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Role of Late Sodium Current in the Simulated Low Repolarization Reserve and Ischemic Ventricular Tissue

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Abstract: Late sodium current I_{NaL} is largely enhanced in failure and ischemic hearts. However, its role in the failure in combination with ischemic heart is poorly understood. In this study, a transmural computer model was created by considering the most significant effect of ischemia on different cellular types along the fiber. By completely blocking I_{Kr} while enhancing I_{NaL}, the low repolarization reserve situations in Heart Failure (HF) were also simulated. The results showed that when I_{NaL} was elevated 4 times, repolarization and Transmural Dispersion of Repolarizing (TDR) were both enlarged with rate dependence. Further enhancement of I_{NaL} could amplify the rate adaptation. For 5 relative to 4 times I_{NaL}, TDR raised 14.5, 18.3 and 21.5% for basic cycle lengths of 500, 1000 and 2000 m sec, respectively. Moreover, Early After Depolarization (EAD) could be induced by enlarging I_{NaL} to 10 times while considering a 4-fold increase of L-type calcium current I_{CaL} to mimic adrenergic stimulation observed in HF. Therefore, the study indicated that in failure in combination with ischemic heart, the enhancement of I_{NaL} could favor the occurrence of either the reentrant or the triggered arrhythmia. Accordingly, selective blockade of I_{NaL} was suggested to be a potential target for antiarrhythmic therapy.

Key words: Late sodium current, heterogeneity, repolarization reserve, ischemia

INTRODUCTION

LQT syndrome is a repolarizing disorder with obvious prolongation of QT interval. It is susceptible to induce sudden cardiac death due to the formation of Early Afterdepolarization (EAD) and a polymorphic Ventricular Tachycardia (VT) named as Torsades de Pointes (TdP) (Cardona *et al*., 2010). It is known that normal cardiac repolarization depends critically on the interplay of multiple ion currents and these provide reserve to protect against excessive QT prolongation (Milberg *et al*., 2007). However, some pathological situations in combination with the use of drugs may reduce the repolarization reserve (Varro and Baczko, 2011).

Pure class III antiarrhythmic drugs (rapidly activating delayed rectifier K^+ current I_{Kr} blocker) is known to be frequently associated with an increased incidence of EAD and even TdP because it prolongs Action Potential Duration (APD) in a reverse rate dependent manner in which the APD shortens as heart rate increases (Wu *et al*., 2011). Additionally, repolarizing disorder has been observed under pathological situations, such as Heart Failure (HF) in which K^+ current is down-regulated Scho while the late sodium current (I_{NaL}) is elevated (Maltsev and Undrovinas, 2008). Recently, more and more evidences suggest an important role of I_{NaL} during repolarization under pathological conditions (Lowe *et al*., 2012; Moreno and Clancy, 2012). Several studies have demonstrated a potential role of suppression repolarization abnormalities by inhibition I_{NaL} using antiarrhythmic drugs (Saint, 2008).

Despite recent concerns about I_{NaL}, its role under ischemic condition is poorly understood. Ischemia not only can cause arrhythmias, but also usually occurs accompanying other pathological situations such as HF. It was reported that I_{NaL} was enhanced both in ischemic and HF. The inhibition of I_{NaL} could reduce electrical and mechanical dysfunction of ischemic myocardium (Shryock and Belardinelli, 2008; Saint, 2006). Therefore, the main goal of this study is to investigate the effects of I_{NaL} enhancement on the dispersion of repolarization and EAD formation in failure in combination with ischemic ventricle in order to reveal its potential role for antiarrhythmic therapy.

MATERIALS AND METHODS

Heterogeneous 1-d multicellular model: Based on a canine single cell model (Benson *et al*., 2008), a heterogeneous transmural strand consisting of 150 cells was developed to approximate properties of endocardial, midmyocardial (M) and epicardial cells. The left-hand

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50 cells were characterized with endocardium. The middle 50 cells were M myocytes while the others were epicardium. As reported in our previous study (Zhang *et al*., 2014), electrical propagation was described by the non-linear cable equation with the impermeable boundary conditions. ECG was computed from the transmembrane potential using an integral expression given by Gima and Rudy (2002). The operator splitting method was used to solve the model.

Simulation of pathological conditions: To mimic ischemia, the extracellular K^+ concentration $[K^+]_o$ was elevated since accumulation of $[K^+]_o$ was considered to be the most important characteristics in ischemia (Carmeliet, 1999). It was reported that despite a greater susceptibility of endocardium to metabolic effects of ischemia, the electrophysiological changes evoked by ischemia in epicardium were actually greater (Okumura *et al*., 1983), therefore, along the developed fiber $[K^+]_o$ was raised 10, 20 and 30% for endo-, mid- and epi-myocytes, respectively. In addition, to model the low repolarization reserve caused by class III antiarrhythmic drugs (Cardona *et al*., 2010), I_{Kr} was completely blocked.

RESULTS

Pathologically-induced action potential change: Figure 1 shows action potentials of ischemia combined with a complete block of I_{Kr} (broken line) and normal action potentials (solid line) of three cellular types. Obviously, the major effects of ischemia on action potentials were the elevation of resting potential and significant shortening of APD. Although I_{Kr} block should prolong APD since it is an outward current, however, compared with the normal situation in which M cell presented the longest APD, with deterioration of ischemia along the fiber from endo-to epi-myocytes, APDs were dramatically reduced because APD shortening caused by ischemia exceeded its lengthening induced by I_{Kr} block. Therefore, in the simulated pathological situations, resting potentials were raised 3.5, 5.9 and 7.3% while APDs were reduced 23.4, 38.3 and 63.3% for endo-, mid- and epi-myocytes, respectively.

Effects of I_{NaL} on dispersion of repolarization: Figure 2 displays action potentials of three type myocytes and their corresponding ECG waveforms at pacing rates of 500, 1000 and 2000 m sec when I_{NaL} was enhanced 4 times. As denoted, QT was defined as the time from the onset of the QRS to the end point of the T wave. T_{p-e} was defined as the time from the peak to the end of the T wave. We noticed that compared with the normal situation in which M cell presented a longest APD, thus the last one to repolarize, in the ischemic situation in Fig. 2, the endocardium repolarized last, resulting in that T_{p-e} aligned with complete repolarization of the epi and endo-myocardium while QT coincided with the upstroke and repolarization of the endocardial action potential.

From Fig. 2 we noticed that after 4 times enhancement of I_{NaL}, APDs prolonged significantly. Meanwhile, APD and T_{p-e} showed rate dependent characteristics. Taking the M cell as an example, compared with results at BCL = 500 m sec, for BCL of 1000 and 2000 m sec, APD prolonged 5.9 and 11.3%, respectively.

Figure 3 displays the T_{p-e} interval (A) and the ratio of T_{p-e}/QT (B) versus BCL for different enhancement of I_{NaL}. Open circle-denoted curves represent the results of 4 times I_{NaL} while the curves with solid triangles are the results of 5 times I_{NaL}. Obviously, T_{p-e} interval and T_{p-e}/QT ratio not only exhibited rate dependence but also showed

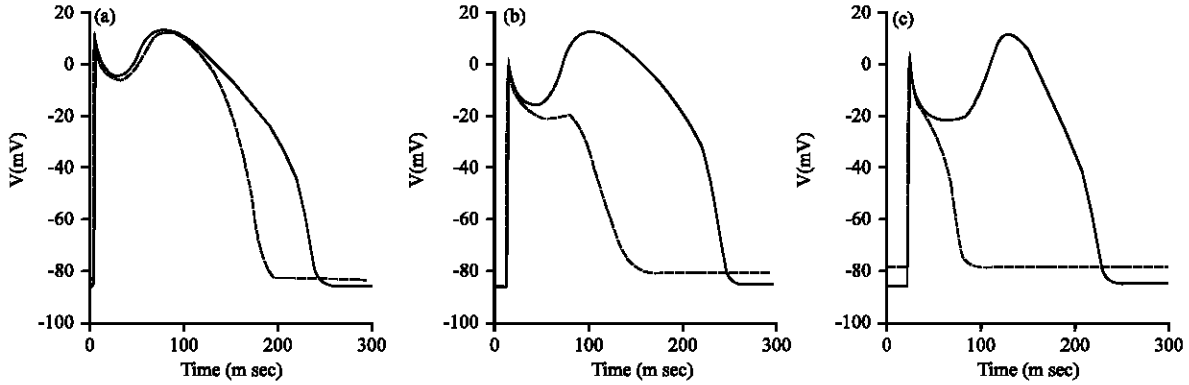

Fig. 1(a-c): Action potentials of the normal (solid lines) and ischemia combined with I_{kr} block (broken line). (a-c) Correspond to endo-, mid- and epi-myocytes located in the middle of each layer

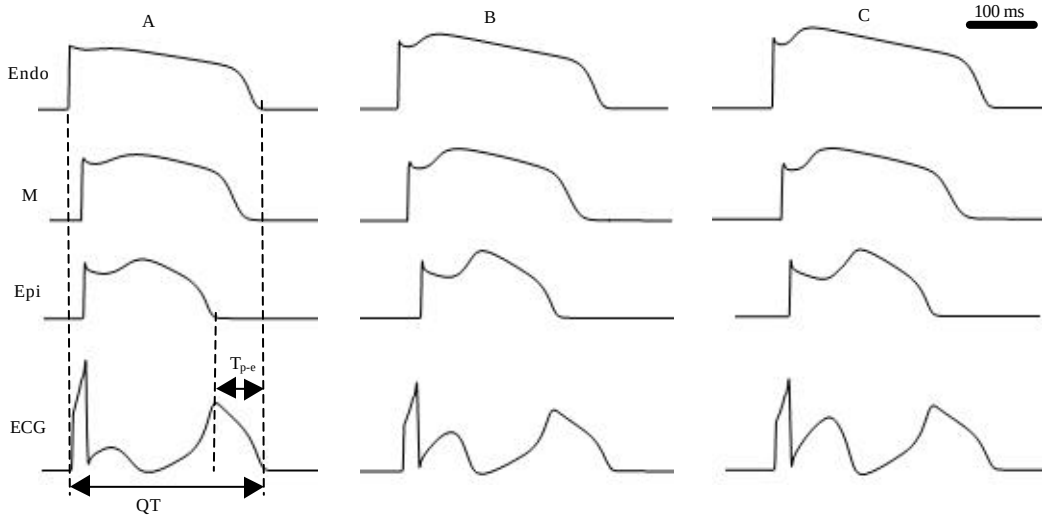

Fig. 2(a-c): Action potentials at different pacing rates when I_{NaL} was enhanced 4 times. (a-c) Correspond to BCLs of 500, 1000 and 2000 m sec, respectively. In each panel, action potentialsof end-, mid-, andepi-myocytes as well as the ECG are aligned from the top to the bottom

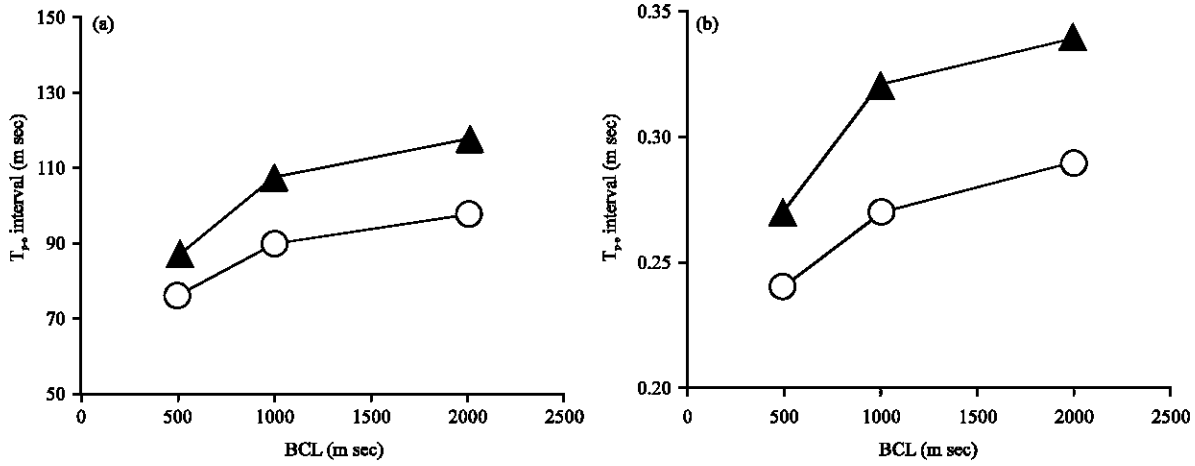

Fig. 3(a-b): (a) T_{p-e} interval and (b) Ratio of T_{p-e}/QT versus BCL for 4 (open circle labels) and 5 (solid triangle labels) times of I_{NaL}

increasing tendencies with enhancement of I_{NaL}. In contrast, for 5 vs. 4 times I_{NaL}, T_{p-e} interval raised about 14.5, 18.3 and 21.5% for BCLs of 500, 1000 and 2000 m sec, respectively. Since the Transmural Dispersion of Repolarization (TDR) across the tissue can be approximated by T_{p-e} (Antzelevitch *et al*., 2007), the results indicated an important effect of I_{NaL} on TDR. Besides, the increase of T_{p-e}/QT ratio also suggested a high probability of TdP in that this ratio was reported to be an important arrhythmic index particularly relevant to the TdP risk (Gupta *et al*., 2008).

Effects of I_{NaL} on EAD generation: In order to characterize the role of I_{NaL} in the firing of EAD, a 4-fold increase of L-type calcium current (I_{CaL}) was considered as well to simulate adrenergic stimulation observed in HF situation (Tomaselli and Marban, 1999). Figure 4 displays effects of I_{NaL} enhancement on EADs in mid-myocytes. After I_{NaL} was enlarged 7 times, APD was prolonged markedly (broken line). But no obvious voltage oscillation appeared during the repolarizing phase of the action potential. When I_{NaL} was further elevated to 10 times (solid line), an EAD like voltage oscillation

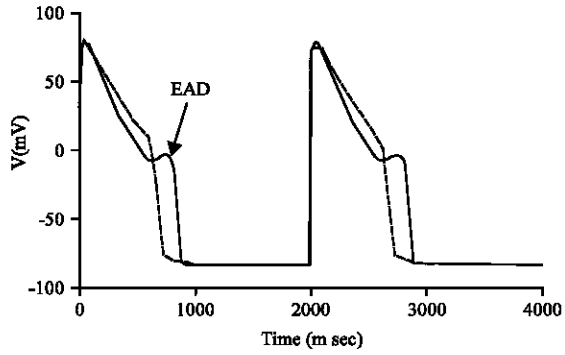

Fig. 4: Effects of I_{NaL} enhancement on EAD generation in M cells. Solid line and broken line correspond to 10 and 7 times of I_{NaL}, respectively

occurred at the late stage of the plateau, suggesting a proarrhythmic effect of I_{NaL}.

DISCUSSION

It is known that the prolongation of APD is usually related to conditions of low repolarization reserve in which an unbalance among currents could lead to repolarizing disorder, such as EAD and LQT symptom. These phenomena have been observed in HF situation where I_{NaL} plays an important role (Cardona *et al*., 2010; Maltsev and Undrovinas, 2008). Recent report suggested that I_{NaL} was also enhanced during ischemia. However, the role of I_{NaL} in HF in combination with ischemic situations is poorly understood. In this study, a transmural heterogeneous model by considering the most significant effect of ischemia on different cellular types along the fiber has been developed. The low repolarization reserve situations were created by completely blocking I_{Kr} while enhancing I_{NaL} with different degree. The developed model demonstrated that although I_{Kr} was a repolarizing current which would prolong the APD after it was inhibited, however, since accumulation of $[K^+]_o$ caused by ischemia not only raised the resting potential, but also shortened the APD dramatically (Fig. 1), the APDs for three cellular types were actually reduced markedly, specifically for the epi-myocytes that suffered ischemia seriously.

After enhancing I_{NaL}, we found that compared with the normal situations in which the effect of I_{NaL} on APD prolongation became significant after 2 times of I_{NaL}, in ischemia this effect was not found remarkable until I_{NaL} was increased 4 times. However, when I_{NaL} was enhanced further, its impacts on action potentials were similar to the normal situations. Figure 2 and 3 illustrated that APD, repolarization and TDR all showed rate dependence, that is, tachycardia made them short while bradycardia made them long. Besides, the enhancement of I_{NaL} was demonstrated to amplify the repolarization prolongation and dispersion of repolarizing at the same time. It is well known that TDR plays an important role in forming reentrant arrhythmia (Antzelevitch *et al*., 2007), therefore, the increase in TDR at enhanced I_{NaL} favored the possibility of the occurrence of TdP.

Additionally, in order to evaluate the role of I_{NaL} in the firing of EAD, besides a large increase of I_{NaL}, a 4-fold elevation of I_{CaL} was also considered to simulate adrenergic stimulation observed in cases of HF. Figure 4 indicated that for a same I_{CaL}, only when I_{NaL} was large enough, EAD was induced,suggesting a contribution of I_{NaL} to triggering arrhythmia by causing EAD.

CONCLUSION

The study revealed that in failure in combination with ischemic heart, the enhancement of I_{NaL} could favor the occurrence of either the reentrant or the triggered arrhythmia. Accordingly, selective blockade of I_{NaL} was indicated to be a potential target for antiarrhythmic therapy.

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