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Role of CaMKII in CaMKII/[Na+]i/[Ca2+]i Feedback in Myocardial Ischemia and Reperfusion Injury: A Simulation Study

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Myocardial ischemia and reperfusion injury (MIRI) is a serious complication after percutaneous coronary intervention, which leads to heart failure, increased infarction size, and severe arrhythmias [1,2]. Various signaling pathways were found to be participated in the process of MIRI, such as phosphatidylinositol 3-kinase (PI3K)/AKT, extracellular signal-regulated kinase (ERK), endothelial NO synthase (eNOS), etc[3-5]. Recently, more and more studies demonstrate that Na^+/Ca^{2+}/Calmodulin-dependent protein kinase II (CaMII) feedback plays vital role in heart failure [6]. Over-activity of CaMKII enhanced the late Na^+ current(I_{NaL}), caused intracellular Na^+ ($[Na^+]_i$) increasing, changing the equilibrium of the Na^+-Ca^{2+} exchanger (NCX) to impair forward-mode (Ca^{2+} extrusion), and aggravating reverse-mode (Ca^{2+} influx) exchange. Subsequently, this Ca^{2+} overload further activate CaMKII and cause a feedback loop of CaMKII/$[Na^+]_i$/$[Ca^{2+}]_i$ in heart failure. However, the role of CaMKII/$[Na^+]_i$/$[Ca^{2+}]_i$ feedback in MIRI is still unclear. In the present study, we took the published MIRI action potential model [7,8], 50% blocking the voltage-dependent sodium current(I_{Na}) and CaMKII, to observe the effect of I_{Na}(-) and CaMKII(-) on MIRI.

To ensure the influence of I_{Na} and CaMKII on MIRI, we used Roberts-Christini MIRI AP model [7,8], which combined the dynamic changes of intracellular pH (pH_i), extracellular pH(pH_e), 13 ion currents and 6 pump exchangers. All simulations were run using a pacing rate of 1 Hz. Four groups were set as: Control (MIRI only), I_{Na} 50% block, CaMKII 50% block and both (I_{Na} 50% and CaMKII 50% block), respectively.

As we showed in **Figures 1A-1C**, during ischemia stage, intracellular and extracellular pH were reduced to 5.8 and 6.2 from pre-ischemia stage(pH_e 7.4, pH_i 7.2), respectively. The AP amplitude was decreased alternatively, which were consistent with the previous report [9]. In **Figures 1D-1G**, we can see that sodium overload existed in 10-minutes ischemia stage, compared with pre-ischemia, exacerbating in 10-minutes reperfusion stage. I_{Na} 50% block (blue line) slightly reduced intracellular sodium concertration ($[Na]_i$), while activated CaMKII 50% block (green line) and both block (black line) reduced $[Na]_i$ more significantly. Calcium overload were found in control (red line) and I_{Na} 50% block(blue line), while it was reduced significantly in CaMKII 50% block and both block **(Figure 1H)**, which reveals that CaMKII is essential to keep calcium overload, not I_{Na}. Consistently, we found NCX current were also reduced in CaMKII 50% block and both block **(Figure 1I)**, which suggested that NCX played downstream role of CaMKII and calcium overload.

To further explore the mechanisms of CaMKII and I_{Na} on MIRI, we analysed various currents which might be related with sodium and calcium overload. As we showed in **Figures 2A-2I**, during pre-ischemia stage, we can see that Peak I_{Na} keeps in 350 uA/uF in normal, while it reduced half (175 uA/uF) in I_{Na} 50% block and both groups. All other currents, such as calcium-sodium exchanger (I_{CaNa}), I_{NaL}, background sodium current (I_{Nab}), sodium-potassium exchanger (I_{NaK}), ATP-inactivated potassium current (I_{Katp}), sodium-calcium exchanger (I_{NCX}), sodium-bicarbonate symporter (I_{NBC}), sodium-exchanger (I_{NHE}), are nearly the same values in these four groups. During 10-minutes ischemia stage, Peak I_{Na} among the four groups were reduced significantly (40-60 uA/uF). Peak I_{Nab} increased in CaMKII 50% block and both I_{Na}-CaMKII block groups, while all other currents kept the simular values among four groups. During 10-minutes of reperfusion stage, Peak I_{CaNa} were significantly increased in CaMKII 50% block and both I_{Na}-CaMKII block groups, which reveals that more calcium ions were transferred from inside to outside of cells in these two groups, while other currents changed little. Therefore, I_{CaNa} takes responsibility for reducing calcium overload in MIRI.

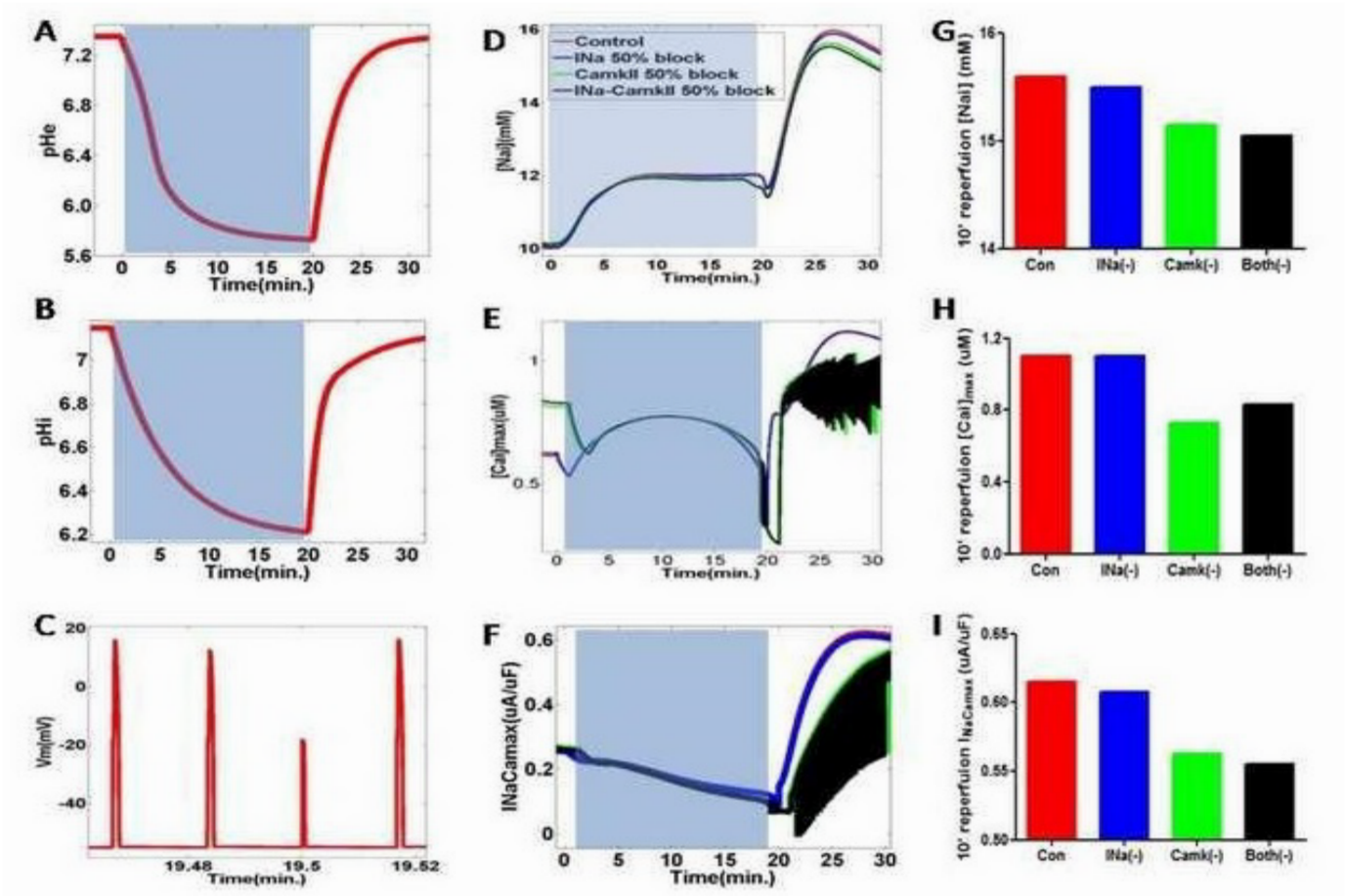

Figure 1 Summary of simulations. Changes in (A) intracellular pH (pH_i), (B) extracellular pH (pH_e), (C) action potential, (D) intracellular sodium (Na^+_i), (E) maximum intracellular calcium (Ca^{2+}_i), (F) I_{NaCa} current during simulated ischemia (gray region) and (G) Na^+_i (H) Ca^{2+}_i (I) I_{NaCa} at 10 minutes reperfusion during four simulations: Control(with no I_{Na} and CaMKII inhibition) (red), I_{Na} inhibition at 50 percent (blue) , CaMKII inhibition at 50 percent (green) and both I_{Na} and CaMKII inhibition at 50 percent (dark).

As for the limitation, we used Roberts-Chritini MIRI AP model, which was the latest AP model describing the acidosis state and various currents' changes in MIRI, more information might be focused on the Markov state of ion channels.

Conclusion

The mechanisms of MIRI is complicated, considering the system is combined with various nonlinear components and frequently exhibit non-intuitive behavior, using the dynamic MIRI model showed in the present study will provide a powerful method to reveal the vague secrets. Here we used the MIRI model to provide a solve to the interesting question, what is the focus of CaMKII/$[Na^+]_i$/$[Ca^{2+}]_i$ feedback, which is more important between CaMKII and I_{Na}. Our study indicate that CaMKII plays a key role in calcium overload in MIRI, not I_{Na}, blocking of CaMKII activated I_{NCX} and I_{CaNa} currents, transferred more Ca^{2+} to the outside of cell, subsequently reducing calcium overload, and finally alleviated MIRI. Inhibited activation of CaMKII might be a potential treatment in protection against myocardial ischemia and reperfusion injury.

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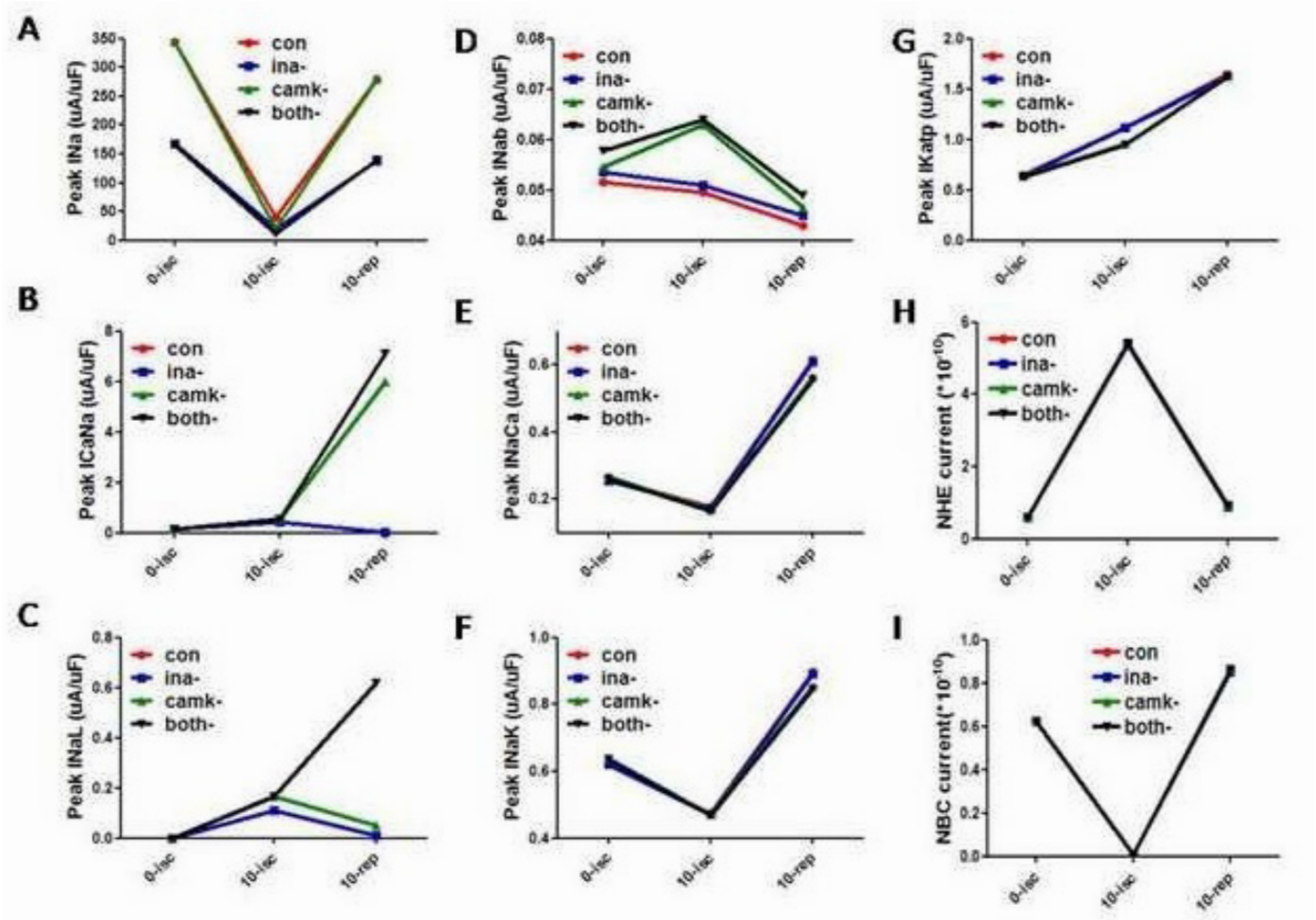

Figure 2 Changes of maximum currents and exchangers during four simulations: Control (with no INa and CaMKII inhibition) (red), I_{Na} inhibition at 50 percent (blue), CaMKII inhibition at 50 percent (green) and both I_{Na} and CaMKII inhibition at 50 percent (dark). (A) peak I_{Na}, (B) peak I_{CaNa}, (C) peak I_{NaL}, (D) peak I_{Nab}, (E)peak I_{NaCa}, (F)Peak I_{NaK},(G)Peak I_{Katp}, (H)I_{NHE} , (I)I_{NBC} during pre-ischemia(0-isc), 10 minutes ischemia(10-isc) and 10 minutes reperfusion(10-rep) stages.

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