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REVIEW

Atrial fibrillation and inflammation

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Abstract

Atrial fibrillation (AF) is the most common clinical arrhythmia. Recent investigations have suggested that inflammation might have a role in the pathophysiology of AF. In this review, the association between inflammation and AF, and the effects of several agents that have anti-inflammatory actions, such as statins, polyunsaturated fatty acids, corticosteroids and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, have been investigated.

Key words: Atrial fibrillation; Inflammation; Statins

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EPIDEMIOLOGY AND PATHOPHYSIOLOGY OF ATRIAL FIBRILLATION

Epidemiology

AF is the most common clinical arrhythmia and affects > 2.3 million people in the United States. Its prevalence increases with age and is as high as approximately 10% by the age of 80 years. It is associated with increased risk of stroke, heart failure and mortality[1].

Pathophysiology

Conventionally, the presence of multiple re-entrant circuits that originate in the atria and rapidly firing atrial activity in the pulmonary veins have been described as potential mechanism for atrial fibrillation (AF)[1]. Recent studies have also shown that there is an association between inflammation and AF[2]. The frequent occurrence of AF in patients with inflammatory conditions such as myocarditis and pericarditis has raised the possibility that AF is associated with local inflammation[3,4]. The finding of marked inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies of patients with lone AF, but not in control patients[5], and the presence of circulating autoantibodies against myosin heavy chain[6] supports this hypothesis. Further evidence on this issue has come from the increase in inflammatory markers such as C-reactive protein (CRP), high-sensitivity CRP (hs-CRP) and interleukin-6 in both paroxysmal and persistent AF, compared to control subjects[7-14]. In a multivariate analysis of The Cardiovascular Health Study that included 5806 individuals, CRP levels predicted both the presence of AF at baseline and the development of AF during follow-up, even after adjustment for potential confounding factors[7]. Moreover, longer duration of AF has been found to be associated with higher hs-CRP levels compared with shorter duration of AF, which indicates that there is a link between AF burden and systemic inflammation[8,15]. Similarly, hs-CRP has been found to be a significant predictor of early AF recurrence after cardioversion[11,16-20].

In this review, we focus on the evidence that supports systemic inflammatory mechanisms that might initiate and perpetuate AF. AF has been shown to be associated with inflammation, therefore, the question of whether anti-inflammatory agents can decrease AF rates has been raised. The effects of several agents that have anti-inflammatory actions, such as statins, polyunsaturated fatty acids (PUFAs), corticosteroids and angiotensin-converting en-

zyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), have been investigated in AF in observational and randomized studies.

STATINS AND AF

Observations

The role of inflammation on atrial electrophysiological and structural changes and the effects of atorvastatin on AF were first evaluated by Kumagai *et al*[21] in a canine sterile pericarditis model. They found that the atorvastatin group had lower CRP levels, less pronounced fibrosis in the atrial myocardium, and a shorter duration of AF.

Hypotheses

Since AF has been shown to be associated with inflammation, the question of whether anti-inflammatory agents could decrease AF rates has been raised. Therefore, the effects of statins, which have anti-inflammatory actions, have been investigated in observational and randomized studies.

Small studies

In the canine pericarditis model[21], canine rapid atrial pacing model[22] and canine ventricular tachy-pacing model[23], treatment with statins resulted in decreased inducibility and sustainability of arrhythmia. In human studies, statins have been effective in preventing AF after electrical cardioversion[24,25], in patients with stable coronary artery disease (CAD)[26], acute coronary syndrome[27,28], and pace makers[29], and in patients undergoing coronary artery bypass surgery[30-33]. In a randomized placebo-controlled study, Patti *et al*[30] have shown that atorvastatin at a dose of 40 mg significantly decreased AF rates after bypass surgery compared with placebo. Although peak CRP levels were no different between placebo and atorvastatin groups, CRP levels were higher in patients who developed AF compared to those who did not[30]. Kourliouros *et al*[34] have shown that the benefits of statins on postoperative AF are dose-related.

In contrast to these findings, several studies were unable to show any positive effects of statins on AF. Tveit *et al*[35] and García-Fernández *et al*[36] did not find any benefit of pravastatin and atorvastatin in reducing recurrence rates of AF after electrical cardioversion. Humphries *et al*[37] showed that, although there was no association with statin use and recurrence of AF, recurrence rate was significantly lower in patients who were also taking β-blockers. Richter *et al*[38] were unable to show any positive effects of statins after AF ablation in a retrospective study.

Larger studies

In a retrospective large study of 4044 patients who were undergoing coronary artery bypass grafting (CABG) surgery, Virani *et al*[39] showed that statins had no positive effects on the occurrence of AF. In analyses of two large randomized trials (PROVE IT-TIMI 22 and A to Z trial), McLean *et al*[40] demonstrated high-dose statins did not decrease AF risk. In a large retrospective study, Adabag *et al*[41] found no difference in AF incidence with statin treatment (P = 0.09) in CAD patients. However, statins decreased AF incidence in a subgroup of patients with heart failure (P = 0.04). In contrast, Hanna *et al*[42] showed that statin treatment decreased AF rates in patients with left ventricular dysfunction.

Meta-analyses

Several meta-analyses have been performed to investigate the effects of statins on AF and have indicated conflicting results depending basically on the selection of studies. Fauchier *et al*[43] have performed a meta-analysis that included six studies with 3557 patients. Three studies investigated the use of statins in patients with a history of paroxysmal AF (n = 1) or persistent AF undergoing electrical cardioversion (n = 2), and three investigated the use of statins in primary prevention of AF in patients undergoing cardiac surgery or after acute coronary syndrome. Overall, the use of statins was significantly associated with a decreased risk of AF compared with controls (OR = 0.39). The benefit of statins was more marked in secondary prevention of AF (OR = 0.33) than for new-onset or postoperative AF (OR = 0.60). In the meta-analysis of Liu *et al*[44], six randomized and 10 observational studies with 7041 patients were analyzed. The analysis of randomized controlled trials showed no significant effect of statins on AF development, and significant heterogeneity between individual studies. Subgroup analysis revealed that differences in AF detection methodology might have been the cause of heterogeneity. The analysis of observational studies demonstrated that statin use reduced the relative risk for AF significantly without significant differences between the trials. This favorable effect was greatest in the postoperative patients. A more recent meta-analysis of seven hypothesis-generating trials with 3609 patients and 15 hypothesis-testing trials with 68 504 patients showed a 30% reduction in relative risk of AF in the hypothesis-generating trials and no effect in the hypothesis-testing trials. There was no difference in the effects of statins on primary or secondary prevention of AF[45]. Patel *et al*[46] included 14 trials with 7402 patients in their meta-analysis and showed that statins decreased AF rates by 45%, new-onset AF by 32%, recurrent AF by 57%, recurrent AF after cardioversion by 42%, and postoperative AF by 58%.

Conclusion

The studies that have evaluated the benefits of statins on AF were mainly retrospective and observational, and the results are controversial. The results of meta-analyses are also controversial, depending on the selection of the studies that included different patient populations and different agents at different doses. The data are not yet sufficient to recommend these agents for the treatment of AF outside their approved indications.

Table 1 Statins and atrial fibrillation

Ref.	Study design	Subjects	Conclusion
Kumagai *et al*[21]	Prospective	Interventional canine sterile pericarditis model; atorvastatin	Atorvastatin group had lower CRP, shorter duration of AF, less inflammation in atrial tissues
Siu *et al*[25]	Retrospective	62 lone persistent AF, statin *vs* control	Lower recurrence rate in the statin group
Tveit *et al*[35]	Prospective	114 patients undergoing electrical cardioversion; pravastatin *vs* none	Pravastatin did not reduce the recurrence rate of AF
Young-Xu *et al*[26]	Prospective	449 patients with CAD were followed for 5 yr	Development of AF was lower in statin group
Ozaydin *et al*[24]	Prospective	48 patients undergoing cardioversion; atorvastatin *vs* none	81% relative risk reduction in AF recurrence
Ozaydin *et al*[31]	Observational	264 patients undergoing CABG surgery; any statin	Statin group had lower AF rates
Patti *et al*[30] (ARMYDA-3)	Prospective	200 patients undergoing CABG surgery; atorvastatin *vs* placebo	61% reduction in the odds of AF
García-Fernández *et al*[36]	Prospective	52 patients undergoing cardioversion; atorvastatin *vs* none	No significant difference in recurrence rate of AF
Ramani *et al*[27]	Retrospective	1526 patients with ACS; various statins	43% reduction in the odds
Humphries *et al*[37]	Prospective, observational	625 patiens undergoing cardioversion; any statin	74% reduction in the odds of AF with β-blocker; no effect alone
Hanna *et al*[42]	Data from a multicenter registry	25 268 patients with LVEF ⩽ 40%	Lipid-lowering drug use was associated with reduced odds of AF
Fauchier *et al*[43]	Meta-analysis	Six studies with 3557 patients	Statins were significantly associated with a decreased risk of AF (P = 0.02) Benefit of statins was more marked in secondary prevention of AF
Liu *et al*[44]	Meta-analysis	Six randomized and 10 observational studies with 7041 patients	No significant effect of statins on AF development (P = 0.09). Observational studies showed that statin use decrease the relative risk for AF by 23%. This effect was greatest in the postoperative patients
Patel *et al*[46]	Meta-analysis	14 trials with 7402 patients	Statin decreased AF rates by 45%. Decrease was most prominent in postoperative AF
Marín *et al*[32]	Prospective, observational	234 patients undergoing CABG surgery; any statin	48% reduction in the odds of AF
McLean *et al*[40]	Two large, randomized trials: PROVE IT-TIMI 22 and A to Z trial	8659 patients with ACS; low- *vs* high-dose statin therapy	Neither study showed decreased AF risk with high-dose statin therapy
Lertsburapa *et al*[33]	Observational	555 patients undergoing CABG surgery; any statin	40% reduction in the odds of AF
Kourliouros *et al*[34]	Retrospective	680 patients undergoing CABG surgery; atorvastatin and simvastatin	Improving benefits with higher dose
Virani *et al*[39]	Retrospective	4044 patients undergoing CABG surgery; any statin	No effect
Adabag *et al*[41]	Cohort	13 783 CAD patients	No difference in AF incidence with statin treatment (P = 0.09). However, AF was reduced in a subgroup of patients with congestive heart failure (P = 0.04)

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CRP: C-reactive protein; ACS: Acute coronary syndrome; LVEF: Left ventricular ejection fraction.

Future directions

Future large randomized, placebo-controlled clinical trials are required to clarify the effect of statins on AF. A summary of the studies that have been performed on the effects of statins on AF is given in Table 1.

PUFAs AND AF

Observations

The observation that PUFAs reduce asynchronous contractile activity in rats suggests that they have antiarrhythmic effects on atrial muscle[47].

Hypotheses

The effects of PUFAs that have anti-inflammatory actions have been investigated in several studies.

Small studies

The reports about the effects of PUFAs on AF are more controversial. Calò *et al*[48] showed that pretreatment of 160 patients with fish oil capsules for 5 d before bypass surgery reduced the occurrence of postoperative AF. Saravanan *et al*[49] showed that fish oil 2 g/d did not reduce postoperative AF burden. PUFA supplementation in a randomized fashion in patients with implantable cardioverter defibrillators did not demonstrate any significant beneficial effect on ventricular tachyarrhythmias[50].

Larger studies

Two epidemiological studies have shown that PUFAs decrease the risk of AF[51,52]. Mozaffarian *et al*[51] reported that there was a negative correlation between the consumption of fish oil and risk of AF in a prospective study of 4815

Table 2 Polyunsaturated fatty acids and atrial fibrillation

Ref.	Study design	Subjects	Conclusion
Physicians' Health Study[54]	Prospective	17679 patients (epidemiological study)	Although statistically insignificant, AF risk is higher in PUFAs group
Danish study[53]	Prospective	47949 patients (epidemiological study)	Although statistically insignificant, AF risk is higher in PUFAs group
Rotterdam study[55]	Prospective	5184 patients (epidemiological study)	Although statistically insignificant, AF risk is higher in PUFAs group
Mozaffarian *et al*[51]	Prospective	4815 patients (epidemiological study)	Although statistically insignificant, AF risk is higher in fried fish/fish sandwich group Significantly, AF risk is lower in broiled/baked fish group
Calò *et al*[48]	Prospective	160 patients undergoing CABG surgery	AF risk is significantly lower in PUFAs group
Saravanan *et al*[49]	Prospective	Patients undergoing CABG surgery	AF risk is significantly lower in PUFAs group

PUFAs: Polyunsaturated fatty acids; AF: Atrial fibrillation; CABG: Coronary artery bypass grafting.

adults aged ⩾ 65 years. The study of Macchia *et al*[52] supported these findings and showed that n-3 PUFA reduced the risk of hospitalization for AF. In contrast to these findings, the Danish Diet, Health and Cancer Study[53], Physicians' Health Study[54] and Rotterdam study[55] were unable to show any beneficial effects of fish consumption on AF.

Conclusion
The question of whether PUFAs have beneficial effects on AF development cannot be answered with the current evidence. Therefore, the use of PUFAs in the prevention of AF cannot be supported.

Future directions
More research is needed in this area to yield clearer evidence. A summary of the studies that have been performed on the effects of PUFAs on AF is given in Table 2.

CORTICOSTEROIDS AND AF

Observations
The first observation of the possible relationship between corticosteroids and AF rates came from the study of Ueda *et al*[56].

Hypotheses
The effects of corticosteroids that have anti-inflammatory actions on AF have been investigated in several studies.

Small studies
Chaney *et al*[57] found no difference in the incidence of postoperative AF between the those treated and untreated with methylprednisolone. Yared *et al*[58] have shown that dexamethasone decreases the incidence of new-onset AF in patients undergoing heart surgery. Similarly, in a small study, low-dose methylprednisolone decreased plasma CRP levels and AF recurrence after electrical cardioversion[17]. On the other hand, a randomized double-blind study did not show any beneficial effects of corticosteroids on postoperative AF and inflammation[59]. However, in a randomized study, Halonen *et al*[60] showed that corticosteroids decreased the incidence of postoperative AF and serum CRP levels. In a canine sterile pericarditis model, Goldstein *et al*[61] found that prednisone significantly attenuated the increase in CRP, reduced neutrophil infiltration, and eliminated atrial arrhythmia inducibility.

Meta-analyses
A meta-analysis of nine randomized controlled trials has suggested positive effects of perioperative corticosteroid use on AF occurrence and on length of stay after cardiac surgery[62].

Conclusion
Data are not yet sufficient to recommend corticosteroids for the treatment of AF.

Future directions
Large randomized studies are required to clarify this issue of corticosteroid treatment of AF. A summary of the studies that have been performed on the effects of corticosteroids on AF is given in Table 3.

ACEIs AND ARBs

Observations
In an animal study, it has been shown that angiotensin Ⅱ inhibitors might prevent atrial electrical remodeling[63].

Hypotheses
The effects of ACEIs and ARBs that have anti-inflammatory actions on AF have been investigated in observational and randomized studies.

Small studies
ACEIs or ARBs have been shown to decrease AF in left ventricular dysfunction[64,65] and left ventricular hypertrophy[66], and after cardiac surgery[67-70] and cardioversion[71-73]. In contrast, two previous studies were unable to show any beneficial effect of ACEIs and ARBs on postoperative AF[74,75] and patients in AF rhythm control strategy[76].

Larger studies
In larger studies, ACEIs or ARBs were effective in reducing AF incidence in left ventricular dysfunction or heart failure[77-79]. In a retrospective large study of 10023 con-

Table 3 Corticosteroids and atrial fibrillation

Ref.	Study design	Subjects	Conclusion
Chaney *et al*[57]	Prospective	60 patients undergoing CABG surgery; methylprednisolone	No effects of steroids on in the incidence of AF
Yared *et al*[58]	Randomized	235 patients undergoing CABG or valve surgery	Dexamethasone decreased incidence of new-onset AF
Yared *et al*[59]	Randomized	78 patients undergoing CABG or valve surgery	Dexamethasone did not decrease incidence of new-onset AF and inflammation
Dernellis *et al*[17]	Randomized	104 patients undergoing electrical cardioversion	Methylprednisolone decreased plasma CRP levels and AF recurrence
Goldstein *et al*[61]	Animal study	Canine sterile pericarditis model	Prednisone treatment decreased inflammation, and eliminated atrial arrhythmia inducibility
Halonen *et al*[60]	Randomized	241 patients undergoing CABG or valve surgery	Corticosteroids decreased the incidence of postoperative AF and serum CRP levels
Baker *et al*[62]	Meta-analysis	Nine studies with 990 patients undergoing CABG or valve surgery	Positive effects of perioperative corticosteroid use on AF occurrence

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; CRP: C-reactive protein.

Table 4 Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and atrial fibrillation

Ref.	Study design	Subjects	Conclusion
Murray *et al*[76]	Prospective study, retrospective analysis	732 patients; AF rhythm control	No difference in AF recurrence
Madrid *et al*[71]	Prospective (electrical cardioversion)	154 patients; amiodarone only *vs* amiodarone + irbesartan	Recurrence of AF lower in irbesartan group
Zaman *et al*[73]	Prospective (electrical cardioversion)	47 patients; ACEI *vs* no ACEI group	Number of defibrillation attempts required for successful cardioversion was less in ACEI group
Ueng *et al*[72]	Prospective (electrical cardioversion)	125 patients; amiodarone only *vs* amiodarone + enalapril	Enalapril group had decreased rate of recurrence
Pedersen *et al*[65]	Prospective (post-MI)	1577 patients with LV dysfunction post-MI; trandolapril *vs* control	Trandolapril reduces AF
SOLVD[66]	Prospective study, but retrospective analysis (heart failure)	374 patients with depressed LV function; enalapril *vs* control	AF rate lower in ACEI group
Val-HeFT[78]	Prospective study, retrospective analysis (heart failure)	4409 patients with; valsartan *vs* control	ARB lower incidence of AF
CHARM[77]	Prospective study, retrospective analysis (heart failure)	5518 patients; candesartan *vs* control	ARB lowers incidence of AF in both normal and depressed ejection fraction
L'Allier *et al*[79]	Retrospective (hypertension)	5463 patients receiving ACEI *vs* 5463 patients receiving CCB	The incidence of AF was lower in ACEI group
Miceli *et al*[80]	Retrospective (post-CABG)	10023 patients undergoing isolated CABG; ACEI *vs* non-ACEI	ACEI treatment is associated with an increased risk of post-operative AF
Madrid *et al*[81]	Meta-analysis	Seven trials involving a total of 24849 patients	There was a significant statistical difference in the development AF with ACEI/ARB treatment
Kalus *et al*[82]	Meta-analysis	Four trials	There was a significant statistical difference in the development AF with ACEI/ARB treatment
Anand *et al*[83]	Meta-analysis	Nine randomized controlled trials	The use of ACEIs and ARBs had an overall effect of 18% risk reduction in new-onset AF across the trials and 43% risk reduction in patients with heart failure
Jibrini *et al*[84]	Meta-analysis	11 randomized trials	Overall, inhibition of the RAAS reduced the RR of AF by 19%. Reduction in AF was greatest in patients after electrical cardioversion and in patients with heart failure
Healey *et al*[85]	Meta-analysis	11 randomized trials	Overall, ACEIs and ARBs reduced the relative risk of AF by 28%. Reduction in AF was similar between ACEI and ARB and was greatest in patients with heart failure. Overall, there was no significant reduction in AF in patients with hypertension

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; MI: Myocardial infarction; CCB: Calcium channel blocker; LV: Left ventricle; RAAS: Renin angiotensin aldosterone system; RR: Relative risk.

secutive patients undergoing isolated CABG (3052 of whom received preoperative ACEI), Miceli *et al*[80] showed that the risk of new-onset postoperative AF ($P < 0.0001$) increased in patients treated with ACEI. They have stated that preoperative administration of ACEI in patients undergoing CABG might lower systemic vascular resistance and vasoplegia in the early postoperative phase, which results in hypotension and requires administration of more

fluids and inotropic and/or vasoconstrictor drugs that might increase the risk of AF.

Meta-analyses

Meta-analyses that have evaluated the benefits of ACEIs and ARBs have shown that, although their use is associated with low AF rates, efficacy rates differ between subgroups of patients mainly due to inclusion of different studies[81-85].

Conclusion

Both ACEIs and ARBs decrease AF incidence. However, the evidence is not sufficient to recommend these agents for the treatment of AF.

Future directions

Large randomized studies are still required to clarify the beneficial effects of ACEIs and ARBs on AF. A summary of the studies that have been performed on the effects of statins on AF is given in Table 4.

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