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STATE-OF-THE-ART PAPER

Role of Inflammation in Initiation and Perpetuation of Atrial Fibrillation

A Systematic Review of the Published Data

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Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. Recent studies have indicated that inflammation might play a significant role in the initiation, maintenance, and perpetuation of AF. Inflammatory markers such as interleukin-6 and C-reactive protein are elevated in AF and correlate to longer duration of AF, success of cardioversion, and thrombogenesis. Furthermore, the inflammatory process might be modulated by the use of statins, angiotensin-converting enzyme inhibitors, or glucocorticoids. The purpose of this study is to analyze the current published reports on the relationship between inflammation and AF and the potential therapeutic options available to modulate the inflammatory milieu in AF. (J Am Coll Cardiol 2007;50:2021–8)

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. It is often rapid, irregular, and might arise from multiple ectopic atrial foci (1,2). Twenty percent of patients with paroxysmal atrial fibrillation (PAF), defined as lasting <7 days (and spontaneous conversion), progress to chronic (persistent or permanent) AF, defined as lasting >30 days (1,2–5). The prevalence of AF—affecting more than 2.3 million people in the U.S.—increases dramatically with age and is seen in as high as 9% of individuals by the age of 80 years (1). In high-risk patients, the thromboembolic stroke risk can be as high as 9% per year and is associated with a 2-fold increase in mortality (1,2). The purpose of this study is to analyze the current published reports on the role of inflammation in the perpetuation and maintenance of AF and potential therapeutic options available to modulate this inflammatory process.

Methods

A comprehensive search of published reports with PubMed was done on the topics of AF and inflammation. Additional key words included interleukin (IL)-6 and C-reactive protein (CRP). Criteria for consideration were abstracts and journals written in English between 1995 and 2007. A total of 65 journal articles were reviewed in this paper. Emphasis was placed on abstracts and journals linking AF to inflammation and potential treatment modalities such as statins, angiotensin-converting enzyme (ACE) inhibitors, and glucocorticoid therapy.

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Pathophysiology

Although the pathophysiological mechanism underlying the genesis of AF has been the focus of many studies, it only remains partially understood. Conventional theories focused on the presence of multiple re-entrant circuits originating in the atria that are asynchronous and conducted at various velocities through tissues with various refractory periods (2). Recently, rapidly firing atrial activity in the muscular sleeves around the pulmonary veins ostia have been described as potential mechanism for AF (3).

The development of AF leads to structural and electrical changes in the atria, a process known as remodeling. These changes further perpetuate the existence and maintenance of this arrhythmia (i.e., "atrial fibrillation begets atrial fibrillation") (4). Electrical remodeling has been reported to begin within a few hours after the onset of AF, whereas the structural changes begin to develop after several weeks, thus cardioversion after 24 h becomes increasingly difficult (5).

Much attention has been devoted in the past few years to assess the role of inflammation in AF. The contribution of the inflammatory cascade to the onset of AF is suggested by the high incidence of AF in post-operative cardiac surgeries, a state of intense inflammatory process (6,7,8). Other studies have suggested that inflammation leads to "atrial myocarditis" with subsequent electrical and structural atrial changes, resulting in initiation and maintenance of AF (5,9). Also left atrial dysfunction has been described in patients with increased CRP but without AF, suggesting that inflammation per se affects left atrial function (10).

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AERP = atrial effective refractory period
AF = atrial fibrillation
ARB = angiotensin receptor blocker
CABG = cardiac bypass surgery
CRP = C-reactive protein
DCCV = direct current cardioversion
IFN = interferon
IL = interleukin
PAF = paroxysmal atrial fibrillatioin
RAS = renin-angiotensin system
SEC = spontaneous echo contrast
TGF = transforming growth factor
TNF = tumor necrosis factor

Inflammatory Biomarkers

Cytokines are intracellular polypeptides produced by activated cells, usually monocytes and macrophages, in response to inflammatory stimuli. They are paramount in activating the inflammatory cascade and in the production of acute-phase proteins. The primary inflammatory-mediated cytokines include IL-6, tumor necrosis factor (TNF)-α, IL-1β, interferon (IFN)-γ, transforming growth factor (TGF)-β, and IL-8. Interleukin-6, however, is the primary stimulator of acute-phase proteins. One such acute-phase protein that is the center of much research is CRP. Measurement of acute-phase proteins, such as CRP, can provide a window into the current inflammatory status of a patient (6–9).

Many studies have related an increase in CRP and IL-6 in both PAF and persistent AF (9–12). Studies have already correlated elevation of CRP in healthy individuals to an increased future risk of cardiovascular disease, cerebral vascular events, and peripheral arterial disease (13–16). Elevation of CRP and IL-6 might also contribute to generation and perpetuation of AF, as evidenced by marked inflammatory infiltrates, myocyte necrosis, and fibrosis found in atrial biopsies of patients with lone AF (7–11). Complement activation has also been described in a cohort of patients with AF without other associated inflammatory diseases (8). It has been suggested in 1 population-based cohort of 1,011 patients who were followed up to 4 years that, in the absence of high baseline complement component levels (C3 and C4), a high baseline CRP level is not significantly associated with a high incidence of AF (17).

The exact mechanism of inflammation leading to tissue remodeling in AF patients is unclear and warrants further research. It is thought that AF leads to myocyte calcium overload, promoting atrial myocyte apoptosis. C-reactive protein might then act as an opsonin that binds to atrial myocytes, inducing local inflammation and complement activation. Tissue damage then ensues and fibrosis sets in (9,16,18). Specifically, in the presence of Ca^{2+} ions, CRP binds to phosphatidylcholine. Long-chain acylcarnitines and lysophosphatidylcholines are generated from phosphatidylcholine and can further contribute to membrane dysfunction by inhibiting the exchange of sodium and calcium ions in sarcomeres. This can eventually lead to the maintenance of AF (9,16,17).

AF in post-operative inflammation. The inflammatory cascade and catecholamine surge associated with surgery might play a prominent role in initiating atrial tachyarrhythmias after cardiac surgery. It has been reported to occur in up to 40% of patients undergoing cardiac bypass surgery (CABG) or up to 50% of patients undergoing cardiac valvular surgery (3,4). After cardiac surgery, the complement system is activated and pro-inflammatory cytokines are released. Bruins et al. (8) found that IL-6 rises initially and peaks at 6 h after surgery and a second phase occurs in which CRP levels peak on post-operative day 2, with complement-CRP complexes peaking on postoperative day 2 or 3. The incidence of atrial arrhythmias follows a similar pattern and peaks on post-operative day 2 or 3 (4–8). Another study correlated leukocytosis to an increased incidence in AF in post-operative cardiovascular patients (18).

At a molecular level, Burzotta et al. (19) discovered that the development of postoperative AF was linked to 174G/C polymorphism of the IL-6 promoter gene. In this particular study of 110 patients undergoing CABG, genetic analysis revealed that the GG genotype was associated with higher IL-6 plasma levels and, subsequently, a greater inflammatory burden. Similarly Gaudino et al. (20) established a genetic link between inflammation and AF and found that the GG genotype was an independent predictor of post-operative AF.

AF in nonoperative inflammation. Current evidence suggests that inflammation might also play a prominent role in both the etiology and maintenance of nonoperative onset of AF (21). Numerous studies (Table 1) have reported specifically on the association of CRP with the development and maintenance of AF. The study by Chung et al. (10) was one of the first to demonstrate an association in elevated CRP levels with the onset of AF in a nonoperative setting. The CRP levels were more than 2-fold higher in patients with AF than in the control subjects. Furthermore, patients with persistent AF had higher CRP levels than those with PAF, suggesting that inflammation plays a role in the maintenance of AF.

Around the same time, Dernellis and Panaretou (16) reported similar results. They demonstrated that CRP elevation was present in patients with PAF and that CRP levels were higher in patients who failed cardioversion with amiodarone. Many studies have since drawn similar conclusions (Table 1), thus validating the notion that inflammation plays a viable role in the perpetuation and maintenance of AF. It is now known that CRP levels in patients with persistent AF are higher than in those with paroxysmal AF, and levels in both groups are higher than those in the control group (9,16). Moreover, lower CRP levels have also been correlated to increased success rate of electrical cardioversion and subsequent maintenance of normal sinus rhythm (16,21–28). Dernellis and Panaretou (22) reported that for every 1-mg/dl increase in serum CRP, the risk for recurrent AF is increased 7 times and the risk for permanent AF is 12 times greater than control. Currently, it remains