Effects of the Antiarrhythmic Drug Dofetilide on Regional Heterogeneity of Action Potential Duration: A Computer Modelling Study

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Abstract

Different experimental studies have shown that ventricular cells present several differences between epicardium, endocardium and M-cells. M-cells have longer APDs and higher sensitivity to agents with class III actions and they could contribute to APD heterogeneity in the ventriculum. However, in-vivo studies have observed that the strong cellular coupling reduces the APD dispersion in intact heart. We used the Luo and Rudy model (LRd00) of AP and the model of IKr blockade by the action of dofetilide developed previously by our group to study the effect of dofetilide (a class III antiarrhythmic drug) on the APD dispersion in a strand of ventricular tissue. Our results show that dofetilide increases dramatically the APD dispersion and may modify the transmural gradient of APD even in normal coupling conditions such as those in intact heart. Higher dispersion and, a more complex behaviour, such as 2:1 block, could appear when the coupling decreases.

1. Introduction

The regional heterogeneity in action potential duration (APD) within the ventricular myocardium seems to be related to the origin of different cardiac arrhythmias associated with abnormal repolarization such as long-QT syndrome (LQTS) [1,2].

In some 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) [1,3].

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 in this kind of cells by class III antiarrhythmic drugs.

Different experimental studies using isolated cells have shown that M cells display longer APDs and higher sensitivity to agents with class III actions than cells from epicardium or endocardium [4-6]. These studies also observed that the increment of APD when the frequency decreased is steeper in M-cells than in epicardial or endocardial cells [4]. These properties suggest that M-cells play an important role in the repolarization heterogeneity in ventricular cells.

On the other hand, in the intact heart there are no significant differences in repolarization between the different ventricular cell layers, indicating that there is little heterogeneity in APD distribution across the free wall [7-9]. It has been suggested that the strong intercellular coupling reduces the dispersion in repolarization time and, thereby, the heterogeneity of APD in normal hearts [9]. However, different studies show that more marked heterogeneity should appear in pathological conditions, in which the cells are partially uncoupled, [10,11] such as myocardial infarction or ischemia.

Therefore, controversy still exists about the response in APD heterogeneity across ventricular wall to the action of class III drugs in both normal coupling and in the partially uncoupling observed in pathological situations.

Dofetilide is a class III antiarrhythmic drug commonly used to induce prolongation of APD [6]. 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) [9-11].

The aim of this work is to study the effect of Dofetilide (a class III antiarrhythmic drug) on APD dispersion in a strand of ventricular tissue both with normal coupling and under strong uncoupling.

2. Methods

The one-dimensional heterogeneous fiber used in this study is composed of 190 ventricular cells. The fiber models an endocardial region (cells 0 to 79), a M –cell region (cells 80 to 109) and an epicardial region (cells 110 to 189). The coupling conductance between cells is homogeneous. Values of intercellular resistance R_j of

$3\Omega cm^2$ (normal coupling) and of $30\Omega cm^2$ (strong uncoupling) are used in this study. 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 (1 ms in duration and twice the diastolic threshold in amplitude) were applied to cell 0 with two basic cycle lengths (BCL) of 300 and 1000 ms until the steady-state was obtained. Then APD_{90} of the last AP was calculated at 90% of repolarization. In control, a train of 20 pulses was enough to get the steady-state. However, under drug conditions reaching drug binding steady-state requires more pulses. In order to discard the border effect, we discard 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 I_{Krb} that takes into account the fraction of channels blocked by the drug (b), which depends on the concentrations of dofetilide ([D]), expressed by the following equations:

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

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

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 ($k=0.4137\ mM^{-1}s^{-1}$) 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 three specific cells each one belonging to a different cells type (right part of the figure), in two different conditions: (a) before the application of dofetilide, we will call "control" to this condition, and (b) when the steady-state in the drug-binding was reached after the application of dofetilide (1 mM).

Our results show that in a well coupled strand ($R_j=3\Omega cm^2$) and using a BCL of 300 ms, in control conditions (a) the M cell zone presents a maximum APD_{90} of 160 ms, only 11 ms and 24 ms longer than the duration of the shortest AP of the endocardial (149 ms) and epicardial zones (136 ms), respectively. The application of dofetilide (1mM) (b) increases slightly the APD dispersion (difference between the maximum and the minimum APD of the fiber) from 24 ms to 54 ms, being the maximum APD also recorded in the M zone.

In Figure 2, the effect of increasing the BCL to 1000 ms is shown. In normal conditions (a) AP along the strand becomes longer than that for BCL=300ms, and the maximum APD90 increases to 213 ms (observed in the M-cell zone) while the shortest AP presents an APD_{90} of 181 ms (in the epicardial zone).

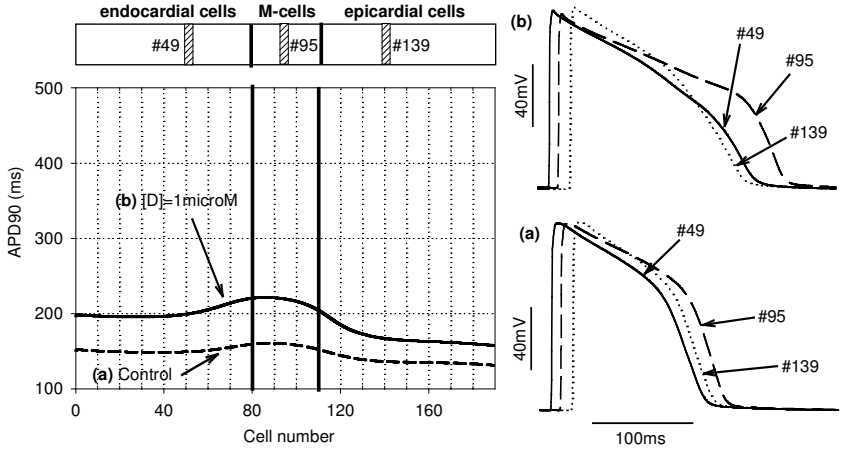

Figure 1. Action potentials and APD_{90} distribution in a well coupled ($R_j=3\Omega cm^2$) heterogeneous fiber for a BCL=300 ms, in two situations: (a) before (control) and (b) after the application of dofetilide (1μM).

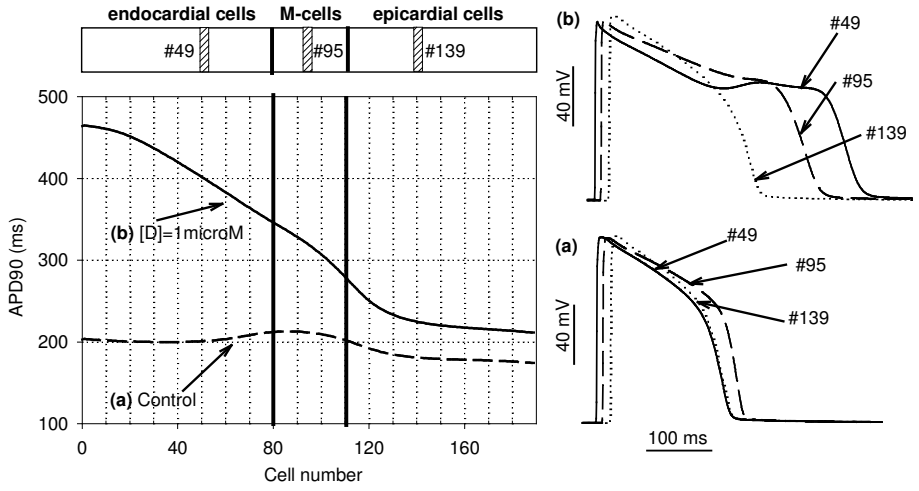

Figure 2. Action potentials and APD_{90} distribution in a well coupled (R_j= 3Ωcm^2) heterogeneous fiber for a BCL=1000 ms, in two situations: (a) before (control) and (b) after the application of dofetilide (1μM).

Thereby, under normal conditions, the APD dispersion increases slightly with the BCL (from 24 to 32 ms). However, for a BCL of 1000 ms the effect of dofetilide is very different compared with that observed for BCL=300ms. For BCL=1000 ms, dofetilide induces early after-depolarizations in part of the tissue, see figure 2(b), and increases dramatically the APD dispersion to 175 ms, being the endocardial cells those that present the higher APD.

The effect of decreasing the intercellular coupling for a BCL=1000 ms is shown in figure 3. Under strong uncoupling (Rj= 30Ωcm^2), in control conditions (a) the observed APD dispersion (65 ms) approximately doubles that obtained under normal coupling (32 ms). A similar behavior was observed when a BCL=300 ms was used (not shown).

Even more, the effect of dofetilide under uncoupling conditions depends strongly on BCL. For long BCLs (1000 ms) the APD_{90} presents a steeper distribution along the fiber and APD dispersion increases to 392 ms.

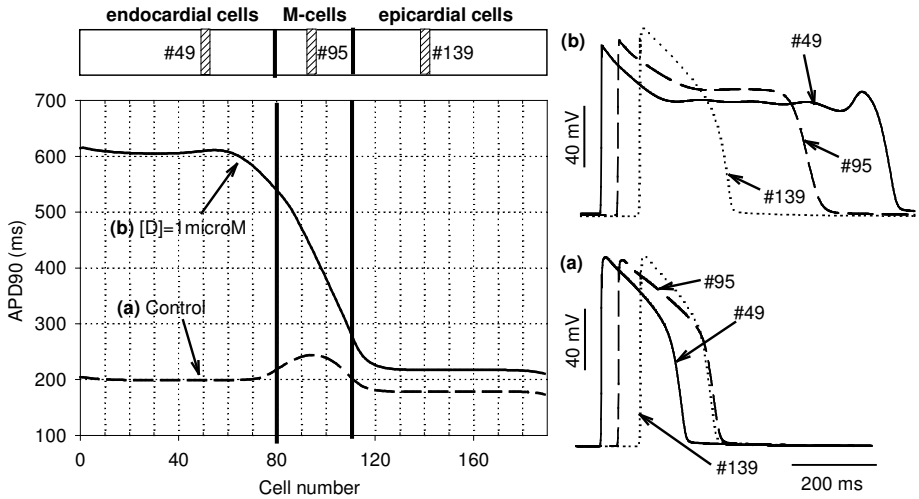

Figure 3. Action potentials and APD_{90} distribution in strong uncoupled (R_j= 30Ωcm^2) heterogeneous fiber for a BCL=1000 ms, in two situations: (a) before (control) and (b) after the application of dofetilide (1μM).

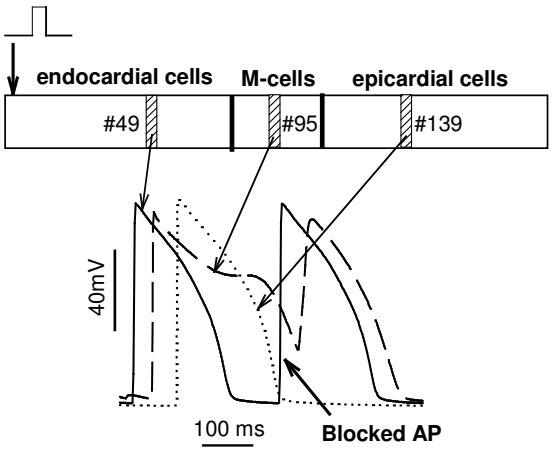

Figure 4. Action potentials in a strong uncoupled (R_j= 30Ωcm^2) heterogeneous fiber for a BCL=300 ms after the application of dofetilide (1μM).

But, for BCL=300 ms (see figure 4) the APD of M cells was prolonged more than 300 ms provoking a 2:1 block.

4. Discussion and conclusions

The main conclusion of our study is that the action of the antiarrhythmic drug dofetilide in combination with electrotonic interactions between cells increases dramatically the APD dispersion and may modify the transmural gradient of APD even in normal coupling conditions such as those present in intact heart. Higher dispersion and, a more complex behaviour, such as 2:1 block, could appear when the cellular coupling decreases.

Acknowledgements

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References

[1] Shimizu W, Antzelevitch C. Celular basis for the ECG features of the LQT1 form of the Long-QT syndrome. Effects of the β-adrenergic agonist and antagonists and sodium channel blockers on transmural dispersion of repolarization and Torsade de Pointes. Circulation. 1998;98:2314-2322.

[2] Vos MA, Gorenek B, Verduyn SC, Van der Hulst FF, Leunissen JD, Dohmen L, Wellens HJ. Observations on the onset of Torsade de Pointes arrhythmias in the acquired long QT syndrome. Cardiovascular Research. 2000;48:421-429.

[3] Restivo M, Caref EB, Kozhevnikov DO, El-Sherif N. Spatial dispersion of repolarization is a key factor in the arrhythmogenicity of Long QT syndrome. J Cardiovasc Electrophysiol. 2004;15:323-331.

[4] Liu D, Antzelevitch C. Characteristics of the delayed rectifier current (I_{Kr} and I_{Ks}) in canine ventricular epicardial, midmyocardial, and endocardial myocytes. Circulation Research. 1995;76:351-365.

[5] Wolk R, Cobbe SM, Hicks MN, Kane KA. Functional, structural, and dynamic basis of electrical heterogeneity in healthy and diseased cardiac muscle: implications for arrhythmogenesis and anti-arrhythmic drug therapy. Pharmacology and Therapeutics. 1999;84:207-231.

[6] Fenichel RR, Malik M, Antzelevitch C, Sanguinetti M, Roden DM, Priori SG, Ruskin JN, Lipicky RJ, Cantinena LR. Drug-induced Torsades de Pointes and implications for drug development. J Cardiovasc Electrophysiol; 2004;15:323-331.

[7] Anyukhovsky EP, Sosunov EA, Rosen MR. Regional differences in electrophysiological mproperties of epicardium, midmyocardium and endocardium. Circulation. 1996; 94:1981-1988.

[8] Bauer A, Becker R, Freigang KD, Senges JC, Voss F, Hansen A, Müller M, Lang HJ, Gerlach U, Busch A, Kraft P, Kübler W, Schöls W. rate- and site-dependent effects of propafenone, dofetilide, and the new I_{Ks} blocking agent chromanol 293b on individual muscle layers of the intact canine heart. Circulation. 1999;100:2184-2190.

[9] Conrath CE, Wilders R, Coronel R, de Bakker JMT, Taggart P, de Groot Jr, Opthof T. Intercellular coupling through gap junctions masks M cells in the human heart. Cardiovascular Research. 2004; 62:407-414.

[10] Viswanathan PC, Shaw RM, Rudy Y. Effects of I_{Kr} and I_{Ks} heterogeneity on action potential duration and its rate dependence. A simulation study. Circulation. 1999; 99:2466-2474.

[11] Viswanathan PC, Rudy Y. Cellular arrhythmogenic effects of congenital and acquired Long-QT syndrome in the heterogeneous myocardium. Circulation. 2000; 101: 1192-1198.

[12] Lu HR, Vlaminckx E, Van Ammel K, De Clerck F. Drug-induced long QT in isolated rabbit Purkinje fibers: importante of action potential duration, triangulation and early afterdepolarizations. European J of Pharmacology. 2002; 452: 183-192.

[13] Faber MG, Rudy Y. Action potential and contractitility changes in $[Na^+]_i$ overloaded cardiac myocytes: a simulation study. Biophys. J. 2000;78:2392-2404.

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