Simulation Study of the Protective Effect of Drugs in Acute Myocardial Ischemia

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Abstract

Increased extracellular potassium concentration (hyperkalemia) and electrical alternans in the action potential (AP) have been shown experimentally to be highly proarrhythmic during the acute phase of myocardial ischemia (AMI), which is a leading cause of death worldwide. However, there is no drug specifically designed to effectively address the electrophysiological and arrhythmogenic consequences of AMI. In this work, computational simulations have been used to study the efficacy of 95 drugs against arrhythmias of ischemic origin. A modified version of the O'Hara et al. computational model has been used to simulate the AMI and the effect of the drug at the cellular level. After defining a series of biomarkers and classification criteria, the results indicate that such classification is possible and Nitrendipine is determined as the most promising drug, standing out for its ability to establish hyperkalemic and electrical conditions compatible with an anti-arrhythmic tendency in all the biomarkers defined. In conclusion, the work demonstrates the feasibility of in-silico experiments to perform a classification capable of minimizing the vulnerability to arrhythmias in AMI.

1. Introduction

It is known that one of the three main components responsible for triggering all other alterations following coronary occlusion during acute myocardial ischemia (AMI) is the increase in extracellular potassium concentration ($[K^+]_o$) [1,2]. This accumulation, commonly referred to as hyperkalemia, is highly proarrhythmic because it increases the likelihood of unidirectional block and subsequent reentry [3,4]. The time course of $[K^+]_o$ in AMI is characterised by three phases [5-8]. The first corresponds to a very rapid rise in $[K^+]_o$ immediately after coronary occlusion and lasts approximately 5-7 minutes. This is followed by a plateau phase. Finally, the third phase corresponds to a second, slower increase in $[K^+]_o$.

A closer examination of the influence of hyperkalemia and the other two main components (acidosis and anoxia) on the dynamic changes in AP morphology shows electrical alternans in cardiac cells. The alternans begin to appear from about the third or fourth minute of post-occlusion, i.e., in the acute phase, and disappear by the eighth minute. Alternans correspond to consecutive APs that differ significantly in both amplitude and duration [9]. This alternans phase promotes, together with hyperkalemia, a completely heterogeneous scenario during the AMI process and constitutes a factor for life-threatening cardiac arrhythmias.

The aim of this work is to assess the effect of different drugs on the time-course of extracellular potassium concentration ($[K^+]_o$) and dynamic changes of the AP during ischemia using computational simulation, and to identify new biomarkers that help to characterize the efficacy of a drug under ischemic conditions.

2. Methods

A modified version of the O'Hara *et al.* model was used in the simulations. To simulate the effects of AMI at the cardiomyocyte membrane level, changes as in [10] were implemented. First, I_{KATP} is added to the model as it was not originally considered and is formulated by adapting Ferrero's model [11] to human cardiomyocytes using data from Babenko [12]. Second, the effects on the ionic pumps of $[ATP]_i$ and $[ADP]_i$ are modelled considering the data of [13] and [14], which introduce different scaling factors affecting the sodium/potassium pump (I_{NaK}), the sarcolemmal calcium pump (I_{pCa}) and the SERCA pump (I_{up}). Third, we introduced the effects of intracellular and extracellular acidosis to the model as in [15] by applying different multiplicative factors on pH-dependent channels such as I_{Na}, I_{CaL} and I_{NaK} and on the sodium/calcium exchanger (I_{Ca-Na}). Additionally, the effects of lysophosphatidylcholine (LPC) on I_{Na} and I_{NaL} were modelled using data from [16]. Finally, the necessary modifications were made to incorporate the effect of drugs on the current of each family of channels, I_S. To this end, a multiplicative factor, f_d, was added to the families of channels affected by the drugs. The effect of 95 different drugs was modelled using the data collected by [17] of their corresponding IC50s, Hill coefficients and effective free therapeutic plasma concentrations (EFTPC) calculating the drug factor, f_d, as shown in Eq. 1. For each drug, different simulations were performed by modifying

the drug concentration according to the EFTPC on an isolated ventricular endocardial cardiomyocyte model stimulated for five minutes under control conditions followed by thirty minutes of progressive acute ischemia.

$$f_d([D]) = \frac{1}{1 + \left(\frac{[D]}{IC50}\right)^H} \qquad \text{Eq. 1}$$

Specifically for each drug, three simulations were carried out with drug concentrations of x1, x2 and x10 the EFTPC. The model inputs for initialisation are based on experimental and simulated data taken from different studies [14, 16, 18, 19]. The periodic stimulation consisted of pulses of 1 millisecond duration and an amplitude twice the normoxic diastolic threshold with a stimulus frequency of 1 Hz.

For the analysis of the results, several biomarkers (BM) defined on the model state variables corresponding to the time course of $[K^+]_o$ and membrane potential have been considered. The main BMs used for the classification of the drugs are shown in Figure 1 on the simulated curves of the time course of $[K^+]_o$ (1A) and APD90 (1B) under control conditions.

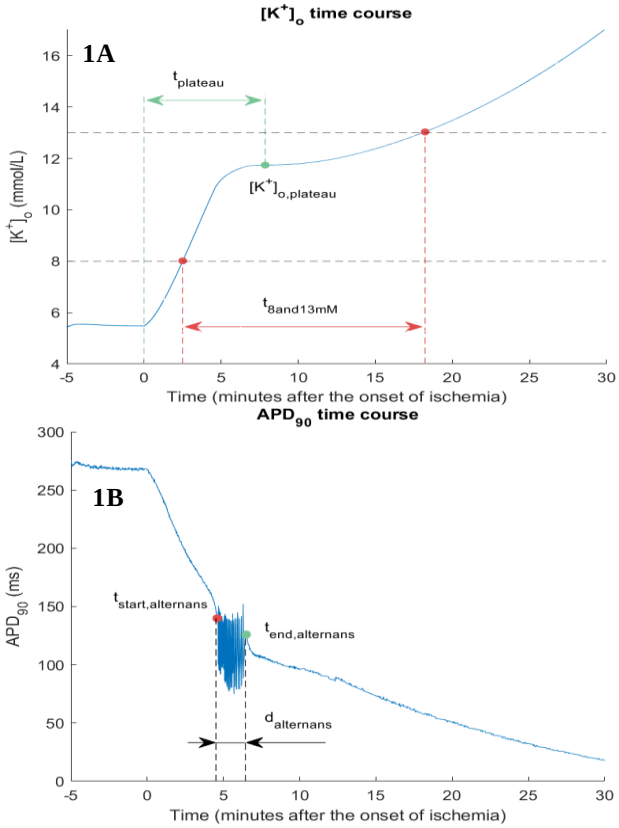

Figure 1. Biomarkers defined on the time course curves of $[K^+]_o$ (upper panel) and APD90 (lower panel).

The BMs in Figure 1A correspond to the $[K^+]_o$ value at the plateau, the time it takes to reach the plateau and the time the cell spends exposed to concentrations between 8 and 13 mM of extracellular potassium, which is considered the most proarrhythmic concentration window. The BMs in Figure 1B correspond to the start, end, and duration of the alternans period.

The criteria used to classify the drugs were as follows. Regarding the duration of the alternans period, if the drug reduces the duration with respect to the control it is considered an antiarrhythmic trend and vice versa. As for the onset of this alternans period, it is considered an antiarrhythmic trend if it starts later than the control and vice versa, ruling out as proarrhythmic all those drugs that generate alternans in the period of normoxia prior to AMI. Regarding the extracellular potassium concentration, a drug with an antiarrhythmic tendency is any drug that reduces and/or reaches the plateau value earlier than the control. Finally, regarding the time spent within the most dangerous window of 8 mM and 13 mM, any drug that reduces the time spent within this window is considered to have an antiarrhythmic tendency.

All anti-arrhythmic tendencies have been assigned a value of (+1) while pro-arrhythmic tendencies have been assigned a value of (-1). A similar value to the control has been assigned with a (0). In this way, the individual (I) performance of each of the three simulations carried out with each drug was added up to obtain the global value (G) of its performance and, thus, to obtain the drug classification.

3. Results

Analyzing the results obtained from the BMs, which are shown in Figure 2, and applying the classification criteria explained above, the classification of drugs is obtained. The classification results allow us to identify those drugs that have a proarrhythmic tendency in normoxia and are therefore immediately discarded as suitable drugs for AMI (Quinidine, Amiodarone and, Ibutilide). On the other hand, it allows to identify the most pro-arrhythmic drugs in AMI (Quetiapine, Pentobarbital and, Propanolol), but more interestingly, it allows to identify the drugs with the highest anti-arrhythmic tendency in AMI. Table 1 shows the three drugs with the highest scores.

4. Conclusions

Nitrendipine may be a good candidate as a protective drug in acute ischemia, as it eliminates the alternans period. The results obtained show promising indications in terms of efficacy of drugs in acute ischemia and serve as a preliminary identification step to model the effect of drugs in arrhythmia vulnerability using cardiac 3D models.

Acknowledgments

This project has received funding from the European

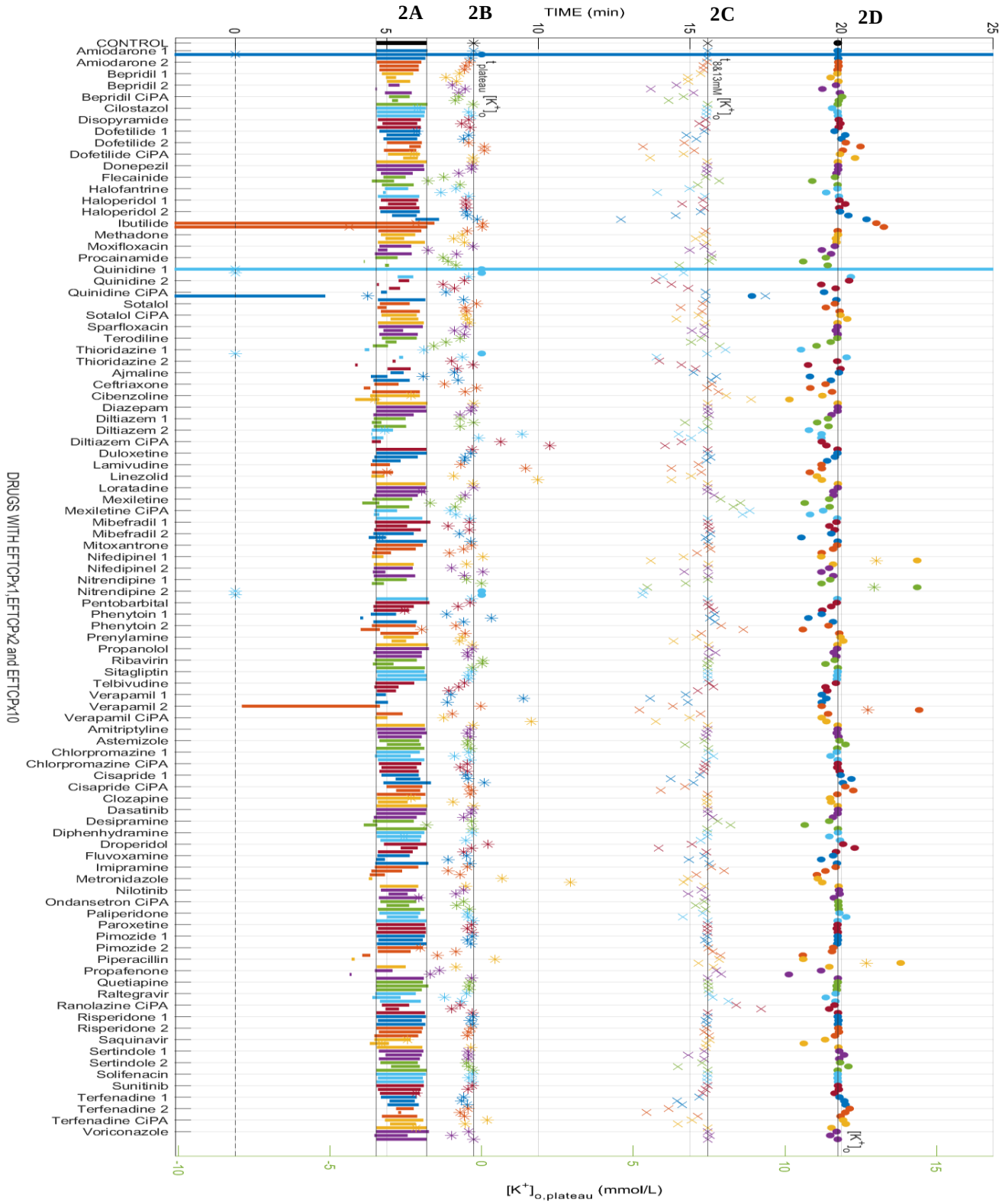

Figure 2. The five main BMs used for drug classification are represented. In all cases the CONTROL is shown in black on the left-hand side. Each of the drugs has been simulated with concentrations 1, 2 and 10 times the EFTPC. (2A) The bars represent the onset and duration of the alternation period. (2B) The '*' symbols indicate the time to reach the potassium plateau. (2C) The 'x' symbols indicate the time of $[K^+]_o$ between 8 and 13 mM. (2D) The '·' symbols indicate the value of the extracellular K^+ plateau concentration.

Table 1. Top 3 of the drug classification.

Drug	[D]	$[K^+]_{o,plateau}$	$t_{plateau}$	$t_{start,alternans}$	$d_{alternans}$	$t_{8and13mM}$	I	G
Nitrendipine II	1xEFTPC	14,36	21,.7	-	-	13,59	3	13
	2xEFTPC	-	-	-	-	13,47	5	
	10xEFTPC	-	-	-	-	13,42	5	
Dofetilide CiPA	1xEFTPC	11,91	8,21	4,91	1,07	15,14	2	8
	2xEFTPC	11,81	5,89	5,04	1,05	14,79	3	
	10xEFTPC	12,31	7,84	5,54	0,48	13,68	3	
Terfenadine 2	1xEFTPC	12,00	7,64	5,02	1,03	14,74	2	8
	2xEFTPC	12,13	7,67	5,31	0,58	14,29	3	
	10xEFTPC	11,99	7,42	5,37	0,10	13,56	3	

Union's Horizon 2020 research and innovation programme under grant agreement No. 101016496 (SimCardioTest) and from the Spanish State Programmes for Knowledge Generation and Scientific and Technological Strengthening of the R&D&I System and R&D&I Oriented to the Challenges of Society (PID2019-104356RB-C41).

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