

Arrhythmogenic Ablation Lesions Underlie Atrial Fibrillation Recurrence: A Longitudinal Bi-Atrial Digital Twin Study

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Abstract

Atrial fibrillation (AF) recurrence following catheter ablation remains a significant clinical challenge. This study investigates whether recurrence could result from the incomplete elimination of the native arrhythmogenic substrate or from new pro-arrhythmic substrates created by ablation. Patient-specific computational models of the atria (i.e., digital twins; DTs) constructed from pre- and post-ablation delayed-enhancement magnetic resonance imaging (MRI) scans were used to assess the arrhythmogenic substrate before and after the procedure. Our findings reveal that the ablation procedure had a differential effect on the substrate of patients whose AF did and did not recur, and suggest that recurrence may be facilitated by ablation lesions themselves. This work presents a novel framework using longitudinal bi-atrial DTs and demonstrates the value of computational models in elucidating the mechanisms underlying AF recurrence.

1. Introduction

Atrial fibrillation is characterized by disorganized electrical activity in the atria, leading to ineffective atrial contraction and loss of the normal rhythm of the heart. Catheter ablation is a key treatment for AF aimed at disrupting abnormal electrical activity to restore normal rhythm. However, many patients experience recurrence [1], highlighting a significant clinical challenge in achieving long-term rhythm control.

The mechanisms underlying AF are complex and multifactorial, involving a combination of ectopic triggers, structural remodeling, and other factors. Fibrotic remodeling leads to regions of slow conduction that could harbor reentrant circuits [2], creating an arrhythmogenic substrate for AF. Ablation lesions lead to further remodeling (scarring) of the atrial myocardium, which may inadvertently create new arrhythmogenic substrates. The relationship between ablation-induced scars and AF recurrence is

complex and not fully understood.

Due to the limited ability to assess patient-specific electrophysiological (EP) effects of structural remodeling in vivo, computational heart models offer a valuable tool for mechanistic studies of cardiac arrhythmias [2, 3]. In this study, we employed bi-atrial computational models to investigate whether AF recurrence could be due to the incomplete elimination of the native arrhythmogenic substrate or the creation of new pro-arrhythmic regions by the ablation lesions. We constructed bi-atrial DTs from pre- and post-ablation MRI scans of AF patients and evaluated the arrhythmogenic propensity of the atrial substrate before and after the procedure. Our results shed new light on the role of ablation scarring in substrate arrhythmogenesis and AF recurrence.

2. Methods

2.1. Clinical Data

Patients with symptomatic AF undergoing first-time catheter ablation as part of routine care underwent cardiac MRI before and three months after ablation. The ablation procedure was conducted following established techniques for pulmonary-vein isolation and posterior wall debulking [4]. The clinical outcome measured was AF recurrence one year post-ablation. Twenty-two patients with good-quality pre- and post-ablation MRI were included in this study. MRI quality was independently assessed by two experienced analysts, with inclusion requiring consensus on the absence of major artifacts and adequate contrast, especially in the right atrium.

2.2. Construction of Bi-Atrial DTs

The bi-atrial DTs were constructed from pre- and post-ablation MRI scans. In short, automatic segmentation of the right and left atrium (LA) was done using a convolutional deep neural network [5], followed by manual quality control. Using personalized image intensity ratio, the

atrial wall was characterized as non-fibrotic, fibrotic (subdivided into interstitial and dense fibrosis), and exclusively in the post-ablation LA, also as ablation scar. Volumetric meshes, incorporating patient-specific atrial geometry and fibrosis/scar distribution, were generated. Then, atrial fibers, computed from diffusion tensor MRI data, were mapped onto the patient-specific meshes using Universal Atrial Coordinates [6]. Non-fibrotic and fibrotic cells were assigned EP parameters as described previously in detail [2]. We used a modified version of the Courtemanche model [7], and in fibrotic regions, we decreased IK1, ICaL, and INa conductance by 50%, 50%, and 40%, respectively. In contrast to previous studies, here we differentiate between two types of fibrosis – interstitial and dense fibrosis – representing different degrees of structural remodeling and differing only in their conductivity (the conductivity of dense fibrosis was 50% of that of interstitial fibrosis). Scar regions were modeled as non-conductive.

2.3. Assessment of the Arrhythmogenic Propensity of the Substrate in DTs

We assessed substrate arrhythmogenicity through EP simulations using openCARP [8] and followed our previously described sequential pacing protocol using 40 pacing sites [2] (Figure 1). For each DT, the substrate was deemed arrhythmogenic if at least one reentry (i.e., rotational activity sustained for at least three seconds) was observed upon cessation of pacing. For each patient, substrate ar-

rhythmogenicity was first assessed in the pre-ablation DT. If the pre-ablation DT was arrhythmogenic, then substrate arrhythmogenicity was assessed in the corresponding post-ablation DT; otherwise, the DT pair was excluded from further analysis.

For each DT, we quantified the vulnerability – calculated as the ratio of pacing sites that induced a reentry to the total number of pacing sites used in the pacing protocol – as well as the potential reentry-sites (PRs) – representing the unique locations capable of sustaining reentries.

It is important to note that substrate arrhythmogenicity represents a measure of the substrate's likelihood of developing an arrhythmia, which may not necessarily represent the patient's current AF status (or lack thereof), as the manifestation of AF may be influenced by other factors such as ectopic triggers, parasympathetic and sympathetic inputs, etc.

3. Results and Discussion

3.1. Vulnerability to Reentry in DTs

Out of the twenty-two pre-ablation DTs, three had no PRs following the pre-ablation inducibility test; of these, two belonged to the no-recurrence group. For the remaining nineteen DTs, the pre-ablation vulnerability to reentry was similar between the recurrence ($14.2 \pm 10.2\%$) and no-recurrence groups ($15.0 \pm 11.2\%$; $p=0.880$; Figure 2). However, following the procedure, the DTs of patients whose

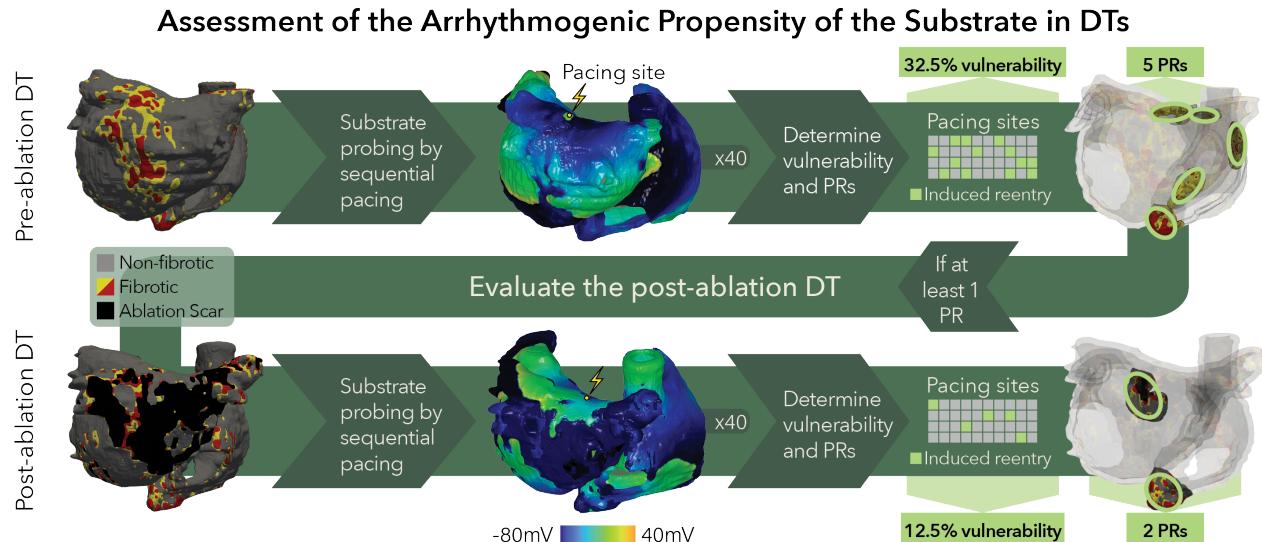


Figure 1. Protocol for assessing the arrhythmogenic propensity in DTs. First, the pre-ablation DTs were probed by sequential pacing from 40 different sites. If at least one reentry was induced in the pre-ablation DT, the corresponding post-ablation DT was evaluated using the same pacing protocol. The arrhythmogenic propensity of each DT was quantified by two metrics: vulnerability and number of PRs. In this example, the pre-ablation DT had 13/40 pacing sites that induced reentry (vulnerability=32.5%) in 5 different PRs, and the post-ablation DT had 5/40 pacing sites that induced reentry (vulnerability=12.5%) in 2 different PRs.

AF recurred post-ablation (R-DTs) exhibited an increase in vulnerability (Δ vulnerability= $9.0\pm17.2\%$), while the DTs of patients whose AF did not recur (N-DTs) exhibited a decrease (Δ vulnerability= $-8.3\pm8.4\%$; $p=0.014$). As a result, the post-ablation vulnerability was significantly higher in the recurrence group ($23.2\pm17.5\%$) compared to the no-recurrence group ($6.7\pm6.1\%$; $p=0.015$). These findings reveal that the ablation had opposite effects on substrate arrhythmogenicity in the two groups: it reduced the substrate's susceptibility to reentry in N-DTs, but increased it in R-DTs.

Our results indicate that high vulnerability observed at three months post-ablation is indicative of AF recurrence occurring within the first year following the procedure. This metric could serve as a tool for post-procedure risk stratification, helping to identify patients who may benefit from closer monitoring or adjunctive therapy after the ablation.

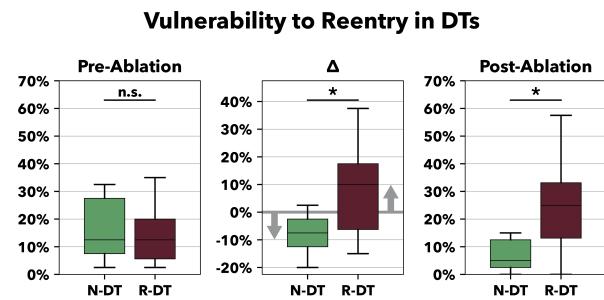


Figure 2. Vulnerability in N-DTs and R-DTs. Δ is the difference from pre- to post-ablation. Data are presented as median [IQR]. Statistical significance is indicated by an asterisk ($p < 0.05$); *n.s.* denotes non-significant differences.

3.2. Potential Reentry-Sites in DTs

In pre-ablation N-DTs, the average number of PRs was 3.9 ± 2.8 (grey bars in Figure 3A), each induced by 1.5 ± 1.0 pacing sites. In contrast, R-DTs exhibited a lower average of 2.3 ± 1.5 PRs, each induced from 2.5 ± 2.2 pacing sites. This suggests that despite fewer PRs in R-DTs pre-ablation, they were more easily inducible than in N-DTs, indicating that PRs in R-DTs were more arrhythmogenic.

From pre- to post-ablation, the average number of PRs in N-DTs decreased significantly (Δ PRs= -2.7 ± 2.2), in contrast to R-DTs, where the average number of PRs decreased only slightly (Δ PRs= -0.2 ± 1.8). This reduction in the number of PRs following the procedure was significantly different between the two groups ($p=0.017$), emphasizing their differential responses to ablation.

Post-ablation PRs were classified as residual (i.e., persisted from pre- to post-ablation) or emergent (i.e., seen only post-ablation). The number of residual PRs was low

and similar in both groups: 3 out of 35 (9%) in N-DTs and 2 out of 23 (9%) in R-DTs, indicating that the ablation procedure eliminated most pre-ablation PRs in both groups. In contrast, there was a high incidence of emergent PRs, particularly in R-DTs. Most R-DTs had 2 or 3 emergent PRs (solid red bars in Figure 3A), while most N-DTs had only 1 (except for P9 with 2; solid green bars in Figure 3A).

Our findings show that a reduction in the number of PRs correlates with a favorable outcome post-ablation (i.e., no-recurrence). Our analysis reveals that the ablation procedure was effective in eliminating most of the pre-existing PRs in both groups, but there was significant latent arrhythmogenicity in the recurrence group (i.e., emergent PRs), which could explain why AF recurred in these patients.

3.3. Scar-Anchored Reentries in Post-Ablation DTs

Approximately half of post-ablation PRs harbored reentries anchored around ablation scars. These scar-anchored reentries (ScAREntries) were nearly three times more prevalent in the recurrence group (11 ScAREntries in 7 R-DTs) than in the no-recurrence group (4 ScAREntries in 3 N-DTs; Figure 3B). Importantly, ScAREntries were 2.7 times more inducible than reentries not anchored around scar (ScAREntries were inducible by 5.3 ± 4.7 pacing sites vs. 2.0 ± 1.7 pacing sites for reentries not anchored around scar; $p=2\cdot10^{-5}$), thereby contributing to higher vulnerability in post-ablation DTs.

From the post-ablation MRI scans, the absolute volume of ablation scar was greater in R-DTs ($9.5\pm2.4\text{ cm}^3$) than in N-DTs ($6.7\pm2.0\text{ cm}^3$; $p=0.014$). However, the relative volume of ablation-scar (i.e., the ratio of scar volume to LA atrial wall volume) did not differ significantly between the two groups ($14.7\pm5.6\%$ in N-DTs vs. $17.1\pm4.9\%$ in R-DTs; $p=0.079$).

These findings demonstrate that ablation scars can create new arrhythmogenic substrates, as evidenced by ScAREntries. The heightened arrhythmogenic propensity in post-ablation R-DTs is largely attributed to ScAREntries, which contributed to emergent PRs and a heightened vulnerability post-ablation. Our results suggest that the presence of ScAREntries may be a key factor in the clinical recurrence of AF after ablation. This underscores the clinical importance of recognizing the potential for ablation scars to create arrhythmogenic substrates and supports the need for further investigation into strategies that minimize these iatrogenic pro-arrhythmic effects of ablation lesions.

4. Conclusion

In this study, we developed the first longitudinal bi-atrial DT framework to investigate the mechanisms underlying

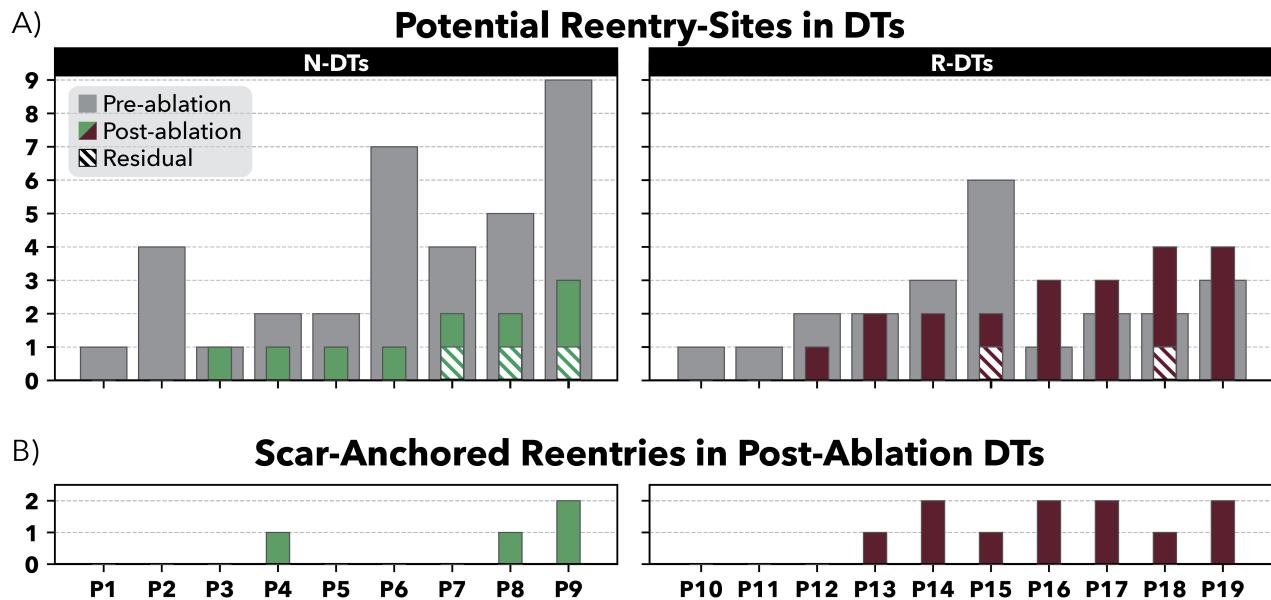


Figure 3. A) Number of pre- and post-ablation PRs. B) Number of post-ablation PRs with ScAReentries.

AF recurrence before and after catheter ablation. Our analysis reveals significant differences between the DTs of patients who did and who did not experience AF recurrence and suggests that the recurrence of AF may be facilitated by ablation lesions themselves. Our work demonstrates the value of computational models in elucidating the mechanisms underlying AF recurrence and highlights their potential for non-invasive, patient-specific risk stratification.

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