Mechanisms of Atrial Fibrillation

Subjects: Physiology
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Atrial fibrillation (AF) is a very common arrhythmia that mainly affects older individuals. The mechanism of atrial fibrillation is complex and is related to the pathogenesis of trigger activation and the perpetuation of arrhythmia. The pulmonary veins in the left atrium arei confirm that onfirm the most common triggers due to their distinct anatomical and electrophysiological properties.

atrial fibrillation | fibrosis | triggers | inflammation oxidative stress

1. Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia and is linked with remarkable mortality and morbidity, which are caused by thromboembolism, heart failure, and impaired cognitive function [1]. The prevalence of AF was estimated in the first years of the 21st century to lie within a range between 0.5% and 1% in the general population, but currently it seems to range between 2% and 4% in developed countries [2]. A threefold increase in its prevalence has been observed over the last 50 years [3]. The risk of AF increases with each decade and exceeds 20% by the age of 80 years [4].

The main ECG characteristics of AF include a lack of discrete P waves and the rapid appearance of fibrillatory (or f) waves that vary in amplitude, morphology, and rate. The QRS complexes demonstrate irregular R–R intervals. The atrial rate may be between 350 and 600 beats per minute (bpm) or unmeasurable.

Fibrillatory waves are usually best seen in the inferior leads and in V1. They may be identified between QRS complexes and are sometimes visible superimposed on the ST segment and T waves [5]. The recording of AF in a single-lead ECG for ≥30 s or in a 12-lead ECG results in the explicit diagnosis of AF [6]. Furthermore, AF is classified as follows: (a) paroxysmal, if it terminates spontaneously or with either (i) electric or (ii) pharmacological cardioversion within a week of onset; (b) persistent, if it is ceaselessly sustained beyond a week, including episodes terminated by intervention after ≥7 days; (c) long-standing and persistent, if it is continuous for over a year and a rhythm-control strategy is adopted; or (d) permanent if it is accepted by the patient and physician, and no other medical intervention with the aim of restoring/maintaining rhythm is conducted [7]. However, this classification does not refer to the underlying atrial substrate, which determines long-term sinus-rhythm maintenance, in cases in which a rhythm-control strategy is selected. The disorganized atrial contractions of AF lead to a 20–30% reduction in stroke volume and cardiac output in healthy individuals. A considerable decline in

output occurs in cases of diastolic dysfunction in which atrial contraction contributes more than normal to left ventricular diastolic filling [8].

The basic pathophysiological pathways leading to AF's onset and perpetuation involve triggers, abnormal atrial substrates, neurohormonal hyperactivation and, finally, a genetic predisposition (**Figure 1**).

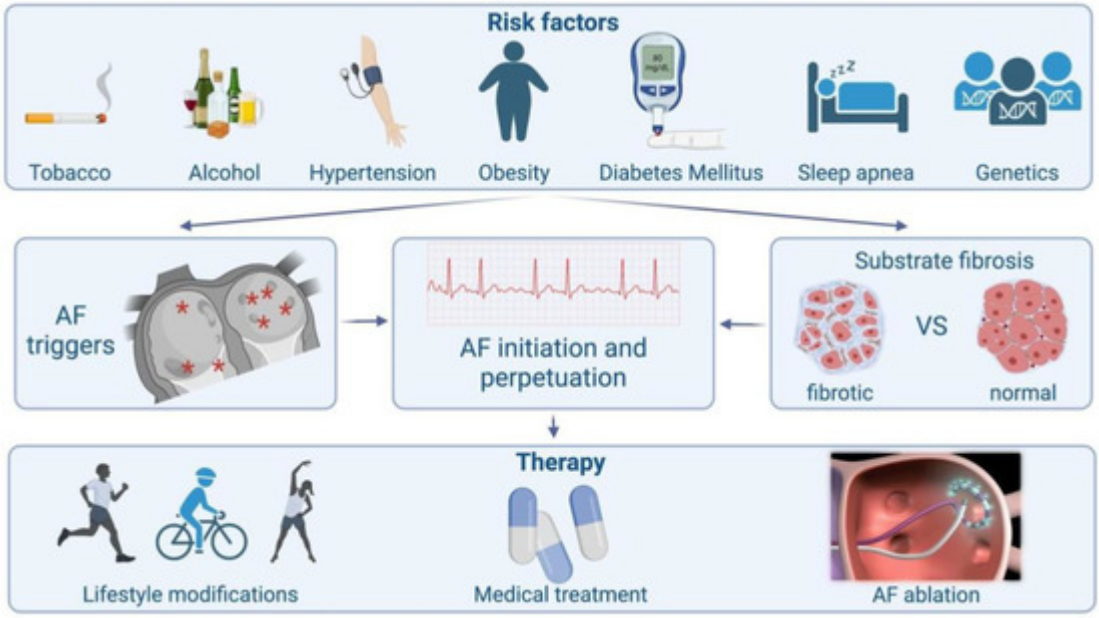


Figure 1. Schematic presentation of atrial fibrillation from causes to treatment.

2. Triggers

Typically, premature atrial beats are the main triggers that convert sinus rhythm to AF. According to Haïssaguerre et al., the vast majority of these ectopic foci inside the atria originate in the pulmonary veins (PVs). The myocardial sleeves within the PVs appear to have specific properties that are both similar to and different from those of the rest of the atrial myocytes in terms of cellular electrophysiology, anatomical characteristics, and myofiber structure and orientation. The main aim of AF catheter ablation is the electrical isolation of the PVs from the rest of the atrium. This therapeutic strategy constitutes the cornerstone of AF catheter ablation [9]. Arrhythmogenesis has a predilection toward PV cardiomyocytes due to their action-potential characteristics, which renders them more susceptible to enhanced normal automaticity and triggered activity.

It is accepted that the acceleration of phase 4 depolarization results in enhanced normal automaticity, reaching an earlier threshold and an elevated automatic rate. On the other hand, delayed after-depolarization is the outcome of intracellular Ca^{+2} overload. In this process, he calcium-overloaded sarcoplasmic reticulum excretes Ca^{+2} in the diastole, activates Ca^{+2}-dependent depolarizing currents (such as the Na^{+}/Ca^{+2} exchange current) and, subsequently, produces a transient inward current that provokes membrane depolarization. The delayed after-depolarization reaches its threshold and a triggered ectopic action potential ensues. Early after-depolarizations originate from disproportionate action-potential prolongation caused by (a) the loss of repolarizing K^{+} currents, (b)

excessive late components of Na^+ currents and (c) the reactivation of plateau Ca^{+2} currents, which produce secondary arrhythmic depolarizations [10]. It is apparent that PV cells fulfill these criteria. The PVs have a depolarized resting membrane potential—which facilitates enhanced normal automaticity. Furthermore, PVs also provide an action potential with a lower amplitude, a shorter duration, and a smaller maximum phase 0 upstroke velocity. Slow and rapid delayed K^+ rectifier currents are augmented in the PVs, whereas transient outward K^+ currents and L-type Ca^{2+} currents are attenuated. Furthermore, animal studies have demonstrated that the diminished activity of the IK1 current facilitates trigger activity during the late phase of depolarization based on an afterdepolarization effect [11].

What is, however, the crucial stimulus that provokes the premature atrial beats in the pulmonary veins? The main AF comorbidities, such as hypertension, ischemic cardiomyopathy, diabetes mellitus, congestive heart failure, and advanced age alter left ventricular elastic properties and subsequently increase left atrial pressure [12]. The most common last step in this pathophysiologic cascade is the development of tissue stretch, which can also induce afterdepolarization and, thus, ectopic activity. This is facilitated by alterations in Ca^{+2} handling induced by increased Ca^{+2} excretion from the sacroplasmatic reticulum and enhanced Na^+/Ca^{+2} exchange, particularly in the setting of b-adrenergic stimulation. Additionally, angiotensin II contributes similarly to Ca^{+2}-handling changes by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is a significant downstream effector in cellular oxidative stress. It is known that NADPH oxidase generates reactive oxygen species (ROS). In turn, ROS products induce early afterdepolarization (EAD) and delayed afterdepolarization (DAD) as a trigger activity through the enhancement of late Na^+ currents. Angiotensin II and ROS enhance abnormal Ca^{+2} handling and Ca^{+2} overload, which cause increased atrial contractility and upregulate Ca^{+2}-dependent signaling. The subsequent alteration of the intracellular calcium balance encourages early after-depolarization. The Ca^{+2}-induced activation of the nuclear factor of activated T cells (NFAT) suppresses the L-type Ca^{+2}-current function, decreases action-potential duration (APD), and facilitates AF-induced electrical remodeling [13] (**Figure 2**).

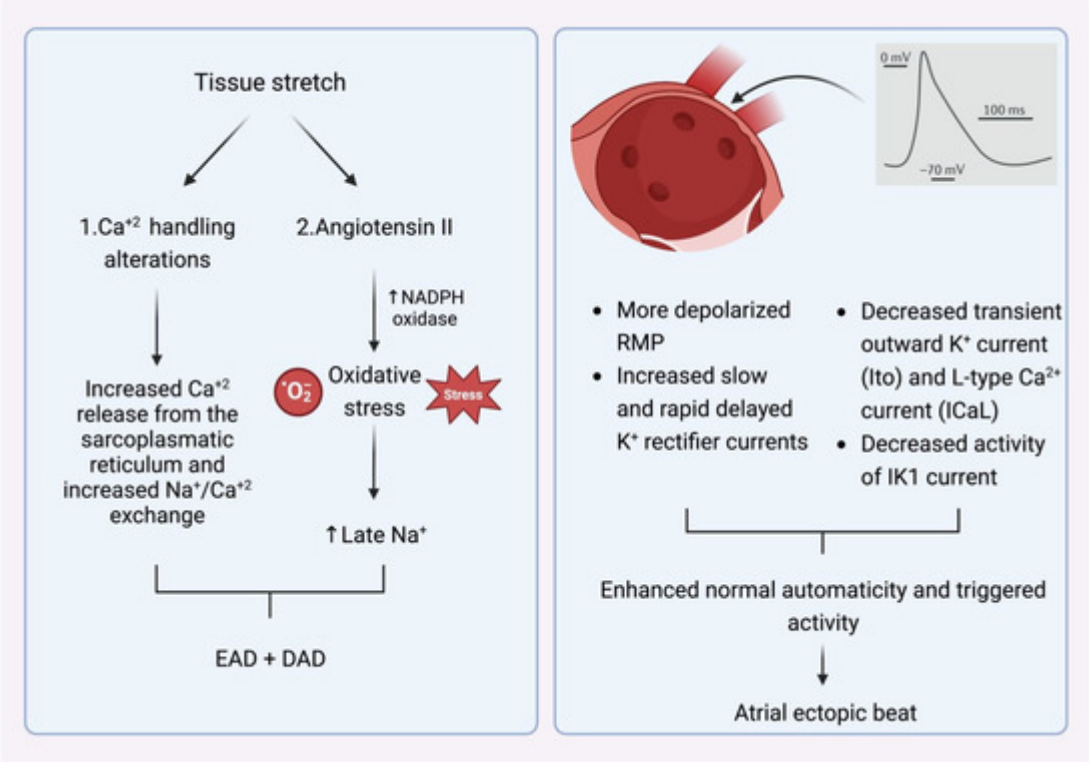


Figure 2. (**Left**) Mechanism that explains how tissue stretch promotes atrial premature beats, mainly through afterdepolarization. (**Right**) Specific electrophysiologic properties of the pulmonary veins render them more likely to be the origin of atrial ectopic beats. *NADPH oxidase* (nicotinamide adenine dinucleotide phosphate oxidase) EAD: early afterdepolarization. DAD: delayed afterdepolarization. RMP: resting membrane potential.

Triggers may originate from different regions (non-PV triggers), including the superior vena cava, crista terminalis, coronary sinus, left atrial appendage, left atrial posterior free wall, and ligament of Marshall [14]. Specific mapping protocols and isoprenaline have been used to address the significance of inducing, locating, and eliminating such non-PV triggers as a means to achieving better results in AF ablation in comparison to empirical PVI. However, this therapeutic strategy has not been established as a common practice [15] (**Figure 3** and **Figure 4**).

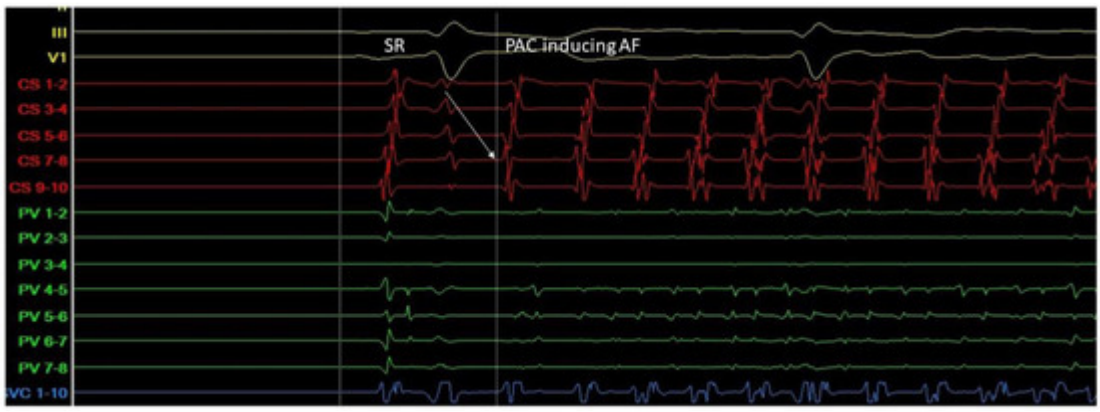


Figure 3. A. Atrial ectopic beat originates from the proximal aspect of the coronary sinus (arrow at the CS 7-8 electrogram)—a non PV trigger—and induces atrial fibrillation (G. Leventopoulos' archive). PV: pulmonary vein.

CS: coronary sinus.

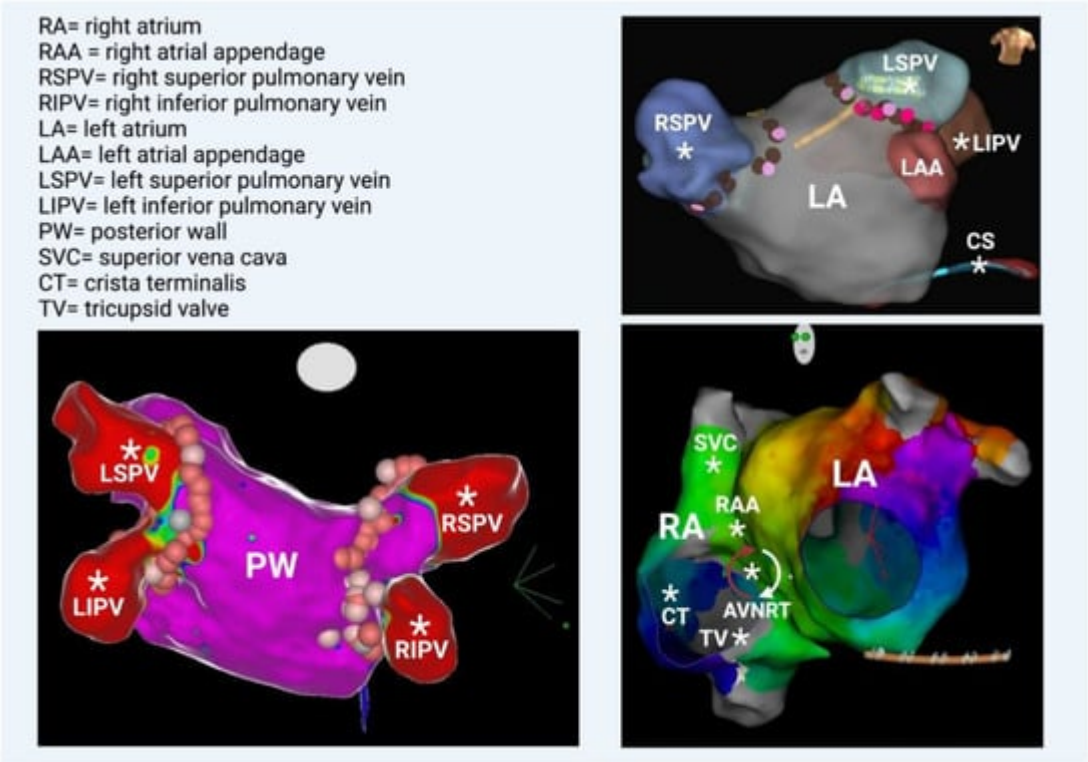


Figure 4. (**Bottom left**) Left atrium—posterior view. All 4 veins and the posterior wall are illustrated; they share the same embryologic origin.

Recently, the role of posterior-LA-wall isolation has emerged. The posterior LA wall should be viewed as an extension of the PVs with clear arrhythmogenic potential, considering its embryological, electrophysiological, and anatomical properties. During human embryogenesis, PVs initially have no link with the fetal heart. At later stages, they converge and form a common PV (at about the fifth or sixth month in utero), which becomes incorporated into the left atrium (LA) by connecting to the embryological LA on the posterior aspect. Subsequently, a smooth posterior LA is formed [16]. It is known that the posterior wall serves as an area in which AF triggers are located. Different stimulation protocols using atrial burst with or without isoprenaline have shown ectopic atrial beats that originate from the posterior wall and lead to AF initiation. Thus, there is a long-standing debate over whether empirical posterior wall isolation (PWI) on top of PVI would have an additional beneficial effect on arrhythmia-free patients' outcomes. This proposal has advocated most strongly for patients with persistent AF. Most often, posterior wall isolation is achieved by creating a roof and a posterior line through continuous RF lesions. A multipolar catheter is used for the verification of electrical isolation. The ablation therapy aims to electrically isolate the posterior wall [15]. However, in the most recent randomized CAPLA study, patients with persistent AF underwent catheter ablation for the first time. It was proven that the patients who were treated with PWI in combination with PVI did not show significant improvements in freedom from atrial arrhythmia at one year compared with those treated with PVI alone. In light of the outcomes of this trial, the empirical inclusion of PWI for the ablation of persistent AF was not supported [17]. Lastly, regarding the additional PV triggers, it should be underlined that in some cases, AF is related to AVNRT or AVRT, and this scenario should be given particular consideration in young

individuals in whom the “traditional” AF risk factors are absent. The atrial activity in these well-defined reentrant circuits can be easily degenerated, transforming regular QRS tachycardia (AVNRT/AVRT) into chaotic atrial propagation, which is indicative of atrial fibrillation [18].

3. AF Perpetuation

Although triggers are required for AF initiation, a vulnerable atrial substrate is equally important. Structural and electrophysiological atrial abnormalities assist AF perpetuation. Reentry constitutes a fundamental mechanism in the maintenance of AF in two possible ways: (a) reentrant rotors or (b) multiple independent wavelets. Multiple wavelets are multiple, simultaneous re-entrant circuits within the atria [19]. The electric dissociation of epicardial and endocardial layers has also been considered to promote reentry and contribute to the perpetuation of AF [20]. Rotors are self-sustaining rotational circuits with a spiral-wave morphology. In the propagation of models shaped in this way, the greatest curvature—at the inner part of the spiral—has the slowest propagation velocity, creating an area of functional conductional blockage at the center of the rotor as the wavelet constantly confronts an unexcitable core. However, this model proposes that the rotor is not stationary, but instead rotates around the atrial tissue. By contrast, the less accepted theory of the “leading circle” includes a stationary unexcited core. Stable rotors can anchor at certain sites—often around PVs and in areas of heterogeneous atrial tissue—forming wavefronts that spread away from the center of the rotor and then fragment, inducing chaotic and fibrillatory activity within the rest of the atrium [21].

Based on the considerations above, FIRMap (focal impulse and rotor modulation) uses phase mapping to identify the locations of up to three rotors or focal sources. This is achieved by a 64-lead basket catheter, which provides endocardial unipolar electrograms. The FIRM maps of AF reveal electrical rotors defined as sequential clockwise or counterclockwise activation contours around a center of rotation emitting outward to sustain AF activation, or focal impulses defined by centrifugal activation contours from an origin. The CONFIRM study revealed for the first time that AF may be perpetuated by localized sources in the form of electrical rotors and focal impulses. The use of FIRM ablation at patient-specific AF-sustaining sources terminated or consistently prolonged the cycle length in persistent or paroxysmal AF compared to conventional ablation in 86% of patients, and substantially increased long-term AF elimination using extremely careful monitoring compared to conventional AF ablation alone. Consistently, favorable outcomes were also reported by three other small single-center studies [22][23][24]. However, multicenter trials, recent systematic reviews, and meta-analyses of AF-rotor and -driver ablation have shown high variability and discrepancy in success rates, which do not seem to be superior to conventional pulmonary vein ablation alone. A similar approach was attempted with a 252-electrode body-surface vest in order to obtain electrocardiographic imaging (ECGi) and to demonstrate rotors that—as opposed to the previous FIRM method—were transient for several cycles only [25].

Structural and electrical remodeling are necessary for the creation of the appropriate substrate and the initiation of reentrant rotors or fragmented wavelets with AF perpetuation as the final result. Ausma et al. noted that rapid pacing induced significant cellular structure changes, such as the formation of enlarged and disordered fibers, enlarged nuclei, giant mitochondria, and a dilated sarcoplasmic reticulum [26]. Similarly, abnormal histological

findings were uniformly found in multiple atrial biopsy specimens in all patients with lone AF by Frustaci et al. [27]. Structural remodeling is characterized by changes in tissue properties and cellular ultrastructure, leading to atrial dilatation, which is the most common echocardiographic finding in patients with AF. Atrial fibrosis has a major role in structural remodeling and it is caused by the deposition of extracellular matrix proteins in the myocardial interstitial tissue. These changes predispose patients to defects in conduction, predominantly contributing to reentry and rotor formation. Atrial fibrosis is caused by the transformation of fibroblasts into myofibroblasts after the activation of transcription factors, and has classically been ascribed to ageing, comorbidities, and cardiovascular risk factors [28].

Many pathways are responsible on a molecular level for fibrosis formation. The renin–angiotensin–aldosterone system is involved in myocardial fibrosis, which is induced by medical conditions such as heart failure, cardiomyopathies, hypertension, and ischemic heart disease. Angiotensin II (Ang II) activates the production of (a) transforming growth factor-β (TGF-β) and (b) extracellular matrix (ECM) proteins, which form AF-promoting fibrous tissue.

The TGF-β1 is a major established profibrotic signaling molecule and a positive regulator of cardiac fibrosis. Its specific overexpression in the heart leads to atrial fibrosis and, in turn, increased susceptibility to AF. Exposure to Ang II or TGF-1 influences cardiac fibroblast function. Excessive fibroblast proliferation leads to the increased synthesis, secretion, and deposition of extracellular-matrix protein and subsequent fibrosis in the interstitial and perivascular space [29]. Both AngII production and AT1-receptor expression are increased during remodeling in fibroblasts in vivo. Increases in Ang II and activated TGF-1 concentrations reciprocally enhance each other's production, the transformation of fibroblasts into collagen-secreting myofibroblasts as the final step in this process. As a result, collagen deposition and fibrosis facilitate AF perpetuation. Moreover, mechanical stretch induces collagen synthesis, along with increased Ang II and TGF-1 expression in cardiac fibroblasts. Thus, chronic atrial dilation may contribute to structural remodeling and the maintenance of AF [30][31].

Apart from myofibroblast proliferation, ion-channel remodeling may also contribute to AF pathogenesis. Cardiac fibroblast proliferation and differentiation is regulated by Ca^{+2}-permeable transient receptor potential (TRP) canonical-3 (TRPC3) channels. It was proven that TRPC3 expression is increased in the atria of AF patients. In turn, AF enhances TRPC3-channel expression by causing the NFAT-mediated downregulation of microRNA-26 and results in the TRPC3-dependent enhancement of fibroblast proliferation and differentiation. In vivo, TRPC3 blockade was demonstrated to prevent AF-substrate development in a dog model of electrically maintained AF. These findings suggest the role of TRPC3 in AF, which involves its mediation of fibroblast pathophysiology, and it can be considered a novel potential therapeutic target [32].

Reactive oxygen species (ROS) refer to low-weight molecules, which constitute derivatives through oxygen metabolism. In heart-failure patients, ROS results in increased calmodulin-dependent protein kinase II (CAMKII) oxidation in the left posterior atrium, which encourages conduction delay and increased conduction heterogeneity, creating appropriate substrates for reentry circuits. Furthermore, superoxide and H_2O_2 products promote myocyte-apoptosis fibrosis and inflammation [33].

ROS production can be estimated and measured by stable markers in the circulation, including markers of lipid peroxidation (isoprostanes), malondialdehyde, oxidized phospholipids, myeloperoxidase, nitrotyrosine, and aminothiol compounds. A 10% increase in glutathione (Eh GSH) levels was linked with a 30% increase in AF incidence. Several therapeutic approaches to AF management have been designed. The use of oxygen-radical scavengers for ROS suppression, such as vitamin C, vitamin E, ebselen, tempol and N-acetyl-cysteine, have been considered. In this direction, therapeutic agents for use against the sources of ROS generation and their key signaling mediators have also been tested [34][35].

Several immune cellular mediators are involved in the fibrotic process that creates the appropriate substrate for AF sustainability. Following myocardial injury, monocytes initiate their differentiation into inflammatory macrophages, which play a significant role in the initiation and progression of fibrotic responses. Resident macrophages contribute to inflammatory myocardial microenviroments by recruiting other inflammatory leukocytes and by secreting metalloproteinase (MMP) 2, MMP 9, and inflammatory markers (IL-6), which regulate fibroblast function [36].

IN addition to macrophages, T-cell infiltration of and recruitment to injured areas as an outcome of cytokine release play a crucial role in atrial fibrosis. For instance, Th1 cells demonstrate antifibrotic action by releasing IFN-γ, inhibiting the TGF-β pro-fibrotic activity and suppressing collagen I and its expression. On the other hand, Th2 cells release pro-fibrotic mediators, such as IL4 and IL13, stimulating collagen synthesis. Furthermore, CD8+ T-cells are involved in the activation of the removal of necrotic debris and collagen-scar formation mediated by macrophages [37].

Furthermore, mast cells have been proven to participate in atrial fibrosis. They produce significant fibrosis mediators, including proteases (i.e., tryptase and chymase) and growth factors (e.g., TGF-β1, TNF, and IL-1) [38]. Tryptase and chymase (a significant protease in the conversion Ang I into Ang II) are major mediators of fibroblast physiology and exert modulatory effects on the atrial substrate and the increase in fibroblast proliferation. Consequently, collagen synthesis and myocardial fibrosis are induced [39][40].

Apart from structural remodeling, other changes in electrophysiological atrial properties, referred to as electrical remodeling, are among the most significant driving factors in AF perpetuation. Electrical remodeling consists of (a) the suppression of the Ca^{+2} current, which shortens the refractory period, (b) the enhancement of outward K^{+} currents, leading to the accelerated repolarization and hyperpolarization of atrial cells, and (c) the modified expression and localization of connexins, resulting in conduction abnormalities. The efficacy of antiarrhythmic drugs in AF, such as class I agents (which block Na^{+}), class III agents (which block K^{+}), or class IV agents (non-dihydropyridine Ca^{++} blockers), is explained by these mechanisms [41]. Electric remodeling is characterized by AF-induced shortening in action-potential duration (APD) and increases in delayed afterdepolarization (DAD) risk. By shortening the APD, atrial reentry rotors appear more stable, increasing AF vulnerability and sustainability. In addition, alterations in Ca^{+2} handling encourage diastolic Ca^{+2} release and ectopic activity. Electrical remodeling can explain why AF can recur early after cardioversion, progress from paroxysmal to more persistent forms, or develop drug resistance [42].

Connexin-40 and connexin-43 are gap-junction proteins, responsible for cell-to-cell electrical conduction [43]. Their expression is changed in AF patients, potentially assisting re-entry-encouraging conduction abnormalities. There is controversy among studies over whether reduced or increased connexin-40 expression at the transverse cell membrane encourages heterogeneous conduction. Abnormal connexin amounts, along with fibrosis deposits, account for zig-zag conduction delays, which encourage the induction of reentry arrhythmias through regions of slowing conduction velocity and unidirectional block. These are the fundamental principles of reeentry circuits.

It is apparent that all the above-mentioned pathways affect AF perpetuation and lead to the established perception that *AF begets AF* [44] (**Figure 5**).

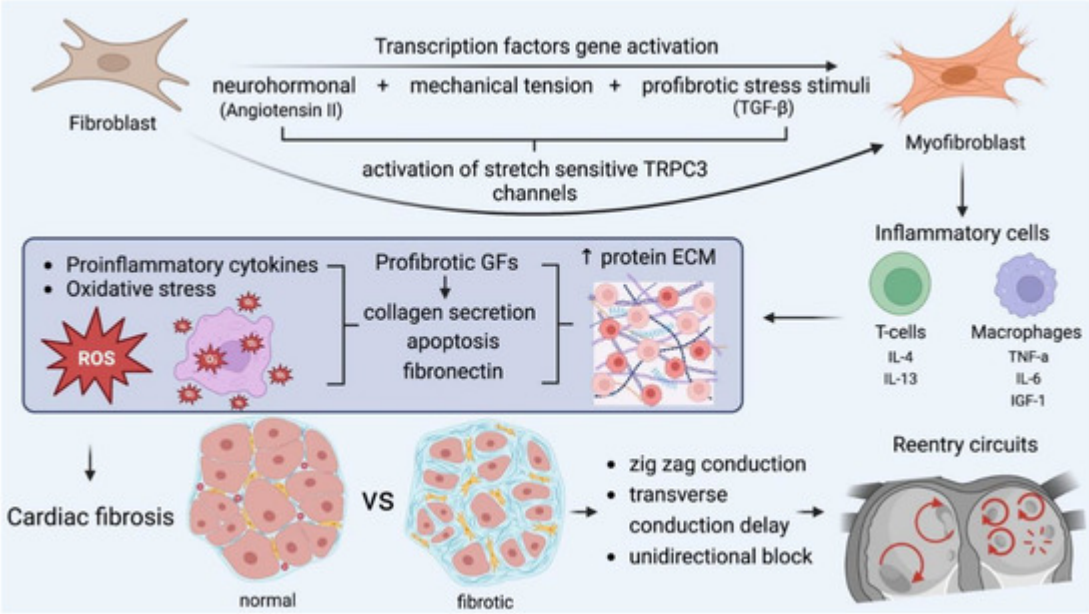


Figure 5. The key role of myofibroblasts in fibrosis formation and the main pathophysiologic cascades. Mechanical stress accounts for myocardial injury, oxidative stress, and neurohormonal activation, which transform fibroblasts into myofibroblasts, which, along with other inflammatory cells, encourage fibrotic substrates. In this microenviroment, all the required conditions for the formation and perpetuation of reentry circuits are fulfilled and further enhanced. GF: growth factor, IL: interleukin, TGF: transforming growth factor, TNF, tumor necrosis factor. IGF: insulin growth factor.

From this perspective, the extent of atrial fibrosis is an adverse prognostic sign in AF treatment, as shown in the DECAAF study, which used late gadolinium enhanced (LGE) MRI to provide a noninvasive means of estimating atrial fibrosis [45]. Based on this, the DECAAF II randomized trial supported the hypothesis that the addition of image-guided fibrosis ablation to conventional PVI results in higher procedural success rates in patients with persistent AF due to fibrotic-tissue debulking. Trial findings revealed that baseline fibrosis predicted AF-ablation outcomes, especially when fibrosis was present at increased levels, but no statistically significant differences were observed in the primary endpoint (time to first arrhythmia recurrence) between groups in the total study population. The subgroup analyses revealed a tendency towards a lower rate of atrial arrhythmia recurrence in the intervention

group for patients with a lower extent of fibrosis at baseline. This is another example of how the understanding of the pathophysiology of fibrosis still cannot be translated into clinical benefits by current therapeutic tools [46].

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