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CLINICAL REVIEW

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Inflammation and atrial fibrillation: A comprehensive review

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Abstract

Atrial fibrillation (AF) has different underlying substrates. Atrial remodeling involves electrophysiological and structural abnormalities that promote the development and perpetuation of AF. Experimental and clinical data indicate that inflammation is implicated in the pathophysiology of atrial remodeling. The mechanistic links between atrial remodeling and inflammation are complex while diverse underlying diseases and conditions may affect these pathways. Inflammatory markers have also been associated with AF development, recurrence, perpetuation, total AF burden as well as with thromboembolic complications. The development of specific anti-inflammatory interventions in this setting seems to be challenging and complicated. Several agents with pleiotropic properties, including anti-inflammatory, have been tested in experimental and clinical settings with variable results. This updated review provides a concise overview of all available data regarding the role of inflammation in AF including the predictive role of inflammatory markers. Also, current knowledge and future directions on anti-inflammatory strategies are critically discussed.

KEYWORDS

anti-inflammatory interventions, atrial fibrillation, atrial remodeling, C-reactive protein, inflammation

1 | INTRODUCTION

Atrial fibrillation (AF) represents the most frequent arrhythmia encountered in clinical practice, and its prevalence has been continuously increasing during the last few decades mainly due to aging of the population and improved survival of patients with other cardiovascular diseases.[1,2] AF is a major health problem associated with significant morbidity and mortality as well as increased healthcare costs.[1,2] AF is a complicated and heterogeneous arrhythmia occurring in diverse clinical settings. Besides local triggers, atrial electrophysiological and structural abnormalities that constitute atrial remodeling seem to play an important role in AF development and persistence.[2–4] The pathophysiology of atrial remodeling is very complex, and the molecular pathways implicated in the initiation and

perpetuation of AF show a high diversity and variability across different underlying substrates.[2–4] Moreover, in recent years the concept of atrial cardiomyopathy has been evolved. This concept expands the principles of structural and electrical remodeling incorporating the processes of mechanical dysfunction and procoagulant state and suggesting that AF is part of a progressive fibrotic atrial cardiomyopathy.[5] Recently, the role of pathophysiologic pathways that involve inflammatory and oxidative processes is under meticulous investigation.[6,7] Given that most of the published data on this subject regards the study of specific biomarkers, the cause-effect relationship with atrial remodeling is not very clear.[6,7] Possibly, both procedures are operative in this setting. Bearing in mind that most of the associated cardiovascular conditions are associated with oxidative stress and inflammation, the study of inflammatory aspects of atrial remodeling becomes more complicated.

2 | RISK FACTORS FOR AF AND INFLAMMATION

Major cardiovascular risk factors and conditions associated with AF have also been linked to low-grade inflammation.[7,8] These include hypertension, congestive heart failure, coronary artery disease, and diabetes.[7,8] Indeed, an increasing body of evidence suggests that these conditions facilitate AF, at least in part, by inflammatory and oxidative mechanisms. Specifically, inflammation and oxidative stress represent pivotal mechanisms of endothelial dysfunction and arterial damage in the setting of hypertension.[9] Angiotensin II which is a major mediator of vasoconstriction in hypertension induces the production of proinflammatory cytokines and activates immune cells.[7] In heart failure, apart from hemodynamic and neurohormonal alterations, several immune inflammatory dysregulations are involved in the progression of ventricular dysfunction and fibrosis as well as in other maladaptive responses.[10] Therefore, these inflammatory pathways may promote AF in this setting.

Patients with AF have an increased prevalence of coronary artery disease.[8] Besides ischemia-induced arrhythmogenesis, atherosclerosis is a chronic inflammatory disease that may promote AF.[11] Indeed, epidemiological evidence links AF with markers of atherosclerotic burden such as carotid intima-media thickness, ankle-brachial index, and coronary artery calcium, factors that do not have direct atrial ischemic effect.[11] Furthermore, inflammation and oxidative stress seem to play a critical role in the pathogenesis of AF in obesity and other metabolic disorders such as diabetes.[12] Diabetes mellitus is associated with atrial electrical and structural remodeling[13] while inflammation seems to be a central mediator.[12]

Chronic obstructive pulmonary disease (COPD) represents a novel risk factor for AF.[14] COPD is associated with inflammation, oxidative stress, hemodynamic abnormalities, hypoxia, hypercapnia, and autonomic imbalance, processes that promote atrial electrical and structural remodeling.[15] Indeed, COPD-related sympathetic overdrive, systemic inflammation and oxidative stress, as well as decreased oxygen saturation, seem to play an important role in AF promotion in this setting.[15] On the other hand, COPD in AF is associated with AF progression, success of cardioversion, recurrence of AF after catheter ablation, and increased cardiovascular and all-cause mortality. Also, smoking which is a major risk factor for COPD has been associated with a modest increased risk of incident AF.[16] The underlying pathophysiological mechanism are very complex given that smoking is implicated in several cardiovascular and respiratory diseases, but the induction of oxidative stress and inflammation could be a common pathogenetic pathway.

Obesity is involved in AF given that general and abdominal adiposity, as well as higher body fat mass, increases the risk of AF.[17] Obesity induces and aggravates several cardiometabolic abnormalities while it exerts adverse hemodynamic effects, and increases systemic inflammation, as well as local inflammation in the heart through excessive epicardial tissue formation.[17,18] Moreover, obesity is a major risk factor for obstructive sleep apnea (OSA) a condition that further increases AF burden.[19] In fact, OSA further aggravates neurohormonal, hemodynamic, and inflammatory abnormalities associated with atrial remodeling.[20]

Air pollution has also been associated with increased AF risk although some inconsistent results have been published. A recent meta-analysis showed that gaseous or particulate pollutants are associated with new-onset AF.[21] Although the underlying mechanisms are not completely known, an increasing body of evidence links air pollution to inflammation, oxidative stress, cardiac ischemia, increased right atrial pressures, and autonomic tone changes.[21] Moreover, chronic kidney disease and end-stage renal disease represent chronic inflammatory conditions that have been associated with increased prevalence of AF.[22,23] Finally, gastroesophageal reflux disease has been associated with increased risk for AF, especially in the presence of esophagitis.[24] In support of this association, therapy with proton pump inhibitors seems to ameliorate symptoms and decrease AF burden in affected individuals.[24] Besides autonomic changes in ganglionated plexi due to anatomic proximity between esophagus and left atrium, local inflammatory processes have also been implicated in this setting.[24]

3 | INFLAMMATION IN ARRHYTHMOGENESIS AND ATRIAL REMODELING

Inflammation may lead to AF, but AF promotes inflammation as well leading to a vicious cycle.[7] Early histologic studies showed that even in patients with so-called "lone AF" local atrial inflammatory infiltration compatible with myocarditis was present in 2/3 of affected individuals.[25] In support of the role of chronic inflammation in atrial arrhythmogenesis, several studies have indicated the association between autoimmune disorders, especially rheumatoid arthritis, and AF.[26,27] Despite the increased risk for coronary disease and heart failure, rheumatoid arthritis-associated inflammation may affect atrial electrophysiology. An increasing body of evidence indicates that inflammatory mediators promote structural and electrical atrial

remodeling.[27] The underlying mechanisms include atrial fibrosis, gap junction modulation, and intracellular calcium-handling abnormalities. These abnormalities increase atrial ectopic activity and slow atrial conduction, impairing atrial impulse propagation and promoting reentry.[27] Interestingly, in a recent study that included more than 20 000 patients with autoimmune rheumatic disease, indicated that the inflammatory status expressed by CRP levels was related to incident AF.[28]

Indeed, systemic inflammation has been associated with endocardial and endothelial inflammation as well as with atrial remodeling. Several inflammatory mediators seem to be involved in electrical and structural remodeling.[7,29] Tumor necrosis factor (TNF), IL-2, and platelet-derived growth factor (PDGF) regulate calcium homeostasis and provoke abnormal triggering in pulmonary veins as well as shortening of atrial action potential duration.[7] Also, these factors along with myeloperoxidase (MPO) and heat-shock proteins (HSPs) induce atrial fibrosis, connexin dysregulation, apoptosis, and myolysis leading to conduction slowing and increased conduction heterogeneity.[7] Moreover, inflammatory cytokines activate NF-kB a transcriptional factor that further promotes inflammatory reactions leading to fibrosis, apoptosis, and cardiomyocyte death.

Of note, local inflammatory reactions in atrial myocardium or in adjacent tissues may directly cause AF. These mechanisms seem to be operative in pericarditis, myocarditis, as well as in postoperative AF after cardiac surgery. Remarkably, the peak incidence of postoperative AF between the second and third postoperative day coincides with the peak inflammatory and oxidative response after the surgical operation.[30,31]

On the other hand, rapid atrial tachycardia leads to calcium overload inducing oxidative stress, apoptosis, membrane dysfunction, energy depletion, and low-grade inflammation.[7] Also, experimental data indicates that rapid atrial pacing increases CRP and AF inducibility.[32] Further support on the concept of AF-induced inflammation is provided in the following section. Therefore, atrial tachycardia and inflammation are 2 processes that feed each other leading to a vicious cycle. A schematic representation of the inflammatory mechanisms implicated in atrial arrhythmogenesis as well as targeted interventions that will be discussed later is depicted in Figure 1.

4 | INFLAMMATORY BIOMARKERS IN AF

Inflammatory indexes have been associated with future AF development, persistence, AF severity, AF recurrences after cardioversion, success of electrical cardioversion of persistent AF, sinus

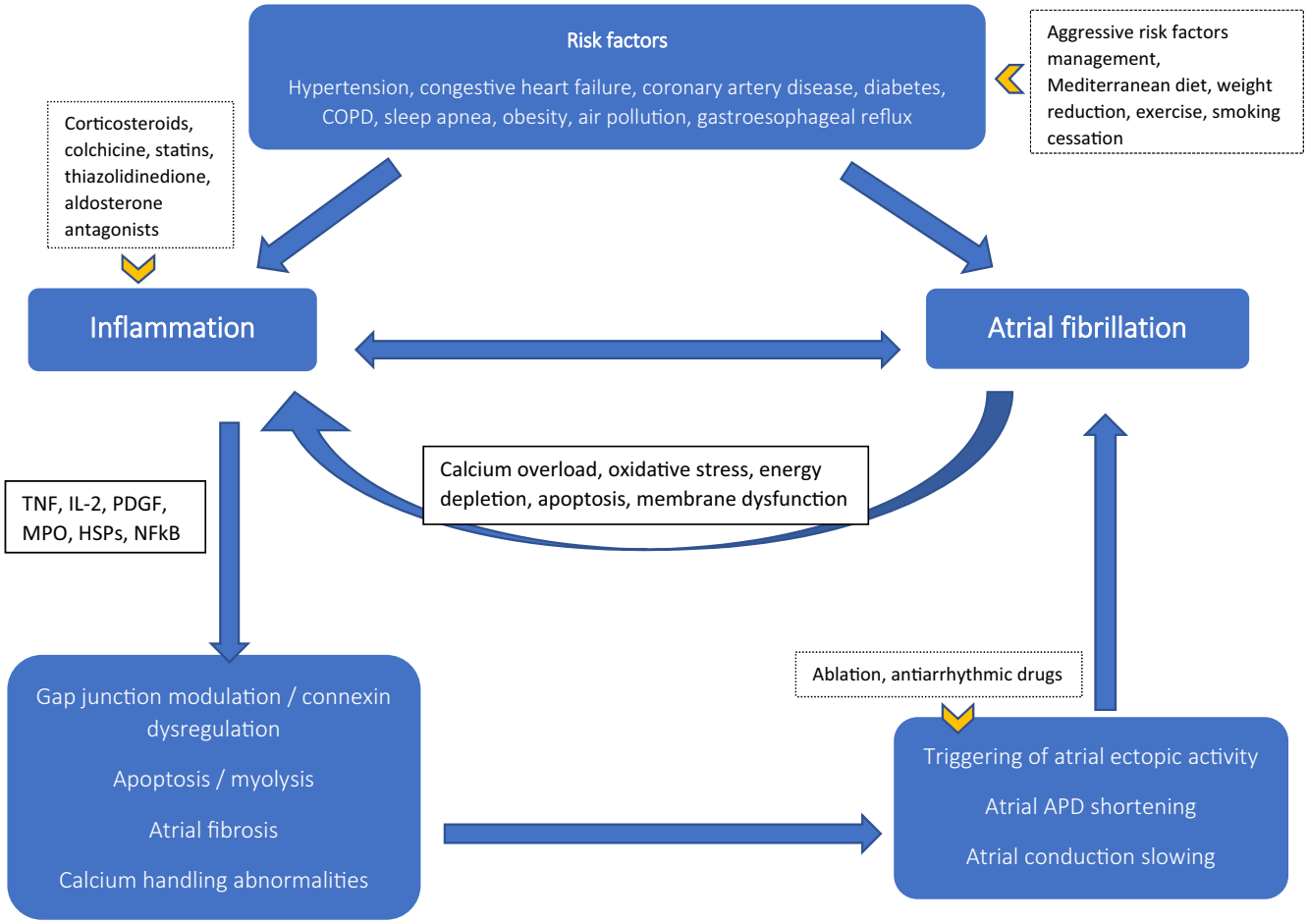

FIGURE 1 Inflammation in arrhythmogenesis and atrial remodeling. In boxes with dotted lines, potential interventions are mentioned

rhythm maintenance after AF ablation, as well as to the associated prothrombotic state.[6,7,33] In support of these findings, several meta-analyses strongly indicate that specific circulating inflammatory markers, such as CRP and IL-6, are associated with greater AF risk in general population and patients who underwent cardiac surgery, as well as with AF recurrence after electrical cardioversion or ablation.[34–36]

It should be stressed that in the majority of published studies only associations between inflammatory markers and AF have been reported and therefore the cause-effect relationship remains unclear. In an older study that included patients with lone AF, it was indicated that CRP a classic marker of systemic inflammation is associated not with the AF per se, but rather with underlying cardiovascular disease.[37] Contrary to this assumption, Marcus et al[38] demonstrated that history of AF does not affect CRP and IL-6 levels while the presence of AF at the time of the blood draw determines an elevation of CRP and IL-6. Moreover, the authors showed that AF results in sequestration of inflammatory cytokines in the heart.[38] In support of the assumption that AF induces an inflammatory response Kallergis et al[39] indicated that restoration and maintenance of sinus rhythm results in gradual decrease of CRP levels. Also, increased levels of inflammatory markers such as CRP and TNF seem to correlate with AF burden and persistence.[7]

In the Framingham Heart Study, an increased white blood cell (WBC) count was associated with incident AF during 5 years of follow-up.[40] We have also shown that WBC count significantly decreases after AF cardioversion in patients who remain in sinus rhythm.[41] A recent meta-analysis showed that WBC count has been related to AF recurrence but not to the presence of AF per se.[42] Neutrophil/lymphocyte ratio (NLR) seems to have a better predictive value than WBC count predicting occurrence and recurrence of AF.[42,43]

Very recently, in a case-control study the proportion of a specific subpopulation of monocytes (intermediate CD14++CD16+) was associated with AF in patients without comorbidities.[44] This subset of monocytes was inversely associated with left atrial appendage velocity during sinus rhythm reflecting functional remodeling of the left atrium.[44] Interestingly, a recent case-control study showed that patients with paroxysmal lone AF had higher eosinophil and neutrophil counts compared to control subjects while during a 12-month follow-up period, left atrial diameter and eosinophil count were independently associated with AF recurrence rates.[45]

Red blood cell distribution width (RDW) represents a marker of anisocytosis of erythrocytes that may be related to inflammation and oxidative stress. In support of these assumption, we have shown in an experimental study that RDW levels are correlated with several biomarkers of oxidative stress and inflammation in a canine model of rapid atrial pacing.[46] Recent data indicate that RDW is clearly higher in patients with new-onset AF as well as in patients with recurrent AF.[42] We have also shown that RDW is an independent predictor of postoperative AF after cardiac surgery[47] and a predictor of AF in patients with sick sinus syndrome undergoing pacemaker implantation.[48] Of note, in a very recent meta-analysis we showed a significant association between baseline RDW levels and AF occurrence or recurrence following cardiac procedure or surgery.[49]

Myeloperoxidase, an enzyme released from activated polymorphonuclear neutrophils, has been linked to atrial fibrosis and remodeling.[50] MPO catalyzes the generation of reactive species like hypochlorous acid, which affect intracellular signaling cascades in various cells and advance activation of pro-MMPs and deposition of atrial collagen resulting in atrial arrhythmias. In an experimental setting, MPO-deficient mice were protected from AF.[51] In the same study, humans with AF had higher plasma concentrations of MPO and a larger MPO burden in right atrial tissue compared to control subjects. Recently, MPO demonstrated to be an independent predictor of AF recurrence after pulmonary vein isolation.[52]

Galectin-3 plays functional roles in the regulation of cell adhesion, immunity, inflammation, and fibrosis. An increasing body of evidence suggests that increased galectin-3 levels are predictive of prevalent and incident AF, as well as arrhythmia recurrence following sinus rhythm restoration although some negative results have been published.[53]

Fibrinogen represents an acute-phase inflammatory protein. We have shown that fibrinogen levels increased significantly in patients who relapsed into AF early after electrical cardioversion.[41] In keeping with these findings, a recent meta-analysis indicated that fibrinogen level was significantly higher in patients with AF compared to those with sinus rhythm.[54]

Collectively, several inflammatory markers have been related to AF burden. However, the inclusion of inflammatory markers such as CRP in predictive models needs further study as there are data indicating that CRP does not improve the predictive value of conventional clinical risk factors for incident AF.[55]

5 | ANTI-INFLAMMATORY INTERVENTIONS IN AF

Several agents with direct or indirect/pleiotropic anti-inflammatory properties have been tested in experimental and clinical settings of AF. Steroid therapy represents a classical anti-inflammatory intervention that has been tested in AF as well. Very recently, in a dog model steroid treatment normalized activation after the atriotomy and decreased the risk of postoperative AF.[56] In the clinical setting, short-term steroid therapy seems to reduce AF recurrence after ablation.[57] In keeping with previous findings, a large clinical study showed that intraoperative dexamethasone administration confers significant protection against AF after cardiac surgery.[58] A recent meta-analysis demonstrated that glucocorticoid therapy not only reduces the incidence of postoperative AF but also reduces the length of stay in the intensive care unit or on the hospital.[59]

Colchicine is an anti-inflammatory agent acting by inhibiting the microtubule polymerization with a well-known efficacy in pericarditis. Accumulating evidence suggests that its short-term use significantly reduces AF burden after ablation/pulmonary vein isolation as

well as after cardiac surgery.[60,61] However, the frequent gastrointestinal side effects may limit its use.

Statins exert several pleiotropic effects, including anti-inflammatory, which may favorably affect atrial remodeling.[62] It has been suggested that statins may be effective in AF prevention especially in the postoperative setting.[63] Indeed, a mounting body of evidence supports this assumption indicating that statin pretreatment reduces AF burden after cardiac surgery along with a modulation of the postoperative rise of CRP.[64] In addition, more limited evidence suggests that especially rosuvastatin and atorvastatin reduce the risk of developing AF and the early recurrences of AF after electrical cardioversion.[65,66]

We have reported experimental evidence showing that thiazolidinedione treatment with rosiglitazone attenuates atrial structural remodeling reducing the interatrial activation time and the atrial interstitial fibrosis as well as AF promotion modulating oxidative stress and inflammation.[67] In the clinical setting, we were the first to report the beneficial effects of thiazolidinedione therapy in paroxysmal AF.[68] Other studies confirmed this assumption although some inconsistent results have been published. Our recent meta-analysis demonstrated that thiazolidinedione use is associated with a lower risk of new-onset and recurrent AF in diabetic patients only in the pooled analysis of observational studies but not in the analysis of randomized trials.[69] Therefore, further large-scale randomized controlled trials are needed to determine whether thiazolidinedione use can prevent AF in the setting of diabetes.

n-3 fatty acids supplementation has been emerged as a promising "upstream" therapy for AF modulating favorably the atrial substrate without proarrhythmic effects. Apart from beneficial electrophysiological effects, n-3 fatty acids exert anti-inflammatory actions in experimental settings. However, inconsistent results have been published regarding efficacy of n-3 PUFA to prevent AF in various settings, such as after cardiac surgery or after cardioversion.[70] Also, a recent clinical study showed that in patients with paroxysmal or persistent AF, treatment with n-3 fatty acids 4 did not reduce the recurrence of AF, nor was it associated with clinically important effects on concentrations of markers of inflammation and oxidative stress.[71]

We have further suggested that aldosterone antagonists might exert beneficial effects on AF, as aldosterone induces inflammation, oxidative stress, and fibrosis.[72] In a previous meta-analysis, we showed that mineralocorticoid receptor antagonists reduce the risk of AF in both heart failure and after cardiac surgery.[73] Analyzing the relative impact of eplerenone and spironolactone, we showed that only eplerenone significantly reduces AF burden.[73] On the other hand, a more recent meta-analysis which included a larger number of studies showed that these agents significantly reduce new-onset AF and recurrent AF, but not postoperative. Therefore, mineralocorticoid receptor antagonist treatment can be considered an additive therapeutic strategy in AF.[74]

It is clearly evident that the greatest benefit from anti-inflammatory interventions such as steroids, colchicine, and statins is observed in settings associated with a considerable inflammatory reaction due to tissue damage such as cardiac surgery or catheter ablation. It should be acknowledged that examination of combined multitarget anti-inflammatory interventions is lacking. Undoubtedly, more studies are needed to elucidate the exact role of inflammation and to clarify the impact of anti-inflammatory interventions in the setting of AF.

Finally, it should be pointed out that AF ablation is a significant therapeutic strategy in the contemporary era. Yet, this procedure induces a degree of tissue damage initially that can be detected by blood tests. For example, a prospective study of 90 AF patients reported that troponin-T and creatine kinase-MB peaked at day 1, high-sensitivity C-reactive protein peaked at day 3 whereas fibrinogen and D-Dimer concentrations were significantly elevated at 1 week after the procedure.[75] Imaging methods such as magnetic resonance imaging[76] and positron emission tomography[77] are useful for characterizing myocardial edema that suggests the presence of inflammation. The procedure may provoke inflammatory reactions in the short term but has been shown to produce reverse atrial remodeling reflected by decreased fibrosis and inflammation in the long term.[78]

6 | RISK FACTOR AND LIFESTYLE MODIFICATIONS THAT REDUCE INFLAMMATION

Given the aforementioned pathophysiologic considerations, it seems reasonable to assume that weight reduction, low-moderate exercise, management of sleep apnea, smoking cessation, and aggressive management of hypertension and diabetes may have favorable effects on AF burden modulating hemodynamic, neurohormonal, inflammatory, and oxidative pathways.[79,80] In this context, inadequate treatment of risk factors significantly favors AF recurrence.[79] On the other hand, aggressive management of cardiometabolic risk factors, weight control, and aerobic training reduces AF burden, symptoms, and AF recurrence after ablation.[17,79–82]

Interestingly, the adoption of Mediterranean diet enriched with extravirgin olive oil but not with mixed nuts reduces AF risk.[83] It is well known that virgin olive oil has antioxidant and anti-inflammatory properties providing considerable cardioprotection.[84] Finally, the recently released randomized RACE 3 study demonstrated that risk factor driven upstream therapy, including treatment of risk factors and change of lifestyle, is effective and feasible to improve maintenance of sinus rhythm in patients with early persistent AF and HF.[85]

7 | CONCLUSIONS

Inflammatory mechanisms are implicated in various underlying conditions, producing the substrates necessary for AF.[86,87] Given the complexity of AF pathophysiology the relative impact of inflammation in different stages of atrial remodeling remains to be elucidated. Although the prognostic role of inflammatory markers in AF has been well established its additive value beyond conventional clinical

and echocardiographic risk factors needs further study. Undoubtedly, further mechanistic insights in atrial inflammatory processes may lead to specific interventions with a low risk for adverse events. Multitarget pharmacological interventions along with risk factor and lifestyle modifications at an early stage where atrial remodeling is not extensive seems to guide future therapeutic approaches.

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CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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