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The Efficacy of Class III Anti-arrhythmic Drugs in 3D Canine Atrial Models: Is the Blockade of I_{KCa} Pro- or Anti-arrhythmic?

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Abstract

Small conductance calcium-activated potassium channel current, I_{KCa}, has recently been characterized in atrial tissue and linked with atrial arrhythmogenesis. As I_{KCa} does not contribute significantly to the ventricular action potential, there is great interest in developing pharmacological agents targeting these channels. However, experimental data so far have presented conflicting evidence as to whether I_{KCa} inhibition is pro- or anti-arrhythmic.

We have created a new formulation for I_{KCa}, which we included in recently developed heterogeneous and anisotropic 3D canine atrial models. These were applied to investigate the effect of I_{KCa} blockade compared to inhibition of other potassium currents: I_{Kr} and I_{Kur}.

Blocking I_{KCa} led to the termination of AF in the 3D atrial model, in contrast to blockades of I_{Kur} or I_{Kr}. Blocking I_{KCa} prolonged action potential duration, APD, by at least 20 ms in all atrial cell types, whereas I_{Kr} or I_{Kur} blocks did not increase APD by more than 10 ms, thus explaining I_{KCa}'s effectiveness in terminating AF.

Nevertheless, the blockade of I_{KCa} also led to an increase in APD dispersion, which is expected to be pro-arrhythmic. In cases when the APD dispersion effects dominate over the APD prolongation, the blockade of I_{KCa} is expected to be pro-arrhythmic, as seen in experimental models of non-remodelled canine atria.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting 3% of the adult population of developed countries. AF is associated with increased morbidity and mortality and its incidence is expected to rise in the near future, making it an urgent and important health problem [1].

Although anti-arrhythmic drugs (AADs) are the first line therapy for recent onset AF, their cardioversion efficacy can be as low as 50% [1]. AADs often carry significant side effects, namely the potential to induce life-threatening ventricular arrhythmias. These pro-arrhythmic side effects can be minimised if AADs are designed to target atrial-selective ionic channels, which have a negligible contribution to the ventricular action potential.

One of such targets is the K^+ ultra-rapid delayed rectifier current, I_{Kur}, which is expressed in human atrial cells, but not in human ventricles [2]. This is in contrast with the rapid delayed rectifier current, I_{Kr}, which is ubiquitous throughout the heart and the blockade of which may lead to life-threatening *Torsade de Pointes* [2].

Recently, ionic current carried by small-conductance calcium-dependent K^+ channels, I_{KCa}, has been characterised in human and canine atrial cells, but, significantly, not in ventricular myocytes, making I_{KCa} a potentially desirable target of anti-arrhythmic drug action in AF. Genomic associations between I_{KCa} and AF have also been established [3].

Although blocking I_{KCa} is known to increase the action potential duration (APD) in canine atrial cells [3]–[6], there is some controversy as to whether its blockade is pro- or anti-arrhythmic. Blocking I_{KCa} has been found to facilitate the initiation of atrial arrhythmias [3], [6], by increasing both APD and APD heterogeneity in the canine left atrium (LA). Other studies have instead found that I_{KCa} blockade, through prolongation of APD, led to reduced AF duration [4] and AF termination [5]. It is also at the moment not clear whether I_{KCa} is overexpressed in the presence of AF remodelling [4] or not [7].

In this paper, we aim to reconcile the disparate experimental findings about I_{KCa}'s effect on AF using insights from computational models. To this end, we introduce a new mathematical formulation for I_{KCa} and include it in our recently developed canine atrial cell models [8]. We use these updated canine models to investigate the effect on APD of blockades of I_{Kr}, I_{Kur} and I_{KCa} in several atrial remodelling conditions. We then determine the effectiveness of these blockades in realistic 3D canine atrial models [8] and interpret these findings in the light of the drugs' effects on APD and APD dispersion across the entire atria, using the formalism previously applied to investigate the effectiveness of multi-channel-blocking AADs [8].

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3. Methods

3.1. Canine Model of Atrial Fibrillation

In this study we used the 3D canine model successfully employed to study the efficacy of AADs in atrial fibrillation [8], [9]. This model includes a realistic canine atrial geometry and myofibre orientations derived from micro computed tomography [10]. It also includes four region-specific electrophysiological models and can easily incorporate different degrees of AF-induced ionic and structural remodelling [8].

As in the previous study, we solved the monodomain equation in a central finite differences setting with Δt = 5 μs and Δx = 0.3 mm. Conditions mimicking AF were obtained by pacing with an S_1-S_2 protocol near the pulmonary veins (PV) in the presence of moderate or severe ionic remodelling (see [8], [9] for details). We additionally studied a situation of moderate remodelling in the presence of I_{KCa}, according to the new mathematical formulation of this current presented below.

3.2. Formulation of I_{KCa} in Heart Failure

The atrial I_{KCa} was formulated as a time-independent passive K^+ current whose conductance depends strongly on the intracellular calcium concentration, $[Ca^{2+}]_i$, following a Hill equation [11], [12]. Parameterization was achieved by fitting experimental data from isolated ventricular myocytes from HF patients [11], to give Equation (1):

$$I_{KCa} = g_{KCa} \frac{[Ca^{2+}]_i^n}{[Ca^{2+}]_i^n + K_d^n}(V_m - E_K) \qquad (1)$$

with g_{KCa} = 0.07 pA/pF, n = 5.0 and K_d = 3 x 10^{-4} mM. V_m is the transmembrane electrical potential, and E_K is the reversal potential for K^+ ions, typically around -87 mV.

3.3. Modelling the Action of AADs

The initial simulations of AF were run for 5 s, at which time each of the AADs was administered. Each drug action was responsible for an instantaneous 50% block of: 1) I_{Kr}; 2) I_{Kur} or, when the model included it, 3) I_{KCa}. The electrical activity of the atrial model was followed for 5s or until termination of all re-entrant activity.

To shed light into the mechanisms through which AAD action is facilitated, we computed 90% action potential duration, ADP_{90}, in baseline conditions (canine models [8] with I_{KCa}) and in the presence of 50% block of either: 1) I_{Kr}, 2) I_{Kur} and 3) I_{KCa}. This was performed for a basic cycle length (BCL) of 500 ms in single-cells and in realistic 3D atrial models. In the latter case, the canine atrial model was paced twice at 150 ms near the left superior PV before APD in each voxel of the model.

4. Results

4.1. AAD effects in a 3D Model of AF

In our AF model of moderate ionic remodelling, I_{Kr} blockade did not have a significant effect on AF, whereas I_{Kur} blockade led to the creation of an additional rotor in the right atrium (RA). In the advanced AF model, AF was sustained by four rotors in total (Figure 1). Neither I_{Kr} nor I_{Kur} blockade had a significant effect in any of the rotors. The I_{KCa} blockade terminated AF within 500 ms. Both I_{Kr} and I_{Kur} blockades increased the complexity of AF activations, leading to the formation of an additional rotor in each atrial appendage (RAA and LAA). The outcomes of these simulations are summarised in Table 1.

Figure 1: Maps of transmembrane voltage, V_m (left) and intracellular calcium concentration, $[Ca^{2+}]_i$ (right), in the canine atrial model just before the application of the AADs. Black arrows mark the direction of the re-entrant circuits driving AF in the model.

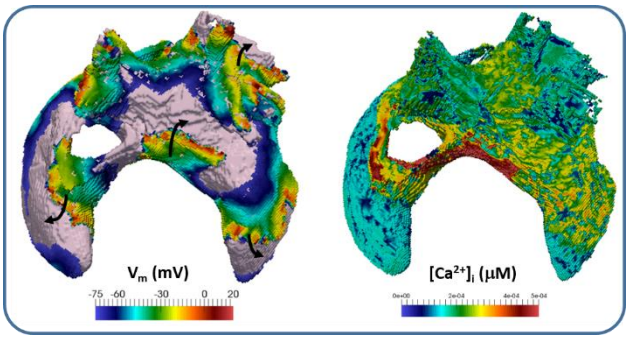


Table 1. Description of the observed re-entrant activity after administration of three different anti-arrhythmic drugs in different conditions.

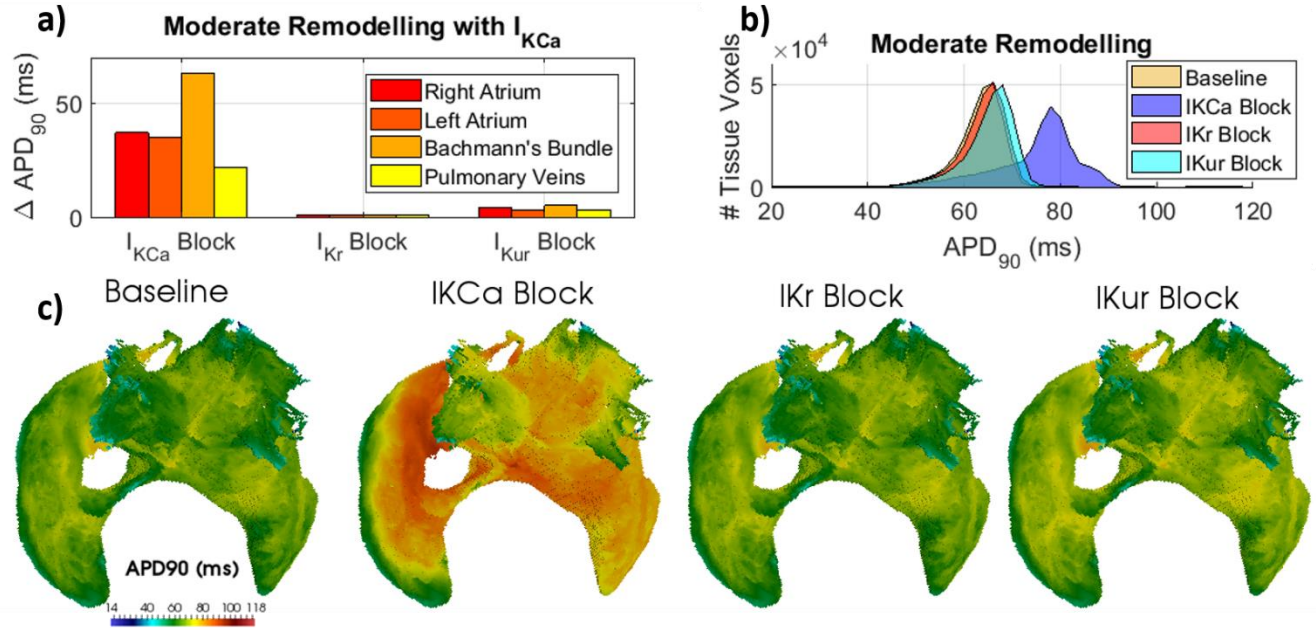
AAD (Channel Blocked by 50%)	Moderate Ionic Remodeling	Severe Ionic Remodeling	Moderate Ionic Remodeling with I_{KCa}
I_{Kr}	No change.	No change.	The rotor divides into two.
I_{Kur}	A new rotor appears in the RAA.	No change.	The rotor divides into two.
I_{KCa}	-	-	All activity is terminated at < 500 ms.

4.2. Effect on APD and APD Heterogeneity

To interpret the different behaviour of the re-entrant activity in the presence of the AADs in the 3D simulations,

we analysed the effect of the AADs on atrial refractoriness, as measured by APD_{90}. Figure 2a shows the increase in single-cell APD_{90} values for different cell types (RA, LA, Bachmann's bundle and PV) in the presence of the I_{KCa} formulation of Eq. (1) for the two levels of ionic remodelling. It is clear that the I_{KCa} block led to the greatest rise in APD_{90}, with I_{Kr} and I_{Kur} having a nearly insignificant effect on APD at the studied pacing rates. The I_{KCa} block also enhances the heterogeneity in APD across cell types, particularly for conditions of moderate remodelling.

Figure 2. Effect of the 50% blockade of different ionic channels on APD_{90} values for the atrial canine model [8] in the presence of I_{KCa} (Eq. (1)) for moderate ionic remodelling. a) Increase in single-cell APD_{90} for each cell type for each AAD (BCL: 500 ms). b) Histogram of APD_{90} in atrial tissue in baseline conditions and after the administration of each AAD (BCL: 150 ms). c) APD_{90} maps in baseline conditions and in the presence of each ionic channel blocker (BCL: 150 ms).



3. Conclusions

In this paper, we extended the computational framework previously presented to study the action of AADs in a realistic 3D model of AF to include the small-conductance calcium-dependent K^+ channel recently characterized in atrial myocytes. Using the new model, we found that blocking I_{KCa} was very effective at terminating AF, in contrast to inhibition of either I_{Kur} or I_{Kr}, which were pro-arrhythmic in these circumstances (Table 1). Even in the absence of I_{KCa}, blocking I_{Kur} or I_{Kr} did not lead to termination in either of the investigated stages of AF remodelling (Table 1).

The differences in the effectiveness of these drugs can be explained by their effect on atrial APD. We found that blocking I_{KCa} led to both an increase in APD and APD dispersion (Figure 2), in contrast with blocks of either I_{Kr} or I_{Kur}, which hardly affected APD in the analysed conditions. We thus hypothesise that the effectiveness of the I_{KCa} block lies in the increase in APD (and therefore wavelength) that it generates. As in Moe's classical theory, this leads to a decrease in the critical volume available to the existing re-entrant circuits, terminating them [13].

In the analysed circumstances, the substantial increase in APD (of more than 60 ms, Figure 2a) brought about by I_{KCa}'s block trumps the concomitant pro-arrhythmic increase in APD dispersion. It is likely that the APD_{90} dispersion induced by I_{KCa} is, at least in part, mediated by the very heterogeneous distribution of Ca_i across the atria, as seen in Figure 1.

This is in contrast to the AAD actions studied previously [8], whose effectiveness was dominated by their effect on APD dispersion over APD prolongation. We propose that the effectiveness of I_{KCa} blockers may depend on the balance between these two anti-arrhythmic and pro-arrhythmic effects. In cases when the APD prolongation dominates (as remodelling conditions in the current study), a block of I_{KCa} is likely to be beneficial. This agrees with anti-arrhythmic effects of I_{KCa} blockade observed in dogs exposed to prolonged atrial pacing [4]. However, if the dispersion in APD it induces is the dominant effect, it is likely that an APD block may be pro-arrhythmic, as seen non-remodelled canine atria [3]. These hypotheses, as well as the congruent earlier ones [14], will be tested in greater detail in future computational studies.

The current study has some limitations. The AAD actions do not model the action of known compounds, instead focusing on mechanisms of drug action. Ion

channel state-dependent binding is therefore not taken into account. We have additionally assumed that the drug action was instantaneous, which is a simplification.

In summary, the current study presents a novel formulation for I_{KCa}, which was incorporated into existing state of the art canine atrial models. We use these updated electrophysiology models to investigate the effectiveness of I_{KCa} blockade in comparison to blockades of other K^+ channels: I_{Kr} and I_{Kur}. We explain the superiority of I_{KCa} blockade by showing how it leads to an increase in APD. The I_{KCa} blockade causes, nevertheless, an increase in APD dispersion, which, in some circumstances, may be pro-arrhythmic, as has been shown in experimental studies.

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References

[1] P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, and E. Al, "2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS," *Eur. Heart J.*, vol. 37, no. 11, pp. 2893–2962, 2016.

[2] J. Tamargo, R. Caballero, R. Gómez, C. Valenzuela, and E. Delpón, "Pharmacology of cardiac potassium channels," *Cardiovasc. Res.*, vol. 62, no. 1, pp. 9–33, Apr. 2004.

[3] C.-H. Hsueh, P.-C. Chang, Y.-C. Hsieh, T. Reher, P. S. Chen, and S. F. Lin, "Proarrhythmic effect of blocking the small conductance calcium activated potassium channel in isolated canine left atrium.," *Heart Rhythm*, vol. 10, no. 6, pp. 891–8, Jun. 2013.

[4] X. Y. Qi, J. G. Diness, B. J. J. M. Brundel, X.-B. Zhou, P. Naud, C.-T. Wu, H. Huang, M. Harada, M. Aflaki, D. Dobrev, M. Grunnet, and S. Nattel, "Role of small-conductance calcium-activated potassium channels in atrial electrophysiology and fibrillation in the dog," *Circulation*, vol. 129, no. 4, pp. 430–440, Nov. 2014.

[5] J. G. Diness, U. S. Sørensen, J. D. Nissen, B. Al-Shahib, T. Jespersen, M. Grunnet, and R. S. Hansen, "Inhibition of small-conductance Ca2+-activated K+ channels terminates and protects against atrial fibrillation.," *Circ. Arrhythm. Electrophysiol.*, vol. 3, no. 4, pp. 380–90, Aug. 2010.

[6] N. Li, V. Timofeyev, D. Tuteja, D. Xu, L. Lu, Q. Zhang, Z. Zhang, A. Singapuri, T. R. Albert, A. V Rajagopal, C. T. Bond, M. Periasamy, J. P. Adelman, and N. Chiamvimonvat, "Ablation of a Ca2+-activated K+ channel (SK2 channel) results in action potential prolongation in atrial myocytes and atrial fibrillation.," *J. Physiol.*, vol. 587, no. Pt 5, pp. 1087–100, Mar. 2009.

[7] L. Skibsbye, C. Poulet, J. G. Diness, B. H. Bentzen, L. Yuan, U. Kappert, K. Matschke, E. Wettwer, U. Ravens, M. Grunnet, T. Christ, and T. Jespersen, "Small-conductance calcium-activated potassium (SK) channels contribute to action potential repolarization in human atria," *Cardiovasc. Res.*, vol. 103, no. 1, pp. 156–167, Jul. 2014.

[8] M. Varela, M. Colman, J. Hancox, and O. Aslanidi, "Atrial Heterogeneity Generates Re-entrant Substrate during Atrial Fibrillation and Anti-arrhythmic Drug Action: Mechanistic Insights from Canine Atrial Models," *PLOS Comput. Biol.*, vol. 12, no. 12, p. e1005245, Dec. 2016.

[9] M. Colman, M. Varela, J. Hancox, H. Zhang, and O. Aslanidi, "Evolution and pharmacological modulation of the arrhythmogenic wave dynamics in canine pulmonary vein model.," *Europace*, vol. 16, no. 3, pp. 416–23, Mar. 2014.

[10] M. Varela, J. Zhao, and O. Aslanidi, "Determination of Atrial Myofibre Orientation Using Structure Tensor Analysis for Biophysical Modelling," in *Lecture Notes in Computer Science*, vol. 7945, pp. 425–432.

[11] P.-C. Chang, I. Turker, J. C. Lopshire, S. Masroor, B.-L. Nguyen, W. Tao, M. Rubart, P.-S. Chen, Z. Chen, and T. Ai, "Heterogeneous Upregulation of Apamin-Sensitive Potassium Currents in Failing Human Ventricles," *J. Am. Heart Assoc.*, vol. 2, no. 1, Jan. 2013.

[12] J. Maylie, C. T. Bond, P. S. Herson, W.-S. Lee, and J. P. Adelman, "Small conductance Ca2+-activated K+ channels and calmodulin.," *J. Physiol.*, vol. 554, no. Pt 2, pp. 255–61, Jan. 2004.

[13] G. K. Moe, W. C. Rheinboldt, and J. . Abildskov, "A computer model of atrial fibrillation," *Am. Heart J.*, vol. 67, no. 2, pp. 200–220, Feb. 1964.

[14] O. Aslanidi and J. Hancox, "Initiation and sustenance of reentry are promoted by two different mechanisms.," *Heart Rhythm*, vol. 12, no. 1, p. e2, Jan. 2015.

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