

The pH Dependence on the Electrophysiological Effect of Lidocaine in Ventricular Myocardium. a Computer Modelling Study

K Cardona¹, J Sáiz¹, JM(Jr) Ferrero¹, M Martínez²,
G Moltó³, V Hernandez³

¹Institute 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 class I antiarrhythmic drug that blocks the sodium channels. This drug is a tertiary amine and exists as an uncharged free amine and cationic protonated form at physiologic pH. Experimental data have shown that the rate of development and recovery of block is slowed at low pH. In this work, a mathematical model of lidocaine effects has been developed. This model has been incorporated to the Luo Rudy model of guinea pig ventricular action potential and we studied the effect of lidocaine on maximum upstroke velocity (dV/dt), action potential duration (APD), conduction velocity (CV) and effective refractory period (ERP) for different values of pH and concentrations of lidocaine. This study demonstrates that 50 $\mu\text{mol/L}$ of lidocaine reduces the dV/dt 36 % and 71 % as well as the CV a 8 % and 17 % for pH 7.4 and 6.4 respectively, while the ERP was increased 1.8 % and 0.6 % for pH of 7.4 and 6.4. The APD does not change when pH was modulated.

1. Introduction

Class I antiarrhythmic drugs exert at least a part of their effect by blocking the inward sodium current (I_{Na}). This drug 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 lidocaine is a tertiary amines and at physiological pH exist as uncharged free amine and as cationic protonated form. The proportion of each species depends on the ambient pH. A number of previous studies in nerve, cardiac, and skeletal muscle have shown that the kinetics of interaction of these drugs with their receptor is critically dependent on pH [2, 3, 4]. It is widely believed that the neutral drug form is thought to come and go from the receptor via a hydrophobic region of the

membrane, while the charged form passes via the hydrophilic region (the inner channel mouth). The hydrophilic pathway is open only when the gates of the channel are open [5].

An earlier study has found that the kinetics of recovery from lidocaine was slowed when the extracellular pH was reduced [6, 7, 8]. This effect is generally believed to result from increase in the fraction of charged drug at receptor site [9, 10].

Furthermore, there have been few published reports of the quantitative analysis of the pH dependence of the recovery from block, but there is only one hypothesis proposed by Starmer and Courtney to explain its pH dependence. It is an interesting model where they used the relatively simple guarded receptor drug-binding theory as well incorporating the equations for the drug and proton dissociation rates. The model assumes that drugs have a fixed affinity for their receptor sites, but access to the binding site is controlled by the voltage-dependent channel gates [11].

A clear understanding of the influence of external pH on the blocking action of class I antiarrhythmic drugs in cardiac muscle is important for a number a reasons. The substantial fall in external pH during myocardial ischemia will change the kinetics of drug binding to the Na^+ channel and may explain the more depressant effect of these drugs during myocardial ischemia [12,13].

The main goal of this work is to introduce the effect of pH in the mathematical model of lidocaine developed previously by our group. We used this model for studying the effect of different drug concentrations on the characteristics of action potentials at different pH.

2. Methods

In this work, the mathematical model of the cardiac action potential developed by Luo and Rudy (phase II)

was used in order to simulate the guinea pig ventricular action potential. The sodium current is expressed as:

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

Where \bar{g}_{Na} is the maximum conductance, m^3, h and j are channel gates, V is the membrane potential and E_{Na} is the reversal potential [14].

In order to model the effect of lidocaine we have used the model proposed by Starmer and Courtney to solve the equations for the drug and proton dissociation [11]. This model is based in the guarded receptor hypothesis (GRH) and the binding and unbinding process is viewed as a hydrophobic process, a hydrophilic process, and a coupling of charged and neutral blocked channels with a proton exchange process.

In our model, we have assumed that the binding and unbinding of charged drug form is controlled by the activation gate, whereas the neutral drug form can bind and unbind in all states of the sodium channel. We assume that the charged form is responsible for the slow component of the block, in agreement with experimental observations [15, 16]. Figure 1 shows the scheme of the interaction of lidocaine and the sodium channel.

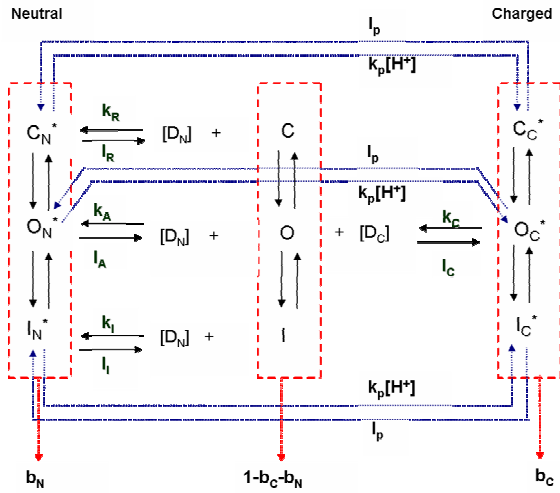


Figure 1. Block diagram for lidocaine in guinea pig ventricular

The association and dissociation rate constants were roughly estimated on the basis of experimental data [9] and subsequently optimized by means of repeated simulations using a genetic algorithm. The process of optimization was run for 400 generations.

The uni-dimensional tissue used in this study is

composed of 200 cells. The excitation was applied to cell # 0, and the action potential characteristics were measured in the centre of the strand when the steady-state was reached as shown in figure 2. We tested the effect of different lidocaine concentrations on the maximum upstroke velocity (dV/dt), the action potential duration (APD), the conduction velocity (CV) and the effective refractory period (ERP). The ERP was obtained to shorten progressively the coupling interval (CI) until the extrastimuli could produce an action potential.

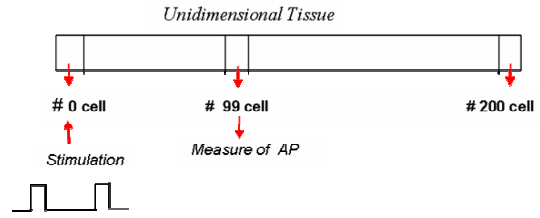


Figure 2. Schematic of the unidimensional tissue and the protocol of stimulation.

3. Results and discussion

In the first place, we measured the effect of different concentrations of lidocaine and pH on the dV/dt ; APD; CV and ERP. We have used the same basic cycle length (BCL) of 500 ms. In our results we obtained a dV/dt reduction of 36 %, 49 % and 71 % for the pH of 7.4; 6.9 and 6.4 when the steady state was reached and with a 50 $\mu\text{mol/L}$ of lidocaine. We can observe this effect in the figure 3.

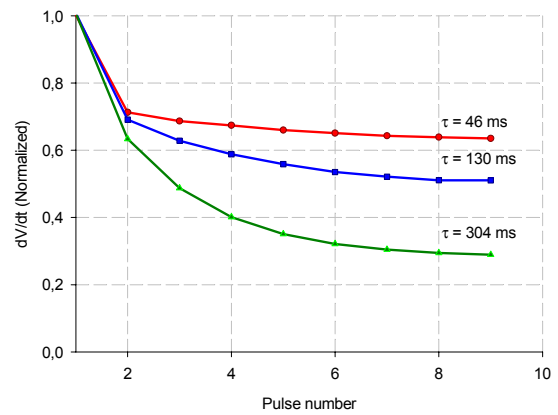


Figure 3. Effect of 50 $\mu\text{mol/L}$ lidocaine on the dV/dt in different pH for a BCL of 500 ms. (pH of 7.4 ●; 6.9 ■; 6.4 ▲).

The values of the time constant (τ) observed in the presence of lidocaine are similar to those previously reported by other authors.

The APD was unaffected by lidocaine when pH was changed using lidocaine 50 $\mu\text{mol/L}$ and a BCL of 200 ms, thus for pH of 6.4 the value of APD was 115 ms while for a pH 7.4 the APD was 112 ms. In table 1, we can observe the effect of lidocaine when the pH and the BCL were changed. Thus, we can say that the APD was not changed when the pH was decreased one unit.

pH	APD		
	BCL 200 ms	BCL 500 ms	BCL 1000 ms
7,4	112,8	151	163,8
6,9	114	151	163,6
6,4	115,9	151	163

Table 1. Effects of the pH on the duration action potential

In order to validate our model, we have to compare our results with experimental data. Broughton [6] evaluated the effect of 15 $\mu\text{mol/L}$ of lidocaine in different pH (6.95 and 7.4). In figure 4, we show the comparison of the experimental data and our results.

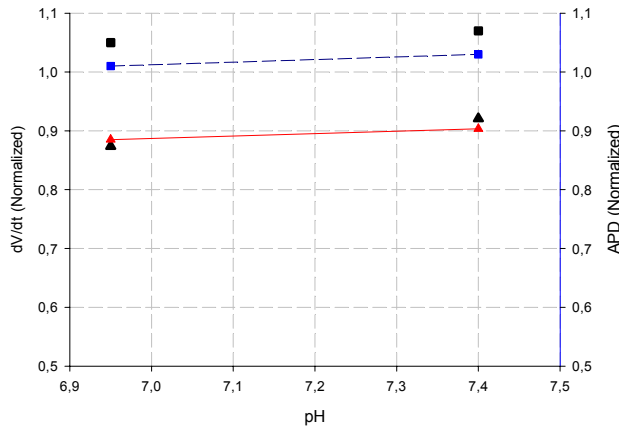


Figure 4. Comparison of the computer predicted values (solid line) and experimental data (data points) for dV/dt (\blacktriangle) and APD (\blacksquare) obtained in the different pH. For BCL 1000 msec and 15 $\mu\text{mol/L}$ of lidocaine

In table 2 we can observe the relative error found. We have compared the experimental data found by Broughton [6] and our results for the dV/dt and the APD in the different pH and obtained a maximum relative error of 3.8 %.

Relative error		
pH	dV/dt	APD
6.95	2,2	3.8
7.4	-1,1	3.7

Table 2. Relative error obtained when we compared the experimental data with our results.

Furthermore, in our simulation, we have found that in absence of lidocaine, the pH does not influence the CV whereas in presence of lidocaine the CV was reduced from 0.30 m/s (without drug) to 0.26 m/s in the highest concentration tested for a pH of 7.4. If we diminished the pH one unit, the CV was decreased from 0.30 m/s (without drug) to 0.23 m/s for the same concentration of lidocaine. We have concluded that if we decrease the pH, the effect of lidocaine on CV is raised.

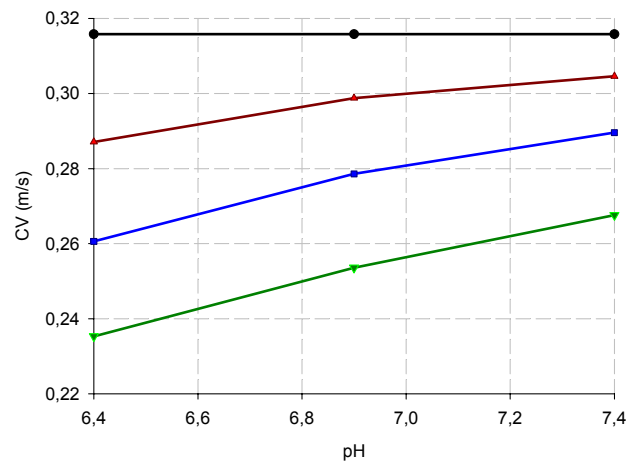


Figure 5. Effect of different concentrations of lidocaine for different pH. In absence of drug (\bullet); 20 $\mu\text{mol/L}$ (\blacktriangle); 50 $\mu\text{mol/L}$ (\blacksquare); 100 $\mu\text{mol/L}$ (\blacktriangledown).

Additionally, the effect of lidocaine on ERP was determined during control and different concentrations of lidocaine and pH. In the absence of the drug and with a pH of 7.4, the ERP was 122 ms, when we increased the concentration of lidocaine, it went up to 2.5 % and 5 % for 50 and 100 $\mu\text{mol/L}$ of lidocaine respectively, for a BCL of 200 ms. In the pH of 6.4, the ERP increased only 0.8 % for the highest concentration tested for the same conditions. Table 3 shows the effect of lidocaine on the ERP in different concentrations, BCLs and pH. Our results suggest that the effect of lidocaine on the ERP is not influenced by changes in the pH.

ERP (ms)			
pH	Lidocaine (μmol/L)	BCL 200 ms	BCL 500 ms
7.4	0	122	158
	50	125	161
	100	128	163
6.9	0	122	158
	50	123	161
	100	124	163
6.4	0	122	158
	50	122	159
	100	123	159

Table 3 Values for ERP in different concentrations of lidocaine, BCLs and pH.

4. Conclusions

In the present study, we have proposed a model to characterize the influence of pH on the effect of lidocaine. Additionally, we validated our results with experimental observations.

Furthermore, the simulation has shown that lidocaine increases its effect on the dV/dt and the CV when the pH is decreased, whereas the effect of lidocaine on the ERP is increased when the pH is raised. The APD does not change its value when the pH is modulated.

Acknowledgements

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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.es