Review

Inflammation and C-Reactive Protein in Atrial Fibrillation:

Cause or Effect?

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Atrial fibrillation is associated with substantial morbidity and mortality rates. The incompletely understood pathogenesis of this cardiac dysrhythmia makes it difficult to improve approaches to primary and secondary prevention. Evidence has accumulated in regard to a relationship between inflammation and atrial fibrillation. Investigators have correlated the dysrhythmia with myocarditis, pericardiotomy, and C-reactive protein levels, suggesting that inflammation causes atrial fibrillation or participates in its onset and continuation. Conversely, other investigators suggest that atrial fibrillation induces an inflammatory response. In this review, we summarize and critically discuss the nature and clinical role of inflammation and C-reactive protein in atrial fibrillation. ***(Tex Heart Inst J 2014;41(5):461-8)***

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Atrial fibrillation (AF) is the sustained cardiac dysrhythmia most often encountered in clinical practice. Despite major advances in management and prophylaxis, AF continues to be associated with a high relative risk of death,[1] and with increased morbidity, repeated hospitalization, and reduced quality of life. Moreover, the prevalence of AF becomes greater as the population ages.[2] Therefore, improved primary and secondary AF prevention is needed to reduce the potentially enormous health burden. This requires a better understanding of the mechanisms underlying AF, with the premise that improved mechanistic insights will lead to innovative and more effective therapeutic approaches. Since the early 2000s, investigators have proposed that AF is caused by inflammatory processes. Study results have shown correlations between markers of inflammation, such as C-reactive protein (CRP), and the onset of AF. However, it remains debatable whether inflammation is only a consequence of left atrial remodeling, or whether inflammation is involved in the pathogenesis of the dysrhythmia. Herein, we summarize and critically discuss the relationship between AF and inflammation.

The Pathogenesis of Atrial Fibrillation

Atrial fibrillation can be induced and maintained by 3 kinds of mechanisms: 1) an irregular atrial response to a rapidly discharging, regularly firing driver that results from local ectopic activity; 2) an irregular atrial response to a rapid, regular discharge that results from a single localized reentry circuit; and 3) multiple functional reentry circuits that vary in time and space.[3] Predisposing factors for all 3 mechanisms include cardiac aging, genotype, ischemic heart disease, and hyperthyroidism.[4]

Basic Mechanisms of Dysrhythmia

Ectopic Firing. Three basic mechanisms underlie ectopic firing: 1) "enhanced automaticity," caused by a decrease in resting potassium (K^+) permeability through the inward K^+ current or by an increase in "funny current" (a pacemaker current manifested in normal human atrial cells during spontaneous phase 4 depolarization)[5]; 2) "early afterdepolarization," a depolarization during the repolarization phase, promoted by action-potential prolongation that enables the L-type calcium (Ca) current to recover from inactivation; and 3) "delayed afterdepolarization," an abnormal diastolic release of Ca from sarcoplasmic reticular Ca stores that causes a net depolarizing inward positive-ion movement.

Reentry. Reentry can maintain AF by producing a single-circuit reentry (a rapidly firing driver with fibrillatory propagation) or by producing multiple irregular reentry

circuits. In both instances, the maintenance of continuous activity depends on atrial (substrate) anatomic and functional properties, with an appropriate balance between refractory and excitability determinants.

Atrial Remodeling. Atrial remodeling results from different kinds of persistent changes in atrial structure (structural remodeling) or function (electrical and neural/autonomic remodeling) that promote the occurrence or maintenance of AF. Inflammation might take part in both kinds of remodeling. Electrical remodeling consists of a shorter atrial effective refractory period, a loss of rate adaptation, and prolonged atrial conductivity.[6] Accumulated Ca within atrial myocytes (related to AF) shortens the atrial effective refractory period and promotes wavelet-reentry circuits.[7] The structural remodeling of the atria occurs in parallel with these changes of electrical remodeling. This process involves left atrial dilation and an increase in atrial fibrosis, particularly consequent to large deposits of collagen and fibronectin between individual cells. The deposition interferes with electrical continuity and slows conduction,[8] whereas the fibroblasts, which can couple electrically to cardiomyocytes, promote reentry, ectopic activity, or both.[9] Finally, autonomic neural remodeling promotes AF by means of vagal discharge that stimulates acetylcholine-dependent K current and reduces action-potential duration that stabilizes reentrant rotors,[10] and by β-adrenoreceptor activation that increases diastolic Ca leak and promotes delayed depolarization-related ectopic firing by the hyperphosphorylating ryanodine receptor channel.[11]

Correlation between Atrial Fibrillation and Inflammation

The pathogenesis of AF is incompletely understood, but more knowledge should lead to new therapeutic approaches (Table I).[12-41] It has been shown that the pathogenesis of several cardiovascular diseases—such as unstable angina and myocardial infarction[42]—involves inflammation. Substantial evidence also links inflammation to the initiation and perpetuation of AF, given the observed onset of AF in inflammatory states such as myocarditis[43] and pericarditis,[44] and the systemic inflammatory response induced by cardiac surgery and cardiopulmonary bypass.[16] This observation was confirmed by histologic findings of atrial myocarditis in patients who had apparently lone AF, but not in persons who were in sinus rhythm.[13] Inflammatory infiltrates, myocyte necrosis, and fibrosis—found in multiple atrial biopsy specimens from patients who had lone AF but no detectable organic heart disease or predisposing factors—were absent in biventricular biopsies of the same patients; this suggested a causative link between inflammation and AF. However, no viral, toxic, or autoimmune cause was established.[13] Maixent and colleagues[15] speculated on the possibility of an autoimmune process after finding circulating antimyosin autoantibodies in the serum of patients who had lone AF. Mandal and associates[17] investigated the effects of heat-shock proteins (HSPs), a group of chaperone proteins that preserve cellular integrity by keeping proteins in their correctly folded state. Their study showed that the inflammation-induced expression of HSPs on the surface of myocytes might lead to cell lysis by circulating anti-HSP65 antibodies, with subsequent structural myocardial changes leading to AF after cardiac surgery. It is likely that the initiation of AF is a consequence of necrosis and fibrosis caused by inflammatory processes, which can trigger atrial dysrhythmias directly through fluctuations in membrane potential.[44] This makes inflammation one of many possible cofactors of AF.

In perpetuating AF, inflammation might participate in the structural remodeling, inducing cellular degeneration, apoptosis, and subsequent atrial fibrosis and dilation. Watanabe and co-authors[39] examined 50 consecutive patients who had paroxysmal AF and 50 control subjects without AF. The authors found that left ventricular mass, left ventricular end-systolic diameter, and left atrial diameter were predictors of elevated CRP and persistent AF. Similarly, Psychari and colleagues,[45] after examining 90 patients with persistent and permanent AF, showed that CRP and interleukin (IL)-6 were positively related to left atrial diameter, and that a significant relationship existed between IL-6 levels and AF duration before cardioversion.

It is also likely that inflammation is involved during electrical remodeling, in particular by increasing the inhomogeneity of atrial conduction and consequently prolonging atrial conductivity. Ishii and associates[19] examined 24 normal dogs and randomly divided them into 4 equal-sized groups: a control group that had anesthesia alone; a pericardiotomy group that had anesthesia and a pericardiotomy; an atriotomy group that underwent anesthesia, pericardiotomy, and a 5-cm lateral right atriotomy; and an anti-inflammatory group that underwent anesthesia, pericardiotomy, and a 5-cm lateral right atriotomy but with 2 mg/kg/d of methylprednisolone administered continuously for one week. Myocardial inflammation was quantified by myeloperoxidase activity, whereas inhomogeneous atrial conduction was quantified by the variation coefficient of the maximal local activation-phase difference. The authors found that inhomogeneous atrial conduction in the atriotomy and pericardiotomy groups was proportionally increased in comparison with the control group, and that anti-inflammatory therapy decreased the inhomogeneity after atriotomy. Moreover, AF duration was longer in the atriotomy and pericardiotomy groups than in the control and anti-inflammatory groups.[19] Ryu and co-authors[21] subjected 5 dogs to sterile pericarditis and showed that inflammation was associated with altered distribution of atrial connexins 40 and 43—major gap-junction proteins in the atrial myocardium that

TABLE I. Current Understanding of Correlation between Inflammation and Atrial Fibrillation

Investigative Findings	Evidence	Supporting References
Inflammation has a role in AF pathogenesis	Histologic evidence of inflammation in atrial biopsy specimen	Morgera T, et al.[12] (1992) Frustaci A, et al.[13] (1997) Narducci ML, et al.[14] (2011)
	Autoimmune myocarditis markers in AF	Maixent JM, et al.[15] (1998)
	Postoperative AF involves inflammatory mediators	Bruins P, et al.[16] (1997) Mandal K, et al.[17] (2004) Lo B, et al.[18] (2005)
	Inflammation contributes to inhomogeneity of atrial conduction	Ishii Y, et al.[19] (2005) Tselentakis EV, et al.[20] (2006) Ryu K, et al.[21] (2007)
	Inflammation markers are good predictors of occurrence and recurrence of AF	Aviles RJ, et al.[22] (2003) Dernellis J and Panaretou M[23] (2006) Marott SC, et al.[24] (2010) Marcus GM, et al.[25] (2010) Lin YJ, et al.[26] (2010) Liu J, et al.[27] (2011) Chang SN, et al.[28] (2012) Acevedo M, et al.[29] (2012)
	Pre-cardioversion hs-CRP levels predict AF relapse	Celebi OO, et al.[30] (2011)
	Anti-inflammatory therapy reduces risk of AF	Deftereos S, et al.[31] (2012) Pena JM, et al.[32] (2012)
AF generates an inflammatory response	Myocyte calcium overload caused by AF may lead to cell death by activation of calpains or binding (in presence of Ca^{2+} ions) of CRP to phosphatidylcholine	Hack CE, et al.[33] (1997) Aimé-Sempé C, et al.[34] (1999) Goette A, et al.[35] (2002)
	AF was the only independent predictor of elevated CRP levels	Yao SY, et al.[36] (2009)
	Restoration and maintenance of sinus rhythm result in a gradual decrease of hs-CRP	Kallergis EM, et al.[37] (2008)
	AF results in sequestration of inflammatory cytokines in the heart	Marcus GM, et al.[25] (2010)
Elevation of CRP levels during AF is a consequence of heart failure	LV end-diastolic pressure is closely associated with CRP	Shah SJ, et al.[38] (2006)
	LV mass, LV end-systolic diameter, and left atrial diameter are predictors of elevated CRP and of paroxysmal AF	Watanabe T, et al.[39] (2005)
	Heart failure is a risk factor for AF	Benjamin EJ, et al.[40] (1994) Ehrlich JR, et al.[41] (2002)
No support for a relationship between AF and inflammation	—	Kallergis EM, et al.[37] (2008) Yao SY, et al.[36] (2009)

AF = atrial fibrillation; Ca = calcium; CRP = C-reactive protein; hs-CRP = high-sensitivity C-reactive protein; LV = left ventricular

are responsible for cell-to-cell conduction of the action potential. Irregular production of these proteins might alter intercellular communication, reducing conduction within the atrial myocardium and creating an arrhythmogenic substrate for AF.[46] This concept was supported by Sawaya and coworkers,[47] who achieved the down-regulation of connexin 40 (but not of connexin 43) in 8 transgenic mice by means of targeted overexpression of tumor necrosis factor in the pericardium.

The most support for correlation between AF and inflammation derives from studies that have related inflammatory biomarkers to the dysrhythmia. Among the first such observations was the correlation between postoperative AF and the degree of systemic inflammatory response after coronary artery bypass grafting (CABG). Lo and co-authors[18] showed that high baseline CRP levels were associated with an increased risk of postoperative AF. Gaudino and colleagues[48] showed that the promoter polymorphism –174G/C IL-6 gene influenced the inflammatory response to CABG and was associated with postoperative AF. In addition, CABG patients who had low IL-2 levels when undergoing CABG had a reduced incidence of postoperative AF.[49] Marcus and associates,[50] in studying 971

coronary heart disease participants in the Heart and Soul Study, found that high levels of IL-6 were associated with the risk of AF. Other investigators associated serum IL-6 levels with AF after CABG,[51] after cardioversion,[52] and after radiofrequency catheter ablation.[53] Aviles and associates[22] performed a cross-sectional study of 5,806 subjects and reported that baseline levels of CRP were higher in patients affected by AF even after adjustment for multiple variables potentially associated with AF, and that CRP level is a strong predictor of future AF. Among 5,491 patients included in the longitudinal study, 897 (16%) developed AF during the follow-up period (median duration, 7.8 yr). Patients in higher CRP quartiles at baseline had a higher risk of developing AF during the follow-up period.[22] Marott and colleagues[24] monitored 10,276 subjects from the Copenhagen City Heart Study for 12 to 15 years for incident AF; CRP levels in the upper versus lower quintiles were associated with a 2.19-fold increased risk of AF after adjustment for age, sex, and statin use.[24] In a population-based cohort of 1,011 patients, Dernellis and Panaretou[23] explored whether the CRP-related incidence of AF was modified by components of the complement systems C3 and C4, with 4 years of follow-up data. Patients with high CRP and high complement levels had a significantly higher risk of AF than did those with normal CRP and low complement levels; conversely, absent a high complement level, high CRP levels were not significantly associated with AF.[23] Acevedo and co-authors[29] compared the baseline CRP levels of 130 patients who had newly diagnosed nonvalvular AF with those of 20 healthy individuals and found that baseline CRP levels were significant and independent predictors of recurrent AF upon one-year follow-up examination, independent of other clinical and echocardiographic variables. Celebi and colleagues[30] evaluated the prognostic value of before- and after-cardioversion CRP levels in predicting the long-term risk of AF. They enrolled 216 patients who had persistent AF; the CRP levels were before cardioversion. After 12 months, basal CRP levels were significantly higher in the patients who had an AF relapse than in those who did not. Other investigators found correlation between baseline CRP levels and the risk of recurrent AF after ablation attempts by circumferential pulmonary vein isolation[27] and catheter ablation.[26]

Inflammation might be involved in the prothrombotic state during AF.[54] Inflammatory cells such as monocytes, macrophages, and lymphocytes produce cytokines and chemokines and can trigger and sustain thrombosis in AF. Interleukin-6 and CRP levels were found to be elevated in patients who had a dilated left atrium and poorly functioning left atrial appendage,[55] and CRP has been correlated with established clinical stroke-risk stratification scores such as $CHADS_2$ and Stroke Prevention in Atrial Fibrillation. The highest CRP levels were found in patients who had a moderate-to-high risk of stroke.[56] Interleukin-6 induces the expression of tissue factor, fibrinogen, factor VIII, and von Willebrand factor, mediating a prothrombotic state. In addition, endothelial function might contribute to inflammation and thrombosis in AF[57]: von Willebrand factor and soluble P-selectin, released by activated endothelial cells, contribute to the development of a proinflammatory and prothrombotic state that mediates the adhesion of leukocytes to the endothelium.

Atrial Inflammation: Cause or Effect?

Inflammatory processes have been associated with AF, but it is uncertain whether this represents the cause or the effect of inflammation. Moreover, it is unclear whether inflammation has the same effect in normal atria and in atria that have undergone substantial structural remodeling.[58]

Factors Favoring a Role of Inflammation in the Initiation of Atrial Fibrillation. Evidence implicating inflammation in the initiation of AF includes the following:

1) The prevalence of AF is higher in the presence of inflammatory states such as cardiac surgery, myocarditis, pericarditis, and sepsis.[59]
2) Baseline CRP levels predict the occurrence and recurrence of AF.
3) Immunosuppressive therapy with glucocorticoids reduces AF recurrence, and this antiarrhythmic effect correlates with a decrease in plasma CRP levels. Ho and Tan[60] performed a meta-analysis of 3,323 patients from 50 randomized controlled clinical trials in which corticosteroids were compared with placebo or an equal volume of normal saline solution, initiated before or at the time of cardiopulmonary bypass. The authors found that corticosteroid prophylaxis reduces the risk of AF in comparison with placebo (25.1% vs 35.1%; $P < 0.01$) and that the prophylaxis was associated with reduced concentrations of IL-6 and high-sensitivity CRP 24 hours after surgery.[60] Similar results have been found with the use of colchicine to reduce AF recurrence after pulmonary vein isolation.[31]
4) Statins have anti-inflammatory properties. In the JUPITER trial, 17,120 individuals without prior histories of arrhythmia were selected for underlying inflammation (high-sensitivity CPR, >2 mg/L) and were randomized to receive either 20 mg/d of rosuvastatin or a placebo. When compared with placebo, allocation to rosuvastatin was associated with a 27% reduction in the relative risk of developing AF during the trial period.[32] Beyond this, a series of studies revealed the efficacy of statins in reducing AF in patients undergoing CABG, to the point that these drugs became a class IIa recommendation in the 2010 European Society of Cardiology Guidelines for CABG.[61]

5) Inflammatory cytokines have an arrhythmogenic effect on atrial myocardium. Tselentakis and colleagues[20] quantified the conduction properties of 6 normal canine right atrial appendages as a function of the direction of impulse propagation with and without 80 μM of arachidonic acid. The inflammatory mediator produced an anisotropic and rapidly reversible decrease in conduction velocity, transverse to the long axis only.

Does C-Reactive Protein Have a Direct Role in the Generation of Atrial Fibrillation?

Marott and colleagues[24] concluded that elevated plasma CRP in itself does not increase the risk of AF. When individuals underwent genotyping for 4 CRP gene polymorphisms, positive results were associated with as much as a 63% increase in plasma CRP levels, but not with an increased risk of AF. Conversely, a direct role of CRP is supported by Narducci and associates.[14] By means of immunohistochemical analysis, they found the intracytoplasmic localization of CRP in isolated atrial cardiomyocytes in 13 of 23 atrial specimens from patients with AF and in no atrial specimens from a control group. Furthermore, CRP in human atrial tissue was unrelated to serum CRP levels in AF patients, which would explain why the results of this study[14] differed from those of Marott and colleagues. It is likely that AF involves a sequestration of inflammatory cytokines in atrial tissue: Marcus and associates[25] found that the difference between left atrial and coronary sinus CRP levels was significantly greater in patients who had AF at the time of the blood draw than in patients who were in sinus rhythm during that time. Chang and coworkers[28] showed that changes in the promoter region regulated the CRP gene that influences the risk of AF: the –390A variant was associated with greater CRP gene-promoter activity, a higher plasma CRP level, and a higher risk of AF. Further analysis showed that CRP significantly increased the inward L-type Ca current in atrial myocytes with no changes in other ionic currents and without affecting expressions of gene-encoding procollagens in atrial fibroblasts. This suggests that CRP increases the risk of the AF-increasing Ca influx in atrial myocytes, but not because of atrial fibrosis.[28]

Factors Not Favoring a Role of Inflammation in the Pathogenesis of Atrial Fibrillation. Evidence against a primary role of inflammation in AF includes the following:

1) The restoration and maintenance of sinus rhythm results in a gradual decrease in CRP levels. Kallergis and colleagues[37] examined 52 patients whose AF had persisted for 3 months and measured their CRP levels before and after successful electrical cardioversion. Those who were in sinus rhythm one month later had significantly lower CRP levels than at baseline; conversely, subjects whose AF recurred had no differences in CRP levels during the study, suggesting that AF by itself induces inflammation.
2) No significant difference was found in CRP levels between persistent AF and episodes of AF in paroxysmal AF, and between the absence of AF in paroxysmal AF and its absence in control subjects. Yao and associates[36] enrolled 411 patients who had lone AF and found that the presence of AF was the only independent predictor of elevated CRP levels.

Although the mechanisms by which AF might cause inflammation are unknown (Fig. 1), it has been hypothesized that the myocyte Ca overload caused by AF leads to cell death[34] mediated by the activation of calpains[35] or by the binding (in the presence of Ca^{2+} ions) of CRP to phosphatidylcholine-generating long-chain acylcarnitines and lysophosphatidylcholines. These mechanisms lead to cellular membrane dysfunction, energy depletion, and apoptosis,[33] and might induce a low-grade inflammatory response—including healing and repair that bring about adverse structural and electrical changes and might also explain the significant difference in CRP levels during AF in the left atrium and coronary sinus.[14]

In some cases, both the elevation of CRP and the onset of AF might be consequences of heart failure; indeed, Shah and colleagues[38] have shown, in 98 patients undergoing cardiac catheterization, that left ventricular end-diastolic pressure is closely associated with CRP level. On the other hand, heart failure is a recognized risk factor for AF.[40,41]

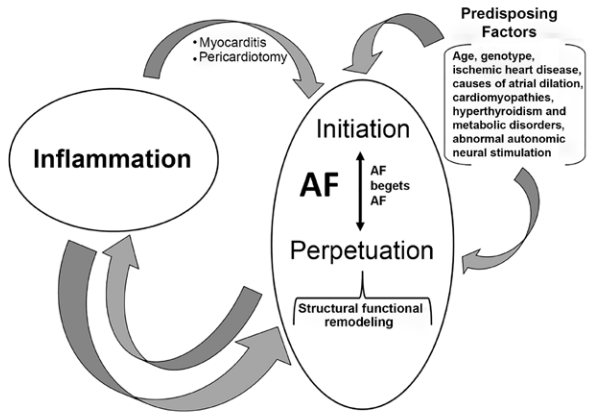

Fig. 1 *Diagram shows the relationship between atrial fibrillation (AF) and inflammation. Inflammation might contribute to initiating AF (as in myocarditis and pericardiotomy) and perpetuating AF (as one of many cofactors that together contribute to remodeling). On the other hand, AF might generate an inflammatory response, as shown by the normalization of C-reactive protein levels after cardioversion.*

Future Directions

Understanding the pathogenesis of AF and the relationships between inflammation and AF is of both academic and clinical interest, because insights might lead to better prevention and treatment of this common but dangerous dysrhythmia. The detailed imaging of inflammation by positron emission tomographic or molecular means[62] might help to clarify the role of inflammation in AF, and microRNA could prove to be of substantial value in the study of tissue and circulating biomarkers.[63] If and when a causal link between inflammation and AF is proved, novel approaches to targeting inflammation, including anti-IL-1 and tumor necrosis factor-α antibodies and microRNA antagonists or mimics,[64-66] might lead to better therapeutic options.

Conclusion

Despite the evidence linking inflammation with AF, the role of inflammation as an initiating event in the development of AF remains debatable. However, on the basis of the current evidence, it is likely that inflammation is involved in electrophysiologic and structural atrial remodeling—processes integral to the development and perpetuation of AF—and that the dysrhythmia subsequently generates an inflammatory response that contributes to remodeling. We need a better understanding of the pathophysiology of AF in order to develop new therapeutic approaches.

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