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Review Article

Association between rheumatoid arthritis and atrial fibrillation: a new perspectives

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ABSTRACT

Rheumatoid arthritis (RA) is a disease with an autoimmune component that directly and indirectly affects various organs, causing significant damage and complications. However, knowledge about the subject and its association with atrial fibrillation (AF) is limited, making its study important due to its close relationship with the incidence of acute coronary syndrome (ACS). AF is the most common cardiac arrhythmia worldwide, showing a significant increase in morbidity and mortality in people who suffer from it. RA characterized by being a systemic inflammatory disease, affects 0.5-1.0% of the adult population. It is associated with a higher incidence of cardiac arrhythmias such as AF. Several epidemiological studies find that the risk of AF is increased in RA compared to the general population. Considering that inflammation plays an important role in AF, RA may be involved in the onset 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

Atrial fibrillation (AF) is the most common clinical arrhythmia. It is a condition in which the atrial electrical signals are fast and disorganized, irregular heartbeats occur accumulating blood which is not ejected correctly, generating blood stasis that favors the formation of clots, which is why it is closely related to a higher risk of death due to its more serious complications such as stroke, peripheral embolism and heart failure.[1] On the other hand, RA represents a chronic, multifactorial inflammatory disease of an autoimmune nature.

It predominantly affects the synovial tissues within small joints and causes limitation of movement.[2]

Peripheral joints are affected symmetrically, and extra-articular manifestations may be expressed. Naturally, RA causes deformity, lung involvement, infections, tumors and joint disability, as well as a reduction in life expectancy, the latter due to the high cardiovascular risk. An early diagnosis, in addition to the use of targeted drugs, leads to an early remission, improving the prognosis of RA, since its pathophysiological complexity, discussed later in the article, requires a multidisciplinary approach with good treatment.[3]

The connection between these two conditions will be pointed out, mainly attributed to the effects of chronic inflammation on the structural and electrical remodeling of the heart. Furthermore, patients with RA have a high

prevalence of cardiovascular risk factors, which reinforces this association. Likewise, understanding the common mechanisms between RA and AF is essential to develop preventive and treatment strategies that improve outcomes in these patients.[4]

EPIDEMIOLOGY OF RA AND AF

Regarding the epidemiology of these conditions, the global burden of disease shows that the estimated prevalence of AF ranges from 2% in the general population to 33.5 million people and affects between 2.5% and 3.5% of the population in several countries. Age plays a crucial role in the prevalence, since 10 to 12% of people aged 80 years or older are affected and its incidence increases with age; approximately 1 in 4 adults develop AF during their lifetime. Likewise, the prevalence of RA varies between 180 and 1,070 per 100,000 inhabitants. AF is the most common arrhythmia among patients with RA, especially in young women under 50 years of age, with sedimentation rates greater than 60 mm/h or anti-TNF-α antibodies.[5]

Some people have AF that comes and goes and lasts from minutes to weeks, while others experience AF continuously and permanently. It is epidemiologically demonstrated that AF is correlated with several factors that, both individually and in combination, promote the initial development of the arrhythmia and exacerbate the episodes. Risk factors include excessive alcohol intake, stress or infection and may go away on their own or in the absence of the underlying trigger. Other risk factors include heart failure, obstructive sleep apnea, obesity, hypertension, chronic kidney disease (CKD), valvular disease, and thyroid disease, in addition, the risk increases with age, as mentioned above, because aging constitutes the main factor responsible for the pathogenesis of arrhythmia.

The Framingham studies have also confirmed that diabetes mellitus and genetic factors significantly predispose the development of the disease, while multiple dietary components play a protective role in reducing the onset of AF.[4] Finally, in another study conducted in the United Kingdom, between 2006 and 2022, participants from the population based biobank were screened for autoimmune diseases. Participants were followed up to detect incident AF, including 494,072 participants free of AF, where the mean age was 58 years, 54.8% of whom were women. The results showed that RA was one of the diseases associated with a higher risk of developing AF, with a higher incidence in women. In a Danish cohort study, arrhythmia was also associated with a 0.8% mortality rate in individuals with RA.[5]

LITERATURE SEARCH

It is a descriptive-exploratory study type of bibliographic review. The literature search period is from 2010 to 2024 in electronic databases such as PUBMED, ELSEVIER, and web of science. The keywords used in the MesH search were: AF, RA, epidemiology, pathophysiology, management. Inclusion criteria: search terms, level of evidence, summaries and keywords, exclusion criteria: not related to the topic, outside the year limit, not available; They will be classified by year, type of study and level of evidence. For eligibility, a critical reading is carried out, level of evidence, documents available for analysis and according to the topic. A total of 22 sources were obtained for analysis and synthesis.

THE ASSOCIATION BETWEEN RA AND AF BETWEEN AUTONOMIC NERVOUS SYSTEM AND RA

The autonomic nervous system (ANS) is part of the peripheral nervous system and is responsible for the involuntary regulation of the body's organs and systems. It is divided into the sympathetic and parasympathetic systems, which act in opposition to one another in certain organs, functioning antagonistically. However, they also work synergistically to achieve a balance that maintains homeostasis in the individual.[6]

In research on RA and the development of fundamental new therapies, the pathophysiology of RA has shown a notable association with an imbalance in the ANS. Dysfunction in this system may precede and even predict the onset of RA.[6] Studies have found that patients with RA exhibit increased sympathetic activity, which is directly associated with greater pain and inflammation.[7]

The ANS operates through visceral reflexes mediated by cholinergic and catecholaminergic pathways. In RA, inflammation is detected by the vagus nerve due to surrounding pro-inflammatory cytokines. Normally, this would reduce inflammation through the "cholinergic anti-inflammatory pathway," which decreases the production of pro-inflammatory cytokines in macrophages via a vagal reflex. However, in RA, this reflex is impaired, leading to the opposite effect. The chronic inflammation of peripheral tissues disrupts this mechanism, causing the ANS and the immune system to respond with various regulatory molecules (cytokines, neuropeptides, neurotransmitters) in a bidirectional manner to the homeostatic disturbances induced by inflammation.[8]

This disruption of the body’s homeostasis and the associated inflammation are directly linked to AF. When the ANS is activated, it induces significant changes in atrial electrophysiology, leading to the onset of AF.[9] Sympathetic nervous activity (SNA) is believed to play a crucial role in provoking AF, making the atria more vulnerable to arrhythmogenic factors from the pulmonary veins.[10,11]

Thus, inflammation, which drives ANS dysfunction, is a shared component in the pathophysiology of both RA and AF. It acts as a common contributor to these two conditions.

RA AND THE RENIN-ANGIOTENSIN SYSTEM

RAS activation has been documented in patients with RA, where a significant increase in angiotensin II type 1 receptors (AT1R) has been observed compared to healthy individuals. This overexpression suggests that the RAS could contribute to the increased cardiovascular risk in these patients. Angiotensin II (Ang II), a central component of the RAS, not only regulates blood pressure but also promotes inflammation by increasing the production of proinflammatory cytokines such as TNF-α and IL-6. This mechanism establishes a vicious cycle where inflammation activates the RAS, which in turn enhances inflammation, thus contributing to a more severe progression of the disease.[12]

IMMUNOLOGICAL MECHANISMS AND INFLAMMATORY EFFECTS

RAS components are present in immune cells, including lymphocytes and macrophages. Ang II acts mainly through AT1R to induce proinflammatory responses. Furthermore, AT1R antagonists have been shown to have direct and indirect anti-inflammatory effects, suggesting that their use could be beneficial in the management of RA. On the other hand, the AT2R receptor appears to have a protective effect by counteracting some of the harmful effects mediated by AT1R.[13]

CLINICAL IMPLICATIONS

Patients with RA have a significantly elevated cardiovascular risk, which cannot be explained solely by traditional risk factors. RAS dysfunction has been associated with changes in vascular structure and an increased incidence of subclinical atherosclerosis. Recent studies have indicated that RAS inhibition by angiotensin receptor blockers (ARBs) or angiotensin converting enzyme inhibitors (ACEi) may offer additional benefits to standard treatment for RA, helping to reduce both inflammation and cardiovascular risk.[14]

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. Anti-TNF-α therapy, a cornerstone of RA treatment, has been demonstrated to improve cardiovascular outcomes.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 an synovial fluid of affected joints. 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.

The underlying mechanisms include atrial fibrosis and atrial electrical remodeling. Considering that the inhibition of IL-6 significantly reduces cardiovascular event rates, patients with AF may benefit from anti-IL-6 therapeutics.

In addition, endothelial function is improved by tocilizumab, an IL-6–blocking agent. This is perhaps a mechanism by which anti-IL-6 therapeutics may improve AF. IL-1β is an independent risk factor of sustained AF.[15]

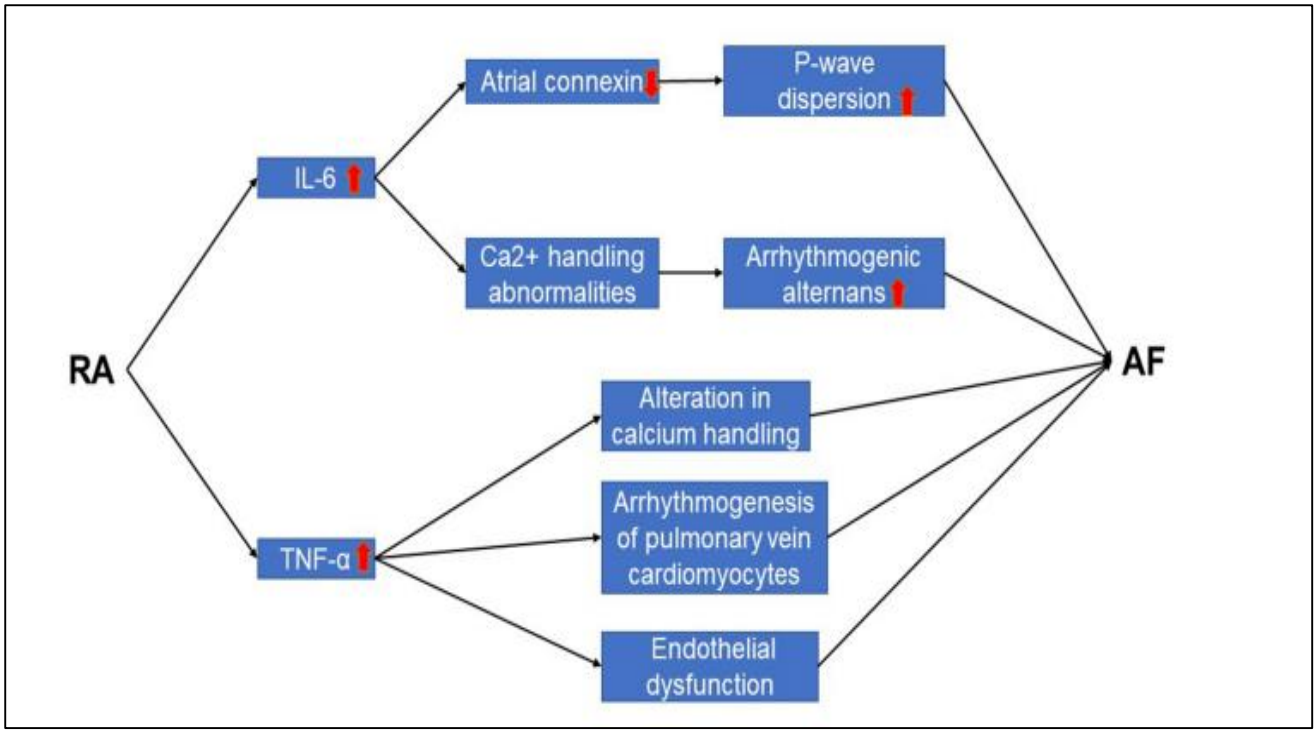

Figure 1: The role of inflammatory factors between RA and AF.[12]

DISCUSSION

RA is a chronic autoimmune disease characterized by joint inflammation, but also has significant extra-articular manifestations, including cardiovascular complications. The pathophysiology of RA involves an autoimmune attack on synovial membranes, resulting in an imbalance of pro- and anti-inflammatory cytokines. This imbalance is not limited, but also contributes to systemic inflammation, which may increase the risk of cardiovascular diseases, such as AF.[16]

Interleukin 6 (IL-6) is one of the most relevant cytokines in this context. IL-6 levels have been shown to be significantly elevated in patients with RA and correlate with disease severity. At the extra-articular level, this cytokine plays a crucial role in atrial remodeling, a process that includes fibrosis, cardiac cell apoptosis, and alterations in the electrical conduction of the heart.[17]

Atrial remodeling is a pathological process characterized by structural and functional changes in cardiac tissue, particularly in the atria. In the context of RA, the chronic effect mediated by IL-6 and other cytokines contributes to atrial fibrosis, a phenomenon that has been identified as a key marker of predisposition to AF. Atrial fibrosis manifests as an increase in the deposition of collagen and other components of the extracellular matrix, which alters the normal architecture of atrial tissue.[18]

Atrial fibrosis not only affects the structure, but also has a significant impact on the electrical function of the heart. The accumulation of fibrous tissue can disrupt the normal propagation of electrical impulses, creating a favorable substrate for the onset of arrhythmias. In experimental studies, it has been observed that the induction of collagenous arthritis in animal models results in an increase in the inducibility and duration of AF, suggesting that inflammation associated with RA may facilitate the onset of this arrhythmia.[19]

Furthermore, cardiomyocyte apoptosis, which has been documented in patients with RA, contributes to atrial remodeling. Programmed cell death of cardiomyocytes can be induced by chronic inflammation and oxidative stress, resulting in decreased cardiac muscle mass and impaired contractile function of the heart. This process, combined with fibrosis, creates an environment conducive to electrical dysfunction and AF.[20]

IL-6, in addition to being an inflammatory mediator, has direct effects on cardiac function. Elevated IL-6 has been shown to induce changes in the expression of connexins, which are proteins essential for the formation of intercellular junctions in cardiac tissue.

These changes can alter electrical communication between myocardial cells, contributing to electrical instability and predisposition to AF.[21]

Studies have shown that IL-6 can induce electrical remodeling in the atria, which results in increased susceptibility to AF, in this context IL-6 not only acts as a marker of inflammation, but may also be a causal factor in atrial remodeling and the appearance of arrhythmias.[22]

CONCLUSION

In conclusion, patients with RA may have higher incidence of AF than patients without RA. Inflammation is a common driver of both disease processes. Compared with the general population, the mortality in patients with RA is increased. 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. 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. The major pathophy siological mechanisms of AF include atrial remodeling, ANS dysfunction, activation of RAS,endothelial dysfunction.

Widely involved in these pathophysiological processes. Controversially, some studies have shown an absence of association between RA and the occurrence of new-onset AF. This may be due to the lack of close surveillance of heart rhythm.

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