Effect of Lidocaine on Reentrant Ventricular Circuits in Acute Ischemic Situations. A Computer Modelling Study

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Abstract

Lidocaine is used as an antiarrhythmic drug, its effectiveness is based on its ability to induce use-dependent block of cardiac sodium channels. This drug has an effect on conduction velocity (CV) and effective refractory period (ERP). Changes in CV and ERP could have an important role in the induction or suppression of reentrant circuits. We have studied the effect of lidocaine on CV, ERP and the characteristics of reentry conduction induced in regional ischemic tissue by computer simulations. The bi-dimensional tissue includes an ischemic zone that corresponds to 9 minutes of ischemia.

This study demonstrates that the lidocaine reduces the CV 40% and 50% and prolongs of ERP 5% and 14% for 50 and 100 μM of lidocaine respectively. As well as, lidocaine can depress 20% and 60% the window vulnerable respectively.

1. Introduction

Class I local anesthetic (LA) such as lidocaine blocks Na^+ current by binding to voltage-gated Na^+ channels. LA drugs exhibits use-dependent block of Na^+ current and it is the hallmark of its antiarrhythmic activity, so this drug is more effective when the frequency of action potentials (AP) is high [1].

The kinetics of the drug can be explained by different experimental studies, where the effect of lidocaine is higher for inactivation and activation state and is lower for rest state. Several attempts have been made to estimate drug affinity for specific channel states based upon hypothetical modelling of channel and drug behaviour: "modulated receptor hypothesis" (MRH) [2] and "guarded receptor hypothesis" (GRH) [3]. Among them, the GRT introduced an analytical method for estimation of rate constants which has an important advantage due to unnecessary precise model of Na^+ channel behaviour.

It is known by different experimental studies that the lidocaine reduces the CV [4] and prolongs the ERP [5,6] in a dose and use dependent manner. The prolongation of refractoriness could be antiarrythmic however; both CV and ERP are major determinants of reentry arrhythmia circuits. Janse [7] and co-workers have found that the prolongation of the ERP in normal tissue can suppress cardiac arrhythmias. Although, the depressant action of the lidocaine on impulse conduction could play an important role in the development arrythmias [8].

The mechanism by which lidocaine suppress o exert arrhythmic effect are still not well understood. Some experiments have shown that the effictiveness of this drug is due to its ability to suppress the re-entrant impulse by prolonged refractoriness. In addition to the reduction of excitability and conversion from uni to bi-directional block it is thought to be one mechanism by which lidocaine prevents arrhythmias [9]. However, limited studies showed occasional proarrhythmic reactions related to strong conduction slowing in the ischemic zone [10]. Basically, depending on the state of the tissue, the additional electrophysiological actions of lidocaine may serve to promote, prevent or have no effect on the induction of re-entrant arrhythmias. [11]

In order to explore the antiarrythmic mechanism of the lidocaine, we investigated the effect on the CV and ERP in normal and ischemic tissue, and we observed the effect of lidocaine on characteristics of reentry conduction induced in ischemic tissue.

2. Methods

The bi-dimensional tissue used in this study is composed of 550 x 550 coupled cells. The mathematical model of the cardiac action potential developed by Luo and Rudy (LRd00) was used in order to simulate the guinea pig ventricular action potential [12]

The effect of lidocaine on sodium current (I_{Na}) was modeled by our group in a previous work. We used the "guarded receptor hypothesis" [3] and assumed that the drug bind to the channel with higher affinity in both the open and inactivated state and it is lower in the rest state.

The interaction between drug and ion channel can be represented by:

$$\frac{db}{dt} = k \cdot [Drug] \cdot (1-b) - l \cdot b \quad (1)$$

Where b represents the fraction of drug bind to the channel, [Drug] is the drug concentration and k y l are expressed by the following equations:

$$k = \left[m^3 hj \cdot k_A + m^3 (1-hj) \cdot k_I + \left(1 - m^3\right) \cdot k_r \right]$$
$$1 = \left[m^3 hj \cdot l_A + m^3 (1-hj) \cdot l_I + \left(1 - m^3\right) \cdot l_r \right] \quad (2)$$

Where k_A, k_I, k_R, l_A, l_I and l_R are the forward and reverse rate constants in the activated (A), inactivated (I) and rest (R) state; m^3, h and j are channel gates [13]. Using an analytical method based upon the GRH, we calculated apparent rate constant describing lidocaine's interaction with the three states of channel (resting, activated and inactivated), and based on the experimental results obtained by Clarkson [14].

We suggest a formulation of the current I_{Na} that takes into account the fraction of channels blocked by the drug (b), as follows

$$I_{Na} = \overline{g}_{Na} \cdot m^3 \cdot h \cdot j \cdot (1-b) \cdot (V - E_{Na}) \quad (3)$$

Where $\overline{g}_{Na}$ is the maximum conductance, V is the membrane potential and E_{Na} is the reversal potential.

The heterogeneity introduced by acute ischemia has been simulated by three main components, hyperkalemia, hypoxia and acidosis. First, hypoxia was taken into account by partially opening of ATP–sensitive K^+ current ($I_{K(ATP)}$), which was formulated as Ferrero Jr. et al [15]. Intracellular values of ATP and ADP were comprised in the range 6.8-4.6 mmol/L and 12-99 µmol/L, respectively. Secondly, hyperkalemia was considered by elevation extracellular K^+ concentrations ($[k^+]_o$), it was set to a value in the range 5.4-12.5 mmol/L. Finally, acidosis was accounted by means of a multiplicative factor (f_{pH}) that reduces up to a 25 % the Ina and the Ca^{2+} current through the L-type channels (I_{CaL}). The distribution of both hyperkalemia and acidosis between normal (NZ) and ischemic (IZ) zone can be observe in figure 1. In our simulations, we have considered the conditions present in the myocardium after 9 minutes of ischemia (The phase Ia of regional ischemia).

To measure the ERP, CV and the vulnerable window, we have paced continuously with basic train of pulses (S1) of 500ms cycle length with a pulse duration of 2 ms. After, we have applied an extrastimuli (S1) which was introduced at different coupling intervals (CI).

The ERP was obtained to shorten progressively the CI until that the extrastimuli could produce an action potential. Measurements of ERP and CV were obtained over range of basic lengths between 200 and 500 ms for different concentrations of lidocaine. The ERP and CV were measured in the middle of the tissue. As well as, the vulnerable window was defined as the interval of time where a momentary stimulus can instigate a reentry circuit [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. (fig 1)

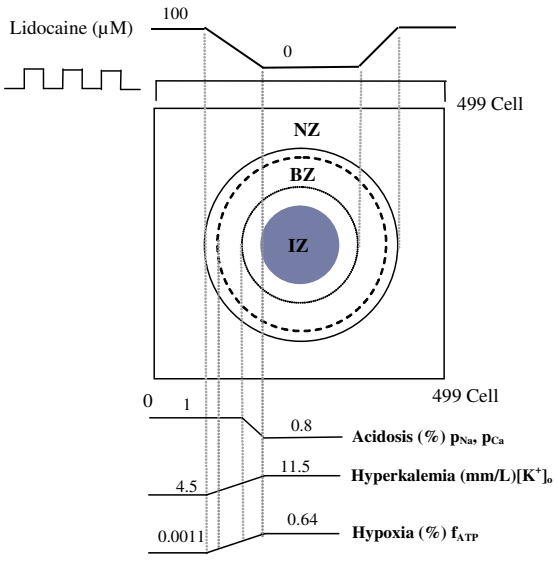

Figure 1. Schematic of the 2D virtual tissue and values of the relevant parameters. The upper trace shows the spatial variation of lidocaine and the bottom traces show the spatial variations of ischemia

3. Results and discussion

In the first place, we measured the effect of different concentrations of lidocaine on the CV and ERP. The ERP was determined as the shortest S1-S1 interval that elicited a propagated action potential.

During normal conditions (without drug), the ERP was decreased in the same way that the cycle length was shortened. When the lidocaine was introduced the ERP was increased from 181 to 191 ms by 50 µM lidocaine and from 181 to 207 ms by 100 µM lidocaine. Figure 2 summarizes the drug effect on the ERP by different concentrations of lidocaine and BCL.

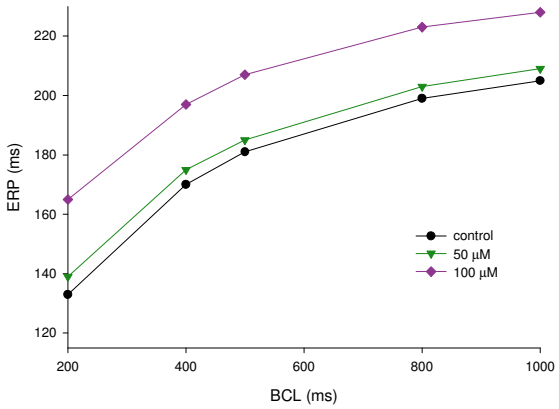

Figure 2.Effect on lidocaine on ERP in different BCLs (• control - ▼ 50µM - ♦ 100 µM)

The ERP was slightly shortened at low concentrations of drug; however these changes were significant at higher concentrations. These effects are similar to those reported by other authors [17]

The effect of lidocaine on conduction velocity was determined during control and different concentrations of lidocaine. In the absence of lidocaine, the conduction velocity was 0.43 and 0.42 m/s for the BCL of 200 and 500 ms respectively. For 100 µM lidocaine the CV decreased 0.198 and 0.194 m/s in the same range of concentrations. Table 1 shows the effect of lidocaine on ERP and CV in different concentrations and BCLs.

Lido (µM)	ERP (ms)		CV (m/s)	
	200 ms	500 ms	200 ms	500 ms
0	133	181	0.43	0.42
50	147	191	0.25	0.24
100	165	207	0.19	0.18

Table 1 Value for ERP and CV in conditions without drug and with 50 and 100 µM lidocaine.

It is known that the minimum size of a re-entrant wave is related to the wavelength, defined as the product between the ERP and CV, therefore some modifications of these parameters could affect the vulnerability to induce or suppress re-entrant circuit. For this reason, we explored the effect of lidocaine on vulnerable window. We have considered an ischemic tissue in phase 1a. In absence of drug we have found a vulnerable window (VW) around 50 ± 5 ms while, with 50 and 100µM lidocaine the VW was 40 and 20 ms respectively. Additionally we have found the inferior and superior boundary changing the S1-S1 delay to identify the most (MPB) and the least premature boundary (LPB). We can observe these values in table 2.

Lidocaine (µM)	MPB (ms)	LPB (ms)	VW(ms)
0	160	210	50
50	170	210	40
100	180	200	20

Table 2. Effect of lidocaine on vulnerable window

Similar results were found by Yin et al [11], they showed that the lidocaine has antiarrhythmic effect because of prolongation of ERP, but a delay in the conduction velocity can generate a proarrhythmic effect. However, other studies with guinea-pig ventricular muscle and rabbit left atrium revealed drug-induced prolongation of the VP due to slow condution. [18,19]. Our results revealed that the vulnerable window was sensitive due to the concentration of the drug.

Figure 3 shows the patron of reentry in the absence of drug (fig. 3A) and in the presence of 100 µM lidocaine (fig. 3B). We used a CI of 190 ms for both simulations. In the first frame, we can observe how the interaction of extrastimuli with the ischemic zone produces a reentry. In the second frame, the reentry is produced as well, but the propagation of the wave front is slower than normal conditions.

4. Conclusions

In summary, these studies in acute ischemic suggest that the lidocaine can depress the vulnerable window in a concentration manner; so we can consider that the lidocaine exerts an antiarrhythmic effect in ischemic tissue. Furthermore, the extension of ERP can be responsible of this effect since the stimuli may find the tissue in state refractory and therefore the stimuli can not propagate.

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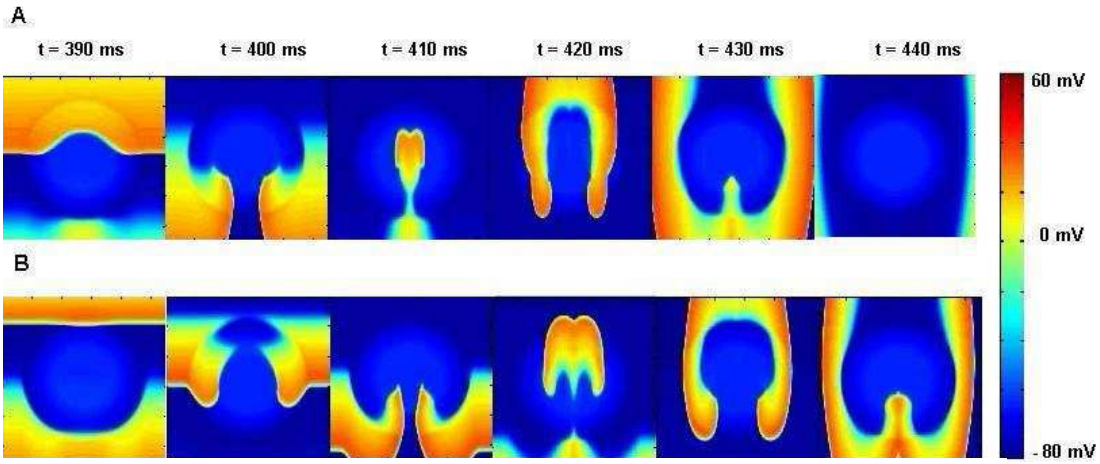

Figure 3. Pattern of reentry. A) in the absence of drug B) in the presence of 100 µM lidocaine

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