Modulation of the Regional Dispersion of Repolarization by the Action of Class III Antiarrhythmic Drug Dofetilide

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Abstract

It is well known that short-long (S-L) sequences frequently precede the onset of malignant ventricular arrhythmias. Experimental studies have shown that a single long coupled extra-beat (L) after a previous basic cycle length resulted in a critical increase of the dispersion of repolarization pattern that promoted re-entrant excitation. However, in normal intact heart little differences in repolarization among different myocardial layers have been observed after abrupt slowing of heart rate. We used the Luo and Rudy model (LRd00) of AP and the model of IKr blockade by the action of dofetilide previously developed by our group to study the effect of dofetilide (a class III antiarrhythmic drug) on the modulation of APD dispersion in a strand of ventricular tissue. Our results show that dofetilide increases dramatically the APD of the strand and that the effect of dofetilide on the modulation of dispersion is complex, indicating that the highest dispersion could appear before the highest effect of the drug is reached.

1. Introduction

Different forms (congenital and acquired) of the long QT syndrome (LQTS) are commonly associated with the occurrence of the malignant ventricular arrhythmia called torsades de pointes [1,2]. LQTS is a syndrome characterized by short-long sequences that are associated with a larger dispersion of repolarization in the ventricles [1,3]. There are different studies that indicate the key importance of spatial dispersion of repolarization in the arrhythmogenic mechanism of LQTS [2]. In experimental studies using LQT3 models based on anthopleurin-A, a single long coupled extra-beat (L) of preceding basic cycle length (BCL) resulted in a critical increase of the dispersion of repolarization pattern [1].

In different species (including human) ventricular cells present several electrophysiological and pharmacological differences between epicardium, endocardium and a group of cells situated between the deep subepicardial to midmyocardial layers (M cells) [3,4].

The higher contribution of I_{Kr} (rapid component of the delayed rectifier potassium current) to repolarization in M-cells compared with endocardial and epicardial cells explains the greater prolongation of APD by decreasing the stimulation frequency and by class III antiarrhythmic drugs, in this kind of cells.

In vitro experiments have shown that after an abrupt lengthening of BCL, the action potential durations (APDs) in M cells reached a new steady state faster than epicardial or endocardial cells, provoking higher dispersion of repolarization. These properties suggest that M-cells play an important role in the dispersion of repolarization in ventricular cells. However, in normal intact heart little differences in repolarization among different myocardial layers has been observed after abrupt slowing of heart rate [4,5].

It has been suggested that the strong intercellular coupling reduces the dispersion in repolarization time and, thereby, the heterogeneity of APD in normal hearts [6]. However, different studies show that more marked dispersion should appear in pathological conditions, in which the cells are partially uncoupled, [7,8] such as myocardial infarction or ischemia, and under the effect of class III drugs, even in normal coupled conditions such as those in intact heart [9].

Dofetilide is a class III antiarrhythmic drug commonly used to induce prolongation of APD [10,11]. Dofetilide is a specific and potent blocker of I_{Kr} with an IC_{50} in the nanomolar range (3.9-31 nM in ventricular myocytes) [10].

The main objective of this work has been to study the influence of dofetilide on the modulation of the regional dispersion of repolarization by the application of a long coupled stimulus after a series of regular rhythm at BCL.

2. Methods

The one-dimensional heterogeneous fiber used in this study is composed of 600 ventricular transversally

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coupled cells. The model comprises an endocardial region (cells 0 to 359), a M–cell region (cells 360 to 539) and an epicardial region (cells 540 to 599), and represents a transmural width of 1.3 cm. The coupling conductance between cells is homogeneous (7.6 μS) and results in a propagation velocity of 0.3 m/s. We used the Luo and Rudy model (LRd00) for the three different cell types: endocardial, M-cells and epicardial, setting a different I_{Ks}:I_{Kr} ratio for each one 15:1, 7:1, and 23:1, respectively.

The stimulation pulses (2 ms in duration and 20% greater than the diastolic threshold in amplitude) were applied to cell 0 with a short basic cycle length (BCL) of 300 ms until the steady-state was obtained. After the last pulse at the short BCL, a single long coupled extra-pulse with coupling intervals of 400, 600 and 2000 ms was applied. The APD_{90} was calculated at 90% of repolarization. In order to discard the border effect, we did not consider data obtained from the first and last 49 cells.

The effect of dofetilide on I_{Kr} current was modeled by our group in a previous work. We used the "guarded receptor hypothesis" and assumed that the drug binds to the channel only in both the open and the inactivated states and that the drug is trapped when the channel closes. We suggested a new formulation of the current IKrb that takes into account the fraction of channels blocked by the drug (b), which depends on the concentration of dofetilide ([Drug]), expressed by the following equations:

$$I_{Krb} = (1-b) G_{Kr\max} X_r R (V - E_{Kr})$$

$$\frac{db}{dt} = \{X_r R + (1-R)\}\{k[Drug](1-b) - rb\}$$

where V is the membrane potential, E_{Kr} is the reversal potential, G_{Krmax} is the maximum conductance of I_{Kr}, X_r is the activation gate, R is the time-independent inactivation gate, k is the association rate constant (k=0.4137 $\mu M^{-1}s^{-1}$) and r is the dissociation rate constant (r=0.0036s^{-1}). For more details of the model see reference.

3. Results

Figure 1 shows the APD_{90} distribution along the heterogeneous fiber and the APs of the long coupled extra-pulse for three specific cells, each one belonging to a different cell type, and for four different coupling intervals: (a) 300 ms (without long coupling), (b) 400 ms, (c) 600 ms, and (d) 2000ms.

Our results show that, before the application of dofetilide, for the extra-pulse at 300ms, the M-Endo dispersion (difference between the maximum and the minimum APD between M and Endo zones) and the M-Epi dispersion (difference between the maximum and the minimum APD between M and Epi zones) are equal to 21 and 19 ms respectively (a). The application of a long coupled stimulus with coupling intervals of 400 ms (b), 600 ms (c) and 2000 ms (d), induces a general increment of APD_{90} but a negligible change in M-Endo dispersion and M-Epi dispersion. For a long coupling interval of 2000 ms the dispersion increases to 22.5 ms for the M-Endo zone and to 20.4 ms for the M-Epi zone.

However, after the application of dofetilide, we observed a complex modulation of M-Endo and M-Epi dispersion that depends on the delay (D) between the application of the drug and the instant in which the abrupt change of coupling interval is introduced (extra long pulse).

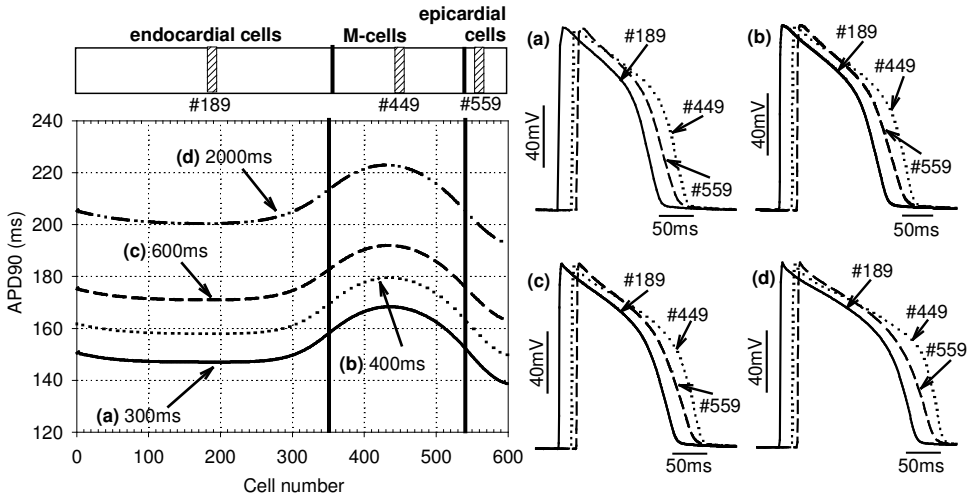

Figure 1. Action potentials and APD90 distribution for a long extra-beat at (a) 300, (b) 400, (c) 600, and (d) 2000ms.

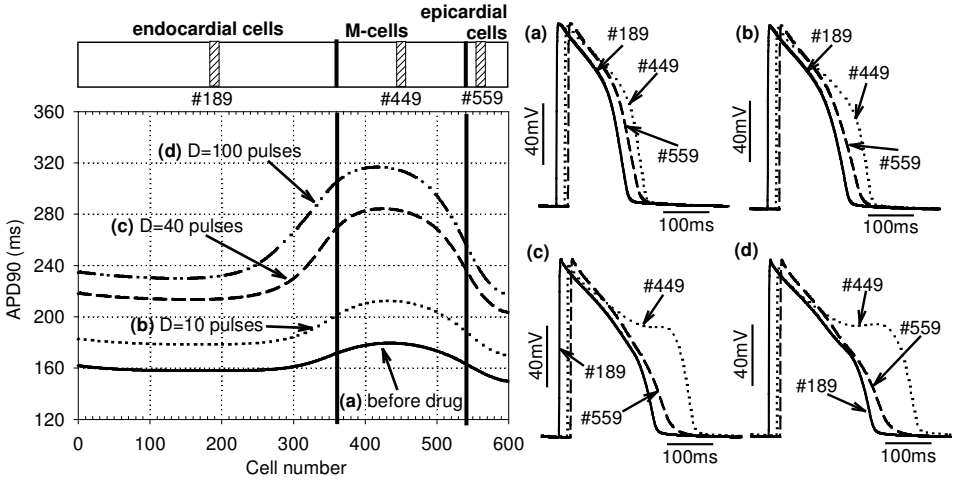

Figure 2. Action potentials and APD90 distribution for an extra-pulse at 400 ms applied: before the introduction of dofetilide (a), and with a delay of 10 pulses (b), 40 pulses (c) and 100 pulses after the application of 1 μM of dofetilide.

Figure 2 shows the effect of applying an extra-pulse with a long coupling of 400 ms, before the application of dofetilide (1μM) (a), and after the introduction of the drug, for different delays (D) between the application of the drug and the instant in which the extra-pulse is introduced: (b) 10 pulses, (c) 40 pulses, and (d) 100 pulses at BCL. After 100 pulses, the effect of drug reached its steady-state. It is possible to observe that the extra-beat at 400 ms induces a monotonic increment of M-Endo and M-Epi dispersion with D from 22 to 87 ms and from 19 to 70 ms, respectively.

A long coupled extra-beat at 600 ms (see figure 3) also induces a monotonic increment of M-Epi dispersion with D (from 19 to 114 ms) but the evolution of M-endo dispersion with D starts at 21 ms, reaches a maximum of 79 ms and decreases to 11 ms (for D= 100 pulses).

For a long coupled extra-beat at 2000 ms, the M-Epi dispersion also increases with D to 120 ms (for D=100 pulses), but M-Endo dispersion becomes negative (endocardial cells have higher APD than M cells).

4. Discussion and conclusions

As expected, dofetilide increases the APD of the cells in the strand with time after its application until the steady-state of drug binding is reached. For all D values, the higher the coupling interval of the extra-beat, the longer the APD of the cells in the strand. However, the effect of dofetilide on the modulation of dispersion is

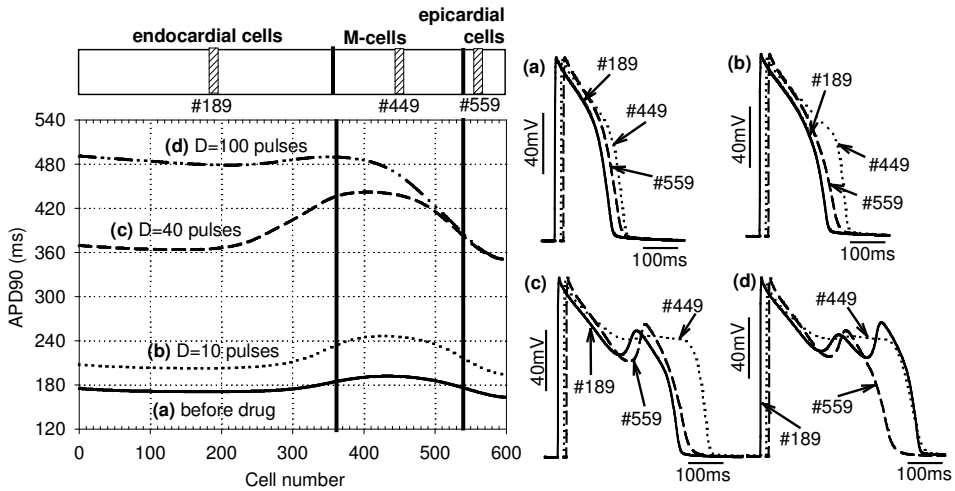

Figure 3. Action potentials and APD90 distribution for an extra-pulse at 600 ms applied: before the introduction of dofetilide (a), and with a delay of 10 pulses (b), 40 pulses (c) and 100 pulses after the application of 1 μM of dofetilide.

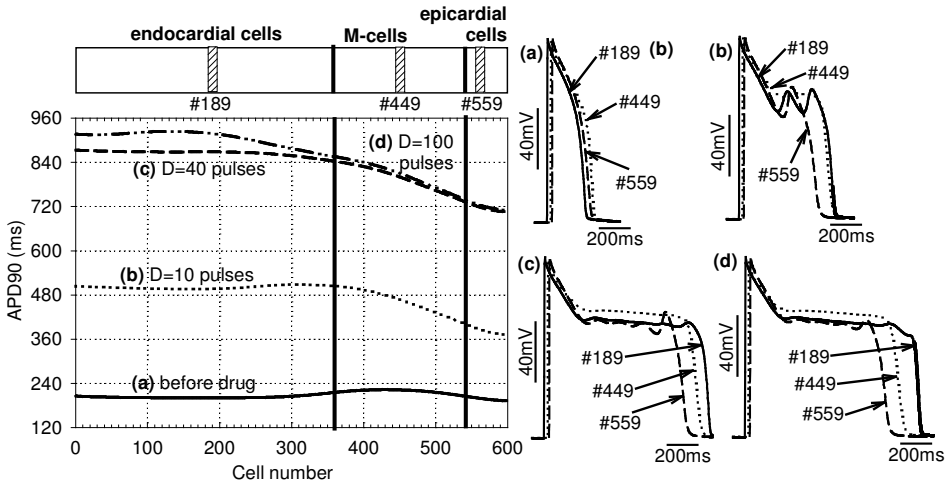

Figure 4. Action potentials and APD90 distribution for an extra-pulse at 2000 ms applied: before the introduction of dofetilide (a) and with a delay of 10 pulses (b), 40 pulses (c) and 100 pulses after the application of 1 μM of dofetilide.

complex, indicating that the highest dispersion could appear before the highest effect of the drug is reached.

Acknowledgements

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