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The relationship between renal oxygen saturation and renal function in patients with and without diabetes following coronary artery bypass grafting surgery

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The approval of the Ankara University School of Medicine ethics committee (23.11.2015/18-763-15).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Acute kidney injury may occur due to renal ischemia and hypoxia during coronary artery bypass surgery. Monitoring of renal regional tissue oxygenation might be useful to determine renal hypoxia. We aimed to investigate whether renal oxygen saturation values differ between diabetic and non-diabetic patients and evaluate the relationship between intra-operative renal oxygen saturation values and postoperative renal function.

Methods: Forty consecutive patients aged 18-65 years, who underwent elective coronary artery bypass grafting, were included in this prospective case-control study. Body mass index ≥30 kg/m^2 and the presence of renal damage were considered the exclusion criteria. Group I consisted of diabetic patients (n = 20), and Group II consisted of non-diabetic patients (n = 20). Near Infrared Spectroscopy (NIRS) recorded renal saturation values just before the intubation as the basal value and every 10 minutes after intubation in all patients. Creatinine clearances and glomerular filtration rates were calculated along with blood urea nitrogen and creatinine values on the postoperative 1st and 3rd days of all patients.

Results: The two groups were similar in terms of gender, age, body mass index, duration of surgery, cross-clamp time, and total cardiopulmonary bypass duration ($P>0.05$). While there was no difference between baseline values, significant differences were found between preoperative BUN and creatinine and POD 3 BUN and creatinine values in Group 1 ($P=0.003$ and $P=0.046$, respectively) and Group 2 ($P=0.018$ and $P=0.030$, respectively). There was no significant difference between two groups in renal oxygen saturation values considering both basal and post-intubation measurements ($P>0.05$ for all). However, an earlier decrease in renal oxygen saturation values was seen in diabetic patients ($P<0.05$). There was no significant relationship between the changes in intraoperative renal oxygen saturation values and postoperative renal function ($P>0.05$ for all).

Conclusion: Although coronary artery graft bypass surgery does not lead to a significant difference in renal saturation values, as determined by Near Infrared Spectroscopy, in diabetic patients compared to non-diabetic patients, NIRS may be helpful and beneficial to show renal ischemia in these patients.

Keywords: Diabetes mellitus, Coronary artery bypass grafting, Near-infrared spectroscopy, Acute kidney injury

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Introduction

Acute kidney injury (AKI) is seen after coronary artery bypass grafting (CABG) with an incidence of up to 45%. It is generally associated with prolonged mechanical ventilation and intensive care unit stay and is probably accompanied by increased mortality [1-4].

Near-Infrared Spectroscopy (NIRS) noninvasively monitors the regional oxygen saturation. It works continuously by measuring the concentration of oxygenated and non-oxygenated hemoglobin in the local tissue area of selected organs [5].

A correlation was shown between urinary biomarkers and low renal saturation values, as detected by NIRS, including the need for renal replacement therapy after cardiac surgery [6]. Contrary to these findings, there was no correlation with the development of AKI [2-4]. Although urinary output amount, blood urea nitrogen (BUN) and creatinine levels have been used as the preliminary indicators for renal function in CABG patients perioperatively, studies which compare renal oxygen saturation values by NIRS with postoperative renal functions are rare [1]. Therefore, evaluation of such a relationship remains controversial.

Even in diabetic patients without nephropathy, a known micro-vascular complication of chronic diabetes, the risk of developing AKI after cardiac surgery is higher than in non-diabetic patients [7]. Therefore, early prediction of the development of AKI in diabetic patients who undergo cardiac surgery may have an impact on the morbidity and mortality.

This study aimed to compare the peri-operative renal oxygen saturation values measured by NIRS in diabetic and non-diabetic adult patients undergoing CABG and evaluate the possible relationship between the peri-operative renal oxygen saturation values with postoperative urinary indicators including urine output, BUN and serum creatinine values.

Materials and methods

This study prospectively investigated patients aged 18-65 years who underwent elective CABG between January 2015 and January 2016 at Ankara University Faculty of Medicine Department of Cardiovascular Surgery after the approval of the Ankara University School of Medicine ethics committee (23.11.2015/18-763-15). The study was conducted in compliance with the Declaration of Helsinki. Written consent was obtained from all patients.

Patients with coronary artery disease and those undergoing elective CABG were included in the study. Emergent surgery, BMI >30 kg/m^2 and diabetes-induced renal micro- or macro-vascular complications were regarded as the exclusion criteria.

The patients were grouped into two as diabetic (Group 1) and non-diabetic (Group 2). Patients with type II diabetes mellitus who were taking oral antidiabetic and/or insulin therapy without any known renal micro- or macro-vascular complications were included in Group I.

An a priori power analysis was conducted using G*Power3 (Faul, Erdfelder, Lang, & Buchner, 2007) to test the difference between two independent group means using a two-tailed test, a medium effect size of d=0.50, and an alpha of 0.05. Result showed that a total of 32 participants with two equal sized groups of n = 16 was required to achieve a power of 0.80. So, it was planned to have at least 20 patients in both groups. Patients were consecutively included in the groups from the beginning of the study, considering the presence or absence of diabetes.

Demographic and clinical features of the patients (age, gender, and BMI) and perioperative (duration of the surgery, cross-clamp time, and total cardiopulmonary bypass duration) and postoperative findings were recorded using a prospectively held database. Hematocrit (%) levels were recorded preoperatively, after induction, pre-CABG, post-CABG, and before the transfer to the intensive care unit in all patients. Urine output was monitored hourly until discharge from the ICU. BUN (mg/dL) and creatinine (mg/dL) values of all patients were measured preoperatively, and on the 1st and 3rd postoperative days (POD 1 and POD 3, respectively). Creatinine clearance (ml/min) and glomerular filtration rate (GFR) were calculated according to following formulas [8]:

- For creatinine clearance, the Cockcroft-Gault formula was used:

  Creatinine Clearance (ml/min) = [[140 - age (years)] x weight (kg)] / [72 x serum creatinine (mg/dL)] (multiply by 0.85 in females).

- For GFR calculation, the simplified Modification of Diet in Renal Disease Study equation was used:

  GFR [ml/ min/1.73 m^2] = 186 x [serum creatinine (mg/dL)]$^{-1.154}$ x [age (years)]$^{-0.203}$ x (0.742 if female).

Peri-operative follow-up

All patients were routinely monitored via electrocardiography, pulse oximetry and non-invasive blood pressure tracing before the induction of anesthesia. Invasive radial artery monitoring was performed before the induction in patients with an ejection fraction (EF) of <50%. Following monitoring, midazolam (0.06 mg/kg) (Demizolam, ampoule, 15 mg/3 ml, Actavis, Istanbul, Turkey) was administered after intravenous access. For induction of anesthesia, 6 mg/kg thiopental sodium (Pentothal Sodium, ampoule, 1 g, Abbott, Istanbul, Turkey), 0.1 mg/kg vecuronium bromide (Norcuron, ampoule, 4 mg, Schering Plough, Istanbul, Turkey) and 1 mcg/kg fentanyl (Fentanyl, ampoule, 0.05mg-ml, 10 ml, Johnson & Johnson, Istanbul, Turkey) were administered. After intubation, oxygen and air mixture was given at 2-4 L per minute. The tidal volumes of patients were set at 6 mL/kg, aiming to have an end-tidal carbon dioxide pressure value of 33-35 mmHg.

Direct blood pressure monitoring with radial artery cannulation was performed in all patients whose blood pressures were non-invasively monitored, and central venous pressure monitoring was performed with right internal jugular vein catheterization. In addition to sevoflurane (Sevoran Liquid, liquid, Abdi Ibrahim, Istanbul, Turkey) with a minimum alveolar concentration of 1.3, remifentanil infusion at a dose of 0.05 mcg/kg/min (Ultiva, vial, 1 mg, Glaxo Smith Kline, Istanbul, Turkey), intermittent doses of midazolam and muscle relaxant vecuronium bromide were used in maintenance anesthesia.

Partial oxygen saturation, lactate, and hematocrit levels were routinely recorded. Renal saturation values were recorded with NIRS at baseline, and every 10 minutes following intubation. After the termination of maintenance anesthesia following CABG, all patients with stabilized vital parameters were transferred to the cardiovascular surgery intensive care unit, intubated.

Renal NIRS technique

NIRS electrodes were placed at the intersection of the posterior axillary line with the 12th rib on both sides of all patients to evaluate intraoperative renal perfusion. To decide the exact value of renal oxygen saturation, the lowest value obtained from both sides was regarded as the final measurement. Renal oxygen saturation (rO_2) values were obtained as the basal measurement before the intubation and 10 minutes after intubation (Figure 1).

Figure 1: Renal NIRS measurement

Statistical analysis

Patients in both groups were compared in terms of gender, age, ejection fraction, BMI, operation time, cross-clamp and cardiopulmonary bypass periods and concomitant disease.

The data were analyzed in the SPSS for Windows 15 package program (SPSS, Inc., Chicago, IL, USA). Mean (standard deviation) values were presented for variables with a normal distribution, median (min-max) values were used for non-normally distributed variables, and the number of cases (%) were used for nominal variables. The significance of differences between the groups was determined by the t-test, and those between the median values was assessed by the Mann Whitney U test. Nominal variables were evaluated by Pearson Chi-Square or Fisher exact test. The paired t-test was used if the variation distribution according to time was normal before and after the treatment, and the Wilcoxon test was used in case of non-normal distribution. Analysis of variance was used for repeated measures if the variation of the distribution of the repeated measures obtained before and during the treatment period was normal. In case of non-normal distribution, the Friedman test was used. Spearman correlation test was utilized when the relationship between continuous variables was non-normal, and the Pearson correlation test was used when it was normal. *P* values of <0.05 were considered statistically significant.

Results

There were 14 males and 6 females in Group 1 and 16 males and 4 females in Group 2. The groups were similar in terms of gender distribution, age, BMI, duration of the surgery, cross-clamp time, and total cardiopulmonary bypass duration ($P>0.05$ for all) (Table 1).

Table 1: Demographic and clinical data of the groups

	Group 1 n=20	Group 2 n=20	*P*-value
Age (year)[¥]	62.2 (10.7)	63.7 (8.2)	0.602
Gender (F/M)	6/14	4/16	0.465
BMI (kg/m^2)[¥]	27.3 (2.1)	26.7 (2.3)	0.289
Duration of surgery (min)[¥]	262.7 (45.2)	264.5 (45.1)	0.640
Cross-clamp time (min)[¥]	56.6 (21.6)	60.1 (19.9)	0.620
Total cardiopulmonary bypass duration (min)[¥]	104.2 (35.8)	116.1 (22.4)	0.149

[¥]: mean (standard deviation), F: Female, M: Male, BMI: Body mass index

There was no significant difference between the groups considering hematocrit values in the preoperative period and during the surgical procedures (Table 2). However, there was a significant decrease in hematocrit values before CABG, after CABG and at the end of surgery compared to the preoperative values in intra-group analyses. In Group 1, the hematocrit value of 39.07 (6.5) % decreased to 32.30 (6.7) % just before CABG, to 24.6 (4.0) % after CABG and to 26.79 (3.7) % at the end of the surgery ($P<0.05$ for all). Such significant decreases were also seen in Group 2 (Table 2).

There was no significant difference between the two groups in terms of BUN, creatinine, creatinine clearance and GFR values during the preoperative period, at POD 1 and POD 3 (Table 3).

Table 2: Hematocrit values (%)

	Preoperative	After induction	Before CABG	After CABG	At the end of surgery
Group 1	39.07 (6.5)	34.98 (6.2)	32.30 (6.7)	24.6 (4.0)	26.79 (3.7)
Group 2	37.07 (8.7)	34.98 (5.4)	33.64 (6.3)	25.60 (3.0)	26.46 (3.5)
P-value[β]	0.862	0.495	0.620	0.429	0.947

[¥]: mean (standard deviation), [β]: *P*-value between the groups

Table 3: Intra- and intergroup comparison of the urinary indicators

Parameter[¥]	Group 1	Group 2	*P*-value [0]	*P*-value [1]	*P*-value [2]
BUN (mg/dL)	16.9 (6.9)	15.4 (5.6)	0.602	--	--
BUN (mg/dL) POD 1	16.7 (6.4)	16.9 (6.3)	0.947	0.920	0.224
BUN (mg/dL) POD 3	22.6 (7.7)	19.8 (7.0)	0.253	0.003	0.018
Creatinine (mg/dL)	1.0 (0.2)	0.9 (0.1)	0.640	--	--
Creatinine (mg/dL) POD 1	1.0 (0.3)	1.1 (0.3)	0.277	0.145	0.014
Creatinine (mg/dL)POD 3	1.1 (0.3)	1.1 (0.3)	0.495	0.046	0.030
CrCl (ml/min)	90.8 (36.2)	90.8 (21.1)	0.820	--	--
CrCl (ml/min) POD 1	87.0 (40.7)	79.6 (27.8)	0.758	0.263	0.027
Cr Cl (ml/min) POD 3	83.5 (39.2)	83.1 (24.8)	0.512	0.126	0.040
GFR (ml/ min/1.73 m^2)	84.3 (27.3)	86.5 (15.9)	0.495	--	--
GFR (ml/ min/1.73 m^2) POD 1	79.7 (28.3)	74.4 (25.9)	0.414	0.247	0.024
GFR (ml/ min/1.73 m^2) POD 3	76.0 (30.1)	78.1 (21.9)	0.461	0.117	0.044

[¥]: mean (standard deviation), BUN: Blood urea nitrogen, POD 1: postoperative day 1, POD 3: postoperative day 3, CrCl: creatinine clearance, GFR: Glomerular filtration rate, [0]: When two groups are compared. [1]: When the values of group I are compared with baseline (preoperative value). [2]: When the values of group II are compared with baseline (preoperative value).

In group 1, there were significant differences between preoperative BUN and creatinine values and POD 3 BUN and creatinine values ($P=0.003$ and $P=0.046$, respectively). However, no significant association was found between creatinine clearance and GFR (Table 3).

Similar to Group 1, significant differences were found between preoperative BUN and creatinine values and POD 3 BUN and creatinine values in Group 2 ($P=0.018$ and $P=0.030$, respectively). In addition, creatinine clearance and GFR values significantly decreased at POD 3 compared to preoperative values ($P=0.040$ and $P=0.044$, respectively) (Table 2), There was no significant difference between Groups 1 2 in terms of urine volume (ml) before, during and after CABG (Table 4).

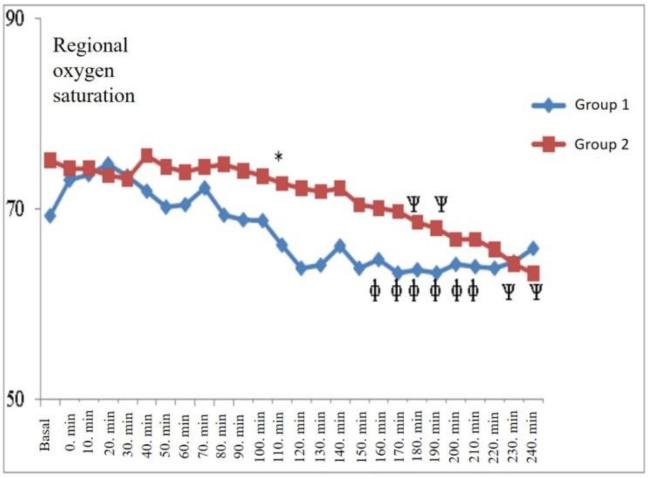
Table 4: Comparison of total urinary volume (ml) during POD 1

	Before CABG[¥]	During CABG[¥]	After CABG[¥]
Group 1	195 (158)	916 (464)	500 (343)
Group 2	195 (180)	1044 (473)	556 (238)
P-value	0.620	0.355	0.383

[¥]: mean (standard deviation)

There was no significant difference between the baseline rO_2 levels of the patients (Figure 2). Although the pattern for the decrease in rO_2 measurements was similar until an average of 110 minutes after the start of surgery, there was a significant difference at this point between Group 1 and 2 ($P<0.05$). In addition, an earlier decrease was observed from the baseline value of rO_2 in Group 1 compared to Group 2 (Figure 2).

Figure 2: rO_2 changes over time



*: $P<0.05$ when compared to Group 1 and Group 2, ϕ: $P<0.05$ when compared to baseline values in Group 1, Ψ: $P<0.05$ when compared to baseline values in Group 2

Discussion

Renal oxygen saturation levels measured by NIRS was lower compared with basal in diabetic and non-diabetic patients undergoing CABG. Although it was significantly lower in diabetics than in non-diabetics, it did not make sense clinically when creatinine and urine output levels were considered.

During open heart surgery, ischemic changes that may occur in splanchnic organs such as the liver and the kidney lead to an increase in postoperative hospital stay, morbidity, and mortality rates. Ascione et al. [9] found that damage to the splanchnic organs was more prominent in patients who were treated with extracorporeal circulation. They also mentioned that more than 24 hours is required for the development of such symptoms. In a case series of 500 patients who underwent cardiopulmonary bypass and who were alive after 24 hours, Khilji et al. reported that acute renal failure rate (creatinine >2.5 mg/dl) was 7%, rate of acute renal dysfunction (creatinine 1.6-2.4 mg/dl) was 20.4% and the mortality rate in patients with AKI was 88% [10]. This shows how important it is to follow the circulation in the splanchnic organs during open heart surgery.

Owens et al. [5] observed renal oxygenation of the patients who underwent pediatric cardiac surgery in the peri-operative and postoperative 48-hour period with NIRS and found that low renal oximetry follow-up was correlated with acute renal failure. In our study, the change in the values of renal oxygen saturation in each patient did not exceed 20%. Reductions of more than 20% from the baseline tissue oxygen saturation values with the NIRS method are considered significant. In addition, there was no significant difference between the baseline measurements of renal oxygen saturation in terms of NIRS values between the diabetic and non-diabetic groups in the present study. No significant correlation was found between changes in intra-operative renal NIRS values and postoperative renal function. However, although there was no significant between the renal NIRS values between the two groups, rO_2 started to fall earlier in Group 1 (the diabetic group) than Group 2 (the non-diabetic group). This decrease reached a significant level at the 110th minutes of the operation. In both groups, the decrease in rO_2 levels was increased as the duration of surgery was prolonged (not given in the text).

This is considered undetected nephropathy, a microvascular complication that develops in diabetic patients. Even 20-30% of the patients undergoing coronary artery surgery have diabetes, the patients with diabetic nephropathy were not included in the study [11, 12]. Although the duration of the diagnosis of diabetes mellitus was not considered in patients with type II diabetes in our study, exclusion of the patients with nephropathy could not be effective to prevent such co-existence.

Although there is no clear and precise information on the use of NIRS in adult patients, we are convinced that NIRS may be useful in monitoring liver and the kidney oxygenation, particularly in patients at risk for renal and ischemic events in appropriate (non-obese patients) cases. The present study was conducted on the diabetic and non-obese patients (BMI <30 kg/m^2) who may be at risk for peri-operative renal ischemia. Therefore, the NIRS method may be a meaningful way to evaluate the somatic oxygen saturation in appropriate adult patients.

Hyperglycemia, which may be present in diabetic patients, is known to adversely affect overall postoperative outcomes [13]. Thus, DM is an independent and potent risk factor for renal insufficiency [14]. In a study by Stallwood and colleagues [15], CABG has been shown to increase the risk of renal insufficiency 2.6-fold. Although this may suggest that the cardiac surgical procedures in diabetic patients may further increase renal insufficiency, there was no significant difference in BUN, creatinine, creatinine clearance and GFR between the diabetic and the non-diabetic groups in our study. Therefore, large-scale prospective studies are needed to clarify this controversial issue.

AKI, a common complication following CABG, is associated with high mortality, extended hospital stays, and increased health expenditures [16]. The frequency of AKI after open heart surgery ranges between 5-48%. The short- and long-term mortality risk increased significantly in the postoperative period in patients with AKI [17]. In the present study, although the longer follow-up periods following CABG were not studied, there was no short-term mortality in both groups.

Serum creatinine level and/or GFR values are used to evaluate the renal functions in the peri-operative periods for almost all types of major surgical procedures. These variables are strong indicators for AKI that can develop postoperatively [18]. In this study, serum creatinine and BUN values were within normal limits in all patients preoperatively due to the inclusion criteria. In addition, there was no statistically significant difference between GFR and creatinine clearance in both groups preoperatively. However, significant increases at POD 3 BUN and creatinine values were observed in both groups. Although creatinine clearance and GFR values significantly decreased at POD 3 in Group 2, the small size of the groups may cause such difference.

Anemia predisposes to AKI [19]. The presence of anemia before CABG alone or in combination with pre- and post-CABG is known to be associated with postoperative AKI development and increased mortality [20]. Prolonged duration of CABG causes an increased rate of hemolysis, and as a result, free hemoglobin acts as an endogenous toxin causing pigment nephropathy. Therefore, the increased duration of CABG also causes an increased risk of AKI [21]. In this study, the decrease in renal NIRS by the duration of the surgery was correlated; therefore, it may have a significant impact on prospective studies.

Some of the challenges we face in this study suggest that there is a need for novel studies on NIRS for evaluation of somatic oxygenation in adult patients undergoing open heart surgery. Since the distance between the somatic organs and the skin is close in pediatric patients, the data obtained with NIRS are reliable, but the reliability of the data obtained with NIRS may be decreased, especially in adult and obese patients. The ideal way to overcome this problem is to locate the NIRS probes where the kidneys are closest to the skin via preoperative ultrasonographic evaluations. That way, it can be possible to find exact points in which the distance between the skin and the kidney is within 2 to 2.5 cm- the optimum distance for these probes. Failure to perform such an evaluation may disturb the interpretation of the results. For that reason, the patients with BMI <30 kg/m^2 were included in the study.

Limitations

This study has some limitations. First, the number of patients in both groups was low, and AKI did not develop in the study group, so the results could not be evaluated in relation to the development of AKI. Second, ultrasound was not used for the placement of renal NIRS probes; therefore, it was not possible to determine whether the distance between the skin and the kidney was 2-2.5 cm. This can have an impact on the reliability of the results obtained.

Conclusion

NIRS may be helpful and beneficial to show renal ischemia in patients following CABG. Although it was significantly lower in diabetics than in non-diabetics, it did not correlate with creatinine and urine output levels. However, large-scale prospective studies including adult obese patients and use of ultrasonography to localize the NIRS probes are needed.

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