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The effect of remifentanil and dexmedetomidine on dynamic thiol/disulfide balance in patients undergoing coronary artery bypass surgery: a prospective case-control study

M. IZGI[1], B. BASARAN[2], T. BAYIR[3], B. AKCA[1], B. CELEBIOGLU[1]

[1]Department of Anesthesiology and Reanimation, Hacettepe University School of Medicine, Ankara, Turkey
[2]Department of Anesthesiology and Reanimation, Karamanoglu Mehmet Bey University, School of Medicine, Karaman, Turkey
[3]Department of Biostatistics, Selcuk University School of Veterinary Sciences, Konya, Turkey

Abstract. – OBJECTIVE: It is established that the balance of serum thiols is disrupted in favor of oxidants in coronary artery disease, and the cardiopulmonary bypass pump used during coronary artery bypass surgery disrupts this balance in favor of oxidants. In this study, we investigated the antioxidant effects of remifentanil or dexmedetomidine on thiol-disulfide balance and paraoxonase-1 (PON-1) levels during on-pump coronary artery bypass surgery.

PATIENTS AND METHODS: A total of 100 patients who underwent on-pump coronary artery bypass grafting surgery between May 2018 and December 2018 were included in the study. Patients were divided into two groups: the remifentanil group (Group R) and the dexmedetomidine group (Group D). Venous blood samples were obtained from the patients after induction of anesthesia [Time 1 (T-1)], then after cross-clamping of the aorta (T-2), after removal of the cross-clamp (T-3), 10 minutes after the end of protamine infusion (T-4), and 24 hours postoperatively (T-5). Serum total thiol, native thiol, disulfide, and PON-1 levels were evaluated.

RESULTS: Total thiol, disulfide, PON-1, native thiol/total thiol, total thiol/disulfide, and native thiol/disulfide levels were similar between the two groups. Native thiol levels were statistically significantly higher in group D compared to group R at T-3 and T-5 ($p = 0.017$ and $p = 0.027$, respectively). When T-1 and T-5 times were compared in intragroup measurements, disulfide levels were significantly lower, and native thiol/total thiol ratios were significantly higher at T-5 ($p < 0.001$).

CONCLUSIONS: In conclusion, in light of the data obtained from this study, it can be concluded that dexmedetomidine used during surgery has a better contribution to oxidant-antioxidant balance than remifentanil in patients undergoing coronary artery bypass surgery with the on-pump method.

Key Words:
Coronary artery bypass graft surgery, Dexmedetomidine, Paraoxonase-1, Remifentanil, Thiol-disulfide homeostasis.

Introduction

Reactive oxygen products are a byproduct of the normal metabolic process in aerobic organisms. Life is sustained by a balance between oxidant and antioxidant mechanisms. Disruption of this balance is defined as oxidative stress (OS). Oxidative products damage many biological molecules, especially proteins, lipids, and nucleic acids[1,2].

Organic compounds containing a sulfhydryl group, which consists of sulfur and hydrogen atoms, are called thiols, and these compounds are organic substances that play an important role in defense against OS with their reducing properties[3]. When oxidative products such as reactive oxygen species form in the organism, these compounds are reduced by transferring their excess electrons to thiol-containing compounds, oxidizing the thiol groups and leading to the formation of disulfide bonds. This is a reversible reaction, and the resulting disulfide bonds can be reduced to thiol groups. Thus, dynamic thiol-disulfide homeostasis (TDH) is achieved. This dynamic TDH plays a critical role in antioxidant defense, detoxification, apoptosis, regulation of enzymatic activity, and cellular signal transduction. Recent studies[1-3] have reported that disruption of this homeostasis can cause various diseases, especially cardiovascular diseases. Paraoxonase (PON) is an ester hydrolase synthesized in the liver, has 3 subtypes, and has both arylesterase

Corresponding Author: Murat Izgi, MD, Ph.D; e-mail: muratizgi@hotmail.com

and paraoxonase activity. Paraoxonase-1 (PON-1) has been reported to protect both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) from oxidation[4]. In the first case-controlled study in humans[5] in 1997, serum PON-1 enzyme levels and activity were found to be low in patients with coronary artery disease independent of other causes, suggesting that PON-1 enzyme activity may be a risk marker for coronary artery disease. The starting point of coronary artery disease and endothelial dysfunction is OS, and the PON1 enzyme reduces OS through its antioxidant effect. PON-1 activity is inversely correlated with atherosclerosis and is lower in diseases that accelerate the development of atherosclerosis.

Continuous passage of blood through the extracorporeal circuit during cardiopulmonary bypass (CPB) leads to an increase in oxidative stress, which is caused by hemolysis, ischemia-reperfusion injury, and neutrophil activation. Oxidative stress plays a crucial role that can affect the function and recovery of organs such as the myocardium, lungs, and kidneys. Administration of antioxidant agents directly intravenously or in cardioplegia solution during surgery may reduce oxidant levels and OS during CPB[6]. Ideal anesthetic management should contribute to reducing the burden of oxidative stress on metabolism. This antioxidant effect is also beneficial to surgical recovery[7]. During cardiovascular surgery, remifentanil or dexmedetomidine are used as adjuvant agents to reduce the need for anesthetic agents by increasing the depth of anesthesia and providing analgesic efficacy and hemodynamic stability. Studies[8-10] supporting that both agents have antioxidant and cardioprotective effects have been published in the literature.

In this prospective observational study, we aimed to evaluate the effect of intraoperative remifentanil or dexmedetomidine on the oxidant-antioxidant balance in patients undergoing coronary artery bypass graft (CABG) surgery through PON-1 and TDH levels. We planned this study with the hypothesis that the effect of dexmedetomidine on the oxidant-antioxidant balance would be more in favor of antioxidants than remifentanil.

Patients and Methods

This study protocol was approved by Hacettepe University Non-Interventional Clinical Studies Ethics Committee on May 3rd, 2018, with the number GO 18/377-20 and funded by Hacettepe University Scientific Research Projects Coordination Unit with the project number THD-2018-17193. This article was written in accordance with the current Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. This study, which we designed as a prospective case-control study, was conducted in the cardiovascular surgery operating rooms of Hacettepe University Hospitals between June 1, 2018, and December 31, 2018, after obtaining ethics committee approval. All patients included in the study were informed about the study during preoperative evaluation, and their written informed consent was obtained.

Patients over 18 years of age who underwent CABG surgery with the on-pump method were included in the study. Patients who did not consent, patients with missing or incomplete data, patients aged < 18 years, patients in which any of the planned blood samples could not be obtained, and patients with an American Society of Anesthesiologists (ASA) score > III were excluded from the study. A total of 108 patients were evaluated for inclusion in the study, and 8 patients who did not consent to participate in the study were excluded (Figure 1). Patients were divided into the remifentanil group (Group R) and the dexmedetomidine group (Group D) according to the adjuvant agent used. A total of 100 patients, 50 from each group, were included in the study (Figure 1). Blood samples were obtained for the measurement of serum PON1, total thiol, native thiol, and disulfide levels at 5 different time points.

Due to the observational nature of our study, patient randomization was not performed, and it was left entirely to the preference of the attending anesthesiologist to decide which of the patients would receive remifentanil and which would receive dexmedetomidine. The attending anesthesiologist of the operations was not directed for any procedure. Patient data and blood samples continued to be collected until a total of 50 patients from each group were included in the study.

In addition to standard ASA monitoring, invasive arterial blood pressure, central venous pressure, urinary catheter, body temperature, and near-infrared spectroscopy (NIRS) monitoring, which is per clinical routine in our clinic, were performed in patients admitted to the operating room for surgery. General anesthesia was induced with midazolam 0.01-0.1 mg/kg, propofol 1-2.5 mg/kg, fentanyl 1-2 mcg/kg, and rocuronium 0.6-1 mg/kg by the attending anesthesiologist per clinical

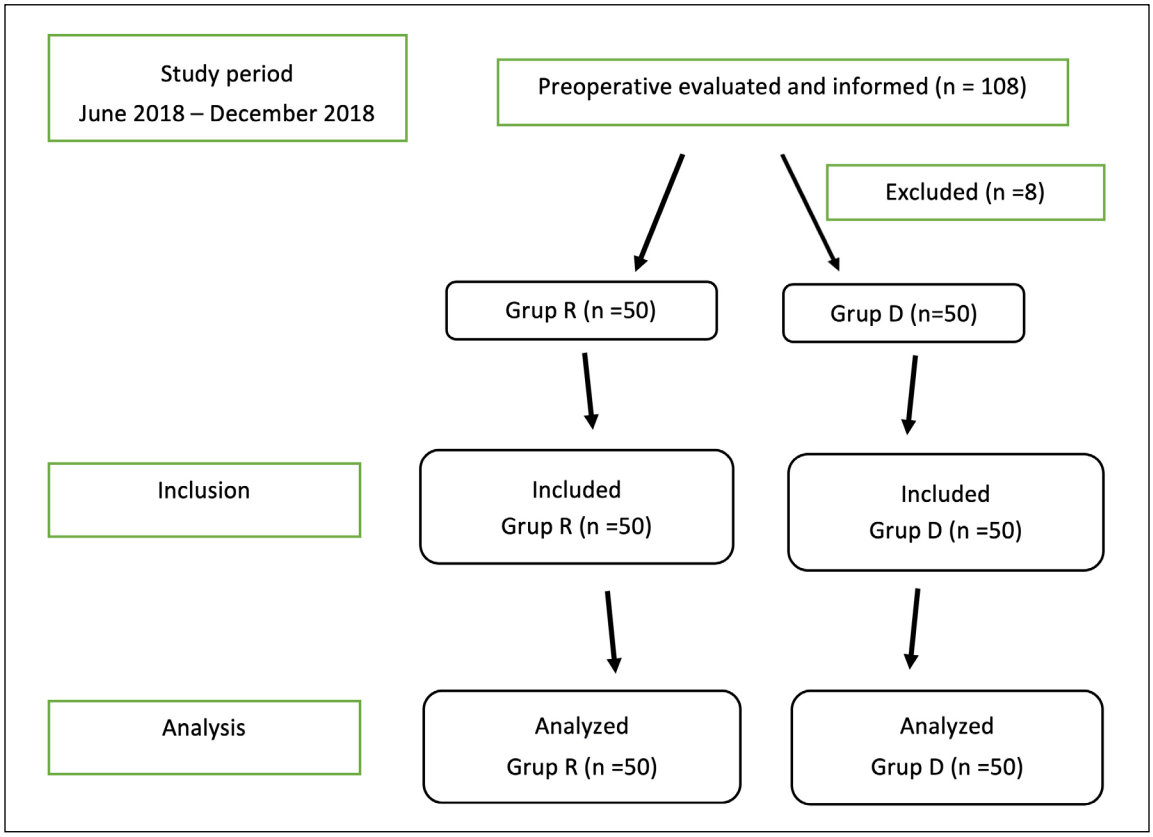

Figure 1. Flow diagram of the study.

routine protocol of our clinic, followed by endotracheal intubation. Remifentanil 0.05 mcg/kg/min or dexmedetomidine 0.4 mcg/kg/h was used intravenously (IV) as an adjunctive agent during the entire maintenance period, starting with induction, according to the preference of the attending anesthesiologist. Each patient received 16 mg of IV dexamethasone. For maintenance of anesthesia, 2% sevoflurane, a 50% O_2/air mixture, and dexmedetomidine or remifentanil were used per the preference of the attending anesthesiologist. All cases undergoing CABG surgery were operated with the on-pump technique, and during the CPB period, maintenance of anesthesia was achieved with 2% sevoflurane administered through the CPB pump and remifentanil or dexmedetomidine administered intravenously. After discontinuation of all anesthetic agents at the end of the surgery, all patients were transferred intubated to the cardiovascular surgery intensive care unit.

In addition to the routine procedures, 5 ml of central venous blood samples were obtained from the patients at 5 different times for the measurement of serum PON1, total thiol, native thiol, and disulfide levels. These blood samples were obtained immediately after induction of anesthesia, following central venous catheterization through the internal jugular vein (T-1), then immediately after removal of the cross clamp (T-2), when the cross-clamp was removed and the patient was started to be warmed (T-3), 10 minutes after the end of protamine infusion (T-4), and 24 hours postoperatively (T-5). Venous blood samples were obtained through a central venous catheter, placed in a red-capped biochemistry tube, and centrifuged at 4,000 rpm for 10 minutes (Hettich Zentrifugen Universal 320 R, Andreas Hettich GmbH & Co; Tuttlingen, Germany), and the plasma was separated. The plasma samples were obtained from the plasma remaining on the top layer of the tube with a micropipette and then placed in Eppendorf tubes and stored at -80°C until they were sent to the laboratory. After all samples were obtained, the relevant parameters were delivered to the laboratory by the cold chain. Commercial kits (Rel Assay Diagnostics, Gaziantep, Turkey) were used to analyze serum PON-1, native thiol, total thiol, and disulfide levels by the Erel method[11]. As a result, the antioxidant activi-

ty of both agents was compared with each other, and it was evaluated whether they were superior to each other in clinical use.

Statistical Analysis

In order to calculate the minimum required sample size before the study, a power analysis was performed with the criteria of type 1 error probability (alpha) = 0.05, power (1-beta) = 0.80, and effect size of 0.3, and it was calculated that the minimum required sample size was at least 92 (46 in each group). The GPower 3.1 (Düseldorf, Germany) program was used for power analysis.

Statistical Package for the Social Sciences (SPSS) software package (Ver. 23.0, IBM Corp., Armonk, NY, USA) was used for statistical analysis. To decide which statistical test to use, the homogeneity of variances was tested by Levene's test, and the normality assumption was tested by the Shapiro-Wilk test. Age and body mass index (BMI) variables were compared using an independent sample *t*-test (Student's *t*-test), and the results were given as mean ± standard deviation. The n and % values of gender and comorbidity variables are given in the table, and comparisons were made using the Chi-square test in the analysis of categorical data. Differences between groups and time were compared using repeated measures analysis of variance (ANOVA) for repeated measures, and results are given as mean ± standard error. A *p*-value < 0.05 was considered statistically significant.

Results

The demographics (age, gender, body mass index) of both groups were similar (Table I). Duration of cross-clamping, duration of CPB, duration of surgery, total duration of anesthesia, and the amount of fluids administration were similar between the groups ($p > 0.05$). However, the difference in urine output between group R and group D was statistically significant ($p = 0.002$) (Table I).

When total thiol, disulfide, PON-1, native thiol/total thiol, total thiol/disulfide, and native thiol/disulfide levels were compared between the two groups, they were similar in all measured periods. Native thiol levels were statistically significantly higher in group D than in group R at T3 and T5 ($p = 0.017$ and $p = 0.027$, respectively) (Table II).

When T1 and T5 times were compared in intragroup measurements, disulfide levels at T5 were significantly lower than T1 (Figure 2). On the other hand, native thiol/total thiol ratios at T5 were significantly higher than T1 ($p < 0.001$) (Figure 3, Table II).

When total thiol, native thiol, disulfide, PON-1, native thiol/total thiol, total thiol/disulfide, and native thiol/disulfide levels were evaluated against time within the group, statistically significant changes were observed in all parameters (Table II).

Table I. Demographics and intraoperative data of patients.

	Group R	Group D	p
Age, year	63.2 ± 9.9	63.4 ± 11.7	0.949
Sex			
Male	41 (82)	36 (72)	0.235
Female	9 (18)	14 (28)	
BMI, kg/m²	27.12 ± 3.19	27.44 ± 3.46	0.634
Comorbidity			
Yes	8 (16)	12 (24)	0.317
No	42 (84)	38 (76)	
Cross-clamp time, minute	64.40 ± 3.62	69.28 ± 3.66	0.345
Cardiopulmonary bypass time, minute	113.26 ± 5.98	117.66 ± 5.64	0.594
Total surgical time, minute	262.90 ± 9.78	278.60 ± 7.39	0.203
Total anesthesia time, minute	298.30 ± 10.10	316.10 ± 7.44	0.159
Total cristalloid given, ml	3,146.00 ± 82.62	3,260.00 ± 91.74	0.358
Urine output, ml	**1,216.00 ± 77.54**	**1,609.00 ± 99.93**	**0.002***

Categorical values are presented as n and %, age and BMI values are presented as mean ± standard deviation, and continuous values other than these are presented as mean ± standard error. The sign *indicates the significant difference between the groups ($p < 0.05$). BMI: body mass index, kg: kilogram, m^2: square meters, ml: milliliter.

Table IV. Evaluation of group, time, and group-time interactions of Total Thiol, Native Thiol, Disulfide and Paraoxanase-1 measurement results and Native Thiol/Total Thiol, Native Thiol/Disulfide and Total Thiol/Disulfide ratios of Remifentanil (R) and Dexmedetomidine (D) groups.

N	Group	Time					Est. Marginals Mean	*p*-value		
		T1	T2	T3	T4	T5		Group	Time	G*T
Total Thiol (µmol/L)	R	296.14 ± 9.82	177.46 ± 9.29	207.68 ± 6.58	338.82 ± 47.54	293.50 ± 8.14	262.72 ± 10.17	0.823	***p* < 0.001**	0.150
	D	320.50 ± 10.32	178.38 ± 10.43	224.08 ± 12.30	284.88 ± 13.16	321.92 ± 14.16	265.95 ± 10.17			
Est. Marginal Means		308.32 ± 7.12[a]	177.92 ± 6.98[c]	215.88 ± 6.98[b]	311.85 ± 24.67[a]	307.71 ± 8.17[a]				
Native Thiol (µmol/L)	R	170.66 ± 6.78	89.80 ± 4.41	**93.32 ± 3.73**	126.82 ± 9.35	**200.36 ± 7.77**	**136.19 ± 5.01[a]**	**0.037**	***p* < 0.001**	0.092
	D	183.92 ± 5.81	100.16 ± 4.90	**108.54 ± 5.04**	127.94 ± 4.49	**235.52 ± 13.59**	**151.22 ± 5.01[b]**			
Est. Marginal Means		177.29 ± 4.46[a]	94.98 ± 3.30[b]	100.93 ± 3.13[b]	127.38 ± 5.19[a]	217.94 ± 7.83[a]				
Disufide (µmol/L)	R	62.74 ± 3.96	43.83 ± 4.07	57.18 ± 2.73	106.00 ± 19.68	46.57 ± 2.87	63.26 ± 4.10	0.312	***p* < 0.001**	0.191
	D	68.29 ± 4.33	39.11 ± 3.94	57.77 ± 5.09	78.47 ± 5.95	43.20 ± 3.85	57.37 ± 4.10			
Est. Marginal Means		65.52 ± 2.93[ab]	41.47 ± 2.83[c]	57.48 ± 2.89[b]	92.24 ± 10.28[a]	**44.89 ± 2.40[c]**				
Paraoxonase-1 (U/L)	R	263.46 ± 33.32	135.00 ± 16.52	133.48 ± 15.85	160.24 ± 18.82	245.30 ± 19.94	187.50 ± 18.28	0.927	***p* < 0.001**	0.934
	D	258.32 ± 25.12	132.82 ± 13.04	131.06 ± 12.39	160.90 ± 13.85	242.48 ± 16.13	185.12 ± 18.28			
Est. Marginal Means		260.89 ± 20.86[a]	133.91 ± 10.52[b]	132.27 ± 10.06[b]	160.57 ± 11.68[c]	243.89 ± 12.82[a]				
Native Thiol/Total Thiol	R	0.58 ± 0.02	0.54 ± 0.03	0.46 ± 0.02	0.45 ± 0.02	0.68 ± 0.02	0.54 ± 0.02	0.069	***p* < 0.001**	0.393
	D	0.59 ± 0.02	0.59 ± 0.02	0.51 ± 0.02	0.48 ± 0.02	0.74 ± 0.02	0.58 ± 0.02			
Est. Marginal Means		0.59 ± 0.01[a]	0.56 ± 0.02[a]	0.59 ± 0.01[b]	0.46 ± 0.02[b]	**0.71 ± 0.01[c]**				
Native Thiol/Disulfide	R	4.21 ± 0.98	2.75 ± 0.43	1.90 ± 0.17	2.09 ± 0.31	7.27 ± 1.99	3.64 ± 0.54	0.175	***p* < 0.001**	0.350
	D	3.17 ± 0.20	3.98 ± 0.55	3.42 ± 0.84	2.50 ± 0.51	10.37 ± 2.37	4.69 ± 0.54			
Est. Marginal Means		3.69 ± 0.50[b]	3.37 ± 0.35[b]	2.66 ± 0.43[b]	2.29 ± 0.30[b]	8.82 ± 1.54[a]				
Total Thiol/Disulfide	R	6.21 ± 0.98	4.75 ± 0.43	3.90 ± 0.17	4.09 ± 0.31	9.27 ± 1.99	5.64 ± 0.54	0.175	***p* < 0.001**	0.350
	D	5.17 ± 0.20	5.98 ± 0.55	5.42 ± 0.84	4.50 ± 0.51	12.37 ± 2.37	6.69 ± 0.54			
Est. Marginal Means		5.69 ± 0.50[b]	5.37 ± 0.35[b]	4.66 ± 0.43[b]	4.29 ± 0.30[b]	10.82 ± 1.54[a]				

Mean ± standard error values are given in the table. The letters a, b, and c indicate the difference between the times ($p < 0.001$). The letters a, and b indicate the difference between the groups ($p < 0.05$). Est.: estimated, µmol: micromole, L: liter, U: unit, G: group, T: time.

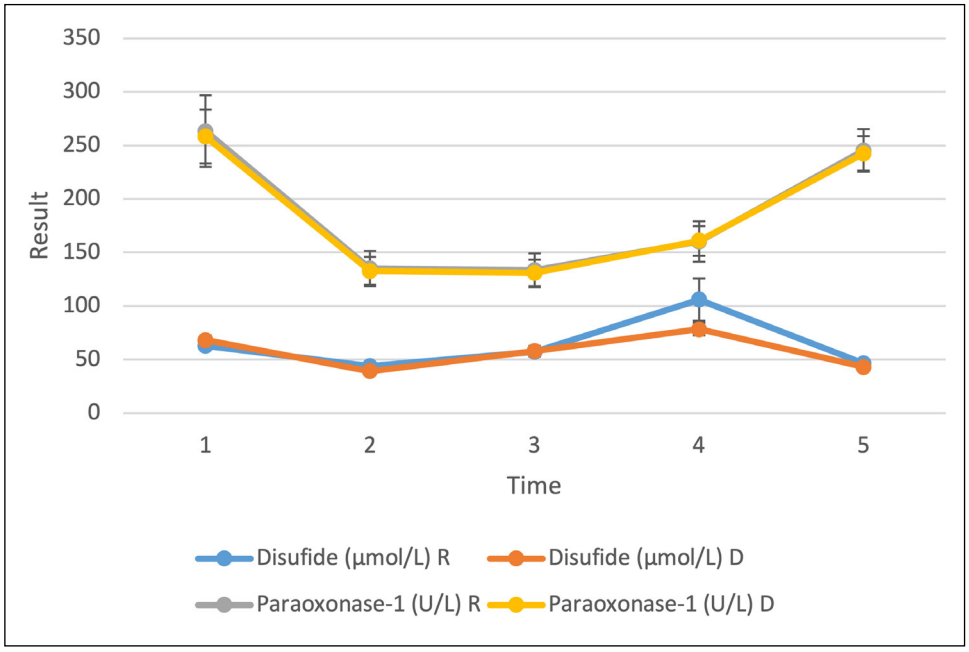

Figure 2. Variation of serum disulfide and paraoxonase levels over time.

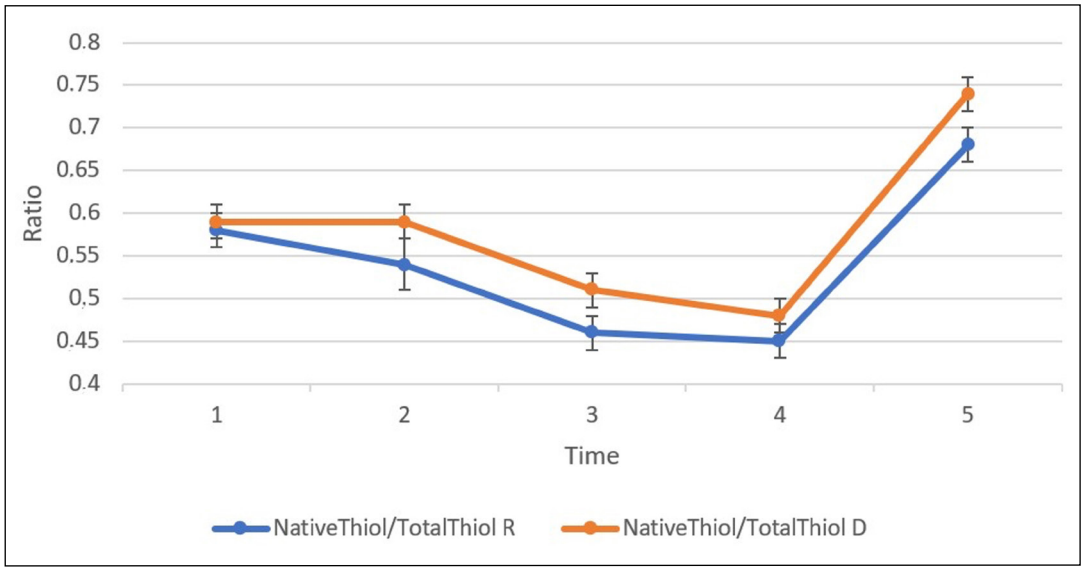

Figure 3. Variation of serum native thiol/total thiol ratio over time.

Discussion

We compared the effects of two anesthetic techniques on TDH and PON-1 activity in patients undergoing CABG. To our knowledge, this is the first clinical study investigating the effect of remifentanil and dexmedetomidine on dynamic THD and PON-1 levels in patients undergoing on-pump CABG. In the dexmedetomidine group, native thiol levels at T3 and T5 times were significantly higher than in the remifentanil group. In addition, when T1 and T5 times were compared in the intragroup measurements, serum disulfide levels were significantly lower at T5 time (Figure 2), and native thiol/total thiol ratios were significantly higher (Figure 3).

A study[12] investigating the relationship between PON-1 activity and complications after coronary artery surgery has reported that integrated models of OS status parameters have the

ability to predict the development of postoperative complications. Wysocka et al[13] reported that PON-1 plasma activity decreased significantly during CABG surgery and increased back in the postoperative period. In this study, similar to the literature, the PON-1 value measured in the intra-operative period was found to be significantly lower than the value measured in the pre-operative period, while the PON-1 value measured in the postoperative period was found to be higher than the pre-operative period (Figure 2). In both groups, the results obtained from the baseline value were found to be very close to each other, and it was determined that the effect of these two agents on PON-1 was similar.

Studies[14,15] evaluating the relationship between the severity of coronary artery disease and serum thiol levels and the relationship between changes in left ventricular systolic function and plasma thiol and disulfide levels[16] have been reported in the literature. Luyten et al[17] showed that antioxidant capacity increased contrary to expectations during CPB but argued that the increase remained lower than the increase in oxidative effect. Sanrı et al[18] reported that they found significant differences between TDH parameters measured at different time points during on-pump CABG surgery. In accordance with the study of Sanrı et al[18], we found that changes occurred between the parameters measured at different times. As a result of the evaluation of the results obtained in the postoperative period compared to the results obtained from the first obtained samples, we found that there was an increase in the antioxidant direction, and this effect was higher in the dexmedetomidine group.

In a study by Zhang et al[19] and in a study by Du et al[20], investigating the role of dexmedetomidine in a myocardial ischemia-reperfusion (I/R) injury model, it was stated that dexmedetomidine may play a protective role in myocardial I/R in mice. It was reported that dexmedetomidine could improve cardiac functions, eliminate free oxygen radicals, and alleviate OS damage. In a meta-analysis[21] evaluating the effects of dexmedetomidine on myocardial I/R injury in patients undergoing cardiac surgery with CPB, it was stated that dexmedetomidine could provide myocardial protection against I/R injury and reduce the duration of intensive care unit stay. A sevoflurane-dexmedetomidine combination was shown to be more effective than a sevoflurane-remifentanil combination in preventing cardiac damage during extracorporeal circulation in a study by Türktan et al[10] investigating the cardioprotective effects of both agents. The reason underlying this effect has been interpreted as more effective protection against ischemia-reperfusion injury. Our results in this study also showed that the anti-oxidant effect of dexmedetomidine was better than that of remifentanil, in accordance with the literature.

Limitations

A limitation of our study is that only one sample was obtained in the postoperative period. A longer follow-up and sampling more than once in the postoperative period would have allowed for better evaluation in the long term. In addition, it would have been better to standardize the groups in terms of comorbidities.

Conclusions

In conclusion, in light of the data obtained from this study, it can be concluded that the contribution of dexmedetomidine to the oxidant-antioxidant balance is more favorable than that of remifentanil. Based on our study and previous literature, we think that the use of dexmedetomidine may be preferred over remifentanil, considering its antioxidant effect.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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Informed Consent

Informed consent was obtained from all participants in this study.

Availability of Data and Materials

The datasets are available from the corresponding author upon reasonable request.

Authors' Contributions

MI, BA, BB and BC conceived the idea. MI, BA, and BB conducted the experimental work. MI, BA, BB, BC, and TB participated in writing, discussion, and data analysis. All authors approved the final version of the publication.

ORCID ID
M. Izgi: 0000-0003-2747-7290
B. Basaran: 0000-0001-5994-3861
T. Bayir: 0000-0001-6381-0324
B. Akca: 0000-0003-4069-2462
B. Celebioglu: 0000-0001-9198-8357

Ethics Approval
This study protocol was approved by Hacettepe University Non-Interventional Clinical Studies Ethics Committee on May 3rd, 2018, with the number GO 18/377-20

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