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Review

Inflammation in the genesis and perpetuation of atrial fibrillation

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The prevalence and persistence of atrial fibrillation (AF) and the relative inefficacy of the currently available pharmacotherapy requires development of new treatment strategies. Recent findings have suggested a mechanistic link between inflammatory processes and the development of AF. Epidemiological studies have shown an association between C-reactive protein and both the presence of AF and the risk of developing future AF. In case–control studies, C-reactive protein is significantly elevated in AF patients and is associated with successful cardioversion. Moreover, C-reactive protein elevation is more pronounced in patients with persistent AF than in those with paroxysmal AF. Furthermore, treatment with glucocorticoids, statins, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers seems to reduce recurrence of AF. Part of this anti-arrhythmic effect may be through anti-inflammatory activity. This article reviews what is known about inflammation in genesis and perpetuation of AF, the putative underlying mechanisms, and possible therapeutic implications for the inhibition of inflammation as an evolving treatment modality for AF.

Introduction

The prevalence and persistence of atrial fibrillation (AF) and the relative inefficacy of the currently available pharmacotherapy requires development of new treatment strategies. Recent findings have demonstrated a mechanistic link between inflammatory processes and the development of AF, a link that may be a target for more effective treatment and prevention strategies. The aim of the present study was to review the literature on inflammation and AF with emphasis on anti-inflammatory therapies as an evolving treatment modality.

Methods

A comprehensive literature search was performed on the topics of AF, atrial flutter, and inflammation. The search was completed using the PubMed, Webspirs, and ISI web of Knowledge databases, which include MEDLINE, BIOSIS, EMBASE, and Web of science. The searches were constrained to articles and abstracts written in English and published between the year 1990 and April 2005. The keywords searched were in the categories of 'text word' and 'medical subject heading' and included: AF, atrial flutter, inflammation, cytokines, C-reactive protein, interleukin-6, tumour necrosis factor (TNF), hydroxymethylglutaryl-CoA reductase inhibitors, and glucocorticoids. One hundred and forty-eight abstracts were reviewed. Additionally, reference lists of identified articles were reviewed. A total of 69 papers that appeared to meet the inclusion criteria were retrieved for review. Criteria for inclusion were: patients or animals with AF or atrial flutter, a marker of inflammation was specified, and the article or abstract was written in English. In addition, the present review covers selected trails on angiotensin converting enzyme inhibitors, ACE-I, angiotensin receptor blockers (ARBs) and AF. These studies do not fulfil the earlier mentioned inclusion criteria as data on markers of inflammation are missing. However, the studies represent an evolving treatment modality for AF highly relevant in the present context.

Results

Inflammation and AF

Since the 1920s, it has been recognized that the greater the duration of persistent AF, the more resistant the AF is to therapy.[1] In 1995, Wijffels *et al.*[2] demonstrated in conscious goats that AF alters the atrial electrophysiological milieu in a way that AF promotes its own maintenance; 'AF begets AF'. The phenomenon was coined 'atrial remodelling' indicating electrophysiological and structural alterations that promote the maintenance and reoccurrence of AF. The first observation linking atrial remodelling to inflammation was made by Frustaci *et al.*[3] who in atrial biopsies from 12 patients with lone AF demonstrated a high prevalence of inflammatory infiltrates, myocyte necrosis, and fibrosis, whereas biopsies from control patients were normal. Similar findings have been reported by Nakamura *et al.*[4] and confirmed in an animal model where dogs with sustained AF demonstrated active atrial perimyocarditis with inflammatory infiltrates, lipid degeneration, and fibrosis.[5]

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Markers of inflammation

A large number of changes, distant from the site of inflammation and involving many organ systems may accompany inflammation. These systemic changes are referred to as the acute-phase response, even though they accompany both acute and chronic inflammatory disorders.[6] The acute-phase response comprises the non-specific physiological and biochemical responses to most forms of tissue damage, infection, inflammation, and malignant neoplasia. In particular, the synthesis of a number of proteins, acute-phase proteins, is rapidly up-regulated, principally in the hepatocytes, under the control of cytokines origination at the site of pathology.[7] An acute-phase protein is defined as one whose plasma concentration increases or decreases by at least 25% during inflammatory disorders. Cytokines are intercellular signalling polypeptides produced by activated cells. Most cytokines have multiple sources, multiple targets, and multiple functions. The cytokines that are produced during and participate in inflammatory processes are the chief stimulators of acute-phase proteins. The initial cytokines in the cascade are (named in order) tumour necrosis factor α (TNF-α), interleukin-6β, interleukin-6 (IL-6), interleukin-1 receptor antagonist, and soluble TNF-α receptors.[8] They are produced by a variety of cell types, but the most important sources are macrophages and monocytes at inflammatory sites.[6] C-reactive protein, named for its capacity to precipitate the somatic C-polysaccharide of *Streptococcus pneumoniae*, was the first acute-phase protein to be described, and is an exquisitely sensitive systemic marker of inflammation and tissue damage. Other acute-phase proteins include proteinase inhibitors and coagulation, complement and transport proteins, but the only molecule that displays sensitivity, response speed, and dynamic range comparable with those of C-reactive protein is serum amyloid A (SAA) protein. The attention focused on C-reactive protein reflects in part the fact that it is a stable analyte in serum or plasma and that immunoassys for it are robust, well standardized, reproducible, and readily available. In cardiovascular medicine, high-sensitive C-reactive protein has received much attention and several studies now support a link between high-sensitive C-reactive protein and future risk of coronary events.[9] The 'high sensitivity' refers to the lower detection limit of the assay procedures being used. The actual C-reactive protein analyte, the plasma protein, being measured is the same regardless of the assay range. In conclusion, inflammation elicits cytokines, which stimulates the expression of acute-phase proteins such as high-sensitive C-reactive protein. Thus, these markers in serum can provide a window to the inflammatory status of the individual, otherwise inaccessible in the intact subject.[9]

Electrophysiology and inflammation in AF

Theories of the mechanism of AF involve two main processes: a triggering mechanism with enhanced automaticity in one or several rapidly firing atrial or pulmonal foci and the development of multiple reentrant circuits of various diameter and conduction velocities in the atria.[10] The development and perpetuation of these circuits depends on the anatomical and electrophysiological substrate of the atria.[11] The anatomical substrate refers to the atrial architecture (fibrosis, fatty infiltration, etc.), whereas the electrophysiological substrate refers to electrical inhomogeneity (refractory period shortening, loss of rate adaptation, prolongation of atrial conduction velocity, etc.).[10] Whether initiation of AF activates direct inflammatory effects or whether the presence of a pre-existing systemic inflammatory state promotes further persistence of AF remains unclear.[12] Both mechanisms may interrelate indicating that inflammation is not only a response to the underlying arrhythmic process but also an integral part of it. Rapid atrial activation has been shown to induce calcium accumulation within the atrial myocytes leading to overload and in some cases to the initiation of apoptotic loss of atrial myocytes.[11] Such damage of atrial myocardium may trigger a low-grade inflammatory response and be part of a structural remodelling with increased persistence of AF.[13] Alternatively, the presence of systemic inflammation with increased circulating C-reactive protein may predispose patients with triggering atrial foci to the development of AF. C-reactive protein may have a direct role in the mediation of local inflammation because of ligand binding and the ability to activate the classic complement pathway.[14] Local atrial complement activation and hence tissue damage further amplifies systemic as well as local inflammation.[15] Furthermore, C-reactive protein binds to phosphocholine, recognizing phospholipid components of damaged cells and some foreign pathogens[16] which can contribute to membrane dysfunction by inhibiting the exchange of sodium and calcium ions in sacrolemmal vesicles and thus lead to the development of arrhythmia.[17] These mechanisms may contribute to the association between increased markers of inflammation and occurrence of AF.

Inflammation and AF post-surgery

The potential role of inflammation in the occurrence of AF post-surgery has been investigated in studies using different markers of inflammation (*Table 1*). Initially, an association between C-reactive protein and arrhythmia was observed in patients who underwent cardiopulmonary bypass surgery.[14] Apart from changes in acute-phase proteins, the inflammatory response is characterized by haematopoietic changes, i.e. anaemia, thrombocytosis, and leukocytosis. The latter was measured in a study on 181 consecutive patients who underwent bypass or cardiac valve surgery and revealed a pronounced and prolonged increase in white blood cell counts in patients who developed post-operative AF.[18]

At the genetic level, Gaudino *et al.*[19] have shown that the 174G/C IL-6 promotor gene variant appears to modulate the inflammatory response to surgery and to influence the development of AF. This observation is an important first link between a gene promotor polymorphism, the inflammatory response, and the development of AF and thus further supports the inflammatory hypothesis. However, two study limitations should be mentioned. First, the study is a *post hoc* comparison of data collected in a prospective investigation. Secondly, no association was found between post-operative AF and C-reactive protein which may be the expression of low statistical power of the study.

Although the aforementioned studies support the role of inflammation in the genesis AF in post-surgery patients, it should be emphasized that several other factors besides

Table 1 Studies on markers of inflammation and occurrence of AF in post-surgery patients

Author	Study design	Intervention	Outcomes	Results
Bruins *et al.*[14]	Prospective, observational, 19 patients with coronary artery disease	CABG	Complement activation products IL-6, C-reactive protein complement-C-reactive protein Clinical symptoms	Peak incidence of arrhythmia on the second to third post-operative day coincides with peak elevation in C-reactive protein
Gaudino *et al.*[19]	Retrospective, observational, 110 patients with coronary artery disease	CABG	174G/C IL-6 promotor gene IL-6 Fibrinogen C-reactive protein AF	Significant correlation between the 174G/C IL-6 promotor gene, IL-6 levels, and development of AF
Abdelhadi *et al.*[18]	Prospective, observational, 181 patients undergoing cardiac surgery	CABG and/or valve surgery	WBC count AF	Significant association between WBC count and occurrence of AF post-surgery

CABG, coronary artery bypass grafting; WBC, white blood cell.

from inflammation can contribute to abnormal atrial conduction and refractoriness as well as to the increased frequency of triggering events. These include atrial incision, atrial ischaemia, associated cardiac disease, pericarditis, increased sympathetic tone, and persistence of atrial electrical activity during cardioplegia.[20]

Inflammation and AF in non-post-operative patients

Two independent clinical trials that appeared almost simultaneously were the first to report an association between C-reactive protein and AF in non-post-operative patients. The first study was a case–control study[21] including 131 patients with atrial arrhythmias. C-reactive protein was significantly elevated in AF patients and C-reactive protein elevation was greatest in patients with more persistent AF. In the second study,[22] 50 patients with paroxysmal AF who underwent pharmacological or electrical cardioversion were compared with age- and sex-matched controls. C-reactive protein was higher in patients with AF and significantly associated with successful cardioversion to sinus rhythm, findings which have been confirmed recently by others.[23] The concept of an association between non-post-operative AF and inflammation was supported by two population-based studies,[12,24] where C-reactive protein was not only associated with the presence of AF but also predicted patients at increased risk for the development of future AF. Furthermore, an association between elevated C-reactive protein and the prevalence of AF as well as the incidence of AF has been confirmed in different study populations.[25,26]

Although the studies suggest the existence of an association between inflammation and AF, it remains unknown whether inflammation is a consequence or a cause of AF. To clarify this issue, Sata *et al.*[27] measured markers of inflammation before and after pharmacological cardioversion in 15 patients with paroxysmal AF (*Table 2*). Levels of C-reactive protein, IL-6, and TNF-α were significantly elevated in AF patients when compared with a control group and remained elevated during the 2 weeks follow-up. On the basis of these findings, the authors suggest that inflammation is the cause rather than the consequence of AF. However, the study is limited by small patient sample size with low statistical power, lack of inflammatory parameters before the onset of AF, and a short follow-up time. Although not statistically significant, all markers of inflammation decreased 14 days after cardioversion compared with levels before cardioversion and a longer follow-up and/or a larger sample size may have changed the present findings. Thus, Acevedo *et al.*[28] reported significantly lower C-reactive protein in patients with sinus rhythm compared with patients in AF during a 1 year follow-up study of 68 patients admitted for newly diagnosed AF.

The fact that elevation was more pronounced in patients with persistent AF than in those with paroxysmal AF led Chung *et al.*[21] to propose that the role of inflammation in AF may be more pathogenetic in promoting persistence rather than initiation of AF. Recent studies have shown that C-reactive protein levels predict arrhythmia inducibility in sterile canine models[29] and C-reactive protein levels have been found to be elevated very early after the onset of AF in patients with paroxysmal AF.[22] Furthermore, elevated C-reactive protein level at admission was an independent predictor of new-onset AF during hospitalization in patients with acute coronary syndromes.[26] On the basis of these observations, inflammation is probably an integral part of both the initiation and the perpetuation of AF.

Inflammation and thromboembolism in AF

AF is associated with a prothrombotic or hypercoagulable state which may increase the risk of stroke and thromboembolism.[30] Furthermore, there is an apparent link between thrombogenesis and inflammation[31,32] where increased levels of inflammatory mediators such as IL-6 and C-reactive protein are associated with an increased risk of vascular events.[33] The significance of inflammation in the prothrombotic state in AF has been investigated in five recent studies[34–38] summarized in *Table 3*. All five studies report elevated C-reactive protein or IL-6 in AF patients. In one study, C-reactive protein and IL-6 were independently related to indices of the prothrombotic state in AF (e.g. C-reactive protein to fibrinogen and plasma viscosity, IL-6 to tissue factor).[35] In addition, IL-6 was an independent predictor of vascular events and stroke in AF[37] and IL-6 was correlated with a point-based score for stroke risk in AF.[38] Furthermore, C-reactive protein was associated with

Table 2 Studies on markers of inflammation and occurrence of AF in non-post-operative patients

Author	Study design	Outcomes	Results
Chung *et al.*[21]	Retrospective, observational case–control study, 131 patients with atrial arrhythmia and 71 control patients	C-reactive protein	C-reactive protein was elevated in AF patients Stepwise C-reactive protein elevation with higher AF burden
Dernellis and Panaretou[22]	Prospective interventional case–control study, 50 patients with pAF undergoing cardioversion and 50 control patients	C-reactive protein Cardiac rhythm	C-reactive protein was elevated in pAF Elevated C-reactive protein[1] was an independent risk factor for unsuccessful cardioversion
Aviles *et al.*[12]	Epidemiologic, cross-sectional study of 5806 subjects; longitudinal study of 5491 subjects followed for 6.9 $\pm$ 1.6 years	C-reactive protein Prevalence of AF Incidence of AF	C-reactive protein independently associated with baseline AF and with future development of AF
Maycock *et al.*[24]	Epidemiologic, prospective, 347 AF patients and 2447 control patients	C-reactive protein Prevalence of AF Incidence of AF	C-reactive protein significantly elevated in AF patients; C-reactive protein independently predicted an increased risk of AF
Asselbergs *et al.*[25]	Epidemiologic, cross-sectional, 8501 subjects	C-reactive protein Prevalence of AF Microalbuminuria	C-reactive protein, microalbuminuria, and the combination of both were independently associated with AF
Sanchez *et al.*[26]	Prospective, observational, 498 patients with ACS	C-reactive protein Incidence of AF	Elevated C-reactive protein, an independent predictor of new-onset AF
Acevedo *et al.*[28]	Prospective, 109 patients with AF, 68 patients were followed for 1 year	C-reactive protein Prevalence of AF	C-reactive protein elevated in AF patients compared with control group at baseline At follow-up, C-reactive protein in patients still in AF was significantly elevated when compared with patients in SR
Dernellis and Panaretou[17]	Prospective, interventional, follow-up (30 months), 104 patients with persistent AF randomized to methylprednisolone or placebo post-cardioversion	Recurrent AF Permanent AF C-reactive protein	C-reactive protein was a risk factor of AF Methylprednisolone successfully prevented recurrent and permanent AF
Sata *et al.*[27]	Prospective interventional, follow-up (14 days); 15 patients with AF undergoing cardioversion and 11 healthy control patients.	WBC count C-reactive protein IL-6 TNF-α	C-reactive protein, IL-6, and TNF-α were elevated in the AF group and remained elevated post-cardioversion
Conway *et al.*[23]	Prospective interventional, follow-up (2 months); 54 patients with AF undergoing cardioversion and 41 normal subjects	Success of DC cardioversion Maintenance of SR C-reactive protein IL-6 P-selectin von Willebrand factor Tissue factor Fibrinogen	C-reactive protein was elevated in AF patients High C-reactive protein was the only independent predictor of cardioversion outcome No significant relation to cardiac rhythm at 2 months.

pAF, paroxysmal atrial fibrillation; ACS, acute coronary syndrome; WBC, white blood cell.

spontaneous echocontrast in the left atrium or the left atrial appendage, which is a well-recognized independent predictor for stroke and thromboembolism in AF.[36]

The studies are limited by their cross-sectional or retrospective design, small sample sizes, and control groups which were non-comparable with the patient groups due to a different distribution of cardiovascular co-morbidities in the AF groups. Accepting these limitations, the finding of elevated markers of inflammation in AF patients is consistent with a potential role for inflammation in AF and the correlations between inflammatory and prothrombotic indexes support a possible relation between inflammation and pathogenesis of stroke in AF.

Glucocorticoid therapy and AF

The anti-inflammatory action of glucocorticoids are well established as one of the major pharmacological uses of this class of drugs.[39] The first observation linking corticosteroid treatment with AF comes from a small number of case reports where high doses of methylprednisolone have been associated with onset of AF.[40–42] In a randomized placebo-controlled study, Chaney *et al.*[40] examined the use of methylprednisolone in patients undergoing coronary artery bypass grafting and found no difference in the incidence of AF between the two groups. The first indication of a positive effect of corticosteroid treatment on AF

Table 3 Inflammation and thromboembolism in AF

Author	Study design	Outcomes	Results
Roldán *et al.*[34]	Cross-sectional observation study of 191 AF patients and 74 age- and sex-matched control subjects Anticoagulation and 3 months follow-up in a subgroup of 43 AF patients	IL-6 E-selectin F 1 + 2	Elevated levels of IL-6 and F 1+2 in AF patients No association between F 1+2 and IL-6 IL-6 levels were associated with previous thromboembolism Anticoagulation did not change IL-6 levels significantly
Conway *et al.*[35]	Cross-sectional observation study of 106 AF patients and 41 healthy control subjects	C-reactive protein IL-6 P-selectin von Willebrand factor Tissue factor Fibrinogen Plasma viscosity Haematocrit	Elevated levels of C-reactive protein, IL-6, and plasma viscosity in AF patients IL-6 significantly higher among AF patients at high risk of stroke IL-6 significantly associated to tissue factor C-reactive protein significantly associated to fibrinogen and plasma viscosity No correlation between C-reactive protein and IL-6
Conway *et al.*[37]	Retrospective of 77 AF patients who were followed for a median duration of 6.3 years	IL-6 C-reactive protein Stroke Death	High IL-6 levels were an independent predictor of stroke or death Trends towards increased risk with high plasma C-reactive protein did not reach statistical significance
Conway *et al.*[36]	Cross-sectional observation study of 37 AF patients and 37 healthy control subjects	TEE risk factors C-reactive protein IL-6 P-selectin von Willebrand factor Tissue factor Fibrinogen Plasma viscosity Haematocrit	C-reactive protein significantly elevated in AF group C-reactive protein, P-selectin, and haematocrit significantly associated with SEC
Roldán *et al.*[38]	Cross-sectional observational study of 191 consecutive patients with non-rheumatic AF lasting for >4 weeks	IL-6 F 1 + 2 Risk score for predicting stroke or death in AF	The risk score was significantly correlated with IL-6 levels, but not F 1 + 2

F 1 + 2, prothrombin fragment 1 + 2, TEE risk factors: dense spontaneous echo contrast in the left atrium (SEC), left atrial appendage thrombus, complex atheromatous plaque, and left atrial appendage peak emptying velocity.

came from a randomized study on 216 patients undergoing coronary or valvular heart surgery.[43] A single dose of dexamethasone after the introduction of anaesthesia was associated with a decreased incidence of new-onset AF in the first 3 days post-surgery. The following limitations are worth emphasizing: AF was a secondary endpoint with low statistical power, patients underwent cardiac surgery and findings cannot readily be extrapolated to the general population of non-surgical AF patients, and finally, the investigators did not measure inflammatory mediators release in response to surgery and the study drug which makes it impossible to correlate the clinical observations to inflammation. However, these preliminary clinical observations was supported by an animal study[29] where prednisone treatment in a canine sterile pericarditis model significantly attenuated the increase in C-reactive protein, reduced neutrophil infiltration in the right atrial appendage, and importantly eliminated atrial arrhythmia inducibility. Currently, only one study has prospectively assessed the relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrence of AF. In the study by Dernellis and Panaretou[17] 104 patients with their first episode of persistent AF were cardioverted (medically or by DC shock) into normal sinus rhythm and received propafenone for the entire follow-up time (30 months). The patients were randomized to either glucocorticoid (methylprednisolone 16 mg for 4 weeks tapered to 4 mg during 4 months) or placebo. C-reactive protein levels were measured during the first hospitalization and after 4 weeks, 4 months, 6 months, and every 6 months afterward for the duration of the trail. The patients in the glucocorticoid group were less likely to develop recurrent AF and importantly this correlated with a significant decrease in C-reactive protein levels. Although the study provides important information, there are some limitations that must be recognized. First, methylprednisolone was used as an add on to propafenone and it is not known whether corticosteroid treatment would have the same benefit when used as monotherapy or in combination with other antiarrhythmic agents. Secondly, the study population consisted of patients with newly diagnosed AF probably of relatively short duration. Patients with AF of longer duration will be

expected to have more extensive electrical and structural changes in the atrial myocardium which may respond less favourably to anti-inflammatory therapy. Thirdly, C-reactive protein was not measured using an ultra-sensitive technique and the reported C-reactive protein levels are not comparable with C-reactive protein levels obtained using ultra-sensitive assays.

In spite of these limitations, the study suggests the intriguing possibility that C-reactive protein lowering therapy may reduce recurrence of AF and thus opens the doors for further investigations on C-reactive protein-lowering drugs, preferentially drugs less burdened with potential serious side effects such as the corticosteroids.

Hydroxymethyl glutaryl coenzyme A reductase inhibitor and inflammation

Numerous trials with hydroxymethyl glutaryl coenzyme A reductase inhibitors, HMG-CoA reductase inhibitors, have demonstrated a significant reduction in cardiovascular events.[44] Although the majority of the effect can be ascribed to a beneficial effect on the lipid profile, the statins have additional non-lipid-mediated effects including anti-proliferative and anti-inflammatory properties.[45] The anti-inflammatory functions of statins is supported in several *in vitro* and *in vivo* studies and has been reviewed by a number of authors.[46–48] In the present context, the following properties should be highlighted:

- statins increase the bioavailability of endothelial NO both by up-regulating endothelial NO synthase and through antioxidant effects.[49,50]
- statins can attenuate oxidant-induced mitochondrial dysfunction in cardiac myocytes.[51]
- statins down-regulate the activity of G proteins in cardiomyocytes and thereby influence surrogate markers of cardiac dysfunction such as atrial natriuretic factor and myosin light chain-2.[52]
- statins diminish the expression and function of inflammatory mediators such as IL-6, TNF-α, C-reactive protein, coclooxygenase 2, and SAA.[46]

These pleiotropic properties may all be involved in the anti-arrhythmogenic activity of the HMG CoA reductase inhibitors. In the context of inflammation, statin therapy significantly reduces C-reactive protein levels and there is a dose-related effect. Jialal *et al.*[53] reported a mean reduction in C-reactive protein levels of 28% in patients treated with 10 mg atorvastatin/day when compared with van Wissen *et al.*[54] and recently Nissen *et al.*[55] who reported reductions in C-reactive protein levels of 45 and 36%, respectively, during intensive (80 mg/day) atorvastatin therapy. Furthermore, Node *et al.*[56] observed a significant decrease in plasma concentrations of both TNF-α and IL-6 in response to simvastatin therapy further supporting the anti-inflammatory properties of statin therapy.

Hydroxymethylglutaryl coenzyme A reductase inhibitor and AF

Data on the effect of HMG-CoA reductase inhibitors on AF are shown in *Table 4*. Kumagai *et al.*[5] evaluated the effect of atorvastatin on AF in a canine sterile pericarditis model. The atorvastatin group had lower C-reactive protein levels, less pronounced fibrosis in the atrial myocardium, and a shorter duration of AF. The study deserves attention as the first study, which evaluates the role of inflammation on atrial electrophysiological as well on atrial structural changes. Recently, these findings have been supported by a study on mongrel dogs subjected to atrial tachypacing and simvastatin treatment.[57] Atrial tachypacing-induced AF promotion was virtually abolished and effective refractory period shortening was significantly suppressed in the simvastatin treated dogs. A major limitation is the animal model which cannot be extrapolated to AF patients.

Three studies have investigated the association between statin use and incidence of AF. Two were observational non-randomized studies. The first demonstrated that statin therapy reduced the rate of recurrence after successful cardioversion of the arrhythmia.[58] The second study showed that the use of statins in patients with coronary artery disease was associated with a reduced risk of developing AF.[59] In contrast to these findings, Tveit *et al.*[60] in a randomized study found no reduction in the recurrence of AF after electrical cardioversion in patients treated with pravastatin 40 mg/day compared with patients on standard therapy. A limitation in all the three studies is that none of the studies have measured markers of inflammation.

In conclusion, data on HMG CoA reductase inhibitors and AF are sparse and inconclusive. Currently, the most convincing data stem from the animal study by Kumagai *et al.*[5] and cannot be extrapolated to AF patients.

ACE-I and ARBs in AF

There is growing evidence, both from animal work[61–63] and from clinical studies,[64–68] of the involvement of the angiotensin system in the phatophysiology of AF (*Table 5*). Recently, Madrid *et al.*[69] have published a meta-analysis of randomized controlled clinical trails that compared ARBs and ACE-I with either placebo or conventional therapy in patients with cardiovascular diseases. The study included 24 849 patients and treatment with ACE-I/ARBs markedly reduced the risk of development or recurrence of AF (odds ratio 0.57, with 95% confidence interval 0.39–0.82). There are multiple possible mechanisms by which ACE-I/ARBs may have anti-arrhythmic efficacy. These include decrease of wall stress, modulation of refractoriness, interference with ion currents, modification of sympathetic tone, stabilization of electrolyte concentrations, and regression of myocardial fibrosis.[61,70,71] Furthermore, the renin–angiotensin system has important modulatory activities in the inflammatory process. Recent work has shown that angiotensin II has significant pro-inflammatory actions, inducing the production of reactive oxygen species, inflammatory cytokines, and adhesion molekyles.[72] In agreement with these observations, angiotensin II receptor blockade significantly reduces multiple markers of inflammation (C-reactive protein, TNF-α, IL-6, and monocyte chemotactic protein-1) in hypertensive patients.[70] Thus, the beneficial anti-arrhythmic effects of ACE-I/ARBs could be attributed, at least in part, to their anti-inflammatory action. However, it should be emphasized that none of the reviewed studies have shown data on serological markers of inflammation.

Table 4 Statin therapy and AF

Author	Study design	Intervention	Outcomes	Results
Kumagai *et al.*[5]	Blinded, randomized, interventional canine sterile pericarditis model on 20 mongrel dogs of either sex	Two groups 10 control dogs 10 dogs receiving atorvastatin	AF duration AERP CT Histology	The atorvastatin group had significantly Lower CRP Shorter duration of AF Longer AERP Shorter CT Less inflammation in atrial tissues
Tveit *et al.*[60]	Randomized, longitudinal (9 weeks), open-label multicentre, interventional study on 114 patients with AF $>$ 48 h.	Two groups DC and standard therapy DC, standard therapy, and pravastatin 40 mg/day	Recurrence of AF	No significant difference in recurrence rate of AF
Siu *et al.*[58]	Retrospective follow-up of 44 $\pm$ 1 months; 62 patients with lone AF lasting $\geq$3 months	Two groups DC and standard therapy ($n = 52$) DC, standard therapy, and statin ($n = 10$)	Recurrence of AF	Significant decrease in recurrence rate of AF
Young-Xu *et al.*[59]	Retrospective follow-up of $\geq$1 year; 449 patients with CAD[5]	Two groups Users of statins ($n = 263$) Non-users of statins ($n = 186$)	Occurrence of AF	Statin therapy was associated with a significantly reduced risk of developing AF
Shiroshita-Takeshita *et al.*[57]	Randomized interventional study on 39 mongrel dogs	Six groups subjected to atrial tachypacing for 7 days Non-paced control group Paced only group C-vitamin E-vitamin Simvastatin C-vitamin sustained-release	Duration of induced AF AERP CRP	Simvastatin prevented AF promotion and significantly attenuated AERP in right atrium No effect of vitamin C or E. No significant change in CRP

AERP, atrial effective refractory period; CT, intra-atrial conduction time; DC, direct current cardioversion; CAD, coronary artery disease.

Conclusion

The idea that inflammatory processes are involved in the pathogenesis of AF is not new, but has attracted renewed focus because of combined clinical, epidemiological, pharmacological, and histological observations. These observations are as follows:

- histological studies have demonstrated inflammatory infiltrates in AF patients and in animal models of AF.
- epidemiological studies have shown a solid association between C-reactive protein and both the presence of AF and the risk of developing future AF.
- In case–control studies C-reactive protein is significantly elevated in AF patients and is associated with successful cardioversion. Moreover, C-reactive protein elevation is more pronounced in patients with persistent AF than in those with paroxysmal AF.
- treatment with glucocorticoids, statins, ACE-I, and ARBs seems to reduce recurrence of AF. Part of this anti-arrhythmic effect may be through anti-inflammatory activity.

Although the reviewed studies support the existence of an association between inflammation and AF, several issues remain unsolved and require further investigation. A major limitation is the lack of inflammatory parameters in patients before the onset of AF; such information requires large cohort studies which should be encouraged. Secondly, the currently available data do not answer whether inflammation is an initiator or a perpetuator of AF, i.e. reflects an epiphenomenon of AF or is a causal pathway. However, it should be emphasized that both mechanisms may interrelate indicating that inflammation is not only a response to the underlying arrhythmic process but also an integral part of it. Thirdly, although drugs with anti-inflammatory action seem to reduce the incidence of AF, it is not known whether these findings are limited to patients with AF of an inflammatory aetiology. At present, these findings cannot be extrapolated to the general population of patients with AF, but require further testing and confirmation in larger randomized clinical trials. Furthermore, the reduction in the incidence of AF observed using drugs with anti-inflammatory action do not clarify whether inflammation is a perpetuator or an initiator of AF as anti-inflammatory drugs would be expected to ameliorate AF in both circumstances. Finally, the electrophysiological mechanisms by which inflammation promote AF have not been fully delineated and need further investigation.

It should be emphasized that although studies of serum markers of inflammation may provide substantial insight into the pathophysiology of AF, the clinical utility of measuring these markers remains uncertain. For a novel marker to have a clinical role, there must be widely available

Table 5 ACE-I or angiotensin II receptor blocker therapy and AF in selected trials

Author	Study design	Intervention	Outcomes	Results
Pedersen *et al.*[64]	Retrospective analysis of a non-pre-specified variable in 1577 patients with reduced LVEF secondary to AMI	Placebo group ACE-I (trandolapril) group	Development of AF during 2–4 years follow-up	Trandolapril reduced the incidence of AF
Nakashima *et al.*[61]	Interventional, placebo-controlled study in a canine model of atrial electrical remodelling	Rapid atrial pacing in four groups: Saline group ACE-I (captopril) group ARB (candesartan) group Ang-II group	AERP	AERP shortening was prevented by candesartan and captopril but increased by Ang-II
Madrid *et al.*[65]	Prospective, randomized open-label interventional study on 154 patients with persistent (>7 days) AF	Electrical cardioversion and: Amiodarone Amiodarone + ARB (irbesartan)	Recurrence of AF DC shock number Required DC energy	Amiodarone + irbesartan had lower rate of recurrence of AF than amiodarone alone
Cardin *et al.*[63]	Prospective, interventional, longitudinal (5 weeks) in a canine model of congestive heart failure	Ventricular tachypacing for up to 5 weeks with and without ACE-I (enalapril) treatment	Apoptosis MAPK expression Caspase-3 activity Ang-II concentration Histopathology	Atrial cell death associated with inflammatory response 24 h after onset of tachypacing; ACE-I only partially prevents atrial structural remodelling
Ueng *et al.*[66]	Prospective, randomized open-labelled interventional study of 159 patients with chronic (>3 months) AF.	Electrical cardioversion and: Amiodarone Amiodarone + ACE-I (enalapril)	Time for first recurrence of AF	The addition of enalapril to amiodarone decreased the rate of immediate and subacute arrhythmia recurrence
Vermes *et al.*[67]	Retrospective analysis of a non-pre-specified variable in 391 patients with reduced LVEF or overt HF	ACE-I (enalapril) Placebo	AF detected at a mean follow-up (mean 2.9 years)	ACE-I significantly reduced the risk of development of AF
Anné *et al.*[68]	Retrospective study of 196 patients with atrial flutter	Atrial flutter ablation	Incidence of AF after ablation	Blockade of the RAS and diuretics was associated with significantly less AF

LVEF, left ventricular ejection fraction; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; Ang-II, angiotensin II; AERP, atrial effective refractory period; CT, intra-atrial conduction time; DC, direct current; MAPK, mitogen-activated protein kinase; ERP, extracellular signal regulated protein kinase; HF, heart failure.

diagnostic test with reproducible assay characteristics appropriate for patient-related purposes. For the time being, only high-sensitive C-reactive protein fulfil these requirements. Furthermore, there must be a consistent series of prospective studies that indicate that elevation of a given inflammatory marker predicts future AF. And finally, whether inflammation *per se* represents a modifiable risk factor is currently uncertain, although preliminary data suggest that several drugs with anti-inflammatory action seem to reduce the incidence of AF. Keeping these limitations in mind, inflammation may provide a potential target for pharmacological interruption or reversal of atrial remodelling and thus form the basis for new, better pharmacological approaches for treating AF. As in all cases of cardiac disease, the best long-term hope lies with therapies that provide protection against AF by preventing the initial development of atrial fibrosis and remodelling.[73] Given the fact that the burden of AF will continue to increase as the population ages and the relative inefficacy of the currently available pharmacotherapies identifying interventions that can prevent or postpone the development of AF deserves high priority.

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