ERP Differences Required for a PV Single Extrasystole to Induce Atrial Fibrillation. An In Silico Study

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Abstract

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and is frequently initiated by ectopic activity originating from the pulmonary veins (PVs). Shortened effective refractory periods (ERPs) in these structures have been reported and identified as key risk factors for AF initiation in clinical studies. In this work, a three-dimensional atrial model was developed to investigate the impact of PV ERP relative to the surrounding atrial tissue ERP (baseline ERP: 220 ms) on AF inducibility. Single premature stimuli were delivered within the PV region, and the resulting arrhythmic responses were evaluated across a range of coupling intervals and ERP configurations. The results demonstrate that when PV ERP is reduced to 150 ms or below, single ectopic beats are sufficient to induce sustained reentrant activity leading to AF. In contrast, longer PV ERP values do not result in arrhythmia initiation. These findings indicate that the ERP gradient between the PVs and atrial tissue plays a key role in enabling the transition from a single ectopic beat to sustained reentrant activity.

1. Introduction

In the current clinical setting, atrial fibrillation (AF) is known as the most prevalent cardiac arrhythmia, affecting nearly 40 million individuals worldwide [1]. This abnormal rhythm, characterized by rapid and disorganized atrial activation, is commonly associated with symptoms such as fatigue, palpitations, and dizziness [2].

AF is thought to originate most commonly from the pulmonary veins (PVs) within the left atrium (LA), primarily due to triggered ectopic activity in these structures. In particular, autonomic ganglia located near the PV ostia have been implicated as potential sources of these triggering events [3,4]. Differences in effective refractory period (ERP) between PV tissue and the posterior atrial wall have been reported in canine models prior to the onset of atrial tachycardia [5]. However, it remains unclear whether similar electrophysiological heterogeneities are present in the human atria and to what extent they contribute to the initiation of paroxysmal AF [6]. In this context, shortened ERPs have been associated with an increased susceptibility to AF initiation [7,8].

Computational simulations constitute a powerful framework for evaluating specific electrophysiological properties in isolation under fully controlled conditions, enabling the comparison of equivalent scenarios in which only the variable of interest is modified. Despite their substantial contribution to AF research, many computational studies rely on simplified or non-physiological parameter values, often derived from measurements obtained under conditions that do not preserve in vivo electrophysiological behavior (e.g., isolated cells), and therefore may not accurately reflect clinical observations [9–12]. Several models adopt markedly shortened refractory periods to represent AF remodeling [13-16], thereby further reducing direct comparability with in vivo data.

Although obtaining accurate in vivo measurements of ERP in specific structures such as the PVs remains challenging in humans, improved characterization of PV electrophysiological properties and their role in AF initiation could enhance patient stratification based on the underlying electrical substrate and support the identification of individuals at increased risk of developing AF. In this context, computational models have demonstrated that regions exhibiting action potential heterogeneities relative to atrial wall morphology may serve as anchoring sites for rotors in AF [17]. In addition, with respect to ERP, spatial dispersion of this parameter within atrial tissue has been shown to significantly influence reentrant dynamics [18]. Nevertheless, the specific impact of these electrophysiological properties when focused on the pulmonary vein (PV) region has not yet been systematically investigated.

Therefore, the objective of this study is to adapt a computational model, within the scope of our methodological framework, incorporating human in vivo

data, and to identify a threshold in effective refractory period (ERP) differences between PV tissue and the posterior atrial wall that enables AF initiation. This approach further aims to assess whether the ERP heterogeneities previously reported in canine models [5] are also present in humans and to evaluate their potential role as a mechanistic substrate for AF initiation when specific refractory conditions are met.

2. Methods

2.1. Electroanatomical model generation

A patient-specific anatomical model of the atria was reconstructed from CT images provided by the Hospital Universitari i Politècnic La Fe (Valencia, Spain). The resulting biatrial mesh incorporated heterogeneous wall thickness, implemented according to previously published methods [19]. The three-dimensional model comprised 1,613,915 hexahedral elements and 1,851,520 nodes, with a spatial resolution of 300 µm. A fixed conduction velocity of 0.7 m/s was assigned, consistent with values reported in clinical studies of AF patients [20], and a uniform anisotropy ratio of 0.5 was applied throughout the tissue. These simplifications were intentionally introduced to minimize the influence of conduction heterogeneities, thereby preventing wavefront fragmentation, the artificial induction of AF, or the spurious stabilization of reentrant activity, which could confound the assessment of ERP differences on arrhythmia initiation. Indeed, it has been shown that variations in anisotropy [21] or conduction velocity [22,23] can strongly influence rotor dynamics in computational simulations.

2.2. Effective refractory period adaptation

For the simulation of the action potential, the Courtemanche-Ramirez-Nattel model [24] was applied, incorporating the acetylcholine-mediated calcium current proposed by Grandi et al. [25]. All electrophysiological models were first stabilized in a 0D context for 1 minute at a basic cycle length (BCL) of 1000 ms. The stabilized model was then assigned to the region of interest within the mesh. For this study, only two regions were considered: the pulmonary veins (PVs) and their antrum, with the remaining mesh representing the rest of the tissue (Figure 1). This approach enables the isolated study of the ERP differences required for AF initiation between the PVs and the surrounding atrial tissue. Finally, the 3D mesh was stabilized with the assigned models over five pacing cycles at the same BCL.

Effective refractory periods (ERP) in each region were determined by applying a circular extrastimulus with a radius of 0.2 cm at the left superior PV (Figure 1) at specific intervals following the last stabilized sinus beat, while monitoring the simulation's response. The initial coupling interval (CI) between the last sinus stimulus and the extrastimulus was set at 250 ms and then decreased in 10 ms steps until the tissue failed to capture. The first CI at which no capture occurred was defined as the ERP.

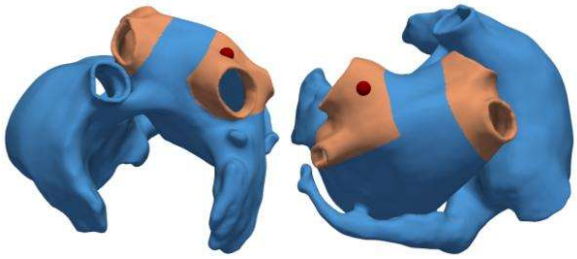

Figure 1. Representation of the pulmonary vein (PV) ectopic focus location (red dot), and ostial and antral regions (orange) versus the remaining atrial tissue (blue) from an anterior view (left) and a posterior view (right).

In this study, a baseline ERP of 220 ms was assigned to the atrial myocardium, based on mean values reported in several human in vivo studies [9–12]. As a proof of concept, and in the absence of precise data on expected ERP ranges for the PVs relative to the surrounding atrial tissue, AF inducibility was evaluated by assigning a range of ERP values to the PV region, specifically 210, 200, 190, 180, 170, 160, 150, and 140 ms.

2.3. AF inducibility study

After the model had reached a stable state, a stimulus was delivered within the PVs region, and the simulation was allowed to run for 1 second. Consistent with previous computational studies [14], AF was considered to have occurred if the resulting arrhythmia exhibited its characteristic features—rotational, rapid, and disorganized activity—and persisted for the duration of the simulation. The premature stimulus was applied at various coupling intervals (CIs) relative to the last sinus beat, allowing assessment of whether the electrical activity at each interval degenerated into sustained AF or self-terminated.

3. Results

3.1. Induced arrhythmias

Using this methodology, each simulation resulted in one of three outcomes: the atrial tissue failed to capture the extrastimulus; the electrical activity spontaneously terminated, with the wavefront colliding with itself in the mitral isthmus region (Figure 2A); or stimulation of the targeted region initiated atrial fibrillation–type arrhythmias (Figure 2B). These outcomes are summarized in Table 1.

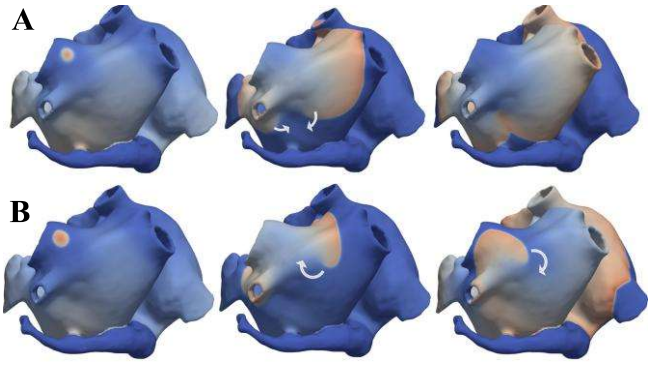

Figure 2. Comparison of outcomes following an extra stimulus where atrial tissue captured the electrical activity: (A) spontaneous termination and (B) induction of AF–type arrhythmias.

Table 1. Induced atrial fibrillation (AF) episodes sustained for 1 second or longer as a function of the effective refractory period (ERP) set for the pulmonary veins (PV) and the coupling interval (CI) from the last sinus beat. Three possible outcomes are reflected: non capture (n.C., grey), atrial fibrillation (AF, orange) and capture (C, green).

CI	ERP PV (ms)							
(ms)	140	150	160	170	180	190	200	210
250	n.C	n.C	n.C	n.C	n.C	n.C	n.C	n.C
260	AF	C	n.C	n.C	n.C	n.C	n.C	n.C
270	AF	AF	C	n.C	n.C	n.C	n.C	n.C
280	AF	AF	C	C	n.C	n.C	n.C	n.C
290	AF	C	C	C	C	n.C	n.C	n.C
300	C	C	C	C	C	n.C	n.C	n.C
310	C	C	C	C	C	C	n.C	n.C
320	C	C	C	C	C	C	C	n.C
330	C	C	C	C	C	C	C	C
340	C	C	C	C	C	C	C	C

3.2. Pulmonary Vein ERP and AF Vulnerability

Table 1 presents the results of arrhythmia induction for each PV ERP and extrastimulus CI relative to the last sinus depolarization. As expected, as the ERP increases, the CI required for the tissue to "capture" the extra stimulus—propagating it to the rest of the atrium—also becomes longer. The atrial tissue did not capture stimuli with a CI shorter than 250 ms from the sinus beat. As can be observed, when ERP are long and comparable to those of the surrounding atrial tissue (220 ms), a single extrasystole originating within the pulmonary veins is not sufficient to induce a spontaneous episode of atrial fibrillation in the developed model. Once the refractory period in the pulmonary veins decreases to around 150 ms, AF episodes begin to occur, and with ERP below 150 ms, they can be triggered across a wide range of CI.

4. Discussion

Induced arrhythmias were classified as atrial fibrillation based on their disorganized pattern and their maintenance through continuously shifting rotational activity within the atrium. It should be noted, however, that clinically, AF is typically associated with even greater wavefront fragmentation, resulting from factors such as regions with heterogeneous conduction velocities, fibrotic or scarred tissue, and multiple ectopic foci. The present study therefore focuses solely on computationally testing the theoretical concept—widely observed in clinical practice—that spontaneously arising ectopic activity from the pulmonary veins can serve as a trigger for AF, and on evaluating whether differences in ERP may account for this phenomenon, as well as the critical magnitude of ERP disparities required to induce it.

In agreement with computational studies on the influence of regions of action potential and ERP heterogeneity on AF dynamics [17,18], the results show a similar trend, indicating that areas exhibiting abrupt changes in this parameter may, at least, act as initiators of AF due to wavefront fragmentation, and may even serve as anchoring sites for rotors.

Furthermore, the inability to achieve tissue capture with CI shorter than 250 ms from the onset of the last sinus depolarization is attributable to the ERP set for the atrial tissue outside the PV, which is 220 ms. Consequently, these regions remain refractory during this period.

The results obtained from the computational model suggest that, with a baseline ERP of 220 ms in the atrial tissue, shorter ERP values in the PVs and their antra—specifically 150 ms or less—represent a risk factor for the development of spontaneous AF episodes following a single extrasystole originating in these structures. The presence of such reduced ERPs, differing by approximately 70 ms from the surrounding atrial tissue, facilitates the formation of transient conduction blocks at the interface between these regions, which can give rise to rotational activity capable of sustaining AF. These findings highlight the importance of integrating computational studies with clinical investigations to further elucidate the mechanisms underlying this highly prevalent arrhythmia.

5. Conclusion

The computational model developed in this study suggests that an ERP of approximately 150 ms in the pulmonary veins (PVs), relative to an effective refractory period (ERP) of around 220 ms in the surrounding atrial tissue, represents a critical threshold at which a single extrasystole originating in these structures can degenerate

into atrial fibrillation (AF). Whether validated with clinical data, these findings may help identify a potential arrhythmic risk factor and predictors of AF recurrence in patients, thereby informing both risk stratification and therapeutic strategies.

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