Computational Study of Drug Effects on Different Atrial Fibrillation Stages

Violeta Puche-García[1], Lucía Romero[1], Javier Saiz[1],

[1]Centro de Investigación e Innovación en Bioingeniería, Universitat Politècnica de València, Valencia, Spain

Abstract

Long-term antiarrhythmic drug therapy is used to reduce the incidence of Atrial Fibrillation (AF), but its efficacy is limited. This study aims to investigate the effect on the vulnerable window (VW) of drugs commonly used to treat AF (dofetilide, flecainide, vernakalant) at its different stages. Atrial electrophysiology was simulated using the Courtemanche model on a 2D left atrial patch, including the parameters to reproduce healthy, LA-paroxysmal AF (pAF), persistent AF (peAF) and peAF with slowed conduction (peAF+↓σ_L) tissues. The VW was computed through an S1-S2 protocol for each drug and AF stage. Under control conditions, the healthy tissue failed to initiate sustained rotors. In comparison, pAF (VW=34ms) and peAF (VW=38ms) remodeling led to a substrate more susceptible to re-entrant activity and generated sustained rotors. In pAF tissues, all drugs reduce the VW in a use-dependent manner. Due to the severe remodeling in peAF and peAF+↓σ_L tissues, drugs had a lower impact or even caused a slight increase in VW. In addition, drugs contributed to destabilizing the rotor activity in pAF, while this effect is not observed in peAF or peAF+↓σ_L. The results support that drug efficacy depends on the AF stage, being greater in pAF tissue.

1. Introduction

Atrial Fibrillation (AF) is the most common cardiac arrhythmia, affecting nearly 2% of the general population. It can progress from short episodes (≤7 days) of paroxysmal AF (pAF) to longer and more frequent episodes of persistent AF (peAF). This long-term process is promoted by changes in the atrial tissue, including alterations in several ionic currents (electrical remodeling), slower conduction (structural remodeling) and shorter refractory periods. This remodeling promotes the susceptibility and maintenance of reentry circuits of AF ('AF begets AF') [1].

Long-term antiarrhythmic drug (AAD) therapy is used to reduce the incidence of fibrillatory activity in the atria. However, its effectiveness is far from optimal and may depend on the degree of AF-induced remodeling. This approach holds great potential for cardioprotecting the atria by preventing new AF episodes to avoid further atrial remodeling. Therefore, it is necessary to consider the remodeling degree of the atria to understand its impact on the mechanisms of drug action and effectiveness.

In this study, an *in-silico* approach is taken to assess the effect of three widely used AADs (dofetilide, flecainide and vernakalant) using a 2D mesh of LA tissue reproducing different degrees of AF. The aim is to investigate the effect on the vulnerable window (VW) for these drugs at different stages of AF-induced remodeling and under a healthy scenario.

2. Methods

2.1. Modelling electrical substrates

The Courtemanche-Ramirez-Nattel model [1] was used to reproduce the human atrial electrophysiology. The K$^+$ current activated by acetylcholine ($I_{K,ACh}$) proposed by Grandi *et al.* [2] was included ([ACh] = 0.005 µM). Both atrial heterogeneity related to LA tissue and AF-induced electrical remodeling were considered by modifying the maximum conductances of several ionic currents, as summarized in Table 1 [4].

Table 1. Scaling factors applied over the baseline model (healthy right atrium) to implement the LA heterogeneity and AF remodeling.

	G_{CaL}	G_{Kr}	G_{Ks}	G_{Kur}	G_{to}	G_{K1}	$G_{K,ACh}$
LA healthy	0.9	2	-	-	-	-	-
LA pAF	0.9	2	-	-	-	2	2
LA peAF	0.9*0.35	2	2	0.55	0.25	2	2

2.2. Drug formulation

The drug effects were reproduced using the simple pore model by which ionic conductances are reduced according to the Hill equation:

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

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. This translates into a blocking factor that multiplies the maximum conductance (G_i), reducing the final conductance in the presence of the drug to $g_{i,drug}$. The IC_{50} and nH values of the drugs for the different currents are shown in Table 2 [5].

Table 2. IC50 values (µM) and Hill coefficient (if different than 1, values in parentheses) for the different drugs.

	G_{CaL}	G_{Kr}	G_{Ks}	G_{Kur}	G_{to}	$G_{K,ACh}$	G_{Na}
Dofetilide	2.3 (5.4)	0.004 5	100	-	0.02 (0.8)	-	1460 (5.1)
Flecainide	26.35 (1.2)	1.5 (0.88)	20	2.9	9.27 (0.7)	-	5.8
Vernakalant	84	20	-	15	15	10	90

Four different concentrations were studied within a clinical range of therapeutic concentration [5, 6] for each drug: dofetilide 0.002 µM, 0.004 µM, 0.01 µM, and 0.02 µM; flecainide 1.5 µM, 3 µM, 4.5 µM and 6 µM; vernakalant 3 µM, 6 µM, 15 µM and 30 µM.

2.3. Tissue simulations

Computational simulations were performed using a 2D mesh replicating an atrial tissue patch to elicit and characterize the occurrence of reentry circuits. The monodomain problem was solved using the Elvira software [7].

Before the 2D simulations, the model was stabilized in a single-cell environment by applying 50 beats with a Basic Cycle Length (BCL) of 400 ms. Stimuli of twice the diastolic threshold amplitude and 2 ms duration were applied. In tissue simulations, the 2D domain consisted of a 5x5 cm^2 grid with a spatial resolution of 300 µm, longitudinal conductivity of 0.0022 S/cm·pF and an anisotropy ratio of 0.35. Versions of the models included the drug formulation to study the drug effect and compare the different compounds and concentrations.

Four different AF-induced remodeling tissues were implemented: healthy, pAF, peAF and peAF+↓σ$_L$. To account for the electrical remodeling, the cell model included the scaling factors to reproduce the electrical remodeling in pAF and peAF conditions. In addition to lone electrical remodeling in peAF, the longitudinal conductivity was reduced by 15% to replicate the slowed conduction observed in peAF (peAF+↓σ$_L$) [4] to investigate the influence of structural remodeling usually present in peAF patients [1].

For each condition, rotor activity was induced by performing an S1-S2 cross-field protocol. The tissue was stabilized by applying 10 planar pulses of 100 pA/pF and 2 ms duration. After the 10th planar stabilization pulse (S1), an extra stimulus (S2) was applied on the lower left corner, varying the S1-S2 coupling interval (CI) with a precision of 1 ms. Temporal vulnerability to reentry was quantified as the width of the vulnerable window (VW) estimated as the totality of CIs leading to rotor activity lasting at least 1s. Simulations were run for 6 sec. To characterize the self-sustained rotor activity, the corresponding spectral and phase analysis for the last 5 sec were performed to compute the dominant frequency (DF) and track the rotor tip trajectories [4]. The ERP was calculated as the shortest S1-S2 CI that allows propagation of the second stimulus.

3. Results and discussion

3.1. AF remodeling characterization

AF-induced electrical remodeling impacts the electrophysiological proprieties of the tissue [1]. Table 3 summarizes the main properties of each substrate in the absence of drugs. By modifying the maximum ionic conductances, APD$_{90}$ shortening and reduction in ERP and CV were reproduced as experimentally observed [1, 4]. As expected, the structural remodeling slowed the CV when comparing peAF and peAF+↓σ$_L$.

Table 3. Effect of the AF-induced electrical and structural remodeling in electrophysiological properties. APD$_{90}$, ERP and CV were computed for the last beat of stabilization in the tissue simulations at the central node of the 2D mesh. VW and DF were calculated as described in methods. For VW, * indicates that the re-entries lasted less than 1 second.

	healthy	*pAF*	*peAF*	*peAF+↓σ$_L$*
APD$_{90}$ (ms)	212	115	88	88
ERP (ms)	203	125	98	98
CV (cm/ms)	70	66	65	60
VW (ms)	19*	35	36	39
Meandering area (cm^2)	-	1.31	0.34	0.22
DF (Hz)	-	9.3	11	11

To quantify the vulnerability to initiate and maintain fibrillatory activity for each substrate, VWs were computed. The healthy tissue could not sustain any re-entry lasting more than 1 second. In comparison, tissues undergoing AF-induced remodeling led to a substrate more susceptible to re-entrant activity. These generated sustained rotors (lifespan > 1 second) due mainly to the reduction of APD_{90}, ERP and CV [8]. These known proarrhythmic mechanisms worsen as the AF-induced remodeling progresses. Therefore, the more severe the remodeling, the higher the VW and the likelihood of inducing rotor activity in the tissue. Comparing the peAF substrates, the inclusion of structural remodeling favors the vulnerability by worsening the slowdown in conduction. Moreover, sustained rotors for both peAF tissues exhibited a higher DF and lower meandering area, leading to more stable reentries.

3.2. Drug effect on vulnerability

The different AF substrate proprieties previously described were considered to investigate how they can affect the drug effectiveness in reducing the VW. Figure 1 shows the VW widths for healthy, pAF, peAF and peAF+↓σ_L tissues in the absence (control) and the presence of drugs for the four concentrations.
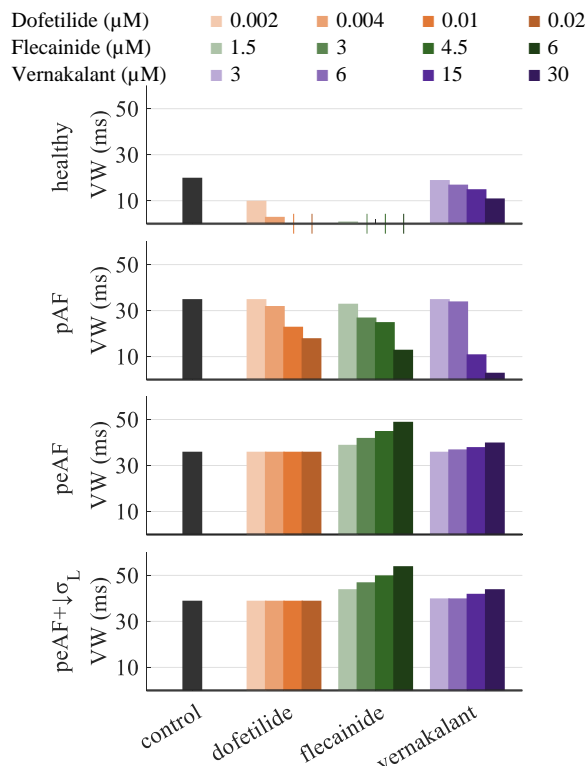

Figure 1. VW (ms) values for healthy, pAF, peAF and peAF+↓σ_L tissues in the absence (control) and the presence of drugs.

For healthy tissues, all the VW widths were composed of rotor activity lasting less than 1 second. Regardless of the drugs, healthy tissue failed to initiate a sustained re-entry. Dofetilide 0.01μM and flecainide 3μM completely eliminated the VW, while vernakalant did reduce the VW, but its effectiveness was lower. For pAF tissues, all drugs managed to reduce the VW in a use-dependent manner. Dofetilide 0.01μM reduced VW by 12ms, flecainide 3μM by 8ms and vernakalant 15μM by 24ms. In peAF and peAF+↓σ_L, the severe remodeling caused a lower impact of drugs or even a slight increase in VW and the generation of more stable rotors compared with pAF.

3.3. Drug effect on sustained activity

Rotor destabilization has been described as an antiarrhythmic mechanism since it promotes the termination of reentrant activity [8, 9]. The tip trajectory and dominant frequency of the sustained rotors were computed. Figure 2 shows the tip trajectory of simulations in pAF and peAF+↓σL in the absence (control) and the presence of drugs: 0.01 μM dofetilide, 1.5 μM flecainide, 15 μM vernakalant.
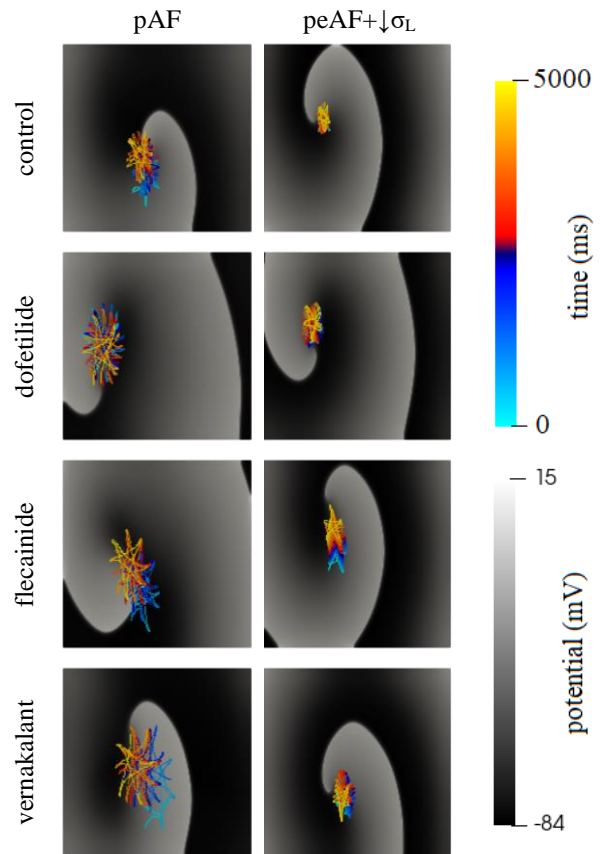

Figure 2. Tip trajectories in pAF and peAF+↓σ_L in the absence (control) and the presence of drugs: 0.01 μM dofetilide, 1.5 μM flecainide, 15 μM vernakalant.

For both pAF and peAF+↓σ_L, all drugs caused a reduction of DF and an increase in the meandering area of the rotor in comparison with simulations without drugs. However, this effect was insufficient in peAF+↓σ_L to destabilize the rotor activity. Comparing pAF with peAF+↓σ_L, the meandering area was decreased respectively by 0.61 and 0.15 for 0.01 µM dofetilide, 1.4 and 0.6 for 1.5 µM flecainide, and 2.1 and 0.3 for 15 µM vernakalant. In addition, the decrements in DF values are more significant on pAF than peAF+↓σ_L. Considering the VW, DF and meandering area outcomes, vernakalant showed greater efficacy than dofetilide and flecainide in pAF. Flecainide and vernakalant should be limited in severe degrees of AF-induced remodeling.

3.4. Limitations and future perspectives

The approach of this study could be used to complement *ex-vivo* and clinical investigations to provide new insights into the mechanisms of existing and novel drugs, as well as compounds in clinical development. To have a more realistic view of pharmacological effects, the model can be extended to real 3D atria models to consider how structural differences may affect their effectiveness.

4. Conclusions

This study is a step forward in understanding the ionic mechanisms underlying AF at different tissue substrates and its response to pharmacological treatment. Our results suggest that the initiation, maintenance and response of AF to drug treatment largely depend on the degree of AF-induced remodeling on the tissue, which is greater in pAF tissue. As AF remodeling worsens, the tissue becomes more vulnerable to rotor activity and lowers drug efficacy. Drugs contribute to destabilizing the rotor activity in pAF, while this effect is insufficient in peAF+↓σ_L. This work shows how *in-silico* studies in personalized medicine can help in predicting and understanding the impact of drugs to reduce the vulnerability to suffering from AF.

Acknowledgments

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Address for correspondence:

Javier Saiz
jsaiz@ci2b.upv.es
Centro de Investigación e Innovación en Bioingeniería (Ci2B),
Universitat Politècnica de València (UPV)
Camino de Vera s/n, 46022 Valencia, Spain