What type of drug would be antiarrhythmic in acute myocardial ischemia? Insights from simulations

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Abstract

Acute myocardial ischemia (AMI) can lead to life-threatening arrhythmias. Hyperkalemia is a major contributing factor, increasing the risk of unidirectional block and re-entry. It also causes dynamic changes in the shape of the action potential, along with acidosis and anoxia. During the AMI process, this heterogeneity creates a vulnerable window (VW) in which re-entry may arise due to an ectopic stimulus. Nevertheless, there is no drug with specific purpose to target the electrophysiological and arrhythmogenic outcomes of AMI. Based on our previous research, an ideal drug with calcium channel blocker properties could be effective. Hence, this study aims to assess the impact of calcium channel blockade on the efficacy of drugs in reducing VW and preventing arrhythmias during AMI using 3D computational simulations. A modified version of the O'Hara et al. computational model was used to include the effects of AMI and drugs. Simulations were carried out on a biventricular 3D anatomical model including a realistic shape of the ischemic and border zone, transmural heterogeneity, and anisotropy. The results suggest a biphasic behavior of calcium blockade on VWs: moderate-low or high blockade prevents arrhtyhmias, whereas low or medium-high blockade exacerbates them. Control Reentrant Probability Index (RPI) is X whereas a RPI of T, Q, Y, and Z is observed at calcium blocking percentages of 20%, 40%, 60%, and 80% respectively. In conclusion, this study demonstrates the feasibility of in-silico experiments for classify and test the drug efficacy in reducing susceptibility to arrhythmias in AMI.

1. Introduction

Coronary artery occlusion causes AMI, triggering electrophysiological alterations that lead to a highly heterogeneous environment. This environment increases the risk of potentially lethal arrhythmias, such as ventricular tachycardia or fibrillation, which can occur within minutes and often result in sudden cardiac death. One of the three primary factors responsible for causing these changes is hyperkalaemia, which is highly proarrhythmic as it increases the chance of unidirectional block and subsequent reentry [1-4]. Along with acidosis and anoxia, leads to dynamic changes in (AP) morphology showing electrical alternans in cardiac cells during the acute phase. Alternans correspond to consecutive APs that differ significantly in both amplitude and duration [5]. This heterogeneous scenario during the AMI process creates a vulnerable window (VW) where re-entry, due to an ectopic stimulus, can be generated. However, there is no drug with specific purpose to target the electrophysiological and arrhythmogenic outcomes of AMI. According to our previous work at the cellular level [6,7], such ideal drug should have calcium channel blocking characteristics. This work aims to study the effect of calcium channel blockade and present evidence of drug efficacy in reducing the VW and preventing arrhythmias during AMI using 3D computational simulations.

2. Methods

"0D simulation" corresponds to a virtual single isolated ventricular endocardial cardiomyocyte, and "3D simulations" to an anatomical model of the ventricles including a realistic geometry of the ischemic region previously developed by our group [8]. This later volume transmural heterogeneity, myocardial anisotropy with fiber orientation and the three ischemic regions: the ischemic central zone (ICZ), the border zone (BZ) and the normal zone (NZ), has been implemented as in [9] (Fig 1A).

A modified version of the O'Hara et al. model was used to simulate the effects of AMI at the cardiomyocyte membrane level. In that way, changes as in [10] were implemented in the model. Furthermore, the channel conductance optimization proposed by [11] have been included in the model to better reproduce the effect of drugs. Finally, the necessary modifications as in [6,7] were made to incorporate the effect of drugs on the current of each family of channels. To this end, a multiplicative factor was added to the families of channels affected by the drugs. The effect of 95 different drugs were modelled using the data collected by [12] of their corresponding IC50s, Hill coefficients and effective free therapeutic plasma concentrations (EFTPC). Single cell simulations were performed as in the previous work [6,7]. In accordance with the same criteria defined, the two biomarkers of the time spent by the cell exposed to concentrations between 8 and 13 mM of extracellular potassium and the duration of alternans were used to identify the most promising drugs. Each 0D simulation consisted of 5 min of normoxia followed by 30 min of acute ischemia. During this last period, hypoxia and acidosis are progressive and the time evolution of the ischemic-related parameters is based on

same experimental and simulated data recollected in [10] (Figure 1C-G). The 0D simulations were also used to obtain the temporal evolution of the extracellular potassium concentration, which will be used as a input in the three-dimensional model simulations (Figure 1B). With this and the time course of the other 5 metabolites, the 3D simulations can be triggered by setting the conditions at given instant of times.

The 3D simulations consisted of six consecutive beats with a cycle length of 600 ms. In these simulations, the Purkinje system used in [9] has not been considered, but the location of the Purkinje muscle junctions and their activation instants have been replicated to apply the sinus pulses (S1). After the fifth S1 beat, a premature stimulus (S2) was applied to a region of the epicardial BZ in the mid-posterior LV wall, highlighted in yellow in Figure 1A. This stimulus mimics the earlier epicardial activity that has been experimentally observed in the myocardium adjacent to the border zone after a premature beat in acute ischemia [3]. The time interval between the fifth S1 and S2 (coupling interval or CI) was varied with a resolution of 5 ms to determine the VW duration for re-entry. The CI interval that produced at least two re-entry cycles in the biventricular model was defined as the VW. To determine the VW over time, and considering computational limitations, only the odd minutes have been simulated. VVs have been calculated for the control and for four different calcium channel blocking factors corresponding to 20, 40, 60 and 80%. To compare the VVs with each other, a re-entry probability index (RPI) has been defined as shown in Eq. 2 and is calculated to each VV case:

$$RPI = 1 - \prod_{i=1}^{n}\left(1 - \frac{VV_{minute_i}}{600}\right)$$
$$where\ i = 2k - 1, for\ k = 1,2,\dots,\left[\frac{n+1}{2}\right] \quad \text{Eq. 2}$$

The single cell simulations were performed with a custom-made script in MATLAB (MathWorks, Natick, MA) using an adaptive time step method. On the contrary, the three-dimensional simulations were run using ELVIRA software [13], where the electrical propagation throughout the ventricles was computed by solving the reaction-diffusion monodomain equation. The complete system of differential equations arising from the computation of the model was solved using the finite element method (FEM).

3. Results

After incorporating the [11] modifications, results from 0D simulations of both the real [6] and ideal [7] drugs indicate that a blockade of calcium channels is a highly promising anti-arrhythmic feature. It effectively reduces the cardiac cell's exposure time to extracellular potassium concentrations ranging from 8 to 13 mM and promotes the removal of the alternans period completely. Therefore, this calcium block is simulated in a three-dimensional isolated manner to verify its effect at the organ level.

The results of the 3D simulations show the 5 VV obtained in figure 2A, corresponding to the control, shown in black, and for the low (20%), medium-low (40%), medium-high (60%), and high (80%) blockages on the

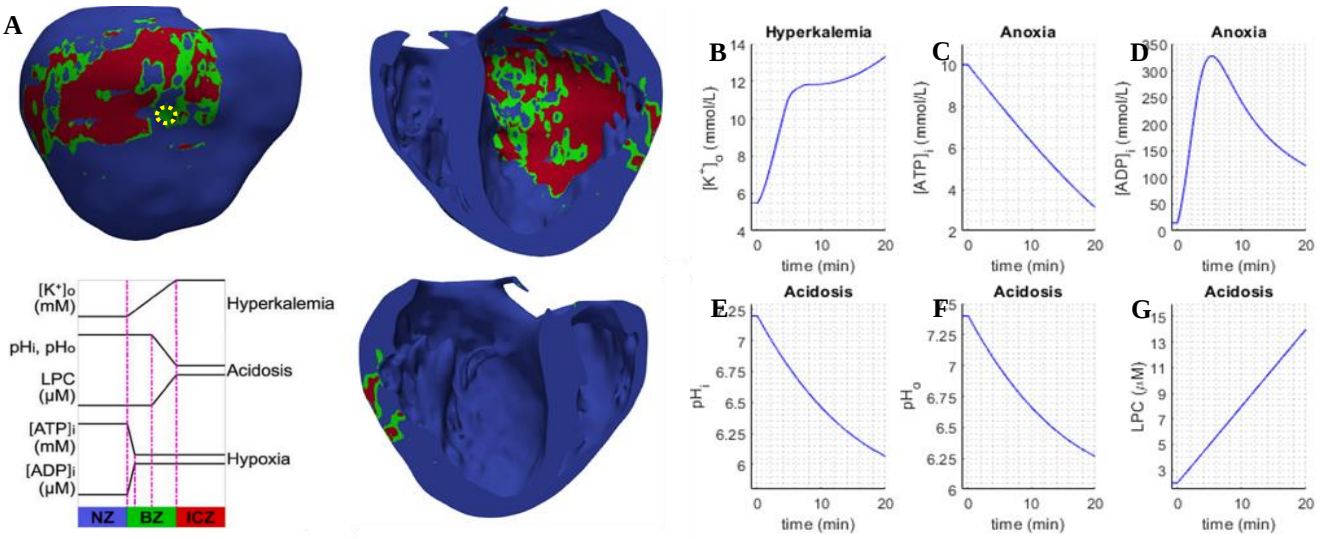

Figure 1. (A) Labelling of ischemic regions (ICZ in red, BZ in green and NZ in blue) and the diffusion of metabolites through them. Highlighted in yellow, the ectopic beat stimulation zone. (B) Time course of extracellular potassium concentration. (C-G) Time course of ischemia-related parameters during the first 20 min of acute ischemia. B to G parameter values before arterial occlusion (t = 0) correspond to healthy conditions.

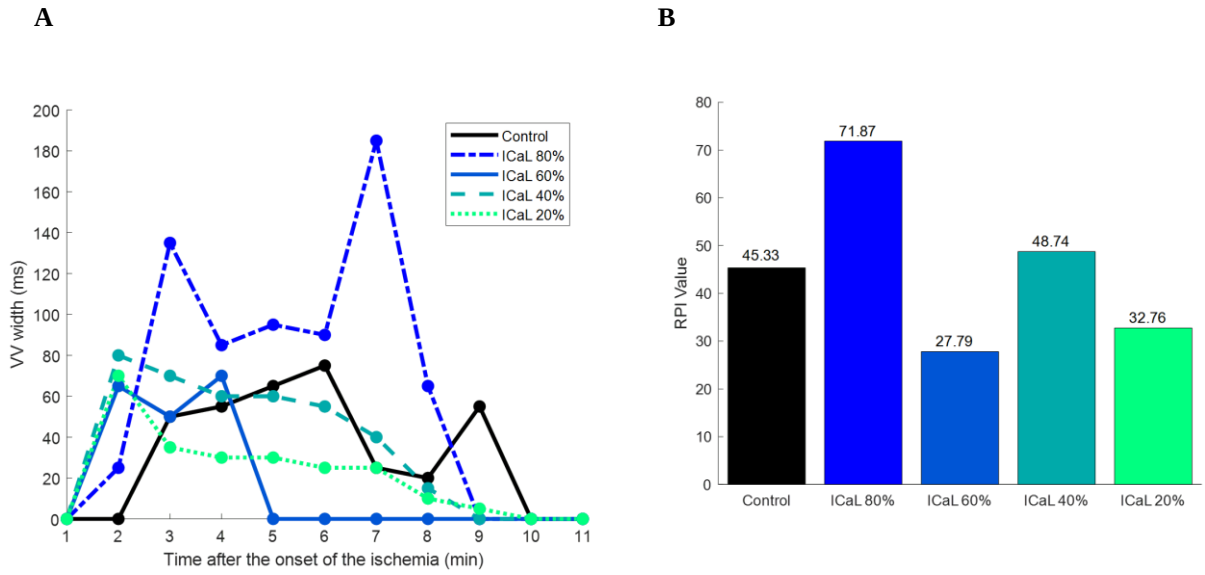

Figure 2. Vulnerable Windows (A) and RPIs (B) for control, low, medium-low, medium-high and high calcium block

calcium channel. The x-axis represents the time in minutes since the occlusion occurred. The y-axis represents the duration in ms of the VV. The latter duration refers to the time under which re-entries occur. The RPI obtained for the different cases is shown in figure 2B. The x-axis shows the cases, and the y-axis shows the RPI value. Above each bar, the RPI value is indicated. Figure 3 illustrates a comparison between two cases of 3D simulations. Case A shows the control against low blockade for minute XXX, with an S2 at YYY ms where re-entry occurs due to the blockade. Case B displays the control versus high blockade for minute BBB, with an S2 at CCC ms where re-entry is prevented by the blockade.

There is a biphasic/triphasic behaviour, i.e., a low or medium-high blockage has higher VV with an associated higher RPI, while a medium-low or high blockage achieves lower VV and therefore lower RPI. As the degree of calcium blockade and minute of ischemia increases, the central ischemic zone is transformed from functional to an anatomical obstacle. Further blocking at each type of obstacle is advantageous with the mechanism restarting when the obstacle type changes. This may explain the biphasic/triphasic behaviour.

The limitations of this work can be found in the resolution the three-dimensional simulations due to the high computational cost. The joint electro-mechanical effect of the drug at the organ level should also be studied.

4. Conclusion

Calcium medium-low or high blockage have been shown to be a candidate at ventricular levels and therefore may be a good characteristic for the candidate protective drug in acute ischemia, as it eliminates the alternans period and drastically reduces VW. The results obtained show promising indications in terms of drug efficacy in acute ischemia and serve as a basis for further study in conjunction with mechanistic simulations. In addition, the new RPI biomarker allows for clearer identification of how different mechanisms affect the likelihood ofre-entry.

Acknowledgments

This project has received funding from the European 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). The authors also thankfully acknowledge the computer resources at MareNostrum and the technical support provided by Barcelona Supercomputing Center (IM-2021-1-0001,IM-2021-1-0003, IM-2022-1-0002, IM-2023-1-0002).

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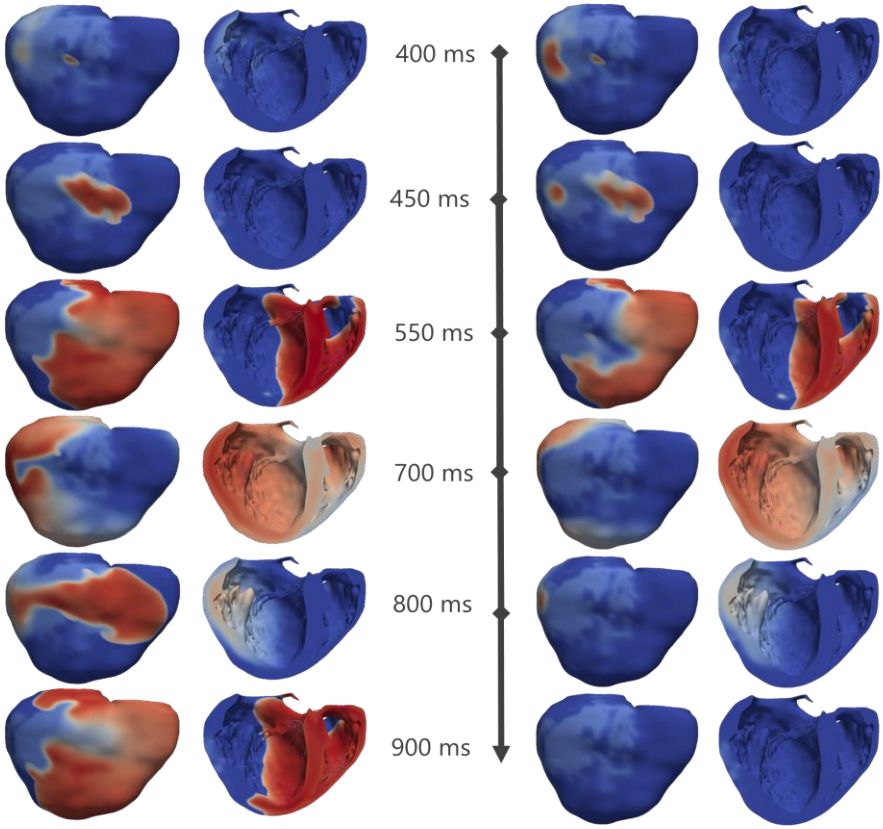

Figure 3. Simulation of an S2 pulse at 390 ms, 5 minutes after the onset of ischemia. Left: control. Right: same case but with calcium channels at 60%. Snapshots correspond to instants shown in middle bar

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