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Inflammation and Atrial Fibrillation

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LIST OF ABBREVIATIONS:

ACEI: Angiotensin-converting enzyme inhibitors
AF: atrial fibrillation
ARB: angiotensin II receptor blockers
CRP: C-reactive protein
IL: interleukin
PUFA: omega-3 polyunsaturated fatty acids
RAAS: renin-angiotensin-aldosterone system
TNF: tumor necrosis factor

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ABSTRACT

There is accumulating evidence pointing to an important association between inflammation and atrial fibrillation (AF). Elevated plasma levels of several markers of the inflammatory cascade have been shown to predict future risk of AF. Inflammation is likely to represent a novel target for both the treatment and prevention of atrial fibrillation.

INTRODUCTION

Recent advances have raised the hope of effective pharmacological or non-pharmacological treatments of atrial fibrillation (AF), and of better understanding of the pathophysiological mechanisms involved in the initiation and persistence of the arrhythmia. The pathophysiology of AF is complex and multifactorial. The underlying etiology is likely different in different patient subpopulations. The development of AF leads to many structural and electrical changes contributing to its perpetuation [1]. Atrial fibrillation also confers a prothrombotic or hypercoagulable state, which may contribute to the risk of thromboembolism [2].

Acute phase response is an innate biological response to a disturbance in homeostasis (infection, inflammation, tissue injury, neoplasm, or immune disturbance). A local reaction at the site of injury or infection leads to an activation of cytokines, specifically interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interferons. Cytokines then trigger systemic responses, which include leukocytosis; increases in glucocorticoid production; increases in erythrocyte sedimentation rate, fever, activation of complement and clotting cascades and an increase in plasma levels of acute phase proteins, C-reactive protein (CRP), serum amyloid A, fibrinogen, and other proteins [3].

C-reactive protein is one of the two most abundant acute phase reactants in humans: levels rapidly increase in the circulation as a result of either trauma or infection. Manufactured in the liver and deposited in damaged tissue, CRP is found in high levels in inflammatory fluids and in both the intimal layer of the atherosclerotic aortic artery and the foam cells within the lesions of atherosclerotic plaque [4,5]. C-reactive protein stimulates mononuclear cells to release tissue factor, a protein that is central to the initiation of coagulation reactions, complement activation, and the neutralization of platelet-activation factor. Together, these reactions promote a thrombotic response [6]. C-reactive protein has been traditionally thought of as a bystander marker of vascular inflammation, without playing a direct role in the inflammatory process. However, recent evidence suggests that CRP may contribute directly to the proinflammatory state [7,8]. An increased CRP plasma concentration is strongly associated with the

risk of serious cardiovascular events, being the measure of a generalized atherosclerotic inflammatory process [9].

INFLAMMATORY MARKERS

There is accumulating evidence pointing to an important association between inflammation and AF. Of all the plasma markers of inflammation, CRP has been the most extensively investigated in clinical studies. The first observation relating inflammation to AF after cardiopulmonary bypass surgery was made in 1997 by Bruins et al. They proposed a direct link between inflammation and AF by observing an increased frequency of AF after coronary artery bypass surgery. The peak incidence of AF occurred on the 2nd-3rd postoperative day, coinciding with the maximal elevation of CRP [10].

Inflammatory changes have also been reported in patients with non-postoperative AF. Marked inflammatory alterations have been observed in atrial specimens obtained from patients with isolated persistent AF [11]. Furthermore, Chung, et al found that CRP levels were significantly higher in patients with paroxysmal and chronic AF than in normal controls, and that the level was higher in the chronic AF than in the paroxysmal AF group. Thus, they showed that inflammation is involved in the onset of AF. However, they stated that whether inflammation is a consequence or a cause of AF remains unknown [12]. Some authors suggested the role of inflammation in atrial remodelling which promotes the initiation and perpetuation of AF [13]. It has been shown that plasma CRP concentration is higher in patients with AF, both paroxysmal and persistent, compared with the general population [12-14]. An increased baseline CRP level is also a risk factor for the development of AF during a long-term follow-up period [15]. In one study, the combination of microalbuminuria and an elevated hs-CRP increased the risk of subsequent AF development by up to four-fold [16]. It has also been demonstrated that CRP represents a robust and significant predictor of early AF relapse after successful cardioversion in patients with AF even after adjustment for multiple risk factors, such as hypertension and coronary artery disease [14,17,18]. Interestingly, two recent studies indicated that CRP relates to the left atrial size and AF duration before cardioversion, providing evidence of an association between inflammation and atrial structural remodelling [19,20].

Another established marker of the inflammatory cascade is IL-6. IL-6 is a circulating cytokine produced by monocytes, macrophages, lymphocytes and endothelial cells. IL-6 can induce a prothrombotic state by increasing expression of fibrinogen, tissue factor, factor VIII and von Willebrand factor, as well as by activating endothelial cells and increasing platelet production [21]. IL-6 is the main hepatic stimulus for CRP production [22]. Higher blood levels of IL-6 and fibrinogen after coronary artery bypass were observed in patients who de-

veloped AF after surgery. The -174G/C Interleukin-6 promoter gene variant appeared to modulate the inflammatory response to surgery and to influence the development of postoperative AF, suggesting an inflammatory component of postoperative atrial arrhythmias and a genetic predisposition to this complication [23]. Similar data have recently been reported for patients with non-postoperative AF. Several studies found increased levels of IL-6 in patients with AF compared with healthy controls [17,19,24-26].

Tumor necrosis factor- α (TNF- α) is a multifunctional circulating cytokine derived from endothelial and smooth muscle cells as well as macrophages [27,28]. TNF, along with interferon- γ and IL-1, stimulates IL-6 production by smooth muscle cells [29,30]. Sata et al measured TNF- α and other indices of inflammation during episodes of paroxysmal AF and after the restoration of sinus rhythm in the same patients, to clarify the relationship between inflammation and the onset of AF. Levels of hs-CRP, IL-6, and TNF after cardioversion were significantly higher than those in controls. Furthermore, the levels of these indices did not differ significantly even at 24 hours and 2 weeks after cardioversion. They concluded that inflammation is a causative agent of paroxysmal AF [25].

A prothrombotic or hypercoagulable state has been described in AF, which leads to the high risk of stroke and thromboembolism in this condition [1,31-33]. There is an apparent link between thrombogenesis and inflammation [34-36]. This supports the concept that the observed inflammation in AF increases the risk of thromboembolism as has been demonstrated for atherosclerotic models. High plasma IL-6 levels have been shown to be an independent predictor of stroke and the composite end point of stroke and death in a prospective study of patients with AF, suggesting that inflammation in AF may predict a poor prognosis. Interestingly, trends toward increased risk with high plasma CRP did not reach statistical significance [37]. Similarly, Thambidorai et al were able to demonstrate in 104 patients with AF that clinical and transoesophageal risk factors for stroke were greater for patients with elevated CRP compared with those with normal levels [38]. This observation is consistent with the results reported by Conway et al [26]. A risk score for stroke in AF has been correlated with IL-6 [24]. Given the evidence so far, the association between markers of inflammation and AF suggest that inflammation plays a role in the pathogenesis of this arrhythmia.

ANTI-INFLAMMATORY INTERVENTIONS

Drug therapy to prevent AF has traditionally targeted atrial electrophysiological mechanisms; however, the proarrhythmic effects of such drug therapy have limited its safety. An alternative strategy for the prevention of AF would be to prevent inflammation.

GLUCOCORTICOIDS

Glucocorticoids are used to treat a wide variety of inflammatory diseases. The first observation of a favourable effect of corticosteroid treatment on AF was made in 2000 by Yared et al [39]. Patients undergoing elective coronary or valvular heart surgery were randomized to receive dexamethasone or placebo after induction of anesthesia. They found that, compared with placebo, patients receiving dexamethasone had a lower incidence of new-onset atrial fibrillation during the first 3 days postoperatively. However, in another randomized, double-blinded, placebo-controlled study, dexamethasone failed to decrease the incidence of postoperative atrial fibrillation [40]. Dernellis and Panaretou demonstrated that the use of low dose glucocorticoids not only improved the efficacy of sinus rhythm maintenance postcardioversion but was also followed by a fall in CRP levels [14].

STATINS

The use of HMG-CoA reductase inhibitors (statins) in the treatment of dyslipidemia has been shown to improve survival and significantly reduce the appearance of cardiac events, both in primary and secondary prevention [41,42]. Statins also have so-called pleiotropic effects, which improve endothelial function, reduce inflammation, enhance angiogenesis and vasculogenesis, limit oxidative processes, stabilize atherosclerotic plaques, and inhibit the thrombogenic response [43,44].

An association between inflammation and AF is undoubtedly present. Therefore, therapeutic approaches targeting inflammation and oxidative stress may exert favourable effects on the risk of AF. Statins have both antiinflammatory and antioxidant properties [45,46]. In an animal study, simvastatin attenuated AF promotion by atrial tachycardia in dogs, an effect not shared by antioxidant vitamins [47]. The available evidence tends to prove that statin therapy, which poses anti-inflammatory properties and reduces CRP levels protects patients with coronary artery disease from developing AF. This effect appears to be distinct from its cholesterol lowering ability [48,49]. Hanna et al analyzed data from Advancent, a large multicenter registry of patients with reduced left ventricular ejection fraction, to explore the relationship between lipid-lowering therapy and AF. Lipid-lowering therapy was strongly protective against the development of AF. This benefit appeared to be independent of the lipid profile and additive to the protective effects of β -blockade and angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) [50]. Similar benefits have been observed in patients undergoing coronary artery bypass grafting [51]. C-reactive protein lowering with atorvastatin appears to be effective in eliminating PAF during daily life in a significant proportion

of patients [52]. However, in a recent post hoc analysis of a large randomized clinical trial, MIRACL study, intensive statin treatment did not appear to prevent new AF in the 16 weeks following acute coronary syndrome [53]. Tveit et al also reported that pravastatin did not reduce the recurrence rate of AF after electrical cardioversion [54]. Further clinical research will determine whether the more widespread use of statins will become an important component of the treatment of patients with atrial fibrillation.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEI) AND ANGIOTENSIN II RECEPTOR BLOCKERS (ARB)

Activation of the rennin-angiotensin-aldosterone system (RAAS) has been implicated in the pathogenesis of a broad spectrum of cardiovascular diseases [55]. Equally, interruption of the RAAS by either ACEI and/or ARBs is highly effective in reducing the known cardiovascular outcomes of these diseases [56]. In AF, the RAAS can influence both electrical and structural remodelling associated with this arrhythmia [55]. There is evidence to date in support of a role for RAAS activation as an important factor in the association between inflammation and AF. Experimental studies have revealed that angiotensin II possesses several proinflammatory properties, such as the activation of various inflammatory mediators (eg, CRP, TNF, IL-6, monocyte chemoattractant protein, nuclear factor-kappaB and nuclear factor-alpha), as well as stimulating the recruitment and infiltration of neutrophils [57,58]. Furthermore, Cardin et al were able to demonstrate that increased atrial expression of angiotensin II is linked with increased atrial cell death and leukocyte infiltration, again supporting a potential link between the RAAS, inflammation and AF [59]. RAAS blockade elicits anti-inflammatory and anti-aggregatory effects in patients with coronary artery disease and prevents atherosclerosis and vascular inflammation [60]. Both ACE-inhibitors and ARBs appear to have significant anti-inflammatory actions [61].

Given the potential role of the RAAS in AF, it would be rational to suspect that RAAS blockade by ACE inhibitors and ARBs may have beneficial effects in AF. Among patients enrolled in the SOLVD study of enalapril in left ventricular dysfunction, only 5.4% of the patients on enalapril experienced AF compared with 24% in the placebo arm. In multivariate analysis enalapril was the strongest predictor of reduced AF incidence [62]. Healey et al conducted a meta-analysis of the available 11 randomized clinical studies on RAAS blockade and AF, which included a total of 56,308 patients. They concluded that ACE inhibitors/ARBs reduced the overall risk of AF by 28% ($P=0.0002$). Furthermore, the reduction in AF was similarly 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) [63]. More impressive are the data from CHARM and Val-HeFT studies, showing an overall 44% relative risk reduction in the development of AF among patients with heart failure (P=0.007). The authors also noted a clear relationship between worsening heart failure (and greater activation of the RAAS system) and greater AF prevention [64,65]. Unfortunately, none of the randomized AF trials analyzed levels of known inflammatory markers simultaneously with the observed beneficial effects in preventing either new onset AF or arrhythmia relapse.

POLYUNSATURATED FATTY ACIDS (PUFA)

Evidence from epidemiologic and clinical prevention trials suggest that the omega-3 polyunsaturated fatty acids (n-3 PUFAs) may have a significant role in protecting against death from cardiovascular disease [66-69]. The n-3 PUFAs have been shown to exert a range of anti-inflammatory actions which include decreased production of arachidonic acid-derived prostaglandins and leukotrienes, decreased production of inflammatory cytokines, decreased expression of adhesion molecules and decreased expression of degrading proteinases that can erode plaque caps [70,71]. As AF has an important inflammatory component and n-3 PUFAs are potent anti-inflammatory agents, recent attention has focused on the possible antiarrhythmic effects of PUFA. In cultured rat atrial myocytes, n-3 fatty acids reduce induced asynchronous contractile activity, suggesting that n-3 fatty acids from fish may have antiarrhythmic effects on atrial muscle [72]. Besides direct electrophysiological effects, it has been proposed that the anti-inflammatory effects of these natural compounds may favourably affect atrial remodelling [73]. In a large, prospective study among elderly adults, greater consumption of tuna or other broiled or baked fish was associated with lower risk of incident AF. This observed relationship persisted after adjustment for a variety of demographic, clinical, lifestyle, laboratory, and dietary characteristics, including preceding myocardial infarction and congestive heart failure [74]. However, in the Danish Diet, Cancer, and Health study consumption of n-3 fatty acids from fish was not associated with a reduction in risk of atrial fibrillation or flutter [75].

ASCORBIC ACID

Antioxidant interventions with vitamin C might have an impact against AF-associated inflammation. Carnes et al were the first to show that an antioxidant intervention with vitamin C ameliorates atrial electrical remodeling in experimental animals and significantly reduces the incidence of postoperative AF in patients undergoing coronary bypass

surgery [76]. In a subsequent report examining 46 patients, Korantzopoulos et al demonstrated that treatment with vitamin C reduced the early recurrence of AF after cardioversion of persistent AF. In the vitamin C group, CRP levels were lower on the seventh day postcardioversion when compared with baseline [77].

CONCLUSION

Inflammation plays an important role in the development of AF [78-80]. Therefore inflammation may be a new therapeutic target in the management of AF. More studies are needed to clarify this important issue.

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