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Role of Inflammatory Pathways in Arterial Fibrillation Initiation and Progression

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Abstract

Atrial fibrillation (AF) is the most common persistent cardiac rhythm disturbance, and a top cause of stroke, congestive heart failure, dementia, and death. Historically, atrial fibrillation has been considered to have a pathophysiology that involves electrical, structural, and autonomic derangements within the atrial myocardial substrate. However, increasingly over the past twenty years, inflammation has emerged as a key, underlying, and unifying pathophysiologic link between initiation and maintenance of atrial fibrillation. This literature review examines both animal and human studies to illustrate how inflammatory pathways regulate atrial electrical instability, structural fibrinosis, and atrial fibrillation. Various pro-inflammatory cytokines, including interleukin-6, interleukin-1β, tumor necrosis factor-α, and C-reactive protein, have long been linked with atrial fibrillation development, burden, and recurrence, and have direct pathologic effects on various ion channel and calcium-handling mechanisms and gap junction integrity. Stimulation of immune pathways, especially the NLRP3 inflammsome, integrates cell stress, oxidative damage, and atrial mitochondriopathy with persistent atrial arrhythmias. Furthermore, inflammation leads to the activation of fibroblasts and subsequent deposition of extracellular matrix and atrial fibrinosis, which maintains re-entrant atrial arrhythmias and promotes persistent to paroxysmal atrial fibrillation conversion. The anti-inflammatory treatments such as colchicine, corticosteroids, statins, antioxidants, lifestyle changes, and newer molecular therapies focused on IL-6 and NLRP3 signaling pathways are showing varied yet promising results based on the stage and phenotype of patients. There is evidence to totally redefine AF from being simply a cardiac condition to being a systemic inflammatory disease, which can provide promising leads in the future for the prevention and treatment of AF.

Keywords: Atrial Fibrillation, Inflammation, Atrial Remodeling, Nlrp3 Inflammasome, Cytokines Cardiac Fibrosis

Introduction:

Atrial Fibrillation, also known as AF, is an arrhythmia. "AF can be unpredictable and very hard to control, and it is the most common typical AF case among patients around the globe. Primary characteristic of AF is the rapid and irregular conduction of the atrial activations. These irregular activations occur due to inappropriate contra electrical activity, which in turn obstructs the effective contraction of the atria. The condition is becoming increasingly common. increasingly common so that, nowadays, it has become a question of millions of people around the world and that also imposes a huge burden on the medical industry in terms of cost and medical effort. AF is a major contributor to serious illness and death, as it is accompanied by the highest probability of causes like stroke, heart failure, cognitive decline, and poor quality of life. If the elder population continues to grow and if the risk factors for developing cardiovascular diseases—like high blood pressure, overweight, and diabetes—continue to be prevalent, the rate of the occurrence of AF will even get higher than current projections. This will call for a more in-depth analysis of its mechanisms and for the development of more specific treatments [1,2].

The pathophysiology of atrial fibrillation has been explained through a combination of electrical, structural, and autonomic remodeling of the atrial myocardium. Electrical remodeling involves shortened atrial refractory periods and altered dynamics of ions, while structural remodeling consists of atrial dilation and connective tissue buildup that are favorable for the creation of reentry circuits. Everyday life with its stresses and regular activities can influence the heart;

sometimes, these influences are strong enough to be classified as auto control, and they are especially sympathetic and parasympathetic interventions that further change the stability of the atrial myocardium. Although classical mechanisms have played and are still playing the most important role, they do not explain the variability that AF has when diagnosed in a patient and its nature as a progressive condition. Inflammation has been investigated more and more over the last twenty years, and it has been recognized as an important factor that adds up to the other mechanisms by way of interaction [3].

The inflaming process is in no way related to the fear of losing an electronic functionality over time, and therefore the feedback produced by the entire immune activity around would be attached to electrical and electrochemical aspects in a very complicated way. Originally, the concept of initiating factors in AF development included factors like electrolytes, drugs and substances abuse. Among the whole bunch of obstinate classic factors, there is one that still is rarely mentioned – emotional stress, which in fact has already been proven to be contributing to the onset of AF over the years. However, it should be noted that the best classic causes still remain in various forms with factor being the least obvious to notice, and thus introducing new players in the game of AF escalating. Nevertheless, inflammation mediators are among the culprits in case of an event like ventricle defibrillation or percutaneous coronary interventions (PCI) where myocardial hypoxia may occur already by the use of lighting-fast primary reperfusion techniques. Two electropathophysiologies methods were accounted for: conduction and reentry and their relation to the cycle of AF episodes is very subtle and complex [4,5].

Background:

Many people believe that inflammation is always bad, but new research indicates that it can actually be beneficial to the body [6,7]. This concept dates back to the 19th century, when research started to characterize inflammation as a healing and defensive mechanism [8]. Understanding the distinction between acute and chronic inflammation is helpful in comprehending how inflammation functions. Clear characteristics of acute inflammation are crucial to its operation. Increased blood flow, for example, results in redness and makes the inflamed area feel warmer than the surrounding healthy tissue [9].

Oedema, or swelling, occurs when materials and liquids seep into tissues; the injury itself may cause pain, or the swelling may stretch surrounding tissues [9]. These indicators demonstrate how crucial the body's natural inflammatory response is to the healing of injured tissue. Since pro-inflammatory cytokines are involved in the signaling pathways that control metabolism, they are essential to this process. But there needs to be a resolution phase before the inflammation goes away and the body returns to normal. In this stage, macrophages are triggered to eliminate dead cells and aid in the removal of excess fluid, and white blood cells receive a signal to cease [10].

Acute inflammation is a defensive reaction that aids in tissue healing by eliminating dangerous substances. In contrast to chronic inflammation, which can persist for months or even years, it typically begins within minutes and lasts for hours [6,7]. The primary distinction is that while acute inflammation uses anti-inflammatory signals to regulate its duration, chronic inflammation can develop and persist for much longer if these signals are absent [7]. Key pro-inflammatory substances, cytokines can be a sign of chronic inflammation, which can result in heart disease, if they remain in the blood for an extended period of time. In addition, inflammation can lead to oxidative stress and calcium imbalance, which can either aid in tissue repair or result in tissue damage [11].

Cardiac hypertrophy, or the thickening of the heart walls, cardiac fibrosis, or the stiffening of the heart tissue, and atherosclerosis, or the accumulation of plaque in the arteries, are all directly caused by chronic inflammation. This demonstrates how a normal healing response can develop into a chronic issue that causes tissue damage, like cardiac fibrosis and cell death (apoptosis) [11]. Systemic inflammatory disease is the term used when there is no resolution phase. Heart function may be irreversibly harmed if the pericardium is impacted by persistent inflammation [10]. Tamponade, or the accumulation of fluid or pressure, is frequently the first stage of the process, which progresses to chronic fibrosis, in which the tissue thickens, stiffens, and calcifies. The heart may eventually become stuck in a hard tissue shell, which prevents it from adequately filling with blood.

Inflammatory Response:

Cytokine and Immune Signalling Pathways

Inflammation is the main risk factor for atrial fibrillation [12,13]. This is because the cytokines, which are the immune molecules, take part in the mechanisms. Examples include tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and C-reactive protein (CRP) because they are among the cytokines that take part in the inflammation in the body [13,14]. In human beings, the result is the increase in the concentration of the cytokines in the blood and the inside of the atria [13,14]. The concentration of the molecules is proportional to the severity, tendency to recur, and progression [13,14]. Therefore, all the mentioned result in the creation of the inflammatory state, leading to arrhythmia. In addition, this can be at either the atrial or the systemic level [12,15].

There is a specific mechanism known as the NLRP3 inflammasome which is activated in these conditions [16,17]. The NLRP3 inflammasome associates deficits in cells which are cardiac muscle cells to the immune system's response

[12,18]. The protein complex is able to detect damage signals such as stress, mitochondria problems, and changes to ions in the cell [12,18]. The complex will initiate the processing of pro-IL-18 and IL-1β to their active forms [16,18]. These cells will begin to exhibit greater signs of inflammation due to the NLRP3 inflammasome [16–17]. Preventing these through genes and medications assists in reducing the risk of developing atrial fibrillation, yet experiments conducted showed that in cases of NLRP3 activation, especially in the atria, it will trigger the development of atrial fibrillation on its own [16,17].

When the cytokines have been produced, the transcriptional signalling systems become very active, especially mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) [12,15]. The NF-κB pathway causes a feedback loop that keeps inflammation going by encouraging higher production of mediators that create fibrosis, molecules for adhesion, and cytokines that cause inflammation [15]. Stress can change gene expression, leading to changes in extracellular matrix processing, bigger signalling, and survival of cardiac muscle cells through MAPK systems like the p38, ERK, and JNK [15]. These molecular pathways also affect proteins of gap junctions, those handling calcium and ion channels, making immune signalling tied to instability of electrophysiology [12,15].

Furthermore, inflammatory cytokines directly affect the electrical function of the heart [12,19]. Because IL-6 and TNF-α reduce the presence of potassium channels and interfere with connexin movement, they can cause heterogeneous action potential duration and slow conduction [13,19]. By increasing calcium leakage from the sarcoplasmic reticulum and altering calcium regulation within cells, IL-1β increases the risk of abnormal atrial activity and delayed extra beats [12,16]. Immune signals consequently transform inflammation from a secondary effect to a primary cause of arrhythmias [12].

Inflammation-Driven Electrical and Structural Remodeling

The atria display a high level of remodeling, both structurally and electrically, as a result of remodeling by the above-stated inflammatory mediators, and thus the creation of a substrate for atrial fibrillation is guaranteed [12,13]. The fibrosis found in the atria, resulting from the activation of the fibroblasts by the inflammation, is the predominant outcome measured as a result of remodeling by the inflammation [13,15]. TGF-β, IL-6, and TNF-α remain some of the most potent or proinflammatory agents. They have the effect of inducing fibroblast growth, the transformation of fibroblasts into myofibroblasts, and accordingly, the idiopathic deposition of the ECM proteins themselves due to fibrosis, as well as electric barriers due to fibrosis-related remodeling, hence competing with ECM proteins, namely collagen and fibronectin, for the recreating of the homogeneous environment created by the atria.

Fibrosis has both structural and electrical elements. Cell proximity for myocytes is hindered by collagen, thereby reducing the velocity and augmenting myocyte conduction resistance [13]. Fibrosis, therefore, creates dynamic, insecure, and non-homogeneous regions, concealing an inflammatory background for arrhythmias and, together with other paths for death, including inflammatory myocyte apoptosis and necrosis, resulting in fibrosis [12,13]. Circuits of re-entry are produced because of anything happening in an action potential, due to reduced velocities of conduction because of an excess of collagen and fibronectin deposits. Neighboring myocytes undergo apoptosis and necrosis, with no pacemaker function, because of the normal path for compensation [13]. The principal known path for maintaining AF has presently been proclaimed as the circuit of re-entry [13].

In this particular phase of the relationship between the components of the heart, electrical remodeling and structural changes are interlinked since they occur concurrently [12]. Secondly, the expression level and lateral localization of the gap junction proteins connexin-40 and connexin-43 are altered owing to the presence of inflammation [15,19]. Conduction velocity and atrial recovery are reduced if the level of expression of connexin is reduced or laterally mislocalized across membranes, which propagate the impulse [19]. To underscore the volatile – but unfortunate – link between the presence of inflammation and the problem of electrical remodeling, research has shown that IL-6-induced reversible downregulation of connexin expression occurs [19].

Dysregulation of calcium handling is the final factor that plays a significant role in the progression of AF due to the inflammatory condition [12,16]. The most prevalent mediators of atrial cellular death start downstream from NLRP3 inflammasome activation, whereas the most potent cytokines act on ion channels [12,16]. Ryanodine receptor phosphorylation can be increased by the corresponding signaling, and phosphorylation-mediated sarcoplasmic reticulum calcium leak highlights dysregulated calcium cycling and spontaneous calcium release events [12,16]. Focal atrial ectopy and delayed afterdepolarizations are brought on by spontaneous calcium release events [16]. Due to sustained re-entrant arrhythmias, slow conduction further highlights trigger likelihood when these happen after the fact in a fibrotic microenvironment downstream of inflammation-induced progression [12,13].

Ultimately, both structural and electrical remodeling are self-reinforcing because the process of remodeling indicates electrical heterogeneity, while electric instability favors more membrane stress and dynamic changes, which accelerate the chances of inflammation activation [12,17]. This explains how the process of paroxysmal changes is converted to sustained changes, thereby making AF progressive in nature [12,13].

Stress from Oxidation and Endothelial Dysfunction

Reactive oxygen species (ROS) are produced more frequently in AF due to inflammatory activation, primarily through NADPH oxidase (NOX), mitochondrial malfunction, and uncoupled nitric oxide synthase. The sympathetic nervous system, metabolic stress, and the renin-angiotensin-aldosterone system (RAAS) all increase the production of ROS. In addition to shortening the atrial effective refractory period (AERP) and promoting delayed afterdepolarizations, excess ROS also directly affects ion channel function and calcium handling proteins, increasing arrhythmogenicity.

ROS also activate redox sensitive transcription factors such as NF-κB and the NLRP3 inflammasome, leading to the release of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemokines, which drive atrial myocyte injury, apoptosis and fibroblast activation [20-25].

Endothelial dysfunction is both a result of and a further exacerbating factor for the underlying inflammation and oxidative stress seen in AF. Endothelial activation leads to increased expression of adhesion molecules, including VCAM-1 and ICAM-1, which promote leukocyte adhesion and migration into the atrial wall.This infiltration of the immune cells continues to perpetuate local inflammation, hence promoting fibroblast activation and the synthesis of the extracellular matrix, resulting eventually in fibrosis and structural remodeling of the atria [21,22,26]. The ROS also increases vascular permeability and reduces the availability of the nitric oxide, hence promoting the prothrombotic state. These events perpetuate the vicious cycle of oxidative damage, endothelial dysfunction, and inflammation, hence the progression and maintenance of AF [21,22,24-27,29].

Recently discovered research describes that mitochondrial dysfunction is also pathophysiologically relevant to persistent AF. Herein, increased activity and calcium overload result in metabolic stress and decreased ATP production, as well as further ROS release. Upstream treatments with a focus on reducing risk factors and modulating the RAAS as well as antioxidants are suggested by the American College of Cardiology [20,21,26,27].

Autonomic and Immune System Interactions

The link between the autonomic nervous system and immune signaling is being increasingly understood to play a role in arrhythmogenic remodeling in patients with AF. The sympathetic component increases ROS production and cytokine release, with parasympathetic dysfunction causing atrial refractoriness and promoting ectopic beats. Immune cell infiltration, especially by macrophages and lymphocytes, leads to local release of cytokine and chemokine production, with a resultant effect on ion channel function, calcium handling, and junctions, resulting in electrical remodeling and arrhythmia susceptibility [20-22,24,28,29].

Macrophages and lymphocytes secrete cytokines (e.g. IL-6, TNF-α) that stimulate fibroblast activation and extracellular matrix production, driving structural changes in the atrial myocardium. Additionally, the epicardial adipose tissue also plays a part in this condition by releasing pro-inflammatory adipocytokines that further augment the inflammatory responses within the myocardium. Therefore, the overall modifications that occur in the architecture and conductivity of the atrium form a natural conduit for the triggering of AF [20-29].

NLRP3 inflammasome activation, specifically the NLRP3 inflammasome, is an important link between immune activation and atrial fibro-inflammation and electrical remodeling. NLRP3 silencing eliminates inducibility of AF in animal models; drugs targeting NLRP3 are also being developed. This is how the American College of Cardiology identifies the upstream mechanisms of AF pathogenesis. It also recommends continued research into novel targets of therapy [20,22].

Therapeutic Approaches Targeting Inflammation in AF

Growing evidence has linked anti-inflammatory therapies as promising ways to manage atrial fibrillation. A variety of approaches have been clinically studied, ranging from conventional pharmacological agents to lifestyle modifications and emerging targeted therapies. Colchicine is an anti-inflammatory agent that acts on the downregulation of inflammatory pathways and modulation of innate immunity through tubulin disruption mechanisms [30]. Although several studies have evaluated colchicine against AF, results have shown variable results. A randomised study by Deftereos et al. initially suggested a reduction in postoperative AF recurrence following a 3-month colchicine administration [31]. However, a more recent and large trial conducted by Conen et al. found no statistically significant reduction in perioperative AF with colchicine and adversely noted increased gastrointestinal symptoms of diarrhea [32]. The variability of these results provides an unclear determination on the efficacy of colchicine in AF therapies and require more specific analysis of patient conditions or operative settings.

Similarly, corticosteroids produce anti-inflammatory and immunosuppressive effects that lead to the reduction of proinflammatory molecules, thus possibly reducing inflammatory responses in AF [33]. A study conducted by Koyama et al. investigated the effects of intravenous hydrocortisone and oral prednisolone pre and post pulmonary vein isolation (PVI) procedures [34]. Results showed that corticosteroid use may help prevent very early AF incidents after PVI, which may improve mid-term outcomes. However, corticosteroids do not help prevent late recurrence of AF. Another study by Kim et al. [35] looked at short term methylprednisolone therapy immediately after PVI and found that while early recurrence was also reduced, late recurrence was not prevented. While short-term treatment of AF is consistent in both studies and suggests opportunities for better atrial remodeling, it lacks long-term benefits. It can also be noted that

dosage variability can be accounted for and requires further analyses.

Furthermore, statins may have a role in inflammation suppression through the reduction of C-reactive protein and LDL-cholesterol [36]. A study by Aydin et al. illustrated the serum LDL-C levels in preoperative patients as a way of predicting postoperative AF independently of statin use. It was found that lower LDL-C was related to AF development, which underlines a possible association between lipid levels and inflammation [37]. Furthermore, this is supported by the JUPITER trial analysis, which demonstrated that rosuvastatin therapy significantly reduced the incidence of AF in individuals with elevated CRP levels.This suggests an anti-inflammatory effect rather than lowering LDL-C alone [38]. Both findings support a possible linkage between statin therapy and its role in lessening AF risk through its inflammatory pathways. In addition to statins, lessening oxidative stress and inflammation through antioxidant reinforcement represents another promising approach. For instance, in a randomized trial by Rodrigo et al., n-3 polyunsaturated fatty acids and antioxidant vitamin administration showed a significant reduction in postoperative AF [39]. Together with statin therapy, it further supports the decrease in inflammatory and oxidative stress markers.

In addition to pharmacological therapies, lifestyle modifications can play an equally important role in reducing inflammation and thereby the recurrence of AF. Particularly, studies found that aerobic interval training has been associated with an improvement of inflammatory biomarkers and endothelial dysfunction through the reduction in oxidative stress and von Willebrand factor [40]. These findings may be more beneficial as a long-term approach, especially used in conjunction with other therapies for substantially reducing AF risk.

Finally, preclinical studies targeting inflammatory mediators implicated in AF, such as the NLRP3 inflammasome and interleukin-6 (IL-6) have been showing potential as a future method. These multiprotein complexes that play a primal role in the immune system regulation, can be modified to downregulate the specific inflammatory pathways that contribute to the structural changes seen in AF [41]. Yao et al. showed that enhanced NLRP3 inflammasome signaling within the cardiomyocytes directly contributed to atrial fibrillation, supporting the potential of using an NLRP3 inhibitor [16]. Similarly, the IL-6 pathway was found to be elevated in cases of AF, while experimental inhibition of IL-6 reduced AF [42]. Although these models are still preclinical, understanding these inflammation-targeted pathways can provide useful directions on future anti-inflammatory treatment strategies [41].

Therapeutic approach	Representative study (author, year)	Mechanism of action	Reported efficacy in AF	DOI
Colchicine	Deftereos et al., 2014	Inhibits microtubule polymerization; suppresses neutrophil activity and NLRP3 inflammasome signaling	Reduced early AF recurrence after pulmonary vein isolation; inconsistent benefit in broader populations	10.1016/jhrthm.2014.01.005
Colchicine	Conen et al., 2023 (COP-AF trial)	Anti-inflammatory via innate immune modulation	No significant reduction in perioperative AF; increased gastrointestinal adverse effects	10.1016/S01406736(23)02071-5
Corticosteroids	Kim et al., 2015	Short-term immunosuppression and attenuation of acute atrial inflammation	Decreased early but not long-term AF recurrence after catheter ablation	10.1161CIRCEP.115.003206
Statins	Peña et al., 2012 (JUPITER analysis)	Reduction of CRP and inflammatory signaling independent of LDL lowering	Lower incidence of new-onset AF in patients with elevated CRP	10.1093/eurheartj/ehr368
Antioxidants	Rodrigo et al., 2013	Reduction of oxidative stress and ROS-mediated inflammatory signaling	Significant reduction in postoperative AF	10.1016/j.jacc.2013.07.014

Lifestyle modification (exercise)	Kim et al., 2023	Improves endothelial function; reduces oxidative stress and inflammatory biomarkers	Improved endothelial dysfunction and AF burden over 1 year	10.2169/ internalmedicine.0812-22
IL-6 pathway inhibition	Yu et al., 2025	Blocks IL-6–mediated inflammatory and fibrotic signaling	Preclinical and early translational evidence suggests reduced AF susceptibility	10.1007/s11596-024-2826-7
NLRP3 inflammasome inhibition	Yao et al., 2018	Prevents IL-1β and IL-18 activation; reduces atrial inflammation and fibrosis	Eliminated AF inducibility in animal models; emerging therapeutic target	10.1161/ CIRCULATIONAHA.118.035202

table

Discussion

Atrial fibrillation (AF) is now acknowledged to be a multifactorial so it is an ongoing condition that is caused by multiple interacting factors like including structural, electrical and autonomic as well as more classical dysregulations in the system. The linkage of these diverse areas is inflammation. Inflammation can cause AF, perpetuate it, and make it worse over time — more than a side effect of heart damage or some other medical condition. This is because inflammation leads to changes in heart tissue composition, electric transmission between cells and in calcium levels. Moreover, the balance among hormones and signals is affected by too much inflammation. The view changes our understanding of AF from electrical problem to a disease affecting part and whole body, more active and multifaceted than we might have thought [4,43].

Recent lines of evidence show there are inflammatory molecules that are crucial in stimulating immune functions and disrupting electrical equilibrium in the heart atria such as interleukin-6, TNF-alpha, or interleukin-1β. These cytokines aren't just markers. The association between high levels of these molecules in the blood and within heart cells makes AF worse at the same time as it is more frequent which also increases the probability for another recurrence. So do these molecules alter the connections among heart cells and stop potassium and calcium from flowing, or they even let calcium leak out of cells' storage areas. That alone makes it easier for abnormal electrical signals to occur and spread. Researchers also discovered that an immune system-majestic switch called the NLRP3 inflammasome can indeed drive AF, via itself, in laboratory models. That helps explain why AF is so common in cases of high inflammation, such as after heart surgery or heart attacks, and in individuals with obesity, diabetes or metabolic disorders [16,43].

If inflammation lasts a long time, it will affect how the heart's atria are built. When you expose your heart cells — called fibroblasts — to large quantities of inflammatory materials for months or years, they proliferate and differentiate into the next type of cardiac cell, the myofibroblasts. These cells then start creating tons more supporting material, including collagen. That process leads to scarring, or fibrosis, that makes the heart impossible to use, generating the loops of odd electrical activity that keep AF going. In addition, anatomical changes in the heart and changes in the electrical signals continue to compound one another, in a sort of self-reinforcing vicious cycle [44,45].

It's a second key relationship embedded to all this, and the thing in question is something called oxidative stress — a state when the heart over-produces reactive oxygen species (ROS) in the body. These are unstable molecules that can, when they accumulate, damage cells. Mitochondria become dysfunctional, some enzymes get into trouble, and even hormone systems can go awry — which can cause another thing: the generation of excess ROS. These molecules then change how heart cells interact with electricity and calcium — and they turn on genetic switches that crank up inflammation even more. To worsen matters, damage to the lining of blood vessels (endothelial dysfunction) lowers the levels of so-called protective molecules, like nitric oxide and allows more immune cells to enter the heart, making blood vessels leakier. The net result is a feedback loop in which inflammation and the consequent oxidative stress feed off one another, and AF gets less and less manageable [46,47].

The body's nervous system also plays an enormous role in the way inflammation governs the heart's electrical signals. Too much activity from the 'fight or flight' (sympathetic) part of the nervous system causes more ROS output and more inflammatory molecules to be produced; a disruption of the 'rest and digest' (parasympathetic) system can cause less time for the heart cells to reset after every beat, and the heart's rhythm becomes more irregular. Immune cells like macrophages and lymphocytes can infiltrate the heart muscle, which can trigger an even greater release of inflammation and activate fibroblasts, which transform the tissue. Fat surrounding the heart, particularly among overweight people, also generates inflammatory signals which further complicate the situation. Many metabolic changes as well — all together with immune system, the nervous system and metabolism — combine to make AF complex with

many subdeterminants [46,47].

As we study AF, we have learned more about how much inflammation is of crucial importance, and that what can be done is often even more complex than merely trying to set the same rhythm in the heart or regulating heart rate. Drugs intended to stop inflammation — from colchicine to steroids, statins and antioxidants — have been tested in studies, as have dietary and exercise changes. Results have been patchy, particularly among those who recently had surgery or are early in their disease. This gives an idea of how hard it can be to target treatments against inflammation in real life, and how much success could hinge on the right patients, the right timing and the right stage of disease. Emerging therapies that target the earliest phases of inflammation, like NLRP3 inflammasome inhibitors or drugs that arrest interleukin-6, look intriguing in early trials, but they don't exist in the form of drugs of daily use [4,47].

Inflammation in AF causes complications apart from heart condition. Individuals with this kind of AF are at higher risk for suffering a stroke, making heart failure worse and dying of heart disease. Inflammation also damages the lining of the heart's chambers, triggers platelets that help blood clot, and reduces levels of nitric oxide (which helps keep blood vessels from being crowded and become damaged). All of this only makes it that much easier for dangerous blood clots to form. Some researchers say that based on these risks, when we think about how risky AF might be to a patient, we should be using markers for inflammation; early anti-inflammatory treatments are also needed to alleviate trouble in the heart and potentially complications caused by clots. Naturally, we have their limitations. Inflammation doesn't act in the same way for everyone with AF, and it's not easy to know exactly what the cause was — especially since many with AF have other diseases as well [1,43].

Medications that reduce inflammation can also have side effects. These cause them to not be used widely in the long run. Efforts to research further will have to look at determining which forms of inflammation matter the most to people in whom they are taking them. Also, developing tests that are more effective in people of various types; testing more accurately — there has to be a concentration on which group of tissue inflammation should be able to produce such results; improving tests to determine which kind of medication is best in particular situations. Inflammation, therefore, lies at the heart of what we know about AF at the present time [4,44].

To conclude, inflammation is the connection point between the immune system and changes in the heart's structure, electrical activity due to chemokines, and also to provide us a broad perspective of AF as one that impacts all of the body and worsens over time. More research on therapies that counteract inflammation, as well as more individual treatments, can revolutionize the fate of a person with atrial fibrillation.

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