

Sulfur Dioxide Effects on Human Atrial Action Potential: In Silico Study

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Abstract

Exposure to air pollutants agents, like sulfur dioxide (SO₂), has significant effects on the cardiovascular system. Studies have shown that SO₂ blocks I_{CaL} and increases the I_{Na}, I_{K1} and I_{to} currents, which implies action potential duration (APD) decrease, favoring the initiation of atrial arrhythmias. This study aims to assess the effects of the SO₂ at different concentrations on human atrial action potential, using computational simulation. For this, based on experimental data, we developed concentration-dependent equations to simulate the SO₂ effects on the currents. They were incorporated in the Courtemanche model of human atrial cell and in a 2D model of atrial tissue. S1-S2 cross-field protocol was applied to initiate a rotor. SO₂ concentrations from 0 to 100 μM were implemented. Our results are in agreement with results from non-human in vitro and in vivo studies. The SO₂ causes APD shortening and loss of plateau phase in a fraction that increases as the concentration increases. In the 2D model, a rotor can be generated from 50 μM of SO₂ concentration, showing a pro-arrhythmic effect.

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]. Human exposure to air pollutants agents, like sulfur dioxide (SO₂), has significant effects on the cardiovascular system [2]. SO₂ is an invisible gas that has a nasty, sharp smell. The main source of SO₂ in the air is industrial activity that involves processing materials that contain sulfur. It causes

cardiovascular diseases and cardiovascular mortality [3]. Studies have shown that SO₂ blocks the L-type calcium channel (I_{CaL}) [4], [5] and increases the sodium channel (I_{Na}) [6], the transient outward potassium current (I_{to}) and the inward rectifying potassium current (I_{K1}) [7]. These effects could cause an action potential duration (APD) decrease, increasing the risk of initiation and maintenance of cardiovascular disease such as atrial arrhythmias. Certain types of atrial arrhythmias can be attributed to stable high-frequency spiral waves (rotors) [8].

This study aims to assess the effects of the SO₂ at different concentrations on human atrial action potential and rotor generation, using computational simulation.

2. Methods

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:

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

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

2.2. Models of SO₂ effects on the ionic currents

Using Hill's equation, we developed concentration-dependent equations to simulate the SO₂ effects on I_{CaL}, I_{Na}, I_{to} and I_{K1}. Based on an experimental study [4, 5], the mathematical relationship between the concentration of SO₂ and the blocking of the current I_{CaL} was:

$$b_{SO_2CaL} = \frac{1}{1 + \left(\frac{35.99}{D_{SO_2}}\right)} \quad (2)$$

Equations of the increase generated by SO₂ in the I_{Na}, I_{K1} and I_{to} currents were developed according to experimental studies [6, 7]:

$$e_{SO_2Na} = \frac{0.841}{1 + \left(\frac{10.97}{D_{SO_2}}\right)^{1.07}} \quad (3)$$

$$e_{SO_2K1} = \frac{1}{1 + \left(\frac{28.5}{D_{SO_2}}\right)} \quad (4)$$

$$e_{SO_2to} = \frac{1}{1 + \left(\frac{17}{D_{SO_2}}\right)} \quad (5)$$

where D_{SO₂} is the SO₂ concentration in μM. The factors (1 - b_{SO₂CaL}), (1 + e_{SO₂Na}), (1 + e_{SO₂K1}) and (1 + e_{SO₂to}) were introduced to the I_{CaL}, I_{Na}, I_{K1} and I_{to} equations in the cell model.

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

A 2D model of human atrial tissue was developed, it consists of a 6 x 6 cm matrix, discretized at a spatial resolution of 312,5 μm, to form a square mesh of 192 x 192 elements.

The monodomain model described by the reaction-diffusion equation defined the electrical propagation of action potential in the tissue:

$$\frac{1}{S_v} \nabla \cdot (D \nabla V_m) = C_m \frac{\delta V_m}{\delta t} + I_{ion} + I_{stim} \quad (6)$$

where S_v is the surface/volume ratio, D is the conductivity tensor. The equation was solved using a semi-spectral scheme [10] in a program developed 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 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. The APD at 90% of the repolarization (APD₉₀) and the different currents were measured on the 10th beat.

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

SO₂ concentrations from 0 to 100 μM were implemented. The simulations ran for 2 s.

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 -π to π, converge and it is estimated through the topological charge density [11].

3. Results

The SO₂ causes the APD shortening and loss of plateau phase of the action potential in a fraction that increases as the concentration increases (Figure 1).

For the highest SO₂ concentration (100 μM), the I_{CaL} peak decreases by 63%, the I_{Na}, I_{to} and I_{K1} peaks increases by 71%, 118% and 78%, respectively, and the APD₉₀ decreases by 71% (Table 1). The RMP does not show significant changes.

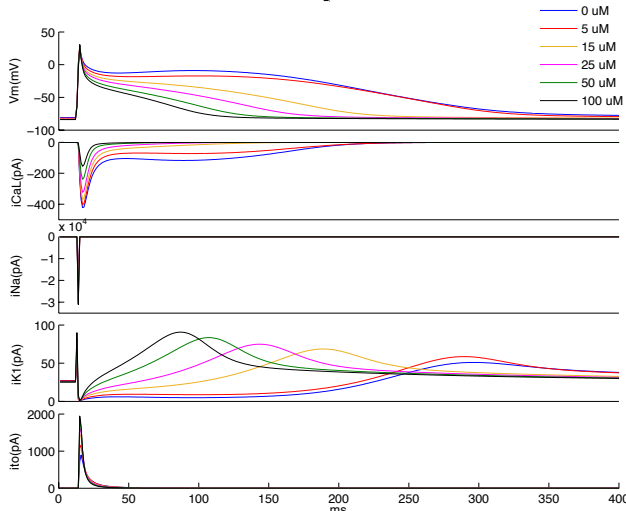


Figure 1. Action potential and I_{CaL} , I_{Na} , I_{K1} and I_{to} currents, at different concentrations of SO_2 .

Table 1. APD values and peaks of the currents, at different SO_2 concentration.

[SO_2] (μM)	APD (ms)	I_{CaL} peak (pA)	I_{Na} peak (pA)	I_{to} peak (pA)	I_{K1} peak (pA)
0	314	-422	-18143	894	51
5	303	-402	-21965	1160	59
15	200	-369	-27098	1439	69
25	153	-323	-29101	1615	75
50	115	-239	-30660	1812	83
100	92	-155	-31091	1946	91

By applying the S1-S2 cross-field protocol in the 2D model at SO_2 concentrations of 0, 5, 15, 25 μM , it was not possible to generate a rotor, the wavefront generated by S2 turns on itself, but it collides with its own refractory tail (inexcitable tissue) and it extinguishes, because the refractory period is greater than the turning trajectory.

On the other hand, when we applied SO_2 concentrations of 50 and 100 μM , the wavefront (having a shorter refractory period) encounters excitable tissue and continues to turn on itself, generating a rotor in the tissue (Figure 2).

The singularity phases of the rotors indicate stable activity in both cases, where the core zones have about 0.9 cm of diameter.

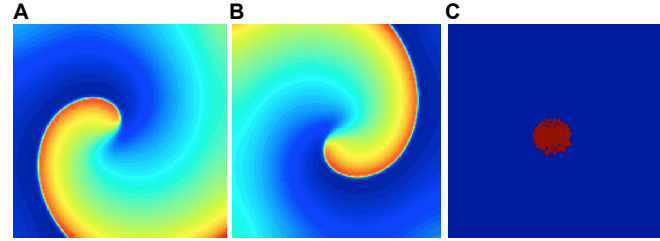


Figure 2. (A-B) Rotor and (C) the singularity phase by SO_2 concentration of 50 μM .

4. Discussion

Clinical studies have shown that air pollution increases the risk of cardiovascular disease mortality by 76 % [12]; such deaths are mainly related to ischemia, arrhythmias and heart failure. Sufficient evidence has been found to conclude that a brief exposure to high levels of pollutants increases the cardiac mortality. Recent studies have been able to demonstrate that cardiac arrhythmias present higher probability of occurrence after the exposure to air pollutants, thus concluding that air pollution is an acute "trigger" of these arrhythmias [13].

Our results in a human atrial cell model are in agreement with results from non-human in vitro and in vivo studies. Experimental studies in isolated rat ventricular myocytes [4]–[7] showed that exposure to SO_2 derivatives causes a decrease of the I_{CaL} current and an increase of the I_{Na} , I_{to} and I_{K1} currents, in a greater fraction as the concentration increases, which can produce damage in cardiomyocytes and result in hypoxia and ischemia.

Our results are consistent with these studies; when the concentration of SO_2 increases, the APD decreases, which is a proarrhythmic effect. When the APD decreases the refractory period it is also shortened, causing that spiral wave encounters excitable tissue and continues to turn on itself, generating a rotor. At the inner tip of the spiral wave, the source–sink relationship is critical and excitation fails. The failure to excite the central zone produces a region of excitable, but non-excited, tissue within the rotating spiral wave called the 'core'. Anchoring at this zone stabilizes the rotor. Reduced I_{CaL} and increased

I_{K1} accelerate and stabilize rotors by abbreviating APD and refractory period [14]. The singularity phases shown in our results indicate stable activity of the rotors generated by applying SO_2 concentrations of 50 and 100 μM .

There are no in silico studies of the effects of SO_2 on human atrial action potential. Despite the existence of studies of 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. 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 such as arrhythmias.

5. Conclusion

Our results show pro-arrhythmic effects of SO_2 expressed through APD shortening and a rotor generation, during normal electrophysiological conditions.

Acknowledgements

This work was supported by the “Departamento Administrativo de Ciencia, Tecnología e Innovación – Colciencias” of Colombia; and the “Dirección General de Política Científica de la Generalitat Valenciana” of Spain (PROMETEU2016/088).

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