THE ROLE OF INTERLEUKINS IN THE PATHOGENESIS OF ATRIAL FIBRILLATION: LITERATURE REVIEW

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Abstract

Relevance. Atrial fibrillation (AF) is the most common arrhythmia, which negatively affects the quality of life and significantly increases the risk of thrombosis, strokes and cardiovascular diseases. The pathogenesis of AF is a complex and multifactorial process in which inflammatory and immune mechanisms play an important role. In recent years, special attention has been paid to interleukins, cytokines that regulate the immune response, which may influence the development and maintenance of AF.

The study of the role of interleukins in the pathogenesis of AF may provide new perspectives for understanding the mechanisms of the occurrence of this arrhythmia and the development of effective methods of its prevention and treatment.

The study aimed to evaluate the influence of interleukins on the pathogenesis of atrial fibrillation and to identify possible mechanisms of their action.

Methods. data concerning the role of interleukins in the pathogenesis of atrial fibrillation were analyzed during the analysis of scientific publications. A systematization of existing studies, including both clinical and experimental data that show a link between the levels of interleukins (IL-1, IL-6, IL-17 and others) and the development of AF was performed. Search methods included analyzing publications in PubMed, Scopus and Web of Science databases over the last ten years and using keywords related to interleukins and AF.

Results. The results indicate that interleukins such as IL-1, IL-6, IL-17 and IL-18 play a significant role in the inflammatory processes associated with AF. Elevated levels of IL-6 correlate with worsening cardiac function and an increased likelihood of developing AF. In addition, IL-1 may contribute to myocardial remodeling, which is a key factor in the pathogenesis of AF.

Other interleukins, such as IL-17, are also associated with inflammatory processes affecting cardiac electrical stability. Accumulating evidence suggests that interleukins can affect cellular hypertrophy and fibrosis, leading to changes in cardiac structure and contributing to the development of AF.

The inclusion of interleukins in risk prediction models for the development of AF may improve preventive strategies and individualize the treatment of patients at risk.

Conclusion. the analysis shows that interleukins play a key role in the pathogenesis of atrial fibrillation by participating in inflammatory processes and abnormalities in cardiac electrophysiology. Further studies are needed to clarify their mechanisms of action and to develop new therapeutic strategies aimed at reducing interleukin levels and improving the prognosis of patients with AF.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Moreover, it is cited as one of the important causes of cardiovascular mortality. Almost one in four people between the ages of 40 and 55 years will experience AF at some point in their lives [1].

Ischemic heart disease and stroke are the leading causes of death according to WHO world statistics and may result from complications of AF [2]. Among

patients with chronic heart failure (CHF), 24% are diagnosed with previous or concomitant AF. The rate of diagnosed CHF in patients with PD is markedly higher than the rate of diagnosed CHF in participants with primary CHF [3]. Thus, AF generates CVD to a greater extent. AF is also associated with an increased risk of stroke and transient ischemic attack; in addition, AF -related strokes increase the risk of long-term disability or death. The attributable risk of AF in relation to stroke is 1.5% among 50-59 year olds and 23.5% among 80-89 year olds [3].

According to international data in the long-term follow-up period, recurrence of atrial arrhythmia is observed in 33% and 43% of patients after 12 and 24 months, respectively. There is no significant difference in arrhythmia-free survival between different ablation strategies [4].

According to global epidemiological studies, the number of AF cases has a worldwide increasing trend due to increased detection and increased life expectancy of the population [5].

In recent years, the study of interleukins (ILs), essential cytokines involved in immune response and inflammation, has received much attention in the field of cardiovascular disease (CVD). Studies have elucidated the involvement of ILs in the development of various CVDs including arrhythmias, myocardial infarction, atherosclerosis and heart failure (HF) [6,7,8].

Studies have shown a highly significant association between IL-1 and PD, with the persistent form being associated with higher IL-1 levels than the paroxysmal form. High IL-1 levels induce rapid electrical remodeling of the atria and also contribute to the development of persistent form of AF as a result of ventricular overload [7,8].

Atrial fibrillation is significantly associated with elevated IL-6 levels, indicating the unique influence of IL-6 on the pathophysiology of AF [1,6]. Thus, IL-6 is involved in the development of atherosclerosis, hypertension, aortic dissection, cardiac fibrosis and cardiomyopathy; stimulates cardiomyocyte hypertrophy, promotes apoptosis and impairs cardiac contractile function; regulates genes involved in inflammation and immunity through multiple signaling pathways, and therefore, like the other interleukins in the present study, is a potential target for the development of therapeutic treatment approaches [9].

Members of the interleukin-12 family, including IL-12, IL-23, are closely associated with the progression of various CVDs entailing inflammatory processes. The mechanism of atrial fibrillation development may be closely related to the occurrence of atrial fibrosis as a result of inflammation [10].

For example, IL-17A promotes the attraction of inflammatory cells to the lumen wall, leading to the development of plaques and cardiovascular events. The IL-17 signaling pathway plays an important role in the pathogenesis of AF, and some genes can be used as potential therapeutic targets in AF; elevated levels are also associated with CHD [11].

The role of IL-28 in the pathogenesis of AF has not been studied [6,7].

The study aimed to evaluate the influence of interleukins on the pathogenesis of atrial fibrillation and to identify possible mechanisms of their action.

Material and methods: This literature review includes articles and review studies on the role of interleukins in the pathogenesis of atrial fibrillation (AF). Data were searched in MEDLINE, Embase, Scopus, PubMed, and Cochrane Central Register of Controlled Trials databases using the keywords 'interleukins', 'atrial fibrillation', and 'inflammation'.

A total of 103 publications from the last 10 years were retrieved, of which 19 sources were included in this review. The authors adhered to PRISMA requirements for systematic reviews in the design and conduct of the study.

Source inclusion criteria:

- Studies addressing the role of interleukins in the pathogenesis of atrial fibrillation.
- Articles published in peer-reviewed scientific journals within the last 10 years.
- Works containing empirical data on the relationship between interleukins and AF.

Source exclusion criteria:

- Studies containing no data on the effects of interleukins on AF.
- Publications outside the field of

cardiology and immunology.

- Studies not published in peer-reviewed scientific journals or published more than 10 years ago.

The analysis identified key interleukins such as IL-1α, IL-1β, IL-6, IL-12/IL-23, IL-17A and IL-28A and their role in inflammatory processes and myocardial remodeling, providing a holistic view of the pathophysiology of AF and its relationship with immunological aspects.

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Results: AF, the most common cardiac arrhythmia, is the result of electrical and structural remodeling of the atria, encompassing interactions between cellular and neurohormonal mediators [12]. Postoperative AF (POAF), defined as first-onset PE in the immediate postoperative period, is associated with hemodynamic instability, increased risk of stroke, an eightfold increase in the risk of subsequent AF and cardiovascular death [13].

The mechanisms leading to PO AF are not fully understood, but it is likely a consequence of both pre-existing factors related to atrial remodeling and perioperative triggers that cause AF in the presence of a vulnerable substrate. Inflammation may be one of the most potent triggers of AF, and activation of myocardial inflammasome by NACHT, LRR and PYD-domain-containing protein 3 (NLRP3) through production of the proinflammatory cytokines interleukin (IL)-1β and IL-18 is associated with the pathogenesis of AF, contributing to atrial structural and electrical remodeling. Elevated levels of IL-1β gene expression are associated with atrial remodeling and sustained AF. IL-1β plays an important role in the inflammatory cascade and coordinates the cellular response to tissue damage, promoting inflammatory cell recruitment and increased production of other cytokines [14].

A group of Italian scientists conducted studies to investigate the relationship between interleukin (IL)-1β secreted by epicardial adipose tissue (EAT), atrial remodeling and the development of post-operative atrial fibrillation (POAF) in patients with coronary heart disease (CHD) [15]. In this work, atrial biopsy and EFT samples were collected from 40 patients undergoing cardiac surgery. Analyses were performed on both serum level and EJT-conditioned media samples to assess IL-1β and IL-1ra content. Atrial fibrosis was determined by histological method, and the role of NLRP3 inflammasome activation in the development of fibrosis was studied in vitro by exposing human atrial fibroblasts to interleukins IL-1β and IL-18.

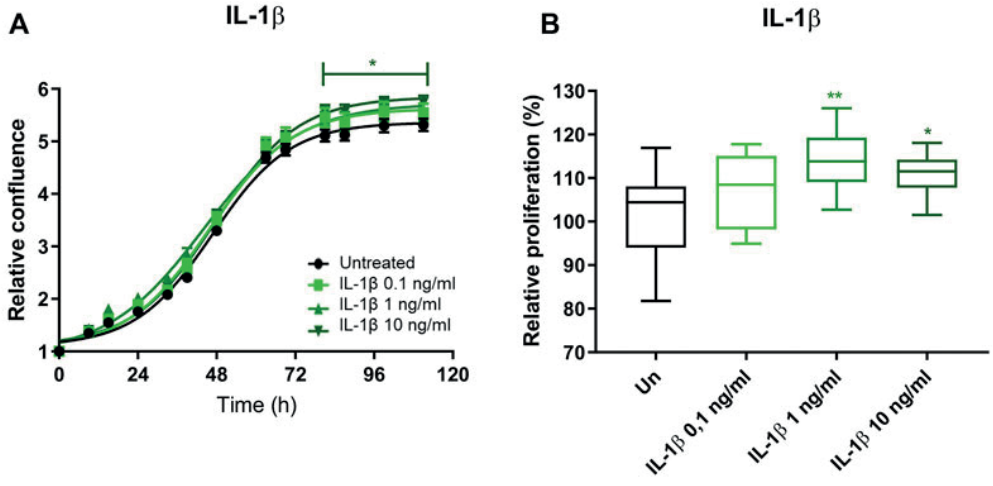
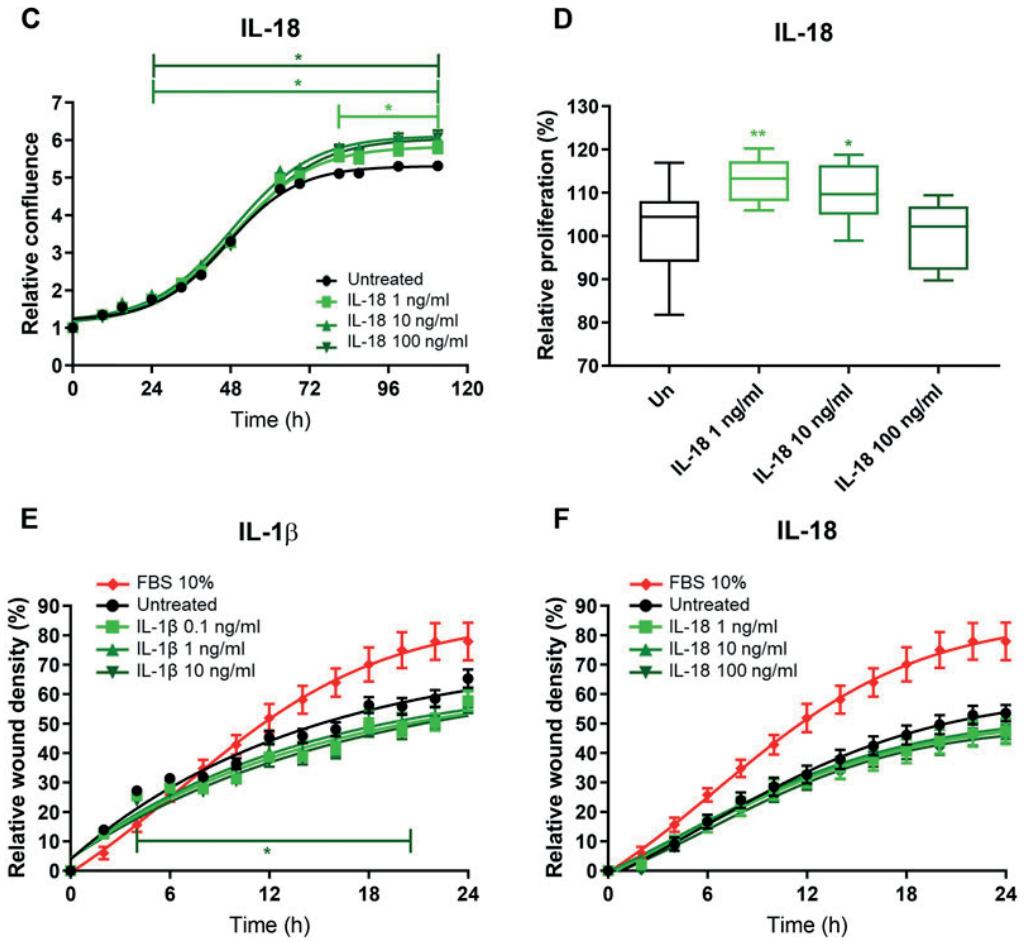


Table 1.
Effect of IL-1β and IL-18 on proliferation and migration of cardiac fibroblasts. (A-B) Relative confluence normalised by T0 and relative proliferation (B-D) versus untreated (set at 100%) and (E, F) relative wound healing density normalised by T0 of immortalised human fibroblasts exposed to different concentrations of (A, B-E) IL-1β and (C, D-F) IL-18 (n = 8). Data are expressed as mean ± SEM. *p < 0.05; **p < 0.01 compared to untreated [15].



The results of the study showed that 40% of patients developed POAF. Patients with and without POAF were similar in clinical and echocardiographic parameters such as left atrial volume and LV thickness. Histological analysis showed no association between POAF and atrial fibrosis. Serum IL-1ß and IL-1ra levels also showed no significant differences between patients with and without POAF. However, EFT-mediated IL-1ß secretion and expression was significantly higher in patients with PAAF compared with the group without POAF.

Additionally, in vitro experiments showed that exposure of atrial fibroblasts to IL-1ß and IL-18 promoted their proliferation and increased collagen synthesis. Stimulated cells continued to support inflammatory processes and fibrosis development by producing IL-1ß and transforming growth factor (TGF)-ß [15].

A large number of studies have confirmed that IL-6 exerts both pro-inflammatory and anti-inflammatory effects through various IL-6Rs. IL-6 receptor complexes consist of IL-6R or soluble IL-6R and gp130. The proinflammatory effect seems to be mainly dependent on sIL-6R-mediated signaling and the anti-inflammatory effect mainly depends on membrane-bound IL-6R (4-7). IL-6 induces Th17 differentiation, suppresses Treg differentiation and stimulates M2 macrophage polarization (8-10). Lymphocytes, monocytes/macrophages, adipocytes, and hematopoietic and endothelial cells are cellular sources of IL-6 (11). The gp130 protein is expressed in almost all tissues (16).

Amdur et al. found that elevated IL-6 levels were associated with an increased risk of AF in patients with chronic kidney disease (CKD), suggesting that IL-6 may serve as an inflammatory biomarker of AF in patients with CKD (17). In addition, IL-6 levels are associated with AF in patients with CHD. An increased incidence of AF was observed in elderly patients treated with recombinant human IL-11. OSM is elevated in atrial tissue in pa-

tients with AF and thrombus. Patients with higher CT-1 levels have a higher incidence of recurrent AF. The relationship between the IL-6 family and AF requires further investigation [18].

The Rotterdam study presented a large population-based cohort study. The study of 10943 participants with pneumonia and chronic obstructive pulmonary disease (COPD). During the one-year follow-up among 99242 patients, 804 participants developed atrial fibrillation. The incidence of AF was 14 cases per 1000 person-years in participants with COPD and 8 cases per 1000 person-years in participants without COPD. The adjusted hazard ratio (HR) for the development of AF in patients with COPD compared with those without COPD was 1.28 [95% CI 1.04, 1.57]. In a random sample of patients with measured plasma IL6 levels at baseline (n=599), patients with COPD with IL6 levels ⩾ median 1.91 pg/ml had a 2.5-fold higher risk of developing AF than patients without COPD (adjusted OR 2.49 [1.18, 5.28]). There was no increased risk of developing AF in COPD patients with IL6 levels below the median (adjusted OR 0.53 [0.14, 1.97]) [19].

The study focuses on the role of the IL-17 inflammatory pathway in the pathogenesis of AF. Inflammation has been shown to lead to myocardial remodeling and fibrosis development, which contributes to the occurrence of AF. A study in Sprague Dawley rats with an aseptic pericarditis model found that IL-17A and other members of the IL-17 family stimulate inflammation and fibrosis, increasing the risk of AF. Administration of drugs such as colchicine and curcumin has been shown to reduce IL-17 expression and improve myocardial health. Comprehensive analysis of the transcriptome has identified key genes (e.g. IL17a, Mapk13) that are significantly active in the model of AF and suppressed by drug therapy [11].

Discussion: Atrial fibrillation is the most common heart rhythm disorder and an important clinical cardiovascular disease. It significantly increases the risk of complications such as stroke, arterial embolism and heart failure. Complex mechanisms underlie this condition, among which the inflammatory process plays a key role. Loss of effective atrial contraction and impaired diastolic function leads to reduced pumping function of the heart and irregularity of ventricular rhythm. A growing body of research confirms that inflammation is an important mechanism in the development of AF, and inflammatory response pathways may be potential therapeutic targets. Inflammatory responses lead to atrial electrical and structural remodeling, as well as thrombogenesis, which creates favorable conditions for the initiation and maintenance of AF.

Some of the major inflammatory mediators that play an important role in the pathogenesis of AF are interleukins. For example, IL-1α and IL-1β are potent pro-inflammatory cytokines that contribute to the development of AF. Their elevated levels are associated with the processes of electrical remodeling of the atria and the development of persistent AF. IL-1β, in particular, activates important signaling cascades, such as the NF-κB pathway, which regulates inflammatory processes and leads to ventricular overload. Importantly, these cytokines influence the development of chronic inflammation, maintaining an unfavorable environment for the maintenance of arrhythmias. IL-6, being a central mediator of inflammation, is actively involved in myocardial remodeling and is associated with the risk of developing AF. Elevated levels of IL-6 correlate with the progression of diseases such as atherosclerosis, arterial hypertension, myocardial fibrosis and cardiomyopathy, making it an important target for further study in the context of AF. This cytokine regulates the expression of genes associated with inflammation and immune response, which holds promise for the development of novel therapeutic approaches.

Other interleukins, such as IL-12 and IL-23, also play a significant role in the development of inflammation in AF. They stimulate inflammatory processes that promote atrial fibrosis, which in turn creates favorable conditions for the onset and maintenance of AF. Particular attention in studies is paid to the p40 subunit common to IL-12 and IL-23, which plays a key role in the regulation of inflammatory responses and may be-

come a target for future therapeutic interventions.

IL-17A is a key factor responsible for the recruitment of inflammatory cells to the vascular wall, contributing to atherosclerotic changes and associated cardiovascular events. In the context of AF, IL-17A activates inflammatory responses, leading to atrial remodeling and increasing the risk of arrhythmias. Its elevated levels are associated with coronary heart disease and atherosclerosis, making it a promising therapeutic target. Notably, the effects of IL-17A on myocardial fibrosis and inflammation are already being studied in the context of anti-inflammatory drugs such as colchicine and curcumin, which have shown the ability to reduce the expression of this interleukin and reduce inflammation.

IL-28A is also an important area of research, although its role in the pathogenesis of AF is still poorly understood. However, evidence points to its possible involvement in immune reactions associated with AF. Studies of IL-28A may open new perspectives for the development of therapeutic strategies aimed at modulating the immune response and reducing the frequency of arrhythmia recurrence.

One of the interesting areas of study of cytokines in PD AF is the investigation of their role in postoperative atrial fibrillation (POAF) in patients undergoing aortocoronary bypass surgery (ACS). For example, a study showed that the onset of PO AF was not associated with clinical or echocardiographic parameters, but the level of secreted EAT-IL1ß, but not circulating IL-1ß, was associated with the development of PO AF. This confirms the important role of local inflammatory processes in the pathogenesis of PO AF after surgery.

Another study from the Rotterdam Study found that patients with chronic obstructive pulmonary disease (COPD) had a 28% higher risk of developing AF compared to patients without COPD. Particular attention was paid to IL-6 levels, which have shown to be a significant predictor of AF risk. Patients with COPD and high IL-6 levels had a 2.5-fold higher risk of developing AF, emphasizing the important role of inflammatory processes in the pathogenesis of arrhythmias in this category of patients.

Studies of the IL-17 pathway also show its importance in the development of AF. IL-17A and IL-17F activate fibroblasts, provoking myocardial fibrosis and inflammatory responses. Administration of agents such as colchicine and curcumin significantly reduce the expression of these cytokines, which is associated with reduced inflammation and atrial remodeling. Studies suggest that genes such as IL17a, Mapk13 and Ccl20 may be potential therapeutic targets in the future, opening new perspectives in the treatment of AF.

What's known: Atrial fibrillation (AF) is the most common arrhythmia, leading to severe complications such as stroke and heart failure. Inflammation and immune responses, particularly those involving cytokines like interleukins (ILs), are recognized as significant contributors to AF pathogenesis. Elevated levels of interleukins such as IL-1 and IL-6 have previously been linked to atrial remodeling, promoting cellular changes that increase the likelihood of AF.

What's new: Recent research highlights a broader role for various interleukins, including IL-17 and IL-18, in AF pathogenesis. These cytokines contribute to atrial fibrosis and electrical instability, setting the stage for AF onset and maintenance. Furthermore, new insights reveal that targeting specific interleukins might offer innovative approaches for AF prevention and treatment, especially among patients with inflammatory risk factors like chronic kidney disease and chronic obstructive pulmonary disease.

Limitations: This study is limited by its reliance on existing literature rather than primary experimental data, which restricts the ability to establish direct causal relationships between interleukin levels and atrial fibrillation (AF) pathogenesis. Finally, while this review identifies promising targets for potential therapies, further experimental and clinical research is needed to validate these findings and develop effective treatment strategies.

Conclusion: Our literature review demonstrated the crucial role of inflammation and key cytokines in the pathogenesis of AF. We examined the

influence of proinflammatory molecules such as IL-1ß, IL-6, IL-17A and others on the processes of electrical and structural atrial remodeling, as well as their contribution to the development of myocardial fibrosis. These cytokines not only participate in the maintenance of chronic inflammation, but also create a favorable environment for the development of arrhythmias. Nevertheless, despite the accumulated data, many aspects of their role in the mechanisms of AF remain poorly understood, emphasizing the need for further research.

As part of our grant project, we plan to further investigate these cytokines to assess in detail their impact on the development and maintenance of AF. Using state-of-the-art equipment and scientific techniques, including analyzing cytokine expression and studying their relationships with inflammatory processes in cardiac tissue, we intend to further investigate their mechanisms of action. These studies will help identify potential therapeutic targets that can be used to develop more effective approaches to the treatment and prevention of AF, especially in patients at high risk of recurrence.

Authors' contributions: contribution to the concept – A.A; scientific design - A.A; execution of the stated scientific research - A.A., B.A., Y.I., B.K.; interpretation of the claimed scientific research - A.A., R.L., B.N, S.A.; creation of scientific article - A.A., R.L., S.A.

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