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Computer Simulation Analysis of Shock Intensity- and Phase- Dependence of High-Intensity DC Stimulation Aftereffects on Action Potential of Ventricular Muscle

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Abstract: The shock intensity- and phase-dependence of high-intensity DC stimulation aftereffects was studied by using Luo-Rudy's dynamic action potential model. Shock-induced transient rupture (electroporation) of the cell membrane was represented by incorporation of non-selective ionic pores. Application of DC shocks during the plateau phase caused a prolongation of the action potential. Diastolic phase shocks resulted in an activation of action potential with similar delay in repolarization. Oscillatory membrane potentials and single or multiple spontaneous excitations were induced by DC shocks with intermediate intensity and these were accompanied by activation of L-type calcium current during the plateau phase. These results are consistent with observations in animal experiments. The Luo-Rudy's dynamic action potential model with reversible electroporation-mediated pores may provide useful tools to investigate membrane potential changes and underlying ionic mechanisms following electrical shocks.

Key words: defibrillation, electroporation, computer simulation, action potentials

Direct current (DC) shock is one of the most effective treatments for ventricular fibrillation but it also causes undesirable postshock aftereffects including initiation of new arrhythmias. The cellular and subcellular mechanisms underlying antiarrhythmic and proarrhythmic effects of DC shocks remain controversial (Jones and Jones, 1980; Ideker el al, 1991; Dillon and Kwak, 1998; Chen et al., 1998; Al-Khadra et al., 2000). We previously investigated postshock aftereffects on the transmembrane potential in isolated ventricular muscles and Langendorff-perfused whole hearts of the guinea pig, and we observed that high-intensity DC shocks (>15 V/cm) caused a delay of action potential repolarization, membrane potential oscillations and repetitive spontaneous activities (Kodama et al., 1994; Kodama et al., 1999; Kodama et al., 2000). Based on these findings, we suggested that reversible formation of membrane pores (electroporation) may play important roles in the DC shock-induced changes in the membrane potential.

Our previous study using a Beeler-Reuter action potential model partially represented the aftereffects observed in animal experiments (Sakuma et al., 1998) and, the subsequent simulation study using a Luo-Rudy model suggested a major contribution of high-intensity shock-induced electroporation for the genesis of action potential aftereffects resulting from early and delayed afterdepolarizations (EAD and DAD) (Ohuchi et al., 2002). In these studies, however, DC shocks were always applied at 0 mV, and the influence of the membrane potential level just before the application of DC shocks on the action potential aftereffects was not examined.

Recently, DeBruin and Krassowska (1999a; b) have investigated the effects of field strength and membrane potential on the DC shock-induced aftereffects using a passive membrane model, and they have concluded that aftereffects are independent of the membrane potential level at the onset of DC shocks because ionic currents through membrane pores are several orders of magnitude larger than ionic channel currents stabilizing the resting membrane potential. Additionally, after the electric field is removed, the shock-induced membrane potential discharges quickly (within 2 μs), whereas the membrane pores persist for several seconds and, therefore, it is possible that the variability of the action potential phase has negligible effects on ionic conductivity through the pores. The aim of this simulation study was to investigate shock intensity- and phase-dependence of high-intensity DC stimulation aftereffects using a dynamic action potential model.

Materials and Methods

1. Cell Model and Electroporation:

The Luo-Rudy dynamic (LRd) model of the mammalian ventricular action potential (Luo and Rudy, 1994 a; Luo and Rudy, 1994 b; Zeng et al., 1995; Viswanathan et al., 1999) was used for the simulation in this study. This model is

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numerically described based on experimental data mostly from guinea pig myocytes. Included in the model are the membrane ionic channel currents as well as ionic pump and exchanger currents. Moreover, the LRd model describes processes that regulate intracellular ion such as intracellular calcium dynamics between the sarcoplasmic reticulum (SR) and the buffering site.

We assumed that small membrane pores are formed instantaneously at the onset of DC shock application as a result of electroporation (Ohuchi et al., 2002). The pore size during DC shock was kept constant ($\overline{S_{pore}}$; maximum size of pore) and then reduced exponentially with a certain time constant (τ_{pore}) to simulate the resealing process of the cell membrane. These are based on the following assumptions: 1) electric field potential created by DC shocks can be discharged instantaneous to membrane potential, and 2) membrane pores need several seconds for complete resealing. In the simulation, pore size (S_{pore}) indicates the percentage of the total pore area to the total geometric membrane area. Ion flux through the pore is calculated based on the Goldman-Hodgkin-Katz equation for various ions.

2. Simulation Protocols:

In our previous study using a LRd model (Ohuchi et al., 2002), the results revealed that either an increase of $\overline{S_{pore}}$ or a prolongation of τ_{pore} has comparable influence on the aftereffects. Therefore, in this study, we varied values of $\overline{S_{pore}}$ (0.12, 0.2, 0.24 and 0.34% of total geometric membrane area) with fixed τ_{pore} of 600 ms. Sixty basic stimuli (S1) were applied at a cycle length of 1000 ms and a DC shock (S2) was given either at the action potential plateau phase with S1-S2 coupling interval (CI) of 110 ms or at the diastolic phase with CI of 350 ms.

Results

Fig. 1 shows simulated action potentials and ionic currents for plateau phase shock (A) and diastolic phase shock (B) with various $\overline{S_{pore}}$ (from 0.12% to 0.34%). During S1 stimulation, the maximum diastolic potential (MDP) was –83 mV and the action potential duration at –60 mV (APD_{-60}) was 164 ms without S2 shock (Control).

Application of a plateau phase shock with pore size ($\overline{S_{pore}}$) at 0.12% caused an inhibition of terminal repolarization and a prolongation of APD_{-60} to 206 ms (Fig. 1, trace a). Plateau phase shocks with $\overline{S_{pore}}$ of 0.2% and 0.24% caused oscillations of membrane potential around –10 to –25 mV and EAD-like spontaneous excitations (Fig. 1, trace b,c). Further elevation of $\overline{S_{pore}}$ (0.34%) resulted in a greater delay of repolarization with minimal membrane potential oscillations (Fig. 1, trace d). The prolonged action potential plateau and membrane potential oscillations following the plateau phase shocks were

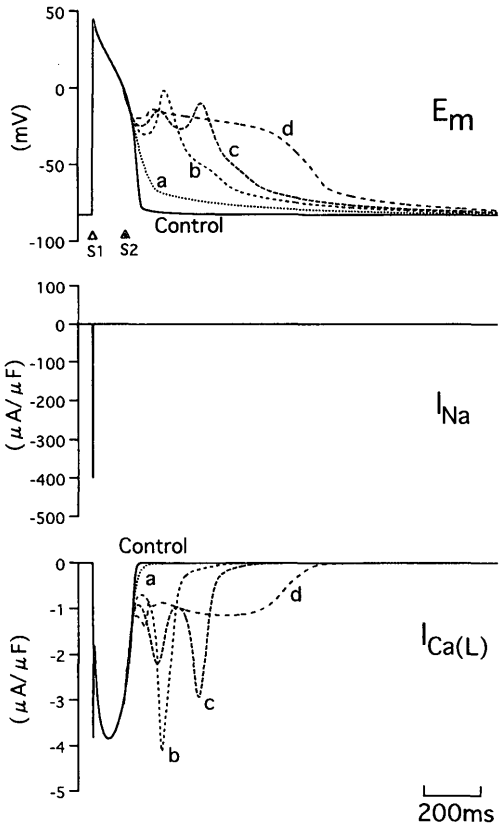

Fig. 1 Membrane potential aftereffects induced by plateau phase shocks. After 60 basic stimuli (S1, 1000 ms intervals), a 10 ms shock (S2) was applied with a coupling interval of 110 ms. Top, superimposed traces of the shocked action potentials with various shock intensity; $\overline{S_{pore}}$, 0.12% (a), 0.2% (b), 0.24% (c) 0.34% (d) of the total cell membrane area. Middle and bottom, fast sodium current (I_{Na}), and L-type calcium current ($I_{Ca(L)}$), respectively.

associated with activation of the L-type calcium current ($I_{Ca(L)}$) (Fig. 1, bottom panel) but there was no activation of the fast sodium current (I_{Na}) at the depolarization phase of oscillatory potentials (Fig. 1, middle panel).

A shock with $\overline{S_{pore}}$ at 0.12% elicited a new action potential from the resting potential (Fig. 2, trace a). The diastolic phase shock-induced action potential showed slow repolarization at the terminal phase and the APD_{-60} was similar to that with a plateau phase shock. Diastolic phase shocks with $\overline{S_{pore}}$ at 0.2% and 0.24% induced action potentials with EAD-like potential changes during the prolonged plateau phase (Fig. 2, trace b and c). Further elevation of $\overline{S_{pore}}$ to 0.34% caused a marked prolongation of the action potential (APD_{-60}, 691 ms) but this was not associated with EAD-like depolarizations (Fig. 2, trace d).

Plateau phase shocks always activated I_{Na} and the maximum I_{Na} increased with an increase of pore size. (Fig. 1, middle). The similar increase was observed in peak $I_{Ca(L)}$ at the onset of shocks (Fig. 2, bottom). EAD-like action potentials induced by diastolic phase shocks were accompanied by the activation of $I_{Ca(L)}$.

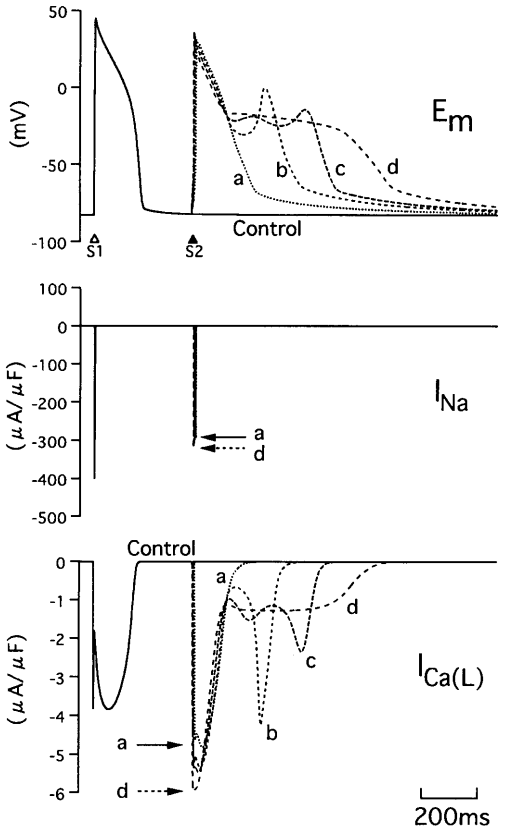

Fig. 2 Membrane potential aftereffects induced by diastolic phase shocks. A S2 shock (10 ms) was applied with a coupling interval of 350 ms. Top, superimposed traces of the shocked-induced action potentials with various shock intensity; $\overline{S_{pore}}$, 0.12% (a), 0.2% (b), 0.24% (c) 0.34% (d) of the total cell membrane area. Middle and bottom, fast sodium current (I_{Na}), and L-type calcium current ($I_{Ca(L)}$), respectively.

Discussion

In the present simulation study, the Luo-Rudy dynamic action potential model with reversible electroporation pores represents membrane potential changes following high-intensity DC shocks applied during the plateau- and diastolic-phase. The shock-induced membrane potential aftereffects included prolonged action potentials, membrane potential oscillations and single or multiple spontaneous excitations, and these changes are similar to experimental observations in our previous study (Kodama et al., 1994). Moreover, in this study, oscillatory membrane potentials and EAD-like spontaneous excitations were induced only by shocks with intermediate intensity ($\overline{S_{pore}}$, 0.2% and 0.24%) and such biphasic effects of shock intensity on spontaneous excitation are qualitatively similar to experimental observations (Kodama et al., 1994). It was also possible in this study to investigate ionic mechanisms underlying the shock-induced action potential aftereffects because we employed one of the most reliable action potential models of mammalian ventricular myocytes currently available; the simulation revealed that activation of $I_{Ca(L)}$ is associated with shock-induced oscillatory membrane potentials and EAD-like spontaneous excitations. In addition, the higher was the intensity of the diastolic shocks, the greater was the peak amplitude of I_{Na} and $I_{Ca(L)}$ at the shock-induced action potential upstroke. This could be the result of complex interactions between changes in the intracellular ionic concentrations and various sarcolemmal ionic currents including electroporation-mediated membrane pores, but further investigations will be required to clarify the detailed mechanisms.

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