Effects of Cardiac Sodium Channel Mutations on the Vulnerable Period in Heterogeneous vs Homogeneous Models of Ventricular Wall

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Abstract

In this study we compare the effects of Na^+ channel mutations on vulnerable period (VP) in hetero- versus homogeneous model of ventricular wall. According to several articles, some Na^+ channel mutations and class I antiarrhythmics prolong VP in homogeneous models and increase risk of reentrant arrhythmias. Here more realistic model is used by introducing physiological transmural heterogeneity into a one-dimensional cable of the Luo-Rudy model cells. We propose a generalized formula for VP and describe new phenomena pertaining to VP not reported with the uniform models. Our simulation results show that the homogeneous models cannot adequately reproduce the effects of loss of Na^+ channel functions on VP. Differences in results are significant both qualitatively and quantitatively. The proarrhythmic effect may not be, therefore, due to extended VP.

1. Introduction

According to [1], drugs blocking Na^+ channels (class I antiarrhythmics) increased risk of sudden cardiac death in post-infarction patients. Both experimental [2, 3] and numerical [4, 5, 6, 7] studies followed that trial and postulated that the proarrhythmic effect is due to increased VP (the time window in which a single premature stimulus can initiate unidirectional propagation and sustained reentrant arrhythmia). However, the studies neglected physiological transmural heterogeneity of the ventricular wall. Growing experimental evidence suggests that the electrophysiological heterogeneity is an important property of the heart and has to be taken into account while explaining several phenomena [8]. In particular, action potential duration (APD) at epicardium is significantly shorter than at midmyocardium and endocardium. As a result the repolarization wave does not follow the depolarization wave. Our numerical studies here show that Na^+ channel loss of function can have opposite effects on VP in such heterogeneous model as compared to a homogeneous one.

2. Methods

Fiber model: Action potential (AP) propagation from endocardium to epicardium during normal ventricular excitation is simulated in a one-dimensional fiber of the Luo-Rudy dynamic model cells. The source code for the single cell was downloaded from [9]. The fiber is 1.65cm long (165 cells) and the corresponding partial differential equation is solved using Crank-Nicolson method with space resolution $\Delta x = l_{cell} = 100\mu$m and time resolution $\Delta t = 5\mu$s. Transmural heterogeneities of ion channel densities are introduced to represent the 3 ventricular cell types: endocardial (cells 1 to 60), midmyocardial (M cells, cells 61 to 105), and epicardial (cells 106 to 165). Density of I_{Ks} (slow-delayed rectifier potassium current) is varied by different scaling constants of maximum conductance g_{Ks}. The transient outward potassium current (I_{to}) is introduced in epicardial and M cells (fig. 1a) [10]. Loss of Na^+ channel function associated with ischemia and arrhythmogenic mutants of SCN5A is simulated as in [7] by modifying maximum channel conductance g_{Na}, recovery rate α_j and inactivation rate β_h. Reduced g_{Na} can also simulate steady-state drug-induced Na^+ channel blockade. *Protocols:* To achieve steady state, four conditioning stimuli S1 are applied at basic cycle length $BCL = 800$ms to the first cell at the endocardial end. A premature test stimulus S2 is applied at different locations and variable time $T2$ (relative to the last S1) during the last repolarization. S1 and S2 have width of 3 cells, duration 0.5ms and amplitude $-600\mu\text{A}/\mu\text{F}$. Vulnerable period is calculated as:

$$VP = (T2_{max} + T2_1)/2 - (T2_{min} + T2_0)/2, \quad (1)$$

where $T2_{max}$ and $T2_{min}$ are respectively maximum and minimum times $T2$ that initiate unidirectional block, $T2_1$ - minimum time for bidirectional propagation, $T2_0$ - maximum time for total block. VP uncertainty due to discrete steps of $T2$ is measured as $(T2_{max} - T2_1 + T2_{min} - T2_0)$ and displayed as error bars together with VP. Action potential duration is measured as the time delay between the occurrence of maximum dV_m/dt and 90% repolarization.

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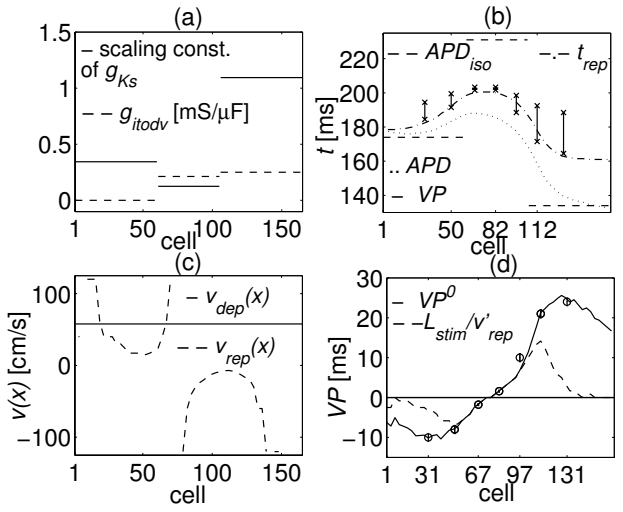

Figure 1. (a) Step changes in maximum conductance g_{itodv} of I_{to} and scaling constant of g_{Ks} simulated physiological transmural heterogeneities of I_{to} and I_{Ks} densities. I_{Ks} density ratio 35:4:11 in epi-/M-/endocardial cells. (b) APD of isolated cells (APD_{iso}) and dispersion of APD in the cable (dotted line). t_{rep} (dash-dot line) - repolarization times along the cable. VP - VP limits along the cable. (c) Local velocities, measured at 3-cell distance, of depolarization, v_{dep}, and repolarization, v_{rep}, waves. (d) 'o' - VP measured in the heterogeneous cable model using paired S1-S2 stimulation. VP^0 - zeroth order approximation of VP according to formula 3. Negative values of v and VP indicate retrograde propagation.

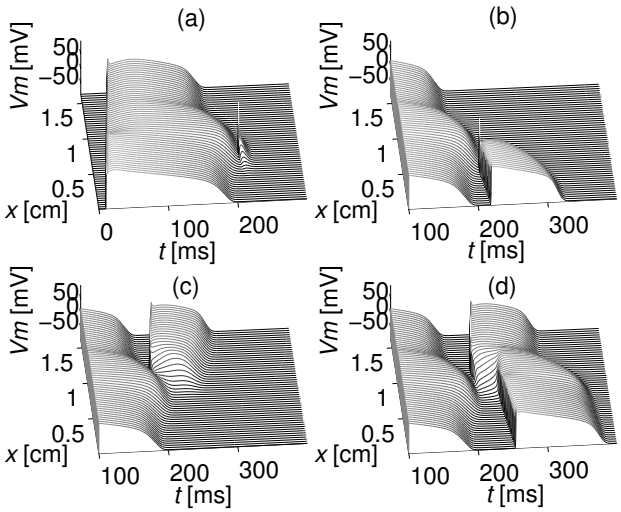

Figure 2. Computed action potentials along the heterogeneous fiber of the LRd model cells ($g_{Na} = 16\text{mS}/\mu\text{F}$). Supra-threshold stimuli are applied at the endocardial end ($x = 0$). The one-dimensional vulnerability is examined by applying test stimuli S2 at different locations in the wake of the last conditioning wave. (a) Bidirectional block ($T2 = 199$ms). (b) Unidirectional propagation in retrograde direction (S2 at cell 50). (c) Unidirectional propagation in antegrade direction (S2 at cell 112). (d) Bidirectional propagation.

3. Results

If APD of all cells in the cable are the same, the depolarization and repolarization waves have exactly the same direction and velocity. However, this is not the case in cardiac ventricles. Action potentials of epicardial cells are shorter than APs at endocardium more than delay between depolarization of endocardium (initiated by Purkinje fibers) and epicardium (fig. 1b and 2a). As a result there are two recovery waves, the first one from epicardium to midmyocardium and a bit delayed the second one from endocardium to midmyocardium. The two waves have opposite directions and changing magnitudes of the local velocities (fig. 1c). The excitation wave propagates with constant local velocity $v_{dep} = 56$cm/s equal to the mean depolarization velocity. We can say that in general v_{rep} is different from v_{dep}, although dependent on it. There are several important qualitative and quantitative differences between uniform and heterogeneous models. In our heterogeneous cable the unidirectional propagation can be either in antegrade or retrograde direction, depending on location of S2 relative to M cells (fig. 2). On the contrary, in a homogeneous cable a premature stimulus can initiate only retrograde propagation (fig. 5d). Magnitude of VP is practically constant over the length of a uniform cable and has zero-order approximation:

$$VP^0_{homo} = L_{stim}/v_{dep}, \tag{2}$$

where L_{stim} is effective test electrode length [11]. In heterogeneous cable the magnitude depends on location of S2. Figure 1d depicts VP measured in the model cable. We introduce here negative value of VP to distinguish between unidirectional propagation in retrograde direction ($VP < 0$) and antegrade direction. To account for the varying VP due to abrupt changes in APD, we generalized formula 2 into:

$$VP^0(x) = \tag{3}$$

$$= \begin{cases} -(t_{rep}(x_l) - t_{rep}(x + L_{stim}/2) - (x_l - (x+ \\ +L_{stim}/2))/v'_{dep}) - L_{stim}/v_{rep}(x) \\ \text{if } 0 \le x < x_l - L_{stim}/2, \\ -L_{stim}/v_{rep}(x) \\ \text{if } x_l - L_{stim}/2 \le x \le x_r + L_{stim}/2, v_{rep} \neq 0, \\ t_{rep}(x_r) - t_{rep}(x - L_{stim}/2) - (x - L_{stim}/2- \\ -x_r)/v'_{dep} - L_{stim}/v_{rep}(x) \\ \text{if } x_r + L_{stim}/2 < x \le 1.65cm, \end{cases}$$

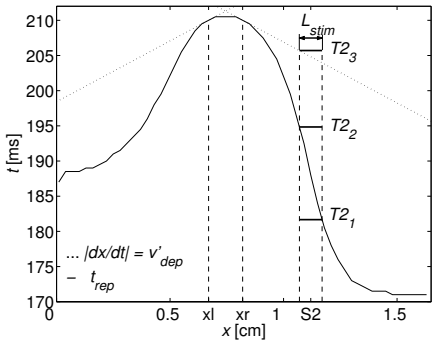

Figure 3. The geometrical interpretation of formula 3. $VP^0 = T2_3 - T2_1$ is the total VP at a given position x. We can distinguish within the total VP local vulnerability $(T2_2 - T2_1) \approx L_{stim}/v_{rep}$ and global vulnerability $(T2_3 - T2_2)$.

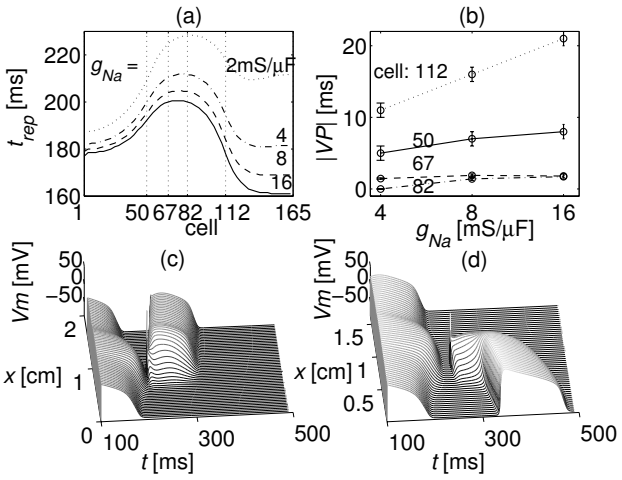

Figure 4. (a) Repolarization times along the cable for different g_{Na}. (b) VP vs g_{Na} at four representative locations. (c) $g_{Na} = 8\text{mS}/\mu\text{F}$, $T2 = 209$ms, cell 82: S2 initiates antegrade propagation. (d) $g_{Na} = 2\text{mS}/\mu\text{F}$, $T2 = 248.39$ms, cell 82: S2 initiates this time retrograde propagation.

where $x_l = 0.64$cm, $x_r = 0.85$cm, v'_{dep} is depolarization wave velocity initiated by S2 and in general $v'_{dep} < v_{dep}$ due to partial recovery of the cells. $L_{stim} = 0.1$cm and $v'_{dep} = 33$cm/s were selected experimentally to fit the measurements of VP. Figure 3 shows the geometrical interpretation of the generalized formula 3. The effects of reduced Na^+ channel density on VP were explored by reducing g_{Na} from control $16\text{mS}/\mu\text{F}$ to 8, 4 and $2\text{mS}/\mu\text{F}$ (fig. 4). Smaller g_{Na} diminishes fast sodium current and membrane excitability and slows down AP propagation (as in homogeneous models). It reduces dispersion of repolarization times between endo- and epicardium and shortens VP, figure 4b. A different repolarization

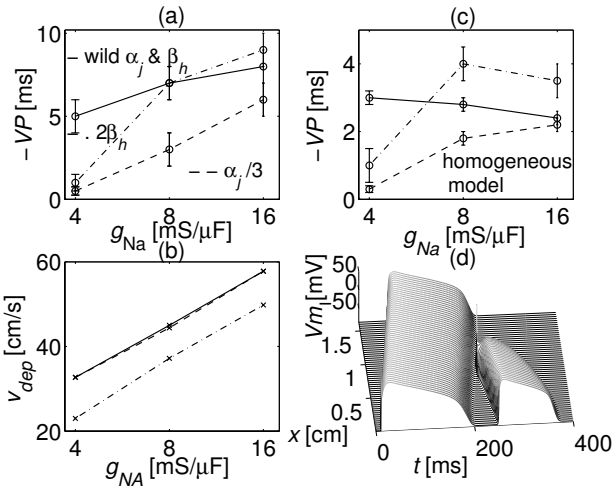

Figure 5. The effects of reduced g_{Na}, reduced recovery rate α_j and increased inactivation rate β_h on: (a) VP in heterogeneous model at cell 50; (b) depolarization wave velocity v_{dep}; (c) VP in homogeneous model. (d) Computed action potentials along the homogeneous fiber and unidirectional propagation initiated by a premature stimulus within VP ($g_{Na} = 4\text{mS}/\mu\text{F}$ and control α_j, β_h).

sequence can result from further AP conduction slowing due to reduction of g_{Na} to $2\text{mS}/\mu\text{F}$, overriding the intrinsic APD differences. Then in some locations the unidirectional propagation switches from antegrade to retrograde direction (fig. 4c and 4d). Such behavior is not possible in homogeneous models. Figure 5 compares the effects of reduced g_{Na}, reduced recovery rate α_j and increased inactivation rate β_h on VP in heterogeneous (fig. 5a) and homogeneous (fig. 5c) models. Changes in g_{Na} have opposite effects in the two models. Accelerated inactivation β_h reduces the peak Na current, thus slowing conduction (fig. 5b) [7]. We have also found a vary narrow (<0.1ms) time window between VP and total block when a premature stimulus initiates a bidirectional propagation (fig. 6) at several locations and parameters of our heterogeneous model. Such behavior was not reported in homogeneous models. Normally bidirectional propagation is initiated directly by a premature stimulus as on panel 6d. However, the 'premature' bidirectional propagation from figure 6b first starts from S2 only in antegrade direction and about 100ms later in retrograde direction by the depolarized cells rather than S2.

4. Discussion and conclusions

From VP point of view, M cells are less likely to initiate unidirectional propagation and reentry as compared to endo- and epicardial cells (fig. 1d). Interestingly, according to [12], when cells are well coupled, endocardial

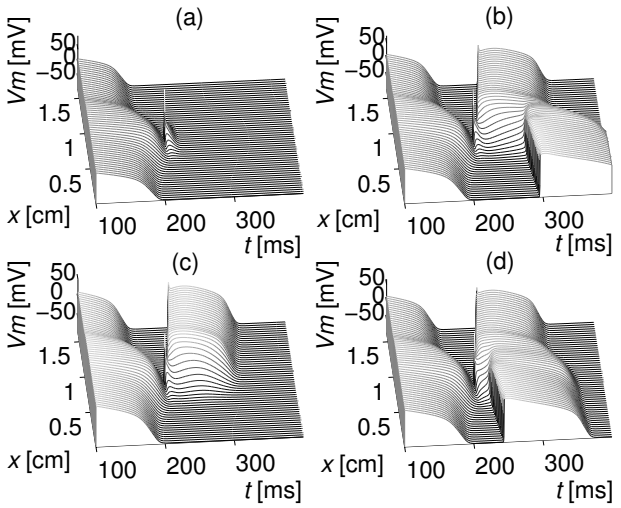

Figure 6. $g_{Na} = 16\text{mS}/\mu\text{F}$, cell 82. (a) Total block at $T2 = 201.5$ms. (b) 'Premature' bidirectional propagation at $T2 = 201.6$ms (also within <201.56ms, 201.60ms>). (c) Antegrade propagation at $T2 = 201.8$ms. (d) Bidirectional propagation at $T2 = 203.4$ms.

cells are more susceptible to EAD development than M cells and experimental findings demonstrated that focal activity in the subendocardium generates the initial beat of polymorphic tachycardias in the LQTS [13] or in ventricular arrhythmias in patients with idiopathic dilated cardiomyopathy [14]. We conclude that homogeneous models used until now cannot adequately reproduce effects of loss of Na^+ channel functions on vulnerable period. The discrepancy in results from homogeneous and transmural models is not only quantitative but also qualitative:

- reduction of sodium channel conductance causes VP shortening in heterogeneous model but VP prolongation in homogeneous models;
- unidirectional propagation induced during VP can be in antegrade or retrograde direction but in uniform model it is always in retrograde direction;
- in the heterogeneous model a narrow time window between VP and total block exists, when a premature stimulus initiates a bidirectional propagation, behavior not reported in homogeneous models.

Proarrhythmic effect of class I antiarrhythmics or Na^+ channel mutations may not be, therefore, due to extended vulnerable period as postulated until now.

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