Balance between sodium and calcium currents underlying chronic atrial fibrillation termination: An \textit{in silico} intersubject variability study

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\textbf{BACKGROUND} Atrial remodeling as a result of long-standing persistent atrial fibrillation (AF) induces substrate modifications that lead to different perpetuation mechanisms than in paroxysmal AF and a reduction in the efficacy of antiarrhythmic treatments.

\textbf{OBJECTIVE} The purpose of this study was to identify the ionic current modifications that could destabilize reentries during chronic AF and serve to personalize antiarrhythmic strategies.

\textbf{METHODS} A population of 173 mathematical models of remodeled human atrial tissue with realistic intersubject variability was developed based on action potential recordings of 149 patients diagnosed with AF. The relationship of each ionic current with AF maintenance and the dynamics of functional reentries (rotor meandering, dominant frequency) were evaluated by means of 3-dimensional simulations.

\textbf{RESULTS} Self-sustained reentries were maintained in 126 (73\%) of the simulations. AF perpetuation was associated with higher expressions of $I_{\text{Na}}$ and $I_{\text{CaL}}$ ($P < .01$), with no significant differences in the remaining currents. $I_{\text{CaL}}$ blockade promoted AF extinction in 30\% of these 126 models. The mechanism of AF termination was related with collisions between rotors because of an increase in rotor meandering ($1.71 \pm 2.01 \text{cm}^2$) and presented an increased efficacy in models with a depressed $I_{\text{Na}}$ ($P < .01$).

\textbf{CONCLUSION} Mathematical simulations based on a population of models representing intersubject variability allow the identification of ionic mechanisms underlying rotor dynamics and the definition of new personalized pharmacologic strategies. Our results suggest that the underlying mechanism of the diverging success of $I_{\text{CaL}}$ block as an antiarrhythmic strategy is dependent on the basal availability of sodium and calcium ion channel conductivities.

\textbf{KEYWORDS} Atrial fibrillation; Ionic currents; Rotor dynamics; Calcium current; Mathematical modeling

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\section*{Introduction}

Pharmacologic treatment of atrial fibrillation (AF) has modest efficacy in terminating the arrhythmia and sustaining sinus rhythm in patients with long-standing persistent AF.\textsuperscript{1,2} One of the explanations for this lack of success in chronic AF patients is the remodeling process of atrial tissue. Prolonged periods of AF result in changes in the characteristics of AF drivers (e.g., dominant frequency [DF], rotor meandering, wavefront curvature) and promote AF maintenance.\textsuperscript{3} Understanding the ionic mechanisms that govern AF drivers will allow the development of more effective antiarrhythmic drug treatments in remodeled substrates. However, the remodeling process and its effects on the interaction between ion channel currents depend on the underlying clinical scenario and genetics of each patient,\textsuperscript{4,5} which may result in perpetuation mechanisms that differ among patients.

Pharmacologic treatments have traditionally attempted to prolong the action potential duration (APD) and refractory period of cells, resulting in an increase of wavelength. However, this strategy has limited efficacy for AF termination and sinus rhythm maintenance.\textsuperscript{1} Another potential strategy, based on most recent knowledge about perpetuation...
of AF by rotors, is to focus on destabilizing rotor cores. An increase in rotor core movement may promote its extinction by collision with other wavefronts or anatomic obstacles and thus appears to be an attractive target for antiarrhythmic drugs. Therefore, an in-depth understanding of the ionic mechanisms that govern self-sustained reentries under remodeled conditions is needed. The voltage-dependent sodium current \( I_{\text{Na}} \) probably is the main ionic current governing wavefront propagation properties during sinus rhythm and reentrant activity. Blockade of this current results in deceleration of reentrant activity and increase in reentry meandering, which facilitates termination of the arrhythmia. However, \( I_{\text{Na}} \) block can increase vulnerability to ventricular fibrillation caused by decreased conduction velocity. In addition, the role of the l-type calcium current \( I_{\text{Cal}} \) in rotor dynamics remains controversial. It has been observed that \( I_{\text{Cal}} \) blockade can result in acceleration of fibrillation activity, consistent with APD shortening, and in a reduction of fibrillation frequency. The specific mechanisms for these discrepancies remain unclear and can be related to the role of \( I_{\text{Cal}} \) in terms of propagation. Our hypothesis is that the effect of \( I_{\text{Cal}} \) block on atrial rotor dynamics is modulated by the strength of \( I_{\text{Na}} \) in the specific tissue preparation. Consequently, the specific mechanisms that govern functional rotors may change between patients depending on the relative expression of sodium and calcium currents, opening new venues for personalized pharmacologic strategies to terminate the arrhythmia.

In order to validate this hypothesis, a population of 173 mathematical models capturing variability in experimental measurements from 149 AF patients was used to evaluate the role of each ionic current in the dynamics of functional reentries. The effect of \( I_{\text{Cal}} \) blockade on reentrant biomarkers and its efficacy for AF extinction by destabilizing the core of rotors were evaluated. Intersubject variability allows identification of the mechanisms that produce diverging effects on AF characteristics by the same antiarrhythmic treatment depending on the basal expression of ion channels.

**Methods**

**Experimental dataset and biomarkers**

Action potential (AP) recordings in atrial trabeculae samples \((n = 215)\) of right atrial appendages from 149 patients diagnosed with chronic AF were available. The following AP biomarkers were quantified at 1 Hz (Figure 1): APD

![Figure 1](image-url)  
**Figure 1** Parameters and biomarkers evaluated in the study. A: Koivumaki model. Atrial fibrillation modifications are depicted in red and blue. Currents sampled to obtain the population of models are shown in green. B: Action potential biomarkers: APD20, APD50, APD90, action potential amplitude (APA), resting membrane potential (RMP), and V20. C: Membrane voltage in sphere simulations according to color scale. Insets show transmembrane voltage and power spectral density for a given node, illustrating the dominant frequency (DF). D: Phase maps in Aitoff projection of the sphere. Left: Detection of the rotor core. Right: Meandering of the core according to color scale. APD = action potential duration.
at 20%, 50%, and 90% of repolarization (APD_{20}, APD_{50}, APD_{90}, respectively), action potential amplitude (APA), resting membrane potential, and AP plateau potential at 20% of APD_{90} (V_{20}).

In addition to AP recordings at 1 Hz, a subset of the preparations (n=9) was used to characterize rate dependency in human atrial APs by quantifying rate-sensitive biomarkers (APD_{50/ratio} and APD_{90/ratio}) as the ratio between APD at each frequency (2, 3, and 4 Hz) and at 1 Hz for APD_{50} and APD_{90}.

Population of models
An experimentally calibrated population of human AF models was generated from the experimental data described earlier, the Latin hypercube sampling methodology described in by Britton et al.\(^1\),\(^2\) and the baseline “AF model” by Koivumaki et al.\(^8\). Therefore, ionic conductances highlighted in green (Figure 1A) took random-sampled values between -100% to +200% of their original value.

The 173 models of the initial population of 16,384 mathematical models that satisfied at all pacing frequencies the physiologic range of biomarkers (as identified in the experimental recordings) constituted the AF population (see Online Supplementary Material).

Role of ionic currents on AF reentrant mechanisms
The impact of intersubject variability in ionic properties in AF-related rotor dynamics was evaluated using 173 computer simulations (one for each of the models in the AF population) conducted in a 3-dimensional (3D) spherical atrial tissue model with membrane kinetics. Fibrillation or rotor activity was characterized using DF and the area of rotor meandering (RM) (Figure 1 and Online Supplementary Material).

In order to identify the main ion channel conductivities involved in the perpetuation of reentries, the 11 modified conductivities were compared between the groups of models with sustained vs unsustained reentries. Relations between modified ionic currents, 1-Hz AP biomarkers, and AF reentrant characteristics (DF, RM) also were analyzed.

Effects ICa\(_\text{L}\) blockade in the population of models
Simulations described in the previous section were analyzed during basal conditions and after a 50% reduction in calcium conductivity (g\(_\text{Ca}\)). The 3D models in which ICa\(_\text{L}\) reduction terminated the arrhythmia were compared with those that maintained reentrant activity. The effect of ICa\(_\text{L}\) block in both DF and RM and its relationship with the modified ionic currents and 1-Hz biomarkers were evaluated.

Statistical analysis
The Mann–Whitney U test, which is robust against non-Gaussian distributions, was used to evaluate statistical significance between variables (P < .01).

To evaluate the role of each of the modified currents on rotor dynamics (RM, DF), partial correlation coefficients (PCr) were used.\(^1\),\(^2\)

**Results**

**Role of ionic currents on reentrant AF mechanisms**

The simulation of 173 different physiologic atrial tissue models allowed us to identify (1) differences between models that do and do not allow AF maintenance and (2) the role of each ion current conductance on AF characteristics (i.e., DF and RM).

Arrhythmias were self-terminated in 47 (27%) of the models during the first seconds of simulated reentrant activity. The temporal evolution of phase maps for representative examples in each subgroup is shown in Figure 2. Note that in the example on the left, reentries were stable during the entire simulation. However, in the example on the right, although reentries start in a similar position, rotor cores drifted up to collision, where the arrhythmia terminated. This mechanism of termination (i.e., collision between rotors due to larger RM) was present in all the 47 simulations in which the arrhythmia was not perpetuated. This result suggests that ion channel currents involved in RM may play a fundamental role in the perpetuation or termination of AF rotors.

A comparison of the distribution of each ionic current parameter between the models in which the fibrillation terminated and those in which it was perpetuated is depicted in Figure 2B. Sodium and calcium conductivities (g\(_\text{Na}\) and g\(_\text{Ca}\)) were the only 2 parameters that presented significant differences between both groups, highlighting their relevance as possible antiarrhythmic targets. Interestingly, no significant differences were observed on potassium repolarizing currents, which previously have been proposed as potential antiarrhythmic targets for AF.\(^1\),\(^2\)

Specific AF characteristics of the models in which the arrhythmia was perpetuated are shown in Figure 3. Significant variability can be observed in the distribution of DFs and RMs, which indicates that the developed population of models allows for the simulation of multiple AF scenarios. Because of the intersubject variability introduced by this database, the relationship between ion channel parameters and AF biomarkers can be identified. Despite the low direct correlation observed between DF and RM (R\(^2\) = -.44), the scatterplot indicates that high DFs are most often related with low RMs, whereas low DFs can be found with any RM value. This result takes on additional relevance when related with the partial correlation analysis between AF biomarkers and ion channels properties (Figure 3B). Sodium conductance plays a main role in both parameters. Although an increase of g\(_\text{Na}\) is correlated with an increase of DFs, it also is related to a reduction of RM. However, the lack of a strong correlation between DF and RM indicates that the effect of g\(_\text{Na}\) in both AF biomarkers is significantly affected by other conductivities. Specifically, our results suggest that, in addition to g\(_\text{Na}\), DF is mainly governed by gK1, whereas RM is inversely related to g\(_\text{Ca}\). None of the remaining studied parameters of the model presented a significant partial correlation with AF characteristics.

Regarding the relationship between AF characteristics and AP biomarkers, our results indicate that APA is the only
biomarker related with both RM and DF. The large dependence of reentrant biomarkers with $g_{\text{Na}}$ is in accordance with the dependency of APA with $g_{\text{Na}}$ (see Online Supplemental Figure 2). In addition to APA, both APD$_{20}$ and AP$_{90}$ presented minor correlations with DF, but we found no strong correlation between any biomarker and RM.

**I$_{\text{Cal}}$ blockade effects in the population of models**

The findings that RM plays a relevant role in the termination of AF as a result of rotor collisions, and that RM is mainly governed by $g_{\text{Na}}$ and $g_{\text{Cal}}$ (PCR $= -0.36$ and $-0.42$), raise questions regarding the efficacy of I$_{\text{Cal}}$ blockers depending on the relative expression of other ion channel currents.

Specifically, effects of a 50% reduction of $g_{\text{Cal}}$ on AF characteristics were evaluated in the 126 models that maintained fibrillation during basal conditions. The juxtaposed effect of this reduction on AF characteristics in 2 examples is depicted in Figure 4. Note that the reduction of $g_{\text{Cal}}$ produced a significant increase in RM (from 1.59 to 3.49 cm$^2$) and a decrease in DF (4.4 vs. 3.8 Hz) (Figure 4A), whereas the reduction of $g_{\text{Cal}}$ resulted in an increase in DF (4.6 vs. 5.1 Hz) (Figure 4B).

The reduction of $g_{\text{Cal}}$ also had different degrees of success on AF termination depending on the specific characteristics of each model. After 7 seconds of simulation under the effects of $g_{\text{Cal}}$ block, 38 of the 126 reentrant processes (30%) terminated. The differences between ion channel properties in the cases of abolished and persisting arrhythmias are shown in Figure 5. Models in which I$_{\text{Cal}}$ block resulted in reentry termination presented lower expressions of I$_{\text{Na}}$ and I$_{\text{K1}}$ (Figure 5A). This is suggestive of the potential implication of patient-specific ratios between $g_{\text{Cal}}$, $g_{\text{Na}}$, and $g_{\text{K1}}$ on the antiarrhythmic effects of I$_{\text{Cal}}$ blockers.

The important role of this balance between ion currents in the specific mechanisms by which calcium block terminates AF is shown in Figure 5B. The reduction in $g_{\text{Cal}}$ resulted in an average increase in RM. However, this effect was not uniform in the entire population, in some cases resulting in a reduction of RM and therefore stabilization of the arrhythmia. Regarding the modifications on DF, no clear trends were observed. In addition, as during basal conditions, a weak inverse relationship between DF and RM was observed ($R^2 = -0.48$). The partial correlation between changes in DF and RM and each of the model parameters can shed some light on
the characteristics of calcium blockers responders and non-responders. As shown in Figure 5C, $g_{Na}$ was the main parameter correlated with both DF and RM changes. According to these results, the inverse correlation between $g_{Na}$ and the change in RM indicates that calcium blockers produced an increase in RM mainly in models in which the basal conductance of $I_{Na}$ was low. This result confirmed that the antiarrhythmic effect of calcium blockers could be subjected to the degree of expression of the sodium current in each patient.

In the case of DF, a more complex behavior is observed. The direct correlation between changes in DF and $g_{Na}$ is suggestive of an increase in DF due to calcium block in models with higher sodium channel conductance. However, the inverse correlation between the change in DF and $g_{K1}$ points to a reduction of DF in models in which $g_{K1}$ was high, as the strong repolarizing effect of $I_{K1}$ is not compensated by $I_{CaL}$. This multifactorial response to calcium block may explain the controversial correlation between calcium blockers and modifications on DFs reported in the literature.7,9,10

Discussion

Major findings

In this study, a population of 173 mathematical models that mimics the intersubject variability of 149 AF patients including rate-dependent response was used to evaluate the
role of each ionic current on AF reentry perpetuation mechanisms by means of 3D spherical models. The fundamental and interdependent role of $I_{Na}$, $I_{CaL}$, and $I_K$ currents on AF dynamics has been shown. This physiologic variability in ionic current densities may independently explain the observed disparity of antiarrhythmic drug effects, which can be related to the expression of other currents untargeted by a compound. As shown here, this may be the case of calcium blockers, whose antiarrhythmic effect is dependent on sodium current density.

**AF population of models**

Mathematical models have been used to evaluate hypotheses of AF perpetuation mechanisms and drug response since the late 1950s. During the last decades, as result of the increase in computing power together with more extended research in cardiac ionic currents by patch-clamp experiments, more sophisticated electrophysiologic models have been developed. These ionic current models have been used to evaluate the effect of antiarrhythmic treatments on both AP and rotors dynamics.\(^8,13\) However, most of these in silico studies have made use of a single set of parameters fitted to an average of many experiments. Although this approach has allowed the reproduction and better understanding of AF mechanisms, it hides the variability between patients observed in clinical practice. This variability may explain the contradictory responses to pharmacologic treatments reported in the literature. New cardiac simulation platforms such as those used in this work\(^14\) allow performance of simulations of populations of models, accounting for the variability observed across subjects. Furthermore, this is the first study in which a population of models has been used to determine the ionic currents linked to arrhythmia perpetuation in a 3D model of AF.

AP markers from experimental recordings allowed us to select ionic current combinations that result in APs covering the observed experimental range. As in previous studies,\(^5,12\) variability in ionic parameters reproduces AP variability in agreement with the biomarkers obtained from the recorded preparations. In order to account for the rate dependence of atrial electrophysiology, we included restrictions in our population reproducing the observed trends. Of note, the
Strategies for the development of new pharmacologic therapies and reentrant biomarkers

Clinical and research studies on AF have demonstrated the importance of rotors on AF maintenance.\textsuperscript{6,10,16} Overexpression of repolarization currents, such as $I_{K_1}$ or $I_{K_{ACH}}$, resulted in rotor acceleration as a consequence of APD shortening,\textsuperscript{1,17} whereas $I_{K_1}$ block has been shown to reduce DF.\textsuperscript{18} However, studies on pharmacologic block of these currents have reported a modest effect on AF termination and sinus rhythm maintenance.\textsuperscript{1} Our simulations in the population of models show a significant correlation of $I_{K_1}$ with DF, and no relationship with $I_{K_1}$, $I_{K_{ACH}}$, $I_{K_{UR}}$, or $I_{K_S}$ in terms of AF maintenance (Figure 2B).

These results suggest that AF maintenance, as previously hypothesized,\textsuperscript{6,9,10} may be more strongly related to the depolarizing currents $I_{Na}$ and $I_{Ca_{L}}$ which increase RM when decreased while yielding a reduction on APD$_{90}$. Reduced $I_{Na}$ or $I_{Ca_{L}}$ availability results in decreased excitability, forcing the rotor core to drift. This increased RM may facilitate annihilation of rotors due to collision, as found in the present study and others.\textsuperscript{6,9,10}

According to these results, AF termination might be approached by pharmacologic reduction of $I_{Ca_{L}}$. However, the role of $I_{Ca_{L}}$ as an antiarrhythmic drug is controversial, as both acceleration\textsuperscript{1} and deceleration\textsuperscript{6,10} of fibrillatory behavior have been reported. This controversy has been also previously discussed in terms of the lack of specificity of some drugs, such as verapamil, which also blocks $I_{Kr}$.\textsuperscript{19} In contrast, simulations allowed us to specifically block $I_{Ca_{L}}$. Yet, a significant number of models could not maintain the arrhythmia even though a significant correlation between $I_{Ca_{L}}$ block and DF was not found. This could be explained by the simultaneous effect of $I_{Ca_{L}}$ on APD and RM\textsuperscript{6} (see Online Supplementary Material) because it shortens APD (which would tend to increase DF) but at the same time increases RM (which, in turn, tends to decrease DF). The balance between these 2 opposing effects has been shown to be multifactorial but strongly related to $I_{Na}$ availability. Therefore, $I_{Ca_{L}}$ may be effective for AF termination in cases of low availability of $I_{Na}$.

According to the results of our study, the antiarrhythmic effect of calcium channel blockers may be more prominent in some patients than others, depending on their specific balance of ion channel currents, particularly $I_{Na}$.

These results allow us to suggest personalized antiarrhythmic treatments based on the patient’s expression of different ion channels. For example, low expression of $I_{Na}$ could indicate a positive responder to $I_{Ca_{L}}$ block antiarrhythmic treatment, whereas calcium blockers may be ineffective in patients with a high expression of $I_{Na}$. Thus, protein expression techniques might help in the stratification of patients depending on $I_{Na}$ levels in atrial tissue to select appropriate candidates for $I_{Ca_{L}}$ block therapy.

Populations of models highlighted differences between responders and nonresponders to treatments ($I_{Ca_{L}}$ block in this case). These analyses will be helpful in the development of new antiarrhythmic strategies and in the selection of responder patients to both established and novel treatments, such as $I_{Na}$ block or multichannel drugs. Furthermore, our results reinforce the development of drugs that partially block both $I_{Ca_{L}}$ and $I_{Na}$.

Study limitations

Mathematical models are partial representations of real objects, so their results can be conditioned by gaps in knowledge. Additional repolarizing currents, such as small-conductance calcium-activated potassium channels, are increasingly recognized as contributors to AF remodeling.\textsuperscript{20} However, the inclusion of such channels should not alter the main findings of this study, based on the balance between atrial depolarizing currents and tested here against a wide range of possible repolarization reserves. Whereas extrapolation of results requires caution and future validation against refined models of human electrophysiology, the introduction of intersubject variability approximates in silico experiments to more realistic clinical scenarios.

Because of technical limitations, tissue samples were obtained from the right atrial appendage and thus may not be representative of the entire atria. The left atrium has been reported as more frequently involved in AF maintenance in paroxysmal AF\textsuperscript{16,17}, whereas right atrial tissue of those patients may harbor reentries with lower DFs. This may be one of the mechanisms of our reported frequencies, which are lower than those typically found in AF patients.

In addition, structural disarrangements (e.g., fibrosis or decreased tissue coupling) play a relevant effect in excitability and rotor maintenance.\textsuperscript{11,21} Channel kinetics also have an important role in the initiation and maintenance of atrial arrhythmias, as in the case of late $I_{Na}$.\textsuperscript{22} Further studies investigating the relationship between these parameters and the properties of reentrant activity are needed.

Finally, the morphology of simulated atrial tissue does not reproduce the complex atrial anatomy in humans. Nevertheless, introduction of anatomic heterogeneities would most likely increase the incidence of collisions and annihilation of wavefronts under increased RM.

Conclusion

Experimentally calibrated populations of models are presented as a useful tool for understanding the ionic mechanisms related to rotor dynamics and defining new pharmacologic targets for AF. This study showed that the
same pharmacologic treatment can produce different effects on AF dynamics for cells modeled under the same variability found in human experimental data. By using this computational framework, our results suggest that I_{Ca,L} block can be an efficient antiarrhythmic treatment in AF patients with depressed I_{Na} current. This methodology will be very helpful in the selection of responder patients and the development of new antiarrhythmic treatments, such as I_{Na} block or drugs that affect multiple channels.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2016.08.028.

References

1. Pandit SV, Zlochiver S, Filgueiras-Rama D, Mironov S, Yamazaki M, Ennis SR, Nougiam SF, Workman AJ, Berenfeld O, Kalifa J, Jalife J. Targeting atrioventricular differences in ion channel properties for terminating acute atrial fibrillation in pigs. Cardiovasc Res 2011;89:843–851.
2. Wettwer E, Christ T, Endig S, Rozenariu I, Matschke K, Lynch JJ, Pourrier M, Gibson JK, Fedida D, Knaut M, Ravens U. The new antiarrhythmic drug vernakalant: ex vivo study of human atrial tissue from sinus rhythm and chronic atrial fibrillation. Cardiovasc Res 2013;98:145–154.
3. Climent AM, Guillem MS, Atienza F, Fernandez-Aviles F. Electrophysiological characteristics of permanent atrial fibrillation: insights from research models of cardiac remodeling. Expert Rev Cardiovasc Ther 2015;13:1–3.
4. Walsmsley J, Rodriguez JF, Mirams GR, Burrage K, Elnov IR, Rodrigue B. mRNA Expression levels in failing human hearts predict cellular electrophysiological remodeling: a population-based simulation study. Plos One 2013;8:e56359.
5. Sanchez C, Bueno-Orovio A, Wettwer E, Loose S, Simon J, Ravens U, Pueyo E, Rodriguez B. Inter-subject variability in human atrial action potential in sinus rhythm versus chronic atrial fibrillation. PLoS One 2014;9:e105897.
6. Kneller J, Kalifa J, Zou R, Zaitsev A, Warren M, Berenfeld O, Vignond E, Leon L, Nuttel S, Jalife J. Mechanism of atrial fibrillation termination by pure sodium channel blockade in an ionically-realistic mathematical model. Circ Res 2005;96: E35–E47.
7. Chorro F, Canoves J, Guerrero J, Manar L, Sanchis J, Such L, Lopez-Merino V. Alteration of ventricular fibrillation by flecainide, verapamil, and sotalol: an experimental study. Circulation 2000;101:1606–1615.
8. Koivumaki JT, Seemann G, Maleckar MM, Tavi P. In silico screening of the key cellular remodeling targets in chronic atrial fibrillation. PLoS Comput Biol 2014;10:e1003620.
9. Samie F, Mandapati R, Gray R, Watanabe Y, Zuur C, Beaumont J, Jalife J. A mechanism of transition from ventricular fibrillation to tachycardia: effect of calcium channel blockade on the dynamics of rotating waves. Circ Res 2000;86: 684–691.
10. Climent AM, Guillem MS, Fuentes L, Lee P, Bollensdorff C, Fernandez-Santos ME, Suarez-Sancho S, Sanz-Ruiz R, Sanchez PL, Atienza F, Fernandez-Aviles F. The role of atrial tissue remodeling on rotor dynamics: an in vitro study. Am J Physiol Heart Circ Physiol 2015;309:H1964–H1973.
11. Shaw R, Rudy Y. Ionic mechanisms of propagation in cardiac tissue: roles of the sodium and L-type calcium currents during reduced excitability and decreased gap junction coupling. Circ Res 1997;81:727–741.
12. Britton OJ, Bueno-Orovio A, Van Ammel K, Lu HR, Towart R, Gallagher DJ, Rodriguez B. Experimentally calibrated population of models predicts and explains intersubject variability in cardiac cellular electrophysiology. Proc Natl Acad Sci U S A 2013;110:E2108–E2105.
13. Pandit S, Berenfeld O, Anumonwo J, Zaritski R, Kneller J, Nuttel 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.
14. Garcia-Molla VM, Liberos A, Vidal A, Guillem MS, Miltet J, Gonzalez A, Martinez-Zaldivar FJ, Climent AM. Adaptive step ODE algorithms for the 3D simulation of electric heart activity with graphics processing units. Comput Biol Med 2014;44:15–26.
15. Bueno-Orovio A, Sanchez C, Pueyo E, Rodriguez B. Na/P pump regulation of cardiac repolarization: insights from a systems biology approach. Pflugers Arch 2014;466:183–193.
16. Rodrigo M, Guillem MS, Climent AM, Pedron-Torrecilla J, Liberos A, Miltet J, Fernandez-Aviles F, Atienza F, Berenfeld O. Body surface localization of left and right atrial high-frequency rotors in atrial fibrillation patients: a clinical-computational study. Heart Rhythm 2014;11:1584–1591.
17. Atienza F, Almendral J, Jalife J, Zlochiver S, Ploutz-Snyder R, Torrecilla EG, Arau J, Kalifa J, Fernandez-Aviles F, Berenfeld O. Real-time dominant frequency mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. Heart Rhythm 2009;6:3340.
18. Warren M, Guha P, Berenfeld O, Zaitsev A, Anumonwo J, Dhamaon A, Bagwe S, Tafet S, Jalife J. Blockade of the inward rectifying potassium current terminates ventricular fibrillation in the guinea pig heart. J Cardiovasc Electrophysiol 2003;14:621–631.
19. Zhang ST, Zhou ZF, Gong QM, Makelski JC, January CT. Mechanism of block and identification of the verapamil binding domain in HERG potassium channels. Circ Res 1999;84:989–998.
20. Skibsbye L, Poulet C, Dinnes JG, Bentzen BH, Yuan L, Kappert U, Matschke K, Wettwer E, Ravens U, Grunnet M, Christ T, Jepsersen T. Small-conductance calcium-activated potassium (SK) channels contribute to action potential repolarization in human atria. Cardiovasc Res 2015;103:156–167.
21. Zlochiver S, Muñoz V, Vikstrom KL, Taffet SM, Berenfeld O, Jalife J. Electrototoxic myofibriloblast-to-myocyte coupling increases propensity to reentrant arrhythmias in two-dimensional cardiac monolayers. Biophys J 2008;95:4469–4480.
22. Morotti S, Koivumaki JT, Maleckar MM, Chiamvimonvat N, Grandi E. Small-conductance Ca^{2+}-activated K^{+} current in atrial fibrillation: both friend and foe. Biophys J 2016;110:274a.