Mechanical Translation of Electrical Abnormalities with a New Electromechanical Model of Human Ventricular Cell

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Abstract

Investigating cardiac electrical abnormalities using computational models of cardiomyocytes is nowadays established. However, less attention has been paid, until recently, on how these abnormalities impact contractility. We here present a novel electromechanical model, developed by introducing a recently published contractile element in our electrical model Bartolucci-Passini-Severi. Our electromechanical model is able to reproduce delayed afterdepolarization, early afterdepolarizations, and contraction abnormalities in terms of aftercontractions triggered by either drug action or specific pacing protocols.

Our findings confirm the experimental evidence that both delayed and early afterdepolarizations can trigger aftercontractions. In addition, we hypothesize that there is not a 1:1 afterdepolarizations-aftercontraction correspondence as aftercontractions appeared only in the presence of specific electrophysiology mechanisms.

Hence the proposed electromechanical model is suitable to assess drug safety and investigate drug arrhythmic risk not only in terms of electrophysiology but also in contractility.

1. Introduction

Cardiac electrical signals and myocyte contraction are strongly related and the complex interplay between cardiac electrophysiology and mechanics makes it challenging to assess their relative and combined relationship. During the last decade, several human cardiomyocyte electrophysiology models have been developed. Still, not much attention was paid to their contractile properties. Some contractile elements have been developed, with different complexity, both for animals [1] and human cardiomyocytes [2], and they are suitable for integration into the classical cardiomyocyte cellular models simulating action potentials (APs) and Ca^{2+} transients.

Recently, some advances have been done also to simulate the electromechanics of human adult cardiomyocytes [3,4] and human-induced pluripotent stem cell cardiomyocytes [5]. Margara et al. [4] coupled the gold standard human ventricular action potential O'Hara-Rudy model (ORd) [6], and their new ToR-ORd model [7] with the contractile element proposed by Land et al. [2] to simulate the active tension. Lyon et al. [3] coupled the ORd model with the MedChem model of sarcomere mechanics [8].

In this study, we want to expand the applicability of our recent Bartolucci-Passini-Severi (BPS) model [9] of the human ventricular AP, by using it as the electrical component for a new electromechanical model as the level of improvement in the electrophysiology department of BPS model necessitates further computational investigations on the contractility of human ventricular cardiomyocytes as well.

We coupled BPS with the Land contraction model [2], which was built on novel measurements of tension in human cardiomyocytes.

Our aim is to investigate electrical abnormalities such as early-afterdepolarization (EADs) and delayed afterdepolarizations (DADs) and their translation into mechanical dysfunction like aftercontractions.

2. Methods

In this work, both BPS and the Land contractile element have been chosen since they are human models validated against experimental human data. First, our new electromechanical model (BPSLand) was calibrated both on active tension (TA) and AP experimental biomarkers. For the calibration, an optimization procedure has been implemented following a hybrid approach including first genetic algorithms, and then a simplex optimization step as in [10].

To investigate the occurrence of afterdepolarizations and aftercontractions, we first applied a protocol designed to trigger delayed afterdepolarizations (DADs), as reported by Li and Rudy [11]: we fast-paced BPSLand for 1500 beats at a short cycle length (CL=275ms) and then triggered one log beat (CL=10,000ms).

To simulate the occurrence of early-afterdepolarization (EADs) in BPSLand, we applied the same protocol used

in [9]. We simulated 0.1 μM dofetilide administration at CL=4,000ms and set the extracellular concentrations as in in the vitro experiments: ($[K^+]_o$ = 5 mM, $[Ca^{2+}]_o$ = 2 mM, $[Na^+]_o$ = 137 mM) [12]. As with the original BPS models, BPSLand produced a remarkable AP duration (APD) prolongation, but no EADs. This confirmed that the BPS electrophysiology has not been affected by the integration of the Land model. Therefore, we extracted the coefficient sets corresponding to models responding to dofetilide with EADs from the experimentally calibrated population of models presented in [9], which used BPS as the baseline. We used such coefficient sets to modulate the BPSLand main currents, pumps, exchangers, and Ca^{2+} fluxes between 20% and 200% of their baseline values, and then we applied the EADs protocol, observing the occurrence of both EADs and aftercontractions.

3. Results

Figure 1 shows the behaviour of the BPSLand model in terms of AP, Ca^{2+} transient in the cytosol and subspace, and the active tension.

The BPSLand model was able to translate the electrical abnormalities, such as DADs and EADs in the aftercontraction mechanical anomaly. By applying the DAD protocol describes in the Methods, BPSLand triggered an unpaced beat followed by several DADs (Fig. 2). An accumulation of Ca^{2+} in the sarcoplasmic reticulum (SR) arises from the fast pacing, which was spontaneously released by the Ca^{2+} flux (J_{rel}) through the RyR SR channels during the diastolic phase of the last long beat. As already described in [9], these releases triggered the anticipated AP and DADs, and now also aftercontractions in BPSLand (Fig. 2).

Like BPS, the baseline BPSLand model did not produce EADs by blocking I_{Kr} or simulating the dofetilide, only showing an extreme APD_{90} prolongation of over 250% (Fig. 3 left). Conversely, we observed EADs in the eight models generated by modulating BPSLand baseline parameters. In Figure 3 we reported an example of membrane potential (top) and active tension (bottom) traces of a model in control (left) and with the dofetilide simulation (middle) producing both EADs and aftercontractions and producing only EADs (right). Nevertheless, in correspondence with EADs, we observed aftercontractions only in six models. We can see this in Figure 3 central and right columns. In both cases, we detected a similar reactivation of the L-type Ca^{2+} current (I_{CaL}), but only in the right column, we observed also spontaneous Ca^{2+} release from SR, which pours enough Ca^{2+} to trigger the aftercontraction into the cytosol.

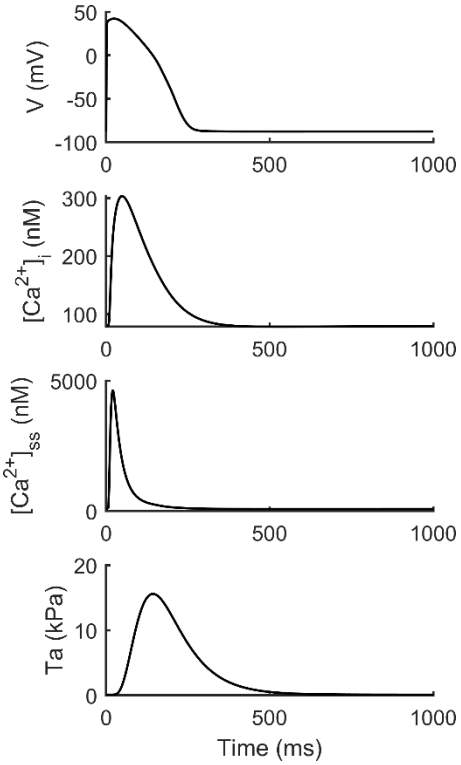

Figure 1. Illustrative traces simulated by BPSLand. Top: action potential. Middle: cytosolic and subspace Ca^{2+} concentration. Bottom: active tension.

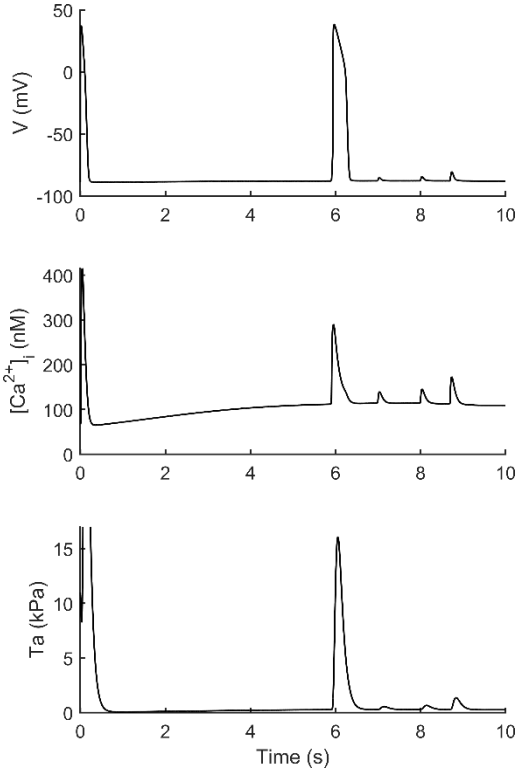

Figure 2. Aftercontractions triggered by an anticipated beat and delayed afterdepolarizations. The action

potential at t=0 is the long beat at BCL = 10,000 ms, following 1,500 beats at BCL = 275 ms. The action potential at t ~6 s is triggered by the spontaneous Ca^{2+} release from the sarcoplasmic reticulum, not by external pacing. Top: membrane potential. Middle: cytosolic Ca^{2+} concentration. Bottom: active tension with aftercontractions.

4. Discussion and Conclusions

It is well established nowadays that cardiac single-cell models can reproduce arrhythmogenic phenomena to study the mechanisms of cardiac arrhythmias in humans and simulate interventions such as drugs. How these electrical abnormalities translate into contractile irregularity is less investigated by models. Nguyen et al. [13] stated that EADs and DADs can trigger aftercontractions. The proposed BPSLand model can help investigate this relationship and simulate both EADs/DADs and the corresponding aftercontractions.

BPSLand was carefully built to preserve the electrophysiology of BPS, so it only produces APD prolongation by dofetilide simulation. In our previous study [9], by using the population of in silico models approach we were able to trigger EADs. Therefore, we extracted from that population the parameter set which produces EADs as a response to dofetilide. Using them with BPSLand, we obtained not only EADs but also aftercontractions. From our results, we hypothesize there is not a 1:1 EAD-aftercontraction correspondence. In fact, we have already observed that EADs can be triggered by two mechanisms: I_{CaL} reactivation or spontaneous Ca^{2+} release from RyRs (Fig. 3). The corresponding aftercontraction appears only in the case of spontaneous release (Fig. 3 red traces).

BPSLand also simulated DADs as a source of aftercontraction, as experimentally reported [14], using a protocol to stress the model.

In conclusion, this new electromechanical model can simulate abnormalities from the electrical point of view but also by translating them into abnormal active tension phenomena, thus expanding the spectrum of application of in silico models from electrophysiology to contractility.

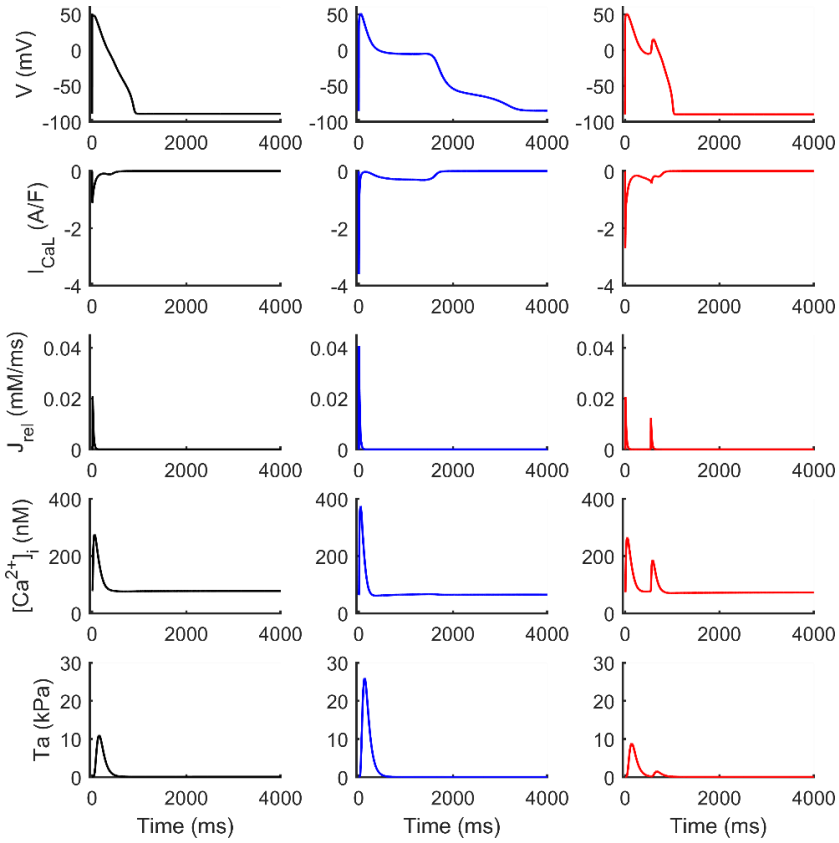

Figure 3. Effects of 0.1 μM dofetilide on the electrophysiology and contractility simulated by BPSLand (left panel) and by two models obtained modulating the maximum conductances/currents with the parameter sets extracted from a population of models (middle and right panels). The middle panel shows an I_{CaL}-driven EAD and the absence of aftercontractions. The right panel shows a spontaneous release from SR-driven EAD and its corresponding aftercontraction.

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