

Using Computational Modelling to Define the Ideal Characteristics of Antiarrhythmic Drugs in Acute 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 ischemic pathology. In this work, computational simulations have been used to define the characteristics of an "ideal/theoretical" drug that, by affecting several families of cellular ion channels, protects the myocardium against ischemic arrhythmias. A modified version of the O'Hara *et al.* computational model has been used the AMI and the effect of the drug at the cellular level. After defining a series of biomarkers and conditions to be met by a population of drug models, the results show that, from the initial population ($N=10,000$), 17 drug models pass all the established criteria. Of the latter, two stand out for their ability to establish hyperkalemic and electrical conditions compatible with an anti-arrhythmic trend in all the biomarkers defined. In conclusion, the work demonstrates the feasibility of *in-silico* experiments to define an "ideal/theoretical" drug capable of minimizing 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 define the characteristics of an "ideal/theoretical" drug with multichannel effect that counteracts these two proarrhythmic conditions in AMI using computational modelling.

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 in order to incorporate the effect of drugs on the current of each family of channels, I_S , following the simple pore-block model:

$$I_S = G_s \cdot f_d([D]) \cdot f_v(V_m) \cdot f_l([L]) \cdot (V_m - E) \quad [1]$$

where G_s is the maximum conductance of the family, f_d , f_v and f_l are the factors corresponding to the drug-, voltage- and ligand-dependent gates respectively, V_m is the membrane potential and E is the reversal potential of the channels.

To define a population of candidate theoretical drugs, the selected ionic currents were multiplied by random factors (f_d) between 0 and 2 to mimic the inhibitory/excitatory effect of drugs on ion channels. The drug was supposed to affect I_{Kr} , I_{NaL} , I_{CaL} , I_{Na} and I_{Ks} currents. In this way, a population of 10,000 drug models was generated. For each drug, five minutes of normoxia followed by 30 minutes of progressive ischaemia were simulated on the single cell model. 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. 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.

Not all the models generated were considered valid, as they may not be faithful representations of real situations. To validate each of these models, they are filtered so that in normoxia they must meet the conditions of having positive depolarisations, resting membrane potentials of ± 3 mV with respect to control potentials ($RMP_{control} = -87.53$ mV) and APD90 values of $\pm 10\%$ with respect to control values ($APD90_{control} = 270$ ms). These values defined for the constraints are stricter criteria than the range of physiological values found in the literature [20]. This implies that the results obtained meet more stringently the physiological needs in normoxia. Subsequently, valid drug models are searched for those in which the BM of the alternans period duration is equal to 0, i.e., this proarrhythmic period is eliminated. From this point, a wide range of filters can be applied in search of the ideal drug. In this case, we searched for drug models that are most beneficial for cardiac function where the I_{Kr} channel is not blocked, and the blockage in the I_{CaL} channel does not exceed 80%.

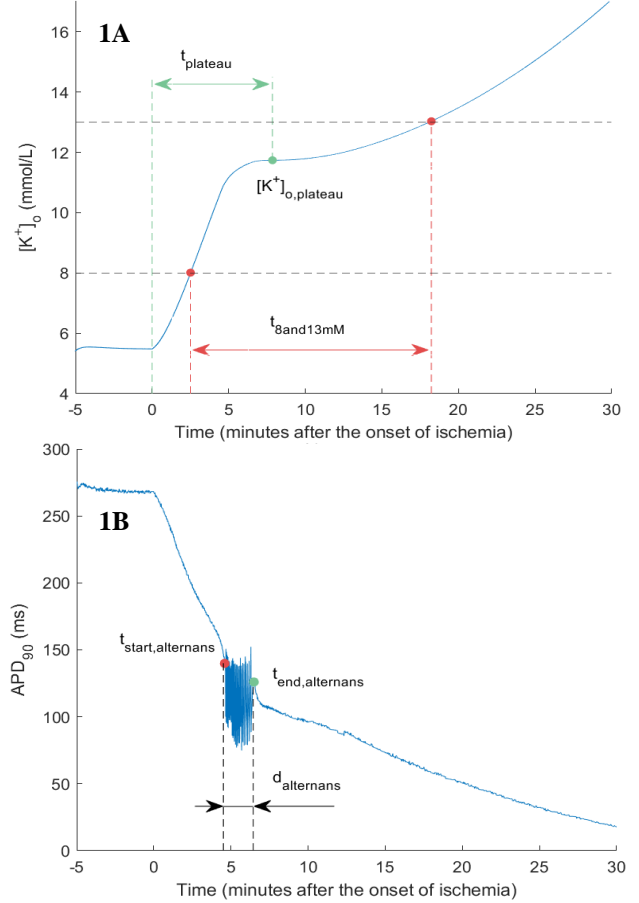


Figure 1. Biomarkers defined on the time course curves of $[K^+]_o$ (1A) and APD90 (1B).

3. Results

Of the population of 10,000 initial drug models, only 1,661 passed the normoxic conditions filter. Of the latter, 184 are the cases in which the alternating period was eliminated and are shown in Figure 2 where the control curves are depicted in black.

In order to see if there is any trend or requirement that these combinations must meet, a box plot representation was made for each of the factors individually (Figure 3). It can be noted that, for a drug to pass the normoxia and alternans elimination filter, there must be a clear inhibitory effect on the I_{CaL} channel current, while the rest of the currents accept a wider range of possibilities.

Finally, the drug models that contained positive factors on the I_{Kr} channel and a blockade on I_{CaL} of no more than 80% were identified. Figure 4 shows these cases (N=17) represented in green, compared to the rest of the factor combinations of the filtered drug models (N=167), represented in black.

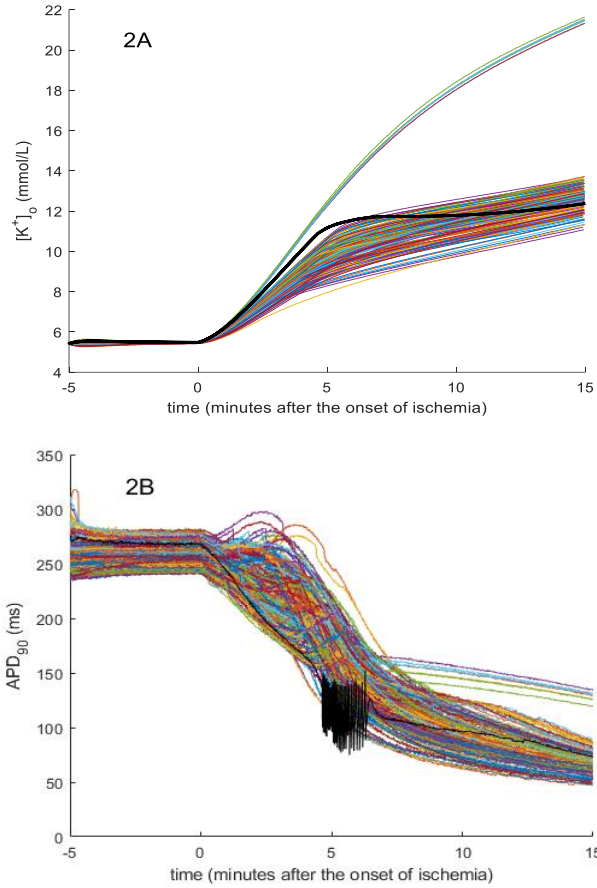


Figure 2. Result of the time course curves of $[K^+]_o$ (2A) and APD90 (2B) of the drug model population (N=184) overcoming the normoxic conditions filter and eliminating the alternans period.

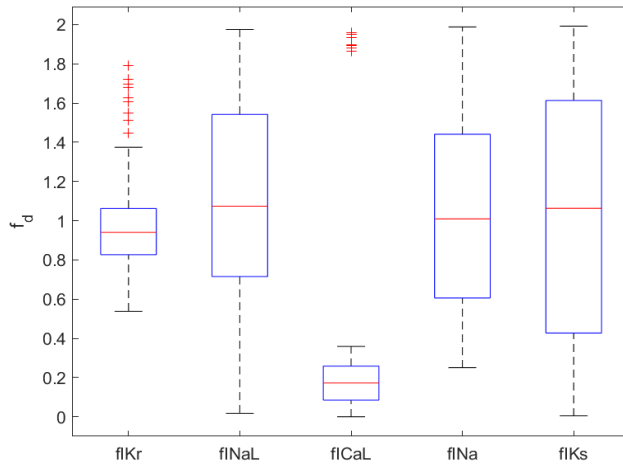


Figure 3. Boxplot for each of the factors

A total of 17 candidates were identified to pass all the defined filters. The factor combinations of these 17 candidates are listed in table 1 together with the BM value of the time spent by the cell between 8 and 13 mM of

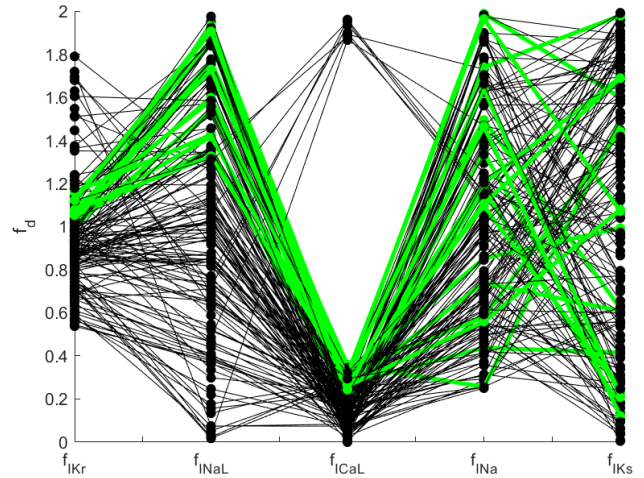


Figure 4. Combinations of factors for valid drugs. Those with positive factors in I_{Kr} and a blockage of no more than 80% on I_{CaL} are marked in green.

Table 1. Combinations of factors that meet all defined filters together with their corresponding value of the t_{8y13mM} BM.

N.º	f_{IKr}	f_{INaL}	f_{ICaL}	f_{INa}	f_{IKs}	t_{8y13mM}
1	1.02	1.93	0.30	1.98	1.59	9,29
2	1.13	1.85	0.27	0.44	0.42	14,45
3	1.01	1.77	0.20	1.34	0.24	13,25
4	1.12	1.86	0.34	1.49	0.62	11,45
5	1.00	1.54	0.33	0.58	1.44	16.92
6	1.06	1.77	0.36	0.26	1.49	12,99
7	1.05	1.36	0.20	1.17	0.17	14,06
8	1.14	1.86	0.32	0.85	0.99	11,23
9	1.12	1.92	0.29	1.74	1.97	10,99
10	1.09	1.58	0.26	0.74	0.67	11,69
11	1.04	1.73	0.25	1.20	1.69	11,07
12	1.05	1.42	0.32	1.96	1.07	10,14
13	1.07	1.73	0.27	1.11	1.67	12,64
14	1.06	1.60	0.26	0.56	1.08	11,92
15	1.16	1.43	0.27	1.09	0.25	11,42
16	1.08	1.33	0.30	1.64	0.21	9,93
17	1.12	1.91	0.24	1.46	0.12	12,68
Control	1	1	1	1	1	15,67

extracellular potassium concentration (t_{8y13mM}). The rest of the BM were discarded.

It can be seen that, except for the fifth combination, all of them manage to reduce the BM value t_{8y13mM} , which is considered an anti-arrhythmic trend. Therefore, these 16 combinations show the desired anti-arrhythmic trend. It is worth noting the performance of combinations 1 and 16,

which reduce the BM t_{8y13mM} value by more than 5 minutes compared to the control (6.38 and 5.74 minutes respectively).

4. Conclusion

Our results demonstrate the feasibility of using AP simulation to define an "ideal/theoretical" drug that reduces the defined ischaemic BM values and thus minimises vulnerability to arrhythmia in acute myocardial ischaemia. The efficacy of drug candidates could be further assessed in a 3D biventricular model.

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