

Effect of Lidocaine in Acute Ischemic Situations: A Computer Modelling Study

K Cardona¹, J Saiz¹, JM(Jr) Ferrero¹, M Martinez²,
G Molto³, V Hernandez³

¹Center for Research and Innovation on Bioengineering, UPV, Valencia, Spain

²Grupo Predictive Control and Heuristic Optimization Research Group, UPV, Valencia, Spain

³High Performance Networking and Computing Group, UPV, Valencia, Spain

Abstract

Lidocaine is a drug that blocks the sodium channel in a pH, frequency and concentration dependent manner. In this work, we have used a mathematical model of lidocaine developed by our group and incorporated it into the Luo Rudy model of ventricular action potential. We have studied the action of lidocaine on the sodium current (I_{Na}), maximum upstroke velocity (dV/dt) and conduction velocity (CV) in ischemic tissue. Additionally, we measured the block window (BW) in different concentrations of drug. Our results show that 100 $\mu\text{mol/L}$ of lidocaine under simulated acute ischemic conditions reduces the I_{Na} , dV/dt and CV a 42 %, 41 % and 24 % in the normal zone (cell 54), respectively while in the border zone (cell 94) the decreased was 37 %; 44 % and 18 % for the same parameters. Finally, we have found that lidocaine diminished de BW, thus the drug tends to eliminate the UDB.

1. Introduction

Lidocaine is a class Ib antiarrhythmic drug that blocks the sodium channels. The blockade of these channels produces a decrease in the sodium current (I_{Na}) as a result of it reduction the conduction velocity (CV) is diminished too [1,2]. The actions of lidocaine on the sodium channel are a dose and use dependent manner

The possible mechanism for drug-associated arrhythmogenesis could be related with the delayed recovery of cellular excitability which can introduce a nonuniform dispersion of refractoriness along the cardiac fiber and could serve as a substrate for initiating re-entrant rhythms [3]. Carsson has proposed that the failure in the propagation can favour a unidirectional block of wave front of the stimuli [4,5].

Under ischemic conditions the action of lidocaine is modified. The substantial fall in external pH during myocardial ischemia changes the kinetics of drug binding to the Na^+ channel and may explain the more depressant

effect of these drugs during myocardial ischemia [6]. A study has found that the kinetics of recovery from lidocaine were increased and slowed when the extracellular pH was reduced [7,8].

On the other hand, the mechanism by which drugs like lidocaine suppresses or exerts arrhythmic effect is still not well understood. Some experiments have shown that the reduction of excitability promotes the proarrhythmic effect and in ischemic conditions its action is increased due to dispersion of the conduction [9-11]. However, limited studies have demonstrated that lidocaine can prevent arrhythmias as a result of its ability to prolong the refractoriness [12].

To understand the nature of this paradox, we first explore the action of lidocaine on the characteristics on action potential (sodium current (I_{Na}), maximum upstroke velocity (dV/dt) and conduction velocity (CV)) in ischemic tissue. And then, we studied the effect of lidocaine on the block window (BW) defined as the range of delays between the premature stimuli can not propagate around all tissue.

2. Methods

We use the mathematical model of lidocaine developed previously by our group where it is included the pH and use dependent. This model is based in the guarded receptor hypothesis (GRH) and the binding and unbinding process is assumed as a hydrophobic process, a hydrophilic process, and a coupling of charged and neutral blocked channels with a proton exchange process [13].

Additionally, we have used the Luo Rudy model (LRd00) of guinea pig ventricular cells in order to modelling the electrical activity of myocardial [14].

The simulated tissue was composed of a strand of 370 cells in acute ischemic conditions. To introduce the heterogeneity produced by acute ischemia, we have simulated three main components: hiperkalemia (increase in the extracellular K^+ concentration ($[\text{K}^+]_o$)), hypoxia (activation of the $\text{K}[\text{ATP}]$ current) and acidosis

(reduction in the availability of Na^+ and Ca^+ channels) [15,16].

We have assumed that the lidocaine should be able to get in of the ischemic zone the same degree as potassium can get out of the ischemic zone.

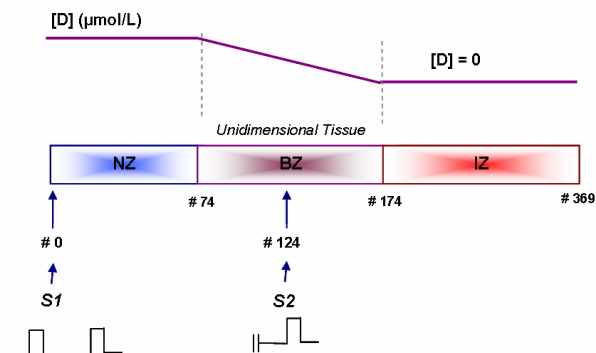


Figure 1. Schematic of unidimensional tissue under ischemic conditions.

The excitation was applied to cell # 0, and the action potential characteristics were measured in the different zones of the tissue when the steady-state was reached as shown in figure 1. We tested the effect of different lidocaine concentrations on the sodium current (I_{Na}), maximum upstroke velocity (dV/dt) and the conduction velocity (CV). In order to explore the cell excitability, we used the concept of the block window (BW), which was obtained with the protocol S1-S2. A basic stimulus (S1) of 500 ms cycle length (BCL) with pulse duration of 2 ms has been used and the premature pulse (S2) was applied at a different location from the basic stimulus (cell # 124).

3. Results and discussion

Initially, we measured the effect of different concentrations of lidocaine on I_{Na} , dV/dt and CV for BCL of 200 and 500 ms under ischemic conditions. In the figure 2, we can observe the reduction on I_{Na} in the different zones of the tissue.

In the normal zone (cell # 54), the I_{Na} was decreased a 42 % for 100 $\mu\text{mol/L}$ of lidocaine. In the border zone, the decrease in the cell 94 was a 37 %, whereas in the cell 174, it was a 1 %. Finally, the I_{Na} was unaffected at the ischemic zone.

When we varied the BCL under ischemic conditions, the action of lidocaine on I_{Na} was modulated, so if we decreased the BCL the reduction was increased. In normal tissue, in presence of 100 $\mu\text{mol/L}$ lidocaine the I_{Na} was reduced a 54 % and 41 % for BCL of 200 and 500 ms, respectively. In the border zone, the decline was of 48 % and 36 % for the same BCLs.

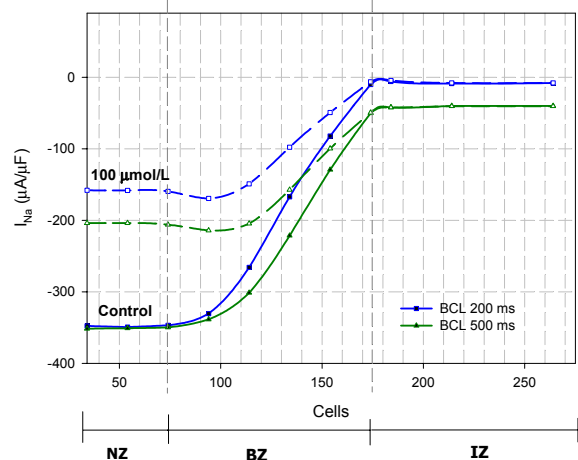


Figure 2. Effect of 100 $\mu\text{mol/L}$ (dashed line) lidocaine on the I_{Na} and in absence of the drug (solid line) in different cells for a BCL of 200 (■) and 500 ms (▲).

In respect to the dV/dt , we found the same effects that the sodium current, the reduction on dV/dt was higher at the normal zone than at the ischemic. In our results we have obtained that in the normal zone the dV/dt was decreased 20 %, 36 % and 50 % for the concentrations of 20, 50 and 100 $\mu\text{mol/L}$ of lidocaine, respectively. We can observe this effect in the table 1.

		dV/dt (%)		
		Concentration of drug ($\mu\text{mol/L}$)		
	Cell	20	50	100
NZ	54	20	36	50
	74	19	35	49
BZ	134	10	21	34
	194	0.7	4	4.5

Table 1. Effect of different concentrations of lidocaine on dV/dt in the several zones of the ischemic tissue

Additionally, the action of lidocaine on CV was increased when we grow up the concentration. In the figure 3, we show the effect of lidocaine on CV in the different zones of the tissue. In the normal zone, the reduction was similar for all cells whereas in the border zone the reduction depends on the considered cell, in the middle of the zone there is an increase in the value of CV which is maintained in the presence of lidocaine.

We found few studies where the action of lidocaine on the characteristics of action potential was evaluated. However, our results were consistent with experimental recordings where is expressed the dispersion on the CV when the ischemic conditions and the drug were mixed. [17, 18].

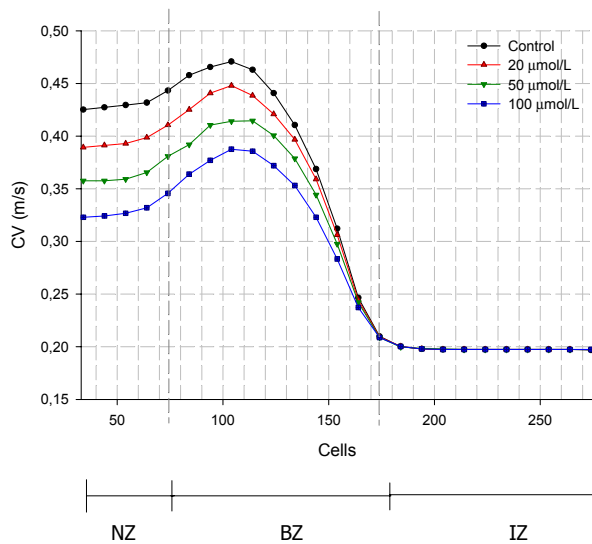


Figure 3. Effect of different concentration of lidocaine on the CV. Control (●); 20 (▲); 50 (▼) y 100 (■) $\mu\text{mol/L}$ lidocaine.

It is well known that slow conduction and unidirectional block (UDB) set the stage for reentry after a premature stimulation. Our previous results have demonstrated that lidocaine changes the CV. For this reason, we explore the effect of drug on excitability under ischemic conditions through the concept of block window (BW). We used the protocols s1-s2, the basic stimulation was applied in the cell 0. To the stimuli premature (s2) we applied in cell 124. We obtained the limits of the BW varied the coupling interval (CI).

With this protocol, we found three pattern of activation: no propagation (the tissue was still refractoriness state and the stimuli premature can not propagate), UDB and complete propagation.

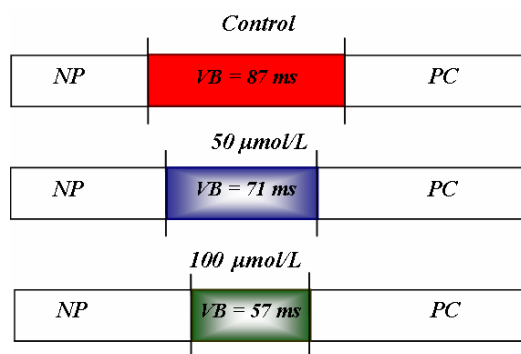


Figure 4. Width of the block window for different concentrations of lidocaine.

In the figure 4 shows the BW and its superior and inferior limits obtained for a control, 50 and 100 $\mu\text{mol/L}$

of lidocaine.

In absence of drug we have found a BW around 87 ms while, with 50 and 100 μM lidocaine the BW was 71 and 57 ms, respectively. Additionally, we have observed that the two limits were modulated in presence of both concentrations of drug due to the action of lidocaine on the slow CV and the effective refractory period. Table 2 shows the values for the limits and BW founded.

Concentrations ($\mu\text{mol/L}$)	IL (ms)	SL (ms)	BW (ms)	BW (%)
0	155	242	87	
50	163	234	71	18
100	173	230	57	34

Table 2. Values for the inferior (IL) and superior (SL) limit, block window (BW) in different concentrations of lidocaine under simulated acute ischemic conditions.

4. Conclusions

In conclusion, our simulations have shown that the action of lidocaine on the I_{Na} , dV/dt and CV under ischemic conditions depend on the zone of the tissue. As well as, we can observe that the blockade in all zones of the tissue is frequency dependent when the tissue is modified for the acute ischemia. Furthermore, our simulations are consistent with experimental observations where the lidocaine and acute regional ischemic modulate the dispersion of the CV due to different action on the diverse zones of the ischemic tissue.

Finally, we have observed that the BW was decreased for the different concentrations of the drug studied. Therefore, we can say that lidocaine reduces the start of UDB, thus it could be an antiarrhythmic effect of drug.

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Address for correspondence

Karen Cardona Urrego
 Instituto de Investigación e Innovación en Bioingeniería, UPV
 Valencia- Spain

E-mail: kacarur1@doctor.upv.