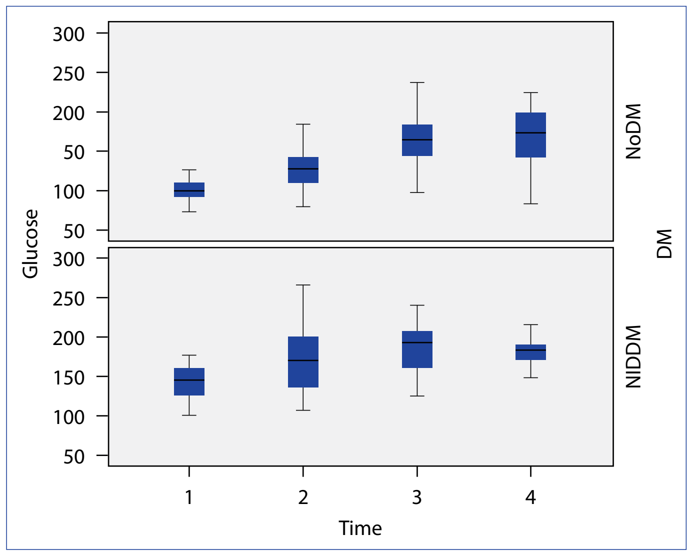


**Figure 1.** Blood glucose levels during four intraoperative time points.

dL$^{-1}$ 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 intraoperative 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 are 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<0.001) as expected. NIDDM group patients had 1.67 times higher blood glucose values than those with NoDM group (p<0.05) (95% CI: 1.47, 1.91). In general, time has a positive and statistically significant effect on blood glucose levels (p<0.001). As time progress-

**Table 2.** Intraoperative data during time points

| Variables | Group NoDM (n=64) | Group NIDDM (n=19) | p | p□ |
|---|---|---|---|---|
| Glucose | | | | <0.001* |
| T1 | 101.5 (128) | 153 (167) | <0.001*¥ | |
| T2 | 127.5 (127) | 170 (159) | <0.001*¥ | |
| T3 | 165 (182) | 193 (115) | 0.015*¥ | |
| T4 | 171 (186) | 182 (104) | 0.599¥ | |
| Lactate | | | | 0.426 |
| T1 | 0.90 (2.3) | 0.90 (1.5) | 0.568¥ | |
| 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¥ | |
| $DO_2$ | | | | 0.609 |
| T1 | 915 (1954) | 798 (1562) | 0.229¥ | |
| T2 | 525 (388) | 473 (266) | 0.095¥ | |
| T3 | 497 (492) | 450 (303) | 0.237¥ | |
| T4 | 729 (1315) | 647 (718) | 0.186¥ | |
| $VO_2$ | | | | 0.575 |
| T1 | 256 (537) | 243 (444) | 0.803¥ | |
| T2 | 166 (206) | 179 (179) | 0.862¥ | |
| T3 | 136 (204) | 118 (219) | 0.061¥ | |
| T4 | 204 (455) | 211 (599) | 0.786¥ | |
| $O_2ER$ | | | | 0.004* |
| T1 | 0.28 (0.32) | 0.31 (0.27) | 0.201¥ | |
| 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 | | | | 0.378 |
| T1 | 1295 (2430) | 1270 (1280) | 0.978¥ | |
| T4 | 820 (1460) | 940 (1090) | 0.165¥ | |
| $ScvO_2$ | | | | 0.080 |
| T1 | 0.73 (0.36) | 0.71 (0.29) | 0.198¥ | |
| 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 | | | | 0.063 |
| T1 | 13.70 (8.5) | 13 (4.6) | 0.132¥ | |
| 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 | | | | 0.606 |
| T1 | 76.33 (53.0) | 81 (44) | 0.380¥ | |
| T2 | 62 (50) | 63 (40) | 0.438¥ | |
| T3 | 70 (40) | 76 (33) | 0.368¥ | |
| T4 | 68.67 (42) | 73 (33) | 0.213¥ | |
| Heart rate | | | | 0.624 |
| T1 | 68±14 | 69±9 | 0.696ʋ | |
| T4 | 85±13 | 86.±14 | 0.944ʋ | |
| Urine output (cumulative) | | | | 0.753 |
| T1 | 50 (350) | 20 (500) | 0.660¥ | |
| 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 resistance; $ScvO_2$: Central venous oxygen saturation; MAP: Mean arterial pressure; ¥: Mann–Whitney U-test; Ŧ: GEE method; ʋ: Independent two-sample test; *: P<0.05.

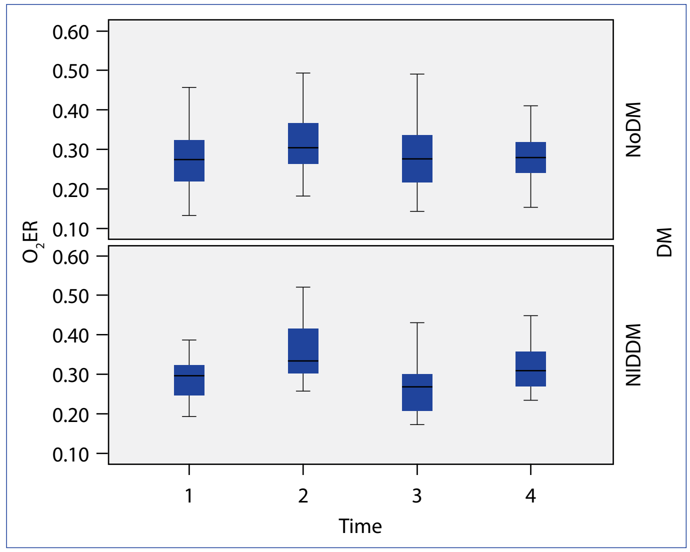


**Figure 2.** The $O_2ERs$ during four intraoperative time points.

es, 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 (Fig. 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) (Fig. 2). There is a statistically significant difference between the groups at the 4$^{th}$ time point (p=0.022). 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 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, post-operative complications, and mortality data were not statistically different, as shown in Table 3.

## Discussion

This study hypothesized that stress hyperglycemia may cause increased oxygen extraction ratio and may differ in non-diabetic and non-insulin-dependent diabetic patients undergoing cardiac surgery. The stress-induced hyperglycemic response during cardiac surgery was more severe in noDM patients than in patients with NIDDM (1.14 vs. 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.

**Table 3.** Intraoperative and postoperative variables of the study population

| Variables | Group NoDM (n=64) | | Group NIDDM (n=19) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Intraoperative transfusion | 9 | 14.1 | 3 | 15.8 | 1.000 |
| Intraoperative inotropic infusions | | | | | – |
| 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 | 6 | 9.4 | 2 | 10.5 | 1.000 |
| Cerebrovascular accident | 1 | 1.6 | 1 | 5.3 | 1.000 |
| Tamponade | 1 | 1.6 | 1 | 5.3 | 0.408 |
| Respiratory complications | 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.

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, and 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 levels in the NoDM group which stress hyperglycemia ratio was found 78% reached their highest values at 2nd and 3rd time points when CPB and hypothermia effects were strongest. In the NIDDM group, blood glucose levels were peaked during 2nd and 3rd time points, similar to the NoDM group. 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.[17] In another coronary surgery patient group, when a blood glucose target of 90–120 mg $dL^{-1}$ and 121–180 mg $dL^{-1}$ was achieved, no difference was observed in deep sternum wound infection, pneumonia, perioperative renal failure, or mortality.[18] 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.[19,20] 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 post-operative 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.[21]

In general, global body oxygen delivery in anesthesia practice is mathematically formulated by $DO_2$, that is, the product of CO 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, 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, the same study indicated that high blood glucose level is not suitable for use as a perioperative marker for global tissue hypoperfusion.[22] 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.[23] 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.[24,25] 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.[26] 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; and abnormal circulation, such as cyanotic shunt and arteriovenous malformation. In our study, the reason for the relatively high $O_2ER$ from the beginning of the operation in anesthetized patients may be due to 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, non-pulsatile 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 appear 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. Moreover, it would be more valuable if we had chance to measure cortisol levels to determine catabolic stress.

The stress-induced hyperglycemic response during cardiac surgery was more severe in NoDM patients than in patients with NIDDM. In terms of the $O_2ER$ parameter that reflects tissue oxygenation, NIDDM patients had significantly higher $O_2ER$ values than NoDM patients. When taken into account, $O_2ER$ reflects the total outcome of small changes on microcirculation, we can highlight the conclusion that NIDDM patients undergoing cardiac surgery have greater tissue oxygen demand/supply imbalance compared to NoDM patients.

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**Disclosures**

**Ethics Committee Approval:** The study was approved by The Ankara Türkiye Yüksek İhtisas Training and Reasearch Hospital Ethics Committee (Date: 11/01/2019, No: 29620911-929).

**Informed Consent:** Written informed consent was obtained from all patients.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Authorship Contributions:** Concept – A.D., E.B., H.Y.Ö.; Design – A.D., M.B.; Supervision – A.D., E.B.; Materials – E.B., H.Y.Ö.; Data collection &/or processing – E.B., H.Y.Ö.; Analysis and/or interpretation – A.D., M.B.; Literature search – A.D., E.B., H.Y.Ö., M.B.; Writing – A.D., E.B.; Critical review – H.Y.Ö., M.B.

**Etik Kurul Onayı:** Çalışma Ankara Türkiye Yüksek İhtisas Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylandı (Tarih: 11/01/2019, Numara: 29620911-929).

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**Hakem değerlendirmesi:** Dışarıdan hakemli.

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