Modeling Calcium Dynamics in Human Atria

Inma R Cantalapiedra[1], Carlos Lugo[1,2], Angelina Peñaranda[1], Leif Hove-Madsen[3], Blas Echebarria[1]

[1]Departament de Física Aplicada, Universitat Politècnica de Catalunya, BarcelonaTech, Barcelona, Spain
[2]Centro de Astrobiología (CSIC/INTA), Instituto Nacional de Técnica Aeroespacial, Madrid, Spain
[3]Cardiovascular Research Centre CSIC-ICCC, Hospital de Sant Pau, Barcelona, Spain

Abstract

Mathematical models of cardiac electrophysiology are an important tool to investigate the underlying mechanisms responsible of arrhythmias. In particular, an important question is the origin of atrial fibrillation (AF). Often, AF initiation is preceded by action potential duration (APD) alternans, i.e., beat to beat oscillations in the APD, that arise at slower rates in patients with persistent AF than in those without AF or with paroxymal AF. Most of these arrhythmias appear as a consequence of malfunctions in calcium dynamics that produce oscillations in intracellular calcium, inducing subsequent APD alternans through electromechanical coupling. The aim of this work is to present a human atrial mathematical model that gives insight into the presence of calcium alternans. For that the model by Nygren et al was modified in order to reproduce calcium alternans at high pacing rhythms, as has been observed in experiments. The model reproduces the nonlinear dependence of gain and fractional SR Ca release upon SR Ca load. At fast pacing rates it presents alternans, due to slow recovery from inactivation of the RyR. Finally, we compare the results from this new model with other human atrial models well established in the literature.

1. Introduction

Atrial fibrillation (AF) is a highly prevalent disease that constitutes the most common arrhythmia, with a prevalence approaching 20% in patients over 85 years of age. AF can produce structural and/or electrophysiological changes in the atria that often progresses to chronic or persistent atrial fibrillation [1]. To treat it, invasive and non-invasive methods, such as tissue ablation, electrical cardioversion and pharmacological therapy have been applied. Unfortunately, antiarrhythmic drugs have moderate effectivity and often present adverse effects. The complications produced by AF and its contribution to the population morbidity and mortality, makes essential a better understanding of the electrophysiological mechanisms of AF initiation and maintenance. In a recent study Narayan et al. [2] showed that action potential duration (APD) alternans preceded every AF episode, yet was absent when AF was not induced, concluding that alternans may provide an AF substrate. Initiation of alternans occurs at slow rates and can not be explained in terms of action potential restitution curves, being calcium alternans the alternative underlying mechanism.

Calcium alternans has been observed in both experimental and numerical simulation studies. A posible explanation of their generation is based on the alternation of sarcoplasmic reticulum (SR) calcium content. At fast pacing rates the Sarco/Endoplasmic Reticulum Ca-ATPase (SERCA) pump, that loads calcium from the cytosol to the SR, has not enough time to refill the SR. This effect together with a steep relationship between SR calcium release and SR calcium load produces sustained alternans [3,4]. But experiments where alternans are obtained without SR calcium content oscillations, as well as alternans appearing at slower pacing rates, suggest an alternative mechanism, based on refractoriness of release [5], as has also been observed in numerical studies [6–8].

To date, several mathematical models of human atrial myocytes have been proposed [9–11]. They differ greatly in their constituents (number of compartments, presence or absence of t-tubules, etc), and in their dynamical response [12]. In fact, two of the most widely used, the models by Nygren et al. [10] and by Courtemanche et al. [9] do not present calcium alternans. The latter presents action potential alternans, but just in a very narrow range of pacing periods and for a particular geometry (in a ring of tissue) [13]. In this paper we analyze a new human atrial model that produces calcium alternans due to RyR refractorinness [14]. It is based in the model by Nygren et al. [10], where we have modified the number of compartments and the RyR2 dynamics. With this, the model has been shown to present cytosolic calcium alternans without concurrent SR calcium content fluctuations [15]. Furthermore, this model reproduces recent experiments by Shkryl et al. [16] on re-

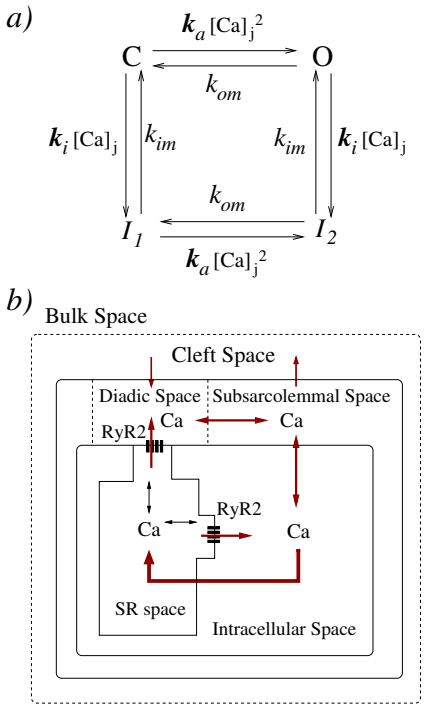

Figure 1. a) Representation of RyR2 gating dynamics. The four markovian states of RyR2 are O (open), I_1 and I_2 (inactivated) and C (closed). Respective rates for transition between states are represented. The recovery time is defined as $1/k_{im}$. b) Different compartments including a distinction among dyadic, subsarcolemmal and intracellular spaces. Release from the SR goes both to the dyadic and intracellular spaces, but in the latter there is no entrance of L-type calcium current.

fractorinness of release [15]. In this paper we present the main characteristics of the model, and compare it to other atrial models in the literature.

2. Materials and methods

In our study we used a human atrial myocyte based on the model described by Nygren et al. [10]. The original model does not reproduce calcium alternans, so we made some changes in order to account for experimental results. The modified model includes three different compartments i) a dyadic (junctional) space with the presence of LCC and RyR2 channels, ii) a subsarcolemmal space where the other transmembrane currents act, and iii) the bulk cytosolic compartment where the calcium concentration transient is caused by diffusion from the subsarcolemma and luminal calcium efflux from the SR through the RyR2 channels. For the RyR2 dynamics we consider a markovian four state model. The SR Ca release includes inactivation/adaptation and SR Ca load dependence of activation and inactivation.

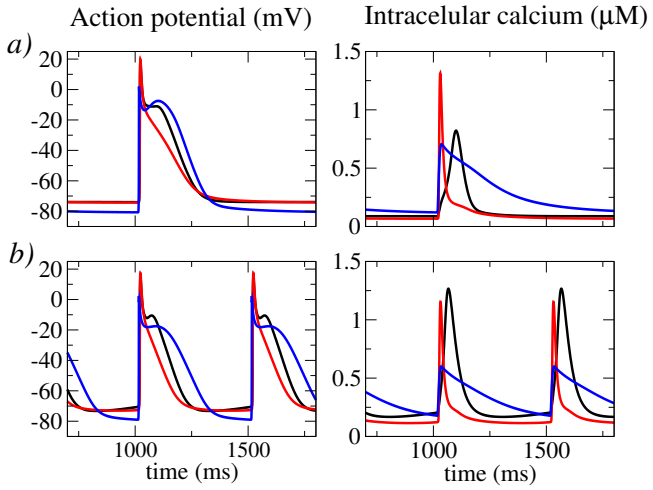

Figure 2. Action potential and calcium transient at several pacing periods a) BCL=1000 and b) BCL=500 ms for our model (black line) and the models by Nygren et al. (red line) and Courtemanche et al. (blue line).

A schematic representation of dynamics of RyR2 channels and cellular compartments is shown in Figure 1.

We have simulated the model for a single cell and in a one-dimensional strand of tissue. We have checked the dependence of action potential duration (APD) and intracellular calcium peak to a change in the strength of the L-type calcium current conductande g_{cal}. We have also calculated dynamic restitution curves for the APD and conduction velocity (CV) in the one-dimensional case, pacing at different basic cycle lengths (BCLs) until steady state was reached, and compared with other human atrial models.

3. Results and comparison with other models

In Figure 2 we show the action potential and cytosolic calcium transient from our model and compare it with the results from the models by Nygren et al. [10] and Courtemanche et al. [9]. At a pacing rate of 1Hz the action potential duration (APD) of the present model is similar to Nygren et al., and slightly shorter than the APD from Courtemanche et al., particularly at faster pacing periods (BCL=500 ms, Figure 2b). Due to the different calcium transient, phase 2 in our model is different from Nygren et al, showing a dome, similar to Cortemanche et al. and experimental APs in human atrial cells [17, 18]. The differences among the models become more apparent looking at the calcium transients (Figure 2). Due to the different RyR2 dynamics, the intracellular calcium peak is broader in our model and occurs at a later time than in Nygren et al. It also increases as one decreases the pacing period,

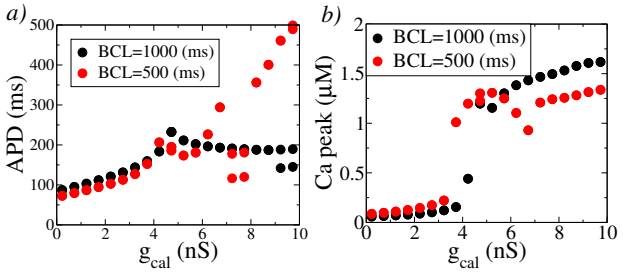

Figure 3. Dependence of the a) APD and b) cytosolic calcium peak on the strength of the L-type calcium current at pacing periods of BCL=1000 ms (black circles) and BCL=500 ms (red circles). In b) it can be seen that depending on the conductance g_{cal} the are two branches, one with low and the other with large release.

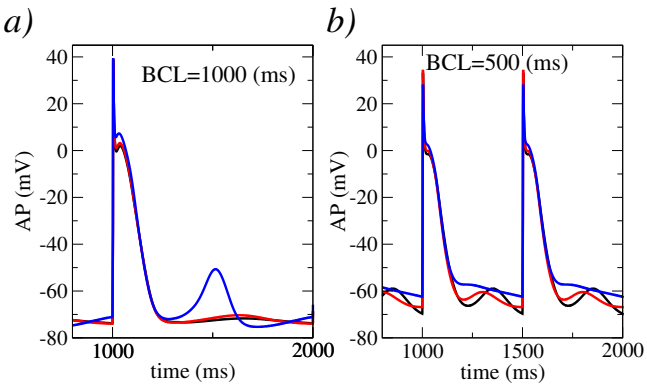

Figure 4. Action potential at basic cycle lengths of a) BCL=1000 ms and b) BCL=500 ms and for several values of the L-type calcium current conductance: g_{cal} = 6.5 nS (black line), g_{cal} = 7 nS (red line) and g_{cal} = 9 nS (blue line).

contrary to what occurs in other models.

To check this latter point we have calculated both the APD and intracellular calcium peak in our model as a function of the L-type calcium current conductance g_{cal} and for two different pacing periods, BCL=1000 ms and BCL=500 ms (see Figure 3). From these plots, it is apparent the existance of two branches, one with small release, at lower values of g_{cal}, the other with large release, at higher values of g_{cal}. This has also a reflection in the APD curve, that presents a discontinuity linked to the jump in the intracellular calcium peak branch. From the figure it can also be observed that the calcium peak decreases with increased pacing period in the lower branch, and the opposite in the higher one. In our simulations in Figure 2 we take the value $g_{cal} = 4.05$ nS, somewhat intermediate between both. A much larger value is not posible to consider because then the AP starts to present delayed afterdepolarizations and the APD becomes very large (Figure 4). For values of g_{cal}

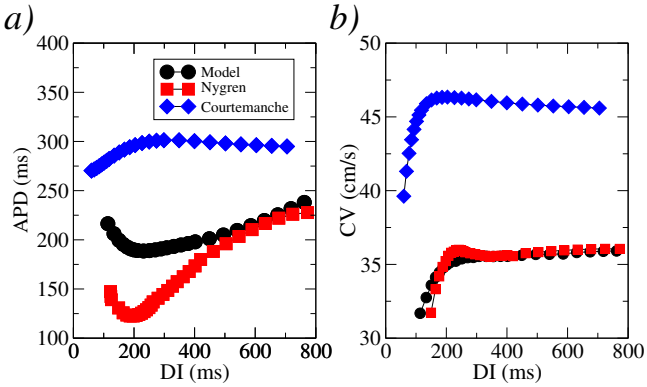

Figure 5. a) APD and b) CV restitution curves as a function of the diastolic interval (DI) for our model (black circles) and the models of Courtemanche et al. (blue diamonds) and Nygren et al. (red squares).

close to the jump in the branches, the model presents alternans at pacing periods smaller than BCL=500 ms.

We have further compared our model to those in Nygren et al. and Courtemancje et al. computing the dynamic APD and CV-restitution curves in a one-dimensional strand of tissue. For the APD, our model presents a restitution curve that is flatter than that in Nygren so, at fast pacing rates, our APDs are larger than in Nygren. The model by Courtemanche et al. presents also a flat curve but with larger APDs. The conduction velocity is similar to Nygren, as one would expect, since the main different between both models lies in the dynamics of calcium. One should notice that the CV calculated in Figure 5 has been done for the same diffusion constant as used in Nygren et al, that gives CVs lower than those measured in human atrial tissue [13].

4. Conclusions

Atrial fibrillation is the most prevalent cardiac arrhythmia, particularly on aged persons. Recent experiments seem to suggest that calcium alternans plays an important role in its origin. Thus, a good understanding of the latter seem of big importance to unveil the mechanisms that give rise to sustained AF. We have analyzed a new model that presents calcium alternans due to refractoriness in release, and compared it with other human atrial models. Since the present model is based in the model by Nygren et al, with modified calcium handling dynamics, it presents similar values of the CV. However, both the form of the AP and its dependence with pacing frequency departs from the behavior observed by Nygren et al., being the main difference the presence of calcium alternans and irregular rhythms at fast pacing rates in our model.

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Address for correspondence:

Inma R. Cantalapiedra

Departament de Física Aplicada, UPC. BarcelonaTech, EPSEB, A. Dr. Marañón, 08028 Barcelona

E-mail: inma@fa.upc.edu