

Acquired Brugada-like Symptoms of Cyanide-caused Cardiac Toxicity: A Computational Study

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Abstract

A high performance computational study of the cellular processes of ventricular cardiac tissue exposed to cyanide (CN) is presented. The model used was based on the Luo-Rudy formalism with modifications. To account for the CN-caused changes, the model used ion concentrations based on published metabolic studies with CN used as a blocking agent. The model included a cell swelling-activated chloride current, and a membrane current activated by the decline in the ATP concentration. The calculations show the rise in the resting voltage and the connection between the abbreviated AP duration and the modulation in the pseudo-ECG. Similarities in the ECG of tissue affected by CN and tissue exhibiting the Brugada syndrome suggest that fundamental mechanism responsible for the generation of polymorphic VF observed in both cases share a commonality with implications for treatment.

1. Introduction

The use of cyanide in the metal forming industries is widespread and accidents in its use are common. The effect of CN on human tissue is profound and immediate. CN interferes with the oxygen utilization of the cells. One of the first manifestations in the heart is bradycardia that soon changes to Torsade de Pointes and culminates in ventricular fibrillation. On the ECG, the P-wave, the atrial depolarization is eliminated, ST-segment deviation, usually a rise in the slope, becomes noticeable followed by modulation of the T-wave. The changed morphology is expressed in steepening and coalescing of the QRS and the T-waves. A J-wave becomes noticeable. See Katzman et al. [1] and Wexler et al. [2] for additional details.

On the cellular level, changes in the ion concentrations become important, especially calcium overload of the cell and increase in $[K^+]_o$. The cell's energy homeostasis, Balaban [3], is profoundly disturbed, and several compensatory membrane currents are activated. Three of

the most important currents are the ATP-dependent I_{KATP} , Elliott et al. [4], the osmotic swelling-activated $I_{Cl,sw}$, and the calcium-dependent potassium current. $I_{Ca(L)}$ declines. The disequilibrium in the membrane currents caused by the cyanide has important implications for the cell's electrophysiology. CN-caused cardiac toxicity shares some commonality with ischemia but is different in the level of acidity of the tissue and the nature of some of the activated currents. A number of the known effects, including enhanced catecholamine secretion, the effect of the increase in free Mg^{2+} , and pH changes are not addressed in this paper. More details are given in Baskin et al. [5], Leimdorfer [6] and Van der Heyden et al. [7].

To gain insight into the cellular processes a computational study of the behavior of ventricular cells under the influence of CN was performed. The next section describes the methods used followed by the results and a brief discussion of the similarity in some aspects to acquired Brugada-like and CN-caused cardiac modulation of the electrophysiology.

2. Methods

The effect of the presence of CN in the tissue was modeled by changing the tissue parameters to those measured in CN-caused metabolic blockade of cardiac tissue available in the open literature and including the currents activated under these conditions. Two of the more important ones for this model are the activation of I_{KATP} due to decline in the ATP stores and $I_{Cl,sw}$ when the cell volume is modulated. Change in cellular ion concentrations is also an important aspect of CN toxicity. Calcium overload causes the activation of K^+ channels, Ionue [8]. Rise in $[Na^+]_i$ and $[Ca^{2+}]_i$ enhance the I_{Ks} current that is activated at voltage values much higher than for I_{Kr} . I_{Kr} is reduced by acidification and the presence of external divalent cations, noticeable in CN-affected tissue.

For these numerical simulations cardiac tissue cells of three kinds were considered: epicardial, midmyocardial and endocardial representing the ventricular wall. The

important distinction among these cells for these calculations is in the value of the maximum cell conductance. Using the conditions of Table I, first a baseline action potential and then a pseudo-ECG were calculated. The former used the Luo-Rudy model of the cellular processes as described in Ferrero et al. [9], Shaw et al. [10].

The model of Vandenberg et al. [11] for osmotic swelling-activated chloride current was modified and incorporated into the simulations. It accounts for the expression of some of the changes in the membrane currents caused by CN-caused lesions, Suzuki [12]. Cell swelling contributes to the rise of the resting membrane potential and the shortening of the AP.

A pulse of 200 mA/cm² of 0.5 ms duration initiated the action potential. Using the formulation of Plonsey et al. [13], with the pseudo-ECG electrode at 2.0 cm from epicardium, the extra cellular unipolar potential generated by the fiber in the surrounding field was calculated from

$$\Phi_e = \frac{a^2 \sigma_i}{4\sigma_e} \int \left(-\nabla V_m \right) \left[\nabla \frac{1}{r} \right] dx.$$

where a is the radius of the fiber, r the distance from the source to the field point, V_m the transmembrane potential and σ_i/σ_e the ratio of the intracellular to the extra cellular conductivities.

The mathematically-generated ECG was calculated on a strip of cardiac tissue made up of three types of cells, endocardial, midmyocardial (M), and epicardial. A distinctive difference among these cells is the maximum value of the channel conductance for the I_{Kr} and the I_{Ks} currents. The conductance ratios for these cells were set at 11:1, 4:1 and 35:1 respectively following experimentally obtained values, Viswanathan et al. [14].

For the calculations reported here, a monodomain approach was adopted with fiber orientation (one of the diffusion matrix entries) assumed to be uniform. The propagation of the action potential was based on the following cable equation:

$$\frac{\partial V}{\partial t} = -I_{ion}/C_m + D \left(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V}{\partial y^2} \right)$$

In this equation, V is the membrane voltage and I_{ion} the transmembrane ionic current, mainly made up from the sodium, potassium, calcium and chloride currents, and pumps and exchangers. D is the diffusion constant and C_m the membrane capacitance. Appended are the gating variables of the ionic channels and equations for the change of the ion concentrations. No flux boundary conditions were used. After determining the baseline in these simulations, the approach was to vary the ion

channel conductivities thought to be affected in CN-affected tissue. In addition, a series of simulations were performed increasing the extra cellular potassium concentration, the calcium concentration in the cell and the internal sodium level. Two additional currents, the ATP dependent potassium current and the cell volume dependent chlorine current were activated in the simulation of severely affected tissue.

3. Results

Fig. 1 gives the baseline electrophysiological behavior of the tissue. The action potential cycle length (CL) is 220 ms. Next, in Fig. 2, the AP of a CN affected ventricular cell is shown. The CL is considerably shortened, an indication of tachycardia. The resting potential is higher. When the I_{KATP} current is activated due to the decline in ATP, the energy source, and $I_{Cl,sw}$, the chloride current is activated by the change in the cell volume, Fig. 3, the changes in the markers of the electrophysiology are notable. CN-affected cardiac tissue shows similarity in appearance to Brugada-like markers on the ECG, Fig. 4. The mathematically generated ECG shows the J-wave as well as an ST-denivelation. The maximum amplitude of the AP is lower and the QRS portion of the ECG shows widening and is joined with the T-wave. Next, the effect of calcium overload of the cardiac cell with reduced ATP concentration of 3.0 is shown by the green trace. The full effect of the presence of CN in the tissue is shown there. The ECG is modulated, the short CL indicates the experimentally observed ventricular tachycardia and possible onset of fibrillation. The inversion of the T-wave indicates abnormal repolarization of the ventricles. The internal Ca^{2+} concentration was 0.0009 mM/L and the $[ATP] = 1.0$. Pharmacological intervention, restoring the baseline ion concentrations, can reverse these trends as shown in Fig. 5.

4. Discussion

A condensed overview of the effect of CN on cardiac tissue was presented. CN has severe consequences for the electrophysiology by modulating the balance of currents in the exposed tissue thereby also mimicking aspects of the Brugada syndrome in its expressed effects. I_{Na} , I_{to} , and I_{Ca} are modified in the epicardial tissue with a loss of the dome in phase II of the action potential. On the ECG the ST-denivelation is noticeable and the J-wave is visible.

The simulations were able to reproduce in situ measured CN-caused ECG modulations as reported in ref. [2]. Computer experiments show that to reverse the effect

of CN, restoration of the depolarizing sodium current and the calcium homeostasis should be among the primary targets of a pharmacological intervention.

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Table I. Initial values.

	Baseline	CN-affected Cell	Ischemia
Model Quantity	(mM)	(mM)	(mM)
[Na ⁺] _i	10.0	Incr. ~2.5 x	10 - 20
[Na ⁺] _o	145.0	134.0	140.0
[K ⁺] _i	150.0	125.0	125.0 (acidic env.)
[K ⁺] _o	4.0	10.0	4 -16
[Ca ²⁺] _i	0.0003	Incr. >3 x	0.0003 – 0.0009
[Ca ²⁺] _o	1.8	2.0	~2.0
[ATP]	5.0	3.0	3.0 <

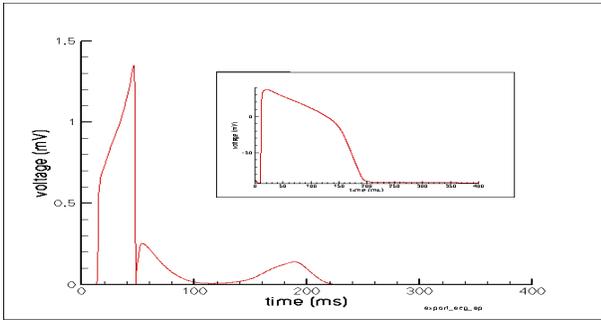


Figure 1. The baseline mathematically generated ECG of the cardiac tissue with action potential shown in the insert.

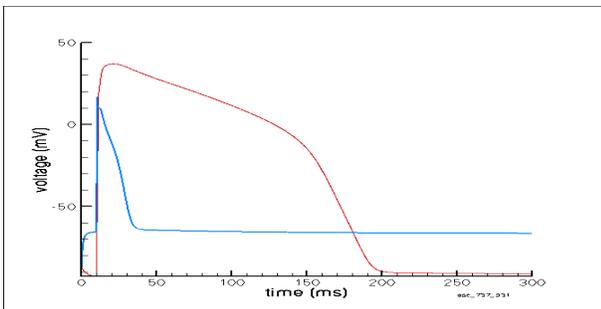


Figure 2. CN notably shortens the cycle length of affected tissue (blue trace) in comparison with the baseline (red trace).

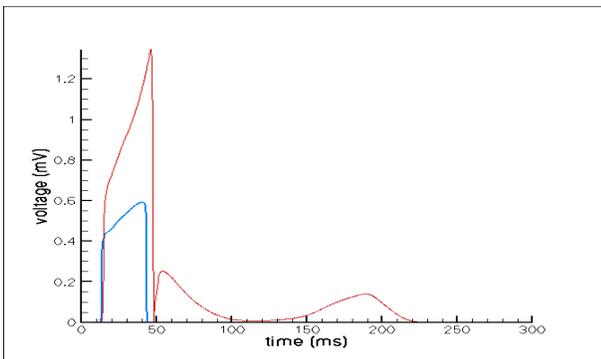


Figure 3. Simulated ECG (blue trace) of severely CN-affected cardiac tissue. $[Ca^{2+}] = 0.0009$, $[ATP] = 1.0$, $K^+_o = 12.0$ mM/L. The baseline is shown in red.

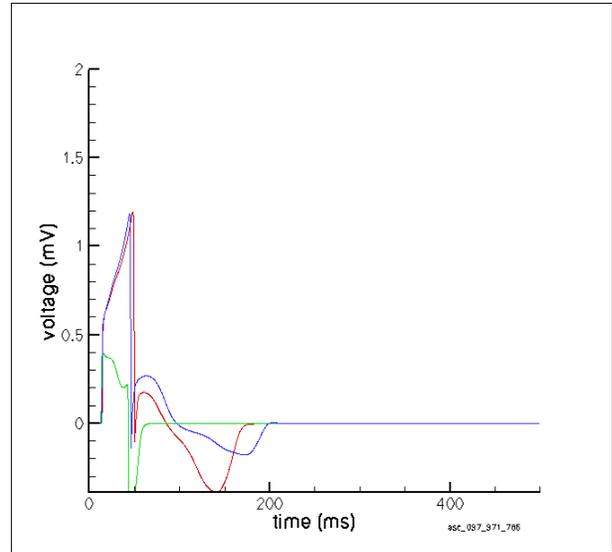


Figure 4. The effect of calcium overload, reduced availability of ATP and high external potassium concentration. The red trace shows the effect of a 50% overload of internal sodium. The blue curve represents potassium and calcium overload. The green ECG trace shows the effect of the activation of the chloride channel under ion concentration overload conditions. The reversal from normal direction of the membrane currents was noted.

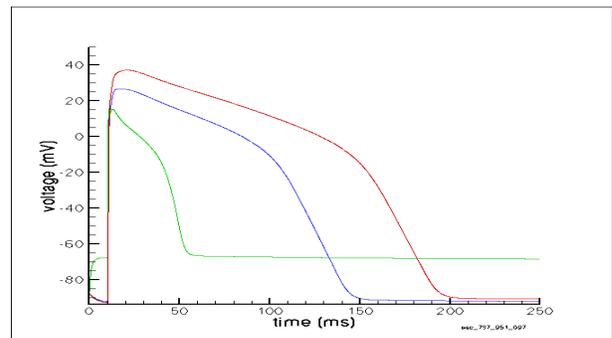


Figure 5. Simulated pharmacological intervention: the red trace shows the baseline, blue the case with ion concentrations restored except for sodium, showing a 50% cell overload.