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Investigating the Effect of Inflammation on Atrial Fibrillation Occurrence by Measuring Highly Sensitive C-reactive Protein (hs-CRP)

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ABSTRACT

Introduction: Atrial fibrillation (AF) is the most prevalent cardiac arrhythmias that cardiologists and internists encounter. The goal of this article is to clarify an overview of the evidence linking inflammation to AF existence, which may highlight the effect of some pharmacological agents that have genuine potential to reduce the clinical burden of AF by modulating inflammatory pathways.

Materials and Methods: In a case-control study, 50 patients with atrial fibrillation (AF) with different etiologies and 50 patients with sinus rhythm and similar bases were selected. Sampling for highly sensitive c-reactive (hs-CRP) was done on the patients presenting with AF to the Ghaem hospital between October 2006 and June 2007.

Results: Mean age of the patients was 62 years with maximum of 90 and minimum of 36 and standard deviation of 13.80. The most frequent age group was 71-80years. Fifty-four percent of patients were male and 46% were female. Mean serum hs-CRP levels in AF patients with hypertension (HTN), Ischemic heart disease (IHD), Valvular heart disease (VHD), HTN+IHD and hyperthyroidism were 8.10, 9.40, 8.68, 10.16 and 5.98 mg/Lit; respectively. There was significant difference between hs-CRP levels in hypertensive patients in the two groups (P=0.010). Similar results were observed in IHD patients, VHD patients and HTN+IHD patients in two groups (P=0.015, P=0.037, P=0.000).

Conclusion: In addition to some risk factors like baseline cardiac diseases, aging, thyrotoxicosis, pulmonary embolism, pneumonia and cardiac surgery, there also appears to be consistent links between hs-CRP, a marker of inflammation, and the pathogenesis of AF.

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Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmias that cardiologists and internists, encounter. It may be paroxysmal or sustained. The prevalence of AF is age-dependent, affecting approximately 1% of people aged ≤65 years and 5% of individuals older than 65 years (1).

AF is also associated with an increase in the mortality relative risk—ranging from 1.3 to 2.34, as well as an increasing morbidity and adversely affects quality of life (2). Patients who present with stroke in the base of AF have a significantly worse outcome, which is defined by a higher mortality, morbidity, and longer hospital stays (3, 4). Even patients with paroxysmal (self-terminating) and persistent AF (lasting more

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Table 1. Demographic data in AF and sinus rhythm group

		Age				Sex	
	Number of patients	Mean	Max.	Min.	S.D.	Male	Female
AF	50	62	90	36	13.80	54%	46%
Control	50	55.9	82	29	12.39	68%	32%

than 7 days or requiring cardioversion) have a risk of stroke that is similar to patients with permanent AF.

Lately, in Western countries, hospitalizations for AF have increased by approximately two- to three-folds (5). This is largely explained by the acceleration of population aging, the predominance of AF among the elderly, and improved survival of patients with cardiovascular disease CVD (6).

Indeed, the age-adjusted prevalence of AF among patients with ischemic stroke has already risen by greater than 40% over the last 30 years (7). So, there is a growing need for improved primary and secondary AF prevention strategies to reduce this potentially great health burden. There is now an increasing evidence linking inflammation to a broad spectrum of cardiovascular conditions, such as coronary artery disease (CAD), insulin resistance and diabetes mellitus, and also hypertension. Additionally, there is emerging data to support the association between inflammation and AF (8).

Highly sensitive C-reactive protein (hs-CRP) has evolved as the most robust and reproducible marker of vascular inflammation (9). CRP is a circulating acute-phase reactant named initially for its capacity to bind to the c-polysaccharide of streptococcus pneumonia (1). CRP is synthesized primarily by the liver in response to Interlukin-6 and Interlukin-1 and is a part of acute phase proteins. It aggregates to the outer layer of the organisms and consequent activation of complement cascade. The result is organism lysis and some other biologic acts such as CRP acts as opsonic (10).

Of note, there is a consistent and significant correlation (in all populations) between baseline hs-CRP levels and risk of future cardiovascular events (stroke, peripheral vascular disease, sudden cardiac death, AF, plaque rupture and recurrent ischemia, and myocardial infarction) (10).

The precise mechanism for the increased circulating hs-CRP in AF is uncertain, but it might reflect active participation of CRP in the local inflammatory response within the atrial myocardium. In patients with AF, CRP may localize in atrial tissue, possibly binding to the membranes of myocardial cells in inflamed tissues and activating complement, leading to tissue damage (11).

The vascular markers which has been more studied have are (hs-CRP) and interleukin (IL)-6 which have had higher levels in AF group, compared with the control group with sinus rhythm (1). The goal of this study is to clarify an overview of the evidence linking inflammation to AF existence and inherence which may highlight the effect of some pharmacological agents that have genuine potential to reduce the clinical burden of AF by modulating inflammatory pathways.

Materials and Methods

In a case-control study, 50 patients with AF rhythm plus different etiologies and 50 patients with sinus rhythm and similar underlying diseases were selected. Sampling was done on the patients presenting with AF to the Ghaem hospital between October 2006 and June 2007. Inclusion criteria were: AF rhythm in the time of study entry (which is upholded by physician examination and electrocardiographic monitoring simultaneously), not given any other recognized inflammatory disease, without using any anti-inflammatory drugs and appetency to collaboration, and normal sinus rhythm at the time of the study for control group.

C-reactive protein was measured on the Hitachi 912 (Roche Diagnostics, Indianapolis) assay system using photometric method (mg/dl). Demographic data like age, sex, concomitant diseases, AF duration, ventricular response, Ejection Fraction in echocardiography and hs-CRP level (in AF group) and age, sex, concomitant disease and hs_CRP levels (in control group) were collected. All patients provided written informed consent approved by the ethical committee of the Mashhad University of Medical Sciences.

Statistical Analysis

Continuous variables are reported as means± standard deviation whereas categorical variables are reported as numbers and percentages. T and X2 tests were used for comparison.

Results

A total of 100 patients with and with no AF were included in the study. In the AF group mean age of the patients was 62 years. The most frequent age group was 71-80 years old. In the control group, the mean age of the patients was 55 years old. The most frequent age group was 51-60 years. Demographic data is shown in Table

Table 2. Other demographic data in Atrial fibrillation group

	Mean.(Months)	Min.(Months)	Max.(Months)	S.D.
AF duration	40.49	0.5	144	34.90
Ventricular response	94.32	75	130	16.42
Ejection fraction	55.06	40	70	7.60

AF: Atrial fibrillation

Table3. Level of hs-CRP in AF and sinus rhythm group

		Hs-CRP level(mg/lit)			
	Numbers	Mean	Max.	Min.	S.D.
AF	50	8.87	19.4	2	3.54
Sinus rhythm	50	5.09	11.7	0.77	2.55

Table 4. Hs-CRP levels in different subgroups

	AF group		Control group		total	
	No.	Mean hs-CRP level	No.	Mean hs-CRP level	No.	Mean hs-CRP level
HTN	7	8.10	21	5.02	28	5.79
IHD	15	9.40	12	5.73	27	7.77
VHD	12	8.68	9	5.36	21	7.26
HTN+IHD	11	10.16	8	3.98	19	7.56
Hyperthyroidism	5	5.98	0	--	5	5.98

HTN:Hypertensions
IHD:Ischemic heart disease
VHD:Valvular heart disease

1. There was significant difference between age in 2 groups but it has not negative effects on the results since it does not have any effect on hs-CRP levels.

The least duration of AF was 2 weeks and the longest period was 12 years old. Mean duration of AF was 40 months (Table 2).

After statistical analysis, we found a significant difference between hs-CRP levels in two groups (P=0.00).

Mean serum hs-CRP levels in AF patients with Hypertensions (HTN), Ischemic heart disease (IHD), Valvular heart disease (VHD), HTN+IHD and hyperthyroidism were 8.10, 9.40, 8.68, 10.16 and 5.98; respectively. These levels were 5.02, 5.73, 5.36 and 3.98 in control group; respectively (there were no hyperthyroid patient in control group) (Table 4).

There was a significant difference between hs-CRP levels in hypertensive patients in the two groups (P=0.010). Similar results were observed in IHD patients, VHD patients and HTN+IHD patients (P=0.015, P=0.037, P=0.000). But, there was not significant difference between hs-CRP levels in different concomitant diseases without respect of AF or sinus rhythm (P=0.256). Also, there was not significant correlation between AF duration and hs-CRP levels (P=0.0604).

Discussion

Inflammation has been shown to have a direct role in the initiation, maintenance, and recurrence of atrial fibrillation (AF) although the underlying mechanisms are unknown. Similarly, it is unclear if inflammatory markers are elevated due to the AF alone or the coexisting cardio-vascular diseases that increase the risk of AF.

Our study, like prior studies, demonstrated that AF is typically a disease of aging and follows the acquisition of cardiovascular diseases such as hypertension, diabetes and valvular heart disease. These data provide insight into hs-CRP elevation both with cardiovascular disease in general and with AF. Our data showed that the average hs-CRP level was higher in patients with AF in comparison to those without it. These data show the incremental and independent nature of AF and inflammation.

In general, the association between AF and inflammation is well established, and several prior studies have documented the relationship with CRP (12-18). In the cross-sectional study, Chung *et al* first reported that permanent AF was associated with higher levels of CRP than paroxysmal AF, implying that CRP levels may be related to the burden of AF (12). But this was a cross-sectional study and, therefore, did not address whether inflammatory marker elevation was the cause or the consequence of AF. On the contrary, Pellegrino *et al* reported significantly increased CRP levels in subjects with paroxysmal AF compared to subjects with persistent AF (19). Finally, CRP has been reported as a risk factor for recurrences of lone AF, whereas elevated CRP levels have been related to AF recurrences after successful cardioversion (20).

Importantly, AF also increases other inflammatory markers as well, including complement (C3, C4), prothrombin fragments, and IL-6 (13, 14). Interestingly, Marcus *et al* found that CRP and IL-6 levels were significantly higher when blood was drawn during AF than during sinus rhythm, regardless of a history of AF (21). Liuba *et al* assessed IL-6 and hs-CRP levels in a small group of patients referred for

radiofrequency catheter ablation, and concluded that there were no differences in plasma levels of both markers between paroxysmal AF and permanent AF (22). In a case-control study involving 305 patients with AF and 150 controls, Li *et al* found that IL-6, IL-8, and Monocyte Chemoattractant Protein-1 (MCP-1) levels were not different in paroxysmal, persistent, or permanent AF after adjusting for age, sex, race, body mass index, heart failure, and statin use; however, the investigators reported higher tumor necrosis factor-α (TNF-α) concentrations in patients with persistent AF and in patients with permanent AF than in patients with paroxysmal AF. Indeed, a graded increase in TNF-α was seen among the subgroups of paroxysmal, persistent, and permanent AF, respectively (23). The difference of inflammatory markers related to clinical subtypes of AF might be interrelated with different role of inflammatory markers in the pathogenesis of AF.

In our study, AF was associated with the increased mean CRP level across all concomitant the diseases. CRP and other inflammatory marker elevations in patients with AF have been associated with worse outcomes such as death, stroke, and arrhythmia recurrence after cardioversion (15-18). Furthermore, these data assist in defining AF as a risk factor in addition to a risk marker of other diseases.

These data improve our understanding that AF is independently associated with inflammation, but what remains unclear is if targeting inflammation in patients with AF will improve outcomes or help to promote sinus rhythm. Statins which have pleiotropic effects, including reducing inflammatory markers, have been shown to decrease the risk of postoperative AF when given prior to cardiac surgery (24). Use of statins has also been shown to decrease the recurrence of AF postcardioversion (25). Unfortunately, however, statins have not been shown to decrease recurrence rates of AF following catheter ablation (26). Other anti-inflammatory agents have also been studied. Hydrocortisone, but not dexamethasone, has been shown to reduce the incidence of AF following cardiac surgery (27). Methylprednisolone has been shown to decrease CRP as well as to prevent recurrent and permanent AF (28). Fish oil, when given 2 g/day for 5 days prior to coronary artery bypass graft surgery, showed a reduction in postoperative AF (29), but studies evaluating dietary consumption of fish oil in the general population have shown mixed results in preventing AF (30). These data suggest that targeting inflammation as a possible underlying mechanism of is feasible, but longterm treatment and follow-up studies are required to assess durable outcomes.

Conclusion

Risk factors associated with AF were associated with higher CRP in an incremental manner. However, the presence of AF was also associated with higher CRP despite associated comorbidities. These data support the concept that AF is an inflammatory process and thereby may convey independent risk.

Study limitations

Our data needs to be confirmed in larger studies with extended follow-up durations to investigate the effect of inflammation on AF and its treatment process by anti-inflammatory drugs.

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Conflict of Interest

The authors declare no conflict of interest.

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