SLOW PULSE DUE TO CALCIUM CURRENT INDUCES PHASE-2 REENTRY IN HETEROGENEOUS TISSUE

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Abstract:
Phase-2 reentry is a basic mechanism for the transition to VT and VF in the heart. It is thought to underly many causes of idiopathic ventricular arrhythmias as, for instance, those occurring in Brugada syndrome. Reentry is usually linked to heterogeneity in tissue repolarization. We study some circumstances under which a region of depolarized tissue can reexcite adjacent regions that exhibit shorter action potential duration (APD), eventually inducing reentry. Simulations are performed using a simplified ionic model that reproduces well the ventricular action potential (AP). We analyze first the conditions that lead to very short action potentials (APs). Then, we show that reexcitation takes place via a slow (calcium current induced) pulse that propagates into the region of short APs until it encounters excitable tissue. In two dimensions, this may give rise to reentry with the formation of counter-rotating spiral waves.

1. INTRODUCTION

In patients with structurally normal hearts polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) account for 4% to 12% of the total sudden deaths each year. Most arrhythmias, including VT and VF, are associated with the formation of rotors (spiral or scroll waves), that impose a fast, and often irregular, cardiac rhythm. A possible mechanism for the formation of rotors is based on the existence of dispersion of AP repolarization in a region of cardiac muscle. This provides the substrate for reentry via, for instance, conduction block under rapid pacing, or phase-2 reexcitations . In this latter mechanism, the AP dome is lost at some regions of tissue, but not at others, that can therefore reexcitate the already repolarized tissue. Often, the loss of dome results from the interplay between the fast sodium current INa responsible of the depolarization of the cell (phase 0 of the AP), and the transient outward current Ito, that creates the notch of the action potential (phase 1). If, as a result of the competition of these two currents, the transmembrane voltage remains below the threshold value for activation of the L-type calcium current ICaL, then the dome of the AP is lost. This is particularly relevant in the right ventricle (RV), where Ito has been shown to be stronger. Phase-2 reentry due to regions with loss of dome has been observed in situations resembling ischemia, or under conditions of elevated extracellular calcium with rapid pacing. Another prominent example is Brugada syndrome [1]. Theoretical studies show that an inhomogeneous distribution of Ito can give rise to very disparate values of action potential duration (APD) in neighbouring cells, leading to reexcitation. This takes place via phase-2 reentry, where electrotonic currents from a depolarized region of tissue (during calcium current entrance, or phase-2 of the AP) are enough to provoke the firing of an AP in an adjacent area. However, in these studies INa is never triggered at the exact same point of the fiber where the discontinuity is located [2]. At the discontinuity point, rather, the recovery of the dome due to the activation of the L-type calcium current ICaL produces a gradient of

transmembrane voltage, which results in a front in voltage that propagates slowly into the region of short APs. This proceeds until the front reaches a point where the sodium gates have had enough time to recover, producing an influx of INa and a fast depolarization pulse. In the present paper we use two-dimensional simulations to study the formation of phase-2 reentry in tissue with heterogeneity in electrophysiological properties. We perform the analysis using a simplified cardiac model [2] that allows us to gain further insight into the mechanisms of reexcitation, although the results do not depend on the specific cardiac model considered.

2. MATERIALS AND METHODS

We study propagation of transmembrane potential in a 2D cardiac tissue by means of the standard monodomain propagation model:

$$\frac{\partial V}{\partial t} = \nabla \cdot (D \nabla V) - (I_{ion} + I_{stim}) / C_m , \quad (1)$$

where is the nabla operator, V is the membrane potential, Cm is the membrane capacitance, D = σ /(SCm) is the anisotropic conductivity tensor, σ is the electrical conductivity and S ≡ S/V is the cell surface to volume ratio. Cardiac excitation and propagation are simulated using a simple five-variable model [2]. We decompose the total membrane current into four components, i.e., Iion = Ifi+Isi+Iso+Ito, where the sum contains a fast inward current Ifi (Na+current plus the fast part of the Ca2+ current); a slow inward current, Isi (correspondingly, Ca2+ current); a slow outward time-independent current, Iso; and a fast transient outward current, Ito, these last two corresponding to the sum of several K+ currents in detailed models. Note that it is important to take it into consideration if one is interested in describing the Brugada syndrome. Indeed, the Ito current is responsible for counteracting the effect of the sodium entry into the myocytes. In the Brugada syndrome, due to the weakness of sodium fluxes, the entrance of Ito is often enough to result in a loss of dome of the action potential. The model is simulated first for a single cell, to study the change of action potential duration (APD) as a function of several parameters. Then, we simulate it in a patch of epicardial tissue of dimensions L= 6cm x 6cm, with reduced Na current inactivation time, τ_{h-}, and increased transient outward current conductance, gto, except in a circular central region of radius 0.675 cm where gto takes its normal value [3]. The cable equations are then solved using a simple Euler method with dt = 0.01 ms and dx = 0.015 cm. We use the same values of the parameters as in Ref.[3].

3. RESULTS

We have computed the action potential duration (APD) as a function of both Ito conductance gto and sodium current INa inactivation time τ_{h-}. A fast sodium inactivation time is thought to underly many cases of Brugada syndrome, while an increase in Ito has been related to epicardial dispersion of repolarization leading to VT via phase-2 reentry in isolated canine ventricular myocytes. As both effects alter the equilibrium that results in the phase 0 of the AP, it is to be expected an increased notch and, eventually, the lose of the dome. It can be observed that in both cases the transition from large to short APs is very sharp. This suggest that small changes of the electrophysiological properties can have a big effect, making tiny spatial variations potentially proarrhythmic.

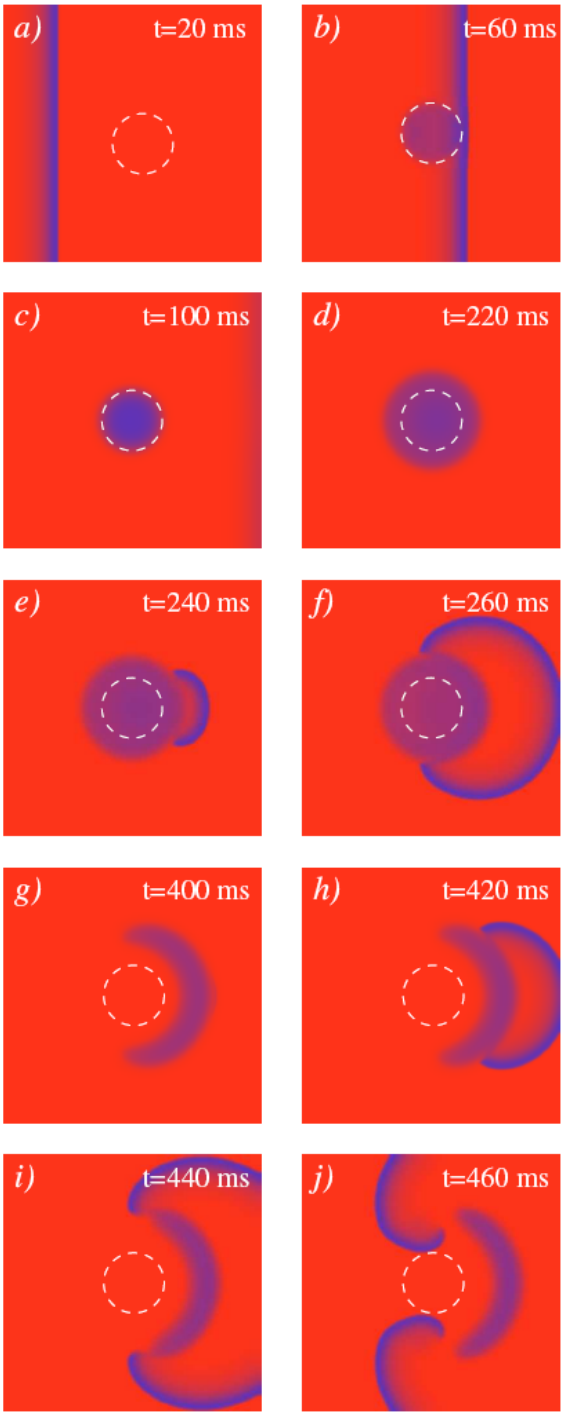

Figure 2. Action potential propagation in a square tissue of size 6 cm x 6 cm with fast sodium inactivation and a heterogeneous g_{to} distribution. The dashed white circle denotes the limits of the central region of lower g_{to}. The tissue is stimulated from the left side. We show frames at different times after stimulation.

We confirm this point with numerical simulations of the cable Eq. (1) in two-dimensional tissue, stimulated from the left hand side, and with the distribution of gto explained previously. As the excitation propagates from left to right in the tissue, the resulting AP is very short everywhere (due to increased gto), except in the central region, where it recovers the dome (see Fig. 2). The size of depolarized tissue then increases beyond the boundaries of this central region (marked by a discontinuous line in Fig. 2), as calcium current during phase-2 activates. This region of depolarized tissue thus continues expanding until it encounters newly recovered tissue, where a (short) AP fires due to the opening of INa.

One interesting point to notice is the appearance of a slow pulse, due to the calcium current (Fig. 2g), that produces fast reexcitations repetitively. This increases greatly the possibility of forming reentrant waves. Typically, the speed of the slow pulse is an order of magnitude lower than that of the sodium induced fast excitations (for details, see the calculation in [3]). This gives a speed of the order of a few centimeters per second. Thus, in the current configuration, the slow pulse persists for a time interval close to a second. Considering that the sodium inactivation gates recover in a time scale of the order of 50-100 ms, it has time to give rise to about ten reexcitations before it disappears.

In the present simulations, in fact, after several reexcitations, two counter rotating reentrant waves are formed (see Fig. 2j).

In the initial stages, the stimulus propagates along the domeless region (short APD), but recovers the dome as it enters the central area with low gto. Depolarization persists in the central zone and a voltage pulse, induced by the calcium current, spreads to the

adjacents regions, until it encounters tissue able to be excitated. Excitation can be produced in the direction of initial stimulus propagation, named as reexcitation, or in the opossite direction, named as reflection.

4. DISCUSSION AND CONCLUSSION

Phase-2 reentry is a basic mechanism for the transition to VT and VF in the heart. In this respect, a good understanding of the relevant ingredients that participate in its appearance may contribute to the development of treatments to prevent it. As discussed in the paper, reexcitation due to phase-2 reentry needs two conditions to be met: first, that a heterogeneous loss of dome is produced in tissue and, second, which the spike-and-dome regions are able to reexcitate the loss-dome areas. The complication with respect to treatment is that, conditions that diminish the probability of losing the dome may also increase the probability of reexcitation. For instance, drugs that increase the strength of ICaL may eventually help recovering the dome, and decrease dispersion of repolarization, but until this occurs, they increase the probability that a reexcitation occurs (see, for instance, Fig. 7 in Ref. [10]). This happens because an increase in gCaL stabilizes the slow calcium pulse, which then is able to reexcitate adjacent tissue.

Thus, drugs that decrease Ito would seem more suitable candidates to avoid dispersion of repolarization while maintaining a low probability of reexcitation, as they do not change much the stability of the slow pulse.

In this paper we have used a simplified five-variable model of the action potential to study the occurrence of reexcitations in a tissue with dispersion of repolarization. We have focused on the case where it appears as a result of a heterogeneous distribution of fast outward current Ito (together with modified sodium recovery kinetics), but similar results would be obtained if this heterogeneity was created by a variation of other suitable electrophysiological parameter, as for instance the fast inward sodium inactivation time. The origin of reexcitation is based on the existence (often transiently) of a slow pulse that propagates into the region of short APs until it reaches excitable tissue. One interesting thing to notice is that the region of APs with dome can be very small, and still give rise to reexcitations. Finally, we would like to emphasize the utility of considering simplified descriptions of the cardiac dynamics that, although they cannot provide complete description of the molecular mechanisms involved in the origin of channelopaties, they provide very valuable tools to study wave dynamics, and the origin of wave instabilities.

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