Potential Pharmacological Therapies for Atrial Fibrillation. A Computational Study

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Abstract

Ionic mechanisms underlying atrial fibrillation (AF) generation and propagation are unclear. In this study, we investigate the dependence of AF related properties to changes in human atrial ion channel characteristics by systematically conducting a sensitivity analysis. Cell and tissue simulations are performed using the Maleckar action potential computational model for control and AF remodeling conditions, and are validated using experimental data from the literature. Inward rectifier K^+ current is shown to play a key role in many of the analyzed cell properties: action potential duration (APD), resting membrane potential and APD restitution slopes; as well as in tissue refractory period and wavelength. Na^+/K^+ pump is essential in APD adaptation to heart rate changes and important in the tissue refractory period as well. Fast Na^+ current is proven to be of great significance in tissue simulations, especially altering tissue excitability and, consequently, conduction velocity. Ionic mechanisms underlying electrophysiological properties are similar in control and AF. Sensitivity of AF related properties to changes in ion channel characteristics can help in the design and screening of new multi-channel action anti-AF drugs.

1. Introduction

Cardiac arrhythmias, defined as conditions associated with abnormal electrical activity in the heart, are a serious health problem in our society. The most commonly diagnosed cardiac arrhythmia is persistent atrial fibrillation (AF), especially in developed countries. AF is mainly sustained by reentrant wavelets propagating through excitable tissue, but its underlying ionic mechanisms are not totally clear yet, despite the extensive research conducted over the past decades. In this study we quantify the sensitivity of properties related with arrhythmic risk to changes in human atrial ion channel properties. Simulations are performed using a detailed action potential (AP) model [1] and its extension to tissue, and are validated using experimental data from the literature.

2. Methods

2.1. Action potential model

The human atrial cell model developed by Maleckar *et al* [1] is used for AP simulation in control conditions. AF-induced electrical remodeling is simulated by altering ion channel properties, specifically modifying ionic current conductances (G_i) implying equivalent alterations in the corresponding ionic currents (I_i), as reported in previous studies [2]: 70% reduction of I_{CaL} (L-type Ca^{2+} current); 50% reduction of I_{to} (transient outward K^+ current); 50% reduction of I_{Kur} (ultrarapid rectifier K^+ current); and 100% increment of I_{K1} (inward rectifier K^+ current) (Figure 1).

The forward Euler method with a time step of 0.02 ms for time integration is used to solve ordinary differential equations in single cells. In tissue simulations, finer time steps of 0.005 ms and 0.01 ms are used to solve ordinary differential equations and partial differential equations, respectively. The spatial resolution is set to 250 μm to ensure convergence of the numerical results. The open source software package Chaste (www.comlab.ox.ac.uk/chaste) is used to conduct the tissue simulations on grid computing facilities through the use of the middleware platform Nimrod/G [3].

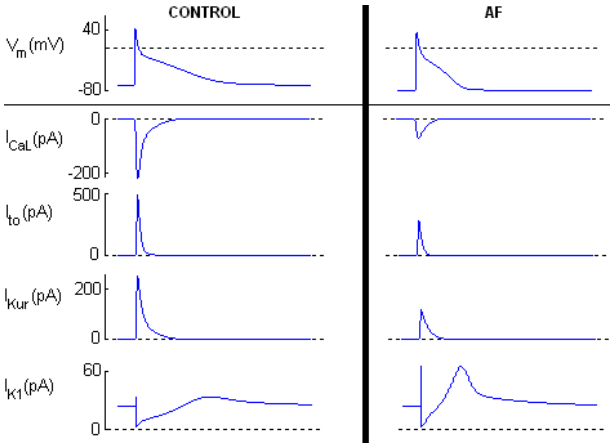

Figure 1. Control (left) vs. AF-remodeling (right) AP and modified ionic currents.

2.2. Single cell biomarkers

Different stimulation protocols are simulated to properly characterize the electrophysiological biomarkers described next. A 2-ms square stimulus pulse and twice diastolic threshold amplitude is applied to single cells in all cases:

- Action potential duration (APD) measured at 90% repolarization and resting membrane potential (V_{rest}) are obtained after 20 min of periodic stimulation at a cycle length (CL) of 1000 ms.
- APD adaptation to sudden changes in heart rate (HR=1/CL) is characterized by calculating the time constants, τ_{fast} and τ_{slow}, associated with fast and slow phases of APD adaptation following HR acceleration and deceleration. The cell is stimulated for 10 minutes at CL=1000 ms, then CL is suddenly changed to 600 ms and maintained for 10 minutes, and finally back to CL=1000 ms for other 10 minutes. A delayed APD rate adaptation has been previously related to higher arrhythmic risk [4].
- APD restitution (APDR) slope has been suggested as an arrhythmic risk biomarker in the literature [5]. The S1S2 protocol, consisting of 10 S1 stimuli applied every 1000 ms followed by an S2 extra-stimulus applied at varying diastolic interval (DI) after the last generated AP, and the dynamic protocol, consisting of series of 100 stimuli applied at progressively decreasing CLs, are simulated to calculate the corresponding slopes, S_{s1s2} and S_{dyn}, of the APDR curves.

2.3. Tissue biomarkers

The monodomain equation is used to simulate electrical propagation in atrial tissue for both control and AF electrical remodeling conditions. The intracellular conductivity is defined as 1.75 mS/cm, in both longitudinal and transversal directions. The tissue size used in this study is 1x1 cm^2 for characterization of electrophysiological properties of atrial tissue such as effective refractory period (ERP), conduction velocity (CV) and wavelength (WL), whose changes can be pro- or anti-arrhythmic:

- ERP is calculated as the shortest coupling interval between two stimuli applied in the center of the tissue that makes propagation of the second stimulus possible.
- CV is obtained by applying one stimulus in one of the borders of the tissue and measuring the time taken by the wavefront to propagate in the centre of the simulated mesh.
- WL is directly calculated from ERP and CV, and is the shortest path required by a rotating reentrant wavefront to propagate [6]: WL=ERP*CV.

2.4. Sensitivity analysis

To assess the role of ionic currents properties in modulating each of the analyzed arrhythmic risk biomarkers, absolute ($S_{m,p}$) and relative ($R_{m,p}$) sensitivities of each biomarker "m" to $\pm$30% variations in parameter "p", which can be either an ionic current conductance or a time constant of the model, are calculated:

$$D_{m,p_0 \pm 30\%} = \frac{C_{m,p_0 \pm 30\%} + C_{m,p_0}}{C_{m,p_0}} 100, \quad (1)$$

$$S_{m,p} = \frac{D_{m,p_0+30\%} - D_{m,p_0-30\%}}{0.6}, \quad (2)$$

$$R_{m,p} = \left| \frac{S_{m,p}}{max_p\{S_{m,p}\}} \right|. \quad (3)$$

In the above equations, C_{m,p_0} and $C_{m,p_0 \pm 30\%}$ are the values of the biomarker "m" in control conditions and when the model parameter "p" is varied by $\pm$30% from its default value. $D_{m,p_0 \pm 30\%}$ is the percentage of change in "m" when "p" is modified by $\pm$30% from its default value. Note that for S_{s1s2} and S_{dyn} biomarkers, absolute sensitivity is calculated by averaging the sensitivity results of maximum slope and slope at a DI of 100 ms in order to account for the APDR curve tendency and not only for the value at a specific point.

3. Results

3.1. Biomarkers: control and AF

APD and V_{rest} after 20 minutes of periodic pacing are 197 ms and -73.75 mV, respectively, in control, and 115.4 ms and -78.96 mV in AF remodeling conditions (Figure 1), consistent with experimental studies. The time constant of fast APD adaptation, τ_{fast}, only calculated after HR acceleration due to the formation of delayed afterdepolarizations (DADs) after HR deceleration in some of the analyzed cases, is 20.5 s in control and 31.7 s in AF, while the time constant of slow APD adaptation, τ_{slow}, is 103.8/136.6 s after HR acceleration/deceleration in control

and 123.6/159.3 s in AF. S1S2 restitution slopes $S_{s1s2,max}$ and $S_{s1s2,DI=100}$ are 0.63 and 0.2, respectively, in control, and 0.31 and 0.09, respectively, in AF remodeling. Dynamic restitution slopes, $S_{dyn,max}$ and $S_{dyn,DI=100}$ are 0.37 and 0.31, respectively in control, and 0.23 and 0.16 in AF remodeling. ERP and CV are also decreased in AF remodeling, being 223 ms and 48.54 cm/s in control, and 151 ms and 45.95 cm/s in AF. As a consequence, WL is reduced from 10.8 cm in control to 6.9 cm in AF.

3.2. Sensitivity analysis

The most significant results in terms of relative sensitivity of the analyzed biomarkers to changes in ionic current properties are shown in Figure 2, for control conditions, and in Figure 3, for AF remodeling conditions. In general, absolute sensitivities in AF are smaller than in control, but the main ionic mechanisms affecting each biomarker are very similar in both conditions.

CONTROL	GK1	GNaK	GNa	GCaL	GKur
APD90	-141%	36%	-9%	31%	-37%
Vrest	28%	18%	-1%	-6%	4%
τfast	100%	6%	-7%	1598%	-334%
τslow	13%	-1005%	13%	-42%	43%
Ss1s2	-90%	86%	5%	90%	-92%
Sdyn	-1364%	400%	-103%	7%	-120%
ERP	-74%	-60%	-37%	32%	-30%
CV	-7%	-6%	71%	0%	1%
WL	-82%	-66%	39%	32%	-29%

$R_{m,p} = 1$
$0.2 < R_{m,p} \leq 1$
$0.04 < R_{m,p} \leq 0.2$
$R_{m,p} < 0.04$

Figure 2. Absolute and relative sensitivity results for control conditions.

Regarding APD and V_{rest}, G_{K1} inhibition by 30% entails an anti-arrhythmic APD lengthening of 121.4 ms in control and 40.2 ms in AF, and an increment in V_{rest} of 9.05 mV in control and 1.87 mV in AF (Figure 4A-B). As regards APD rate adaptation mechanisms (Figure 4C-F), τ_{fast} is mainly determined by G_{CaL} in control (7.2 s smaller under 30% G_{CaL} inhibition than its control value) but by the maximal value of the Na^+/K^+ pump (G_{NaK}) in AF; on the other hand, τ_{slow} is determined in both control and AF by G_{NaK} (30% G_{NaK} overexpression implies much faster APD adaptation, being τ_{slow}=73.14/86.76 s after HR acceleration/deceleration in control and τ_{slow}=46.34/56.46 s after HR acceleration/deceleration in AF). Results in Figures 2 and 3 show

AF	GK1	GNaK	GNa	GCaL	GKur
APD90	-88%	43%	3%	11%	-26%
Vrest	6%	5%	0%	0%	0%
τfast	16%	-154%	-3%	20%	-19%
τslow	0%	-156%	22%	-21%	-18%
Ss1s2	-92%	20%	15%	21%	-38%
Sdyn	-151%	85%	-12%	25%	-42%
ERP	-46%	-22%	-61%	9%	-18%
CV	-9%	-6%	72%	0%	2%
WL	-56%	-28%	21%	9%	-15%

$R_{m,p} = 1$
$0.2 < R_{m,p} \leq 1$
$0.04 < R_{m,p} \leq 0.2$
$R_{m,p} < 0.04$

Figure 3. Absolute and relative sensitivity results for AF electrical remodeling conditions.

that there are notable differences in the mechanisms involved in S_{s1s2} and S_{dyn}, since, in control, G_{Kur} is the most relevant conductance to S_{s1s2}, but G_{K1} is the parameter which mostly affects S_{dyn}. In AF electrical remodeling, both restitution slopes are mainly characterized by G_{K1}, whose inhibition implies steeper APDR slopes that favor wave-breaks generation but may stop reentry propagation (Figure 4G-J).

Analyzing tissue biomarkers sensitivities, ERP is strongly affected by G_{K1} and G_{NaK} in control (ERP is anti-arrhythmically incremented by 64 and 49 ms when G_{K1} and G_{NaK} are respectively inhibited by 30%); however, the strongest dependence of ERP in AF remodeling is on G_{Na} (43 ms increment of ERP under 30% G_{Na} inhibition). Regarding CV, it is mostly determined by G_{Na} in both control and AF electrical remodeling (12.2 and 12 cm/s slower when G_{Na} is decreased by 30% in control and AF, respectively). Despite WL being directly dependent on ERP and CV, WL dependence on G_{Na} is not as notable as on G_{K1} and G_{NaK} because alterations in G_{Na} induce opposite sign changes in ERP and CV (WL is anti-arrhythmically increased by 3.46 and 1.58 cm if G_{K1} is inhibited by 30% in control and AF, respectively).

4. Discussion and conclusion

In this study, we provide a systematic characterization of the changes in ionic current properties that could be key in the development of new anti-AF treatments. Results show slight differences between the mechanisms involved in control and AF remodeling conditions in terms of relative sensitivity of risk markers. A decrement in I_{K1}, important in reentrant rotor stability [2] and closely related

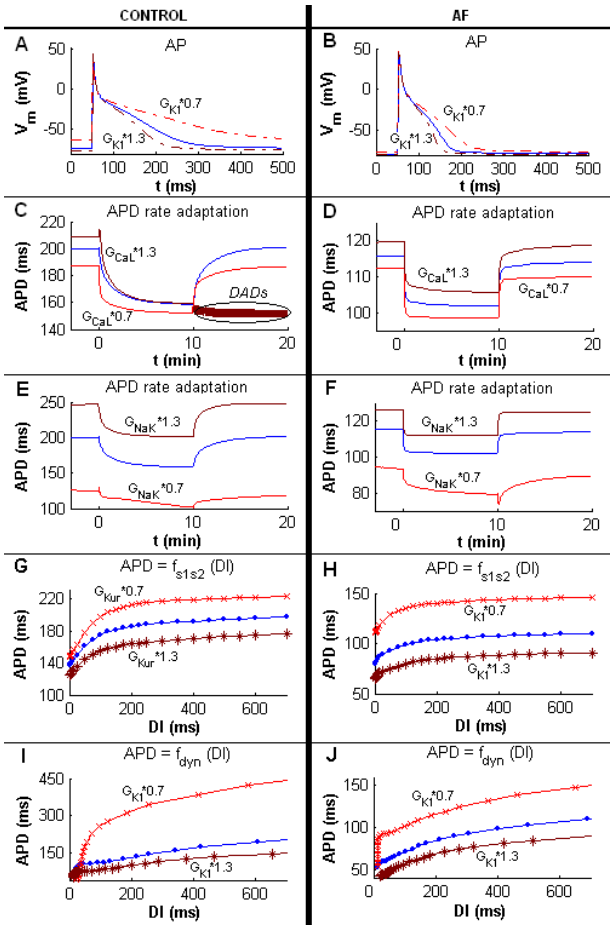

Figure 4. Ionic mechanisms of cellular electrophysiological properties (APD, V_{rest}, τ_{fast}, τ_{slow}, S_{s1s2} and S_{dyn}) in control (left) and AF electrical remodeling (right).

to arrhythmic risk [7], is proven to be anti-arrhythmic in atria, since it substantially increases APD, V_{rest}, restitution slopes, ERP and WL. Inhibition of I_{Na}, responsible for AP initiation, is strongly connected with anti-arrhythmic lower cellular excitability, and leads to notable effects on tissue properties, specifically CV and ERP. Existing anti-arrhythmic drugs blocking Na^+ channels, such as lidocaine and ranolazine, have limitations of use because of their side effects on K^+ channels [6] and on the ventricles [8]. A reduction of the Na^+/K^+ pump activity, which maintains an adequate balance between intracellular and extracellular concentrations of Na^+ and K^+, implies pro-arrhythmic lengthening of APD rate adaptation but anti-arrhythmic increments in ERP and WL.

Some other ionic mechanisms have high relevance for certain properties, like I_{CaL}, important in the fast adaptation phase of APD rate adaptation but whose effects are attenuated in AF conditions [2], or I_{Kur}, a possible target for reentry termination drugs [2] shown to be relevant for restitution slopes as well.

In conclusion, the analysis performed in this study is a step forward in the understanding of the ionic mechanisms underlying AF at cell and tissue levels. Sensitivity of biomarkers related to reentry stability and reentrant properties (APD, V_{rest}, APD rate adaptation, APD restitution, ERP, CV, WL) to changes in ion channel electrophysiology, as provided here, can help in the design and screening of new multi-channel action anti-AF drugs. In particular, drugs inhibiting I_{K1}, I_{Na} and Na^+/K^+ pump activity make atrial tissue more reluctant to propagate arrhythmias.

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References

[1] Maleckar MM, Greenstein JL, Giles WR, Trayanova NA: K^+ current changes account for the rate dependence of the action potential in the human atrial myocyte. Am J Physiol Heart Circ Physiol 2009;297:H1398-H1410.

[2] Pandit SV, Berenfeld O, Anumonwo JMB, Zaritski RM, Kneller J, Nattel S, Jalife J: Ionic determinants of functional reentry in a 2-D model of human atrial cells during simulated chronic atrial fibrillation. Biophys J 2005;88:3806-3821.

[3] Abramson D, Giddy J, Kotler L: High Performance Parametric Modeling with Nimrod/G: Killer Application for the Global Grid?. International Parallel and Distributed Processing Symposium (IPDPS) 2000;520-528.

[4] Grom A, Faber TS, Brunner M, Bode C, Zehender M: Delayed adaptation of ventricular repolarization after sudden changes in heart rate due to conversion of atrial fibrillation. A potential risk factor for proarrhythmia?. Europace 2005;7:113-121.

[5] Kim B-S, Kim Y-H, Hwang G-S, Pak H-N, Lee SC, Shim WJ, Oh DJ, Ro YM: Action potential duration restitution kinetics in human atrial fibrillation. J Am Coll Cardiol 2002;39:1329-1336.

[6] Comtois P, Sakabe M, Vigmond EJ, Muñoz M, Texier A, Shiroshita-Takeshita A, Nattel S: Mechanisms of atrial fibrillation termination by rapidly unbinding Na^+ channel blockers: insights from mathematical models and experimental correlates. Am J Physiol Heart Circ Physiol 2008;295:H1489-H1504.

[7] Kharche S, Garrat CJ, Boyett MR, Inadac S, Holdend AV, Hancoxe JC, Zhang H: Atrial proarrhythmia due to increased inward rectifier current (I_{K1}) arising from KCNJ2 mutation A simulation study. Prog Biophys Mol Biol 2008;98:186-197.

[8] Burashnikov A, Di Diego JM, Zygmunt AC, Belardinelli L, Antzelevitch C: Atrium-selective sodium channel block as a strategy for suppression of atrial fibrillation: differences in sodium channel inactivation between atria and ventricles and the role of ranolazine. Circulation 2007;116:1449-1457.

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