Optimization of Pharmacotherapy for Familial Atrial Fibrillation in a Numerical Model of Human Atrial Electrophysiology

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Abstract

Pharmacological therapy of atrial fibrillation (AF) is still a major clinical challenge. Particularly AF of early onset has a significant familiar component and was associated with various gene mutations. In this study, we designed and optimized antiarrhythmic agents for atrial substrates affected by human ether-à-go-go-related gene mutations L532P and N588K. A virtual multichannel blocker was designed aiming at a restoration of the wild-type (WT) action potential (AP) on the single cell and tissue level. Furthermore, the amiodarone and dronedarone concentrations yielding the smallest difference between WT and mutated APs were identified. The WT AP at a basic cycle length (BCL) of 1000 ms could be restored by significant block of I_{Kr} and I_{Kur} ($\geq 39\%$) and less pronounced block of I_{Ks}, $I_{Ca,L}$, $I_{b,Na}$, and $I_{b,Ca}$ ($\leq 17\%$) for both mutations. Effective dronedarone concentrations of 88 nM for L532P and 40 nM for N588K yielded matches almost as good while amiodarone could not sufficiently restore the WT AP. APD_{90} restitution was effectively restored by the tuned N588K agent whereas differences of up to 34 ms were observed for low BCLs using the tuned L532P agent. Our results provide insight into the pharmacodynamic response of mutated myocytes and may aid in the optimization of patient group-specific therapeutic approaches.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in humans and associated with severe complications such as stroke [1]. In the past years, various gene mutations have been linked to AF ("familial AF") [2]. People carrying these mutations are more susceptible to AF than others. Despite a multitude of available antiarrhythmic agents, pharmacological AF therapy is still a major clinical challenge. Amiodarone is a well-known class III drug with proven clinical efficacy [1]. Dronedarone is a derivative and was designed to reduce adverse effects.

In this work, we aim to revert the action potential (AP) of myocytes affected by human ether-à-go-go-related gene (hERG) mutations N588K and L532P to that of non-mutated, wild-type (WT) myocytes. Towards this end, a virtual multichannel blocker minimizing the difference of the AP courses was designed for each mutation. The restitution of the action potential duration at 90% repolarization (APD_{90}) was assessed for the myocytes under the influence of the newly designed antiarrhythmic agents. Furthermore, the amiodarone and dronedarone concentrations yielding the smallest difference were determined.

2. Methods

The Courtemanche-Ramirez-Nattel (CRN) model of human atrial electrophysiology [3] was used as a reference for WT myocytes. The I_{Kr} formulation was adapted to model the two hERG mutations N588K and L532P as described before [4]. In brief, half activation and inactivation voltages and the slope of the corresponding Boltzmann functions, as well as the time constant of the gate were adjusted according to data measured by McPate et al. [5] to represent the N588K mutation. To model the L532P mutation, a hybrid optimization approach [6] was used to tune 10 parameters of the CRN I_{Kr} formulation to match measured data [7]. To approximate heterozygous expression, a 1:1 mutant to WT ratio was assumed.

For the design of a virtual drug, the maximum conductances g_x of the ionic currents I_{Kr}, I_{Kur}, I_{Ks}, I_{to}, I_{K1}, I_{Na}, $I_{Ca,L}$, $I_{b,Na}$, and $I_{b,Ca}$ channels were inhibited individually by a factor k_x:

$$I_x = g_x \cdot k_x \cdot (V_m - E_x), \quad k_x \in [0, 1] \qquad (1)$$

with V_m being the transmembrane voltage and E_x being the equilibrium potential of the respective ion type. The effect of the pharmacological agents amiodarone and dronedarone was modeled by reducing the maximum con-

ductance of the ion currents according to the Hill equation:

$$\Theta = \frac{1}{1 + \left(\frac{IC_{50}}{D}\right)^{nH}} \quad (2)$$

with Θ being the degree of channel blockage ranging from 0 to 1, IC_{50} being the half maximal inhibitory concentration, D being the free drug concentration, and nH being the Hill coefficient. The respective IC_{50} and nH values were extracted from the literature (see Table 1). The objective function for the minimization was defined as the root mean square error (RMSE) between the mutant and the WT AP over a time span of 500 ms:

$$\Delta AP := \sqrt{\frac{1}{500} \sum_{i=1}^{500} \left(V_{m,mut}(x_i) - V_{m,WT}(x_i)\right)^2} \quad (3)$$

The V_m course of the mutant cell was altered by the vector $\vec{k} \in \mathbb{R}^9$ according to (1) in order to minimize ΔAP or by the scalar concentration D of either amiodarone or dronedarone according to (2) for the dose optimization of these drugs. To compensate for transient oscillations caused by conductance changes, the last AP in a train of 6 was analyzed. APs were elicited by stimuli at a basic cycle length (BCL) of 1000 ms.

Cell models were implemented in *MATLAB* (R2013b, The MathWorks, Nattick, MA, USA) and solved with a variable time step by *ode15s* for simulations on the single cell level. Tissue simulations were conducted in a 1D strand of size $7 \times 0.1 \times 0.1$ mm^3 using the monodomain solver *acCELLerate* [18] and a time step of 10 μs. The finite difference grid had an isotropic voxel side length of 0.1 mm. For the optimization on the single cell level, the trust region reflective algorithm as provided by *lsqnonlin* in *MATLAB* was utilized using uniformly distributed random start vectors. On the tissue level, the constrained Broyden-Fletcher-Goldfarb-Shanno algorithm provided by *SciPy* [19] was used with the optimized parameters from
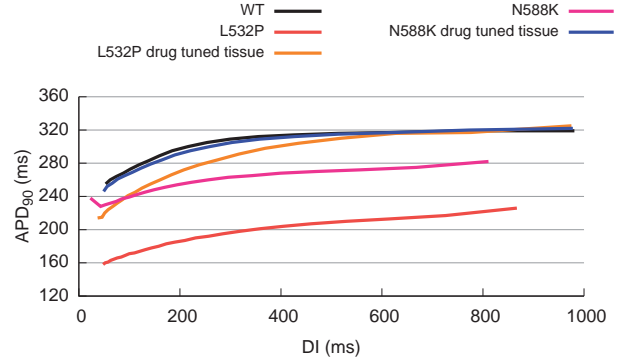

Figure 1. Restitution of the APD$_{90}$ for WT and mutant atrial myocytes. The optimized multichannel blockers (see Table 2) were applied to the hERG mutant cells.

the single cell level as initial guess. Furthermore, APD$_{90}$ was analyzed in tissue for 30 BCLs distributed linearly in the frequency domain ranging from 200 ms to 1300 ms. In this way, the restitution with respect to the diastolic interval (DI) defined as the difference between BCL and APD$_{90}$ was obtained as described before [4].

3. Results

In a first step, a virtual multichannel blocker was designed to minimize the RMSE between the WT and the mutated APs. In the single cell environment, the RMSE could be reduced from 18.15 mV to 0.51 mV for L532P and from 8.34 mV to 0.51 mV for N588K, respectively (see Fig. 2A). The maximum deviation per time step was reduced from 36.18 mV to 3.14 mV and from 17.08 mV to 2.48 mV accordingly. The inhibition factors yielding the lowest RMSE are shown in Table 2. As can be seen in Fig. 2B, the match for L532P using the inhibition vector $\vec{k}$

Table 1. Pharmacological inhibition of cardiac ion channels by amiodarone and dronedarone.

	Amiodarone			Dronedarone		
	IC_{50} (μM)	nH	Ref.	IC_{50} (μM)	nH	Ref.
I_{Kr}	2.80	0.91	[8]	0.0591	0.80	[9]
I_{Kur}	-	-		1.00	1.00	[10]
I_{Ks}	3.84	0.63	[11]	5.60	0.51	[12]
I_{Na}	4.84	0.76	[13]	0.54	2.03	[13]
$I_{Ca,L}$	5.80	1.00	[14]	0.83	2.75	[15]
I_{NaCa}	3.30	1.00	[16]	-	-	
I_{NaK}	15.60	1.00	[17]	-	-	

Table 2. Inhibition factors for atrial ion currents ranging from 1 (no effect) to 0 (complete blockage). The given combinations yielded the lowest RMSE between mutated and WT APs in single cell and tissue simulations.

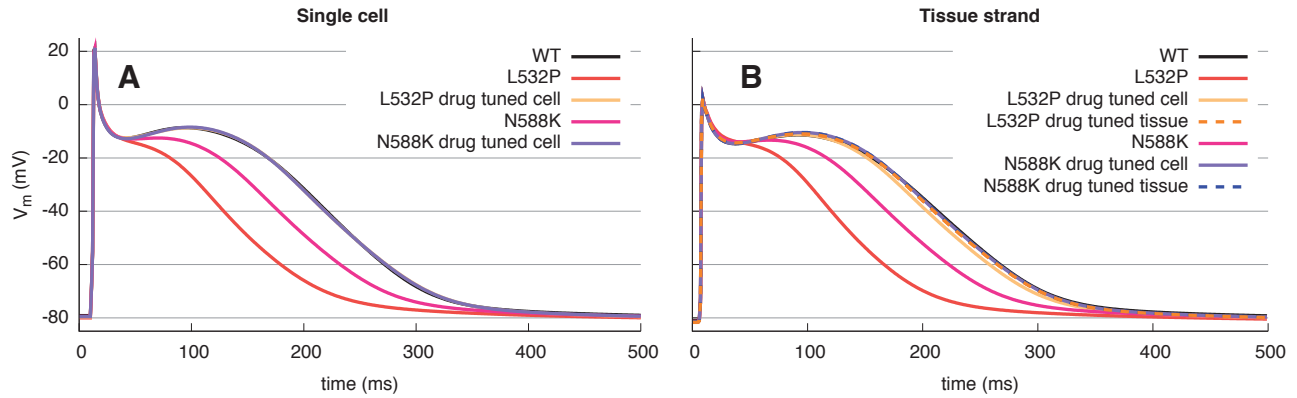|	L532P		N588K	
	Cell	Tissue	Cell	Tissue
k_{Kr}	0.42	0.39	0.56	0.56
k_{Kur}	0.59	0.59	0.61	0.61
k_{Ks}	0.95	0.95	0.88	0.88
k_{to}	1.00	1.00	0.99	0.99
k_{K1}	1.00	1.00	1.00	1.00
k_{Na}	1.00	1.00	0.99	0.99
$k_{Ca,L}$	0.86	0.86	0.83	0.83
$k_{b,Na}$	0.97	0.98	0.96	0.96
$k_{b,Ca}$	0.92	0.92	0.96	0.96

Figure 2. AP curves from single cell (A) and tissue (B) simulations obtained using WT and hERG mutation cell models. Multichannel blockers as defined in Table 2 were applied to mutant myocytes to restore the WT AP. In (A), the curve of the L532P cell under the influence of the tuned drug is covered by that of N588K under drug influence. In (B), the N588K curve under the influence of the drug tuned in tissue is partially covered by that tuned in the single cell environment.
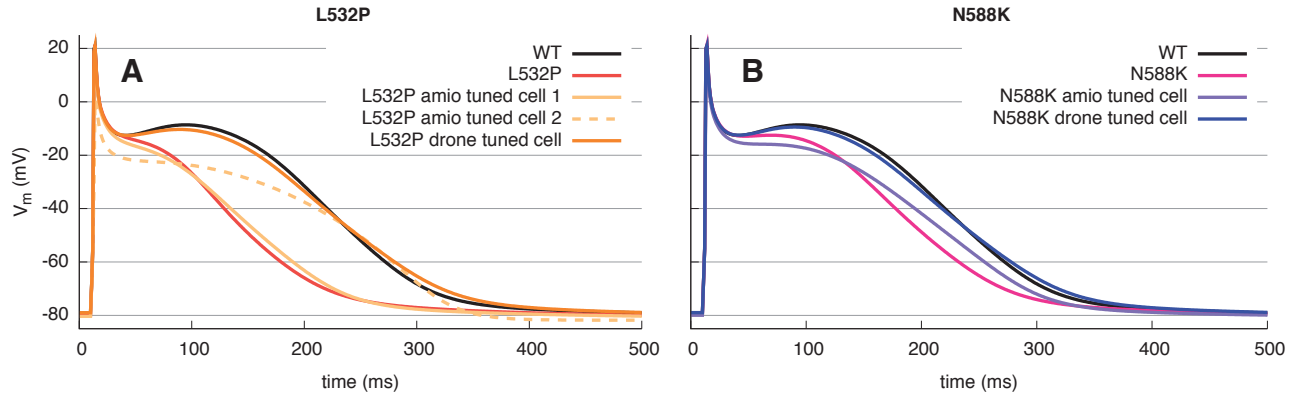

Figure 3. The concentration of amiodarone and dronedarone was optimized to restore the AP of cells affected by hERG mutations L532P (A) and N588K (B) to the WT AP. 2 amiodarone concentrations yielded the same RMSE for L532P.

obtained on the single cell level was not as good in tissue simulations (RMSE 1.76 mV). However, the RMSE could be reduced to 0.63 mV by subsequent optimization in tissue yielding an additional 3% blockage of I_{Kr} and a reduction of $I_{b,Na}$ blockage by 1% compared to the single cell optimum. For N588K, the RMSE of 0.63 mV could not be improved further.

For higher stimulation frequencies, the APD_{90} of the mutated cells under the influence of the optimized multichannel blocker was reduced compared to WT myocytes (see Fig. 1). For N588K, the maximum shortening was 6.2 ms at a DI of 178 ms. For L532P, the maximum deviation compared to WT was 34.2 ms at a DI of 62 ms.

In a second step, the concentration of amiodarone and dronedarone was optimized on the cellular level using the same objective function as above. The resulting AP curves are shown in Fig. 3. For L532P, amiodarone concentrations of $0.658\,\mu$M and $10.72\,\mu$M yielded the low-

est RMSE of 17.21 mV. The optimal dronedarone concentration of $0.088\,\mu$M yielded 1.76 mV, respectively. For N588K, RMSEs were 6.33 mV and 1.33 mV for concentrations of $0.760\,\mu$M and $0.040\,\mu$M, respectively.

4. Discussion

We aimed to restore WT electrophysiology in atrial myocytes affected by hERG mutations L532P and N588K. Towards this end, we minimized the deviation between WT and mutant APs by tuning the inhibition of ionic currents. In a single cell environment, the WT AP could be restored by significant block of I_{Kr} and I_{Kur} ($\geq 39\%$) and less pronounced block of I_{Ks}, $I_{Ca,L}$, $I_{b,Na}$, and $I_{b,Ca}$ ($\leq 17\%$). For L532P, I_{Kr} inhibition had to be slightly reduced to obtain optimal results on the tissue level. APD_{90} restitution was almost restored by the virtual N588K drug. For L532P, shortening of up to 15% could not be prevented

for low BCLs. Our results show that combined reduction of ionic current conductances can counterbalance changes in I_{Kr} kinetics due to e.g. genetic mutations.

Concerning the existing pharmacological agents amiodarone and dronedarone, markedly different potency with respect to the restoration of the WT AP was observed. While dronedarone achieved results close to the hypothetic virtual multichannel blocker, the RMSE could not be significantly reduced using amiodarone. These results underline the importance of the complex, non-linear interaction of different ionic currents and advise against solely considering the main effect (i.e. potassium channel blockage) when characterizing mode of action.

It has to be emphasized that the model of amiodarone represents its acute effects which differ from those seen under chronic administration [20]. Moreover, the pharmacological agents investigated in this work build purely on maximum conductance inhibition and do not consider voltage or state-dependent block providing potential for future optimization of restitution properties.

Zemzemi et al. investigated I_{Kr}, I_{Na}, and $I_{Ca,L}$ blockage in ventricular myocytes all the way from ion channel to body surface potentials [21]. However, our study is — to the best of our knowledge — the first to optimize hypothetic and existing drugs for familial AF comprehensively. Our results provide insight into the pharmacodynamic response of mutated myocytes rendering patients vulnerable to AF and may aid in the design and optimization of patient group-specific therapeutic and preventive approaches.

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