Relationships of High-sensitive C-reactive Protein and P-wave Dispersion in Lone Atrial Fibrillation

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Abstract

Background: Current evidence links atrial fibrillation (AF) to the inflammation. Inflammatory indexes such as high-sensitive C-reactive protein (hs-CRP) have been related to the development and persistence of AF. However, the role of inflammation in the atrial electrophysiological remodeling indexed by P-wave dispersion (P_d) remains unclear.

Methods: The study consisted of 71 patients with lone paroxysmal AF (AF group) and 71 age- and gender-matched controls of paroxysmal supraventricular tachycardia without history of AF (control group). Electrocardiography, P_d, hs-CRP, and other clinical characteristics were compared between the two groups.

Results: There was no significant difference between the two groups regarding age, gender, hyperlipidemia, etc. Compared to controls, left atrial diameter (44 ± 7 vs 39 ± 7 mm), P_d (49 ± 13 vs 26 ± 8 ms), and hs-CRP (2.17 [1.46–2.89] vs 1.12 [0.74–1.41] mg/L) were increased ($P < 0.05$), respectively. Linear regression identified hs-CRP as an independent correlation of P_d level both in the total population and the AF group ($r = 0.464$ and 0.313; $P < 0.001$, respectively). Multiple logistic regression revealed hs-CRP as an independent determinant of AF (odds ratio [OR] =15.430, 95% confidence interval: 6.031–39.476: $P <0.001$). Further adjusted for P_d, both P_d and hs-CRP were independent predictors for AF, but the OR for hs-CRP in predicting AF has been attenuated from 15.430 to 6.246.

Conclusions: In lone AF, P_d and plasma hs-CRP concentration are inter-associated and related to AF. The interaction between hs-CRP and AF may be mediated by P_d, suggesting an important role of inflammation in the atrial electrophysiological remodeling predisposing to AF.

Key words: Atrial Fibrillation; High-sensitive C-reactive Protein; Inflammation; P-wave Dispersion

Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. Although the exact pathophysiology of AF remains unclear, it is accepted that the initiation and maintenance of AF require both a trigger and a susceptible 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. P-wave dispersion (P_d) is defined as the difference between the maximum and the minimum P-wave duration calculated on a 12-lead surface electrocardiogram (ECG). Prolonged P_d has been proposed an independent predictor of atrial remodeling and development of AF in patients with various cardiovascular diseases.[1-9]

An increasing body of evidences has demonstrated that inflammation plays an important role in the initiation and perpetuation of AF. 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.[10-14]

Little is known about the relationship between inflammation and atrial remodeling in AF. Only one previous study evaluated the relationship between hs-CRP and P_d and demonstrated that hs-CRP and P_d are interrelated and associated with AF.[15] However, that study included population with hypertension predisposing to hs-CRP and P_d elevation and the arrhythmia.[16,17] The purpose of this study was to investigate the association between inflammation (as indexed by hs-CRP) and atrial electrophysiological remodeling (as indexed by P_d) and their associations in lone AF patients without hypertension and structural heart disease.

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METHODS

Patients

Between June 2008 and July 2009, 71 consecutive patients with symptomatic paroxysms of lone AF (AF group) were recruited. All the patients in AF group had the paroxysms of AF lasting for <48 h. Furthermore, no patients had received electrical cardioversion before. Seventy-one consecutive subjects of paroxysmal supraventricular tachycardia without history of AF matched for age and gender (control group) [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, including 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 4 weeks) trauma or surgery; none was under treatment with nonsteroidal anti-inflammatory or corticosteroids drugs. For the clear identification of the onset of P-wave deflection on the 12-lead ECG, patients with permanent pacemaker implantation, bundle branch block, abnormal serum electrolyte or ventricular pre-excitation were also excluded.

All AF patients discontinued all anti-arrhythmic drugs treatment at least for 5 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*.

Clinical characteristics

Patients were interviewed, and records were reviewed to determine past medical history, medications, and 12-lead ECG for P_d assessment, a complete echocardiography and plasma hs-CRP levels determination. 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) were determined by echocardiography within 3 days.

Chemical laboratory analyses

Venous blood samples were collected from the antecubital vein in the morning upon admission. Plasma hs-CRP concentration was determined in heparinized plasma with a commercially available enzyme-linked immunoturbidimetric assay (Orion Diagnostica, Finland). The measurement range and detection limit of this test were 0.25–10.00 mg/L and 0.25 mg/L, respectively.

Measurement of P-wave dispersion

The standard 12-lead ECG was recorded at a 50 mm/s paper speed and 1 mV/cm standardization. Recordings were performed during sinus rhythm and spontaneous breathing in the supine position. All P-wave duration was measured blindly by two experienced observers. P-wave on all derivations was measured on 12-lead surface ECGs. The onset of the P-wave was defined as the point of first visible upward slope from baseline for positive waveforms and as the point of first downward slope from baseline for negative waveforms. The return to the baseline was considered as the end of the P-wave. The longest P-wave duration was defined as P_{max} and the shortest P-wave duration as P_{min}. The difference between P_{max} and P_{min} was calculated as P_d. Both the intra- and inter-observer variations for all measurements were <5% and, therefore, nonsignificant.[5]

Statistical analysis

Continuous data are presented as mean ± standard deviation (SD) and categorical variables as percentage. The Kolmogorov–Smirnov statistic was used to test for any deviation from normality and the variables with nonnormally distributed scores were presented as median plus interquartile range. Because of the large range in hs-CRP, results of its log are also reported. The AF group was compared with the control group using the two-sample *t*-test for independent samples when dealing with approximately normally distributed variables and the Wilcoxon rank-sum test otherwise. Categorical variables were compared using the Pearson's χ^2 test.

Linear regression was performed to evaluate the independent relationship of hs-CRP and P_d in the total population and

Table 1: Characteristics of the study population with AF and control group

Variables	AF group (n = 71)	Control group (n = 71)	P
Age (years)	57 ± 8	54 ± 11	0.560
Male (n (%))	51 (71.8)	53 (74.6)	0.610
Smoking (n (%))	29 (40.8)	27 (38.0)	0.340
Hyperlipidemia (n (%))	11 (15.5)	12 (16.9)	0.450
BMI (kg/m²)	25.5 ± 2.1	24.8 ± 2.5	0.047
Systolic blood pressure(mmHg)	131 ± 15	127 ± 15	0.540
Diastolic blood pressure (mmHg)	80 ± 13	77 ± 12	0.410
Heart rate (beats/min)	81 ± 18	76 ± 15	0.290
Fasting glucose (mmol/L)	5.02 ± 0.63	4.85 ± 0.64	0.470
Serum creatinine (μmol/L)	80.6 ± 15.7	79.2 ± 12.6	0.290
hs-CRP (mg/L)	2.17 (1.46–2.89)	1.12 (0.74–1.41)	0.001
Log (hs-CRP)	0.31 ± 0.21	0.02 ± 0.18	0.001
LAD (mm)	44 ± 7	39 ± 7	0.000
LVEDD (mm)	51 ± 4	49 ± 5	0.009
LVEF (%)	62 ± 6	63 ± 7	0.570
P_{max} (ms)	119 ± 17	102 ± 15	0.010
P_{min} (ms)	70 ± 23	76 ± 17	0.120
P_d (ms)	49 ± 13	26 ± 8	0.000

AF: Atrial fibrillation; BMI: Body mass index; hs-CRP: High sensitive C-reactive protein; LAD: Left atrial diameter; LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; P_{max}: Maximum P-wave duration; P_{min}: Minimum P-wave duration; P_d: P-wave dispersion.

the AF group. In addition to hs-CRP, each of other clinical and laboratory variables were also analyzed by multivariate linear regression in the total population.

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 $P < 0.05$ for inclusion and $P \geq 0.05$ 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 and P_d. 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, IL, USA).

RESULTS

Clinical characteristics

In patients with lone AF, the mean age was 57 ± 8 years, and 71.8% were male. They had their arrhythmia for a median duration of 3 years (2–7 years) prior to inclusion in this study. Patients with AF had received a variety of medications for AF, including warfarin in 3 patients, aspirin in 10, β blocker in 15, calcium channel blocker in 6, profenanone in 10, and amiodarone in 5. The subjects in the control group were not taking any routinely cardiovascular medications before enrollment. The clinical and echocardiographic characteristics of the study population are presented in Table 1. Apart from the matched age and gender, no significant differences were observed between two groups with reference to their blood pressure, heart rate, fasting glucose, and serum creatinine ($P > 0.05$). Compared to the control group, the AF patients showed a larger LVEDD and LAD ($P < 0.05$), respectively. There was no statistically significant difference between two groups in LVEF ($P > 0.05$).

Comparisons of high-sensitive C-reactive protein and P-wave dispersion between the two groups

Levels of hs-CRP were significantly higher in the AF group than in the control group. The median hs-CRP in the AF group was 2.17 mg/L, compared to 1.12 mg/L in the control group ($P < 0.05$). The mean log (hs-CRP) values were also significantly higher in the AF group compared to the control group [Table 1].

P-wave dispersion (49 ± 13 vs 26 ± 8 ms, $P < 0.05$) and P_{max} (119 ± 17 vs 102 ± 15 ms, $P < 0.05$) were significantly longer in AF group than in controls. P_{min} was shorter in the AF group compared to controls, although the difference did not reach the statistical significance (70 ± 23 vs 76 ± 17 ms, $P > 0.05$).

In the AF group, the longest P-wave duration was observed in the II lead (118 ± 11 ms) and the shortest duration in V1 lead (68 ± 8 ms).

Multivariate predictors of P-wave dispersion

Regression analysis of hs-CRP level and P_d as a continuous variable revealed a positive relationship between the two variables in the total study population ($r = 0.464$, $P < 0.001$) and in the AF group ($r = 0.313$, $P < 0.001$). Multivariate regression analysis identified hs-CRP level as an independent positive correlate of P_d ($t = 6.278$, $P < 0.001$). Other independent factors included age ($t = 2.040$, $P = 0.030$), BMI ($t = 2.910$, $P = 0.004$), LAD ($t = 3.718$, $P < 0.001$), and LVEDD ($t = 2.226$, $P = 0.028$). The gender, smoking, hyperlipidemia, systolic blood pressure, diastolic blood pressure, heart rate, fasting glucose, serum creatinine, and LVEF showed no significant relationship with P_d and were discarded from the regression model [Table 2].

Univariate and multivariate predictors of atrial fibrillation

In univariate logistic analysis, BMI, hs-CRP, LAD, LVEDD, and P_d were significantly related to AF ($P < 0.05$), respectively [Table 3].

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. The results demonstrated that LVEDD (*OR* = 1.189, 95% *CI*: 1.063–1.332, $P = 0.003$) and hs-CRP (*OR* = 15.430, 95% *CI*: 6.031–39.476, $P < 0.001$) were associated with AF. After adjustment of P_d, both P_d (*OR* = 1.213, 95% *CI*: 1.123–1.310, $P < 0.001$) and hs-CRP (*OR* = 6.246, 95% *CI*: 2.280–17.115, $P < 0.001$) were the independent predictors for AF, but the *OR* for hs-CRP in predicting AF has been attenuated from 15.430 to 6.246 [Table 4].

DISCUSSION

This study demonstrated that lone AF patients have a higher level of hs-CRP and P_d compared to age and gender-matched

Table 2: Multivariate linear regression results for detecting independent factors on P_d in total patients

Variables	t	P
Age	2.040	0.030
Male	0.858	0.392
Smoking	−1.682	0.095
Hyperlipidemia	1.258	0.211
BMI	2.910	0.004
Systolic blood pressure	1.435	0.154
Diastolic blood pressure	0.636	0.526
Heart rate	−0.146	0.884
Fasting glucose	1.258	0.211
Serum creatinine	0.736	0.463
hs-CRP	6.278	0.000
LAD	3.718	0.000
LVEDD	2.226	0.028
LVEF	−0.543	0.588

P_d: P-wave dispersion; BMI: Body mass index; hs-CRP: High-sensitive C-reactive protein; LAD: Left atrial diameter; LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction.

Table 3: Univariate predictors of AF

Variables	OR	95% CI of OR	P
Age	1.027	0.992–1.062	0.128
Male	1.145	0.557–2.355	0.713
Smoking	1.125	0.574–2.207	0.731
Hyperlipidemia	0.901	0.369–2.203	0.820
BMI	1.162	1.002–1.349	0.047
Systolic blood pressure	1.018	0.996–1.042	0.112
Diastolic blood pressure	1.018	0.991–1.046	0.194
Heart rate	1.017	0.997–1.038	0.098
Fasting glucose	1.544	0.912–2.614	0.106
Serum creatinine	1.007	0.984–1.031	0.549
hs-CRP	12.418	5.149–29.946	0.000
LAD	1.106	1.050–1.166	0.000
LVEDD	1.110	1.024–1.203	0.011
LVEF	0.986	0.936–1.039	0.603
P_d	1.223	1.145–1.306	0.000

AF: Atrial fibrillation; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; hs-CRP: High-sensitive C-reactive protein; LAD: Left atrial diameter; LVEDD: Left ventricular end diastolic diameter; LVEF: Left ventricular ejection fraction; P_d: P-wave dispersion.

Table 4: Multivariate predictors of AF

Variables	OR	95% CI of OR	P
LVEDD	1.189	1.063–1.332	0.003
hs-CRP	15.430	6.031–39.476	0.000
Further adjusted for P_d			
P_d	1.213	1.123–1.310	0.000
hs-CRP	6.246	2.280–17.115	0.000

AF: Atrial fibrillation; OR: Odds ratio; CI: Confidence interval; LVEDD: Left ventricular end diastolic diameter; hs-CRP: High-sensitive C-reactive protein; P_d: P-wave dispersion.

controls. Hs-CRP and P_d were positively correlated and in association with AF. The interaction between hs-CRP and AF may be mediated by P_d, suggesting an important role of inflammation in the atrial electrophysiological remodeling predisposing to AF.

P-wave dispersion represents a noninvasive ECG marker that may reflect the prolongation of intraatrial and interatrial conduction time, as well as the discontinuous inhomogeneous propagation of sinus impulses.[1] Previous studies have reported that AF is associated with increased P_d in various clinical settings, including patients with hypertrophic cardiomyopathy,[3] atrial septal defect,[4] rheumatic mitral stenosis,[5] acute myocardial infarction,[6] and postsurgery of coronary artery bypass.[7] In addition, P_d is associated with AF in patients with hyperthyroidism[8] or chronic obstructive pulmonary disease.[9] In patients with lone AF, P_d was also increased and was associated with AF,[1] which is consistent with the present study. Thus, P_d has become a valuable ECG index for atrial remodeling and proven its predicting utility for AF.

Recently, an increasing body of evidence links AF to the inflammatory state. Frustaci et al.[18] demonstrated a high

prevalence of inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies of patients with lone AF. In a canine sterile pericarditis model,[19] AF is associated with initiation of inflammation. Hs-CRP, acting as the major inflammatory index, whose relationship with AF has been intensely studied. Plasma hs-CRP level is increased in AF.[10] In a community-based population,[10] increased hs-CRP levels at baseline independently predicted newly detected AF. Furthermore, baseline hs-CRP levels could predict the risk of new-onset AF after cardiac surgery,[11] and predict AF recurrence after successful electrical cardioversion[12] or catheter ablation.[13] In addition, hs-CRP has been independently related to pro-thrombotic state in AF.[14] Moreover, elevated hs-CRP levels have been reported 2 weeks after successful cardioversion of AF.[20] These studies suggested a pathogenetic role, rather than a consequence for inflammation in AF.

It has been speculated that the process of inflammation and oxidative stress are interrelated and contribute to the atrial remodeling.[21] Notably, atrial remodeling represents the major pathophysiological substrate in AF. Thus, it may be speculated that the association between inflammation and AF may be mediated by atrial remodeling. However, the interrelationship of inflammation with atrial remodeling, as indexed by hs-CRP and P_d, and their association with AF has not been fully analyzed. In one recent study, Tsioufis et al.[15] reported that hs-CRP and P_d are interrelated and associated with AF. However, in that study, the enrolled population were all hypertensive subjects. The exact relationship between hs-CRP and P_d is obscured by the effects of the hypertension because it predisposes both inflammation and atrial remodeling.[16,17] The effect of comorbidities predisposing to both inflammation and atrial remodeling and AF is minimal in lone AF patients and is therefore particularly interesting.

In this study, we demonstrated that the subjects with lone AF have elevated hs-CRP levels and greater values of P_d. We also found that hs-CRP was an independent risk factor of P_d. Furthermore, although hs-CRP was identified as an independent determinant of lone AF, adjustment for P_d attenuates the relationship of hs-CRP with AF. These findings imply that P_d may act as a mediator between inflammation and AF.

Several mechanisms might explain our observation of the association between P_d and hs-CRP. Histological studies noted inflammatory cell infiltration and fibrosis in atrial biopsies of patients with lone AF.[18] Inflammation cell filtration and calcium overload during AF may promote oxidative damage in atrial tissue which promotes atrial fibrosis and facilitates AF continuation.[21,22] Furthermore, inflammation may initiate endothelial dysfunction and activation of rennin-angiotensin-aldosterone axis and play a part in the structural remodeling, including atrial fibrosis, loss of atrial myocytes mass. Furthermore, CRP binds to phosphocholine, recognizing phospholipids components of damaged cells and some foreign pathogens.[23] Binding

CRP may activate the classic complement pathway.[11] These changes may lead to the inter- and intra-atrial conduction heterogeneity and dispersion of the atrial refractory period/velocity, providing the substrate for AF, thus may underlie the prolongation of P_d.

Although our results indicate an association between hs-CRP and AF, the present study was not a prospective cohort design in nature, thus, limits our ability to determine a cause or effect relationship between hs-CRP and AF. Nevertheless, the aim of the present study was to investigate the association between the inflammation and the atrial electrical remodeling in AF. Whether the inflammation was a cause or the consequence of AF remains controversial and deserves further study.

In conclusion, the present study demonstrated that in patients with lone AF, P_d and hs-CRP are inter-associated and in relation to AF. The interaction between hs-CRP and AF may be mediated by P_d, suggesting a crucial role of inflammation in the atrial electrophysiological remodeling predisposing to AF.

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