HOSPITAL CHRONICLES 2009, 4(1): 29–35

REVIEW

The Emerging Role of Inflammation and Fibrosis in Atrial Fibrillation and the Potential of Counter Interventions

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KEY WORDS: *atrial fibrillation; inflammation; fibrosis; renin-angiotensin system; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; statins; thrombo-embolism; C-reactive protein*

ABBREVIATIONS
ACE = angiotensin-converting enzyme
AF = atrial fibrillation
ARB = angiotensin receptor blocker
CAD = coronary artery disease
CHF = congestive heart failure
CRP = C-reactive protein
IL = interleukin
PUFA = polyunsaturated fatty acids
RAAS = rennin-angiotensin aldosterone system
TGF = tissue growth factor
TNF = tumor necrosis factor

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ABSTRACT

There are now emerging data to support the association between inflammation and atrial fibrillation (AF). Initial observations were made after coronary artery bypass surgery, noting a peak incidence of AF on the second and third post-operative days, which coincided with the peak elevation of CRP levels. This association was subsequently shown in several other situations of AF. Data also emerge which link the renin-angiotensin aldosterone system (RAAS) to this inflammatory process. A putative link between inflammation and thromboembolic complications of AF has also been suspected. Given the important role of the RAAS in inflammation and AF, it could be postulated that interruption of the RAAS may exert positive effects upon this process. Statins with their anti-inflammatory action as part of their pleiotropic effects, as well as other anti-inflammatory agents, such as steroids and fish oils, might be of help in AF therapy according to some clinical studies. Finally, there appears to be a connection with atrial fibrosis in AF, as increased atrial fibrosis has been shown to correspond to an increase in conduction heterogeneity and AF vulnerability. Thus, inflammation and fibrosis may constitute new therapeutic targets in the management of AF. More studies are needed to clarify these important issues.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, affecting approximately 0.9% of the population.[1] The prevalence of AF is strongly age-dependent, affecting approximately 1% of persons aged 65 years and 5% of individuals older than 65 years.[2] AF is also associated with an increase in the relative risk of mortality ranging from 1.3 to 2.34, independent of other risk factors as well as an increasing morbidity and adversely affects quality of life.[3-5] Unfortunately, current rhythm control strategies are far from ideal. Data from five comparative studies of a primary rate control vs. rhythm control strategy for patients with a history of AF failed to show a significant superiority of rhythm control.[6-10] In fact, these studies merely emphasized the limited efficacy and high side-effect profile of the currently available anti-arrhythmic drugs.[11]

Presented in part at "**Athens Cardiology Update 2008**", International Cardiology Symposium of Evagelismos General Hospital of Athens, Athens, Greece, April 17-19, 2008

INFLAMMATION AND ATRIAL FIBRILLATION

There is now an increasing body of evidence linking inflammation to a broad spectrum of cardiovascular conditions, such as coronary artery disease (CAD), insulin resistance and diabetes mellitus, and hypertension.[12-16] In addition, there is emerging data to support the association between inflammation and AF.[17-18]

The pathophysiology of AF is highly complex. It is now recognized that the development of AF leads to functional changes within the atria that perpetuate the arrhythmia ('AF begets AF'), by a process known as electrical remodeling.[19] Structural remodeling of the atria occurs in parallel with the changes of electrical remodeling. The structural changes which define this structural remodeling include left atrial dilatation and increasing atrial fibrosis.[20] Key to this fibrotic process is the deposition of increased amounts of connective tissue between individual cells and with the deposition of large amounts of collagen and fibronectin.[21] Bruins et al. were the first to propose the inflammation-AF hypothesis, following their observations of an increased frequency of AF after coronary artery bypass surgery. They noted that the peak incidence of AF occurred on the second and third post-operative days, which coincided with the peak elevation of CRP levels.[22]

Histological evidence to support the association between inflammation and AF has been derived from several sources.[23-27] Results of atrial biopsies taken from patients in AF compared with controls have demonstrated evidence of inflammatory infiltrates and oxidative damage within the atrial tissue. The inflammatory markers that have been most frequently studied are high-sensitivity C reactive protein (hs-CRP) and interleukin (IL)-6. Levels of hs-CRP have been noted to be higher among patients with AF compared with controls in sinus rhythm. Also, persistent AF patients have higher hs-CRP levels than paroxysmal AF patients, and both have higher levels than controls.[28-35] Furthermore, a longer duration of AF is associated with higher hs-CRP levels and larger left atrial dimensions, supporting a link between the burden of AF, inflammation, and structural remodelling. In both cross-sectional and longitudinal studies, hs-CRP has remained a consistent and significant predictor of early AF relapse after successful cardioversion, even after adjustment for risk factors for AF, such as hypertension and CAD. hs-CRP has also been shown to be predictive of subsequent future development of new cases of AF among a large cohort of patients in sinus rhythm.[30-32,34] IL-6 levels would be raised in patients with AF compared with healthy controls.

There have been five studies which have investigated the relationship between IL-6 and AF. Four of these studies found increased levels of IL-6 in patients with AF compared with healthy controls, with one failing to find any association.[28-30,35,36] So far, there has been only one study that has looked into the possible association between TNF-a and AF. This was a very small study and did not adjust for confounding factors; however, it did demonstrate increased levels of TNF-a in patients with AF compared with healthy controls in sinus rhythm.[28] Finally, there appears to be a relationship between elevated white blood cell count as a marker of inflammation and the development of AF after cardiac surgery in 181 consecutive patients undergoing coronary bypass or cardiac valve surgery (AF), even after multivariate analyses.[37]

There is histological evidence to confirm that AF (both persistent and paroxysmal) leads to altered angiotensin II receptor expression. In a key paper, Cardin et al. were able to link increased atrial expression of angiotensin II receptors with increased atrial cell death and leukocyte infiltration supporting a potential link between the RAAS, inflammation, and AF. Furthermore, there is now evidence linking polymorphisms in the renin–angiotensin system (RAS) gene with an increase risk of subsequent AF development, further supporting the role of the RAAS in the development of AF.[38-43]

Although there appears to be a link between inflammation and AF, one of the key questions is whether the observed inflammation in AF increases the risk of thromboembolism as has been demonstrated for atherosclerotic models. Conway et al. were the first to confirm this putative link between inflammation and complications of AF. In a small pilot study, they showed that elevated IL-6 levels were an independent predictor of the composite of stroke or death among a cohort of 77 high-risk AF patients.[44] This observation was complemented by data from Thambidorai et al, which showed that trans-esophageal risk factors for stroke were greater for patients with elevated hs-CRP compared those with normal levels among 104 patients with AF.[45] Hence, there appears to be an established link between inflammation, AF, and thrombosis.

PREVENTING AF BY MODULATING THE INFLAMMATORY STATE

There have been a large number of studies that have analyzed the relationship between **RAAS inhibition and AF**. In a recent large meta-analysis (56308 patients) incorporating 11 of the 12 randomized trials using either ACE-inhibitors or ARBs for the prevention of AF, Healey et al. demonstrated a favorable effect of RAAS inhibition in the primary and secondary prevention of AF. They concluded that ACE-inhibitors/ARBs reduced the overall risk of AF by 28% [95% confidence interval (CI) 15–40%, P: 0.0002] across a broad spectrum of patient subgroups (including patients with hypertension, heart failure, post-myocardial infarction, and post-cardioversion). Furthermore, the reduction in AF was similar independent of whether an ACE-inhibitor or an ARB was the main drug group used (ACE-inhibitors: 28%, P:0.01; ARBs: 29%, P: 0.00002).[46]

There have been several putative mechanisms to explain the favorable actions of ACE-inhibitors and ARBs in the prevention of AF: decreased atrial stretch; lowered end-diastolic left ventricular pressure and subsequent left atrial pressure; the

prevention of atrial fibrosis; the modification of sympathetic tone, alteration in ion currents and atrial refractoriness, and direct anti-arrhythmic effects.[47] However, given the demonstrated important role of the RAAS in inflammation and AF, it could be postulated that interruption of the RAAS may exert positive effects upon the left atrium by reducing atrial inflammation, oxidative stress, and reduce atrial remodelling.

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, remain the most powerful and effective lipid-lowering drugs. A series of landmark clinical trials have established statins as effective agents in the primary and secondary prevention of coronary artery disease. It has become increasingly apparent that the benefits of statins extend to mechanisms beyond their cholesterol-reducing effects. These 'pleiotropic' (multiple) effects include improved endothelial function with increased nitric oxide bioavailability, anti-thrombotic effects, enhanced stability of the atherosclerotic plaque, and decreased oxidative stress and vascular inflammation. If AF is indeed linked to inflammation then statins would offer a potentially preventative role in AF. There have been five studies so far that have analyzed the efficacy of statins in the prevention of AF.[48-52] Four of these studies showed favorable effects of statins to reduce the incidence of AF, with only one study reporting negative results. Siu et al were the first to study the prevention of AF with statins. They retrospectively studied 62 patients with lone persistent AF lasting 3 months who underwent direct current cardioversion, and observed that statin- treated patients (n = 10) had less recurrent AF than the control group of 52 patients (40 vs. 84%, P: 0.0007); however, this was a very small and underpowered observational study.[53] In a much larger observational study, Young- Xu et al. 166 studied a cohort of 449 patients with CAD at high risk of AF. They observed a significantly lower rate of new AF development among statin users (9%) compared with non-users (15%). Of note, the potential impact of statins on AF development was independent of its cholesterol-lowering ability. Also, the efficacy of statins in preventing AF appeared to correlate with the length of statin use, with longer statin use being associated with greater protection against the subsequent development of AF.[54] In the largest study so far, Hanna et al. performed a cross-sectional analysis of 25,000 patients enrolled in the multicenter Guidant-sponsored Advancement Heart Failure Registry; of these patients, 7027 patients (27%) developed AF, and statin therapy led to a 23% reduction in AF, when compared with those not treated, even after multivariate analysis (odds ratio for AF 0.685; P , 0.001).[55]

STEROIDS

In a double-blind study, Dernelis and Panaretou randomized 104 patients with first presentation persistent AF to low-dose glucocorticoid therapy (16 mg methyl prednisolone for 4 weeks tapered to 4 mg for 3 months) or placebo.[56] A primary rhythm control strategy involving amiodarone & cardioversion was adopted in all of the patients as part of the trial protocol. All patients were successfully cardioverted and were commenced on oral propafenone post-cardioversion. The authors found that methyl prednisolone significantly reduced the primary endpoint of AF recurrence (50% in the placebo group vs. 9.6% in the glucocorticoid group) as well as the extended endpoint of permanent AF (29% in the placebo group vs. 2% in the glucocorticoid group). In addition, hs-CRP concentrations were a significant predictor of the primary end-point, with higher hs-CRP levels being predictive of AF recurrence, and vice versa. In addition, methyl prednisolone significantly lowered hs-CRP by an average of 80% within the first month, and this reduction was maintained for the duration of the 30-month study (P=0.001). The authors also demonstrated that the risk of AF recurrence was increased by approximately seven times for each 1 mg/dL increase in plasma levels of hs-CRP, providing a strong link between the degree of inflammation and the burden of AF.

FISH OILS

Dietary intake of polyunsaturated fatty acids (PUFAs), notably omega (n)-3 fatty acids, have been to shown to have favorable effects on cardiovascular outcomes. Their efficacy can only be partly explained by improvement in lipid profile and there is mounting evidence to support potential anti-inflammatory and antioxidant properties of oily fish. Indeed, n-3 fatty acids have anti-inflammatory properties and are frequently used clinically to treat symptoms of inflammatory diseases, such as rheumatoid arthritis or Crohn's disease.[57,58] In a prospective, population-based cohort of 4815 older (>65 years) Mozaffarian et al. demonstrated that consumption of high levels of fish containing n-3 fatty acids was associated with a lower incidence of subsequent AF development.[59] However, these results are challenged by an even larger prospective study of 47 949 participants (mean age: 56 years) which investigated the relation between the consumption of n-3 fatty acids from fish, by use of a detailed semi-quantitative food questionnaire, and risk of AF or flutter, but found that consumption of n-3 fatty acids from fish was not associated with a reduction in risk of AF or atrial flutter.[60] Finally, in a recently published study of 160 patients pre-treatment with omega-3 fatty acids reduced the incidence of AF post-coronary artery bypass surgery by 58% compared with patients treated with usual care only.[61] In this study, 2 g/day of PUFAs was administered at least 7 days before surgery and continued until discharge. In addition, treatment with fish oils reduced the length of hospitalization from 8.2 to 7.3 days (P:0.017).

VITAMIN C

Ascorbic acid (vitamin C) is potent oxygen scavenger, which may potentially modulate the inflammatory and oxidative abnormalities associated with AF.[62] In a novel study, Carnes et al. gave supplemental ascorbate to 43 patients

before, and for 5 days following, cardiac bypass graft surgery, and found that ascorbate significantly reduced the incidence of post-operative AF (16.3% in ascorbate treated vs. 34.9% in control subjects).[63] They also showed that atrial peroxynitrate (a known ROS) formation was increased during rapid atrial pacing and that atrial ascorbate levels were reduced following atrial pacing. The current evidence would thus support the hypothesis that vitamin C attenuates atrial electrophysiological remodelling and reduces AF burden, possibly via the scavenging peroxynitrite and other reactive oxygen species, and reducing the inflammatory substrate.

ATRIAL FIBRILLATION AND ATRIAL FIBROSIS

Which mechanism of AF is characteristic in a setting of atrial fibrosis is unknown, as evidence exists for both reentry and discrete, stable foci as an AF mechanism in dogs with pacing-induced CHF. Li et al showed a mechanism of macroreentry with conduction abnormalities providing the milieu for AF propagation before termination with dofetilide, an IKr channel blocker. In contrast, this study also showed in a model of rapid atrial pacing that multiple wavelets were the likely mechanism, and dofetilide was ineffective in terminating AF. The rapid atrial pacing model has atrial electrical remodeling and little in the way of structural remodeling. The CHF model does not have any significant atrial electrical remodeling (at least none that contributes substantially to the AF substrate) but has substantial atrial structural remodeling.[64,65] Stambler et al suggested that AF in the setting of CHF in dogs was focal in origin caused by triggered activity. This triggered activity was shown to be produced by delayed after-depolarizations initiated by intracellular Ca^{+2} overload. Drugs that reduced intracellular Ca^{+2} levels (verapamil, flunarizine, ryanodine) all terminated AF.[66] Okuyama et al performed high-density mapping of the pulmonary veins during AF in dogs with CHF. In half of the AF episodes recorded in the CHF model, focal activation was seen from within the vein independent of the left atrium. This type of activation was not seen in any of the AF occurring in controls, as the pulmonary veins were activated passively from wavefronts originating from the left atrium.[67]

The precise mechanisms and signaling pathways involved in the development of atrial fibrosis are unknown. It appears, however, that the atrium is more susceptible to atrial fibrosis than is the ventricle, and currently three interrelated pathways appear to be involved the renin–angiotensin system, TGF-1, and the oxidative stress pathways.

Transgenic mouse models of angiotensin- converting enzyme (ACE) over-expression have been shown to result in atrial fibrosis.[68] Several clinical and animal studies have shown that use of ACE inhibitors with CHF reduces the occurrence of AF and AF vulnerability.[69] Use of ACE inhibitors has also been shown to prevent the progression of paroxysmal AF to chronic AF and to increase the efficacy of electrical cardioversion of AF.[70,71] These clinical data suggest that ACE inhibitors may be useful in delaying progression of atrial fibrosis and AF.

In a transgenic mouse model that overexpresses a constitutively active transforming growth factor TGF-β1, selective atrial interstitial fibrosis was observed, but ventricular histology was normal. This occurred despite equal over-expression of TGF-1 in the atrium and the ventricles. The increase in atrial fibrosis was shown to correspond to an increase in conduction heterogeneity and AF vulnerability.[72] Cellular electrophysiology was not affected by the TGF-β1. This study demonstrated that atrial fibrosis alone is a sufficient substrate for AF, and that TGF-β1 may play an important role in the genesis of atrial fibrosis. In another study by the same group, the drug pirfenidone was used to target the expression of TGF-β1. Pirfenidone has been shown to significantly reduce expression of TGF- β1, with a concomitant reduction in tissue fibrosis in multiple experimental animal models.[65] Increases in angiotensin II (AngII) and activated TGF-β1 concentrations reciprocally enhance each other's production[73] and induce expression of additional profibrotic molecules in fibroblasts[74] creating positive feedback cycles for fibrosis. Mechanical stretch induces collagen synthesis[75] along with increased AngII and TGF-β1 expression in cardiac fibroblasts,[76] and thus chronic atrial dilation may contribute to structural remodeling and the domestication of AF.[77] Fibroblast stretch- sensing mechanisms show exquisite sensitivity, with different types of deformation causing differential ECM expression profiles. In addition to profibrotic actions, mechanical stretch of fibroblasts can directly modulate myocyte electrical activity, a potentially proarrhythmic mechanism called mechanoelectric feedback.[78]

CONCLUSION

Inflammation and fibrosis play an important role in the development of AF. Therefore inflammation and fibrosis may constitute new therapeutic targets in the management of AF. More studies are needed to clarify these important issues.

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