Mapping Simulated ECG to Early Acute Kidney Injury Based on Electrolyte Disturbances

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Abstract

Background: Acute kidney injury (AKI) leads to blood electrolyte imbalances, affecting cardiac electrophysiology. However, the specific ECG features associated with early-stage AKI and its underlying ionic mechanism remain unclear. Methods: Serum K^+ and Ca^{2+} levels in mice were measured within 12 hours post-AKI onset. These values were input as parameters into cardiac computational model to simulate action potential duration (APD) at cellular level and ECG at one-dimensional level respectively. Results: Silico study shows that low serum K^+ leads to increased R and S wave amplitudes during the 1-hour post-AKI phase. In the 12-hour post-AKI phase, high serum K^+ causes flattened QRS. The T wave peak, corresponding to APD plateau phase, is delayed. Conclusion: The relationship between ECG features and AKI development within 12 hours is built based on blood K^+ and Ca2+ measurements. ECG can serve as a valuable clinical indicator for identifying cardiac electrophysiological changes in the early stages of AKI.

1. Introduction

Acute kidney injury (AKI) is a global concern due to its high incidence in both high and low-income countries. AKI is determined by the sudden decrease of kidney function [1], expressing as disrupted homeostasis of electrolytes, pH, osmolality and so on. In clinical, AKI is diagnosed by measuring the increase in serum creatinine (Cr) within 48h or 7 days and the decrease in urinary output for 6h according to the KDIGO Clinical Practice Guideline [2]. Severe AKI and its complications have a poor prognosis, where acute heart failure is the most common complication, called type 3 Cardio-Renal Syndrome (CRS-3) [3]. A meta-analysis shows that the risk of heart failure, myocardial ischemia and arrhythmia are increased obviously by AKI [4]. To reduce mortality and improve the prognosis of CRS-3 patients, early diagnosis and timely intervention play a vital role.

However, the underlying mechanism of cardiac injury induced by AKI is not completely clear, especially the temporal relationship between AKI and characteristics of cardiac electrophysiology still remains unknown. The unveiled relationship results in a lack of clinical indicators for early diagnosis of cardiac events caused by AKI. Therefore, determining the characteristics of cardiac electrophysiology is of great significance for the early diagnosis and prevention of cardiac events for AKI patients.

In clinical practice, there are multiple risk factors causing AKI, such as ischemia, post-surgical interventions, volume depletion [1]. Owing to the patient-specific causes, it is difficult to investigate the characteristics of cardiac electrophysiology during the evolving AKI. Combining experimental data and computational models [5] are the optimal method to investigate the temporal-spatial relationship between AKI development and cardiac electrophysiology.

CRS-3 originates from kidney-heart crosstalk, the underlying mechanism include but not limited to hyperkalaemia, metabolic acidosis and systemic inflammation [3]. The hierarchy of the above mechanisms contributing to CRS-3 has not yet been established. Previously, myriad researches [6-10] have related electrolyte abnormalities with the development of AKI and its prediction of endpoints. However, the characteristics of serum electrolytes throughout AKI progression have not been investigated thoroughly and their corresponding properties of ECG tracing have not been declared exhaustively.

Here we refine the common factors of renal-cardio mechanisms (changes in serum K^+ and Ca^{2+}) and focus on unveiling electrophysiological changes and its underlying ionic mechanisms corresponding to early stages of AKI by applying mouse ventricular cell model and one-dimensional transmural model.

Noting that the existence of M cell in mouse heart still remains controversy [11, 12]. In this study, we modified the mouse ventricular cell model [5] to reproduce long APD of the M cell, which is in consistence with experimental findings. The effects of these transmural heterogeneous currents on APD and ECG are also studied by simulation.

In all, this study paves a way for screening electrophysiological indicators and potential ion channels targets for the early diagnosis of cardiac events in AKI and blocking its progress.

2. Methods

2.1. Establish the mouse model of AKI

Renal ischemia is a common cause of AKI and warm ischemia-reperfusion model is the most widely used in AKI study. Briefly, male C57BL/6J mice (8 weeks, 22 g body weight) underwent 35 min of unilateral renal pedicle clamping with contralateral nephrectomy. While in the sham group, male and age-matched mice received the same operative procedure except renal pedicle clamping. After AKI/sham surgery, blood samples were harvested at 1, 3, 6 and 12 h for further serum analysis (Figure 1). Cr, BUN (blood urea nitron), K^+ and Ca^{2+} in sham and AKI groups at the indicated timepoints were measured to evaluate renal function and serum electrolyte levels. Where the Cr and BUN are clinical indices most utilized to assess renal injury.

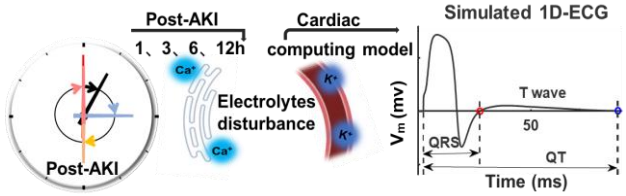

Figure 1. Measuring both serum K^+ and Ca^{2+} to input cardiac model and simulate ECG in early AKI.

In subsequent computational study, serum K^+ and Ca^{2+} in different timepoints are input into mouse cardiac ventricular models to compute corresponding APDs and pseudo-ECG.

2.2. The midmyocardial (M) cell model of mouse ventricles

There is a controversy in the existence of M cells in mouse [11, 12]. To investigate transmural heterogeneity and identify the electrophysiological effects brought by M cells in vivo, we modified the Bondarenko [5] ventricular cell model to simulate M cell APD to match experimental data previously reported [13, 14]. M cell model differs from the Bondarenko model in I_{Na}, I_{Kur} and I_{K1}. The currents ratios of M cell model to the original Bondarenko model are set as shown in table 1.

Table 1. Transmural currents in the M cell model.

Current	M model
I_{Na}	1.2
I_{Kur}	0.55
I_{K1}	0.8

The membrane potential is calculated by equation 1, where V_m is membrane potential, C_m is membrane capacitance.

$$C_m \frac{dV_m}{dt} = I_{CaL} + I_{pCa} + I_{NaCa} + I_{Cab} + I_{Na} + I_{Nab} + I_{NaK} + I_{tof} + I_{tos} + I_{K1} + I_{Ks} + I_{Kur} + I_{Kss} + I_{Kr} + I_{ClCa} + I_{stim} \quad (1)$$

2.3. Transmural One-dimensional ventricular model

The transmural ventricular cable was built by incorporating subendocardial [15], the above M and subepicardial cell models [15]. The proportion of cell numbers in the three layers was 12:8:12, producing about 10 ms of QRS duration. The length in long axis of a cell model was set as 0.1 mm, leading to 0.32 mm length of our cable.

As shown in equation 2, V_m of cell model in our 1D cable was determined by the two items in the right equal. In the first item, I_{tot} represents the summation of membrane currents and the stimulus current applied. The second item indicates intercellular currents. The potential at 1 cm away from subepicardial layer is recorded as our p-ECG.

$$\frac{dV_m}{dt} = -I_{tot} + \nabla \cdot (\nabla V_m) \quad (2)$$

3. Results

As figure 2 shows, both of Cr and BUN values increase with time post-AKI surgery.

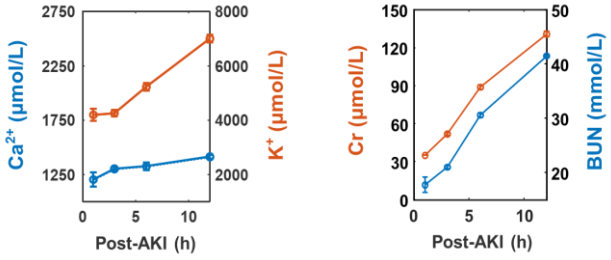

Figure 2. Serum Ca^{2+}, K^+, Cr and BUN at the indicated timepoints measured in post-AKI groups. Cr, Creatine. BUN, Blood urea nitron.

That rising values indicate the degree of AKI becoming more severe. At the same time, serum K^+ and Ca^{2+} levels exhibit changes with time. Where the serum K^+ changing level possesses a broader range and serum K^+ has an obvious increase in 12h post-AKI comparing with 1h post-surgery.

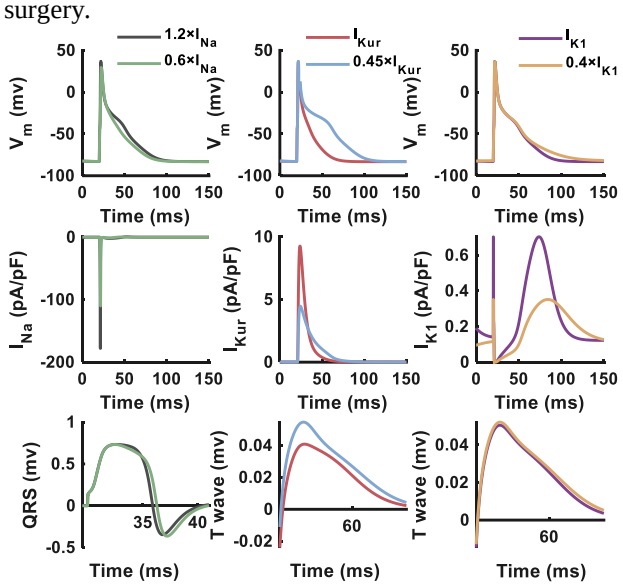

Figure 3. Changes of I_{Na}, I_{Kur}, I_{K1} in the M cell model and the resulted APDs and pseudo-ECG.

I_{Na}, I_{Kur} and I_{K1} are transmural heterogeneous currents. They contribute to depolarizing and repolarizing phases respectively. Figure 3 represents their effects on M cell APD and p-ECG. Specifically, QRS is broaden by decreased I_{Na} ($0.6\times I_{Na}$). The amplitude of T wave increases with smaller I_{Kur} ($0.45\times I_{Kur}$). Varying I_{K1} contributes little to APD and p-ECG.

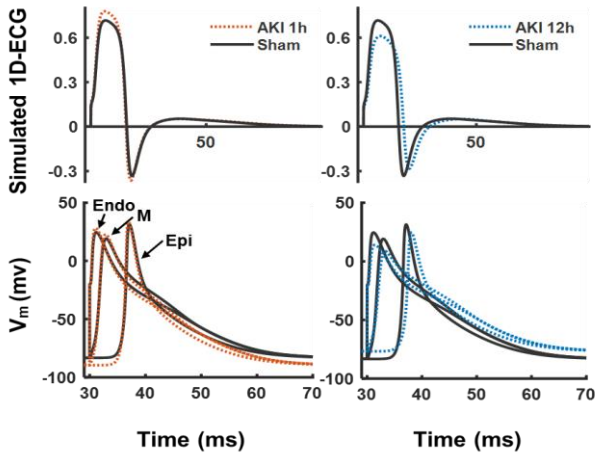

Figure 4. p-ECG and the corresponding transmural APDs in sham, 1h and 12h respectively.

The mouse transmural ventricular model is constructed by contacting cell models of three layers. The magnitude of QRS complex is larger in 1h post-AKI comparing with sham group. As with the increase of serum K^+, QRS magnitude decreases. In 12h post-AKI, QRS is broaden and flatten, thus, the T wave is delayed. Figure 4 delves into underlying ionic mechanisms at cellular level of the electrophysiological changes. On one hand, the increase of QRS magnitude is due to the hyperpolarization in APDs, brought by low serum K^+ in 1h post-AKI. On the other hand, flatten QRS complex originates from conduction delay and depolarization in high serum K^+ in 12h post-AKI.

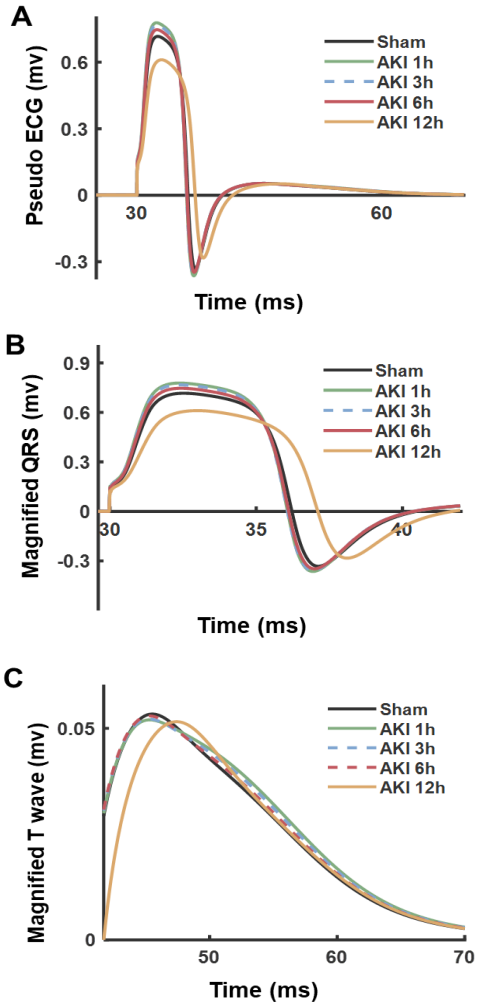

Figure 5. The simulated ECG and the enlarged parts of it in sham, 1h, 3h, 6h, and 12h post-AKI groups. A. Pseudo ECG. B. The enlarged QRS complex in comparison. C. T wave enlarged in the corresponding groups.

The measurements of serum K^+ and Ca^{2+} values in other timepoints post-AKI are also input into the 1D model as initials to compute p-ECG (Figure 5). Furtherly, to make the effects of electrolytes on p-ECG morphology more clearly, magnified QRS complex and T wave are represented in figure 5. Comparing with the p-ECG in 1 and 12h post-AKI, the changes of p-ECG in 3 and 6h post-AKI are relatively slight.

4. Discussion

According to experimental studies, the M cell exhibits transmural differences in membrane ionic currents and results in longer APD. Compared with the two other cell types in myocytes, the M cell has the maximum sodium channel density and relative less I_{K1} [13, 14]. Its long APD is demonstrated to be induced by I_{Kur} and we furtherly confirm the role of I_{Kur} through simulation.

Although both of the serum K^+ and Ca^{2+} levels keep increasing after AKI surgery, the range of serum Ca^{2+} level changes is quite smaller than serum K^+. Serum K^+ is reported to be the key factor predictive of AKI developing [6, 7]. In our study, changes of serum K^+ level is also identified to be related with AKI stages.

The most evident changes of ECG morphology in AKI are the magnitude and duration of QRS complex. In 1h post-AKI surgery, QRS complex exhibits evident increased magnitude. As with time, in 12h post-AKI, QRS complex becomes flatten and broaden, representing high serum K^+ level and indicating the possibility of arrhythmia. In conclusion, QRS complex could not only be a clinical marker representing cardiac electrophysiological changes, but also clinical indices indicating AKI stages.

Acknowledgments

This work was supported by Young Scholar Independent Innovation Science Foundation of Chinese PLA General Hospital (No. 22QNFC116).

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