C–Reactive Protein and Atrial Fibrillation in Idiopathic Dilated Cardiomyopathy

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ABSTRACT

Background: Previous studies have found elevated plasma C-reactive protein (CRP) levels in atrial fibrillation (AF) patients. Most of these studies included AF patients with various heart diseases, but few studies were designed to investigate CRP in idiopathic dilated cardiomyopathy (IDCM) patients with AF.

Method and Results: CRP levels in 242 IDCM patients with AF were compared with CRP levels in 280 control IDCM patients. Among control patients, 70 had atrial premature beats or atrial tachycardia and 210 had normal sinus rhythm. CRP was higher in the AF group than in the control group (median, 4.59 versus 2.81 mg/L; $p<0.001$). The prevalence of AF in IDCM patients increased as plasma CRP levels increased, and the patients with the highest plasma CRP levels had the highest probability of suffering from AF. Outcome of multivariate logistic regression analysis showed body mass index, AF, and white blood cell count significantly correlated with the plasma CRP levels.

Conclusion: Our data demonstrated that the plasma CRP level in IDCM patients with AF was higher than in IDCM patients without AF, and an increase in plasma CRP levels was associated with an increased prevalence of AF in IDCM patients. Also, body mass index, AF, and white blood cell count correlate with plasma CRP levels in IDCM patients. These data suggest there is presence of inflammation in IDCM patients with AF.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia found in clinical practice and is associated with a high risk of morbidity and mortality. Recent epidemiological,[1,2] animal,[3,4] and clinical[5,6] studies have shown that occurrence and recurrence of AF are associated with inflammatory processes. Some researchers have suggested that ongoing inflammation leads to structural remodeling of the atrium, thus promoting persistence or recurrence of AF.[7] This hypothesis has also been supported by histological evidence of myocarditis in patients with AF.[8] Also, a number of inflammatory markers were found to be elevated in patients with AF, including C-reactive protein (CRP), 5 and 6 prothrombin fragments, and interleukin-6.[7] Although the biologic functions of CRP are poorly understood, it has become a popular biomarker for cardiovascular risk. In addition, many studies have proved that CRP was associated with occurrence and recurrence of AF. However, there is no direct evidence to demonstrate the relationship between AF in patients with idiopathic dilated cardiomyopathy (IDCM, a disease of unknown cause that results in an enlarged heart that does not pump properly) and plasma CRP levels. Previous studies have shown that the immune response against viral replication is activated in IDCM and related to the severity of IDCM.[9] Scholars also found a persistent inflammatory state suggesting that a viral origin may induce advanced myocardial damage resulting in the types of heart failure with poor prognosis as seen in IDCM. Elevated CRP level can indirectly reflect this inflammatory state in IDCM patients.[10,11] Therefore, it is hypothesized that the inflammatory reaction in IDCM patients is related to the complication of AF. The aim of the present study was to investigate the relationship between plasma CRP levels and AF in IDCM patients. The results of this study can help us to identify whether there is an inflammatory reaction in IDCM patients with AF; then provide more evidence for whether inflammation plays a role in the induction of AF substrate.

Methods and Material

Populations

IDCM patients often have complications, including heart failure and infectious diseases, that can influence plasma CRP levels. To negate the impact on CRP induced by other clinical factors, 522 patients were selected from 1,371 consecutive patients who were diagnosed with IDCM. The clinical diagnosis of IDCM was based on the criteria of the World Health Organization/International Society and Federation of Cardiology definition of cardiomyopathies. Exclusion criteria included patients with heart failure due to coronary artery disease, valvular or congenital heart disease, infectious disease, hypertensive cardiomyopathy, New York Heart Association (NYHA) heart function class greater than II, autoimmune or inflammatory disease, thyroid disease,

Received: November 22, 2007
Accepted with revision: January 18, 2008

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20430

treatment with corticosteroids or NSAIDs, known coronary artery disease, acute coronary syndromes, surgery within 60 days, a history of infection, hepatic or malignant disease, or chronic renal failure.

In these IDCM patients, 496 patients were treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers F, 173 patients were treated with digitalis, and 387 patients were treated with β-blockers. Detailed medical history, physical examination, and routine biochemical testing were performed in addition to a 12-lead electrocardiogram (ECG). Valvular function, left ventricular size, heart function (ejection fraction), and left atrial diameter (LAD) were evaluated by transthoracic echocardiography. The diameter of the left atrium was measured in parasternal long axis view. The protocol of this study was approved by Fuwai hospital's ethics committee and each patient gave written consent.

Data Collection

According to routine ECG and ambulatory ECG during this hospitalization or before, the patients were divided into a control group (including patients had normal sinus rhythm, atrial premature beat, and atrial tachycardia) and an AF group—the diagnostic criterion of AF was the absence of distinct P-waves and the presence of small irregular oscillations or "fibrillatory" waves and the ventricular response (QRS) was irregular on a ECG, all the arrhythmias were diagnosed by a professional physician according to the patients current or previous ECG. Venous blood was drawn by venipuncture at 6–7 AM on the second day of admission in all subjects with AF. Blood was drawn at the same time from patients in the control group. Blood was collected in tubes containing ethylene diamine tetraacetic acid (EDTA) for analysis of total white blood cell count (WBC) by using the Coulter principle method.

CRP Assay

CRP was assayed by immunonephelometry using a Dade Behring BNII analyzer (Dade Behring Inc, Newark, NJ) according to the manufacturer's protocol. CRP concentrations were determined with a typical detection limit of ≈ 0.175 mg/L.

Statistical Analysis

Because the raw CRP values were skewed and kurtotic, they were log transformed before analysis. Comparison of log CRP levels between subjects with AF and controls was performed using a 2-sample t test. Quartiles of plasma CRP levels were presented. The clinical variables of the AF group were compared with the control group using the 2-sample t test for independent samples when dealing with approximately normal distributed variables. Categorical variables were compared using chi-square or Fisher's exact test. According to the quartile of plasma CRP levels, the IDCM patients CRP levels were divided into 4 ranks. The chi-square test was used to compare the prevalence of AF in patients with different plasma CRP levels. Variables that were significantly associated with plasma CRP levels in univariate analysis were entered into the multivariate logistic model. A p value <0.05 was considered statistically significant. All the analyses were done using SPSS version 13.0 software (SPSS Inc, Chicago, IL).

Results

Patient Population

CRP was assayed in 242 patients with AF and 280 control patients. IDCM patients with AF included 148 patients with paroxysmal atrial fibrillation and 94 patients with persistent atrial fibrillation. Patient characteristics are shown in Table 1. The mean age of IDCM patients with AF was 56.09±13.03 years, while control patients were 50.04±14.97 years old. The white blood cell count in IDCM patients with AF was higher than in the control group. There was no significant difference in body mass index (BMI) between the groups. Subjects with AF (79.8%) included more male patients than in the control group; in addition AF patients had a higher prevalence of diabetes, sick sinus syndrome and a lower prevalence of atrioventricular block and bundle branch block than control patients. The AF group and control group have a similar NYHA class. Except for LAD, there was no significant difference in echocardiography results between control group and AF patients.

CRP and AF

Univariate analysis showed CRP was significantly higher in IDCM patients with AF (median, 4.59 mg/L; inter-quartile range (IQR) 2.41 to 8.11 mg/L) than control patients (median, 2.81mg/L; IQR, 1.25 to 4.95 mg/L; ($p = 0.001$; Figure 1). The difference of plasma CRP levels between the IDCM patients with persistent atrial fibrillation and IDCM patients with paroxysmal atrial fibrillation was not significant (median, 4.35mg/L; IQR, 2.54 to 8.45 mg/L, versus median, 4.74 mg/L; IQR, 2.40 to 7.92 mg/L, ($p = 0.312$; Figure 2).

According to the quartile of all the IDCM patients plasma CRP levels (median, 3.57 mg/L; IQR, 1.84 to 6.86 mg/L), we divided the patients into 4 groups. And then we investigated whether the occurrence of AF correlated with plasma CRP levels. Linear by linear chi-square test showed the difference in prevalence of AF between groups with different plasma CRP levels was significant, and the prevalence of AF increased with the plasma CRP levels (Figure 3). The patients with the highest CRP levels had the highest prevalence of AF.

Multivariable Correlates with CRP Levels

Variables that were significantly associated with high plasma CRP levels in univariate analysis were entered into the multivariate logistic model. Results of multivariate

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20430

Table 1. Patient Characteristics

Variables	Control	AF	*p*
	n = 280	n = 242	
Age, y	50.04±14.97	56.09±13.03	<0.001
WBC × 10^9/L	6.57±1.91	7.32±1.89	<0.001
LAD mm	42.69±7.93	45.22±8.18	<0.001
LVEF %	36.53±11.31	35.19±10.59	NS
LVEDD mm	60.43±10.14	60.23±1.76	NS
BMI (kg/m^2)	24.73±4.22	25.3±3.81	NS
NYHA class <II	95 (33.9%)	75 (31%)	NS
Sex male n (%)	195 (69.6%)	193 (79.8%)	0.008
Hypertension n (%)	43 (15.4%)	45 (18.6%)	NS
Diabetes n (%)	10 (3.5%)	21 (8.7%)	0.016
SSS n (%)	2 (0.7)	9 (3.7%)	0.028
BBB n (%)	61 (21.8)	18 (7.4%)	<0.001
AVB n (%)	39 (13.9)	13 (5.4%)	0.001

Values are mean±SE or n (%). Abbreviations: AVB, atrioventricular block; BBB, bundle branch block; BMI, body mass index; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NS, not significant; SSS, sick sinus syndrome; WBC, white blood cell count.

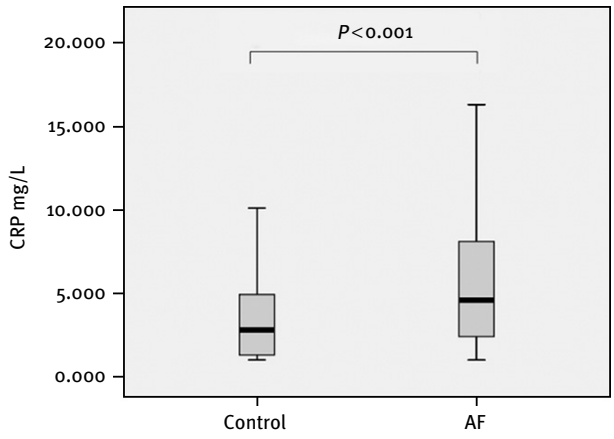

Figure 1. Box plots illustrating CRP levels in controls and in patients with atrial fibrillation. Boxes = interquartile ranges; bars = the 90th and 10th percentiles. Abbreviations: CRP, C-reactive protein.

logistic regression models using clinical variables were listed in Table 2. Multivariate analysis adjusted by age, sex, history of hypertension, diabetes, sick sinus syndrome, atrioventricular block, NYHA class I, and echocardiographic parameters showed that white blood cell counts ($p<0.001$), BMI ($p = 0.021$) were significant predictors of elevated CRP plasma levels. AF ($p<0.001$) was significantly associated with elevated CRP independent of other clinical factors.

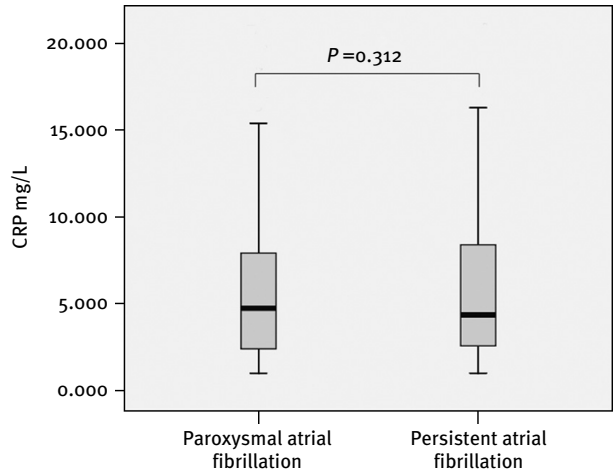

Figure 2. Box plots illustrating CRP levels in patients with paroxysmal atrial fibrillation and in patients with persistent atrial fibrillation. Boxes = interquartile ranges; bars = the 90th and 10th percentiles. Abbreviations: CRP, C-reactive protein.

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DOI:10.1002/clc.20430

Table 2. Multivariate Analysis: Predictors of Elevated CRP in all the Idiopathic Dilated Cardiomyopathy Patients

Variables	B	OR	95% CI for OR	*p*
AF	0.447	2.139	1.453–3.149	<0.001
WBCs	0.169	1.427	1.013–2.171	<0.001
NYHA <II	0.153	0.738	0.431–1.259	0.327
LAD >45 mm	0.034	1.027	0.716–1.474	0.858
LVEF ≤30%	0.113	0.720	0.494–1.048	0.277
Age	0.010	1.010	0.677–1.437	0.120
BMI	0.109	1.214	0.377–1.621	0.021
SEX	0.226	1.181	0.783–1.781	0.287
Hypertension	0.395	1.500	0.926–2.430	0.110
Diabetes	0.199	0.829	0.387–1.774	0.411
SSS	−0.169	0.917	0.249–2.375	0.802
AVB	0.009	0.764	0.407–1.434	0.370

$R^2 = 0.72$; $p<0.001$. Abbreviations: AF, atrial fibrillation; AVB, atrioventricular block; B, regression coefficient; BMI, body mass index; CI, confidence intervals; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; OR, odds ratios; SSS, sick sinus syndrome; WBC, white blood cells count.

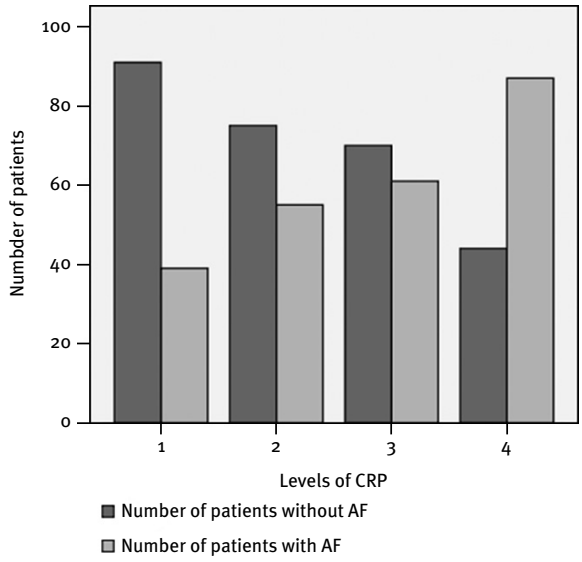

Figure 3. This figure demonstrated that prevalence of AF in IDCM patients increased while the plasma CRP levels were increasing, and the patients with the highest plasma CRP levels had a highest prevalence of suffering from AF. Abbreviations: CRP, C-reactive protein.

Discussion

In the present study, we investigated whether plasma CRP levels and other inflammation factors were related to AF in IDCM patients. The results showed that plasma CRP levels in IDCM patients with AF were higher than the IDCM patients without it. In addition, the prevalence of AF in IDCM patients increased in a stepwise manner with CRP level elevation. BMI and WBC levels were associated with higher plasma CRP levels; AF was significantly associated with elevated CRP independent of the other clinical factors.

We also observed that older age and higher prevalence of diabetes are closely linked to the AF compared with that of control patients. No correlations between CRP and older age or prevalence of diabetes were observed. In addition, CRP was found to be an independent predictor of AF after adjustment for these differences using multivariate analysis.

WBC counts have been considered as a traditional inflammatory factor for a long time. In this study, WBC counts markedly increased in the AF group compared with that of the control group, which was also correlated with plasma CRP levels. These results further proved that an inflammatory reaction existed in IDCM patients with AF. We also found that BMI was correlated with plasma CRP levels. Higher BMI is an indicator of patients with central obesity. The adipose tissue until very recently was considered to be only a fat reservoir; however recent research has recognized that it is an immune-metabolic-endocrine organ. It became evident a decade ago that either the visceral adipose tissue itself or the infiltrating macrophages are able to secrete pro-inflammatory cytokines.[12] These cytokines include interleukin-1, interleukin-6, and tumor necrosis factor;[14] which can increase the plasma CRP levels through an indirect pathway.[14–16] Therefore the higher plasma CRP

levels correlated with BMI were in accordance with the results of previous studies.

AF is frequently precipitated by other acute inflammatory clinical conditions such as pericarditis, general infections, thyrotoxicosis, and alcohol abuse.[17] Chung et al.[1] showed that the CRP levels were elevated in subjects with AF compared with healthy control subjects or subjects with other atrial arrhythmias. They found that the CRP levels gradually increased from control subjects to those with paroxysmal and permanent AF. Other studies with large patient populations have also demonstrated that CRP is not only associated with the presence of AF, but also may predict patients at increased risk for future development of AF.[2] Acevedo et al.[17] got a similar result to Chung's study;[1] they showed that the plasma CRP levels in patients with nonvalvular AF dramatically increased compared with that of control subjects. No differences of CRP levels between patients with paroxysmal and persistent AF were observed. Moreover, clinical studies indicated that CRP was a predictor of recurrence of AF in patients who received successful cardioversion.[18,19] However, Patrick et al.[20] recently demonstrated that there was no difference in CRP levels between subjects with lone AF and healthy controls, while there was a significant increase in CRP levels in subjects with AF and hypertension compared with subjects with lone AF or controls.

Our study is the first to investigate the differences of plasma CRP levels between IDCM patients with and without AF. Previous studies have investigated the relationship between AF and inflammation in a population that contained some IDCM patients; however the controls were healthy people, thus these studies did not eliminate the possibility that increased plasma CRP levels in patients with AF may be caused by structural heart disease. In this study both AF patients and control groups were IDCM patients, therefore our study excluded the potential bias of previous studies.

High levels of plasma CRP were related to increased risk of mortality in patients with IDCM.[9–11] CRP plays an important role in human IDCM, yet no study has previously investigated the correlation between CRP and arrhythmias in IDCM patients. The present study indicates a strong positive correlation between CRP and IDCM patients with AF. Our results are in agreement with that of Chung et al.[1] and Acevedo et al.[17] Based on these results, we concluded that the inflammatory condition may play a role in the occurrence of AF in IDCM patients. This may be due to inflammation-induced direct changes of the electrophysiological characteristics of atrial cells and/or inflammation-mediated structural remodeling in the atrium thereby indirectly affecting the electrophysiological characteristics of the whole atrium.

Furthermore, our findings do not contradict the results reported by Patrick et al.[20] A dual-substrate paradigm of AF has been recognized for a long time, substrates for sources initiating AF and substrates for maintenance of AF seem to underlie the spectrum of clinical atrial arrhythmias observed. Many studies have shown lone AF was always induced by atrial premature beats, usually initiated from focal sources, most commonly located in sleeves of atrial myocardium extending into the pulmonary vein ostia.[21,22] As for the occurrence of AF in IDCM patients, it is probably related to changes of atrial substrate induced by inflammatory reaction, we think it is different from lone AF.

However we still can't exclude the probability that the increased CRP levels in AF patients were caused by AF itself. Because we do not have enough evidence to confirm that AF was induced by inflammation in IDCM patients, we need to do more studies to investigate the relationship between AF and inflammation in these patients. But considering previous studies have suggested increased plasma CRP levels associate with recurrence of AF,[18] inflammation probably plays a role in the occurrence of AF.

In addition, we can evaluate the relationship between the plasma CRP levels and the prevalence of AF because more patients were included in this study. The findings confirmed that the prevalence of AF increased according to the plasma CRP level elevation, a chi-square test demonstrated that the difference of prevalence of AF between the groups with different plasma CRP levels is significant.

Limitations

Although the present study confirmed that CRP was associated with AF in IDCM patients, we did not evaluate whether some drugs such as statins or hormones could prevent occurrence of AF in IDCM patients. Further studies should be carried out to verify whether anti-inflammation treatment could treat AF in IDCM patients. In addition, this study was based on a Chinese population from our hospital and may not be reflective of all IDCM patients with AF.

Conclusion

In conclusion, this study demonstrated the presence of systemic inflammation in IDCM patients with AF. Our data showed that higher plasma levels of CRP were observed in IDCM patients with AF than patients without it. The plasma CRP levels are correlated with increased white blood cell counts and increased body mass index in IDCM patients. These results indicate an inflammatory reaction is associated with atrial fibrillation in IDCM patients.

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20430

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Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20430