Lead and Carbon Monoxide Effects on Human Atrial Action Potential. In Silico Study

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Abstract

Exposure to air pollutants like lead (Pb^{++}) and carbon monoxide (CO), promotes the occurrence of cardiovascular diseases. Experimental studies have shown that Pb^{++} and CO block the L-type calcium channels, decreasing the calcium current (I_{CaL}) and the action potential duration (APD), favoring the initiation of atrial arrhythmias.

Our goal is to study the effects of Pb^{++} and CO at different concentrations, on I_{CaL} and action potential using computational simulation. For this, we developed mathematical models of the air pollutants effects on the atrial L-type calcium channel and they were incorporated in a mathematical model of human atrial cell and in a 2D model of atrial tissue.

Our results suggest that the Pb^{++} and CO block the I_{CaL} current in a fraction that increases as the concentration increases, generating an APD shortening. The combined effect of both air pollutants generated an APD shortening and a stable rotor, which is considered as a pro-arrhythmic effect. These results are consistent with experimental studies.

In silico studies may contribute to a better understanding of the mechanisms by which air pollutants have unhealthy effects on cardiac system.

1. Introduction

Air pollution is defined as the presence in the atmosphere of one or more substances in sufficient quantity to produce health alterations. Air pollution causes 4.3 million premature deaths annually [1]. In 2010, the economic cost of health impacts of air pollution in developing countries was around USD 1.7 billion [1].

Lead (Pb^{++}) is a toxic agent that can exert adverse health effects in humans. According to the United States Environment Protection Agency (EPA), the Pb^{++} is one of the most dangerous air pollutants, affecting multiple human body systems [2]. In general, more than 143.000 people die every year due to illnesses related to Pb^{++} [3].

Carbon monoxide (CO) is a toxic gas, from incomplete combustion. When people breath, the CO binds to hemoglobin and is significantly retained within the blood reducing the amount of oxygen that it can transport [4].

Exposure to these air pollutants contributes to cardiovascular diseases [5]. Epidemiological studies have reported effects such as heart failure, generation of cardiac arrhythmias and decreased heart rate variability [3,5-11]. Experimental studies have shown that the Pb^{++} blocks the L-type calcium channels [12]. A decrease in L-type calcium current (I_{CaL}) is an important mechanism that favors the generation of atrial arrhythmias [13]. Recently, it has been shown that chronic exposure to CO promotes a pathological phenotype of cardiomyocytes, where remodeling leads to an important reduction of the action potential duration (APD) in atrial myocardium increasing the risk of arrhythmias [9,10] and ischemia [14]. This study aims to assess the effects of the Pb^{++} and CO at different concentrations on human atrial action potential, using computational simulation.

2. Methods

2.1. Human atrial cell model

The Courtemanche–Ramirez–Nattel–Kneller [15,16] membrane formalism was implemented to simulate the electrical activity of human atrial cell. A 0.005 μM of acetylcholine concentration was simulated. The transmembrane voltage (V_m) is given by:

$$C_m \frac{dV_m}{dt} + I_{ion} + I_{st} = 0, \qquad (1)$$

where C_m is the membrane capacitance (100 pF), I_{ion} is the total membrane current, and I_{st} is the external stimulus current. The model is considered under normal electrophysiological conditions.

2.2. Model of Pb^{++} and CO effects on I_{CaL}

We developed concentration dependent equations to

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simulate the Pb^{++} and CO effects on I_{CaL} and they were included in the I_{CaL} equation as blocking factors.

To develop a basic model of the Pb^{++} effect on I_{CaL}, we used the steady state fraction of blockade (b_{Pb}). In this model the kinetics of the channel would be considered unchanged in the presence of the Pb^{++}. Hill equation has been used to fit the concentration-response relationship for ligand block. It describes the fraction of the macromolecule saturated by ligand as a function of the ligand concentration; it is used for determining the degree of cooperativeness of the ligand binding with the receptor:

$$b_{Pb} = \frac{1}{\left[1+\frac{IC_{50}}{D_{Pb}}\right]^{h}}, \qquad (2)$$

where IC_{50} is the half maximal inhibitory concentration for the current block by Pb^{++}, D_{Pb} is the Pb^{++} concentration. A Hill coefficient (h) of 1 indicates completely independent binding. For the IC_{50} to block $I_{CaL,}$ we used 152 nM, this value was found in ventricular myocytes [12]. There are no reported values of the IC_{50} for blocking channels by Pb^{++} on atrial myocytes.

Based on an experimental study [14], we established a relationship between the CO concentration and the APD decrease. This study attribute the APD decrease to a blockage of the I_{CaL} current; therefore, we developed a basic model of the CO effect on the I_{CaL} current. The blocking factor (b_{CO}) of the I_{CaL} current by CO is dependent on the concentration of CO (D_{CO}) and has a lineal behavior. This equation was introduced in the I_{CaL} equation of the cell model, and it was adjusted to obtain APD reductions approximately equal to those observed experimentally. Following, the equations to calculate b_{CO} and I_{CaL} are given by:

$$b_{CO} = 0.0002D_{CO} + 0.0827, \qquad (3)$$

$$I_{CaL} = (1 - b_{CO})(1 - b_{Pb})g_{CaL}dff_{Ca}(V_m - 65), \quad (4)$$

where g_{CaL} is the maximum conductance of I_{CaL}, d is the activation gate, f is the voltage-dependent inactivation gate, f_{Ca} is the calcium-dependent inactivation gate and 65 is the value of equilibrium potential for I_{CaL}.

2.3. 2D model of human atrial tissue

A 2D model of human atrial tissue was developed, which consists of a 6 x 6 cm domain. It was discretized at a spatial resolution of 312.5 μm, to form a mesh of 192 x 192 elements.

2.4. Electrical propagation model

In the 2D model, the propagation in cardiac tissue defined by the monodomain model of electrical propagation is described by the following reaction-diffusion equation:

$$\frac{1}{S_v}\nabla \cdot (D\nabla V_m) = C_m\frac{\partial V_m}{\partial t} + I_{ion} + I_{st}, \qquad (5)$$

where S_v is the surface/volume ratio and D is the conductivity tensor. The equation was solved using a semi-spectral scheme [17]. The tissue was considered isotropic. A conductivity of 0.4 S/cm was assigned in order to obtain a conduction velocity of 62.5 cm/s.

2.5. Simulation protocol

We implemented the unicellular models to simulate the sinus rhythm under physiological conditions, using the Cellular Open Resource public CellML OpenCOR® software. Forward Euler method with a time step of 0.001 ms was implemented to solve the equations.

A train of 10 stimuli was applied at a basic cycle length of 1000 ms. Pb^{++} and CO concentrations from 0 to 300 nM and from 0 to 1000 uM were implemented, respectively. The APD at 90% of the repolarization (APD_{90}), I_{CaL} current and the resting membrane potential (RMP) were measured on the 10th beat using a program developed in MATLAB® software.

The S1-S2 cross-field protocol was applied in the 2D model (rectangular pulses of 2 ms duration and 6 mA amplitude). The S1 stimulus was plane and was applied at the left boundary of the model. The S2 stimulus was rectangular (3 cm x 3 cm) and was applied 167 ms after S1 at a corner of the model. The simulation ran for 2 seconds.

3. Results

The I_{CaL} current without Pb^{++} or CO effects shows a peak of -454 pA, the current remains active during the plateau phase of action potential. The APD_{90} has a value of 211 ms under control conditions.

First we applied different Pb^{++} concentrations. As the Pb^{++} concentration increases, I_{CaL} downregulation is observed, which causes an APD shortening and loss of plateau phase. When the highest Pb^{++} concentration was applied (300 nM), the I_{CaL} peak decreased 61% (-179 pA) and the APD_{90} reached a value of 113 ms, which indicates a decrease of 47%.

When different CO concentrations were applied, as the CO concentration increases, I_{CaL} downregulation is also observed, which causes an APD shortening and loss of plateau phase. When the highest CO concentration was applied (1000 μM), the I_{CaL} peak decreased 22% (-356 pA) and the APD_{90} reached a value of 151 ms, which indicates a decrease of 28%.

When we applied both air pollutants, the Pb^{++} and CO

blockade the I_{CaL} current in a fraction that increases as the concentration increases, resulting in APD_{90} shortening. As the Pb^{++} and CO concentrations increases, I_{CaL} downregulation is observed, which causes the APD shortening and loss of plateau phase of the action potential. When the highest Pb^{++} and CO concentrations were applied (300 nM and 1000 uM, respectively), the I_{CaL} peak decreased by 71% (-130 pA) and the APD_{90} decreased by 51% (104 ms). The RMP did not show significant changes (-83 mV approximately).

Table 1 shows the APD_{90} decreasing values in function of the different Pb^{++} and CO concentrations.

Table 1. APD_{90} values at different Pb^{++} and CO concentrations.

[Pb^{++}]	[CO]	APD_{90}
0 nM	0 µM	211
60 nM	200 µM	139
120 nM	400 µM	123
180 nM	600 µM	115
240 nM	800 µM	110
300 nM	1000 µM	104

Figure 1 shows the effects of different Pb^{++} and CO concentrations on I_{CaL} current and atrial action potential.

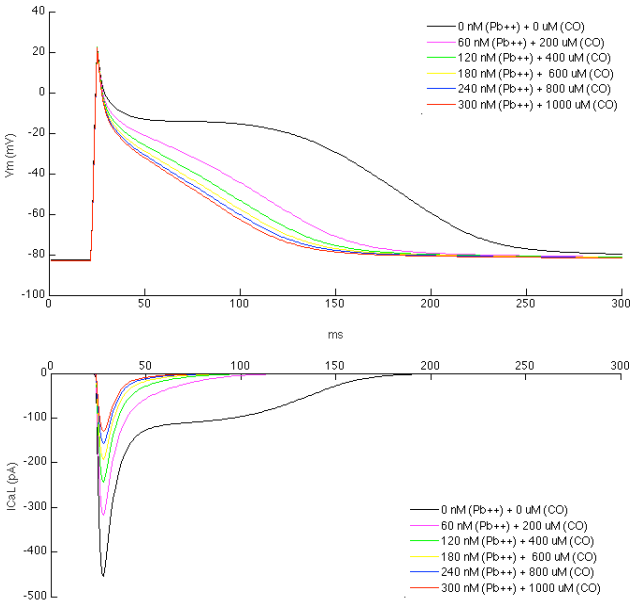

Figure 1. Atrial action potential and I_{CaL} current at different Pb^{++} and CO concentrations.

When S1-S2 cross-field protocol was applied in the 2D model without Pb^{++} or CO effects, a rotor was not generated. However, when the highest Pb^{++} and CO concentrations were applied (300 nM and 1000 uM, respectively), a stable rotor was observed (Figure 2), showing the pro-arrhythmic effect of the pollutants in the atrial tissue.

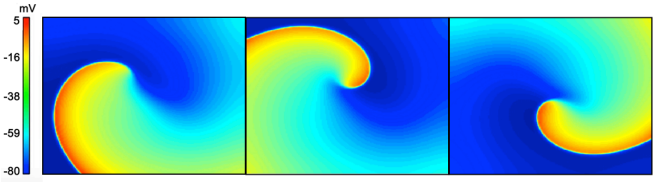

Figure 2. Rotor generated by applying the highest Pb^{++} and CO concentrations.

4. Discussion

Our results showed that Pb^{++} blocks the I_{CaL} current in a fraction greater as the concentration increases, prolonging its action in time, which results in an APD shortening as was demonstrated experimentally [12]. This analysis is consistent with an experimental study in ventricle myocytes of rats [12], where the Pb^{++} blocked the L-type calcium channels, however, its mechanism is not well explained. There are not in silico studies of Pb^{++} effects on human atrial action potential.

Our results also showed that CO blocks the I_{CaL} current, in a fraction greater as the CO concentration increases. These results are consistent with experimental studies. A study in rats [14] showed that CO leads to an important reduction of the APD in atrial myocardium, as well as a significant acceleration of the sinus rhythm and reduction in the force of contraction. Our results are consistent with these studies, as soon as the concentration of CO increases, the APD shortening is observed. There are not in silico studies of CO effects on human atrial action potential.

When we simulated the combined effects on I_{CaL} of the two air pollutants, CO and Pb^{++} at different concentrations, our results showed a significant APD decrease in a fraction greater as the concentrations increase, which is a severe pro-arrhythmic effect. Our results in a human atrial cell model are in agreement with results from non-human in vitro and in vivo studies.

Clinical studies have shown that air pollution increases the risk of cardiovascular disease mortality by 76% [18]; deaths are related to ischemia, arrhythmias and heart failure mainly [19-21]. Sufficient evidence has been found to conclude that a brief exposure to high levels of pollutants increases the cardiac patients mortality. Likewise, it has been shown that prolonged exposures reduce people's life expectancy by several years, and hospital admissions due to cardiovascular diseases increase with high pollutants concentrations [22]. Recent studies have been able to demonstrate a higher probability of occurrence of cardiac arrhythmias after exposure to air pollutants, concluding that air pollution is an acute "trigger" of these arrhythmias [23]. Despite the existence

of studies on the effects of air pollutants on the cardiovascular system in the literature, the mechanisms underlying the effects of acute and chronic exposure to these agents on the heart have not been well established.

5. Conclusion

Our results show pro-arrhythmic effects of Pb^{++} and CO on expressed through shortening of APD, during normal electrophysiological conditions. In silico studies may contribute to a better understanding of the mechanisms by which air pollutants have unhealthy effects on cardiac tissue, promoting cardiac diseases as arrhythmias.

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