

# Inflammation-Induced Remodeling and Atrial Arrhythmias in Systemic Lupus Erythematosus: In Silico Insights

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## Abstract

*We present in silico experiments investigating the potential relationship between atrial arrhythmias in patients with systemic lupus erythematosus (SLE) and the combined effects of structural and electrical remodeling due to chronic inflammation. The study utilized a computational model to simulate the structural and electrical changes in atrial tissue caused by chronic inflammation, with the ultimate goal of shedding light on the mechanisms underlying the development of atrial arrhythmias in SLE patients. The experiment results indicate that electrical remodeling associated with SLE can alter the depolarization pattern and facilitate the emergence of reentry patterns that could initiate arrhythmias. Mild inflammation was found to be insufficient to trigger arrhythmias, while severe inflammation could induce arrhythmias that were not sustained but exhibited a repetitive pattern. This pattern exhibited a 2:1 block of the left atria. These findings provide important insights into the mechanisms underlying the development of atrial arrhythmias in SLE patients and suggest that inflammation-induced structural and electrical remodeling may contribute to this condition. The study offers a valuable starting point for further investigating the complex relationship between SLE, chronic inflammation, and atrial arrhythmias. Furthermore, in the future, this could contribute to the development of new therapeutic strategies for this condition.*

## 1. Introduction

Atrial arrhythmias have been associated with increased risk of mortality and morbidity [1]. While several risk factors for atrial arrhythmias have been identified, such as diabetes, obesity, aging, and chronic inflammation, the initiation of atrial arrhythmia pathogenesis remains unclear [2].

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a clinically heterogeneous presen-

tation and multisystemic involvement. It is characterized by the formation of autoimmune antibodies and different levels of systemic chronic inflammation. It has been suggested that the inflammatory state displayed by autoimmune diseases such as SLE could serve as a trigger to develop atrial arrhythmias through the structural and electrical remodeling of the atria. Studies have shown that patients with SLE have double the risk of developing atrial arrhythmias compared to the general population [3, 4]. In SLE, several possible mechanisms have been proposed as the cause of the development of atrial arrhythmias, such as sinus tachycardia or atrial ectopic beats [2]. However, conclusive evidence on the relationship between SLE and atrial arrhythmias remains uncertain.

Inflammatory mediators such as cytokines and chemokines can directly affect the expression and function of ion channels in cardiac myocytes. In chronic inflammation, pro-inflammatory cytokines such as interleukin-6 can reduce L-type calcium and sodium channel density. Additionally, SLE-associated inflammation can affect the inward-rectifier potassium channels, which stabilizes the resting membrane potential and maintains normal cardiac rhythm [5]. Furthermore, SLE-associated autoantibodies can target other ion channels, including the transient outward potassium channel and the ryanodine receptor, which is involved in the release of calcium from the sarcoplasmic reticulum during excitation-contraction coupling [6]. Lastly, in some cases of SLE, there is a specific autoantibody production that targets ion channels and receptors in the heart. Anti-Ro/SSA and anti-La/SSB antibodies can bind to the L-type calcium channel and reduce its density, impairing cardiac function [2].

Thanks to advances in computational cardiac modeling, different scenarios can be modeled to reproduce various physiological and pathological conditions. Computer models can play a significant role in understanding the mechanisms underlying complex biological processes, such as the relationship between SLE and atrial

arrhythmias. While atrial arrhythmias electrical and structural remodeling have been extensively studied, the effect of chronic inflammation and atrial arrhythmias in patients with SLE still lacks understanding.

This study aims to model different degrees of electrical and structural remodeling due to chronic inflammation in SLE. We will obtain different scenarios to evaluate the link between the SLE inflammatory process and vulnerability to atrial arrhythmias in patients with SLE.

## 2. Methods

Human atrial cardiomyocyte electrophysiology was modeled using the mathematical formulation proposed by Courtemanche et al. [7]. SLE electrical remodeling due to inflammation was modeled by modifying specific ionic channels' maximum conductivity. Based on literature, we modified the maximum conductance of the sodium channel (GNa), the L-type calcium channel (GCaL), the transient outward potassium channel (Gto), the rapid delayed rectifier potassium channel (GKr), the ryanodine receptors (RyR), and maximum calmodulin concentration (Cmdn) to simulate electrical remodeling due to mild and severe inflammation (Table 1) [2, 5, 6]. Additionally, SLE fibrosis exhibits an interstitial pattern [4] modeled by splitting the nodes of the tetrahedral mesh following the main fiber direction. Eikonal-based simulations were carried out using a bi-atrial geometry [8] with an average edge length of  $900 \mu\text{m}$  as described in Barrios et al. [9].

	GNa	GCaL	Gto	GKr	RyR	Cmdn
M	0.5	0.5	0.5	0.5	1.5	1.5
S	0.25	0.25	0.25	0.25	2.0	2.0

Table 1. Factor which increased or decreased the ionic model parameters to simulate mild (M) and severe (S) inflammation due to systemic lupus erythematosus.

## 3. Results

Action potential duration at 90% repolarization was 293.94 ms, 323.07 ms, and 245.08 ms for control, mild inflammation, and severe inflammation, respectively (Figure 2). Interstitial fibrosis alone did not cause atrial arrhythmias. However, the total activation was increased with a higher amount of interstitial fibrosis. The latest activation time was 111 ms, 122 ms, and 132 ms for no interstitial fibrosis, 10% interstitial fibrosis, and 40% interstitial fibrosis (Figure 3).

Additionally, combined electrical and structural remodeling associated with SLE changed the depolarization pattern and allowed a reentry pattern to arise (Figure 4). While fibrosis and mild inflammation did not trigger an

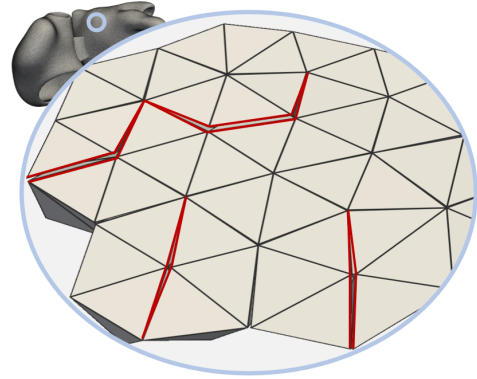


Figure 1. Node splitting of a tetrahedral mesh to model systemic lupus erythematosus interstitial fibrosis in the bi-atrial coarse mesh. Red edges highlight the separation between nodes.

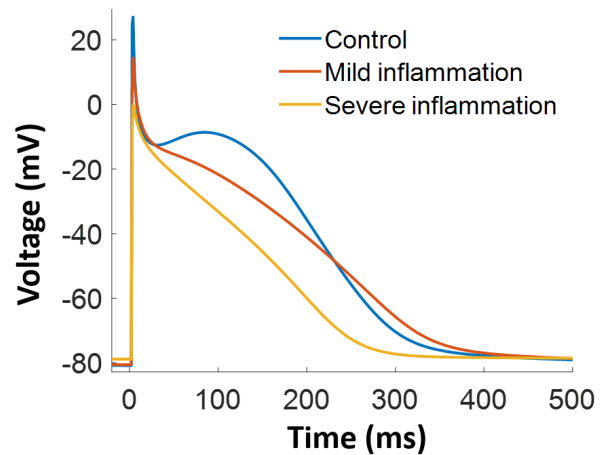


Figure 2. Traces of action potential for control case (non-remodeled) in blue, mild electrical remodeling due to inflammation in red, and severe electrical remodeling due to inflammation in yellow.

arrhythmia, fibrosis and severe inflammation were able to initiate arrhythmias, which were not sustained but showed a repetitive pattern for simulations of 5 s. The pattern exhibits a 2:1 block of the left atria. The arrhythmogenic pattern due to severe inflammation is depicted in Figure 4.

## 4. Discussion

Here we presented in silico experiments to understand the risk of developing atrial arrhythmias in SLE. We showed that electrical remodeling due to inflammation creates a vulnerable substrate to initiate and maintain atrial arrhythmias. Interstitial fibrosis alone does not increase the vulnerability to atrial arrhythmias but slows the wavefront propagation, delaying the latest activation.

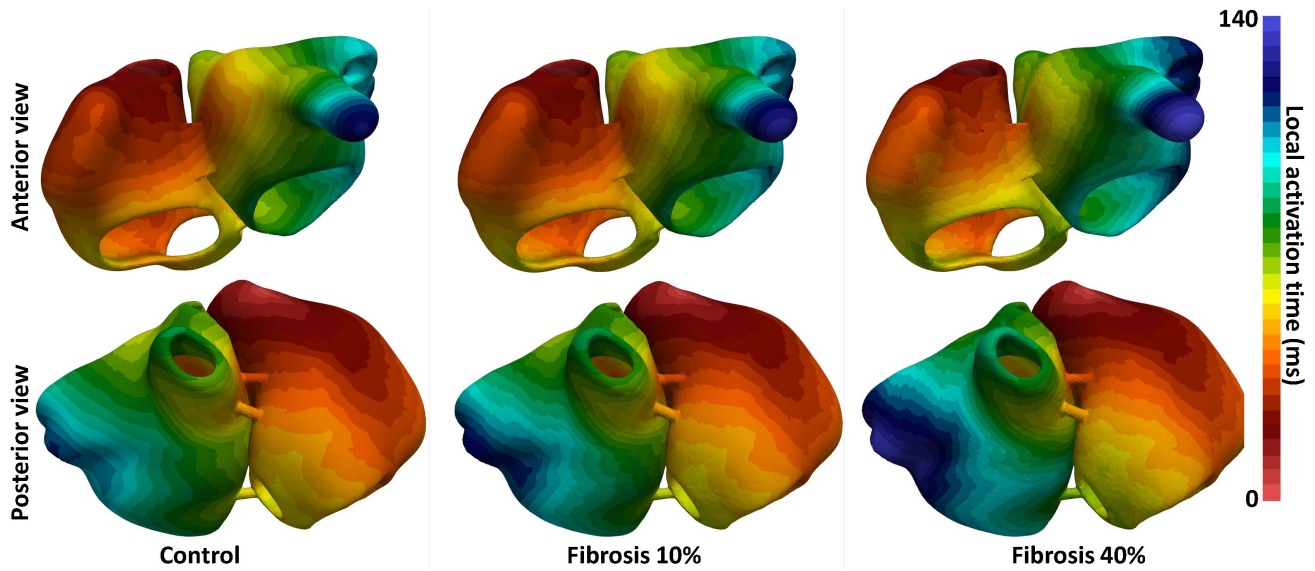


Figure 3. Anterior and posterior view of the local activation time map for control case, for 10% of interstitial fibrosis, and 40% of interstitial fibrosis. Due to fibrosis, the total activation time increased from 111 ms for control case, to 122 ms and 132 ms for 10% fibrosis and 40% fibrosis, respectively.

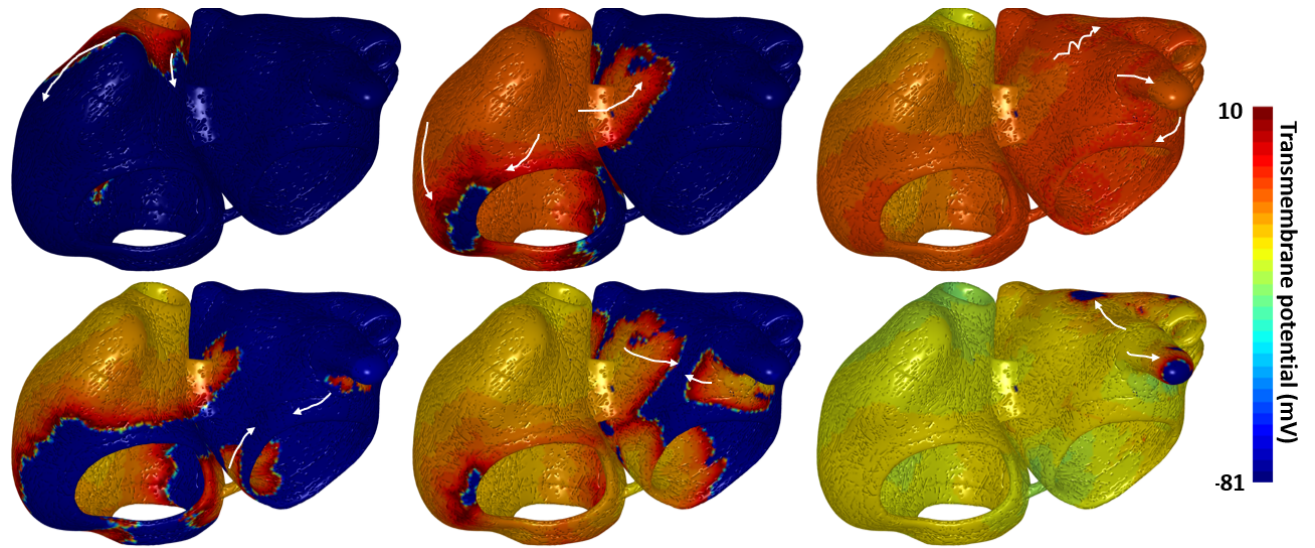


Figure 4. Snapshot of the depolarization pattern arising due to structural and electrical remodeling in systemic lupus erythematosus. White arrows show the depolarization direction. The pattern exhibits a 2:1 block due to the prolonged action potential duration.

Several studies have shown that fibrosis increases the vulnerability to atrial arrhythmias. However, not all fibrosis exhibits the same pattern due to different etiologies (e.g., diabetes, obesity, aging, chronic inflammation, etc.) [10]. In the case of autoimmune diseases, fibrosis could be exhibited in a patchy pattern, for example in systemic sclerosis or an interstitial pattern as in SLE [2]. Our findings showed that interstitial fibrosis, characteristic of SLE, does not increase the spontaneous occurrence of

atrial arrhythmias following a sinus rhythm activation.

We found that a combination of electrical and structural remodeling due to inflammation in SLE increases the vulnerability to atrial arrhythmias. While interstitial fibrosis slows the conduction in the cardiac tissue, it does not increase spontaneous initiation to atrial arrhythmias. However, the vulnerability to atrial arrhythmias was increased in the presence of electrical remodeling due to chronic inflammation. McDowell et al. [11] showed that a

combination of fibrosis and electrical remodeling increases the vulnerability to atrial fibrillation. Moreover, Varela et al. [12] showed that action potential duration heterogeneity is a key player in initiating atrial arrhythmias, which aligns with our results from the inflammation remodeling increases the action potential duration heterogeneity.

This study was performed in one atrial anatomy. Further studies can include population of atrial cellular and anatomical models that could provide more insight in the relationship between SLE and anatomical differences. Additionally, cellular infiltration plays a role in the dynamics of atrial arrhythmias and in the electrical remodeling where myofibroblasts [13] and macrophages [14] are found and should be studied in a mesh with a higher resolution to reduce the effect of the homogenization. However, here we present potential mechanisms that could trigger atrial arrhythmias in patients with SLE. These experiments could help clinicians understand the pathophysiology behind atrial arrhythmias in SLE patients. Furthermore, it could provide key information for the specific treatment of these patients and therefore therapies could be tailored to individual patients in the future.

## 5. Conclusions

We present here an in silico experiment which can serve as starting point to elucidate the link between atrial arrhythmias and SLE as a consequence of the combined effects of structural and electrical remodeling due to chronic inflammation.

## Acknowledgments

This project is part of the grant I+D+i PLEC2021-007614, funded by MCIN/AEI/10.13039/501100011033 and by the “European Union NextGenerationEU/PRTR” and by the European Union’s Horizon research and Innovation programme under the Marie Skłodowska-Curie grant agreement No. 860974.

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