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Associations of big endothelin-1 and C-reactive protein in atrial fibrillation

Li-Hui ZHENG*, Wei SUN*, Yan YAO, Bing-Bo HOU, Yu QIAO, Shu ZHANG

State Key Laboratory of Cardiovascular Disease, Clinical EP Lab & Arrhythmia Center, Fuwai Hospital, Beijing, China

Abstract

Background Atrial fibrillation (AF) is associated with inflammation and endothelial dysfunction. However, the association between inflammation (as indexed by high-sensitivity C-reactive protein, hs-CRP) and endothelial function [as indexed by big endothelin-1 (ET-1)] in AF patients remains unclear. **Methods** We enrolled 128 patients with lone AF, among which 83 had paroxysmal AF, and 45 had persistent AF. Eighty-two age- and gender-matched controls of paroxysmal supraventricular tachycardia without AF history were evaluated. Plasma hs-CRP, big ET-1 levels and other clinical characteristics were compared among the groups. **Results** Patients with persistent AF had higher hs-CRP concentrations than those with paroxysmal AF ($P < 0.05$), both groups had higher hs-CRP level than controls ($P < 0.05$). Patients with persistent AF had higher big ET-1 level than those with paroxysmal AF, although the difference did not reach the statistical significance ($P > 0.05$), and both groups had higher big ET-1 levels than controls ($P < 0.05$). Multiple regression analyses revealed hs-CRP as an independent determinant of AF ($P < 0.001$). Further adjusted for big ET-1, both big ET-1 and hs-CRP were independent predictors for AF ($P < 0.001$), but the odds ratio for hs-CRP in predicting AF attenuated from 8.043 to 3.241. There was a positive relation between hs-CRP level and big ET-1 level in paroxysmal AF patients ($r = 0.563$, $P < 0.05$), however, the relationship in persistent AF patients was poor ($r = 0.094$, $P < 0.05$). **Conclusions** Both plasma hs-CRP and big ET-1 levels are elevated in lone AF patients, and are associated with AF. In paroxysmal lone AF patients, there were significant positive correlations between plasma hs-CRP level and big ET-1 level.

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Keywords: Atrial fibrillation; C-reactive protein; Endothelin; Inflammation

1 Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. It has been reported that lone AF accounted for about 2.7%–11.4% of all AF.[1] Although the exact pathophysiology of AF remains unclear, it is accepted that the initiation and maintenance of AF requires both a trigger and a substrate. The trigger is mainly the ectopic beats or repetitive foci from pulmonary veins or atrium. The heterogeneous atrial effective period, atrial enlargement and atrial fibrosis constitute the main process of atrial remodeling, which provide the substrate of atrial inhomogeneous conduction predisposing AF. An increasing body of evidences has demonstrated that AF is closely associated with inflammation. Increased inflammatory markers [mainly high-sensitivity C-reactive protein (hs-CRP)] are increased in AF, and could predict new-onset AF and AF recurrence after cardioversion or catheter ablation.[2–6] Endothelin-1 (ET-1) is an endothelium-derived vasoconstrictor peptide, and plays important roles in the pathophysiology of AF via membrane ion channels and atrial remodeling.[7,8] Big ET-1 is a 38-amino acid precursor of ET-1, has a much longer half-life, and has been proven a better approach for the investigation of the secretory activity of the endothelial system.[9]

Previous studies showed that ET-1 concentrations are elevated in some inflammatory pathology, and the ET-1 level was positively related to C-reactive protein concentration as in chronic obstructive pulmonary disease,[10] diabetes mellitus,[11] and acute ischemic stroke.[12] However, an isolated study showed that plasma CRP is not positively related with ET-1 in stable coronary artery disease.[13] In AF patients, little is known about the relationship between inflammation and the endothelin system. This study aimed to investigate the relationship between inflammation (indexed by hs-CRP) and endothelial dysfunction (indexed by big ET-1) in lone AF patients.

*The first two authors contributed equally to this manuscript.

Correspondence to: Yan YAO, MD, PhD, State Key Laboratory of Cardiovascular Disease, Clinical EP Lab & Arrhythmia Center, Fuwai Hospital, 167 Beilishi Road, Xicheng District, Beijing 100037, China. E-mail: ianyao@263.net.cn

Telephone: +86-10-8839-8460 **Fax:** +86-10-6833-4688

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2 Methods

2.1 Study populations

One hundred and twenty-eight consecutive patients with lone AF (AF group) were recruited, of which 83 had paroxysmal AF, and 45 had persistent AF. Paroxysmal AF was defined as self-terminating AF, lasting for ≤ 7days. Persistent AF was defined as AF lasting at least 7 days. The control groups consisted of 82 consecutive subjects of paroxysmal supraventricular tachycardia without history of AF and structural heart disease (Table 1).

We aimed to include a population with lone AF and no comorbid conditions with hypertension and various structural heart diseases. The following conditions were also excluded: coronary artery disease, hepatic or renal dysfunction, acute or chronic pulmonary embolism, chronic obstructive pulmonary disease, thyroid dysfunction and established diagnosis of diabetes mellitus or sleep apnea. In addition, none of the participants had any history of inflammatory or infection disease or recent (within the last four weeks) trauma or surgery; none was under treatment with nonsteroidal anti-inflammatory or corticosteroids drugs.

All AF patients discontinued all anti-arrhythmic drugs treatment at least for five half-lives prior to enrollment in the study. Informed written consent was obtained from all patients, and this study was approved by the Ethics Committee of Fuwai Hospital and clinical investigations are conducted according to the principles expressed in the Declaration of Helsinki.

Table 1. Characteristics of the study populations with AF and control group.

	Controls (*n* = 82)	Paroxysmal AF (*n* = 83)	Persistent AF (*n* = 45)
Age, yrs	54 ± 11	57 ± 8	56 ± 9
Male	55 (67.1%)	61 (73.5%)	32 (71.1%)
Smoking	32 (39.0%)	36 (43.4%)	20 (44.4)%
BMI, kg/m^2	24.2 ± 2.7	25.8 ± 2.1	25.3 ± 2.4
AF history, yrs	-	3 (1–4)	4 (2–8)$^{\#}$
Systolic blood pressure, mmHg	124 ± 13	125 ± 12	122 ± 11
Diastolic blood pressure, mmHg	77 ± 10	78 ± 11	74 ± 11
Heart rate, beats/min	75 ± 15	80 ± 18	77 ± 10
Fasting glucose, mmol/L	4.88 ± 0.66	5.01 ± 0.64	5.08 ± 0.59
Serum creatinine, μmol/L	79 ± 12	80 ± 16	81 ± 13
Hyperlipidemia	14 (17.1%)	11 (13.3%)	8 (17.8%)
LAD, mm	36 ± 4	42 ± 5*	45 ± 6*$^{,\#}$
LVEDD, mm	49 ± 4	51 ± 4*	52 ± 4*
LVEF, %	63 ± 6	62 ± 6	61 ± 5
WBC, × 10^9/L	5.40 ± 1.32	5.34 ± 1.36	5.31 ± 1.15
ESR, mm/h	7 ± 4	8 ± 4	8 ± 4
Hs-CRP level, mg/L	0.94 ± 0.44	1.77 ± 1.08*	2.25 ± 0.88*$^{,\#}$
Big ET-1 level, fmol/mL	0.43 ± 0.27	1.07 ± 0.59*	1.10 ± 0.59*

Data are presented as mean ± SD, *n* (%) or median (interquartile ranges). *P < 0.05 compared to controls; $^{\#}P$ < 0.05 compared to paroxysmal AF. AF: atrial fibrillation; BMI: body mass index; ESR: erythrocyte sedimentation rate; ET-1: endothelin-1; Hs-CRP: high-sensitivity C-reactive protein; LAD: left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; WBC: white blood cell.

2.2 Clinical characteristics

Patients were interviewed and records were reviewed to determine past medical history, medications, and 12-lead ECG, a complete echocardiography and plasma hs-CRP and big ET-1 levels determined. The body mass index (BMI) was calculated as body weight (kg) divided by the square of the height (m) at the time of the admission. After admission, left atrial diameter (LAD), left ventricular end diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF) was determined by echocardiography within three days.

2.3 Chemical laboratory analyses

Venous blood samples were collected from the antecubital vein in the morning upon admission. Plasma hs-CRP and big ET-1 concentrations were determined in heparinized plasma with a commercially available enzyme-linked immunoturbidimetric assay (Orion Diagnostica, Finland and Biomedica, Australia, respectively). White blood counts (WBC) and erythrocyte sedimentation rates (ESR) were also measured.

2.4 Statistical analysis

Continuous data are reported as mean ± SD and categorical variables as percentage. The Kolmogorov-Smimov statistic was used to test for any deviation from normality and the variables with non-normally distributed scores were presented as median plus interquartile range. With continuous variables, group mean values were compared using the Student *t* test or analysis of variance as appropriate, and otherwise, the Wilcoxon rank-sum test. Categorical variables were compared using the Pearson's χ^2 test. Spearman's correlation test was used for plasma hs-CRP and big ET-1 level correlation analysis. A value of $P < 0.05$ is considered statistically significant.

Bivariate linear regression was performed to evaluate the independent relationship of hs-CRP and big ET-1 in the total AF group and paroxysmal/persistent AF group, respectively.

Multivariate logistic regression analysis was used to determine the effects of various baseline clinical and laboratory variables in AF. A stepwise forward selection algorithm was applied to select determinants of AF, with criteria of a P value < 0.05 for inclusion and a P value > 0.05 for removal from the model to screen covariates in the multivariate analysis. The variables included in the multivariate model were age, gender, smoking, hyperlipidemia, BMI, systolic blood pressure, diastolic blood pressure, heart rate, fasting glucose, serum creatinine, hs-CRP, LAD, LVEDD, LVEF, WBC, ESR and big ET-1. Adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated. $P < 0.05$ is considered statistically significant. All statistical analyses were performed using SPSS software version 13.0 (SPSS, Inc., Chicago, Illinois, USA).

3 Results

3.1 Clinical characteristics

In 128 patients with lone AF, the mean age was 57 ± 8 years, and 93 (72.7%) were male. They had their arrhythmias for a median duration of 3 (2–7) years prior to inclusion in this study. Patients with AF had received a variety of medications for AF, including warfarin in 35 patients, aspirin in 50, β-blocker in 110, calcium channel blocker in 36, propafenone in 85, and amiodarone in 37. The subjects in control group were not taking any routinely cardiovascular medications before enrollment.

The clinical and echocardiographic characteristics of the study populations are presented in Table 1. No significant differences were observed between three groups with reference to their blood pressure, heart rate, fasting glucose, and BMI ($P > 0.05$). Compared to the control group, both paroxysmal and persistent lone AF patients had a larger LAD ($P < 0.05$, respectively). Persistent AF patients had a larger LAD than that with paroxysmal AF. Furthermore, both paroxysmal and persistent AF patients showed a larger LVEDD than controls ($P < 0.05$).

3.2 Comparisons of hs-CRP and big ET-1 among the three groups

Levels of hs-CRP were significantly higher in AF subjects than in controls. These differences persisted when the patients were grouped into persistent AF (2.25 ± 0.88 mg/L), paroxysmal AF (1.77 ± 1.08 mg/L), or controls (0.94 ± 0.44 mg/L). Furthermore, there was a progressive decrease in hs-CRP concentration with persistent AF, paroxysmal AF and control patients, respectively.

Big ET-1 concentrations were significantly higher in AF patients than in controls. These differences persisted when the patients grouped into persistent AF (1.10 ± 0.59 fmol/mL), paroxysmal AF (1.07 ± 0.59 fmol/mL), or controls (0.43 ± 0.27 fmol/mL). However, there was no statistical significance between persistent and paroxysmal AF groups ($P = 0.1$), (Table 1).

3.3 Univariate and multivariate predictors of AF

In univariate logistic analyses, BMI, hs-CRP, LAD, LVEDD and big ET-1 were significantly related to AF ($P < 0.05$), respectively (Table 2).

The following variables including age, gender, smoking, hyperlipidemia, BMI, systolic blood pressure, diastolic blood pressure, heart rate, fasting glucose, serum creatinine, hs-CRP, LAD, LVEDD and LVEF were analyzed using multivariate logistic regression analyses. It demonstrated that BMI, LAD, heart rate and hs-CRP were independently associated with AF. After adjustment of big ET-1, the BMI, LAD, hs-CRP and big ET-1 were the independent predictors for AF, but the OR for hs-CRP in predicting AF has been attenuated from 8.043 to 3.241 (Table 3).

3.4 Correlations between hs-CRP and big ET-1 levels

Plasma hs-CRP levels and big ET-1 concentrations were examined using a bivariate linear regression model. A positive relationship between hs-CRP and big ET-1 level

Table 2. Univariate predictors of AF.

	OR	95% CI	*P* value
Age	1.027	0.997–1.057	0.073
Male	1.304	0.714–2.383	0.387
Smoking	1.215	0.691–2.137	0.499
Hyperlipidemia	0.953	0.454–2.001	0.899
Body mass index	1.263	1.117–1.428	0.000
Systolic blood pressure	1.002	0.980–1.025	0.845
Diastolic blood pressure	1.001	0.975–1.028	0.938
Heart rate	1.016	0.996–1.036	0.108
Fasting glucose	1.457	0.936–2.269	0.096
Serum creatinine	1.005	0.985–1.025	0.620
Hs-CRP	6.260	3.529–11.105	0.000
LAD	1.298	1.199–1.405	0.000
LVEDD	1.115	1.041–1.193	0.002
LVEF	0.967	0.923–1.013	0.158
WBC	0.961	0.776–1.190	0.715
ESR	1.050	0.974–1.132	0.202
Big ET-1	18.608	7.832–44.215	0.000

AF: atrial fibrillation; ESR: erythrocyte sedimentation rate; ET-1: endothelin-1; Hs-CRP: high-sensitivity C-reactive protein; LAD: Left atrial diameter; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; WBC: white blood cell.

Table 3. Multivariate predictors of AF.

Variables	OR	95% CI	*P* value
BMI	1.461	1.187–1.799	0.003
LAD	1.294	1.160–1.445	0.001
Heart rate	1.043	1.010–1.077	0.01
hs-CRP	8.043	3.428–18.874	0.000
Further adjusted for big ET-1			
BMI	1.458	1.172–1.815	0.001
LAD	1.279	1.141–1.434	0.001
hs-CRP	3.241	1.225–8.575	0.018
Big ET-1	6.996	1.671–29.286	0.008

AF: atrial fibrillation; BMI: body mass index; ET-1: endothelin-1; hs-CRP: high-sensitivity C-reactive protein; LAD: left atrial diameter.

was found in the total AF populations ($r = 0.365$, $P < 0.001$), and for the paroxysmal AF($r = 0.563$, $P < 0.001$), respectively. Although there was a statistically significant positive correlation for persistent AF subjects, the linear relationship was not strong ($r = 0.094$, $P < 0.05$), (Figure 1).

4 Discussion

The major findings of this study were: (1) lone AF patients have higher levels of hs-CRP and big ET-1 compared to controls. Higher hs-CRP levels were observed in persistent AF patients compared with paroxysmal AF; (2) the interaction between hs-CRP and AF may be mediated by big ET-1; and (3) Hs-CRP and big ET-1 levels were positively correlated in paroxysmal AF patients. These findings suggest that the endothelin system may play a role in the inflammatory process in lone AF.

4.1 AF and inflammation

Recently, an increasing body of evidence links AF to the inflammation. Frustaci, *et al*.[14] demonstrated a high prevalence of inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies of lone AF patients. In a canine sterile pericarditis model,[15]AF is related with inflammatory initiation. Hs-CRP, acting as the major inflammatory index, and its relationship with AF has been intensely studied. In a community-based population,[2] plasma hs-CRP levels are increased in AF, and increased baseline hs-CRP concentrations independently predicted new-onset AF. Furthermore, baseline hs-CRP levels could predict newly developed AF after cardiac bypass surgery,[3] and predict AF recurrence after successful radiofrequency catheter ablation,[4] and electrical cardioversion.[5] Also, hs-CRP was independently related to pro-thrombotic state in AF.[6] Moreover, increased hs-CRP levels have been reported two weeks after successful cardioversion of AF.[16] These studies imply a pathogenetic role for inflammation in the initiation and development of AF.

4.2 AF and endothelial dysfunction

AF has been reported in association with the endothelial system. In AF patients, the plasma ET-1 concentration was elevated, independent of the underlying structural heart disease.[17] Furthermore, a decrease in the expression of endothlin A-receptor can predict new-onset AF post cardiac bypass surgery.[18] ET-1 shortens the atrial action potential duration and the effective refractory period mainly through inhibiting the L-type calcium current.[7] Also, ET-1 may modulate the rennin-angiotensin-aldosterone system; augment the myocardial inotropic function and stimulated cardiac hypertrophy.[19] ET-1 can also stimulate the production of pro-inflammatory cytokines such as interleukin-6, predisposing inflammation. Elevated big ET-1 mRNA was demonstrated in AF patients.[20] Big ET-1 could predict the

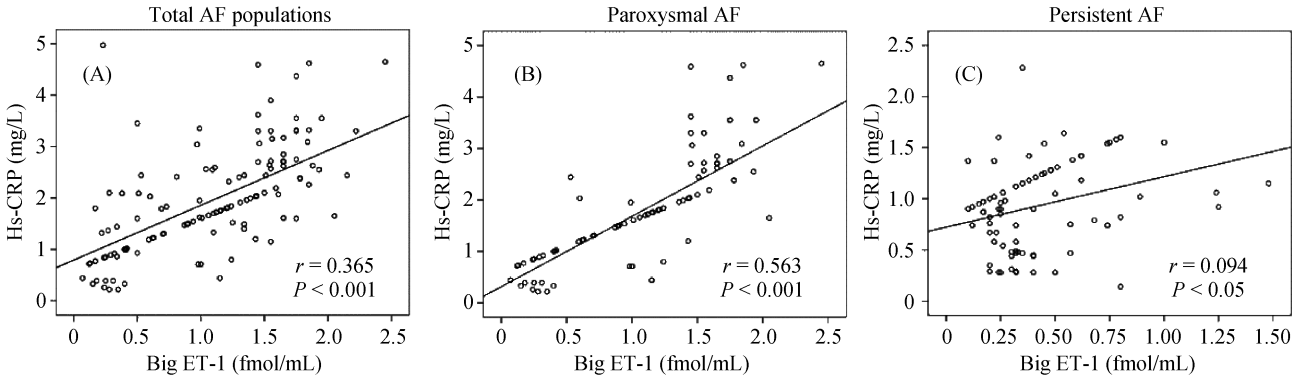

Figure 1. Scatter plots of hs-CRP level and big ET-1 concentrations in total lone AF subjects, paroxysmal lone AF and persistent lone AF patients, respectively. There is a positive relationshihp between plasma hs-CRP and big ET-1 levels in both total AF subjects (A) and paroxysmal AF (B). However, there is a very weak correlation between the above two parameters in persistent AF subjects (C). AF: atrial fibrillation; ET-1: endothelin-1; hs-CRP: high-sensitivity C-reactive protein.

AF independently, and predict recurrence post AF ablation.[21,22] This study demonstrated that the big ET-1 level is elevated in lone AF patients. Thus, ET-1 plays an important role in facilitating electrical or structural remodeling of AF, and causing AF chronicity; big ET-1 has become a valuable index for the ET-1 system in AF patients.

4.3 Endothelial dysfunction and inflammation in AF

Several studies have evaluated the relationship between ET-1 and CRP. Plasma ET-1 levels are found elevated and correlated with CRP in patients with inflammatory pathologies such as exacerbations of chronic obstructive pulmonary disease,[10] acute ischemic stroke,[12] and acute myocardial infarction treated with direct coronary angioplasty.[23] However, the positive relationship between the ET-1 and CRP may be obscured by statin treatment in patients with stable coronary artery disease.[13] Furthermore, increased ET-1 and endothelin converting enzyme activity were found at the site of inflammation in atherosclerotic coronary arteries.[24] CRP could also induce endothelial dysfunction, and endothelin antagonism and IL-6 inhibition attenuate the pro-atherogenic effects of CRP in venous endothelin cells.[25] These studies showed that endothelial dysfunction might play an important role in the inflammatory process. However, little is known about this relationship between the endothelin dysfunction and inflammation in AF patients.

In this study, we enrolled lone AF patients to explore the relationships between inflammation and endothelial function in AF. Previous studies have shown that hypertension and structural heart disease may predispose both inflammation and endothelial dysfunction, thus, lone AF patients are optimal subjects to explore relationship between inflammation and dysfunction in AF. We observed that lone AF patients have a higher level of hs-CRP and big ET-1 compared to controls. Higher hs-CRP levels were observed in persistent AF patients compared to paroxysmal AF. Furthermore, although hs-CRP was identified as an independent determinant of lone AF, adjustment for big ET-1 attenuates the relationship of hs-CRP with AF. These findings implied that big ET-1 may act as a mediator between inflammation and AF. We also determined that hs-CRP and big ET-1 levels were positively correlated in paroxysmal AF pa¬tients. However, in persistent AF patients, we did not find a strong linear relationship between them. The underlying reasons may be attributable to the adaptive down-regulation of the protein expression of endothelin receptors in the presence of persistent AF.[20] Furthermore, accumulating data suggest that the process of atrial remodeling is complex. Activation of rennin-angiotensin-aldosterone axis and sympathetic tone and atrial fibrosis or other factors may also play important roles in AF. Thus, the endothelin role in AF maintenance is of less importance. Future studies will require the investigation of the relationships between inflam¬mation and endothelial dysfunction in different types of AF in larger samples.

4.4 Study Limitations

Although our results indicated an association among hs-CRP, big ET-1and AF, the present study was not a prospective cohort design in nature, thus, limiting our ability to determine a cause or effect relationship between inflammation/endothelial dysfunction and AF. Nevertheless, the aim of the present study was to investigate the association between the inflammation and the endothelial dysfunction in AF. Whether inflammation was a cause or the consequence of AF remains controversial and deserves further study.

The present study did not address the pathophysiological relationship between inflammation and endothelial dysfunction directly, and it also merits further study. However, we did find a positive correlation between the increases in plasma hs-CRP and big ET-1 levels in patients with paroxysmal AF, but not in persistent AF. As many previous studies have demonstrate elevated ET-1 levels in inflammatory pathologies, such as chronic obstructive pulmonary disease,[10] acute ischemic stroke,[12] and acute myocardial infarction treated with direct coronary angioplasty,[23] we felt the results of the present study remains valuable, and such knowledge might provide useful insight into the endothelin dysfunction in the pathophysiology of AF, which was also stated as an inflammation disorder.

4.5 Conclusions

Both plasma hs-CRP and big ET-1 levels are elevated in lone AF patients, and are associated with AF. In paroxysmal lone AF patients, there were significant positive correlations between plasma hs-CRP level and big ET-1 level.

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