C-REACTIVE PROTEIN IN PAROXYSMAL LONE ATRIAL FIBRILLATION

Dowod TAHM[1], Amin AA[2], Al-Sulaiman A[3], Ali JI[4] & Reda M[5]

ABSTRACT

Objective: The objective of the study was to investigate a possible role of the acute phase protein C-Reactive Protein "CRP" in the patho-physiology of paroxysmal lone atrial fibrillation.
Setting: Department of Medicine and Cardiology, Al-Adan Hospital, Kuwait.
Methods and Results: CRP in 20 patients with paroxysmal lone atrial fibrillation (AF group) was compared with CRP in 20 healthy volunteers (Healthy group). CRP was higher in atrial fibrillation group than in healthy group (mean 0.50 versus 0.21 mg/dl; p = 0.0037).
Conclusion: Elevated CRP levels may reflect an inflammatory state that promotes the development of atrial fibrillation.
Key words: Atrial fibrillation, C-reactive protein, inflammation

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INTRODUCTION

Atrial fibrillation (AF) the most common sustained atrial arrhythmia seen in clinical practice is associated with a two-fold increase in total cardiovascular mortality [1] as well as potential for substantial morbidity including stroke, congestive cardiac failure and cardioomyopathy.

AF occurs with increasing frequency as people grow older [2]. It is present in 0.5% of 50 to 59-year-old subjects whereas the lifetime prevalence of AF is nearly 9% among 80-89 year old subjects.[3]

AF is generally classified as either paroxysmal, where the episode terminates spontaneously, persistent, where cardio version is required for termination, or chronic, where cardio version is unsuccessful [4,5]. Lone AF is defined as AF occurring in the absence of structural heart disease with normal metabolic, thyroid, pulmonary function and oxygen saturation [6].

Although a number of risk factors have been associated with AF, acute or chronic hemodynamics, metabolic or inflammatory stressors may lead to structural remodeling of the atria that promote progression and persistence of AF [7]. Evidence for an inflammatory contribution to at least some form of AF was initially suggested by high incidence of AF (25-40%) after cardiac surgery [6].

Inflammatory response triggers the production and release of a multitude of inflammatory mediators. Acute phase response is characterized biochemically by changes in the levels of various acute phase proteins. CRP is the prototypical acute phase protein in humans [8,9]. We focused in our study on a possible role of acute phase protein CRP in the patho-physiology of paroxysmal lone atrial fibrillation.

1. Dr. Tarek Abdel Hamed Mostafa Dowod
Senior Registrar,
Department of Medicine
2. Dr. Amin Al-Sayed Amin
Senior Registrar,
Department of Cardiology
3. Dr. Arafat Al-Sulaiman
Clinical Chemistry Laboratory
4. Dr. Jaffer Ismail Ali
Registrar,
Department of Medicine
5. Dr. Mostafa Reda
Consultant Cardiologist &
Head of Cardiology Department
1-5: Al-Adan Hospital, Kuwait

Correspondence:

Dr. Tarek Abdel Hamed Mostafa Dowod
P. O. Box 47854,
Fahaheel, Kuwait
E-mail: doriya70@hotmail.com

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PATIENTS AND METHODS

CRP in a group of patients with paroxysmal lone atrial fibrillation was compared with CRP in a healthy group of patients in sinus rhythm who were undergoing routine physical examination.

Healthy group: The healthy group consisted of twenty healthy volunteers undergoing routine screening physical examination that included high sensitive CRP determination.

Paroxysmal lone atrial fibrillation group: The AF group included twenty patients seen in CCU and medical department in Adan hospital where high sensitive CRP was routinely measured.

Exclusion criteria: Patients who had surgery within 60 days, a history of infection or an acute coronary syndrome within the month before CRP collection were excluded from the study.

Data Collection: Baseline clinical data was available from all patients, ECG, echocardiogram and additional clinical data was available from the AF group including the presence or absence of AF at the time of CRP sampling.

All the patients in AF group have normal echocardiogram, normal thyroid, metabolic and pulmonary functions including oxygen saturation. Patients who were in sinus rhythm at the time of blood sampling of CRP have been considered to have paroxysmal atrial fibrillation.

CRP Assay: Blood samples were drawn into plain tubes and sent to the laboratory. Samples were allowed to clot and serum separated and analyzed for high sensitive CRP. CRP was determined by immuno-nephelometry method on BN Prospec Analyzer (Dade Behring-Germany). According to the manufacturer's manual, minimum measuring value is 0.017 mg / dl and patient reference value is < 0.3 mg / dl.

Statistical Analysis: The statistical analysis was performed using Excel 2000 software. Quantitative data were reported as mean ± standard deviation and compared using the paired two–tailed student's T test. A probability level of < 0.05 was considered statistically significant.

RESULTS

We studied a possible role of C Reactive Protein in the patho-physiology of paroxysmal lone atrial fibrillation. CRP in 20 patients, 8 Female (40%) and 12 Male (60%) their mean age 45.85±6.5 was compared with CRP in 20 healthy volunteers 10 Male (50%) and 10 Female (50%) their mean age was 33.6± 5.82. Men were 1.5 times more likely to develop AF than women. As the study showed a statistically significant difference in age between the two groups (p= 0.0003). CRP was significantly higher in patients with paroxysmal atrial fibrillation (AF group) than in healthy group (p = 0.0037). The results of the study have been summarized in Table-I

Table 1: Patient's Characteristics

	AF Group (n=20)	*Healthy Group (n=20)*
Age (in years)	45.85 ± 6.50*	33.6 ± 5.82*
Sex: (Male)	8 (40%)	10 (50%)
(Female)	12 (60%)	10 (50%)
CRP (mg / dl)	0.50 ± 0.34*	0.21 ± 0.22*

* Mean ± SD

DISCUSSION

It has become clear in the recent years that important triggers initiating atrial fibrillation arise from focally discharging cells located most commonly at the pulmonary vein ostia [10]. These foci may lead to frequent atrial ectopy and paroxysms of atrial fibrillation. Whether initiation of atrial fibrillation activates direct inflammatory effects or the presence of a pre-existing systemic inflammatory state promotes further persistence of atrial fibrillation remains unclear [6].

The high rate activity of atrial fibrillation may lead to myocyte calcium overload and in some cases to the initiation of apoptotic loss of atrial myocytes [11]. CRP has been shown to act as an opsonin and may participate in the clearance of apoptotic myocytes [12].

Myocyte loss is typically accompanied by replacement fibrosis. This low level inflammatory

response may thus be part of structural remodeling process associated with increased persistence of atrial fibrillation [13-14]. Alternatively, the presence of a baseline elevated level of systemic inflammation may predispose patients with triggering atrial foci to development or persistence of atrial fibrillation.

This worsened progression of arrhythmia in the presence of systemic inflammation may be analogous to that observed in other states in which elevated CRP is associated with increased mortality and left ventricular dysfunction [15].

In our study, men where 1.5 times more likely to develop AF than women. This was in lines with the most prior publications, which have also noted that men are at greater risk to have AF than women [16-18]. The statistically significant difference in age between the two groups (p=0.0003) reflects the increasing frequency of AF with increasing age. This is also in line with Framingham study [2].

We report the association of paroxysmal lone atrial fibrillation, with elevated CRP, a marker of systemic inflammation. These results suggest that the elevated CRP may be related to the burden of atrial fibrillation. CRP was statistically significantly elevated in patients with lone atrial fibrillation in the absence of structural heart disease when compared with healthy subjects (p=0.0037). However, whether CRP elevation is a consequence rather than a cause of atrial fibrillation cannot be determined by these results.

These findings require further testing and confirmation in a larger trial. Nevertheless, these results may provide a potential target for pharmacological interruption or reversal of atrial structural remodeling. Currently available pharmacological treatments for atrial fibrillation have limited efficacy and potentially toxic side effects. Inflammatory mechanisms may form a basis for new better tolerated pharmacological approaches for treating atrial fibrillation. Randomized tests of agents such as anti-inflammatory agents or other CRP lowering drugs may be needed [6].

Supporting this hypothesis is the observation of inflammatory infiltrates, myocyte necrosis and fibrosis in atrial biopsies of patients with lone atrial fibrillation refractory to anti-arrhythmic therapy [10]. In an earlier case control study of patients with atrial fibrillation, it was found that CRP levels were higher in patients with atrial fibrillation than a control group of patients in sinus rhythm [6].

CONCLUSION

CRP, a marker of systemic inflammation was independently associated with the presence of atrial fibrillation at baseline, although a causal relationship cannot be established. These findings support a possible association of an inflammatory state and future development of atrial fibrillation.

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