Cardiac dynamics: modeling the Brugada syndrome

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A B S T R A C T

The Brugada syndrome is associated with an abnormal electrocardiogram (ECG), characterized by an elevation of the ST-segment. Since its discovery in 1992, it has gained increasing recognition, and today is believed to be responsible for 4% to 12% of all sudden deaths and around 20% of deaths in patients with structurally normal heart. Recently it has been discovered that it is caused by a mutation in a specific gene (SCN5A), resulting in dysfunction of the sodium channel in the membrane of cardiac cells. However, the link between this channelopathy and the occurrence of arrhythmias or ventricular fibrillation is, as yet, not completely understood. We have constructed a simplified ionic model that reproduces well the action potential observed in the Brugada syndrome. With its help, possible mechanisms for the induction of reentrant waves (spirals) will be discussed.

Keywords: Cardiac dynamics; Brugada syndrome; Ventricular fibrillation.

INTRODUCTION

Cardiac arrhythmias and sudden cardiac death are among the most common causes of death in the industrialized world. Despite decades of research their causes are still poorly understood. For this, theoretical studies of the mechanisms of cardiac arrhythmias have become a very active area of research.

A normal heart pumps blood throughout the body by means of a coordinated contraction. This is initiated by a change in the transmembrane potential of cardiac cells, starting in the sinoatrial node, whose self-excitatory cells act as the pacemakers of the heart, and spreads then along the atria and ventricles. During normal rhythm, thus, the heart beats regularly, and its electrical activity can be observed in an electrocardiogram (ECG).

In some situations, however, failures in propagation can cause the formation of re-entrant waves (also called rotors), creating regions where excitation propagates in closed loops, with a period two or three times faster than normal. This corresponds to monomorphic or polymorphic tachycardia, depending if there is a single or multiple sources. Although very often tachycardia terminates spontaneously, it may degenerate into fibrillation, a life-threatening cardiac disorder, where rotors are created and destroyed continuously, and synchronous excitation is lost. In this situation, the heart does not pump blood, and death occurs in a few minutes, unless a defibrillatory shock is given.

In patients with structurally normal hearts polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) account for 5% to 12% of the total sudden deaths each year. Approximately half of these are attributed to the Brugada syndrome [1]. This is a genetic disease that produces well recognized changes in the electrocardiogram, characterized by a ST-segment elevation terminating in a negative T wave in the right precordial leads. Often associated with this ECG morphology are episodes of rapid polymorphic VT capable of degenerating to VF.

Nowadays, it is known that Brugada syndrome is due to a mutation in one of the genes regulating the sodium channel across the cell membrane [2].

However, the exact mechanism linking this genetic defect to the genesis of reentrant waves is, as yet, not completely understood.

With this aim, we have performed simulations of a simplified model for the propagation of transmembrane potential in cardiac cells. We have chosen the parameters of the model as to fit the action potential, propagation speed, and wavelength of the pulses obtained with more detailed electrophysiological models. In particular, we are able to reproduce human epicardial, endocardial, and M cell action potentials. Modifying the dynamics of sodium channels to mimic Brugada syndrome, we show possible mechanisms of generation of reentrant waves that could lead to VF.

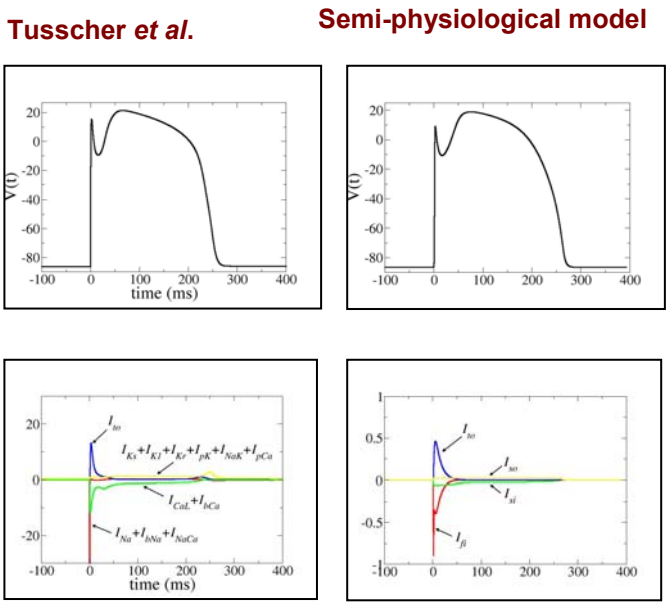


Fig. 1. Comparison of action potential and ionic currents for the simplified model and a detailed ionic model for human ventricular cells given in [3].

MODEL EQUATIONS

Ignoring the discrete character of microscopic cardiac cell structure, a 2D sheet of cardiac cells can be modeled as a continuous system with the following partial differential equation

$$\frac{\partial V}{\partial t} = D\nabla^2 V - I_{ion} / C_m \qquad (1)$$

where V is the potential difference across the cardiac cell membrane, D is a diffusion constant that we take $D=1.2\ x10^{-3}$ cm^2/ms, C_m is the membrane capacitance per unit surface area, with typically takes the value $C_m=1$ μF/cm^2, and I_{ion} is the sum of all transmembrane ionic currents. Thus, the cell membrane is modeled as a capacitor connected in parallel with variable resistances and batteries representing the different ionic currents and pumps.

The ionic current I_{ion} corresponding to each ion is proportional to the difference between

$$I_{ion} = G_x(V - E_x) + \ldots$$

the transmembrane potential and the equilibrium Nerst potential for that ion

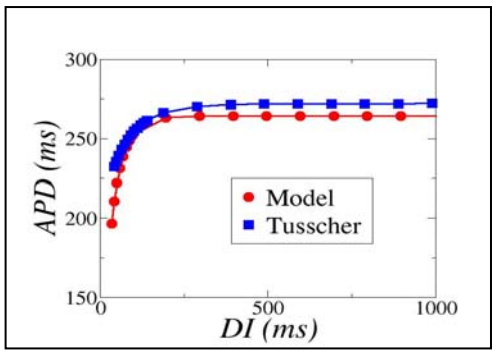
The conductances G_x are not constant, but depend on the state of the gates that regulate the transport of ions between the extra and intracellular medium. Typically, these gates are voltage activated, with characteristic times for opening and closing.

Detailed electrophysiological models [3] include currents and gates for all the possible ions. Following the model proposed in [4] we will rather identify the currents by function into inward and outward ionic currents, these divided again into fast and slow. Thus, we have

$$I_{ion} = I_{fi}(V,v(t)) + I_{to}(V,r(t),v(t)) + I_{si}(V,w(t)) + I_{so}(V)$$

where $v(t)$ and $w(t)$ are the inactivation gates of the fast and slow inward currents, while $r(t)$ is the activation gate of the transient outward current I_{to}, that was not considered in [3].

Fig. 1 shows the comparison of the action potential (form of the $V(t)$ curve during one excitation) and currents in a single cell, obtained with the ten Tusscher model for human ventricular cells [3] and our semi-physiological model [5]. Despite the complexity of detailed electrophysiological models, the simplified model reproduces perfectly the form of the action potential.



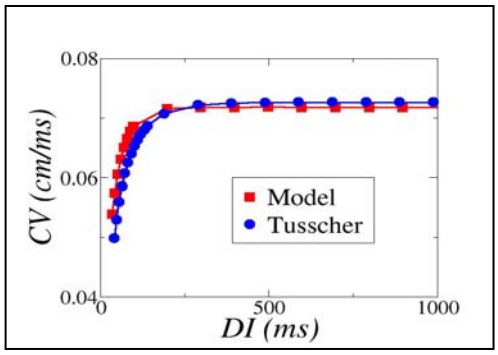


Fig. 2. Action potential duration (APD) and conduction velocity (CV) restitution curve as a function of diastolic interval (DI) for our simplified model and that in ten Tusscher *et al*. [3].

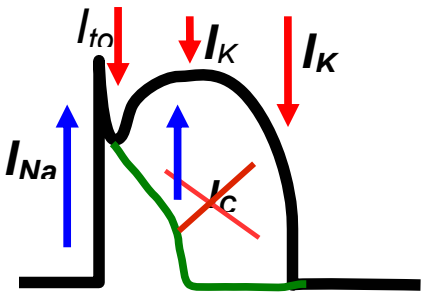


Fig. 3. Mechanism for the loss of dome in a cell with a genetic mutation causing Brugada syndrome. As the gates regulating I_{Na} deactivate faster, the outward current I_{to} produces a larger notch in the action potential. If the transmembrane potential goes below a certain value, the gates regulating the calcium current close, and the system goes back to the equilibrium state without the characteristic dome caused by the influx of calcium.

To check if our model also reproduces correctly the main properties of propagation, we have simulated Eq. (1) in a cable of tissue, and measured both the propagation speed, and the duration of the action potential (APD, time during which the voltage is above a certain threshold, characterizing the duration of the excited state) with respect to the diastolic interval (time elapsed between the end of the previous excitation and the current one). Again, the comparison is good (Fig. 2), so we expect the simplify model to reproduce well wave propagation.

BRUGADA SYNDROME

Brugada syndrome is characterized by a rapid deactivation of the sodium channels, leading to a decrease of the inward current at the initiation of the action potential. In epicardium, where the potassium mediated transient outward current is large, this may result in loss of the characteristic dome of the action potential (Fig. 3), due to inward calcium current. In the presence of heterogeneity in I_{to} distribution, a spatially localized region where the dome is lost may appear. This is a particularly proarrhythmic situation, since the region without dome becomes excitable before the action potential of neighbouring regions has finished, creating the right substrate for reentry and induction of tachycardia.

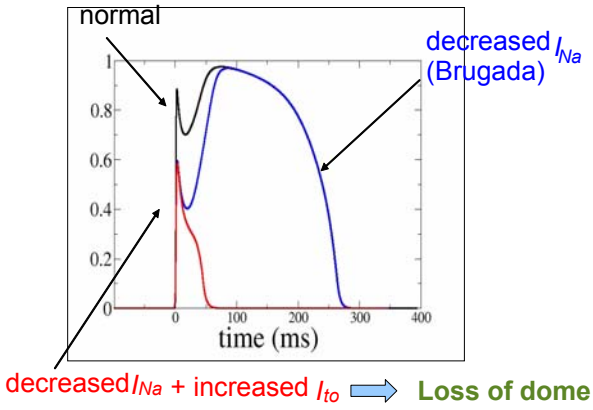


Fig. 4. Action potential obtained with the simplified model for normal epicardium, and epicardium with decreased I_{Na} (mimicking Brugada syndrome), with large and small values of I_{to}.

To check this point, we simulate ventricular endocardial and epicardial action potential with

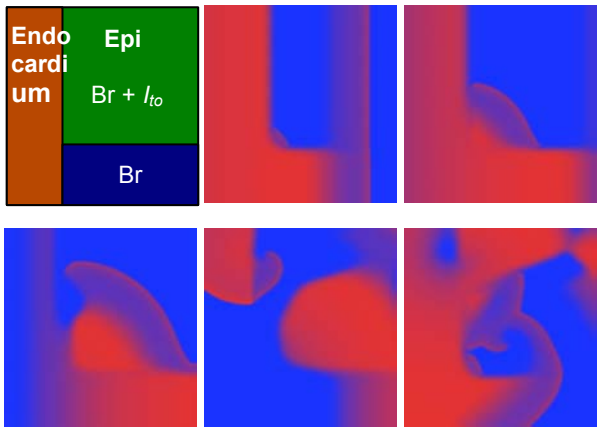


Fig. 5. Intramural conduction. The action potential is generated in the endocardium. In the epicardium there is a region of large I_{to} where the dome is lost, allowing a re-entrant wave to propagate, generating a disordered state.

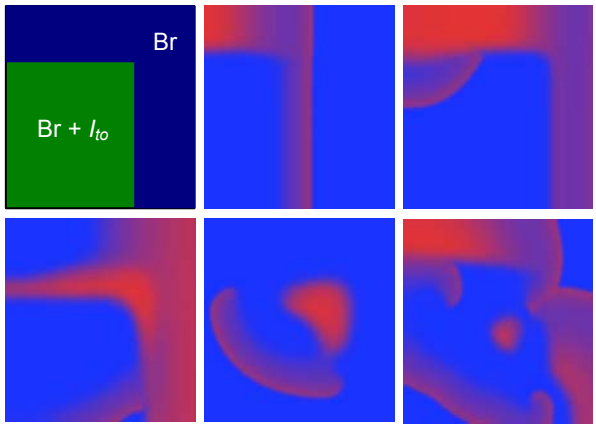


Fig. 6. Propagation within epicardium. The action potential is generated on the left border. In the region with larger I_{to} the dome is lost, resulting in a short action potential, after which the tissue becomes again excitable. It gets again excited by the region with dome, after which a very disordered dynamics entails.

Brugada syndrome by increasing the transient outward current and inactivating quickly the Na current, eventually producing the loss of the dome (Fig. 4).

Then we consider two different geometries: one corresponding to intramural ventricular conduction, with the action potential propagating from the endo- to the epicardium, and two different values of I_{to} in the epicardium (Fig. 5). The other corresponds to propagation along the epicardium, again divided into regions with larger and smaller values of I_{to} (Fig 6). In both situations, reexcitation of the tissue with larger I_{to} results in the formation of reentrant waves, and a very disordered state, similar to fibrillation.

CONCLUSIONS

Cardiac arrhythmias, especially those occurring in the ventricles, are three-dimensional phenomena whereas experimental observations are still largely constrained to surface recordings. Thus the difficulty in identifying the exact nature of the arrhythmic states and the mechanism causing their initiation. In this respect computer simulations of propagation of excitation in the human heart constitute an invaluable tool to get a better inside into these mechanisms.

In this paper we have constructed a semi–physiological model to study the propagation of cardiac stimulus through ventricular tissue. The model reproduces the action potential of different cardiac cells and the restitution curves obtained from a realistic model. It also reproduces the action potential observed in the Brugada syndrome. We have shown that, given the appropriate geometry and heterogeneity of electrophysiological properties, propagation in tissue can generate reentrant waves associated to arrhythmias.

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