Inflammation in Lone Atrial Fibrillation

Shu-Yuan Yao, PhD, Jian-Min Chu, MD, Ke-Ping Chen, MD, Min Tang, MD, Pi-Hua Fang, MD, Fang-Zheng Wang, MD, Shu Zhang, MD

Center of Arrhythmias, Fuwai Cardiovascular Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, People's Republic of China

Address for correspondence:
Shu Zhang, MD
Fuwai Cardiovascular Hospital
Peking Union Medical College
and Chinese Academy of
Medical Sciences
167 BeiLiShi Road
Beijing, 100037, P.R. China
zhangshuysy@yahoo.com

ABSTRACT

Objectives: This study was designed to evaluate the correlation between lone atrial fibrillation and inflammation.

Methods: A total of 411 subjects were enrolled in this study, including 333 patients with lone atrial fibrillation, and 78 controls. C-reactive protein (CRP) and echocardiography were evaluated, and the electrocardiograph was monitored to identify cardiac rhythm at the time of blood sampling. According to the rhythm, paroxysmal atrial fibrillation was divided into presence and absence of atrial fibrillation.

Results: Subjects with lone atrial fibrillation had higher CRP levels than controls (media, 1.00 mg/L; IQR, 1.00–2.54 versus media, 1.00 mg/L; IQR, 1.00–1.55; $p = 0.016$) and subjects with persistent atrial fibrillation had higher CRP levels than those with paroxysmal atrial fibrillation (media, 1.62 mg/L; IQR, 1.00–3.98 versus media, 1.00 mg/L, IQR, 1.00–2.10; $p = 0.022$), and so did presence of atrial fibrillation rather than absence of atrial fibrillation (media, 2.11 mg/L; IQR, 1.00–3.60 versus media, 1.00 mg/L; IQR, 1.00–1.76; $p = 0.000$) in paroxysmal atrial fibrillation. However, there was no significant difference in CRP levels between persistent atrial fibrillation and presence of atrial fibrillation in paroxysmal atrial fibrillation ($p = 0.992$). Neither was there any difference between absence of atrial fibrillation in paroxysmal atrial fibrillation and controls ($p = 0.483$). In patients with lone atrial fibrillation, atrial fibrillation rhythm ($B = 4.85$, 95%CI: 2.61–8.99) was the only independent predictor of elevated CRP levels after adjusted covariants.

Conclusions: Patients with lone atrial fibrillation had elevated CRP levels only when they were in atrial fibrillation rhythm and an elevated CRP level was not related to duration of time or history of atrial fibrillation.

Key words: atrial fibrillation, inflammation, C-reactive protein

Introduction

Recent evidence suggests there is an association between inflammation process and atrial fibrillation.^{1–7} Further studies indicate that ongoing inflammation can lead to atrial remodeling, thus promoting persistence or recurrence of atrial fibrillation.⁸ Several studies have also demonstrated that structural heart diseases themselves are related to inflammatory reaction.^{9–13} Therefore, abnormal inflammatory process in atrial fibrillation patients with structural heart diseases may be related to either structural heart diseases or episodes of atrial fibrillation. Nevertheless, atrial fibrillation patients without structural heart diseases are ideal subjects for us to explore the association between atrial fibrillation and inflammation. In the present study we enrolled a large cohort of lone atrial fibrillation patients to explore correlation between inflammation and atrial fibrillation.

Methods

Patient Selection

The subjects in the case-control study were enrolled from the patients admitted to Center of Arrhythmias in Fuwai Cardiovascular Hospital between January 2002 and April 2006. All patients with lone atrial fibrillation were referred and patients with Wolff-Parkinson-White syndrome as controls were randomly enrolled into the study.

No subjects had any heart abnormalities other than atrial fibrillation or Wolff-Parkinson-White syndrome. Lone atrial

fibrillation was defined as atrial fibrillation in patients without any identifiable heart abnormalities. Paroxysmal atrial fibrillation was defined as having paroxysms of atrial fibrillation that terminated within 1 mo after onset. Persistent atrial fibrillation was defined as atrial fibrillation lasting at least 1 mo, and may include permanent atrial fibrillation. Exclusion criteria for all subjects were any structural heart diseases including coronary heart disease, cardiomyopathy disease, left ventricular ejection fraction $\leq 45\%$ etc., hypertension, chronic obstructive pulmonary disease, recent infectious disease, malignancies, thyroid dysfunction, hepatic or renal failure, surgery or stroke within 6 mo, trauma or vascular events within 4 wk, autoimmune diseases, and being treated with anti-inflammatory drugs such as corticoids, non-steroidal anti-inflammatory medication excluding aspirin. In addition, we also excluded atrial fibrillation secondary to abnormal thyroid function, imbalance of electrolytes, and so on.

According to the criteria of patient selection, all subjects were divided into lone atrial fibrillation group and control group, and the lone atrial fibrillation group was further divided into two subgroups including persistent and paroxysmal atrial fibrillation. In addition, the paroxysmal atrial fibrillation group was divided into presence group (atrial fibrillation was present at the time of blood sampling) and absence group (sinus rhythm was present at the time of blood sampling).

Signed written consent was obtained from all subjects before their participation in the study, and the study was approved by the ethics committee of our institution.

Routine Examinations

All subjects were evaluated by clinical history, physical examination, routine laboratory assays, electrocardiography, chest x-ray, and echocardiography. In order to identify lone atrial fibrillation, thyroid function test, exercise stress test, nuclear cardiac imaging and/or coronary angiography were performed in patients with atrial fibrillation. Transthoracic and/or transesophageal echocardiography were performed to detect the presence of underlying structural heart diseases and evaluate left atrial dimension, left ventricular ejection fraction and left ventricular end-diastolic dimension.

Venous blood was drawn by venepuncture between 6 and 7 AM on the second day of admission from all subjects. All patients were monitored by electrocardiography at the time of blood sampling. The sinus rhythm was shown in all controls at the time of sampling. Blood was collected in tubes containing EDTA (Sarstedt, UK) for counting total white blood cell and neutrophil granulocyte by the Coulter principle method (Beckman-Coulter GEN-S, USA). C-reactive protein (CRP) level was detected by immunoturbidimetric assay (Herrenberg, Germany).

Statistical Analysis

All statistical analyses were performed using SPSS 13.0 for Windows. Categorical data were expressed as frequencies and percentages, and continuous data as means plus/minus standard deviation. Probability values were two-tailed and values were considered significantly different when $p < 0.05$. Distribution of frequencies was evaluated using χ^2 test. Approximately normal distribution variables were analyzed by unpaired t test and one-way ANOVA test respectively, and non-normal distribution variables were analyzed by Wilcoxon rank-sum test. Fisher's exact test was used for categorical variables. Because of skew distribution of CRP level, Spearman correlation analysis was performed to analyze the association between CRP level and continuous variables, including age, body mass index, left atrial dimension etc. The variables which were significantly correlated to the CRP level in the univariate analysis were entered into multivariate analysis. In the logistical regression model, the CRP level was divided into three groups: low (< 1 mg/L), moderate (1–3 mg/L) and high group (≥ 3 mg/L).

Results

Clinical and Echocardiographic Characteristics

According to the inclusion criteria, a total of 333 patients with lone atrial fibrillation, and 78 patients with Wolff-Parkinson-White syndrome were enrolled into the present study. The

lone atrial fibrillation group consisted of 261 paroxysmal and 72 persistent atrial fibrillation patients. The paroxysmal atrial fibrillation group was divided into presence group ($n = 58$) and absence group ($n = 203$) according to cardiac rhythm at the time of blood sampling. Subjects among groups were well matched in terms of sex, age, smoking history, body mass index, diabetes mellitus, and hyperlipemia. The echocardiographic examination indicated that patients with lone atrial fibrillation had larger left atrial dimension ($p = 0.000$) and lower left ventricular ejection fraction ($p = 0.005$) than controls, and so did the persistent atrial fibrillation group more than the paroxysmal atrial fibrillation group ($p = 0.000$, $p = 0.000$, respectively). In paroxysmal atrial fibrillation, the presence group had a larger left atrial dimension than the absence group ($p = 0.024$), and there were no significant differences in other indexes between the two groups. The clinical and echocardiographic characteristics are shown in Table 1.

Inflammatory Indexes

Lone atrial fibrillation group and controls: Patients with lone atrial fibrillation had a higher CRP level than controls (media, 1.00 mg/L; IQR, 1.00–2.54 versus media, 1.00 mg/L; IQR, 1.00–1.55; $p = 0.016$). There were no significant differences in white blood cell count and neutrophil granulocyte count between the two groups (media, 5.69; IQR, 4.83–6.63 versus media, 5.56; IQR, 4.77–6.90, $p = 0.759$ and 3.39 ± 1.15 versus 3.24 ± 1.10 , $p = 0.283$, respectively).

Paroxysmal, persistent atrial fibrillation groups and controls: Persistent atrial fibrillation patients had an elevated CRP level (media, 1.62 mg/L; IQR, 1.00–3.98), which was significantly higher than that in controls ($p = 0.000$), and in paroxysmal atrial fibrillation patients (media, 1.00 mg/L, IQR, 1.00–2.10; $p = 0.022$). The CRP level in paroxysmal atrial fibrillation patients was not significantly higher than that in controls ($p = 0.087$). White blood cell count and neutrophil granulocyte count were not significantly different among paroxysmal, persistent atrial fibrillation groups and the control group (media, 5.66; IQR, 4.80–6.66 versus media, 5.79; IQR, 4.87–6.59 versus media, 5.56; IQR, 4.77–6.90 and 3.38 ± 1.18 versus 3.43 ± 1.02 versus 3.24 ± 1.10 , respectively, $p > 0.05$).

Persistent atrial fibrillation group, presence and absence groups in paroxysmal atrial fibrillation

and controls: There was no significant difference in CRP level between the presence group (media, 2.11 mg/L; IQR, 1.00–3.60) and persistent group ($p = 0.922$), and between the absence group (media, 1.00 mg/L; IQR, 1.00–1.76) and control group ($p = 0.483$). The CRP levels in the presence and persistent groups were higher than that in the control ($p = 0.000$; $p = 0.000$, respectively) and absence groups ($p = 0.000$; $p = 0.000$, respectively) (Figure 1). In the presence group, higher white blood cell count and

TABLE 1: The clinical and echocardiographic characteristics

	Control Group (n = 78)	Lone AF (n = 333)	Persistent AF (n = 72)	Paroxysmal AF (n = 261)	Absence of paroxysmal AF (n = 203)	Presence of paroxysmal AF (n = 58)
Female (%)	20 (25.6)	79 (23.7)	15 (20.8)	64 (24.5)	51 (25.1)	13 (22.4)
Smoking (%)	38 (48.7)	142 (42.6)	26 (36.1)	116 (44.4)	86 (42.4)	30 (51.7)
Hyperlipemia (%)	11 (16.5)	55 (14.1)	13 (18.0)	42 (15.7)	34 (16.8)	8 (13.8)
Diabetes mellitus (%)	4 (5.1)	16 (4.8)	7 (9.7)	9 (3.4)	8 (4.0)	1 (1.7)
Lipid-lowering agents (%)	4(5.1)	29(8.7)	8(11.1)	21(8.1)	13(6.4)	8(13.8)
β -blocker (%)	—	60 (18.0)	19 (26.4)	41 (15.7)	14 (6.9)	27 (44.6)
Digoxin (%)	—	12 (3.6)	7 (9.7)	5 (1.9)	1 (0.5)	4 (6.9)
CCB (%)	—	15 (4.5)	6 (8.3)	9 (3.5)	6 (3.0)	3 (5.2)
Aspirin (%)	6 (7.7)	43 (12.9)	11 (15.3)	32 (12.3)	15 (7.4)	17 (29.3)
Propafenone (%)	—	28 (8.4)	2 (2.8)	26 (10.0)	10 (4.9)	16 (27.6)
Aminodarone (%)	—	37 (11.1)	8 (11.1)	29 (11.1)	14 (6.9)	15 (25.7)
Age (y)	52.8 $\pm$ 8.9	54.2 $\pm$ 12.3	55.4 $\pm$ 14.2	53.9 $\pm$ 11.8	52.9 $\pm$ 11.8	54.2 $\pm$ 11.1
BMI (kg/m ²)	24.8 $\pm$ 3.4	25.2 $\pm$ 3.7	25.7 $\pm$ 3.3	25.1 $\pm$ 3.7	25.0 $\pm$ 3.9	25.2 $\pm$ 2.9
History (y)	—	5.82 $\pm$ 6.49	6.82 $\pm$ 6.53	5.54 $\pm$ 6.46	5.79 $\pm$ 6.69	4.69 $\pm$ 5.56
LAD (mm)	31.4 $\pm$ 3.8	35.4 $\pm$ 5.4	39.0 $\pm$ 5.7	34.4 $\pm$ 4.9	34.1 $\pm$ 4.8	35.7 $\pm$ 5.0
LVEDD (mm)	47.5 $\pm$ 4.6	48.6 $\pm$ 4.5	49.8 $\pm$ 5.2	48.3 $\pm$ 4.2	48.2 $\pm$ 4.2	48.5 $\pm$ 4.3
LVEF	0.66 $\pm$ 0.07	0.63 $\pm$ 0.08	0.60 $\pm$ 0.09	0.64 $\pm$ 0.07	0.63 $\pm$ 0.07	0.64 $\pm$ 0.07

Abbreviations: AF = atrial fibrillation, BMI = body mass index, CCB = calcium-channel blocker, LAD = left atrial dimension, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction.

neutrophil granulocyte count were observed comparing to the absence group (media, 6.13; IQR, 5.31–6.95 versus media, 5.60; IQR, 4.68–6.48, $p = 0.003$ and 3.79 ± 1.29 versus 3.26 ± 1.13 , $p = 0.036$, respectively).

Predictors of elevated CRP level in lone atrial fibrillation: In univariate analysis restricted to all patients with lone atrial fibrillation, including age, sex, body mass index, smoking history, diabetes mellitus, hyperlipemia, taking or not taking lipid-lowering agents, antiarrhythmic drugs and aspirin, duration time of atrial fibrillation, atrial fibrillation history, atrial fibrillation rhythm, left atrial dimension, left ventricular end-diastolic dimension and left ventricular ejection fraction, and predictors of high CRP level were older age, larger body mass index, and atrial fibrillation rhythm. CRP levels had no significant correlation to left atrial dimension, left ventricular end-diastolic dimension, left ventricular ejection fraction, duration time, and history of atrial fibrillation (Table 2). In logistical regression analysis, atrial fibrillation rhythm ($B = 4.85$, 95%CI: 2.61–8.99) was the only independent predictor of high CRP level.

Discussion

The present study demonstrated that: (i) patients with lone atrial fibrillation had higher CRP level than controls, in addition, the CRP level in patients with persistent atrial fibrillation was similar to that in patients with presence of paroxysmal atrial fibrillation, both of which were higher than that in controls and patients with absence of paroxysmal atrial fibrillation; (ii) atrial fibrillation rhythm was the independent predictor of elevated CRP level after adjusting other variables in lone atrial fibrillation patients.

In recent years, accumulating evidence has been presented that there is a possible association between inflammation and atrial fibrillation.^{1–8} However, Conway et al.¹⁴ found that the relationship between atrial fibrillation and elevated inflammatory markers became insignificant after adjusting potential confounding variables. In addition, the study by Ellinor et al.¹⁵ indicated that increased CRP level in atrial fibrillation patients with hypertension might be a manifestation of underlying cardiovascular disease rather

Figure 1: CRP levels in the control, absence, and presence groups in paroxysmal atrial fibrillation and persistent atrial fibrillation group. Middle line indicates media; bottom of box, 25th percentile; and top of box, 75th percentile. Number of patients in each group is indicated within the box. *: $p < 0.000$ versus the control group and absence group, AF: atrial fibrillation.

than the atrial fibrillation itself. Based on previous investigations, atrial fibrillation patients with structural heart diseases are not optimal subjects used to explore the association of inflammation with atrial fibrillation. However, lone atrial fibrillation provides an excellent opportunity for that study because of its unique characteristic that is not complicated with structural heart diseases. Therefore, the present study enrolled lone atrial fibrillation patients to explore the relationship between atrial fibrillation and inflammation, and to our knowledge, it is the largest cohort of lone atrial fibrillation subjects used to study the inflammation.

The results in the present study demonstrated an association between inflammation and lone atrial fibrillation. In our study, patients with paroxysmal atrial fibrillation had only transient elevation of CRP levels, which returned to normal after reversion to sinus rhythm. In addition, the results of white blood cell count and neutrophil granulocyte count were similar to that of CRP level. Although our study cannot elucidate whether an elevated CRP level contributes to precipitating atrial fibrillation or is a consequence of the arrhythmia, it is more probable that the initiation of atrial fibrillation as a stress reaction would lead to inflammation. In addition, previous studies have demonstrated that inflammation promotes the process of atrial remodeling and persistence of atrial fibrillation.⁸ Therefore, in lone atrial fibrillation, especially with normal anatomy and physiological function, the maintenance of sinus rhythm may be very important, which would

TABLE 2: Univariate analysis: predictors of elevated CRP levels in patients with lone atrial fibrillation

Predictors of elevated CRP	<i>r</i>	Sig
Female	0.308	0.336
Age	0.148	0.007
Smoking history	0.066	0.810
Hyperlipemia	0.068	0.855
Diabetes Mellitus	-0.041	0.943
Body mass index	0.119	0.030
Taking lipid-lowering agents	0.504	0.488
Taking Aspirin	0.823	0.061
Atrial fibrillation history	-0.017	0.761
Duration time	0.053	0.764
Left atrial dimension	0.088	0.107
Left ventricular end-diastolic dimension	-0.043	0.437
Left ventricular ejection fraction	0.019	0.727
Atrial fibrillation rhythm	1.132	0.000

attenuate the inflammation process, thus reducing atrial remodeling.

Up to date, only 3 studies have reported the correlation between lone atrial fibrillation and inflammation, and they had different results. Our findings are conducive to explaining different results of CRP levels in controls and patients with lone, persistent, or paroxysmal atrial fibrillation in those studies.^{1,15,16} Those discrepancies were due to the different proportions of patients with paroxysmal atrial fibrillation and with sinus rhythm in all atrial fibrillation subjects when undergoing blood sampling.

Previous studies indicated that an elevated CRP level was associated with age, body mass index, left atrial dimension, left ventricular ejection fraction, and hypertension etc., in patients with atrial fibrillation. The univariate analysis in our study demonstrated that an increased CRP level was significantly associated with age, body mass index, and atrial fibrillation rhythm, which is consistent with previous reports. More importantly, our multivariate analysis for the first time indicated that atrial fibrillation rhythm was the only and independent predictor of elevated CRP level in lone atrial fibrillation patients. These results are also supportive of the association between inflammation and atrial fibrillation.

Limitations

The present study was limited by use of prior medication in subjects such as lipid-lowering agents, although the ratio

of taking lipid-lowering agents was low (8.7%) and these medications were not significantly associated with increased CRP level.

Conclusion

The large cohort study in patients with lone atrial fibrillation indicates that inflammation is significantly associated with atrial fibrillation, and the atrial fibrillation rhythm is the only and independent predictor of elevated CRP level.

References

1. Chung MK, Martin DO, Sprecher D, Wazni D, Kanderian A, et al.: C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001;104(24):2886–2891
2. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Qautaharju P, et al.: Inflammation as a risk factor for atrial fibrillation. *Circulation* 2003;108(24):3006–3010
3. Ishii Y, Schuessler RB, Gaynor SL, Yamada K, Fu AS, et al.: Inflammation of atrium after cardiac surgery is associated with inhomogeneity of atrial conduction and atrial fibrillation. *Circulation* 2005;111(22):2881–2888
4. Kumagai K, Nakashima H, Saku K. The HMG-CoA reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. *Cardiovasc Res* 2004;62(1):105–111
5. Bruins P, te Velthuis H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, et al.: Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation* 1997;96(10):3542–3548
6. Watanabe E, Arakawa T, Uchiyama T, Kodama I, Hishida H. High-sensitivity C-reactive protein is predictive of successful cardioversion for atrial fibrillation and maintenance of sinus rhythm after conversion. *Int J Cardiol* 2006;108(3):346–353
7. Frustaci A, Chimenti C, Bellocci F, Morqante E, Russo MA, et al.: Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997;96(4):1180–1184
8. Carnes CA, Chung MK, Nakayama T, Nakayama T, Nakayama H, et al.: Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. *Circ Res* 2001;89(6):E32–E38
9. Zoccali C, Maio R, Tripepi G, Mallamaci F, Perticone F: Inflammation as a mediator of the link between mild to moderate renal insufficiency and endothelial dysfunction in essential hypertension. *J Am Soc Nephrol* 2006;17(4):S64–S68
10. Luft FC. Angiotensin, inflammatory, hypertension, and cardiovascular disease. *Curr Hypertens Rep* 2001;3(1):61–67
11. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336(14):973–979
12. Sunq KC, Suh JY, Kim BS, Kang JH, Kim H, et al.: High sensitivity C-reactive protein as an independent risk factor for essential hypertension. *Am J Hypertens* 2003;16(6):429–433
13. Saito M, Ishimitsu T, Minami J, Ono H, Ohru M, et al.: Relations of plasma high-sensitivity C-reactive protein to traditional cardiovascular risk factors. *Thrombosis* 2003;167(1):73–79
14. Conway DS, Buggins P, Hughes E, Lip GY: Relationship of interleukin-6 and C-reactive protein to the prothrombotic state in chronic atrial fibrillation. *J Am Coll Cardiol* 2004;43(11):2075–2082
15. Ellinor PT, Low A, Patton KK, Shea MA, Macrae CA: C-reactive protein in lone atrial fibrillation. *Am J Cardiol* 2006;97(9):1346–1350
16. Hatzinikolaou-Kotsakou E, Tziakas D, Hotidis A, Stakos D, Floros D, et al.: Relation of C-reactive protein to the first onset and the recurrence rate in lone atrial fibrillation. *Am J Cardiol* 2006;97(5):659–661