Pinacidil Modifies the Vulnerability to Reentry during Regional Myocardial Ischemia in a Dose Dependent Manner: a Simulation Study

B Trenor, JM Ferrero (Jr), F Montilla

Universidad Politecnica de Valencia, Valencia, Spain

Abstract

Potassium channel openers, such as pinacidil, are known to increase ATP-sensitive potassium current. Its activation changes markedly action potential configuration, specially during myocardial ischemia, creating inhomogeneities and favoring the occurrence of reentry. However, controversial effects of KCOs have been observed. The aim of this work was to analyze the effects of pinacidil on reentry generation in a regional ischemic tissue using Luo-Rudy II model. Our results show that the vulnerable window (VW) width increases to 49 ms and reaches a maximum value of 54 ms for a dose of 0.001 mmol/L and 0.003 mmol/L respectively, compared to 45 ms in the absence of the drug. For higher doses, the VW width is reduced, and no reentry occurs for 0.01 mmol/L. We conclude that pinacidil modifies vulnerability to reentries during the acute phase of regional ischemia in a dose-dependent manner, and has antiarrhythmic effects for elevated doses.

1. Introduction

ATP-sensitive potassium channels (K(ATP) channels) remain closed during normoxia and open under pathological situations, such as myocardial ischemia [1], due to the reduction of intracellular ATP concentration ($[ATP]_i$) [2] and the raise of intracellular ADP ($[ADP]_i$) [3]. The presence of pinacidil, a potassium channel opener (KCO), also activates ATP-sensitive potassium current ($I_{K(ATP)}$) [4]. Many experimental studies have addressed the effect of this drug on arrhythmias caused by reentry. Indeed, the activation of K(ATP) channels accelerates the repolarization of the cell reducing action potential duration (APD). In addition, pinacidil has a major effect on APD in ischemic zones than in normal zones. Alterations and inhomogeneities arise within the tissue during regional ischemia and thus in an ischemic tissue in the presence of pinacidil. Also during ischemia conduction velocity (CV) and refractory period (RP) are affected and postrepolarization refractoriness is present in the ischemic zone [5]. These alterations and inhomogeneities favour the occurrence of unidirectional block and thus reentry [6].

However, many authors sustain the hypothesis that pinacidil has antiarrhythmic and protective effects [7,8] in the sense that they prevent the generation of triggered activity [9] and have been found to prevent the occurrence of fibrillation under specific situations [10]. The action of this drug is controversial and further investigations should be done to elucidate its effects.

The aim of this work was to analyze the influence of pinacidil on reentry initiation and maintenance in a regional ischemic tissue by means of computer simulations.

2. Methods

In order to analyze the effects of pinacidil on reentry initiation and maintenance, we simulated the electrical activity of a prematurely stimulated regional ischemic tissue. Several doses of the drug: 0, 0.001 mmol/L, 0.003 mmol/L, 0.005 mmol/L, 0.007 mmol/L and 0.01 mmol/L were applied. In each case, we carried out a set of simulations stimulating prematurely with different coupling intervals (CIs). Then we measured the width of the vulnerable window (VW) to reentry, i.e. the interval of time including the instants of premature stimulation, which initiate reentry.

As depicted in figure 1, the premature current pulse was applied after the basic stimulus given at t=150 ms, their amplitude was 1.5 times diastolic threshold and the duration was 2 ms.

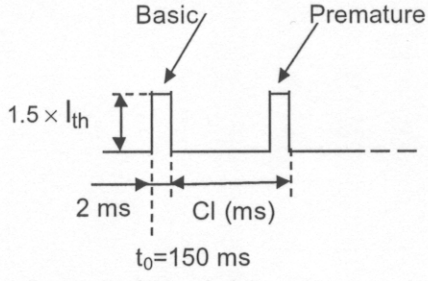

Figure 1. Protocol of stimulation

Both current pulses were applied to the bottom edge of the tissue, as shown in figure 2. We considered a square anisotropic tissue with a 4:1 ratio of anisotropy. The dimensions of the sheet were 5.5×5.5cm and was divided

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550×550 elements of 100μm×100μm.

As depicted in the scheme three different zones were distinguished in order to reproduce regional ischemic electrophysiological conditions. The healthy normal zone (NZ), where metabolical conditions are normoxic conditions: extracellular potassium concentration ($[K^+]_o$) of 5.4 mM, intracellular ATP and ADP concentrations ($[ATP]_i$ and $[ADP]_i$) of 6.8 mM and 15 μM respectively, and sodium and calcium channels unblocked. Along the border zone (BZ), defined as a ring 1 cm wide, metabolical conditions changed progressively until reaching ischemic conditions, which remain stable in the central circular ischemic zone (CZ). $[K^+]_o$ suffers a linear increase from 5.4 mM up to 12.5mM along 1 cm of tissue, while $[ATP]_i$ and $[ADP]_i$ reach the ischemic concentration of 4.6 mM and 99 μM respectively earlier (the metabolical BZ is 1 mm wide). Finally, along the last 0.5 cm of the border zone, the progressive block of sodium and calcium channels begins (due to a decrease in pH) reaching a fraction of open channels in the CZ of 0.75.

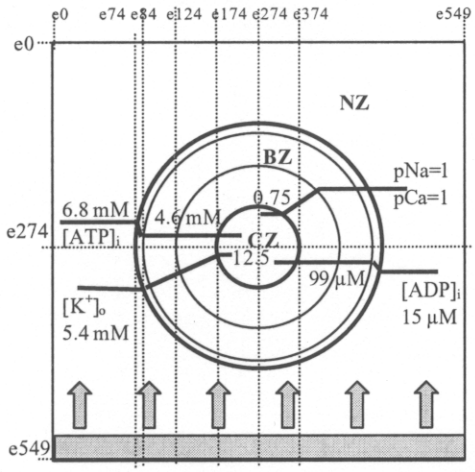

Figure 2. Bidimensional tissue of 550×550 elements with a normal zone (NZ), a border zone (BZ) and a central ischemia zone (CZ).

The cellular model was a modified version of Luo-Rudy phase II formulation [11] of ventricular AP, including IK(ATP) formulation by Ferrero et al. [12] and the effects of pinacidil on this current [13].

3. Results

The first basic stimulation applied to the bottom edge of the regional ischemic tissue propagated in the longitudinal direction (vertical direction in figure 2), reaching the top edge. This propagation was observed for all the applied doses of pinacidil or in the control situation, i.e. in the absence of the drug. In first instance,

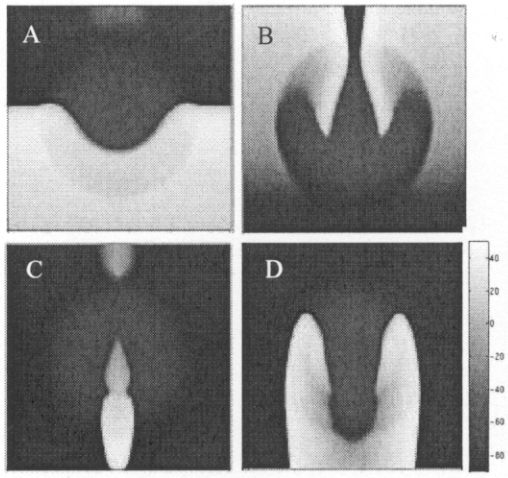

Figure 3. Reentry initiation after the premature stimulation applied at t=362 ms in the absence of pinacidil. These isopotential maps were taken at t=425 ms (A), t=525 ms (B), t=650 ms (C) and t=750 ms (D).

propagation through the NZ was planar. However, a curved pattern of activation was observed when the propagation reached the BZ and the CZ, as shown in isopotential map A in figure 3. This effect can be explained by the differences in conduction velocity in the NZ (492.61 mm/ms), the CZ (303.03 mm/ms) and the BZ (534.75 mm/ms).

Afterwards, premature stimulation had different effects on the electrical activity of the tissue depending on the dose of the drug and on the instant of time of stimulation. On the one hand, if the current pulse was too premature, the bottom fiber was still in refractoriness so that AP propagation could not take place. Was the current pulse applied at an instant of time included in the VW for the considered dose of pinacidil, and was the AP propagation blocked in the proximal CZ, as shown in isopotential map 3A. Then, the whole CZ was surrounded by the wavefront until the distal zone of the CZ was at last excited. Propagation block was subsequently unidirectional and reentry was initiated (see figure 3).

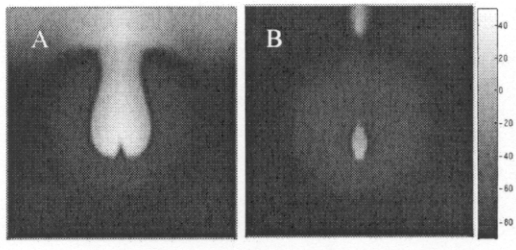

Figure 4. AP propagation block after the premature stimulation applied at t=363 ms in the absence of pinacidil. These isopotential maps were taken at t=590 ms (A), t=665 ms (B).

In contrast, when premature stimulation was applied at instants of time not included in the VW, greater than the upper limit or slightly smaller than the lower limit, block was bidirectional (see figure 4), and no reentry was initiated, neither mantained. In figure 4, the premature stimulation has already propagated and surrounded the CZ. In both isopotential maps the AP is trying to reenter but is finally blocked.

Finally, if the premature pulse was applied much later than the upper limit of the VW, propagation was achieved through the whole sheet.

As afore mentioned, this set of simulations was carried out for different doses of pinacidil and different widths of VW ware obtained. We observed a biphasic behavior of the drug, as depicted in figure 5. In first instance, in the control situation, the VW width was 45 ms. When the dose was slightly raised, a widening of the window was obtained, reaching its greatest width of 54 ms for 0.003 mmol/L. In contrast, with greater doses, the VW was reduced, and disappeared for 0.01 mmol/L or bigger doses.

4. Discussion

During the acute phase of myocardial ischemia, arrhythmias arise very often due to reentrant circuits formation [6,14]. Two conditions are necessary to generate reentry: the existence of a premature stimulus acting as a trigger, and electrophysiological conditions favoring unidirectional block and thus initiation and maintenance of the reentrant circuit. In this work, these two last phases of reentry generation have been addressed: initiation and maintenance, under the effects of pinacidil.

Many experimental studies have analyzed the electrophysiological conditions favoring reentry generation, such as inhomogeneities in action potential duration (APD), conduction velocity (CV), refractoriness [6,15] and anisotropy [16].

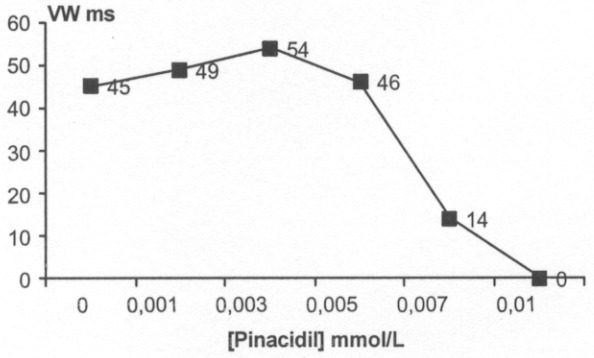

Figure 5. Width of the VW for different doses of pinacidil.

The above described heterogeneities are present in the regional ischemic tissue simulated in this work, and thus initiation and maintenance of reentry could be observed after the action of the triggering premature stimulation.

Much attention has been paid to the influence of pinacidil on arrhythmias and reentry generation. Several experimental works have shown the controversial effects of this drug.

On the one hand, KCOs have beneficial effects on arrhythmias caused by abnormal repolarization. These drugs prevent early after depolarizations (EADs) and delayed after depolarizations (DADs) generation [7], exerting antiarrhythmic effects.

As for reentry generation, experimental results with KCOs depend on the applied doses and heart conditions. Pinacidil was found to be both proarrhythmic [15,17] and antiarrhythmic [7,8].

Simulation studies are a useful tool to analyze in detail these effects. Our results showed that high doses of pinacidil reduced the probability of reentry generation. Indeed, a premature stimulation in the regional ischemic tissue with 0.01 mmol/L pinacidil was blocked bidirectionally. Postrepolarization refractoriness in the CZ [18] can explain the proximal AP block in the presence or in the absence of the drug. However distal AP block can be influenced by the high dose of pinacidil, as in control situation and after a premature stimulation applied at the same instant of time the distal CZ is excited. Indeed, $I_{K(ATP)}$ activation accelerates cellular repolarization and reduces membrane potential, and thus potential gradient in the direction of propagation. Consequently, axial current is reduced and can provoke the AP block. Furthermore, $I_{K(ATP)}$ competes with calcium current, which is responsible for the second phase of cellular depolarization, so that high doses of pinacidil can hamper AP development and propagation.

Low doses of the drug exert an opposite effect: the VW widens compared to the control window. Unidirectional block (UDB) occurs whereas bidirectional block (BDB) takes place in the absence of the drug for the same stimulation conditions. We hypothetize that a slightly higher activation of $I_{K(ATP)}$ reduces slightly APD, and sodium inactivation gates h and j start sooner their recovery from inactivation (results not shown). This gates are responsible for cell refractoriness. Subsequently, when the wavefront reaches the distal CZ, these cells have already recovered and excitation is achieved in the presence of low doses of the drug but not in its absence.

We can conclude that there is a critical dose of pinacidil (0.003 mmol/L in our case) for which the probability of UDB is maximum. This dose may vary for specific tissue conditions. Furthermore, high enough doses of the drug (greater than 0.01 mmol/L in our case) enhance significantly $I_{K(ATP)}$ activity, favoring BDB and hampering reentry generation. If we take into account that pinacidil prevents also EADs and DADs generation,

we can sustain the hypothesis that pinacidil exerts antiarrhythmic effects at high doses.

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Address for correspondence.

Beatriz Trenor.
Universidad Politecnica de Valencia
Camino de Vera s/n
Valencia 46022
Spain.
btrenor@eln.upv.es