The effect of oxidative stress related with ischemia-reperfusion damage on the pathogenesis of atrial fibrillation developing after coronary artery bypass graft surgery

Koroner arter baypas cerrahisi sonrası gelişen atriyum fibrilasyonu patogenezinde iskemi reperfüzyon hasarı sonucu oluşan oksidatif stresin rolü

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ABSTRACT

Objectives: We aimed to investigate the role of oxidative stress related with ischemia- reperfusion damage on the pathogenesis of atrial fibrillation (AF) developing after coronary artery bypass graft (CABG) surgery.

Study design: In our prospective, single-center study, 118 patients who underwent elective isolated on-pump CABG surgery were included. Patients were divided into two groups according to the development of postoperative atrial fibrillation (POAF) as Group 1: Patients who developed POAF, and Group 2: Patients who remained in sinus rhythm. In addition to preoperative demographic, laboratory, echocardiographic, intraoperative, and postoperative clinical characteristics, levels of plasma total oxidative status (TOS) after placement and removal of aortic cross clamp (ACC) were compared between the two groups. Predictors of POAF were also investigated by multivariate logistic regression analysis.

Results: A comparison of preoperative demographic, laboratory, echocardiographic, and postoperative clinical characteristics between the two groups showed that patients in Group 1 were significantly older (65.6±7.20 *vs.* 59.6±9.07, p<0.001), had a lower hematocrit level (37.5±5.16 *vs.* 39.7±5.28; p=0.034), and an enlarged left atrium diameter (39±0.45 *vs.* 3.6±0.48; p=0.006). Changes in plasma TOS levels after placement and removal of ACC were statistically significant in Group 1 [13 (8.6-23), 30 (18.1-47.3); p=0.001 *vs.* 14 (8.8-22.2), 24 (21.4-42.7); p=0.060]. Length of stay in the intensive care unit [3 (2-14) *vs.* 2 (1-58); p=0.001] and length of stay in hospital [7 (6-85) *vs.* 7 (5-58); p=0.001] were prolonged in Group 1. In multivariate logistic regression analysis, aging (odds ratio (OR): 1.088, 95% confidence interval (CI): 1.005-1.177; p=0.036), hematocrit level (OR: 0.718, 95% CI: 0.538-0.958; p=0.025), pump temperature (OR: 1.445, 95% CI: 1.059-1.972; p=0.020), and plasma TOS level (OR: 1.040, 95% CI: 1.020-1.050; p=0.040) were found to be independent predictors of POAF.

Conclusion: Ischemia-reperfusion damage related with ACC placement may be an important factor on the pathogenesis of POAF. Minimizing the oxidative stress occurring intraoperatively should be targeted for preventing mortality and morbidity due to POAF.

ÖZET

Amaç: Çalışmamızda koroner arter bapas cerrahisi (KABC) sonrası gelişen atriyum fibrilasyonu (AF) patogenezinde iskemi reperfüzyon hasarıyla (İRH) ilişkili oksidatif stresin rolünü araştırdık.

Çalışma planı: Çalışmaya elektif koşullarda pompa kullanılarak ve tek başına KABC uygulanan 118 hasta dahil edildi. Hastalar ameliyat sonrası atriyum fibrilasyonu (POAF) gelişimine göre iki gruba ayrıldı. (Grup 1: POAF gelişen hastalar, Grup 2: Sinüs ritminde kalan hastalar). Her iki grup ameliyat öncesi, ameliyat sırasında ve ameliyat sonrasındaki klinik özellikler ile aort kros klemp (AKK) yerleştirilmesi ve uzaklaştırılması sonrası plazma toplam oksidatif durum (TOD) değerleri açısından karşılaştırıldı. POAF öngördürücüleri çok değişkenli lojistik regresyon analiziyle belirlendi.

Bulgular: Her iki grup arasında ameliyat öncesi, sonrası ve ameliyat sırasındaki klinik özellikler açısından yapılan karşılaştırmada grup 1'deki hastaların grup 2'deki hastalara oranla daha ileri yaşta olduğu (65.6±7.20 ve 59.6±9.07, p<0.001), hematokrit seviyelerinin daha düşük olduğu (37.5±5.16 ve 39.7±5.28, p=0.034) ve sol atriyum çaplarının daha geniş olduğu görüldü (39±0.45 ve 3.6±0.48; p=0.006). Grup 1'de yer alan hastaların AKK yerleştirilmesi ve uzaklaştırılması sonrası bakılan plazma TOD değerlerindeki değişimin istatistiksel olarak anlamlı olduğu saptandı [13 (8.6-23), 30 (18.1-47.3), p=0.001 ve 14 (8.8-22.2), 24 (21.4-42.7); p=0.060]. Yoğun bakım ünitesi [3 (2-14) ve 2 (1-58); p=0.001] ve hastanede kalış süresinin [7 (6-85) ve 7 (5-58); p=0.001] Grup 1'deki hastalarda daha uzun olduğu belirlendi. Çok değişkenli lojistik regresyon analizinde yaş (odds oranı [OO]: 1.088, %95 güven aralığı (GA) 1.005-1.177, p=0.036), hematokrit seviyesi (OO: 0.718, %95 GA 0.538-0.958, p=0.025), pompa derecesi (OO: 1.445, %95 GA 1.059-1.972 p=0.020) ve plazma TOD değerinin (OO: 1.040, %95 GA 1.020-1.050, p=0.040) POAF gelişimi için bağımsız bir belirteç olduğu tespit edildi.

Sonuç: Aort kros klemp ile ilişkili iskemi reperfüzyon hasarı POAF gelişiminde önemli bir faktör olabilir. POAF'nin önlenmesinde ameliyat sırasında oluşan oksidatif stresin azaltılması hedeflenmelidir.

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Atrial fibrillation (AF) is the most common arrhythmia after coronary artery bypass graft (CABG) surgery performed with extracorporeal circulation. Its incidence differs between 30% and 50% according to the type of cardiac surgery.[1] Postoperative atrial fibrillation (POAF) is associated with increased morbidity and mortality. Predisposing factors that may be responsible for the pathogenesis of POAF should be identified clearly. Although advanced age, anemia, prior history of AF, heart failure, peripheral arterial disease, obstructive lung disease, obesity, hypertension, and left atrial enlargement are well-known conventional risk factors for AF, their consistency in regard to POAF has not been sufficiently validated in clinical trials. Currently, increasing attention is being given to the role of oxidative stress following cardiac surgery and to whether or not it may contribute to POAF.[2]

Abbreviations:

ACC	*Aortic cross clamp*
AF	*Atrial fibrillation*
CABG	*Coronary artery bypass graft*
CI	*Confidence interval*
ECG	*Electrocardiography*
LA	*Left atrium*
NADPH	*Nicotinamide adenine dinucleotide phosphate*
OR	*Odds ratio*
POAF	*Postoperative atrial fibrillation*
TOS	*Total oxidative status*

Placement and removal of the aortic cross clamp (ACC) during CABG induces ischemia- reperfusion damage and leads to increased oxidative stress. Major structural changes secondary to increased oxidative stress can be explained by increased intracellular calcium storage, activation of mitochondrial caspases, deterioration of intercellular gap junctions, and shortening of the refractory period of myocytes.[3] Postoperative increased levels of oxidative stress indicators, such as xanthine oxidase, nuclear factor kappa b and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, support the impact of oxidative stress on the pathogenesis of POAF.[4] There have been clinical trials that showed conflicting results about the prevention of POAF with medications such as amiodarone, beta blockers, statins, and magnesium sulfate; thus, the optimal method of preventing POAF remains unknown. For this reason, it will continue to be a challenging medical condition.[5]

Although some oxidative molecules have been investigated in POAF, there have been no studies done thus far considering the role of increased plasma total oxidative status (TOS) levels associated with ischemia-reperfusion damage in consequence of ACC manipulation on the pathogenesis of POAF.

We aimed to investigate oxidative stress related with ischemia-reperfusion damage by measuring plasma TOS levels after the placement and removal of ACC during CABG surgery and its effect on the pathogenesis of POAF.

PATIENTS AND METHODS

Study population

The study included 118 patients who underwent elective isolated on-pump CABG surgery in our hospital, Istanbul University Institute of Cardiology, from September 2012 to July 2013. Patients who had a history of preoperative atrial fibrillation, myocardial infarction, cardiac surgery, end stage heart failure, thyroid disease, electrolyte imbalance, chronic inflammatory disease, ejection fraction (EF) <25% and left atrium diameter >70 millimeters were excluded from the study. POAF was defined as an arrhythmia that lasts longer than 30 seconds with irregular RR intervals showing no distinct P waves on the surface electrocardiography (ECG). All patients were followed by continuous ECG monitoring during the postoperative period for the detection of POAF. According to the development of POAF, patients were divided into two groups. Group 1 included patients who developed POAF and Group 2 included patients remaining in sinus rhythm postoperatively. In addition to plasma TOS levels after placement and removal of ACC, other demographic, laboratory, echocardiographic, intraoperative, and postoperative characteristics were compared in both groups. Predictor factors for the development of POAF were also investigated by multivariate logistic regression analysis. Informed consents were taken from all patients, and the study protocol was approved by our local ethics committee.

Blood sample collection

Blood samples were obtained from the jugular vein and placed into dry blood tubes 30 minutes after placement of the ACC and 10 minutes after removal of the ACC during CABG surgery. Samples were separated by centrifugation at 3000 rpm for 10 minutes and plasma was stored at -80°C.

Measurement of total oxidative status (TOS) of plasma

Total oxidative status (TOS) of plasma was measured using a novel automated colorimetric measurement

method for TOS developed by Erel.[6] In this method, oxidants present in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules, which are abundantly present in the reaction medium. The ferric ion makes a colored complex with xylenol orange in an acidic medium. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide, and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H_2O_2 Eq/L).

Statistical analysis

The Statistical Package for the Social Sciences software (SPSS, version 15.0, SPSS Inc, Chicago, IL, USA) was used for all statistical calculations. The Kolmogorov-Smirnov test was used to determine whether the parameters fit with the normal distribution. Data within the normal distribution were expressed as mean±standard deviation (SD), whereas results of data without normal distribution were given by median (interquartile range). Comparisons of data distributed normally were made using unpaired Student t-test. Mann-Whitney U-test was used for comparing the data distributed non-normally. Categoric variables were shown as percentages and compared to Fisher's exact test. The Wilcoxon test was used to compare the levels of continuous variables changing over time in the same groups. Multivariate logistic regression analysis including the variables that showed p values <0.250 in the univariate analysis was performed to identify the independent predictors of POAF. A p value <0.05 was considered statistically significant.

RESULTS

Twenty-nine females and 89 male patients (24.5% vs 75.5%) were enrolled in our study. During the postoperative period, 37 patients (31%) developed POAF and 81 patients (69%) remained in sinus rhythm. Preoperative demographic, laboratory, echocardiographic, intraoperative, and postoperative clinical characteristics are presented in Table 1. The patients who developed POAF (Group 1) differed significantly from those patients who remained in sinus rhythm (Group 2) with regard to age (65.6±7.2 *vs.* 59.6±9; p<0.001), lower hematocrit level (37.5±5.16 *vs.* 39.7±5.28; p=0.034) and enlarged left atrium diameter (39±0.45 *vs.* 3.6±0.48; p=0.006). The postoperative length of stay in the intensive care unit [3 (2-14) *vs.* 2 (1-58); p=0.001] and length of stay in hospital [7(6-85) *vs.* 7(5-58); p=0.001] were longer in Group 1, whereas the other clinical parameters were similar between the two groups (p>0.05).

Plasma TOS levels after placement and removal of ACC were statistically significant in Group 1 [13 (8.6-23), 30 (18.1-47.3); p=0.001 *vs.* 14 (8.8-22.2), 24 (21.4-42.7); p=0.060] (Table 2).

In multivariate logistic regression analysis, aging (odds ratio [OR]:1.050, 95% confidence interval [CI]: 0.992-1.114; p=0.030), hematocrit level (OR: 0.718, 95% CI: 0.538-0.958; p=0.025), pump temperature (OR: 1.445, 95% CI: 1.059-1.972; p=0.020), and plasma TOS level (OR: 1.040, 95% CI: 1.020-1.050; p=0.040) were found to be independent predictors of POAF development (Table 3).

DISCUSSION

In this study, we investigated the relationship between POAF and oxidative stress associated with ischemia-reperfusion damage during ACC manipulation in CABG surgery by measuring plasma TOS levels. In conclusion:[1] Age, left atrium diameter, length of stay in the intensive care unit and length of stay in the hospital were higher in patients who developed POAF;[2] Plasma TOS levels after placement and removal of ACC were statistically significantly different in patients who developed POAF compared with those who remained in sinus rhythm. In multivariate logistic regression analysis, aging, hematocrit level, pump temperature, and plasma TOS levels were found to be independent predictors of POAF.

Postoperative atrial fibrillation (POAF) is the most common arrhythmia after cardiac surgery, and it is an important medical problem associated with increased cost of care, mortality and morbidity.[7] Although there have been clinical and experimental trials that have investigated the pathogenesis of POAF, there are not yet any conclusive studies that satisfactorily explain POAF. The complexity and multifactorial nature of POAF makes it impossible to identify an optimal medical treatment.[8] Well-known conventional risk factors for AF are not always consistent with POAF.

Table 1. Comparison of preoperative, intraoperative and postoperative clinical characteristics between the two groups

Demographic characteristics	Group 1 (n=37)			Group 2 (n=81)			*p*
	n	%	Mean±SD Median (range)	n	%	Mean±SD Median (range)	
Age (years)			65.6±7.20			59.6±9.07	0.000
Gender							0.335
Male	30	81.1		59	72.9		
Female	7	18.9		22	27.1		
Body mass index (kg/m²)*			26 (20-40)			27 (20-57)	0.303
Hypertension	23	62		47	58		0.692
Diabetes mellitus	15	40.5		39	48.1		0.551
Smoking	21	56.8		43	53.1		0.842
Laboratory findings							
Hematocrit (%)			37.5±5.16			39.7±5.28	0.034
WBC count (10³/μL)			7.7±2.66			8.0±2.61	0.440
Platelet count (10³/μL)			238±63			241±75	0.832
LDL-cholesterol (mg/dL)*			105 (72-185)			128 (40-247)	0.065
HDL-cholesterol (mg/dL)*			40 (25-62)			37 (15-131)	0.262
GFR (ml/min)*			79 (40-226)			87 (27-169)	0.129
Potassium (mEq/L)*			4.43 (3.6-5.39)			4.39 (3.59-5.37)	0.470
CRP (mg/L)*			7 (0-110)			6 (0-72)	0.261
Fasting blood glucose (mg/dL)*			120 (71-293)			116 (77-336)	0.692
Medications							
Beta blocker	5	94.6		69	85.2		0.220
ACE/ARB inhibitor	25	67.6		60	74.1		0.511
Statin use	28	75.7		66	81.5		0.470
Echocardiographic findings							
LA diameter (cm)			3.9±0.45			3.6±0.48	0.006
Ejection fraction (%)*			57 (30-60)			60 (28-60)	0.346
LV diastolic dysfunction	34	91.8		77	95		0.624
Intraoperative variables							
Total bypass time (min)*			129 (67-349)			130 (54-275)	0.628
Cross clamp time (min)*			72 (31-90)			69 (25-185)	0.801
Pump temperature (°C)*			31 (28-35)			30 (27-32)	0.115
Total graft number*			4 (1-7)			4 (1-6)	0.855
Usage of LIMA (%)*	33	91.7		68	89.5		1.000
Postoperative features							
Complication (n)	5	13.5		6	7.4		0.317
Hospital stay (day)							
Intensive care unit*			3 (2-16)			2 (1-58)	0.001
Total*			7 (6-85)			7 (5-58)	0.001
Plasma TOS levels*							
After application of ACC			13 (8.6-23)			14 (8.8-22)	0.920
After removal of ACC			30.6 (18.1-47.3)			24.6 (21.4-42.7)	0.900

*Mann-Whitney U-test was used for non-normally distributed variables and expressed by the median-interquartile ranges. ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; CRP: C-reactive protein; GFR: Glomerular filtration rate; HDL: High-density lipoprotein; LA: Left atrium; LDL: Low-density lipoprotein; LIMA: Left internal mammary artery; LV: Left ventricle; TOS: Total oxidative status; WBC: White blood cell; ACC: Aortic cross clamp; SD: Standard deviation.

Table 2. Comparison of plasma TOS levels after placement and removal of ACC in the two groups†

Groups	After application of ACC	After removal of ACC	*p*
Group 1	13 (8.6-23)	30 (18.1-47.3)	0.001
Group 2	14 (8.8.1-22)	24 (21.4-42.7)	0.060

ACC: Aortic cross clamp, POAF: Postoperative atrial fibrillation, TOS: Total oxidative status. †Wilcoxon test was used to compare plasma TOS levels after placement and removal of ACC in the two groups.

Table 3. Multivariate logistic regression analysis of clinical parameters related with POAF

Clinical parameters	*p*	OR (95% CI)
Age	0.036	1.088 (1.005-1.177)
Hematocrit (%)	0.025	0.718 (0.538-0.958)
Low density lipoprotein	0.390	0.990 (0.983-1.007)
Glomerular filtration rate	0.141	1.016 (0.995-1.038)
Usage of beta blockers	0.204	3.680 (0.493-27.493)
Left atrium diameter	0.080	2.440 (0.880-6.777)
Pump temperature	0.020	1.445 (1.059-1.972)
Plasma total oxidative status level	0.040	1.040 (1.020-1.050)

OR: Odds ratio; CI: Confidence interval; POAF: Postoperative atrial fibrillation.

Currently, increasing evidence has implicated the potential role of oxidative stress in the pathogenesis of POAF. Excessive release of oxidative molecules are involved in the structural and electrical remodeling of the heart, contributing to the pathogenesis of POAF.[9] During on-pump cardiac surgery, ACC manipulation is the most attributive resource of oxidative stress secondary to ischemia-reperfusion damage.[10] Increased levels of oxidative stress are associated with inflammatory changes, such as lipid peroxidation, modification of proteins, activation of complement cascades, excessive reactive oxygen radicals, and expression of adhesion molecules.[11]

Oxidative status can be measured separately in the laboratory, but these measurements are time-consuming, labor intensive, costly, and do not reflect the true levels of oxidative stress. Oxidative molecules in human metabolism have an additive effect, so when seeking a specific relationship between oxidative metabolism and suggested diseases, an evaluation of the total levels of oxidative status is essential.[12] Therefore, it was decided to choose plasma TOS levels as an indicator of oxidative stress on the pathogenesis of POAF.

Oxidative stress during coronary artery bypass surgery is related with depression in myocardial function and can be detected in nearly half of the cases.[13] Ramlawi et al.[14] found that postoperative increments in total peroxide levels used as a marker of oxidative stress during cardiac surgery were significantly higher in patients who developed POAF. Kim et al.[15] showed that tissue levels of NADPH oxidase in the left atrium were correlated with lipid peroxidation and were also increased in patients who developed POAF. The findings of this study showed significantly increased plasma TOS levels in the setting of CABG surgery due to the ischemia-reperfusion damage in patients who developed POAF compared with patients who remained in sinus rhythm, supporting a relationship between POAF development and oxidative stress.

In this trial, patients who developed POAF were older than patients who remained in sinus rhythm postoperatively. Aging leads to increased sympathetic activation and left atrial fibrosis, which are the main changes composing reentry focuses.[16,17] Amar et al.[18] reported that in patients older than 60 years, POAF was more common and the length of hospital stay was longer. Hosokawa et al.[19] reported that for

every additional 10-year increment in age, there was an associated 1.5 times increased risk for the development of POAF.

In patients who remained in sinus rhythm postoperatively, preoperative hematocrit levels were higher than in patients who developed POAF. Several studies indicate that anemia is an important contributing factor for the development of POAF.[20] Anemia causes increased adrenergic activation and cardiac output to compensate for reduced oxygen delivery for tissues. The anemia-related adrenergic response may trigger POAF. In Group 1, the intraoperative degree of pump temperature was higher than in Group 2. It has been suggested that mild hypothermia suppresses sympathetic activity, thus preventing neurohormonal- mediated atrial fibrillation.[21] Sun et al.[22] reported that the sympathetic response depends on the depth of hypothermia, and mild hypothermia is recommended by the American College of Chest Physicians for reducing the incidence of POAF.[23]

In conclusion, this is the first study designed to evaluate the effect of oxidative status using plasma TOS levels on the pathogenesis of POAF. The findings of this study suggest that oxidative stress induced by ischemia-reperfusion damage due to ACC manipulation during CABG surgery is a contributing factor for POAF development. To decrease the complication and mortality ratios associated with POAF, there is a need to focus on impaired oxidative response.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Atrial fibrillation/etiology/prevention & control; coronary artery bypass; coronary artery disease/surgery; oxidative stress.

Anahtar sözcükler: Atriyum fibrilasyonu/etiyoloji/korunma ve kontrol; koroner arter baypas; koroner arter hastalığı/cerrahi; oksidatif stres.