In Silico Study of Gaseous Air Pollutants Effects on Human Atrial Tissue

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Abstract

Exposure to gaseous air pollutants such as carbon monoxide (CO), nitric oxide (NO) and sulfur dioxide (SO_2) promotes the occurrence of cardiac diseases. Investigations have shown that CO and SO_2 block the calcium channel (I_{CaL}) of myocytes. The SO_2 also increases the sodium channel (I_{Na}), the transient outward (I_{to}) and inward rectifying (I_{K1}) potassium currents. The NO blocks I_{Na} and increases I_{CaL}. We developed concentration-dependent equations to simulate the gaseous pollutants effects on the ionic currents. They were incorporated in the Courtemanche model of human atrial cell and in a 2D tissue model. A train of 10 stimuli was applied. The action potential duration (APD) was measured. S1-S2 cross-field protocol was applied to initiate a rotor. The CO and SO_2 concentrations from 0 to 1000 uM and NO concentration from 0 to 500 nM were implemented. Six concentration combinations were simulated (cases 1 to 6). The gaseous air pollutants caused an APD shortening and loss of plateau phase of the action potential in a fraction that increases as the pollutant concentration increases. When the highest concentration was applied, the APD decreased by 81%. In the 2D model, from case 4 conditions it was possible to generate rotor, propagating with high stability. These results show pro-arrhythmic effects of gaseous air pollutants.

1. Introduction

Air pollution can produce alterations in health, affecting the quality of life of the population and the degradation of ecosystems. According to the WHO, environmental pollution is responsible for around 4.3 million premature deaths each year [1]. Exposure to gaseous air pollutants like carbon monoxide (CO), nitric oxide (NO) and sulfur dioxide (SO_2) promotes the occurrence of cardiac diseases. There are studies showing that CO and SO_2 block the calcium channel (I_{CaL}) of myocytes [2] [3]. The SO_2 also increases the sodium channel (I_{Na}), the transient outward (I_{to}) and inward rectifying (I_{K1}) potassium currents [3]–[6]. The NO blocks I_{Na} and increases I_{CaL} [7], [8].

The aim of this work is to study the effects of the gaseous pollutants at different concentrations on human atrial tissue, using computational simulation.

2. Methods

Based on experimental data, we developed concentration-dependent equations to simulate the gaseous pollutants effects on the ionic currents. They were incorporated in a model of human atrial cell and in a 2D tissue model.

2.1. Human atrial cell model

The Courtemanche model [9] to simulate the atrial action potential was implemented. The transmembrane voltage (V_m) is calculated by the equation:

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

where C_m is the specific membrane capacitance (100 pF), I_{ion} is the total ionic current that crosses the membrane and I_{stim} is the stimulus current.

2.2. Models of gaseous air pollutants effects

Based on experimental study [2], we established a relationship between the CO concentration and the decrease of the action potential duration (APD). The APD decrease is attributed to a blockage of the I_{CaL} current. Thus, we developed a basic model of the CO effect on the I_{CaL} current. The blocking factor of the I_{CaL} current by CO (b_{CO_CaL}) is dependent on the concentration of CO (D_{CO}) through a linear relationship as follows:

$$b_{CO\_CaL} = 0.0002 D_{CO} + 0.0827, \qquad (2)$$

This equation was introduced on the I_{CaL} equation of the cell model, and it was adjusted to obtain APD reductions that approximate those observed experimentally.

Using the Hill's equation, we developed concentration-dependent equations to simulate the SO_2 effects on I_{CaL}, I_{Na}, I_{to} and I_{K1}. Based on an experimental study [10], the mathematical relationship between the concentration of SO_2 and the blocking of the current I_{CaL} ($b_{SO_2\_CaL}$) is as follows:

$$b_{SO_2\_CaL} = \frac{1}{1+\left(\frac{35.99}{D_{SO_2}}\right)}, \qquad (3)$$

where D_{SO2} is the SO_2 concentration in μM. The equations relating the increment of the I_{Na}, I_{K1} and I_{to} currents due to SO_2 were developed according to experimental studies [6, 7] as follows:

$$e_{SO_2\_Na} = \frac{0.841}{1+\left(\frac{10.97}{D_{SO_2}}\right)^{1.07}}, \qquad (4)$$

$$e_{SO_2\_K1} = \frac{1}{1+\left(\frac{28.5}{D_{SO_2}}\right)}, \qquad (5)$$

$$e_{SO_2\_to} = \frac{1}{1+\left(\frac{17}{D_{SO_2}}\right)}, \qquad (6)$$

In agreement with experimental data [8], the mathematical relationship between the concentration of NO and the blocking of the current I_{Na} is the following:

$$b_{NO\_Na} = \frac{1}{1+\left(\frac{523}{D_{NO}}\right)^{6.8}}, \qquad (7)$$

where D_{NO} is the NO concentration in nM.

To simulate the effect of the NO on the I_{CaL} current, the Michaelis-Menten equation was implemented as follows:

$$e_{NO_{CaL}} = \frac{0.59(D_{NO})}{D_{NO}+0.007}, \qquad (8)$$

where the values 0.59 nM and 0.007 nM are the values of e_{max} and EC_{50} respectively. These equation was fitted using human atrial myocytes data from [7].

The factors $(1 - b_{CO\_CaL})$, $(1 - b_{SO2\_CaL})$, $(1 + e_{SO2\_Na})$, $(1 + e_{SO2\_K1})$ and $(1 + e_{SO2\_to})$ were introduced to the I_{CaL}, I_{Na}, I_{K1} and I_{to} equations in the cell model, respectively:

$$I_{CaL} = \left(1 - b_{CO\_CaL}\right)(1 - b_{SO_2\_CaL})(1 + e_{NO\_CaL})g_{CaL}dff_{Ca}(V_m - 65), \qquad (9)$$

$$I_{Na} = \left(1 + e_{SO_2\_Na}\right)\left(1 - b_{NO\_Na}\right)g_{Na}m^3hj(V_m - E_{Na}), \qquad (10)$$

$$I_{K1} = \frac{(1+e_{SO_2\_K1})g_{K1}\,(V_m - E_{K1})}{1+e^{0.07(V+80)}}, \qquad (11)$$

$$I_{to} = \left(1 + e_{SO_2\_to}\right)g_{to}oa^3oi(V_m - E_{to}), \qquad (12)$$

2.3. 2D model of human atrial tissue and electrical propagation

A 2D model of human atrial tissue was developed through a 6 x 6 cm matrix, discretized at a spatial resolution of 312.5 μm, obtaining a square mesh of 192 x 192 elements. The monodomain model, defined by the reaction-diffusion equation, describes the electrical propagation of the action potential wave in the tissue:

$$\frac{1}{S_v}\nabla \cdot (D\nabla V_m) = C_m\frac{\delta V_m}{\delta t} + I_{ion} + I_{stim}, \qquad (13)$$

where S_v is the surface/volume ratio, D is the conductivity tensor. The equation (13) was solved using a semi-spectral scheme [11] in a program implemented in MATLAB®. 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.

2.4. Simulation protocol

We implemented the unicellular model to simulate the atrial action potential. Forward Euler method with a time step of 0.001 ms was implemented to solve temporal derivatives. A train of 10 stimuli was applied at a basic cycle length of 1000 ms. The APD at 90% of the repolarization (APD_{90}) and the different currents were measured on the 10th beat.

The S1-S2 cross-field protocol was applied to the 2D model in order to initiate a rotor. The S1 stimulus generates a planar wave and it was applied at the left boundary of the model. The S2 stimulus is a square (3 cm x 3 cm) and was applied after S1 at a corner of the model.

The CO and SO_2 concentrations varying from 0 to 1000 uM and NO concentration varying from 0 to 500 nM were implemented. Six cases were generated by combining the gaseous air pollutants concentrations as shown in Table 1.

Table 1. Combinations of gaseous air pollutants concentrations.

Case	[CO]	[SO_2]	[NO]
C1	0 μM	0 μM	0 nM
C2	200 μM	5 μM	1 nM
C3	400 μM	50 μM	10 nM
C4	600 μM	100 μM	100 nM
C5	800 μM	500 μM	300 nM
C6	1000 μM	1000 μM	500 nM

2.5. Phase singularity analysis

The rotor tip motion is defined through phase singularity analysis. A phase map is generated by calculating the Hilbert transform of the membrane

potential time series. The singularity is defined as the point where the phases, from $-\pi$ to π, converge and it is estimated through the topological charge density method [12].

3. Results

Under normal physiological conditions, an APD shortening was observed by increasing the concentrations of gaseous air pollutants, which was accentuated for C3. For C2, a slight increase of the plateau phase was observed. Under the highest concentration (C6), the magnitude of the maximum I_{CaL} peak decreased by 95% (-21 pA), the I_{Na}, I_{to} and I_{K1} peaks increased by 43% (-10300 pA), 96% (100 pA) and 61% (1440 pA) respectively, generating a significant decrease in the APD. The APD_{90} reaches a value of 61 ms, equivalent to a reduction of 81%. The resting membrane potentials did not change significantly.

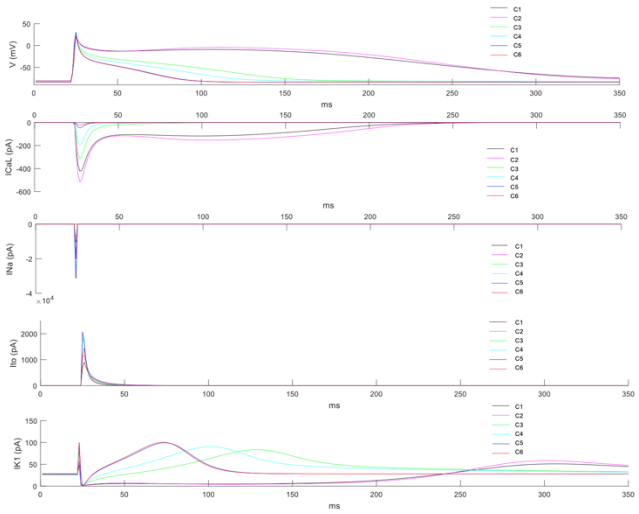

Figure 1. Atrial action potential and I_{CaL}, I_{Na}, I_{to} and I_{K1} currents at concentrations corresponding to C6.

Table 2. Values of APD_{90} and percentage of reduction for the 6 cases of combinations of gaseous air pollutants concentrations.

Case	**APD_{90} (ms)**	**Reduction (%)**
C1	314	0
C2	305	3
C3	126	60
C4	97	69
C5	63	80
C6	61	81

The Table 2 shows the values of APD_{90} for the six cases of combination of gaseous air pollutants concentrations. An increase in the concentration of the gases causes a decrease in the APD, presenting a pronounced shortening from C3.

By applying the S1-S2 cross-field protocol to the 2D model, it was not possible to generate rotors for C1, C2 and C3. Under such conditions, the wavefront generated by S2 turns on itself, but it collides with its own refractory tail (unexcitable tissue) and it extinguishes, because the refractory period is greater than the turning trajectory.

On the other hand, when we applied gaseous air pollutants concentrations of C4 to C6, it was possible to generate stable rotors within vulnerable windows ranging from 34 for C4, to 42 ms for C6. The wavefront (having a shorter refractory period) encounters excitable tissue and continues to turn on itself, generating a stable rotor in the tissue. The rotor tip remains practically at the middle of the tissue. The Figure 2A depicts the rotor sequence obtained by applying the concentrations established in C6 to a coupling interval of 107 ms (corresponding to the middle value of the vulnerable window).

The phase singularity trajectory, that represents the temporal evolution of the rotor tip in the space, indicates high stability, where the core zone has about 0.9 cm of diameter (Figure 2B).

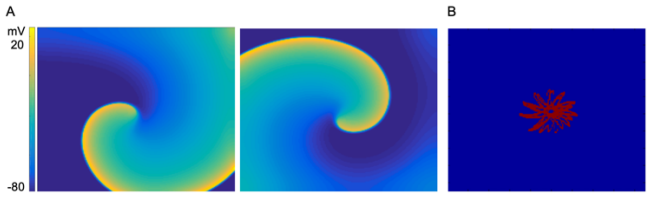

Figure 2. (A) Rotor and (B) phase singularity trajectory generated under C6 conditions.

4. Discussion

The simulation of the combined effects of CO, SO_2 and NO pollutant gases on the I_{CaL}, I_{Na}, I_{to} and I_{K1} currents, showed a significant decrease in APD. At the highest simulated concentrations, the APD reaches up to 81% of reduction under normal physiological conditions. These results suggest a severe pro-arrhythmic effect. Clinical studies have shown that air pollution increases the risk of mortality from cardiovascular disease by 76% [13], deaths are mainly related to ischemia, arrhythmias and heart failure [14]–[16]. Strong evidence has been found about that mild exposure to high levels of air pollution increases mortality in patients with heart problems. Likewise, it has been demonstrated that prolonged exposures reduce the quality of life of people, and high air pollution increases hospital admissions for cardiovascular diseases [17].

Recent studies have shown a higher probability of the occurrence of cardiac arrhythmias after exposure to air pollutants, concluding that air pollution is an acute "trigger" of these arrhythmias [18]. Despite the existence of studies on the effects of air pollutants on the

cardiovascular system, the mechanisms underlying the effects of acute and chronic exposure to these in the heart are not well established.

In a recent study [19], the effect of CO on the ventricular cell by computational simulation was assessed. It is important to highlight that, to date, there are few in silico studies that have evaluated the effect of air pollution on the cardiac system. Computational studies, as the one presented in this work, can contribute to a better understanding of the mechanisms by which these pollutants have harmful effects on cardiac tissue.

5. Conclusion

Our results show pro-arrhythmic effects of gaseous air pollutants on expressed through APD shortening and a rotor generation, during normal electrophysiological conditions.

Acknowledgments

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