Pharmacological Prevention of Paroxysmal Fibrillatory Episodes in 2D Atria Considering Atrial Dominant Frequency

Violeta Puche-García[1], Laura Martinez-Mateu[2], David Filgueiras-Rama[3], Lucía Romero[1], Javier Saiz[1]

[1]Ci2B, Universitat Politècnica de València, Spain
[2]BigMed+, Universidad Rey Juan Carlos, Spain
[3]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Spain

Abstract

The suboptimal success of antiarrhythmic drugs (AADs) in preventing paroxysmal Atrial Fibrillation (pAF) episodes could potentially be addressed by considering how intersubject variability influences the response to the pharmacological treatment choice. This study investigates the impact of the AF dominant frequency (DF) during medication-free periods on the efficacy of two AADs (flecainide and vernakalant) in preventing pAF episodes using 2D pAF left atrial models. Both effectively reduced the vulnerable window (VW_{width}) at low drug-free DF, with vernakalant exhibiting greater efficacy than flecainide. At high drug-free DF, the drugs differed in efficacy such that vernakalant showed a better reduction in VW_{width}, while flecainide caused slight increments. These findings suggest that the drug efficacy in preventing pAF episodes is influenced by drug-free DF, highlighting the potential to enhance personalized pharmacological strategies in pAF patients.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting nearly 2% of the general population. Atrial remodeling begins with the onset of asymptomatic episodes and becomes more pronounced as fibrillation progresses, increasing the likelihood of future episodes leading to the continuous progression of the disease.

It has been observed that patients experiencing short episodes (≤7 days) of paroxysmal AF (pAF) undergo changes in the left atrial (LA) tissue. These changes, such as alterations of different ionic currents and short refractory periods, create conditions that favor the initiation and maintenance of AF reentrant circuits [1]. Pharmacological therapy serves as the first line of treatment, aiming to reduce the incidence of fibrillatory episodes and prevent further atrial remodeling. However, the effectiveness of this therapy remains suboptimal, highlighting the need for improving the personalization of antiarrhythmic treatment.

Recently, in-silico studies have shown the potential of computational models to assess and predict the impact of electrophysiological variability (i.e., ionic profiles and related tissular properties) on the pharmacological prevention [2] and cardioversion [3] of AF episodes.

In this study, an in-silico cardioprotection study is performed using a 2D LA model under pAF conditions to assess the impact of the AF dominant frequency during medication-free periods on the efficacy of two widely used antiarrhythmic drugs (flecainide and vernakalant) in preventing fibrillatory episodes.

2. Methods

2.1. Paroxysmal left atrial model

The Courtemanche-Ramirez-Nattel model [4] was used to reproduce the human atrial action potential (AP). The model was modified to include the acetylcholine-activated K^+ current ($I_{K,ACh}$) proposed by Grandi et al. [5] ([ACh] = 0.005 μM) and to reproduce pAF conditions in LA. The latter was implemented by applying scaling factors to the ionic conductances. For the LA electrical heterogeneity, G_{CaL} was reduced by 10%, and G_{Kr} was increased by 200% [6], while the electrical remodeling for pAF in LA consisted of a 200% upregulation of both G_{K1} and $G_{K,ACh}$ [7].

To investigate the impact of electrophysiological variability, ten ionic conductances (G_i) and tissue longitudinal diffusion (D_L) were individually varied by ±30% and ±40% to build a population. For each profile, different biomarkers were computed in the absence and presence of flecainide and vernakalant. The results of the ±40% variation in the absence of drugs were used to perform a sensitivity analysis to determine the influence of the different parameters on the biomarkers.

2.2. Drug mathematical model

The simple pore model reproduced the drug effects:

$$g_{i,drug} = G_i \cdot \left[1 + \left(\frac{D}{IC_{50,i}}\right)^{nH}\right]^{-1} = G_i \cdot F_{blockeade} \quad (1)$$

Where for each current *i*, $IC_{50,i}$ is the mean inhibitory concentration of the drug, *nH* is the Hill coefficient and *D* is the free drug concentration (in this study, therapeutic concentrations: 1.5 μM for flecainide and 10 μM for vernakalant). Due to experimental IC_{50} variability [8], a preliminary study was performed by examining different virtual versions of each drug (different IC_{50} values) so that the simulated responses could be calibrated to align with experimental studies (data not included). The resulting blocking factors are summarized in Table 2.

Table 2. Blocking factors as function of the therapeutic concentration of each drug.

	G_{CaL}	G_{Kr}	G_{Ks}	G_{Kur}	G_{to}	G_{Na}	$G_{K,ACh}$
Flecainide	0.94	0.50	0.93	0.66	0.78	0.75	-
Vernakalant	0.81	0.67	-	0.60	0.60	0.83	0.50

2.3. Simulations to assess the drug action

For each profile, in the absence and presence of flecainide and vernakalant, the cellular model was stabilized by applying 50 pulses at a pacing period of 400ms. Then, the 2D simulations were performed using a 5x5cm^2 mesh replicating an atrial tissue patch to elicit re-entrant circuits. Spatial resolution was 300 μm, and the longitudinal diffusion and anisotropy ratio were set to 0.0022 mS and 0.35, respectively, to ensure a longitudinal conduction velocity of 68.5 cm/s [6]. The S1-S2 cross-field protocol was applied to induce the rotors. First, a stabilization simulation of 10 planar pulses (S1) with a period of 400 ms was performed. Then, a rectangular extra stimulus (S2) was applied in the lower left corner. Temporal vulnerability was quantified as the width of the time window during which an S2 stimulus initiates a re-entry lasting at least 1 s. The corresponding pseudo-EGM and its Dominant Frequency (DF) were computed for each reentry obtained for the last 5 seconds of the simulation only to consider the self-sustained rotor activity.

Cell biomarkers concerning the Resting Membrane Potential (RMP), AP duration (APD_{90}) and maximum depolarization velocity (dV/dt_{max}) were computed at the last stabilization pulse S1. Tissue biomarkers were also obtained: vulnerable window widths (VW_{width}) and DFs, as well as the Effective Refractory Period (ERP), longitudinal Conduction Velocity (CV_L) and rotor meandering area. Since, for some simulations in the presence of the drug, the VW_{width} was completely reduced, rotor DF and meandering area were only computed for those simulations where AF was inducible.

3. Results and discussion

3.1. Characterization of pAF in left atrium

Figure 1 shows the action potentials and the DF distribution for the population in the absence of drugs (grey), along with the effects of flecainide (green) and vernakalant (purple) on the baseline model (black). In our left atrium paroxysmal baseline model, the APD_{90} values for control and in the presence of flecainide and vernakalant were 113 ms, 142 ms and 145 ms, respectively (Fig. 1-A), thus reproducing the APD_{90} lengthening of these antiarrhythmic drugs [8].

All models were susceptible to sustained rotor activity in the absence of drugs, leading to different VW_{width} and rotor DF, denoting the influence of ionic heterogeneity on AF vulnerability.

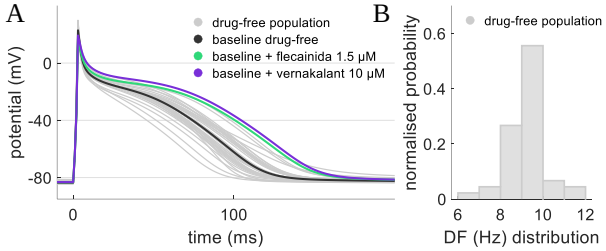

Figure 1. *A) APs for the population in the absence of the drug (grey) and the effect of flecainide (green) and vernakalant (purple) on the AP of the baseline model. B) Distribution of DF values for the population in the absence of the drugs.*

The impact of ionic conductances and longitudinal diffusion on the biomarkers was studied to characterize the properties of the left atrium paroxysmal model in the absence of drugs and the sensitivity results are shown in Figure 2. The conductances that most significantly influenced AF vulnerability were G_{K1}, G_{Na}, G_{CaL}, G_{to}, $G_{K,ACh}$ and D_L, consistent with previous sensitivity studies [2, 9]. The VW_{width} was reduced when G_{Na}, G_{CaL} and D_L were increased and G_{K1}, G_{to} and $G_{K,ACh}$ were reduced. Two antiarrhythmic mechanisms were found, one regarding the prolongation of APD_{90} and ERP and another related to increments in CV_L. The former involved the blockade of outward K^+ currents (G_{K1}, G_{to} and $G_{K,ACh}$) and the increase of inward Ca^{2+} current (G_{CaL}) which had an impact on APD_{90} and ERP lengthening [3]. The increase in both biomarkers mitigates the reduction caused by electrical remodeling relative to pAF and helps to successfully arrest arrhythmias in animal species [10]. Besides, these ionic configurations also influence the AF dynamics, leading to lower DF rotors and meandering areas, hampering the rotor formation and thus reducing the VW_{width} [10].

Regarding the antiarrhythmic mechanism led by conduction, both upregulations of G_{Na} and D_L decreased VW_{width} which may be linked to the increment in CV_L that they cause, since low diffusion and conduction are known

to be one of the main contributions of AF inducibility [2]. The variation in VW_{width} due to G_{Na} was minor, likely because it induced opposite changes in ERP and CV_L. Although the increment on G_{Na} and D_L decreases VW_{width}, the rotor dynamics differ. Both have a positive effect on DF but the opposite regarding the meaning area of the rotor. This difference may be associated with the lower ERP for increased G_{Na}, which leads to a major extent of excitable tissue. It may also explain the lower impact of G_{Na} on VW_{width} compared to D_L which showed no effect on ERP.

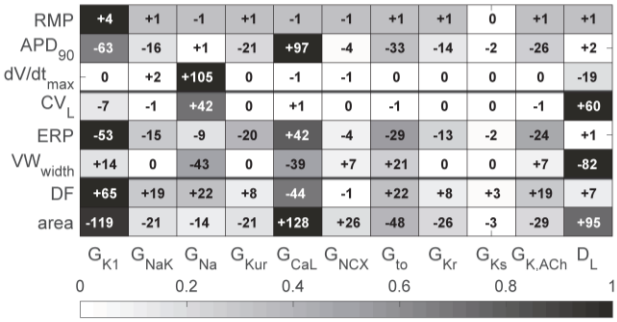

Figure 2. *Absolute (numerical value) and relative (grayscale) sensitivities in the absence of drugs.*

3.2. Pharmacological prevention of AF episodes

Since the aim of this study was to assess whether DF during medication-free periods can be considered as a clinical biomarker to refine the pharmacological choice, two subgroups of the population in the absence of drugs were defined according to their DF, the low (1st percentile) and high (3rd percentile) DF groups. Subsequently, differences in the reduction of VW_{width} between these groups for each drug were analyzed, along with differences in other biomarkers based on the frequency group. Figure 3 illustrates the percentage variation in APD_{90}, ERP, dV/dt_{max}, CV_L and VW_{width} for low DF (transparent color) and with high DF (solid color) models in the absence of drugs compared to the presence of flecainide (green) and vernakalant (purple).

Our results showed that intersubject variability significantly influenced the performance of flecainide and vernakalant. In general, flecainide and vernakalant reduced the VW_{width} and even eliminated it completely in some cases (ΔVW_{width} = -100%).

For the low DF group, both drugs were effective in reducing VW_{width}, although vernakalant exhibited a significantly greater efficacy compared to flecainide. For the high DF group, the drugs differed significantly in efficacy such that vernakalant showed a better reduction in VW_{width}, while flecainide tended to cause slight increments in vulnerability, as other studies reported [2]. These differences between flecainide and vernakalant may be linked to the higher significant increase in APD_{90} and ERP observed when applying vernakalant, along with a stronger reduction of CV_L under flecainide application, independently of the DF group. This outcome was consistent with the sensitivity analysis (Fig. 2), which supported that the model vulnerability decreased when APD_{90}, ERP, and CV_L were increased.

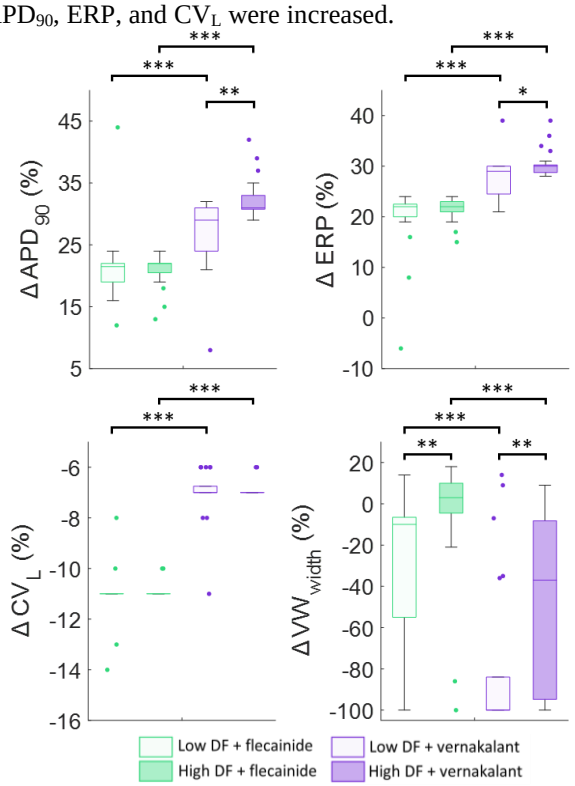

Figure 3. *Percentage variation in APD_{90}, ERP, dV/dt_{max}, CV_L, and VW_{width} due to flecainide and vernakalant. Mann-Whitney U test: *p < 0.05; **p < 0.01; ***p < 0.001.*

Both drugs performed statistically better in reducing VW_{width} at low DF compared to high DF. Regarding vernakalant, there were significant differences between both groups of models in the increase of both APD_{90} and ERP, leading to a reduction in the model vulnerability. There were no significant differences in the variation of APD_{90}, ERP, and CV_L for flecainide, which explained the difference in reducing VW_{width} when comparing low and high DF groups.

Notably, a significant finding was that both flecainide and vernakalant managed to reduce the vulnerability to suffering AF episodes, but they worsened the VW_{width} for some models. Flecainide was not able to reduce the VW_{width} for models where G_{K1}, G_{NaK}, G_{Kur}, G_{Kr}, G_{Ks}, $G_{K,ACh}$ or G_{to} were increased and G_{CaL}, G_{Na} or D_L were reduced, while vernakalant failed when G_{CaL} or G_{Na} where decreased. These results agreed with the sensitivity analysis since the variation of these ionic conductances produced the shortening of both APD_{90} and ERP and the hampering of the conduction, which were proarrhythmic mechanisms that led to higher values of VW_{width} [2, 3].

3.3. Pharmacological effect on AF dynamics

To better comprehend the differences between flecainide and vernakalant, the drug effect on the DF and the meandering area were also analyzed. Figure 4 shows the variation in DF and meandering area due to flecainide and vernakalant only for models where AF was inducible in the presence of the drugs. Both drugs tended to reduce the DF and increase the meandering area of the rotors, which may contribute to the prevention of rotor formation together with the lengthening of both APD_{90} and ERP [10].

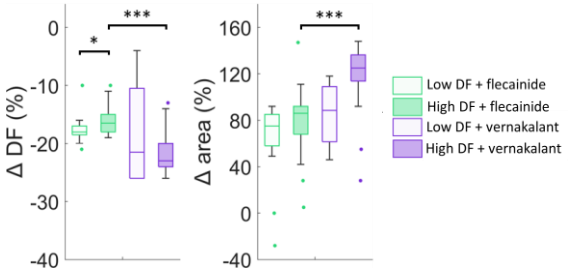

Figure 4. *Percentage variation in DF and meandering area due to the presence of flecainide and vernakalant. Mann-Whitney U test: *p < 0.05; **p < 0.01; ***p < 0.001.*

Regarding flecainide, although the effect on APD_{90}, ERP and CV_L could not explain the difference in reducing VW_{width} when comparing DF groups, there was a significant difference in the reduction of DF between these. This explained the higher performance of flecainide for the low DF models since the drug had a more significant decrease in DF. Besides, the significant differences in high DF between flecainide and vernakalant in reducing DF and increasing area also support the better efficacy of vernakalant for these conditions.

4. Conclusions

This study advances our understanding of the ionic mechanisms underlying AF at the tissue level and its response to pharmacological treatment with flecainide and vernakalant. Our results suggest that intersubject variability significantly influences DF in the absence of drugs and the performance of flecainide and vernakalant. Specifically, both drugs were effective for the low DF group, while vernakalant performed better in the high DF group. This work highlights the potential of in-silico studies to enhance personalized medicine, as they can help to refine the pharmacological strategies in pAF patients.

Acknowledgments

This work has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 101016496 (SimCardioTest) and was partially funded by MICIU/AEI/10.13039/501100011033 and by ERDF/EU. The authors also thankfully acknowledge RES resources provided by the Barcelona Supercomputing Center in MareNostrum5 (IM-2024-1-0010 and IM-2024-2-0015).

References

[1] J. Andrade *et al.*, "The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society comprehensive guidelines for the management of atrial fibrillation," *Canadian Journal of Cardiology*, vol. 36, no. 12, pp. 1847-1948, 2020.

[2] A. Sanchez de la Nava *et al.*, "Artificial intelligence-driven algorithm for drug effect prediction on atrial fibrillation: an in silico population of models approach," *Frontiers in Physiology*, vol. 12, p. 768468, 2021.

[3] A. Dasí *et al.*, "What determines the optimal pharmacological treatment of atrial fibrillation? Insights from in silico trials in 800 virtual atria," *The Journal of Physiology*, vol. 601, no. 18, pp. 4013-4032, 2023.

[4] M. Courtemanche *et al.*, "Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 275, no. 1, pp. H301-H321, 1998.

[5] E. Grandi *et al.*, "Human atrial action potential and Ca2+ model: sinus rhythm and chronic atrial fibrillation," *Circulation Research*, vol. 103, no. 9, pp. 1055-1066, 2011.

[6] R. Belletti *et al.*, "Arrhythmogenic effects of genetic mutations affecting potassium channels in human atrial fibrillation: a simulation study," *Frontiers in Physiology*, vol. 12, p. 681943, 2021.

[7] L. Palacio *et al.*, "In-silico study of the ionic current gradients determining left-to-right atrial frequencies during paroxysmal atrial fibrillation," *Simulation*, vol. 95, no. 12, pp. 1129-1139, 2019.

[8] M. Geng *et al.*, "Revisiting antiarrhythmic drug therapy for atrial fibrillation: reviewing lessons learned and redefining therapeutic paradigms," *Frontiers in Pharmacology*, vol. 11, no. 581837, 2020.

[9] C. Sánchez *et al.*, "The Na+/K+ pump is an important modulator of refractoriness and rotor dynamics in human atrial tissue," *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 302, no. 5, pp. H1146-H1159, 2021.

[10] R. Ramirez *et al.*, "Mechanisms by which ranolazine terminates paroxysmal but not persistent atrial fibrillation," *Circulation: Arrhythmia and Electrophysiology*, vol. 12, no. 10, p. e005557, 2019.

Address for correspondence:

Javier Saiz
jsaiz@ci2b.upv.es
Centro de Investigación e Innovación en Bioingeniería,
Universitat Politècnica de València
Camino de Vera s/n, 46022 Valencia, Spain