Modeling the Mechanism of $[Na^+]_i$ Elevation in Heart Failure by a Canine Ventricular Cell Model

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Abstract

Numerous studies have found the phenomenon of $[Na^+]_i$ elevation in cardiac myocytes in heart failure (HF), which may influence cardiac action potential (AP) and intracellular Ca^{2+} handling to induce cardiac arrhythmias. As one of the most important regulators in the cardiac myocytes, Ca^{2+}/Calmodulin-dependent protein kinase II (CaMKII), which could alter Na^+ channel gating, was found to be over-expressed in HF. It may contribute to $[Na^+]_i$ elevation in HF. For the purpose of this study, we developed a new canine epicardial cell model based on the framework of published Hund-Rudy dynamic (HRd) model. The effects of dynamic CaMKII regulation on fast Na^+ current (I_{Na}) and late Na^+ current (I_{NaL}) were incorporated into our model according to the recent experimental data. Simulation results suggested that the regulation role of CaMKII on I_{NaL} could elevate $[Na^+]_i$. The effect of COE on I_{Na} had a function of lowering $[Na^+]_i$ in fact. However, it could not offset the trend of Na^+ up-regulation by enhanced I_{NaL}. The magnitude of $[Na^+]_i$ elevation was smaller than experimentally measured values. We speculate that other $[Na^+]_i$ elevation mechanisms such as lowered Na^+/K^+ pump (I_{NaK}) or increased Na^+/H^+ exchange may happen in HF.

1. Introduction

Heart failure (HF) is usually characteristic of prolonged APD facilitating cardiac arrhythmias and disturbed Ca^{2+} handling system causing contraction or relaxation dysfunction. Recently, more and more attention has been attracted to the phenomenon of $[Na^+]$ elevation. Due to the interplay with Ca^{2+} by Na^+/Ca^{2+} exchange current (I_{NaCa}), elevated $[Na^+]$ may play a more important role in Ca^{2+} handling in HF. Some researchers even related it with a complementary mechanism for the lowered Ca^{2+} in HF [1]. However, the mechanism of $[Na^+]$ elevation remains not clear. It is difficult for experiments to accurately find the mechanism because the cardiac myocyte is an interactive system and many components of it affect each other. In this context, computer simulations provide an alternative way. Based on the framework of Hund-Rudy dynamic (HRd) model [2], we developed a new canine epicardial ventricular cell model to explore the mechanism of $[Na^+]$ elevation in HF. Dynamic CaMKII kinetics was included. In HF, up-regulated CaMKII may be a possible reason of elevated $[Na^+]$.

2. Methods

In this work, Ca^{2+} handling system was reconstructed. Sarcoplasmic reticulum (SR) Ca^{2+} pump (SERCA) was modeled as a bidirectional pump [3]. SERCA and SR passive leakage current were dependent on both intracellular Ca^{2+} and Ca^{2+} in network SR ($[Ca^{2+}]_{NSR}$). The SR release current was taken from Livshitz et al [4], which incorporated CaMKII dependent facilitation. Augmented I_{leak} by CaMKII over-expression (COE) was consistent with experimental observations [5]. Fast Na^+ current (I_{Na}), late Na^+ current (I_{NaL}), transient outward K^+ current (I_{to}), time-independent K^+ current (I_{K1}), rapid-activating delayed rectifier K^+ current (I_{Kr}), L-type Ca^{2+} current (I_{CaL}) were reformulated using recent experimental data. The conductance of Na^+/K^+ pump current (I_{NaK}) was increased to stop $[Na^+]$ accumulation. CaMKII kinetics was kept the same as in HRd model.

HF settings: Alterations in HF were grouped into two classes. The first class corresponded to acute COE regulated alterations of I_{CaL}, SERCA, I_{leak}, I_{K1}, I_{to}, I_{Na} and I_{NaL}, which alterations could be reversed by CaMKII inhibitor. The second group corresponded to the protein expression remodeling of SERCA, I_{K1}, slow-activating delayed rectifier K^+ current (I_{Ks}) and I_{to}, which alterations could not be reversed by CaMKII inhibitor. In our simulation, SERCA was down-regulated by 50%, in the range of 49% to 52% estimated by Winslow et al [6]. I_{K1} and I_{Ks} were down-regulated by 50% and 57%, respectively [7]. $I_{to,fast}$ was down-regulated by 30% and $I_{to,slow}$ up-regulated by 41% [8]. I_{NaCa} was not changed according to the experimental observations by Xiong et al [9].

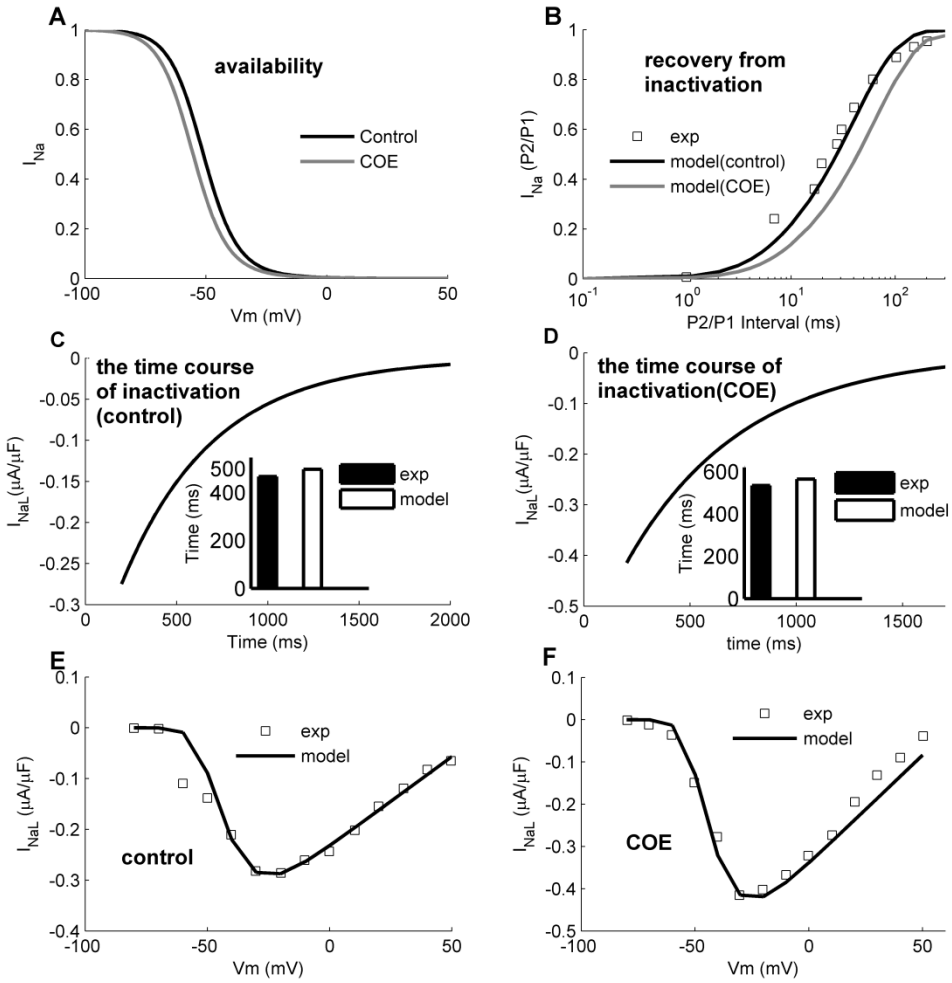

Figure 1. Gating properties of I_{Na} and I_{NaL}. (A) I_{Na} steady state inactivation in control and COE. (B) I_{Na} recovery from inactivation in control and COE. (C) I_{NaL} inactivation kinetics in control. (D) I_{NaL} inactivation kinetics in COE. (E) I_{NaL} I-V relationship in control. (F) I_{NaL} I-V relationship in COE.

3. Results

The gating properties of I_{Na} and I_{NaL} are shown in Figure 1. As shown in Figure 1B, the recovery kinetics of I_{Na} agrees well with experimentally measured values [10]. For I_{Na}, Steady state inactivation (SSI) was left shifted by 4.25 mV (Figure 1A) (-6 mV measured by Wagner et al (11)) and the recovery from inactivation was delayed by 58% (~50% measured by Wagner et al [11] with COE. The conductance of I_{Na} was chosen to match the maximum upstroke velocity and AP amplitude from Lue et al [12]. Inactivation kinetics and I-V relationship of I_{NaL} were reformulated to match the recent experimentally measured values under both control and HF conditions [13] (Figure 1 C-F).

In control, $[Na^+]$ at rest and 2 Hz are 6.65 mM and 10.3 mM respectively, which are in the range of experimentally measured values [14]. As shown in Figure 2, both under the condition of COE and HF, simulated I_{Na} at 1 Hz AP pacing is reduced which could cause lowered $[Na^+]$, whereas I_{NaL} show a trend to increase under the same circumstances. Augmented I_{NaL} would compensate the loss of $[Na^+]$ by reduced I_{Na}. In response to the elevated $[Na^+]$ and lowered intracellular $[Ca^{2+}]$ In HF, I_{NaCa} spends a longer time in the reverse mode (i.e. Na^+ efflux and Ca^{2+} influx state) (Figure 2C). At the same time, I_{NaCa} would tend to limit the $[Na^+]$ accumulation to maintain its original state. However, the elevation of $[Na^+]$ in our simulation (Figure 2D, 0.23 mM at 2 Hz, 0.3 mM at 1 Hz, 0.07 mM at 0.5 Hz) are smaller than experimentally observed values in HF (4 mM in canine [15]). To preclude the possibility that the discrepancy of our simulated $[Na^+]$ elevation and experimental observations is due to the inaccuracy of the experimental

data which we used to model I_{NaL}, we tested another experimental data by Valdivia et al [16]. In that experiment, I_{NaL} in HF has a nearly 3-fold increase compared with control. We implemented a 3-fold increase

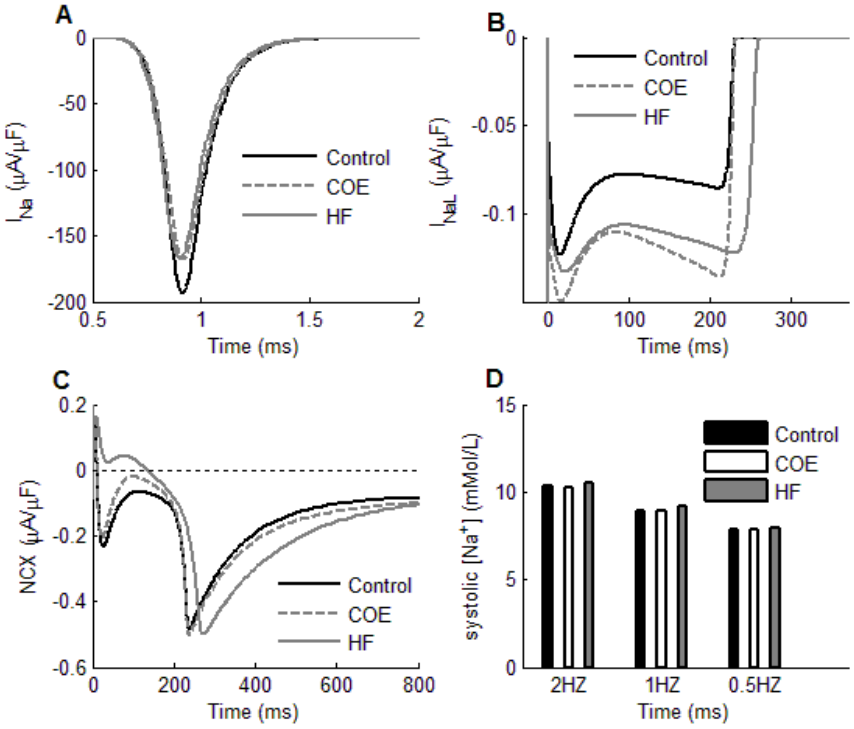

Figure 2. Na^+ related currents and Na^+ elevation. (A-C) I_{Na}, I_{NaL}, I_{NaCa} in control, COE and HF. (D) Na^+ at different pacing rates in control, COE and HF.

in our HF simulation. However, in this simulation, $[Na^+]$ had only another 0.2 mM elevation, still not close to the 4 mM elevation in HF. It suggests that there should be other mechanisms for $[Na^+]$ elevation in HF [17].

4. Discussion

$[Na^+]$ elevation mechanisms deduced from limited experimental data are controversial in some cases. According to Verdonck et al [15], dogs with hypertrophy showed a decrease in Na^+ affinity of I_{NaK}, but Bossuyt et al found that I_{NaK} function was not altered in rabbits with HF [18]. According to experiments [11, 13], intracellular $[Na^+]$ elevation was simulated by enhancing I_{NaL} alone in this work. However, 4 mM elevation was not achieved by our model. There could be several explanations for this. Firstly, $[Na^+]$ elevation may be species dependent and I_{NaK} may be down-regulated as reported [15]. In our model, $[Na^+]$ is really sensitive to I_{NaK}. Even a small change in I_{NaK} could contribute to a big change on $[Na^+]$. Secondly, up-regulated Na^+/H^+ exchange may also be a reason of $[Na^+]$ elevation in HF [17]. In conclusion, we speculate that there should be other $[Na^+]$ elevation mechanisms besides enhanced I_{NaL}.

Acknowledgements

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