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ORIGINAL ARTICLE

The association of plasma oxidative status and inflammation with the development of atrial fibrillation in patients presenting with ST elevation myocardial infarction

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ABSTRACT

Atrial fibrillation (AF) is the most common supraventricular arrhythmia following ST elevation myocardial infarction (STEMI). Oxidative stress and inflammation may cause structural and electrical remodeling in the atria making these critical processes in the pathology of AF. In this study, we aimed to evaluate the association between total oxidative status (TOS), total antioxidative capacity (TAC) and high-sensitivity C-reactive protein (hs-CRP) in the development of AF in patients presenting with STEMI. This prospective cohort study consisted of 346 patients with STEMI. Serum TAC and TOS were assessed by Erel's method. Patients were divided into two groups: those with and those without AF. Predictors of AF were determined by multivariate regression analysis. In the present study, 9.5% of patients developed AF. In the patients with AF, plasma TOS and oxidative stress index (OSI) values were significantly higher and plasma TAC levels were significantly lower compared to those without AF ($p = .003$, $p = .002$, $p < .0001$, respectively). Multivariate regression analysis results showed that, female gender (Odds ratio [OR] = 3.07; 95% Confidence Interval [CI] = 1.26–7.47; $p = .01$), left atrial diameter (OR =1.28; 95% CI =1.12–1.47; $p < .0001$), hs-CRP (OR =1.02; 95% CI =1.00–1.03; $p = .001$) and OSI (OR =1.10; 95% CI =1.04–1.18; $p = .001$) were associated with the development of AF in patients presenting with STEMI. The main finding of this study is that oxidative stress and inflammation parameters were associated with the development of AF in patients presenting with STEMI. Other independent predictors of AF were female gender, left atrial diameter and hs-CRP.

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Antioxidants; atrial fibrillation; inflammation; myocardial infarction; oxidative stress

Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia, affecting 1–2% of the general population. Its prevalence increases with age and is as high as approximately 10% by the age of 80 [1–3]. It is the most common supraventricular arhythmia following acute myocardial infarction (AMI) with an incidence between 6 and 21% [4]. The occurrence of AF is associated with increased mortality, a three-fold increased incidence in congestive heart failure and a five-fold enhanced risk of stroke [5]. Patients with AF generally have been found to be older, female gender and have a low blood pressure, higher heart rate, higher Killip class, history of hypertension, prior myocardial infarction, diabetes mellitus and low ejection fraction [6,7].

The pathophysiology of AF is incompletely understood. Structural heart diseases may trigger structural remodeling in both the ventricles and the atria, which may result in electrical remodeling facilitating the initiation and maintenance of AF [1]. Oxidative stress and inflammation may also cause structural and electrical remodeling in the atria making these critical processes in the pathology of AF [8,9]. In this study, we aimed to evaluate the association between total oxidative status (TOS), total antioxidative capacity (TAC) and high-sensitivity C-reactive protein (hs-CRP) in the development of AF in patients presenting with acute ST elevation myocardial infarction (STEMI).

Methods

Study group

In this prospective study, 369 consecutive patients with STEMI were screened between January 2011 and December 2012. Inclusion criteria included age greater than 18 years and presence of acute STEMI. Exclusion criteria included unstable angina pectoris, non-ST elevation myocardial infarction, hyperthyroidism, history of AF (paroxysmal, persistent, or permanent), moderate to severe heart valve disease, advanced chronic obstructive pulmonary disease, infection, sepsis, rheumatic or inflammatory disease, history of malignancy and use of antiarrhythmic drugs. Out of 369

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consecutive patients with acute STEMI, three patients with hyperthyroidism, five patients with severe heart valve disease, three patients with advanced chronic obstructive pulmonary disease, one patient with sepsis, two patients with a history of malignancy, one patient using antiarrhythmic therapy and eight patients with a history of AF were excluded. Therefore, the study cohort consisted of 346 patients with STEMI. The institutional ethics committee approved the study and all participants provided written informed consent.

Diagnosis of STEMI was made by the rise and/or fall of cardiac biomarker values (preferably troponin) with at least one value above the 99th percentile of the upper reference limit and with at least one of the following; symptoms of ischaemia, new or presumably new significant ST-T changes (ST-segment measured at the J point, should be found in two contiguous leads and be $\geq$0.2 mV in men, or $\geq$0.15 mV in women in leads V2–V3 and/or $\geq$0.1 mV in other leads) or new left bundle branch block [10].

Each patient was questioned about major cardiovascular risk factors including family history of coronary artery disease, current smoking status, hyperlipidaemia, hypertension, diabetes mellitus and obesity. Family history of coronary artery disease was defined as manifestation of the disease in first-grade male relatives younger than 55 years or in female relatives younger than 65 years of age. Hyperlipidaemia was defined as fasting total cholesterol level >200 mg/dL or pharmacotherapy with lipid-lowering agents. Hypertension was defined as systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg measured before hospitalization or pharmacotherapy with antihypertensive drugs. Diabetes mellitus was defined fasting plasma glucose $\geq$126 mg/dL or pharmacotherapy with insulin or oral antidiabetic agents. Obesity was defined as body mass index >30 kg/m^2. Patients who were smoking prior to hospitalization were accepted as smokers.

Clinical data of the patients, their previous medication history and medications started after hospitalization were recorded. The patients were divided into two groups: those with and those without AF. All patients were admitted to the coronary intensive care unit and when their hemodynamic and respiratory functions were stabilized, they were transferred to the wards. Patients were followed with continuous electrocardiography (ECG) monitoring during their stay at the coronary care unit for the occurrence of AF, which was defined as an irregular narrow complex rhythm (in the absence of bundle branch block) with absence of discrete P waves. Patients did not undergo continuous ECG monitoring during their stay at the wards, therefore rhythm follow-up was not evaluated at the wards. An AF episode lasting >30 sec during hospitalization at the coronary care unit was accepted as an endpoint.

All patients were treated according to the currently available guidelines [11]. Primary percutaneous coronary intervention (PCI) was performed in the patients when deemed appropriate. When primary PCI was not an option, thrombolytic therapy was given. The patients underwent transthoracic echocardiography and the left ventricular ejection fraction was calculated by Simpson's method [12].

Blood sampling and analyses

Venous blood samples were obtained upon admission of the patients, drawn from a large antecubital vein without interruption of venous flow, using a 19-gauge butterfly needle connected to a plastic syringe. The contents of the syringe were transferred immediately to polypropylene tubes. These tubes were then centrifuged at 4000 rpm for 10 min at 10–18 °C. Supernatant plasma samples were stored in plastic tubes at −80 °C until analysis. All plasma samples for TAC and TOS were measured by the same and single assay.

Total antioxidative capacity levels were determined spectrophotometrically (Rel Assay Diagnostics, Gaziantep, Turkey). The method is based on the bleaching of the characteristic color of a more stable ABTS (2,2′-azino-bis[3-ethylbenzothiazoline-6-sulfonic acid]) radical cation by antioxidants [13]. The assay has excellent precision with coefficient of variation less than 3%. The results were expressed as mmol Trolox (Rel Assay) equivalent/L.

Total oxidative status levels were measured spectrophotometrically (Relassay, Diagnostics, Gaziantep, Turkey). In this method, oxidants present in the sample oxidized the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction was enhanced by glycerol molecules abundantly present in the reaction medium. The ferric ion produced a colored complex with xylenol orange in an acidic medium. The color intensity, which could be measured spectrophotometrically, was related to the total amount of oxidant molecules present in the sample [14]. The assay was calibrated with hydrogen peroxide and the results were expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H2O2 equivalent/L). The coefficient of variation for individual plasma samples was less than 3%. The levels of TAC and TOS were assayed in an Olympus AU 2700 autoanalyzer (Japan).

The oxidative stress index (OSI) is defined as the ratio of TOS to TAC levels, expressed as a percentage. For the calculation of OSI, TAC units were represented as mmol/L, and the OSI value calculated according to the following formula: OSI (arbitrary unit) = TOS (mmol H2O2 equiv./L)/TAC (mmol Trolox equiv./L).

Serum hs-CRP level was measured by a chemiluminescent immunometric assay within 12–24 h after admission using available commercial kits according to the manufacturer's instructions (Immulite 2000, Siemens Medical Solutions Diagnostics, NJ, US). The intra- and inter-assay coefficients of variation for hs-CRP were <8.7%.

Statistical analysis

Continuous variables were expressed as mean + SD and categorical variables were expressed as numbers and percentages (%). To compare continuous variables, Student's *t*-test or Mann-Whitney *U* test were used where appropriate. Categorical variables were compared with the χ^2 test. We used a receiver operating characteristic (ROC) analysis with area under the curve and OSI cut-off point for prediction of AF. Predictors of AF were determined by logistic regression analysis. The strength of association between variables and

the occurrence of AF was represented by odds ratios (ORs) and their accompanying 95% confidence intervals. Since we have too many variables in the regression analysis, we have performed an epidemiological approach and factors that have been shown to be associated in the development of AF (age, gender, left atrial diameter, ejection fraction, hs-CRP and OSI) were entered in a multivariate regression analysis [6,7,15]. Statistical significance was defined as $p < .05$. SPSS 11 (Chicago, IL) was used for analysis.

Results

A total of 346 patients (mean age: 62 ± 12 years; range, 23–92 years) were included in this study. During the follow-up period, 33 patients (9.5%) developed AF. Demographic and clinical characteristics of the patients with and without AF are listed in Table 1. The patients with AF were older and female when compared to the patients without AF ($p = 0.001$ and $p = 0.003$, respectively). Hypertension and obesity were more common ($p = .008$, $p < .0001$, respectively), but smoking was less common in patients with AF as compared to those without AF ($p = .009$). Diabetes mellitus and hyperlipidemia rates were similar between patients with and without AF (for both parameters $p > .05$).

Total cholesterol levels were lower ($p = .030$), but high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides levels were similar between patients with and without AF (for all parameters $p > .05$). Ejection fraction was lower ($p = .038$) and left atrial diameter was higher in patients with AF than the patients without AF ($p < .0001$). Time to reperfusion and troponin T serum levels at baseline and peak were similar between patients with and without AF (for all parameters $p > .05$).

There were no statistically significant differences between patients with and without AF in regard to previous use of renin-angiotensin system blockers, beta-blockers, acetyl salicylic acid, clopidogrel or statin. In-hospital treatments were similar among the patients with and without AF ($p > .05$). The follow-up duration for the patients in the coronary intensive care unit was about 2.11 ± 0.67 days and this duration was similar in patients with and without AF ($p > .05$). As Table 1 indicates, 33 patients developed AF. Of these 33 patients, 13 patients received thrombolysis, 13 patients received PCI and seven patients received no reperfusion due to late admission. Recanalization methods (thrombolysis vs. primary PCI) were similar between the patients with or without AF ($p > .05$). There was no association between presence and mode of reperfusion and development of AF (Table 2).

Oxidative status and inflammation parameters are presented in Table 3. In the patients with AF, plasma TOS and OSI values were significantly higher and plasma TAC levels were significantly lower compared to those without AF. We calculated the cut-off point of 21.2 for OSI to estimate the presence of AF with a sensitivity of %80 and a specificity of %61 (AUC =0.72, $p < .001$) (Figure 1). Hs-CRP levels were significantly higher in the patients with AF compared to patients without AF.

Factors that were ascertained to be significantly different with univariate regression analysis (age, gender, left atrial diameter, ejection fraction, hs-CRP and OSI) were entered in a multivariate model. Multivariate regression analysis results showed that female gender, left atrial diameter, hs-CRP and OSI were associated with the development of AF (Table 4).

Discussion

The main findings of this study indicate that oxidative stress and inflammation parameters were associated with the development of AF in patients presenting with acute STEMI. Oxidative stress is caused by the increased production of reactive oxygen species and is linked with negative outcomes in cardiovascular diseases such as coronary artery

Table 1. Demographic and clinical characteristics of the patients with and without atrial fibrillation (AF).

	Without AF ($n = 313$)	With AF ($n = 33$)	p-value
Age, year	61.4 ± 12.7	68 ± 12.1	.003
Body mass index	26.02 ± 3.62	28.66 ± 4.28	<.0001
Female gender	49 (15.7)	13 (39.4)	.001
Smoking	205 (65.5)	14 (42.4)	.009
Diabetes mellitus	74 (23.6)	10 (30.3)	.396
Hypertension	124 (39.6)	21 (63.6)	.008
Hyperlipidemia	72 (23)	9 (27.3)	.582
Family history of CAD	53 (16.9)	7 (21.2)	.537
Ejection fraction (%)	45.1 ± 9.58	41.45 ± 10.0	.039
Left atrial diameter (mm)	39.25 ± 3.3	42.18 ± 2.85	<.0001
Localization of MI			.339
Anterior	141 (45.1)	12 (36.3)	
Non-anterior	172 (54.9)	21 (63.6)	
History of MI	33 (10.5)	4 (12.1)	.780
History of PCI	31 (9.9)	2 (6.1)	.475
History of CABG	11 (3.5)	1 (3.0)	.885
History of heart failure	4 (1.3)	0	
Pre-hospital treatment			
Statin	42 (13.4)	1 (3.0)	.085
Beta blocker	46 (14.5)	4 (12.1)	.689
RAS blockers	108 (34.5)	8 (24.2)	.235
Acetyl salicylic acid	87 (27.8)	8 (24.2)	.664
Clopidogrel	10 (3.2)	1 (3.0)	.959
Diuretics	13 (4.2)	4 (12.1)	.126
Hospital treatment			
Beta blocker	292 (93.3)	28 (84.8)	.080
Statin	295 (94.2)	32 (97.0)	.514
RAS blockers	303 (96.8)	31 (93.9)	.392
Acetyl salicylic acid	307 (98.1)	33 (100)	.422
Clopidogrel	313 (100)	33 (100)	
Enoxaparin	311 (99.4)	33 (100)	.645
Tirofiban	29 (9.3)	2 (12.1)	.595
Thrombolytics	150 (48.0)	13 (39.4)	.422
Primary PCI	112 (35.8)	11 (33.3)	.916
Rescue PCI	20 (6.4)	2 (6.1)	.870
Total cholesterol (mmol/L)	4.57 ± 1.03	4.18 ± 1.03	.030
HDL cholesterol (mmol/L)	1.06 ± 0.25	1.01 ± 0.22	.362
LDL cholesterol (mmol/L)	2.79 ± 0.87	2.56 ± 0.83	.158
Triglycerides (mmol/L)	3.78 ± 2.91	2.92 ± 1.15	.094
BUN (mmol/L)	0.49 ± 0.2	0.55 ± 0.16	.08
Creatinine (μmol/L)	95.47 ± 23	99.89 ± 24.7	.286
Troponin T at baseline (μg/L)	0.47 ± 1.18	0.66 ± 1	.36
Troponin T at peak (μg/L)	5.25 ± 7.1	5.59 ± 3.74	.79
Time to reperfusion (hour)	5.18 ± 5.2	6.25 ± 5.43	.26
Duration of hospitalization during coronary intensive care unit (days)	2.09 ± 0.52	2.27 ± 1.50	.163

Data presented as mean + SD or number (%) of the patients. CAD: coronary artery disease; MI: myocardial infarction; RAS: renin-angiotensin system; PCI: percutaneous coronary intervention; BUN: blood urea nitrogen; CABG: coronary artery bypass grafting.

Table 2. Association of reperfusion on development of AF.

	< 24 hour	24–72 hour	> 72 hour	*p*-value
Patients with no reperfusion	2 (6%)	3 (9%)	2 (6%)	0.8
Patient with reperfusion				
Thrombolytics	8 (24%)	3 (9%)	2 (6%)	
Primary or rescue PCI	9 (27%)	4 (12%)	–	

PCI: percutaneous coronary intervention.

Table 3. Comparison of plasma oxidative stress and inflammation parameters in the patients with and without atrial fibrillation (AF).

	Without AF ($n = 313$)	With AF ($n = 33$)	*p*-value
TAC (mmol/Trolox Equiv./L)	1.43 (0.28)	1.28 (0.27)	.003
TOS (μmol H2O2 Eq/L)	28.43 (5.4)	31.67 (5.77)	.002
OSI	20.54 ± 5.72	25.86 ± 7.21	<.0001
Hs-CRP (mg/L)	20.54 ± 5.72	48.29 ± 34.22)	<.0001

TAC: total antioxidative capacity; TOS: total oxidative status; OSI: oxidative stress index; Hs-CRP: high-sensitivity C-reactive protein. Data presented as mean + SD.

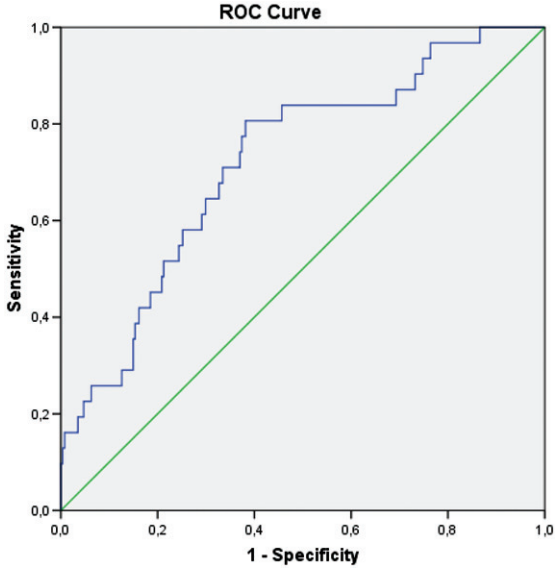

Figure 1. ROC curve with calculated area under the curve and optimal cut-off point for OSI to identify the presence of AF. Optimal cut-off point is 21.2 fL. AUC is calculated at 0.72. ROC, receiver–operating curve; AF, Atrial Fibrillation; OSI, oxidative stress index; AUC, area under curve.

Table 4. Multivariate independent predictors of AF.

	Odds ratio	95% Confidence Interval	*p*-value
Female gender	3.07	1.26–7.47	$p = .01$
Left atrial diameter	1.28	1.12–1.47	$p < .001$
Hs-CRP	1.02	1.00–1.03	$p = .001$
OSI	1.10	1.04–1.18	$p = .001$

Hs-CRP: high-sensitivity C-reactive protein; OSI: oxidative stress index.

disease and AF [16–18]. The use of vitamins and drugs with antioxidant properties in AF prevention indicates that they may have a role in risk reduction of AF [19,20] and postoperative AF [21,22]. Patients with AF exhibit upregulated expression of reactive oxygen species-related genes [23], oxidative injury in atrial myofibrils [24] and increased oxidative stress markers [25–27]. Oxidative stress and inflammation are interrelated and have been implicated in atrial remodelling [28–30].

We have previously reported that postoperative TAC, TOS and WBC were associated with postoperative AF. Carvedilol plus N-acetyl sistein with antioxidant properties reduced oxidative stress and inflammation compared with metoprolol [31]. Borekci et al. [32], have showed that OSI, uric acid and neutrophil to lymphocyte ratio were associated with spontaneous reperfusion in patients with STEMI. Similarly, Turan et al. [33], showed that, plasma levels of TOS and OSI was an important factor related to the complexity and intensity of coronary artery disease in the patients with acute coronary syndrome. In these studies, they were not studied the relationship between AF and oxidative stress markers in patients with STEMI. Our results showed that, plasma levels of TOS and OSI were increased in patients with AF when compared to those without AF in a STEMI patient population. Thus, increased oxidative stress may contribute to pathogenesis in these patients.

An association between inflammation and AF has been indicated in the literature [34]. Inflammation is an important factor related to the initiation and maintenance of AF [15,28,35,36]. Myocyte necrosis, fibrosis and markers of inflammatory infiltrates were found in the atrial biopsies of patients with lone AF, but not in control patients [37]. Hs-CRP and interleukin-6 levels were found to be elevated in patients with paroxysmal, persistent and permanent AF compared to those with sinus rhythm [38]. Moreover, longer duration of AF was found to be associated with higher hs-CRP levels compared to shorter duration of AF [28]. Similarly, hs-CRP has been found to be a significant predictor of early AF recurrence after cardioversion [39]. Colchicine is known a substance with potent anti-inflammatory properties and Deftereos et al. have shown that a short course of colchicine treatment reduced the relative infarct size in patients with STEMI [40]. It is expected that rhythm disturbances such as AF risk would be lower with reduces infarct size. Therefore, anti-inflammatory agents such as colchicine might be promising alternatives that can be used for this purpose in the future. A positive association between increased CRP and new-onset AF in patients with AMI has been shown [15,41,42]. Similarly, in the present study, hs-CRP levels were significantly higher in patients with AF compared to patients without AF. This indicates that higher hs-CRP may be associated with the development of arrhythmia in patients presenting with STEMI.

The overall prevalence of AF among AMI patients has been reported in a range of 6–21% [4]. We have previously reported that among 1000 patients presenting with acute coronary syndrome, the incidence of AF was 8.8% and independent predictors of arrhythmia development included left atrial diameter, age, hypertension, history of AF and the use of statin or renin-angiotensin system blockers [43]. In GISSI-3 study [44], 7.8% of patients developed new AF during their inpatient stay and independent predictors of arrhythmia development were age greater than 70 years, female gender, higher heart rate at admission, higher Killip class, history of hypertension and diabetes. In the present study, 9.5% of patients developed AF and predictors of arrhythmia development in the setting of acute STEMI were female gender, increased left atrial diameter, hs-CRP and OSI.

Gal et al. have shown that serial high sensitivity troponin T plasma levels (at baseline, 24–72 h and >72 h after

admission) were associated with new-onset AF [45]. In the present study, troponin T levels at baseline and peak were not associated with new-onset AF. Gal et al. performed primary PCI to all patients but we performed primary PCI in the only 35% of the cases. Also, they included more patients as compared to the present study. Therefore, we speculated that due to these differences the results of the study by Gal et al. and our study was not in agreement due to these differences.

This study has several limitations. The study population consisted of patients treated with different modes of STEMI treatment and the number of AF patients was too small for definitive conclusions. Additional oxidative stress parameters such as serum prolidase activity, malondialdehyde, superoxide dismutase etc., were not studied. Rhythm follow-up was solely evaluated at the coronary intensive care unit: continuous ECG monitoring as well as rhythm follow-up were not conducted in the patients during their stay at the wards.

Conclusions

The present study suggests that in a patient population with STEMI, oxidative stress and inflammation were significantly higher in patients with AF when compared to those without AF. Further studies are needed to establish the pathophysiological and clinical significance of increased oxidative stress and inflammation, and to investigate the effect of antioxidant and anti-inflammatory agents in patients with AMI.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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