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Effects of Serum Calcium Changes on the Cardiac Action Potential and the ECG in a Computational Model

Abstract: Patients suffering from end stage of chronic kidney disease (CKD) often undergo haemodialysis to normalize the electrolyte concentrations. Moreover, cardiovascular disease (CVD) is the main cause of death in CKD patients. To study the connection between CKD and CVD, we investigated the effects of an electrolyte variation on cardiac signals (action potential and ECG) using a computational model. In a first step, simulations with the Himeno et al. ventricular cell model were performed on cellular level with different extracellular sodium ($[Na^+]_o$), calcium ($[Ca^{2+}]_o$) and potassium ($[K^+]_o$) concentrations as occurs in CKD patients. $[Ca^{2+}]_o$ and $[K^+]_o$ changes caused variations in different features describing the morphology of the AP. Changes due to a $[Na^+]_o$ variation were not as prominent. Simulations with $[Ca^{2+}]_o$ variations were also carried out on ventricular ECG level and a 12-lead ECG was computed. Thus, a multiscale simulator from ion channel to ECG reproducing the calcium-dependent inactivation of I_{CaL} was achieved. The results on cellular and ventricular level agree with results from literature. Moreover, we suggest novel features representing electrolyte changes that have not been described in literature. These results could be helpful for further studies aiming at the estimation of ionic concentrations based on ECG recordings.

Keywords: calcium changes, ECG, action potential, cardiac signals, computational model, ionic concentrations.

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1 Introduction

With a prevalence of 13.1% chronic kidney disease (CKD) is one of the most common diseases in the United States [1]. Due to a failure of the kidneys, CKD patients suffer from an alteration of the blood serum electrolyte concentrations. Sodium, potassium and calcium influence the electrophysiology of the heart. Therefore, patients suffering from CKD are at a higher risk to experience cardiovascular diseases (CVD). The death rate due to CVD is 10 to 30x higher in dialysis patients than in patients without CKD [2]. In order to study the relation between both diseases, the influence of a variation of the electrolyte concentrations on the cardiac signals needs to be investigated. Moreover, recent studies suggest a crucial role of hypocalcemia in the pathophysiology of bradycardic sudden cardiac death in CKD patients [3]. El Sherif and Turito [4] report an action potential duration (APD) prolongation and a QT prolongation during hypocalcemia. However, in vivo studies are generally very limited, expensive and associated with ethical issues, especially when performed in humans. Therefore, computational cardiac modelling is a valuable complementary approach to investigate human cardiology. Pilia et al. [5], studied the feasibility of estimating calcium and potassium levels using simulated ECGs with the ten Tusscher et al. model. This model was able to realistically simulate alterations in extracellular potassium concentration ($[K^+]_o$) on the AP and the ECG. When varying extracellular calcium concentrations ($[Ca^{2+}]_o$), however, the cell model did not show the results expected based on clinical findings, as APD and QT shortening was observed under hypocalcemic conditions. The reason is that the formulation for the calcium-dependent inactivation of I_{CaL} is not precise enough [6]. Summarizing, a computational model which is able to realistically reproduce the effects of serum calcium changes on the ECG is still lacking.

Recently, Himeno et al. [7] presented a human ventricular cell model with refined calcium handling including calcium-dependent inactivation of I_{CaL} based on a spatially-resolved Markov formulation. In this work, we used their model to analyze the effects of serum calcium changes on cardiac action potentials (APs) and embedded it in a bi-ventricular

multi-scale model including a torso to study how the effects on the AP level translate to the body surface ECG.

2 Methods

In the original model presented by Himeno et al., the extracellular sodium concentration ($[Na^+]_o$) was set to 140 mmol/l, $[Ca^{2+}]_o$ to 1.8 mmol/l and $[K^+]_o$ to 4.5 mmol/l. In this study, we varied one of the electrolyte concentrations per setup in the following ranges: 120 - 150 mmol/l $[Na^+]_o$, 0.6 - 3 mmol/l $[Ca^{2+}]_o$, 3 - 9 mmol/l $[K^+]_o$. As the ten Tusscher et al. model showed satisfactory results for $[K^+]_o$ changes in [5] and changes due to $[Na^+]_o$ variations were not pronounced, we present ventricular simulation results only for variation of $[Ca^{2+}]_o$, here.

Single cell simulations were carried out to extract the AP curve by integrating gating variables with the Rush-Larsen method and the remaining differential equations with the forward Euler method. In order to evaluate the effect of an electrolyte variation on the AP, the following AP parameters were evaluated: amplitude, AP duration at 50% and 90% (APD_{50} and APD_{90}), resting membrane voltage (RMV) and the maximum of the time derivative of the transmembrane voltage ($[dV_m/dt]_{max}$) describing the steepness of the AP upstroke.

The initial state for tissue simulations was pre-calculated in a single cell environment to reach steady state conditions. We proposed reformulations of the Himeno et al. model to adapt it for tissue simulations by including apico-basal and transmural heterogeneities as described in [8]. In this study, we worked with the original Himeno et al. model for simulations on cellular level and with the proposed reformulation of the model on tissue level. The excitation spread in the ventricles was simulated by solving the monodomain equation [9]. For each setup, a 12 lead ECG was computed. Since only ventricular simulations were performed, the P-wave was not part of the simulated ECGs.

As described in [5], transformed signals were calculated to combine information from all leads to one signal. 12 features were extracted from the transformed ECG signals to evaluate the effect of electrolyte changes. The literature generally describes QT segment prolongation during hypocalcemia and QT shortening during hypercalcemia. In this work, we analyzed the RT distance, as a variation of the QT segment directly implies a variation of the RT segment. Moreover, we evaluated the following features: peakedness and amplitude of the T wave, slope of the ascending (asc.) part and of the descending (desc.) part of the T wave, ratio of energy of the first half and of the second half of the T wave to the energy of the whole wave, amplitude of the R peak, energy of the R peak, ratio between the energy and the amplitude of the R peak (R ratio en./amp.), amplitude at 130 ms to evaluate ST elevation and QRS complex duration in lead Einthoven II. For further details regarding feature definition, the reader is referred to [5].

3 Results

3.1 Action Potential

The results on the AP level are given in Table 1 and show that a variation of the electrolyte concentration affected almost all analyzed features. When decreasing an arbitrary ionic concentration, the ventricular model responded opposite than during an increase indicating monotonicity. An increase in $[Na^+]_o$ resulted in an increase of amplitude, duration and upstroke slope of the AP and a decrease of the RMV. $[dV_m/dt]_{max}$ showed the highest dependence on $[Na^+]_o$. Hypercalcemia mainly affected the AP by a reduction of the APD. However, a dependence of the upstroke slope and the amplitude was also observed, while the RMV remained unchanged. A decrease of all feature values was observed during an increase in $[K^+]_o$. The value showing the biggest changes during hyperkalemia was $[dV_m/dt]_{max}$ and APD_{50} during hypokalemia.

3.2 ECG

The effects of a $[Ca^{2+}]_o$ variation on the analyzed ECG features are shown in Table 2 and Figure 1. The results can be divided into three groups: features showing a high and a monotonous dependence on the $[Ca^{2+}]_o$ concentration (RT distance, T amplitude, T asc. slope, T desc. slope, R amplitude, R energy, R ratio en./amp. and ST elevation), features showing a high dependence (>4%) on $[Ca^{2+}]_o$ and non-monotonous relation (T ratio 1st half and T ratio 2nd half), features showing a low dependence on $[Ca^{2+}]_o$ and non-mono-

Table 1: Influence of concentration variation on features on cellular level. Values are given as percentage change with respect to the default ionic concentrations defined by Himeno et al. [7].

Conc. (mmol/l)/ Feature	$[Na^+]_o$		$[Ca^{2+}]_o$		$[K^+]_o$	
	120	150	0.6	3.0	3.0	9.0
Amplitude	−2.7	+1.3	−0.8	+0.9	+7.6	−18.3
APD_{50}	−1.8	+4.0	+24.0	−12.8	+14.2	−14.3
APD_{90}	−2.6	+0.8	+16.3	−7.7	+37.3	−22.9
RMV	+0.2	−0.1	0	0	+11.3	−20.1
$[dV_m/dt]_{max}$	−13.0	+9.8	+0.7	−0.6	+8.3	−84.6

Table 2: Influence of $[Ca^{2+}]_o$ changes on features derived from simulated ECGs. Values are given as percentage change with respect to the default ionic concentration defined by Himeno et al. [7].

Conc. (mmol/l)/ Feature	0.6	1.0	1.4	2.2	2.6	3.0
RT distance	+23.31	+12.29	+5.08	−3.81	−7.20	−10.17
T peakedness	−3.42	+0.70	−2.62	−3.82	+1.94	+3.71
T amplitude	+12.01	+5.18	+1.16	−2.45	−5.47	−4.04
T asc. slope	+57.98	+30.17	+13.36	−7.70	−11.63	−15.96
T desc. slope	−32.73	−15.42	−4.00	+6.58	+11.22	+13.94
T ratio 1st half	−7.04	−1.71	+0.09	+0.83	+4.88	+2.44
T ratio 2nd half	+10.57	+2.29	−0.39	−1.21	−7.73	−3.75
R amplitude	-6.56	-3.86	−1.26	+0.98	+1.54	+2.45
R energy	-13.48	-8.15	−2.43	+1.84	+2.62	+4.57
R ratio en./amp.	-7.41	−4.46	−1.19	+0.85	+1.06	+2.07
ST elevation	−62.68	−38.94	−18.23	+15.81	+29.23	+40.58
QRS duration	0	0	0	0	0	0

tonous relation (T peakedness), and finally QRS duration which was invariant during hypo- and hypercalcemia.

4 Discussion

Clinical studies report that the main electrophysiological effect related to hypocalcemia is a prolongation of the APD [4]. Himeno et al. showed that their model is capable to reproduce this effect. However, they only evaluated the results visually [7]. In this work, we studied the changes quantitatively and systematically by taking into account other features and electrolytes ($[Na^+]_o$ and $[K^+]_o$) as well. In our simulations, $[Na^+]_o$ affected all evaluated features slightly. An influence of the $[Na^+]_o$ concentration on the amplitude and the slope of the upstroke has also been reported in [4]. A dependence of RMV on $[Na^+]_o$ has not been reported in the literature to the best of our knowledge. As the $[Na^+]_o$ concentration is taken into account in the Goldman-Hodgkin-Katz equation, we consider that an influence on the RMV plausible, though. APD prolongation was not reported either but we consider it realistic since an increase in the amplitude suggests that the repolarization time is prolonged, too. $[dV_m/dt]_{max}$ is the only value which showed a deviation > 5% with respect to the reference value. The absolute change was very small and almost not visible when analyzing the APs visually.

When varying $[K^+]_o$, APD, RMV and $[dV_m/dt]_{max}$ responded as expected from results described in literature [4].

An alteration of $[Ca^{2+}]_o$ was mainly observed in the APD. A decrease of APD is related to hypercalcemia according to clinical findings. AP amplitude and $[dV_m/dt]_{max}$ showed a very small dependence on the alteration of $[Ca^{2+}]_o$ (<1%). We presume that when using measured signals, these deviations will not be identifiable.

On tissue level, the dependence of RT distance and ST elevation on $[Ca^{2+}]_o$ was clearly visible in the ECGs (see Figure 1). These two changes due to an alteration in $[Ca^{2+}]_o$ were also reported in the literature [4], [10]. T amplitude, T asc. slope, T desc. slope, R amplitude, R energy and R ratio en./amp. also showed a high dependence on $[Ca^{2+}]_o$ changes. However, these features have not been evaluated in literature. We consider these values relevant and suggest to take them into account in future studies. T peakedness showed deviations <4% with respect to the reference value. Thus, we consider it

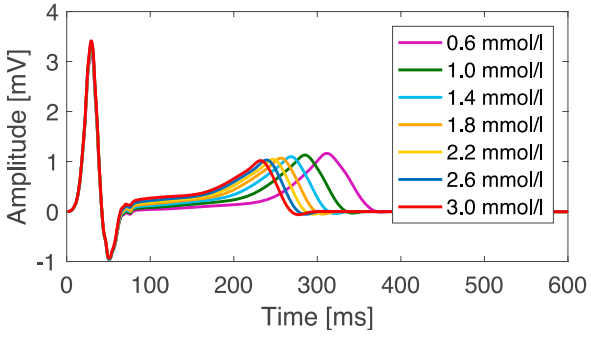

Figure 1: ECG lead II (Einthoven) for $[Ca^{2+}]_o$ variation.

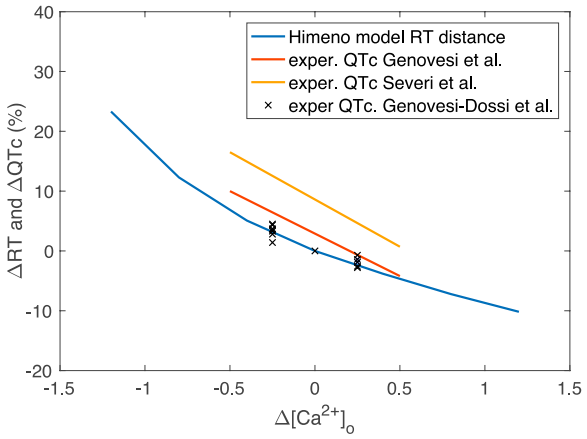

Figure 2: Comparison of simulated and clinical results from Genovesi et al. [11], Severi et al. [12] and Genovesi-Dossi et al. [13].

less relevant for clinical scenarios using noisy measured signals.

To evaluate our results, we compared the simulated RT shortening values due to $[Ca^{2+}]_o$ changes with results from in vivo studies in patients (QTc dependence on $[Ca^{2+}]_o$). Our multi-scale simulator based on the Himeno et al. cellular model showed results within the same range as the results from Genovesi-Dossi et al. [13] and a comparable slope to [11], [12] (Figure 2). Summarizing, the evaluated results are in line with in vivo findings if these were reported in literature. We also showed the dependence of other features on electrolyte concentrations. Several limitations should be considered regarding this study: we computed ECGs based on the ventricular physiology and torso model of one healthy patient. Future studies could consider CKD-induced electrophysiological remodeling and comprise a bigger number of virtual patients. Moreover, the influence of an electrolyte variation on the P wave was not analyzed as only ventricular simulations were performed.

5 Conclusion

Our multi-scale simulator realistically models the effects of $[Na^+]_o$, $[Ca^{2+}]_o$ and $[K^+]_o$ on the AP and how they translate to changes in the ECG. It additionally proves that the Himeno et al. model is capable of simulating realistic APs and ECGs at different extracellular ionic concentrations. This multi-scale simulator could help to understand the relation between CKD and cardiovascular diseases. The results can also be used for further studies based on the idea of considering the ECG as a non-invasive method to estimate the electrolyte concentrations in the extracellular space [5], [14].

Author Statement

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