A Model of Drug Effects on Heart Failure and Hypertrophic Cardiomyopathy in Human Ventricular Cardiomyocytes

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Abstract

Heart failure (HF) and hypertrophic cardiomyopathy (HCM) are two cardiovascular diseases that increase the risk of arrhythmia due to their effects on cardiac electrical activity. However, there is no drug designed for treating the electrophysiological and arrhythmogenic consequences of HF and HCM considering their three stages of severity. In this work, computational modelling has been used to study the efficacy of several drugs against arrhythmogenic phenomena caused by HF and HCM. 95 drugs have been taken into account, of which 28 have been considered as non-arrhythmogenic a priori due to their IC_{50} values. A modified version of the O'Hara-Rudy computational model has been used to simulate both, the pathologies and drugs effect and the influence of sex, cell type and heart rate. Considering the occurrence of early afterdepolarizations (EADs), results show that Diltiazem, Nifedipine and Nitrendipine are the most effective drugs to solve EADs, being Nitrendipine the most effective one without an overdose. Additionally, not only does tachycardia provoke a greater probability of the occurrence of EADs, but also the favourable response to some anti-arrhythmogenic drugs is lower. In conclusion, the risk of HF and HCM developing arrhythmias may be reduced with drugs as identified by our in-silico AP model.

1. Introduction

Cardiovascular diseases are the leading cause of death worldwide and includes a variety of conditions such as HF and HCM. Although they show their own features, they are characterised by triggering electro-physiological alterations promoting, in turn, abnormal electrical impulses. Erratic electrical activity can be promoted by several factors, such as ventricular ectopicity, which is due to a heterogeneity in the repolarization. In such a case, triggered activity is caused by the premature activation of cardiac tissue, which in turn results from EADs. Moreover, there are other arrhythmogenic phenomena promoted by HF and HCM such as a prolongation of the action potential duration (APD), altered triangulation values (APD_{90} - APD_{30}) or electrical alternans which correspond to consecutive APs that are different in amplitude and duration. These conditions prompted by HF and HCM increase the risk of potentially lethal arrhythmias which can result in sudden cardiac death [1],[2]. Nevertheless, there is no drug with specific objective to treat or palliate the electrophysiological and arrhythmogenic consequences of HF and HCM.

The aim of this work is to evaluate the effects of different drugs on HF and HCM-affected hearts considering several conditions such as pathology severity (mild, moderate and severe), sex (female and male), cell type (endocardium, midmyocardium and epicardium) and the heart rate (bradycardia (45 bpm), normal heart rate (75 bpm) and tachycardia (120 bpm)). To achieve this goal, the usage of computational simulation and the determination of biomarkers that help to identify the efficacy of a drug under HF or HCM conditions will be carried out.

2. Methods

"0D simulations" correspond to a virtual single isolated cell, in this case, a human ventricular cardiomyocyte. A modified version of O'Hara-Rudy model has been used in the simulations. The modifications were the following. First, to obtain more realistic values for the rate of depolarisation of the AP and its propagation velocity, the formulation of both, the sodium and L-type calcium currents have been modified as in [3]. Second, different heart rates were modelled using several basic cycle length (BCL) values. Third, to simulate the effect of HF and HCM at the cardiomyocyte membrane level, percentual changes given by Passini et al [4] to integrate the HF and HCM ionic electrophysiological remodelling were implemented. However, as both pathologies are classified according to their several stages (mild, moderate and severe), the percentual changes have been split in three equidistant values in order to model the three stages of each disease. Finally, to incorporate the effect of drugs on the affected currents of each family of channels, I_S, the required modifications were made according to the simple-pore model. For this purpose, a multiplicative factor given by the Eq. (1) as [5] did where the corresponding IC_{50}, Hill coefficients and effective free therapeutic plasma concentrations (EFTPC) collected by [6] for 95 drugs are embedded.

$$f_d([D]) = \frac{1}{1 + \left(\frac{[D]}{IC_{50}}\right)^H} \qquad (1)$$

Moreover, in order to simulate different drug concentrations, different simulations were performed

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by modifying $[D]$ value according to the EFTPC on an isolated human ventricular cardiomyocyte model simulated for one minute. In particular, three drug concentrations were considered for each drug, x1, x2 and x10 the EFTPC. Additionally, it is important to mention that the 95 drugs considered were reclassified into pro- and anti-arrhythmogenic drugs depending on their inhibitory potential on rapid delayed rectifier potassium and L-type calcium currents. Specifically, the drugs considered as non-arrhythmogenic were the ones whose inhibitory potential is greater on the L-type calcium current than on the rapid delayed rectifier potassium current, that means, in those in which $IC_{50}(I_{Kr})$ is greater than $IC_{50}(I_{CaL})$.

For the analysis of the results, several biomarkers related to arrhythmogenicity have been considered. The main biomarkers used for the classification of the pro- and anti-arrhythmogenicity of both, pathologies and drugs, are the following: a positive time derivative of membrane potential during resting phase, a prolongation of APD_{90} value greater than 20%, a resting membrane potential greater than 50 mV, peak values too low or too high (lower than 0 mV or higher than 50mV), the occurrence of alternans, the development of EADs and, finally, a triangulation value greater than 140 ms. In all these circumstances, the probability of arrhythmia occurrence raises. Nevertheless, out of all of these biomarkers, the most determining for identifying arrhythmic risk are the prolongation of APD_{90}, the occurrence of alternants and/or EADs and the triangulation value.

3. Results

Several sets of simulations were run. The first one models control conditions, i.e., without drug effect but considering both sexes, three cell types and three heart rates with and without both pathologies with three different severity stages obtaining 126 simulations. 10 of them showed EADs, all belonging to the midmyocardium and with severe HF and HCM except to severe HF on female and male midmyocardium with tachycardia as Table 1 shows.

Table 1. Summary table of control cases in which EADs occur. Those with a cross (×) in the 'EADs' column means that they have EADs, and the one with permanent EADs has "Permanent" written in it.

No.	Cell type	Sex	Pathology	Severity	Heart rate	EADs
1	Midmyocardium	Female	HF	Severe	Bradycardia	×
2					Normal	×
3			HCM	Severe	Bradycardia	×
4					Tachycardia	**Permanent**
5					Normal	×
6		Male	HF	Severe	Bradycardia	×
7					Normal	×
8			HCM	Severe	Bradycardia	×
9					Tachycardia	×
10					Normal	×

In order to mitigate these effects, the second set of 840 simulations was carried out using the same risk-promoting conditions but with the effect of 28 antiarrhythmic drugs individually. Table 2 shows that 6 drugs prescribed for cardiac symptomology were able to prevent the occurrence of EADs at normal therapeutical doses.

Table 2. Summary of the conditions (✓) in which viable drugs with a concentration equal to EFTPC are effective and viable for treating EADs caused by pathologies

Effective drugs [1xEFTPC] for the treatment of EADs (✓)										
Drug	Female					Male				
	HF		HCM			HF		HCM		
	Bradycardia	Normal	Bradycardia	Normal	Tachycardia	Bradycardia	Normal	Bradycardia	Normal	Tachycardia
Diltiazem 1										✓
Diltiazem 2							✓			✓
Diltiazem CiPA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Nifedipine 1		✓			✓	✓	✓	✓	✓	✓
Nifedipine 2										✓
Nitrendipine 1										✓
Nitrendipine 2	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

In particular, Diltiazem CiPA and Nitrendipine 2 are the most effective ones, palliating the occurrence of EADs in all cases.

Another set of simulations was carried out without pathology effect in order to determine the heart rate impact on the cardiomyocyte response in specific conditions. Once the effect of 95 drugs with three concentrations on both sexes, three cell types and three heart rates have been simulated, giving a total of 5130 simulations, the obtained results have been analysed. Healthy conditions do not provoke any kind of arrhythmia, however, some drugs with certain concentrations under particular conditions enhance the probability of arrhythmia, disrupting some biomarkers associated with arrhythmogenicity such as EADs as Table 3 shows. It is notable that the results indicate that tachycardia is the most affected heart rate. These results are coherent because the heart rate has intense consequences on intracellular Ca^{2+} dynamics. Tachycardia stresses the Ca^{2+} handling system, so, if any of the components that affect intracellular Ca^{2+} dynamics, such as pro-arrhythmic drugs, tachycardia is most likely to lead to an instability of Ca^{2+} influx/efflux, which has a crucial influence in several arrhythmogenic phenomena, like afterdepolarizations, alternans and repolarisation variability in general [7].

Finally, in the last set of simulations that was carried out, a second drug has been simulated in those cases in which one drug (at 1x and 2xEFTPC) had caused EADs, requiring then 5796 simulations. As Table 4 shows, of the total 5796 simulations executed to analyse the drug effectiveness to palliate EADs provoked by another drug, 2184 were run with tachycardia conditions, 1596 with normal heart rate and 2016 with bradycardia. Of these, 181, 415 and 690 simulations respectively, do not present the occurrence of EADs. These values correspond to 8.29%, 26.00% and 34.23% of the total simulations executed per each

Table 3. The occurrence of EADs (×) caused by the effect of some drugs under healthy conditions (without pathology).

EADs (×) caused by the effect of some drugs on healthy cardiac tissue																				
Drug	[Drug]	Female									Male									
		Endocardium			Midmyocardium			Epicardium			Endocardium			Midmyocardium			Epicardium		
		Bradycardia	Normal	Tachycardia	Bradycardia	Normal	Tachycardia	Bradycardia	Normal	Tachycardia	Bradycardia	Normal	Tachycardia	Bradycardia	Normal	Tachycardia	Bradycardia	Normal	Tachycardia
Ajmaline	2xEFTPC				×	×	×							×		×			
	10xEFTPC				×	×	×							×	×	×			
Bepridil 1	10xEFTPC						×												
Bepridil 2	10xEFTPC				×	×	×							×	×	×			
Bepridil CiPA	10xEFTPC				×	×	×							×	×	×			
Cisapride CiPA	10xEFTPC				×		×												
Dofetilide 2	10xEFTPC				×	×	×							×	×	×			
Dofetilide CiPA	10xEFTPC				×	×	×							×		×			
Droperidol	10xEFTPC				×	×	×							×		×			
Flecainide	10xEFTPC				×	×	×							×	×	×			
Halofantrine	10xEFTPC				×		×									×			
Ibutilide	1xEFTPC				×	×	×							×	×	×			
	2xEFTPC				×	×	×							×	×	×			
	10xEFTPC	×	×		×	×	×			×				×	×	×			
Prenylamine	10xEFTPC				×	×	×									×			
Propafenone	10xEFTPC				×	×	×									×			
Quinidine 1	1xEFTPC				×	×	×							×		×			
	2xEFTPC				×	×	×							×	×	×			
	10xEFTPC				×	×	×								×	×			
Quinidine 2	1xEFTPC				×	×	×							×		×			
	2xEFTPC				×	×	×							×	×	×			
	10xEFTPC				×	×	×							×	×	×			
Quinidine CiPA	1xEFTPC				×	×	×									×			
	2xEFTPC				×	×	×							×	×	×			
	10xEFTPC			×	×	×	×	×	×	×			×	×	×	×		×	×
Ranolazine CiPA	10xEFTPC						×												
Terfenadine 2	2xEFTPC				×		×												
	10xEFTPC				×	×	×							×	×	×			
Terodiline	10xEFTPC						×												
Thioridazine 1	1xEFTPC						×												
	2xEFTPC				×	×	×							×		×			
	10xEFTPC				×	×	×							×	×	×			
Thioridazine 2	1xEFTPC				×	×	×							×	×	×			
	2xEFTPC				×	×	×							×	×	×			
	10xEFTPC			×	×	×	×						×	×	×	×			
Verapamil 2	10xEFTPC						×												

Table 4. Relative frequency distribution table by condition of both, the total cases with two drugs effects and the cases without the occurrence of EADs thanks to the effect of the second drug.

Conditions	Frequency	Rel. Freq. (%)	Freq. No EADs	Rel. Freq. No EADs (%)
Total	**5796**	100.00%	1286	22.19%
Cell type				
Endocardium	0	0.00%	0	0.00%
Midmyocardium	5796	100.00%	1286	22.19%
Epicardium	0	0.00%	0	0.00%
Sex				
Female	3276	56.52%	677	20.67%
Male	2520	43.48%	609	24.17%
Heart rate				
Bradycardia	2016	34.78%	690	34.23%
Normal	1596	27.54%	415	26.00%
Tachycardia	2184	37.68%	181	8.29%

heart rate, respectively. These values, together with the conclusions discussed in the previous set of simulations, indicate that not only does tachycardia provoke a greater probability of the occurrence of EADs, but also the favourable response to some anti-arrhythmogenic drugs is lower.

In particular, in these cases, Diltiazem CiPA, Nifedipine 1 and Nitrendipine 2 can be administrated chronically to solve the occurrence of EADs caused by an arrhythmogenic drug. However, as Nitrendipine is the only one which is effective without an overdose, it has been considered as the most effective and viable drug to treat EADs caused by some arrhythmogenic drug administrated to patients with tachycardia

4. Conclusions

According to our simulations, Diltiazem, Nifedipine and Nitrendipine may be great candidates as cardioprotective drugs in both, HF and HCM and under conditions of proarrhythmic drug administration, as they are able to eliminate the occurrence of EADs. Nevertheless, Nitrendipine is the most effective one without an overdose. Moreover, regarding the influence of heart rate, according to the results, the higher the heart rate is, the lower the ability to handle arrhythmogenic mechanisms like EADs. It would be significant to analyse the causes behind this phenomenon.

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