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REVIEW

The Association Between Rheumatoid Arthritis and Atrial Fibrillation: Epidemiology, Pathophysiology and Management

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Abstract: Atrial fibrillation (AF) is the most common cardiac arrhythmia with a significant increase in morbidity and mortality worldwide. Rheumatoid arthritis (RA), as a systemic inflammatory disease, affecting 0.5–1.0% of the adult population, is associated with increased incidence of cardiac arrhythmias such as AF. Several epidemiologic studies find that the risk of AF is increased in RA when compared with the general population. Other studies are inconsistent. Considering that inflammation plays an important role in AF, RA may be involved in the occurrence and development of AF. This review summarizes the epidemiology, pathophysiology, and management of AF in patients with RA.

Keywords: atrial fibrillation, rheumatoid arthritis, epidemiology, pathophysiology, management

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory joint disease, affects 0.5–1.0% of the adult population, and is associated with an increased mortality rate.[1] RA is autoimmune and is generally characterized by autoantibodies to immunoglobulin G (IgG).[2] The utilization of biologic disease-modifying anti-rheumatic drugs (bDMARDs) improves long-term prognosis of RA patients.[3] Besides being a cause of joint structural damage,[4] many diseases are associated with RA, including osteoporosis,[5] depression,[6] pulmonary disease,[7] hypertension,[8] cardiovascular disease (CVD)[9] and cardiac arrhythmias.[10] The association between CVD and RA is well established and the risk of CVD in RA patients is 1.5 times higher compared to the general population.[11,12] CVD is the most common cause of death in RA.[13] In addition to accelerating the development of atherosclerosis, RA is associated with increased incidence of cardiac arrhythmias, especially in women.[14] Inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor- alpha (TNF-α) may play an important role in the cardiac electrophysiology.[15,16]

Atrial fibrillation (AF), as the most common cardiac arrhythmia, affects more than 33 million people worldwide and is associated with a significant increase in morbidity and mortality.[17] The increased risk of stroke, dementia, heart failure, and death are associated with AF.[18] The management of AF mainly includes rate control, rhythm control, and stroke prophylaxis.[19] AF is promoted by advancing age, male sex, heart disease, hypertension, diabetes, obesity, stroke and alcohol overuse.[17,20] However, some individuals develop AF with no apparent risk factors, which suggests some underlying risk factors to AF. In patients with AF, inflammatory infiltrates have been observed in atrial tissues[21] and increased systemic inflammation appears to relate to the persistence of AF.[22] In the general population, inflammatory cytokines such as IL-1, IL-2, IL-6, IL-10 and TNF-α are associated with the presence, persistence and outcome of AF.[23,24]

Under the premise that a systemic inflammatory state may contribute to AF, patients with chronic inflammatory conditions such as RA might be at an increased risk of developing AF. Moreover, growing studies suggest that the

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incidence of AF may be significantly increased in RA than in the general population.[25] Nevertheless, other researches have yielded inconsistent results.[26,27] Since systemic inflammation plays an important role in the pathogenesis of AF and RA is a disease characterized by chronic systemic inflammation, RA may play an important role in the occurrence and development of AF. In this article, we will review the epidemiology, pathophysiology, and management of AF in patients with RA.

Epidemiology

In a Danish nationwide cohort study, Lindhardsen et al report an overall 40% higher incidence of AF in patients with RA compared to the general population.[28] Besides, in patients with RA younger than 50, the relative risk of AF is increased threefold. It is worth noting that the study did not adjust for all cardiovascular risk factors due to the lack of relevant information. Using data from a large US commercial insurance plan, Kim et al show that the incidence of hospitalization for AF in patients with RA is 1.4 times higher than in non-RA patients.[26] After adjusting for various comorbidities, medications and healthcare utilization, the result shows no increased risk of AF associated with RA. These inconsistent findings could be due to a number of differences such as the age of patients, gender composition and duration of follow-up time between the two studies. Bacani et al also adjust the age, sex, calendar year, smoking, and hypertension.[29] Compared with non-RA subjects, the risk of AF during 9.6 years follow-up is higher among patients with RA. However, AF related mortality is equally both in patients with and without RA. In a senior RA cohort from the Korean National Health Insurance Service, a similar risk of AF is found by Jang et al when compared with the control.[27] Although patients in this study could represent the RA patients older than 65 years of age, the similar occurrence of new-onset AF in the senior patients with RA maybe due to the limited close surveillance of heart rhythm. Besides, in a recent study by Argnani et al, RA acts as an independent risk factor for the development of AF.[30] In this study, there are more women in the RA cohort. In conclusion, these studies suggest a link between AF and RA. A routine screening for AF should be part of assessment of patients with RA. The detailed characteristics of the epidemiologic studies are illustrated in Table 1.

Pathophysiological Pathways Between RA and AF

RA and Atrial Remodeling

Structural atrial remodeling is associated with the maintenance and recurrence of AF and electrical remodeling of atria may be the first stage in the onset of AF.[31,32] RA is involved in both atrial electrical and structural remodeling.

P-wave indices (P-wave duration, P-wave dispersion, and P-wave standard deviation) are associated with atrial remodeling[33] and involved in the increased risk of AF.[34] In patients with inflammatory condition such as RA, indices of P-wave dispersion are increased.[24] IL-6-induced downregulation of atrial connexin is responsible for this change. As a systemic inflammatory disease, patients with RA have ten times higher levels of IL-6 in serum than healthy human.[35] Furthermore, IL-6-mediated-Ca2+ handling abnormalities contributes to the development of AF by increasing propensity for arrhythmogenic alternans.[36] Guler et al find that P-wave duration and P-wave dispersion, signs for the prediction of

Table 1 Epidemiologic Studies

Study	Year	Country	Study Design	Number of Cases	Follow-Up	Results	Incidence Rate of AF in RA
Lindhardsen et al[28]	2012	Denmark	Retrospective cohort	18,247	4.8 years	Increased	4.2%
Kim et al[26]	2014	USA	Retrospective cohort	20,852	2 years	No increased	4 per 1000 person-years
Bacani et al[29]	2015	USA	Retrospective cohort	813	9.6 years	Increased	18.3%
Jang et al[27]	2020	Korea	Prospective cohort	4217	5.9 years	No increased	4.01 per 1000 person-years
Argnani et al[30]	2021	Italy	Retrospective cohort	21,201	5 years	Increased	7.01%

AF, are higher in RA patients than healthy control subjects.[37] These rapidly induce atrial electrical remodeling. Prolonged atrial electromechanical conduction is associated with the decreased plasma prolidase activity in patients with AF.[38] Meanwhile, in patient with RA, collagen turnover and fibrosis are decreased with lower prolidase activity.[39] Atrial conduction time is one of the factors that represent left atrial remodeling and is also a predictive factor of AF recurrence.[40] The prolonged atrial conduction time is observed in collagen-induced arthritis (CIA) rat, a widely used animal model to study the pathophysiology of human RA.[41] TNF-α, as a major proinflammatory factor in RA,[42] mediates inflammation-related AF by altering calcium handling and increasing arrhythmogenesis of pulmonary vein cardiomyocytes.[43]

As early as in the 1976, study has observed a link between left atrial enlargement and AF.[44] The late stage of atrial remodeling is mainly characterized by structural remodeling.[45] In CIA rat after primary immunization, atrial structural remodeling is observed and AF inducibility and duration are substantially increased.[41] Through the same animal model, Zhang et al find that the inducibility and duration of AF are significantly reduced by resveratrol, a type of polyphenol antioxidant.[46] Meanwhile, there is a trend for left atrial (LA) enlargement in cardiac asymptomatic RA patients.[47] Atrial fibrosis is a hallmark of atrial structural remodeling.[48] In patients with RA, extensive atrial fibrosis is observed.[49] The degree of LA fibrosis is not only associated with the occurrence of AF,[50] but also a good predictor of AF recurrence post-AF ablation.[51] It is worth noting that when compared with the control group, the degree of fibrosis by cardiac magnetic resonance imaging is similar or lower in RA patients with low to moderate disease activity.[52] Furthermore, insulin resistance (IR) contributes to increased AF susceptibility by engendering both atrial structural remodeling and abnormal intracellular calcium homeostasis.[53] Elevated IR has been observed in patients with RA and is consistent with high disease activity.[54]

RA and Autonomic Nerve System

After activation of the autonomic nervous system (ANS), significant changes in atrial electrophysiology lead to the occurrence of AF.[55] Methods that reduce autonomic innervation or outflow may improve the incidence of AF. At the same time, studies have suggested an imbalance of the ANS in patients with RA.[56] Sympathetic nerve activity (SNA) is thought to play an important role in provoking AF.[57] It makes the atria more vulnerable to arrhythmogenic factors from the pulmonary veins. There is evidence of heightened sympathetic outflow in patients with RA and it's associated with increases in both pain and inflammation in RA.[58] ANS dysfunction in RA is not only present in the resting state, study has shown an enhanced sympathetic response to exercise in post-menopausal women with RA.[59] In addition, the use of tocilizumab, an IL-6 blockade, does have the potential to improve autonomic dysfunction in RA.[60]

RA and Renin Angiotensin System

Renin angiotensin system (RAS) is suggested to play a key role in the occurrence and development of AF through structural and electrical remodeling.[61,62] In addition, RAS blockade therapy has been shown to reduce the relative risk of recurrent AF by 39%.[63] Angiotensin-converting enzyme (ACE) and angiotensin II (Ang II) are the major components of RAS and there is intracellular RAS in cardiac myocytes.[64] The stimulation of angiotensin II may induce AF through inflammation, epicardial fat accumulation, and electrical cardiac remodeling.[65] Previous study has found that the expression of ACE and Ang II are up-regulated in the synovium of the joints from patients with RA.[64] Research shows that in women with RA, serum levels of RAS components such as ACE and Ang II are higher than healthy females and this difference is not altered by the use of ACE inhibitors.[66] Furthermore, the levels of Ang II are higher in active RA when compared with the remission group.[67]

RA and Endothelial Dysfunction

Through years of follow-up, studies have found that endothelial dysfunction is associated with increased risk of AF.[68,69] Besides, the incidence of AF is significantly higher in patients with coronary endothelial dysfunction when compared with those with normal coronary endothelial function and similar AF risk factors.[70] Possible mechanisms include inflammation and oxidative stress.[71,72] From microvascular to macrovasculature, several studies have shown that endothelial dysfunction is observed in patients with RA.[73–75] Increased TNF-α levels induce the endothelial dysfunction

in RA.[76] This is associated with reduced nitric oxide (NO) bioavailability and decreased cyclic guanosine monophosphate (cGMP) levels by increasing vascular oxidized low density lipoprotein (ox-LDL) content and activation of the lectin-like oxidized low-density lipoprotein receptor-1/ nuclear factor-κB/arginase 2 (LOX-1/NFκB/Arg2) pathway. Meanwhile, the addition of TNF-α inhibitors improves endothelial dysfunction in RA.[77,78] Apart from peripheral arteries, Ciftci et al find that coronary endothelial dysfunction is also present in patients with RA.[79] The role of inflammatory factors between RA and AF are shown in Figure 1.

RA and Other Potential Cardiovascular Risk Factors

Epicardial adipose tissue (EAT) is located between visceral pericardium and epicardium surface.[80] Increased EAT thickness is an independent predictor of AF and associated with the severity and recurrence of AF.[81] In patients with RA, EAT thickness is higher than in healthy controls.[82] Furthermore, EAT thickness is positively correlated with the severity of RA.[83] Higher adiponectin concentrations are independently associated with increased risk of AF, specifically among older individuals.[84] Circulating adiponectin levels are significantly higher in patients with RA and they play an important pro-inflammatory role in the pathogenesis of RA.[85,86] The pathophysiological pathways between RA and AF are shown in Figure 2.

Effects of Drugs Used to Treat RA on AF

Biologicals on AF

TNF-α plays an important role in atrial structural, electrical, contractile, and autonomic remodeling.[87] Anti-TNF-α therapy, a cornerstone of RA treatment, has been demonstrated to improve cardiovascular outcomes.[88–90] Therefore, TNF-α antagonists may have a positive effect on the treatment of AF. IL-6, another inflammatory factor in RA, is elevated in serum and synovial fluid of affected joints.[91] On the other hand, IL-6 is a risk factor for AF and high levels of IL-6 predict poor prognosis in patients with AF.[23,92] The underlying mechanisms include atrial fibrosis and atrial electrical remodeling.[93] Considering that the inhibition of IL-6 significantly reduces cardiovascular event rates,[94] patients with AF may benefit from anti-IL-6 therapeutics. In addition, endothelial function is improved by tocilizumab, an IL-6–blocking agent.[95] This is perhaps a mechanism by which anti-IL-6 therapeutics may improve AF. IL-1β is an independent risk factor of sustained AF.[96,97] Besides, it has been found to mediate chronic inflammatory responses in RA.[98–100] In the treatment of RA, IL-1 blockers are

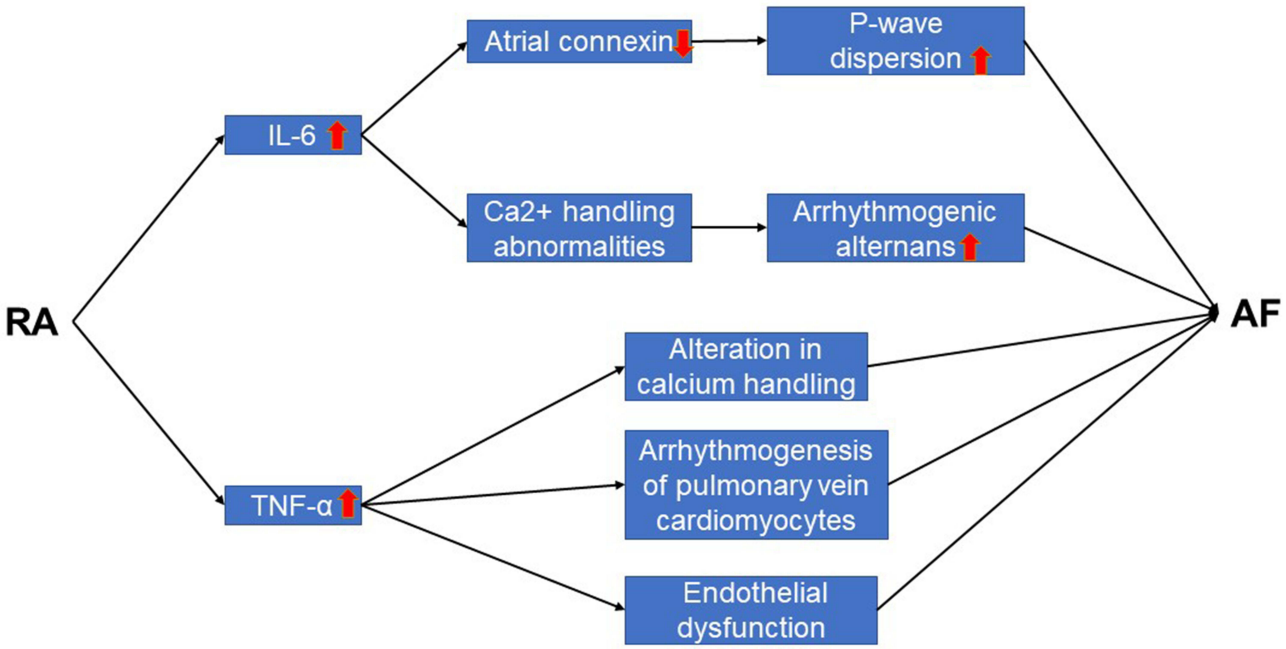

Figure 1 The role of inflammatory factors between RA and AF.
Abbreviations: RA, rheumatoid arthritis; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; AF, atrial fibrillation.

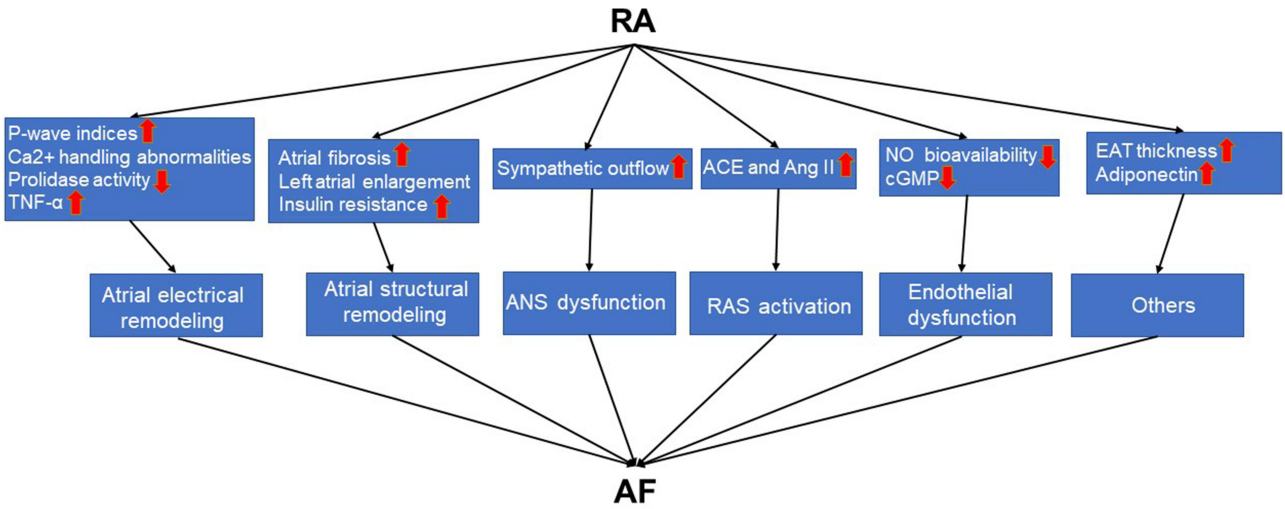

Figure 2 The pathophysiological pathways between RA and AF.
Abbreviations: RA, rheumatoid arthritis; TNF-α, tumor necrosis factor-alpha; ACE, angiotensin-converting enzyme; Ang II, angiotensin II; NO, nitric oxide; cGMP, cyclic guanosine monophosphate; EAT, epicardial adipose tissue; ANS, autonomic nervous system; RAS, renin angiotensin system; AF, atrial fibrillation.

safe and effective.[101] In consideration of the pathogenic role of IL-1β in AF, further studies are needed to determine the effect of IL-1 blockers on AF. Janus kinase (JAK) inhibitor has enabled the treatment of RA to enter a new stage by suppressing the action of JAK, an intracellular tyrosine kinase.[102] On the other hand, JAK signaling pathway plays an important role in cardiac pathophysiology and has been implicated in atrial myocytes hypertrophy, one of the structural remodeling features in AF.[103] The occurrence and development of AF in RA may be affected by JAK inhibitor.

Glucocorticoids and Hydroxychloroquine on AF

Glucocorticoids, as a short-term bridge, have been used for decades to manage symptoms of RA.[104] However, 30 to 50% of patients with RA still use glucocorticoids for long-term treatment.[105] In a large case-control study, current glucocorticoid use is associated with an almost 2-fold increased risk of AF.[106] Subsequent study has shown that glucocorticoid-induced biochemical modification of cardiac ion channels and effective refractory period shortening may be the underlying mechanisms of AF.[107] Hydroxychloroquine is especially used in RA due to its cost-effectiveness, safety and efficacy.[108] In patients with systemic lupus erythematosus, the use of hydroxychloroquine is associated with an 88% decrease in the risk of incident AF.[109] Further studies would be needed to confirm the anti-fibrillatory benefit of this medication in patients with RA.

Managements of AF in RA

Patients with AF have a four-fold to five-fold increase in the risk of stroke.[110] Meanwhile, the risk of stroke is increased in RA, especially in younger patients.[111] However, in an international clinical audit, a large proportion of RA patients with AF who have high risk of stroke do not receive anticoagulant therapy.[112] Anticoagulant treatment among RA patients with AF deserves more attention. Catheter ablation with pulmonary vein isolation (PVI) is an effective treatment for AF.[113] In patients with RA, catheter ablation is safe and effective when compared with non-RA patients.[114,115] However, AF recurrence is more common in RA and is associated with preablation C-reactive protein (CRP) levels and erythrocyte sedimentation rates (ESRs).[115] Inflammation plays a negative role in AF recurrence and maintenance after ablation.[116] Study has shown that glucocorticoids reduce the rate of immediate AF recurrence after catheter ablation by suppressing inflammation.[117] Control of RA disease activity before ablation and use of antiarrhythmic drugs after ablation may help to reduce AF recurrence. Most worthy of mention is that catheter ablation might be considered as the first-line therapy in patients with RA, because some antiarrhythmic drugs are difficult to apply in RA. For instance, both amiodarone and RA cause the development of pulmonary fibrosis.[118,119] In the prevention of AF, patients with hypertension and heart failure may benefit from angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB).[120] Further research is needed to determine whether patients with RA benefit from ACEI and ARB.

Conclusion and Perspective

In conclusion, patients with RA may have higher incidence of AF than patients without RA. Inflammation is a common driver of both disease processes.[121,122] Compared with the general population, the mortality in patients with RA is increased.[123] Elevated incidence of AF due to RA may be one of the reasons. However, two retrospective cohort studies have found no link between AF and RA.[26,27] This may be due to the differences in patient characteristics, follow-up time and treatment.

In addition to synovitis, patients with RA are also at high risk of CVD, including AF.[28–30,124] The major pathophysiological mechanisms of AF include atrial remodeling, autonomic nervous system dysfunction, activation of RAS, endothelial dysfunction, increased EAT thickness, higher adiponectin concentrations and IR.[31,32,53,55,62,68,69,81,84] RA is widely involved in these pathophysiological processes. Controversially, some studies have shown an absence of association between RA and the occurrence of new-onset AF.[26,27] This may be due to the lack of close surveillance of heart rhythm.

Both RA and AF promote stroke,[110,111] but in RA patients with AF, a small proportion of them receive anticoagulant therapy.[112] Given the high risk of stroke, anticoagulation or left atrial appendage closure procedure is important in the management of RA patients with AF when required. Although catheter ablation is safe in patients with RA, a higher rate of AF recurrence is a problem.[115] Systemic inflammation may be responsible, this would need further study in the future.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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