

C-Reactive Protein and Atrial Fibrillation. An Old Marker Looking for of a New Target

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INTRODUCTION

The prevalence and clinical impact of atrial fibrillation (AF), the most common cardiac rhythm disturbance, continues to increase. The pathophysiology of AF is still not well understood and it is generally accepted that the majority of cases are due to fibrosis or degeneration of the atrial muscle, sinus node disease or conduction abnormalities, or to the underlying heart disease itself or ageing. In recent years, a large volume of information has been published on the role of C-reactive protein (CRP) as a predictor of vascular events in cardiovascular disease¹⁻³ and attempts have been made to identify variables that increase or decrease the levels of this inflammatory marker. Elevated CRP levels has been identified as a prognostic marker in healthy individuals and in patients with stable or unstable angina, following myocardial infarction, or after cardiac arrest. The possibility that the association of inflammation with AF could be demonstrated with the help of CRP has recently captured the attention of many researchers. Histologic studies, such as that of Frustaci et al,⁴ have demonstrated that inflammatory infiltrates are present in biopsies from patients with lone AF but absent in control subjects. Likewise, various epidemiologic studies have demonstrated an association between CRP concentration and AF.⁵ Case-controlled studies have shown a correlation between CRP and the outcome of cardioversion.⁶ Additional data is now provided in an article by Zarauza et al⁷ published in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA.

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ORIGIN OF C-REACTIVE PROTEIN

Inflammation generates multiple responses at a distance from the site at which it is presented. Many of these changes are accompanied by the so-called acute-phase reactive proteins (which accompany both chronic and acute inflammatory responses). CRP is a non-disease-specific acute-phase reactant that has traditionally been used to detect acute lesions, infections, and inflammation, as well as to assess the activity of inflammatory diseases. It is mainly produced in the liver under the control of cytokines, particularly interleukin-6, which is a polypeptide used as a cellular signal produced by activated cells, generally macrophages, at the disease site. CRP, so-called due to its ability to precipitate C polysaccharide from *Streptococcus pneumoniae*, was the first acute phase protein to be described and is a good systemic marker of inflammation and tissue damage.

METHODS FOR DETECTION OF CRP

Baseline concentrations of CRP are divided into thirds in the population: less than 1, 1 to 3, and greater than 3 mg/L. It is in these values, previously considered "normal," that the concentration of CRP appears to have a predictive value. The refinement of laboratory techniques to detect CRP (high-sensitivity CRP) has revealed low-level inflammation associated with vascular disease. Those methods have yet to be implemented in a number of laboratories, many of which continue only to provide values greater than 3 mg or even to specify only a "negative" result (qualitative values related to the cutoff). Older analytic methods were only designed to detect high concentrations (>8 mg/L).

CLINICAL GUIDELINES AND CRP

Some clinical guidelines report that cutoff values for CRP concentration of less than 1, 1 to 3, and greater than 3 mg/L correspond to low, moderate, and high risk of future vascular events, respectively.⁸ Analysis of 2 samples separated by at least 2 weeks is recommended because CRP levels tend to normalize within 2 weeks of the disappearance of inflammation. Concentrations of

more than 10 mg/L must be repeated to rule out acute inflammation and, if the values persist, to consider noncardiovascular etiology. In the study of Zarauza et al,⁷ it is noteworthy that the data suggested that almost all of the patients presented concentrations of less than 10 mg/L.

FACTORS THAT ALTER THE CONCENTRATION OF CRP

CRP levels can be altered by various patient characteristics or treatments. Drugs such as statins, fibrates, niacin, and antiplatelet drugs, as well as weight loss and exercise, have proved to be effective in reducing CRP levels. On the other hand, drugs such as statins, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers reduce the recurrence of AF. Part of this possible antiarrhythmic effect may be explained by their antiinflammatory activity. Unfortunately, in the study by Zarauza et al,⁷ data was not collected on concomitant treatment, and consequently, it is not clear whether baseline differences in treatments could have influenced concentrations CRP levels and perhaps even the maintenance of sinus rhythm.

ROLE OF INFLAMMATION IN THE GENESIS AND PERSISTENCE OF ATRIAL FIBRILLATION

Recent studies have indicated a link between inflammatory processes and the development of AF. Inflammation may not be simply a response to underlying arrhythmia but, rather, an integral part of it (Figure).

Frustaci et al⁴ were the first to demonstrate the presence of inflammation in patients with AF. In biopsies from 12 patients with lone AF, those authors observed the presence of inflammatory infiltrates, necrosis, and fibrosis, compared with normal biopsies from a group of control patients. In 2001, Chung et al⁹ performed a retrospective case-control study of CRP levels in 131 patients with atrial arrhythmias. Atrial arrhythmias were associated with a 2-fold increase in CRP levels following adjustment for confounding variables ($P < .001$). However, in that article it was not indicated whether inflammation was the cause or consequence of AF. The same authors demonstrated that CRP levels were significantly higher in patients with paroxysmal or chronic AF than in controls and, in addition, that the concentrations were higher in the group with chronic AF than in those with paroxysmal AF. AF is also a common complication following heart surgery. Following cardiopulmonary bypass surgery, the concentrations of inflammatory markers and complement-CRP complexes increase, with a peak in the second and third days following surgery that coincides with a peak in the incidence of AF.¹⁰

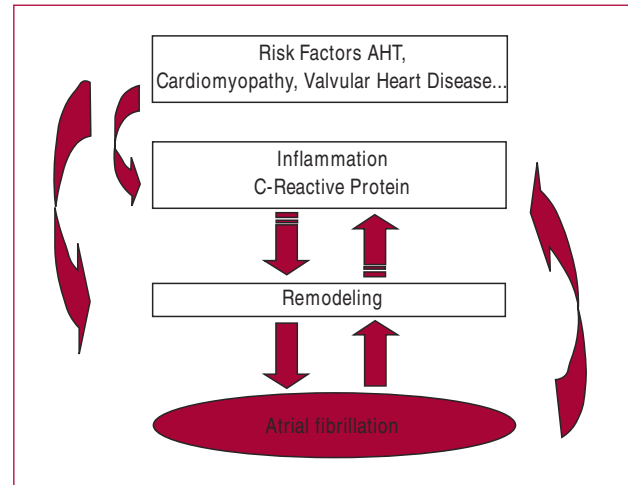


Figure. Role of inflammation in atrial fibrillation: marker, product, or both? It could be the case that the onset of AF directly activates inflammation or that inflammation promotes the onset and perpetuation of AF. It could also be true that the two mechanisms are interconnected. AHT indicates arterial hypertension.

However, this association may be nonspecific and simply reflect the reaction to the acute phase of hemodynamic or surgical stress.

CLASSIFICATION OF ATRIAL FIBRILLATION, INFLAMMATION, AND CRP

Theories of the pathophysiology of AF include that it is initiated by an increase in the automaticity of isolated or multiple ectopic foci, generally located in the pulmonary veins, or the development of multiple reentrant circuits in the atria. The anatomic substrate corresponds to the atrial architecture (fibrosis, necrosis, infiltrates, etc) and the electrophysiologic substrate relates to the heterogeneity of the atrium (shortening of the refractory period, loss of frequency adaptation, slowing of atrial conduction velocity, etc).

The molecular and cellular events that lead to atrial remodeling with fibrosis, characteristic of AF, appear to include hemodynamic, metabolic, oxidative, and inflammatory changes that act in concert with genetic factors. Myosin isoforms, fibrosis, and evidence of oxidative damage mediated by free radicals have been found in the atria of patients with AF. It could be the case that the onset of AF directly activates inflammation or that inflammation promotes the onset or perpetuation of AF. It is also possible that the 2 mechanisms are interconnected. Rapid atrial activation caused by an automatic focus in the pulmonary vein can induce apoptosis of atrial cardiomyocytes. This damage can lead to an inflammatory response that would, therefore, cause structural remodeling and favor the maintenance of AF. On the other hand, the presence of systemic inflammation with increased CRP levels may predispose

patients to developing AF. Local activation of the complement system, mediated by binding of CRP to phospholipid components of the damaged cells and to external pathogens, would amplify local inflammation. CRP also induces secretion of cytokines such as MCP-1, and the expression of adhesion molecules by endothelial cells, as well as directly recruiting monocytes through a receptor for CRP. CRP also sensitizes endothelial cells for histolysis by infiltrating T cells.

In patients with AF, the imbalance between perfusion and metabolic demands can lead to ischemia in atrial cardiomyocytes, microscopic structural changes, and atrial tachycardiomyopathy. Cardiac adaptations to the altered rhythm, known as metabolic, electrical, contractile, and anatomic remodeling, are found to be present in patients with AF, and it is tempting to speculate that inflammation may be at least partly involved in this process. AF generates more AF and positive correlations between inflammatory markers and duration of AF indicate that inflammation may mediate this process. By analogy with the role of CRP in ischemic heart disease, CRP would not only be a marker of inflammation but would also play an active role in its pathophysiology. Alternatively, CRP could be more a consequence than a cause of the pathophysiology. Epidemiologic studies can identify associations but cannot establish causality or mechanisms. It has been proposed that CRP could be a useful marker with which to evaluate the activity of AF and open the door to new pharmacologic interventions to modulate the risk associated with an increase in the levels of this protein.

CRP AND ATRIAL FIBRILLATION, SUCCESS OF CARIOVERSION, AND RECURRENCE

Various studies, almost all of them published recently, have analyzed CRP levels in patients treated by electrical cardioversion for AF (Table).^{6,11-15} Psychari et al¹⁶ analyzed concentrations of CRP and interleukin-6 in relation to the size of the left atrium and the duration of episodes in patients with AF, and unlike Zarauza et al,⁷ observed a correlation between those parameters. CRP was an independent predictor of AF when compared with control subjects and was

positively correlated with atrial size and the concentration of interleukin-6, and negatively correlated with left ventricular function. Interleukin-6 levels positively correlated with the duration of AF prior to cardioversion. The relationship between CRP and interleukin-6 levels with the size of the left atrium and the duration of AF indicate that inflammation may play a role in the process of atrial remodeling. In a study of 106 patients with AF treated by cardioversion in which CRP and rate the recurrence rate were analyzed with a mean (SD) follow-up of 140 (144) days, the concentration of CRP was an independent predictor of AF (odds ratio [OR]=5.30; 95% confidence interval [CI], 2.46-11.5).⁶

However, not all studies have demonstrated the predictive capacity for recurrence of AF following cardioversion. Conway et al¹¹ analyzed the concentrations of CRP and interleukin-6, tissue factor, and fibrinogen, along with platelet activation and endothelial damage in 54 patients. CRP levels were predictive of immediate success of cardioversion (2 mg/L in patients with a successful outcome and 3.2 mg/L in those in whom cardioversion was unsuccessful; $P=.04$) but were not predictive of the result at 2 months following cardioversion (0.29 mg/mL in patients with AF and 2 mg/L in patients in sinus rhythm; $P=.07$). The remaining parameters analyzed did not have predictive capacity for initial outcome or outcome at 2 months. In the study of Zhang et al,¹⁷ CRP levels following surgery were also unable to distinguish between patients with and without AF. In the same study, statins were able to reduce AF independently of CRP concentration. Likewise, in the study of Cosgrave et al¹² undertaken in 81 patients with AF who received electrical cardioversion, CRP concentration did not discriminate between initial success and failure of cardioversion or the recurrence of AF at 2 months. It is noteworthy in the study of Zarauza et al⁷ that CRP levels were not different in the group in which electrical cardioversion failed initially compared with the group in which the treatment was a success. That observation was in spite of the fact that AF was of a much longer duration (more than 2 years in some patients). That finding should make us consider the proposed utility of CRP as a marker of

TABLE. Concentrations of C-Reactive Protein and Recurrence of Atrial Fibrillation in Different Studies*

Author and Reference	Year of Publication	CRP in Group With Recurrence of AF, mg/L	CRP in Group With Maintained SR, mg/L	P	Odds Ratio
Cosgrave et al ¹²	2005	21.6	24	.710	–
Acevedo et al ¹³	2005	12±18	5±1.5	.030	–
Watanabe et al ⁶	2005	1.3±1.7	0.3±0.2	.005	5.3 (95% CI, 2.46-11.5)
Wazni et al ¹⁴	2005	3.95	1.81	.002	–
Malouf et al ¹⁵	2005	10.7±13.7	6.0±15.8	.036	2.19 (95% CI, 1.05-4.55)
Conway et al ¹¹	2004	2.9	2	.057	0.34 (95% CI, 0.11-1.03)

*Data are shown as means±SD. CRP indicates C-reactive protein; AF, atrial fibrillation; CI, confidence interval; SR, sinus rhythm.

inflammatory “activity,” as well as the need to identify changes in CRP levels on an individual basis, assuming that they occur.

Dernellis et al¹⁸ presented a randomized study designed to evaluate the hypothesis that antiinflammatory treatment would reduce recurrence of AF in patients treated in the early stages of the disease. They demonstrated that patients who received methylprednisolone following a first episode of symptomatic persistent AF presented fewer recurrences, and this correlated with lower plasma concentrations of CRP. The mean concentrations of CRP during follow-up correlated with the risk of recurrence of AF. Most importantly, patients from different groups who had similar CRP levels also displayed similar rates of recurrence of AF, a finding that supports the hypothesis that antiinflammatory effects are responsible for reduced rates. The same authors also published a study in 80 patients in which they observed that atorvastatin led to the reduction of both CRP and paroxysmal AF.¹⁹ In that randomized trial, episodes of AF were controlled in 65% of the treated group compared with 10% of the placebo group. Baseline concentrations of CRP were 6.4 mg/L in the placebo group and 5.8 mg/L in the atorvastatin-treated group. Following treatment, the placebo group had values of 6.1 mg/L and the atorvastatin-treated group 2.8 mg/L ($P=.001$). Other studies suggest that angiotensin inhibitors can reduce AF through an antiinflammatory mechanism.²⁰

LIMITATIONS OF THE STUDY

The findings should be interpreted with caution due to the inherent limitations of the design, which may include selection bias and known or as yet unknown confounding factors. Clearly, causality cannot be demonstrated. Furthermore, many studies such as that of Zarauza et al⁷ are based on single baseline measurements of CRP that may not reflect the inflammatory process over time. Another limitation is the lack of data on parameters associated with inflammation in the patients prior to the onset of AF. Current data does not allow conclusions to be reached regarding whether inflammation is a mediator or a perpetuator of AF, that is, whether it is an epiphenomenon or a cause. The correlation of CRP with metabolic risk factors may be indirectly responsible for part of its predictive value and does not clarify treatment strategies.

CLINICAL USEFULNESS

Studies such as that of Zarauza et al,⁷ on which the authors should be congratulated, will provide us with many candidate markers to be used systematically in future patient assessment. Risk stratification is important if it leads us to focus treatment and resources on those groups that will receive the greatest benefit. The clinical usefulness of measuring CRP concentration should be assessed on the basis of whether or not it allows a

pharmacological treatment strategy to be developed for the prevention of AF. This will first require clarification of whether inflammation itself is a modifiable risk factor and could form the basis for the development of new treatments for patients with AF.

CLINICAL IMPLICATIONS AND CONCLUSIONS

CRP may not only be a marker of inflammation in patients with AF but may also play an active pathophysiological role. Alternatively, CRP could be a consequence more than a cause of the pathophysiology of AF. Epidemiologic studies can identify associations but cannot establish causality, which requires other clinical studies. Use of a simple marker for the analysis of inflammatory activity in AF opens new doors towards pharmacological interventions that will modulate inflammation (aspirin, statins, fibrates, angiotensin inhibitors, etc).

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