Levels of Ischemia: Modified Albumin in Patients Undergoing On-pump Coronary Artery Bypass

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ABSTRACT

Objective: To investigate the effect of ischemia-modified albumin (IMA) during cardiopulmonary bypass (CPB).

Study Design: Observational study.

Place and Duration of Study: Department of Cardiovascular Surgery, Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey, between January and April 2018.

Methodology: Patients, who underwent on-pump coronary bypass surgery, were inducted. IMA levels were measured in the preoperative period (IMA-T_1), 30 minutes after removal of aortic X-clamp (IMA-T_2) (ischemic period) and 6th hours (IMA-T_3) after surgery. The groups were formed according to the average value of IMA-T_2 levels measured in the ischemic period. Those with a value above the mean (0.76 U/mL) were grouped as group 1 and those below the mean were grouped as group 2. Postoperative data of the patients were recorded.

Results: There were significant differences between measured IMA levels in different periods of on-pump CABG ($p < 0.001$). The development of postoperative atrial fibrillation (PoAF) was higher in Group 1 and this result was statistically significant ($p=0.004$). High IMA-T2 levels were detected as an independent parameter in predicting the PoAF development ($p=0.04$, logistic regression analysis). ROC curve analysis demonstrated IMA-T2 values of 0.73 or above could predict development PoAF with 82.6% sensitivity and 66.7% specificity (AUC: 0.777, log rank $p=0.001$).

Conclusion: Increased IMA levels during ischemic period may be predictive in PoAF development.

Key Words: *Cardiopulmonary bypass, Myocardial ischemia, İschemia-modified albumin.*

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INTRODUCTION

Damage to the myocardium is inevitable due to the ischemic process created after cardiac surgeries using cardiopulmonary bypass (CPB) and the resulting reperfusion; and oxidative stress comes into play in this process.[1] Ischemia modified albumin (IMA) occurs as a result of ischemic damage due to albumin changes caused by acidosis and increased reactive oxygen derivatives in hypoxic heart tissue.[2] When myocardial ischemia occurs, hypoxia followed by the destruction of acidosis and Na-K pump causes the separation of the first two amino acids (Aspartic acid-Alanine) of the human serum albumin N-terminal thus leading to the formation of IMA.[3]

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Ischemic conditions developing in the body, acidosis associated with ischemia, hypoxia, and free radical damage have been shown to structurally change the albumin N-terminal, thereby reducing the protein's ability to bind transition metal. The new molecule formed after structural changes were called "ischemia modified albumin" by Bar-Or *et al*; and they implemented a quantitative *in vitro* measurement that obtained the presence of IMA in plasma by measuring the cobalt level not bound to the albumin using the albumin cobalt binding test.[4,5]

IMA helps establish the diagnosis in the early stages of ischemia in the pre-necrosis period.[2] It has been approved by the Food and Drug Administration (FDA) as a marker of cardiac ischemia and suspicion of acute coronary syndrome.[6] IMA, which has been reported to detect myocardial ischemia within the first thirty minutes, may make it possible to intervene at an early period to restore myocardial perfusion and thus improve the prognosis of the patient. Markers, such as cardiac troponin I and troponin T, can provide information about perioperative myocardial infarction; but they show the presence of necrosis more.[7]

IMA can occur not only in ischemic myocardial tissue but also in different ischemia models affecting other organs due to high oxidative stress. It has been reported to increase serum IMA levels in many previous studies such as pulmonary embolism, acute ischemic stroke, acute mesenteric ischemia, scleroderma and critical leg ischemia.[8-12]

Coronary bypass surgeries are routinely performed in our clinic using the CPB technique. Whether the surgery and CPB perfusion performed is sufficient for myocardial protection is an important condition and depends on many factors. Knowing the usability of IMA measurements as an ischemia marker for cardiac surgeries will help to review the routine surgeries.

The aim of this study was to evaluate the relationship between hemodynamic parameters and their effects in the postoperative period by measuring the IMA levels before and after CPB.

METHODOLOGY

This prospective and observational randomised clinical study was conducted on 50 patients, who underwent isolated coronary artery bypass grafting (CABG) operation using the CPB technique between January and April 2018 at the Cardiovascular Surgery Clinic of Bursa Yuksek Ihtisas Training and Research Hospital of Health Sciences University. Ethics committee approval for the study was received from the Uludag University (2011-KAEK-26/40, 2017-19 / 41). The necessary consent forms were obtained from the patients for the study.

Patients who underwent isolated CABG using CPB over the age of 18 were included in our study. Firstly, those who would undergo additional surgery for coronary bypass besides CABG, those with a presence of heart valve disease not requiring intervention and those with preoperative heart rhythm disorder were excluded from the study. Besides, those with chronic obstructive pulmonary disease (COPD), cerebrovascular disease, peripheral artery disease, renal failure, and those who needed preoperative inotropic or mechanical support, those who would undergo redo surgery and emergency coronary surgery were not included in the study. All data were recorded as age, gender, history of hypertension and diabetes mellitus, ejection fraction, aortic cross-clamp (X-clamp) time, total CPB time and number of the anastomosis. Also, in the postoperative period, we recorded inotropic drugs support requirement and intra-aortic balloon pump (IABP) requirement, development of postoperative atrial fibrillation (PoAF), intensive care unit (ICU)stay and hospital stay.

A standard median sternotomy was performed in all patients. The patients were heparinised with ACT over 400 seconds (300-400 U/kg). With arterial cannulation from the ascending aorta and two-stage venous cannulation entered the CPB. After aortic cross-clamp, cardiac arrest was achieved with cold blood cardioplegia (10-15 mL / kg) with high potassium and cardiac arrest was sustained with blood cardioplegia, which was applied every 15-20 minutes. Before removing aortic X-clamp, 500 ml of warm blood cardioplegia was given. Proximal anastomoses were performed under the side clamp.

During the operation, a moderate level of hypothermia (28-30 degrees) was applied. Roller pumps and membrane oxygenators were used in all patients (Maquet, Getinge group, Restalt, Germany). Pump flow was provided between 2.2-2.4 lt/min/m2, and non-pulsatile and mean arterial pressure were maintained to remain at the level of 50-60 mmHg during the X-clamping. During CPB, haematocrit was kept between 20-25%. After removing X-clamp, heating was continued until the temperature of the bladder reached 36°C. CPB was terminated after ensuring proper blood pressure and cardiovascular stability. Heparin was neutralized by protamine infusion. After the bleeding control was achieved, tube drains were placed and the layers were closed properly. The patients were followed-up in the intensive care unit in the postoperative period. The first choice was dopamine when the inotropic agent requirement emerged. Following the completion of the surgery, patients were taken to the cardiovascular surgery ICU. Standard postoperative care was given to all the patients. In the case of a new onset of atrial fibrillation, the first choice drug was the amiodarone.

Laboratory parameters were studied from venous blood samples before the surgery except for IMA parameters. For IMA measurements, 10cc blood samples were taken in the biochemistry tubes before entering the CPB (IMA-T_1), 30 minutes after removing the X-clamp (IMA-T_2) and 6 hours after surgery (IMA-T_3) for IMA measurements. In the IMA measurement, 50 µl of cobalt chloride (1 g/l) solution was added to 200 µl of patient serum, mixed and allowed to incubate in the dark for 10 minutes at room temperature. Then 50 µl of dithiothreitol (1.5 g/l) solution was added and mixed. It was incubated for another 2 minutes at room temperature and 1 ml of NaCl 9.0 g/l solution was added. Blind samples were prepared similarly without adding DTT. The absorbance of the mixture was read as 470 nm at Shimadzu UV-1800 Spectrophotometer.

The IMA-T_1, IMA-T_2 and IMA-T_3 values of all patients were measured, and it was observed that the IMA-T_2 levels peaked within 30 min after the removal of X-clamp and decreased to the initial levels after the ischemic period (Figure 1). The effect of the CPB technique on the postoperative period is mostly due to this ischemic period under the X-clamp. Therefore, patients were divided into two groups according to the mean value of the measured IMA-T_2 levels in the ischemic period. For IMA-T_2, those with a value above the mean (0.76 U/mL) were determined as group 1 and those below the mean were determined as group 2.

For statistical analysis, SPSS (IBM SPSS 21.0, Chicago, IL, USA) was used. Continuous variables were expressed as mean±standard deviation and median-IQR (for continuous variables, Mann- Whitney U-test was employed) and nominal variables were expressed as frequency and percentage. Shapiro-Wilk test was used for normality analysis. In the dependent group, paired-samples T-test and repeated measurements-ANOVA test were used to evaluate the relationship between IMA levels with normal distribution measured at different times. In independent groups divided according to the IMA-T_2 level

measured in the ischemic period, the Pearson Chi-square test and Fisher's Exact test were used for nominal data, student t-test was used for continuous data fitting to the normal distribution, and Mann-Whitney U-test was used for continuous data not fitting to normal distribution. The Pearson correlation coefficient test was used to investigate any relationship between the IMA-T_2 levels measured in the ischemic period and the Total CPB Time and X-clamp time. Factors that may affect PoAF development and postoperative inotropic drug support were included in the logistic regression analysis. The receiver-operating characteristic (ROC) curve was applied to predict the effect of IMA-T_2 levels on PoAF development and inotropic drug support. In order to analyse the diagnostic value of IMA-T_2 levels, the sensitivity and specificity of the area under the ROC curve and the measured cut-off value were calculated. In all tests, $p<0.05$ was considered statistically significant.

Table I: Demographic, operative and postoperative parameters of the patients.

	Group 1 (n=26)	Group 2 (n=24)	p-value
Demographic findings			
Age (years), mean S.D	62.35 ±8.04	61.5 ±9.66	0.737 *
Male gender, n (%)	21 (80.8)	22 (91.7)	0.420 #
Hypertension, n (%)	20 (76.9)	18 (75)	0.874 #
Diabetes mellitus, n (%)	15 (57.7)	12 (50)	0.586 #
Ejection fraction %, median (IQR)	50.0 (45.0-60.0)	50.0 (45.0-58.8)	0.984 a
Operative parameters			
Total CPB time (minute), mean S.D	86 ±26.5	96.33 ±21.12	0.136 *
X-clamp time (minute), mean S.D	60.73 ±19.60	69.46 ±22.82	0.152 *
Number of anastomosis, median (IQR)	3.0 (2.0-4.0)	4.0 (3.0-4.0)	0.183 a
Postoperative parameters			
PoAF, n (%)	17 (65.4)	6 (25)	0.004 #
Inotropic drugs support, n (%)	15 (57.7)	10 (41.7)	0.258 #
IABP support, n (%)	2 (7.7)	1 (4.2)	>0.999 #
ICU stay (day), mean S.D	2.5 ±0.58	2.25 ±0.53	0.121 *
Hospital stay (day), mean S.D	7.19 ±0.69	7.17 ±0.76	0.901 *

*Group 1: IMA-T2 levels >0.76, Group 2: IMA-T2 levels <0.76 PoAF: Postoperative atrial fibrillation, IABP: Intra-aortic balloon pump, ICU: Intensive care unit, CPB: Cardiopulmonary Bypass, IQR: Interquartile range, SD: Standard deviation. *Student's t-test, # Pearson Chi- Suquare, [a] Mann-Whitney U-test, [#]Fisher's Exact test was used for values less than five*

RESULTS

This prospective study was conducted with 50 patients according to inclusion criteria. It was observed that all patients' IMA-T_2 levels increased and IMA-T_3 levels decreased to baseline IMA-T_1 levels after the ischemic period ($p<0.001$, Repeated measured-ANOVA (Figure 1). Statistically significant differences were found in T_1-T_2 periods in which rising IMA levels were observed and in T_2-T_3 periods in which decreasing IMA levels were observed ($p<0.001$, paired samples test). There was no difference in periods other than the T2-ischemic period ($p=0.595$, Paired Samples test). For this reason, patients were divided into two groups according to the mean IMA-T_2 level (0.76 U/mL) measured in the ischemic period. Those above this value were determined as Group 1 and those below were determined as Group 2. There were 26 patients in Group 1 (80.8 % males and 19.2 % females , mean age: 62.35 ±8.04 years) and 24 patients in Group 2 (91.7% males and 8.3% females , mean age: 61.5 ±9.66 years). Groups were similar in terms of demographic features which are summarised in Table I.

The operative and postoperative parameters of the groups are shown in Table I. Although Total CPB time and X-clamp time were higher in Group 2 than in Group 1, there was no statistical difference between the groups in terms of X-clamp time which indicated ischemic time ($p=0.136$, $p=0.152$, respectively, Table I). In the postoperative period, the development of PoAF was higher in Group 1, which was statistically significant ($p=0.004$, Table I). There was no significant difference between groups in terms of inotropic drug support, IABP requirement, hospital stay and duration of ICU stay.

The laboratory variables of the patients are summarised in Table II. The difference was statistically significant in terms of this parameter since the groups were divided according to the IMA-T_2 levels ($p<0.001$). There was no difference between groups in other parameters (Table II).

Table II: Laboratory variables.

	Group 1 (n=26) (mean S.D.) / Median (IQR)	Group 2 (n=24) (mean S.D.) / Median (IQR)	p-value
Haematocrit (%)	39.2 (36.1-41.4)	41.1 (38.2-46.7)	0.232[a]
White blood Cell (10^3/µL)	8.14±1.76	8.1 ±2.30	0.959*
Platelet (10^3/µL)	230.0 (203.8-289.8)	222.5 (194.0-240.3)	0.522[a]
BUN (mg/dL)	15.0 (13.8-18.0)	17.5 (12.3-20.0)	0.501[a]
Creatinine (mg/dL)	0.93 (0.7-0.9)	0.98 (0.8-1.0)	0.171[a]
Na (mEq/L)	138.08 ±3.50	138.72 ±2.84	0.483*
K (mEq/L)	4.32 ±0.42	4.34 ±0.45	0.829*
Ca (mg/dL)	9.13 ±0.49	9.18 ±0.6	0.769*
Albumin (mg/dL)	3.89 ±0.42	3.85 ±0.49	0.780*
Fibrinogen (mg/dl)	383.0 (332.3-410.5)	402.5 (323.0-468.5)	0.240[a]
Glucose (mg/dl)	120.0 (104.0-208.3)	119.5 (103.3-153.0)	0.698[a]
C Reactive protein (mg/dL)	5.5 (3.0-9.8)	4.5 (3.0-8.1)	0.619[a]
Total Cholesterol (mg/dl)	204.38 ±48.89	200.96 ±41.73	0.792*
LDL-C (mg/dL)	122.40 ±38.53	120.46 ±34.73	0.853*
HDL-C (mg/dL)	44.81 ±10.12	45.99 ±7.77	0.649*
TG (mg/dL)	121.3 (90.9-207.2)	170.9 (118.9-212.0)	0.214[a]
IMA-T_2 (U/mL)	0.87 ±0.11	0.63 ±0.09	<0.001*
Troponin-I (ng/ml)	0.25 (0.01-4.7)	0.11 (0.02-3.8)	0.892[a]
Creatinine Kinase (U/L)	98.5 (68.8-385.3)	84.8 (70.3-125.9)	0.156[a]

*Group 1: IMA-T2 levels > 0.76, Group 2: IMA-T2 levels <0.76 T:Time courses of plasma concentrations of ischemia-modified albumin levels, T2: 30 minutes after removal of X-clamp, IMA: Ischemia-Modified Albumin, , LDL-C: Low density lipoprotein-cholesterol, HDL-C: High density lipoprotein-cholesterol, TG: Triglyceride, IQR: Interquartile range, SD: Standard deviation. *Student's-t test , [a] Mann-Whitney U-test.*

In correlation analysis between IMA-T_2 levels and total CPB time and X-clamp time, it was found that there was a negative correlation ($rp=-0.341$, $p=0.015$; $rp=-0.276$, $p=0.052$, Pearson correlation).

In univariate logistic regression analysis, the PoAF was significantly correlated with hypertension (OR [Odds Ratio]=6.176, 95% CI [Confidence interval]: 1.184-32.076, $p=0.030$) and IMA-T_2 level (OR=2503.643, 95% CI: 12.85-487515.12, $p=0.004$), but was not correlated with ejection fraction, total CPB time and aortic X-clamp time (Table III).

Parameters which correlated with PoAF in the univariate logistic regression analysis were taken into multivariate logistic regression analysis.

Table III: Logistic regression analysis to identify determinants of PoAF development.

	Univariate analysis			Multivariate analysis		
Variables	**p**	**Exp(B) Odds Ratio**	**95% C.I. Lower - Upper**	**p**	**Exp(B) Odds Ratio**	**95% C.I. Lower - Upper**
HT	0.030	6.176	1.184 - 32.076	0.027	7.885	1.258 - 49.424
DM	0.145	2.344	0.745 - 7.370			
EF	0.759	1.010	0.947 - 1.078			
Total CPB time	0.400	0.991	0.971 - 1.012			
X-clamp time	0.197	0.982	0.955 - 1.009			
İMA (T_2)	0.004	2503.643	12.85 - 487515.12	0.004	5894.602	14.848 - 2340212

PoAF: Postoperative atrial fibrillation, , HT; Hypertension, DM; Diabetes mellitus, EF; Ejection fraxion, CPB; Cardiopulmonary Bypass, IMA: Ischemia-Modified albumin, T:Time courses of plasma concentrations of IMA-T2 levels (T2: 30 minutes after removal of X-clamp).

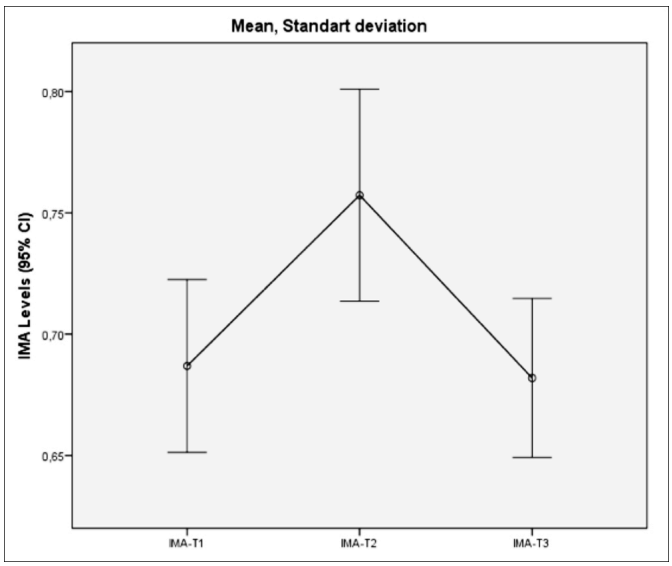

Figure 1. The change in plasma concentrations of IMA values measured before cardiopulmonary bypass (T1), 30 minutes after cross-clamping (T2) and 6 hours after surgery (T3) is shown. (T:Time courses of plasma concentrations of, IMA: Ischemia-Modified Albumin).

We detected that presence of HT (OR=7.885, 95% CI: 1.258-49.424, p=0.027) and high IMA-T_2 level (OR=5894.602, 95% CI: 14.848-2340212, p=0.004) were independent predictors for PoAF development (Table III).

For this reason, the high IMA level is an independent predictor for PoAF development. ROC curve analysis was performed. ROC curve analysis demonstrated that IMA-T_2 values of 0.73 or above could predict development PoAF with 82.6% sensitivity and 66.7% specificity (AUC: 0.777, 95% CI: 0.649-0.905, log rank p=0.001, Figure 2).

DISCUSSION

In the present study, the effect of plasma levels of IMA in patients undergoing isolated on-pump CABG was evaluated. It was found that the development of PoAF was higher in the group with high plasma IMA-T_2 levels which was statistically significant. In logistic regression analyses, it was found that higher plasma IMA-T_2 levels and HT were as independent variables predicting the development of PoAF. It was determined for a cut-off level of 0.73 of IMA-T_2 level for predicting PoAF with a sensitivity of 82.6% and a specificity of 66.7% in ROC analysis.

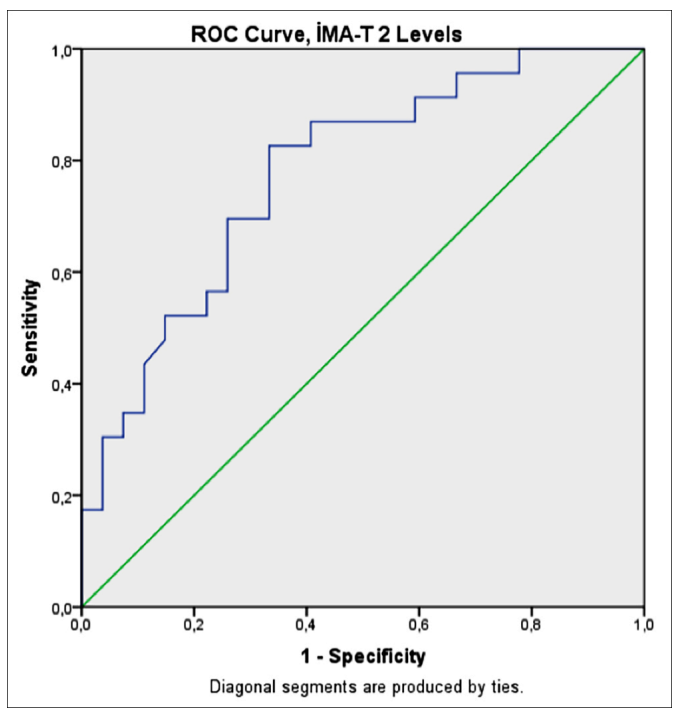

Figure 2: ROC curve and AUC for predicting the development of PoAF for IMA-T_2 levels. (Cut-off level: 0.73, 82.6% sensitivity and 66.7% specificity, AUC: 0.777, log rank p=0.001).

Sbarouni *et al.* stated that IMA peaked in CPB and gradually regressed after surgery and emphasised that whether this situation had a prognostic significance should be investigated.[13] In a study conducted by Kanko *et al.*[2] investigating the use of IMA as a prognostic factor in patients undergoing CABG, it was observed that the IMA levels increased rapidly within the first 30 minutes after cross-clamping and decreased within 6 hours postoperatively. At the end of their studies, they reported that IMA was an early-rising marker of cardiac ischemia and might direct treatment in the early stages. Similar to previous studies, in the study of Karahan *et al* who investigated the effect of N-Acetylcysteine on IMA levels in CABG operations, it was determined that the IMA values increased after X-clamping and decreased after X-

clamp removal, approaching to basal values within 24 hours.[14] In the same study, it was stated that the increase in IMA values was lower in the N-Acetylcysteine-receiving group. In this study, a significant difference was found between the IMA-T_1 values measured at the beginning of the operation and the IMA-T_2 measured 30 minutes after the cross-clamp removal ($p<0.001$), The IMA-T_2 values peaked 30 minutes after the X-clamp was removed. With the elimination of ischemia and coronary revascularisation through CABG operation, a significant decrease was found in the IMA-T_3 values measured at 6th hour postoperatively compared to the IMA-T_2 values measured during ischemia ($p<0.001$). Previous studies and this study showed that IMA values peaked during the ischemia period in CPB, which is an indicator of the ischemic process.

CPB is an important trigger of the inflammatory response and a source of oxidative stress. Myocardial ischemia and reperfusion due to cardioplegic arrest is an important cause of tissue damage and inflammatory response.[15] Oxidative stress caused by CPB and cardioplegic arrest are likely to trigger a cellular change in the atrial tissue causing impaired electrical activity. Atrial remodelling that develops reactive oxygen species (ROS) is responsible for the pathogenesis of PoAF.[16] In studies conducted on samples from the right atrial appendage, NADPH oxidase activity has been shown to be an important independent predictor for the development of PoAF.[17] Myocardial ischemia, inflammatory response, ROS and increased oxidative stress were seen during CPB leading to the formation of IMA.[3] Literature search revealed no evaluation was found between IMA values and development of PoAF among the studies evaluating the relationship between CABG and IMA.[2,7,13,14 18] In this study, the development of PoAF was found to be high in the group with high IMA values $p=0.004$. IMA-T_2 values measured in the ischemia period are independent parameters in predicting PoAF development. In addition, ROC curve analysis demonstrated that IMA-T_2 values of 0.73 or above could predict development PoAF with 82.6% sensitivity and 66.7% specificity. However, total CPB and X-clamp times were lower in Group 1 with high IMA values, and therefore a negative correlation was found between high IMA values and total CPB and X-clamp time. In this study, it was found that the increase in the IMA-T_2 values in the ischemic period in CPB was not associated with the ischemia duration. But it was detected that high IMA values in this ischemic period may lead to the development of PoAF. It can be said that high IMA levels, independent of ischemic time, contribute to the development of postoperative AF. Our study is a rare study that evaluates the development of IMA and PoAF.

Gurumurthy *et al.* stated that IMA was a sensitive biomarker of myocardial ischemia in MI patients, who were admitted to the emergency department.[19] Similarly, Mehta *et al.* investigated the synergism of IMA and high-sensitivity troponin T in the early diagnosis of the acute coronary syndrome and stated that they can be used with better accuracy in the early diagnosis of the acute coronary syndrome.[20] Ozdem *et al.* examined the IMA levels in 41 patients with the acute coronary syndrome,[21] whose troponin and CK-MB values increased 6-12 hours after being admitted to the emergency service and reported that they were normal at the time of admission to the emergency department. When they compared these values with the control group, they reported that serum IMA levels increased immediately after myocardial ischemia and had high sensitivity and a negative predictive value. They stated that IMA may be a useful biochemical parameter in the diagnosis and treatment of myocardial ischemia. In this study, IMA values increased immediately after myocardial ischemia and had high sensitivity and a negative predictive value. There are also publications stating that IMA levels may be a useful diagnostic marker in patients with acute ischemic stroke, apart from myocardial ischemia.[22,23]

In this study, there was no difference between the groups in terms of the postoperative period, inotropic drugs support and IABP requirement, ICU stay and hospital stay. Although there is no comparative study evaluating the effect of IMA levels on postoperative period in patients undergoing CABG in the literature, Karahan *et al.* found in their studies, where they investigated the effect of N-Acetylcysteine on IMA levels, that ICU stay and hospital stay were higher in the group that did not receive N-Acetylcysteine.[14] In another study, Nee *et al.* in their study investigating the relationship between IMA and adenosine plasma concentrations, and systemic inflammatory response syndrome (SIRS) after CPB, found that the levels of IMA and adenosine in the SIRS group increased, and ICU stay time, hospital stay time and mortality rates were higher in this group.[18]

LIMITATIONS OF THE STUDY: This study has several limitations. Firstly, the sample size was small and the study was performed in single centre design. Another limitation may be that authors did not use the albumin-adjusted ischemia-modified albumin level. Thirdly, in this study, troponin levels and other oxidative stress markers were not measured in the postoperative period.

CONCLUSION

The formation of IMA is inevitable as a result of developing ischemia and oxidative stress. This can be seen in any organ; but since intentional ischemia is created in on-pump CABG operations, it is necessary to evaluate the homeostasis of IMA. In addition, it was found that high IMA levels were an independent predictor of the development of PoAF. In the ischemic period, high IMA levels may be one of the reasons for PoAF development. Therefore, more comprehensive studies are needed to evaluate the relationship between IMA values and PoAF development in on-pump

CABG.

ETHICAL APPROVAL:
Ethics committee approval for the study was received from the Uludag University (2011-KAEK-26/40, 2017-19 / 41).

PATIENTS' CONSENT:
The necessary consent forms were obtained from the patients for the study.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
KKÖ: Substantial contributions to the conception or design of the work, or the acquistion, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content.
ABB: Substantial contributions to the conception or design of the work, or the acquistion, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content.
USS: The acquistion, analysis, or interpretation of data for the work, rafting the work or revising it critically for important intellectual content.
OG: The acquistion, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content.
SY: The acquistion, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content. Final approval of the version to be published.

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