Although the use of class I antiarrhythmic agents has decreased after the CAST study because of their proarrhythmic effects,1–3 some antiarrhythmic agents,4–6 including class I agents,7 are administered to patients with implantable cardioverter defibrillators in order to reduce the number of electric shocks. Therefore, it is very important to understand how antiarrhythmic agents affect ventricular vulnerability, but the electrophysiological effects of antiarrhythmic agents on ventricular vulnerability remain unknown.

Recently, virtual electrode polarization (VEP) was proposed as one of the most important mechanisms of ventricular tachyarrhythmia induction (or defibrillation) by electric stimuli or shocks.8–10 Both experimental9,11 and numerical11–13 studies have demonstrated that, because of differences between intra- and extracellular electrical conductivities, the regional shock current via a unipolar electrode generated cloverleaf VEP and caused break excitation (excitation starting just after the shock) with 2 or 4 phase singularities (virtual electrode-induced phase singularities; VEIPS10), resulting in tachyarrhythmias in the form of figure-of-eight or quatrefoil reentry. A change in the refractory (or repolarization) gradient (RG) during the preshock state does not alter the pattern of strong stimulus-induced reentry14,15 because the reentrant wavefronts are generated by the VEIPS, rather than the critical point formation (interaction of excitation wavefront with RG).16 On the other hand, a numerical study demonstrated that the preshock RG pattern alters the vulnerability for reentry induction via VEIPS.13

Previous experiments17–19 demonstrated that a pure sodium channel blocker, lidocaine, increased ventricular vulnerability, but the degree of the increase differed remarkably among those experiments; for example, the magnitude of the increase at the upper limit of vulnerability in voltage varied over the range of 23–69% of the control value. One of the possible reasons for this discrepancy is the difference in the dose of lidocaine20 and another possible reason, we hypothesize, that the differences in the arrhythmogenesis of the sodium channel blockade resulted from the type of preshock RG employed, because it has been shown that the vulnerable window (VW) is altered by the type of preshock RG employed.

The type of preshock RG alters the degree of the increase in ventricular vulnerability under INa blockade. (Circ J 2005; 69: 345–353)

Key Words: Bidomain model; Refractory gradient; Sodium channel blockade; Ventricular vulnerability; Virtual electrode-induced phase singularity
Methods

Simulated Myocardial Tissue and Sodium Channel Blockade

Fig 1A shows the homogeneous and anisotropic biventricular myocardial sheet in which fibers were oriented horizontally. The sheet size was 3.75×2.5 cm and incorporated 93,750 myocardial units. Membrane kinetics were represented by the LR-A model, a modified version of the Luo-Rudy-1 model. The modification and validation of this model have been addressed elsewhere. To investigate the electrophysiological influence of sodium channel blockade on the sheet, we employed 24 mS/cm² as a control value of the maximum conductance of the fast sodium channel, G_{Na}, and employed smaller G_{Na} values of 20, 16, and 12 mS/cm² to mimic the progressive influence of the sodium channel blockade.

The values of the other parameters used in the present study were as follows. The maximum conductances of the slow inward and the time-dependent potassium channels were 0.036 and 0.423 mS/cm², respectively. The spatial discretization step was 0.01 cm in all directions, and the time discretization was varied adaptively between 1.25 and 10.0 s, depending on the value of the first derivative of the transmembrane potential. The longitudinal and transverse conductivities were 3.75 and 0.375 mS/cm in the intracellular space, and 3.75 and 2.14 mS/cm in the extracellular space, respectively; and the surface-to-volume ratio was 3,000 cm⁻¹.

Stimulation Protocol and Definition of Vulnerability

Constant pacing stimuli (S1) of 250-ms basic cycle length were applied transmembranously via a line electrode located at the left (Fig 1B) or top (Fig 1C) border of the sheet, and a plate electrode covering the entire sheet (Fig 1D). Each pacing stimulus had duration of 4 ms and strength twice the diastolic threshold. These S1 stimuli resulted in longitudinally tilted RG (LRG: RG tilted leftwards along the fiber direction), transversely tilted RG (TRG: RG tilted upwards across the fiber direction) and non-tilted RG (NRG), respectively. The 8 pacing stimuli were followed by a 6-ms cathodal monophasic shock (S2) of strength 20 mA with various S1–S2 coupling intervals (CIs). The shocks were delivered extracellularly to the sheet via a unipolar electrode of size 0.1×0.1 cm, which was located near the sheet center. Next we measured the VW as the range of shock timings at which the shock-induced excitation wavefront results in reentry. In the present study, the VW was expressed as the phase in the units of %APD in order to easily compare the shock outcome regardless of the alteration of both action potential duration (APD) and conduction velocity (CV) under sodium channel blockade. The %APD is given in Equation 1:

\[ \%\text{APD} = \frac{C_l d}{\text{APD}} \times 100 \]  

where d (ms) is the period from the onset of the 8th pacing stimulus to the time when depolarization occurred at the shock electrode site. The APD was measured at the shock
Mechanism of Arrhythmogenesis Under INa Blockade

electrode site after the 8th pacing stimulus with no electric shock delivery.

Computations

Numerical calculations were performed using Linux workstations (a cluster of 3.2 GHz Intel Xeon™ processors) at the Center for Computational Cardiac Electrophysiology (C3E) of Shiga University of Medical Science. The other numerical approach has been described elsewhere. The simulation results were color-coded according to the transmembrane potentials.

Results

CV and APD

Fig 2A shows the CV of excitation propagation as a function of GNa. The CV along the fiber orientation was approximately 3-fold greater than that across the fiber orientation. CV was almost linearly decreased to 82.7% along the fiber orientation, and 74.8% across the fiber orientation, of the original value by the reduction in GNa from 24 to 12 mS/cm².

The relationships between APD and GNa under the conditions of LRG, TRG, and NRG are shown in Fig 2B. For each RG case, the APD was measured at the shock electrode site after the 8th pacing stimulus. For the LRG and
TRG cases, the same reduction in $G_{Na}$ progressively and non-linearly shortened the APD by 8.9% and 16.2% of the control value, respectively. The influence of $G_{Na}$ reduction on APD shortening in the case of TRG was comparatively greater than for LRG. In contrast, in the case of NRG, the APD was rather prolonged by 5.8% of the control.

**Preshock RG**

Fig 3A and B show the transmembrane potential distributions around the maximum gradient after the 8th pacing stimulus for LRG and TRG, respectively, under sodium channel blockade. The maximum TRG was steeper than the maximum LRG because of the slower CV. Furthermore, the reduction in $G_{Na}$ from 24 to 12 mS/cm$^2$ caused an increase in the maximum LRG from 33 to 40 mV/cm and an increase in the maximum TRG from 100 to 130 mV/cm.

**VW in LRG**

Fig 4A shows the influence of sodium channel blockade on VW in the case of LRG. We found that the reentry pattern induced by the shock was figure-of-eight or quatrefoil (black and gray bars, respectively), and the former was the dominant pattern. The VW was widened by the reduction in $G_{Na}$ from 24 to 12 mS/cm$^2$ (from 34.4 to 42.4%APD in a duration of phase). Interestingly, the left border of the VW shifted leftwards (to the earlier phase or shorter CI), whereas the right border did not. Snapshots in Fig 4B,C show the typical influence of sodium channel blockade on the wave dynamics of postshock activations in the case of LRG.

When the shock was delivered at 36%APD near the left border of the VW under $G_{Na}$=16 mS/cm$^2$ (panels in upper row of Fig 4B), the shock-induced cloverleaf VEP (81-ms panel) was followed by 2 cathode-break excitation wavefronts (85-ms panel) propagating in opposite directions along the fiber orientation through virtual anodes. The cathode-break excitation immediately and entirely filled the virtual anodes (89-ms panel), and thus no reentry was induced (105 and 123-ms panels). With the reduction in $G_{Na}$ (12 mS/cm$^2$; panels in lower row), the cathode-break excitation wavefront on the left propagated leftwards through the virtual anode with slower CV (81 to 89-ms panels), which allowed the small excitation wavefront (105-ms panel) to escape into the repolarized region near the left border of the sheet and to form a figure-of-eight reentry (213-ms panel). Thus, sodium channel blockade increased the vulnerability for figure-of-eight reentry, with the common pathway aligned along the fiber orientation, and widening of the VW (black bars in Fig 4A).

When the shock was delivered at 74%APD near the right border of the VW under $G_{Na}$=16 mS/cm$^2$ (upper panels in Fig 4C), 2 cathode-break excitation wavefronts initially propagated in opposite directions along the fiber orientation through the virtual anodes (123 and 133-ms panels), after which both wavefronts propagated along the periphery of the repolarized virtual cathode (145-ms panel) and reentered the repolarized region around the shock electrode (189-ms panel), resulting in a quatrefoil reentry (221-ms panel). In this case, however, the same reduction in $G_{Na}$ (12 mS/cm$^2$; in lower panels) altered neither the fundamental wave dynamics of the postshock activations (compare the upper panels with the lower ones in Fig 4C) nor the vulnerability for quatrefoil reentry (gray bars in Fig 4A).

**VW in TRG**

Fig 5A shows the influence of sodium channel blockade...
on the VW in the case of TRG. We found that only figure-of-eight reentry was induced by the shock delivered during the VW. The VW was narrower than in the LRG case (compare Figs 4A and 5A), but again it was widened by the reduction in $G_{Na}$ from 24 to 12 mS/cm$^2$ (from 21.6 to 30.7%APD in the duration of phase). The left border of the VW shifted to the earlier phase, whereas the right border did not shift much. Snapshots in Fig 5B,C show typical examples of the effect of sodium channel blockade on the wave dynamics of postshock activations in the case of TRG.

When the shock was delivered at 51%APD near the left border of the VW under $G_{Na} = 16$ mS/cm$^2$ (upper panels in Fig 5B), the VEP (146-ms panel) was followed by 2 cathode-break excitation wavefronts (150-ms panel) propagating in opposite directions along the fiber orientation through the virtual anodes. These excitation waves immediately and entirely filled the virtual anodes (158-ms panel), and thus no reentry was induced (178 and 258-ms panels). With the reduction in $G_{Na}$ (12 mS/cm$^2$; lower panels in Fig 5B), the cathode-break excitation wavefronts propagated through the virtual anodes on both sides with a slower CV (150 to 162-ms panels) and they escaped into the repolarized region in the upper half of the sheet (182-ms panel). Because the upper wavebreak (end of the wavefront) of the cathode-break excitation on the left collided with that on the right, the cathode-break excitation merged into a wave, resulting in figure-of-eight reentry, the common pathway of which was aligned across the fiber orientation (262-ms panel).

When the shock was delivered at 75%APD near the right border of the VW under $G_{Na} = 16$ mS/cm$^2$ (upper panels in Fig 5C), a rounded-arched wavefront resulting from the organization of cathode-make and cathode-break excitations (173 and 177-ms panels) initially propagated along the periphery of the repolarizing virtual cathode (193-ms panel) and then resulted in a figure-of-eight reentry, the common pathway of which was aligned across the fiber orientation (227 and 265-ms panels). However, the same reduction in $G_{Na}$ (12 mS/cm$^2$; lower panels in Fig 5C) altered neither the fundamental wave dynamics of the postshock activations (compare the upper panels with the lower ones in Fig 5C) nor the right border of the VW (black bars in Fig 5A). In addition, no quatrefoil reentry was observed under $G_{Na}$ ranging from 24 to 12 mS/cm$^2$.

**VW in NRG**

Fig 6A shows the influence of sodium channel blockade on the VW in the case of NRG. We found that the shock-induced reentry pattern was either figure-of-eight or quatrefoil (black and gray bars, respectively), and in this case the latter was the dominant pattern. Contrary to the LRG and TRG cases, the VW was much narrower (compare Fig 6A with Figs 4A and 5A) and was further narrowed by the reduction in $G_{Na}$ from 24 to 12 mS/cm$^2$ (from 18.0 to 14.2%APD in a duration of phase). Snapshots in Fig 6B,C show typical examples of the effect of sodium channel blockade on the wave dynamics of postshock activations with NRG.

When the shock was delivered at 65%APD near the left border of the VW under $G_{Na} = 16$ mS/cm$^2$ (upper panels in Fig 6B), the VEP (78-ms panel) was followed by 2 cathode-break excitation wavefronts (82-ms panel) propagating in opposite directions along the fiber orientation. The excitation waves propagated through the virtual anodes located on both sides of the shock electrode (82 to 110-ms panels).
resulting in quatrefoil reentry (172-ms panel). Interestingly, even with the reduction in G_{Na} (12 mS/cm²; lower panels in Fig 6B) and the slower CV of the cathode-break excitation wavefronts, the excitation waves immediately and entirely filled the virtual anodes (79 to 91-ms panels), and therefore no reentry was induced (111 and 125-ms panels).

When the shock was delivered at 80%APD near the right border of the VW, in both G_{Na} = 16 and 12 mS/cm² cases (the panels in upper and lower rows, respectively, of Fig 6C), 2 cathode-break excitation wavefronts (first and second panels in upper and lower rows) initially propagated along the periphery of the repolarizing virtual cathode (third panels), and then reentered the repolarized region in the vicinity of the shock electrode (fourth panels), resulting in a quatrefoil reentry (fifth panels). In these cases, the reduction in G_{Na} did not shift the right border of the VW, and therefore sodium channel blockade narrowed the VW with decreasing vulnerability for quatrefoil reentry (gray bars in Fig 6A). In addition, a figure-of-eight reentry was also observed when the shock was delivered near the left border of the VW (black bars in Fig 6A) because of the asymmetry of the grounding electrode configuration (Fig 1D); however, the vulnerability for the figure-of-eight reentry was not altered by sodium channel blockade.

Discussion

Major Findings

To the best of our knowledge, the present bidomain simulation study is the first to focus on the preshock-RG pattern in the ventricles as a possible mechanism of the increase in arrhythmogenesis with electric shock under sodium channel blockade. The main findings in this study are as follows.

1. A gradual increase in the degree of sodium channel blockade almost linearly decreased the CV of the excitation wavefronts propagating both along and across the fiber orientation.
2. Together with the gradual increase in the degree of sodium channel blockade, the APD was non-linearly shortened with both LRG and TRG, whereas, with NRG, it was progressively prolonged.
3. The VW for reentry induction because of an electric shock was considerably widened by sodium channel blockade with both LRG and TRG, whereas with NRG, it was considerably narrowed.

Role of the RG in the Influence of Sodium Channel Blockade on CV and APD

The almost linearly-dependent decrease in CV under sodium channel blockade might be simply explained by the reduction in the action potential upstroke (phase 0) and the decrease in overshoot amplitude (phases 0 to 1), as shown in Fig 2C,D. However, because the dependence of the change in APD on the increase in the degree of sodium channel blockade was nonlinear, as shown in Fig 2B, the mechanisms of the decrease or increase in APD under sodium channel blockade might be complex. In the case of NRG, sodium channel blockade resulted in a slight prolongation of the APD (gray line in Fig 2B). The transmembrane potentials in the sheet were uniform and there was no electrotonic interaction between myocardial units. Therefore, it is reasonable to predict that the inherent nature of the myocardial cell resulted in the almost linear prolongation of APD. In fact, we additionally found, at the
cellular level, that the inward rectifier potassium current (I_{K1}) was decreased by the reduction in G_{Na} (data not shown). We believe that this is the case in real myocardial tissue because there is a theoretical grounding that the decrease in sodium channel current during phases 0 to 1 gives rise to the decrease in the outward current via the sodium pump (I_{NaK}), and in the action potential model we used, the I_{NaK} is assumed to be a part of I_{K1}. As a consequence of the decrease in outward current, the slower repolarization took place and the APD was prolonged (Fig 2E).

On the other hand, in the LRG and TRG cases, sodium channel blockade resulted in a non-linear shortening of the APD (Fig 2B). This can be explained by the non-linear electrotonic interactions between depolarizing and repolarized (or repolarizing) regions in the myocardial sheet, which overcomes the aforementioned inherent mechanism of APD prolongation. Because there was a gradient of transmembrane potentials during excitation propagation (Fig 3A,B), the transmembrane potential at the APD recording site (the same site as the shock electrode) was affected by both the regions of overshoot potential following the excitation wavefront (positive electrotonic influence) and the regions of resting potential following the wavetail (negative electrotonic influence). As shown in Fig 2C,D, when G_{Na} was 24 mS/cm², the positive electrotonic influence was strong enough to prolong the plateau phase, resulting in prolonged APD. In contrast, the reduction in G_{Na} to 12 mS/cm² decreased the amplitude of the overshoot potential (a decrease in the positive electrotonic influence) and increased the area of resting potential because of the shorter wavelength resulting from the slower CV, and therefore the APD was markedly shortened.

**Role of RG in the Influence of Sodium Channel Blockade on VW for Reentry Induction**

As shown in Figs 4A,5A and 6A, sodium channel blockade widened the VW for reentry induction in the case of LRG or TRG, but narrowed it in the case of NRG. This discrepancy in response to sodium channel blockade between the different types of RG might be explained by the difference in the first rotation mechanism of the cathode-break excitation wavefront.

Regardless of the RG type, the reentry induced by electric shock delivered near the left border of the VW depended on whether the cathode-break excitation(s) could propagate through the virtual anode and escape into the repolarized region (refer Figs 4B,5B and 6B). In the case of LRG or TRG, sodium channel blockade decreased the CV of the cathode-break excitation wavefront(s), shortened the APD of the preexisting planar wave (Fig 2A,B), and increased the preshock RG (Fig 3A,B), all of which aided the escape of the cathode-break excitation wavefront(s) into the repolarized region; therefore, the left border of the VW shifted leftwards (to earlier phase). However, in the case of NRG, sodium channel blockade decreased the CV of the cathode-break excitation propagation, but increased the APD of the entire sheet except the area of shock-induced VEP (Fig 2A,B); therefore, sodium channel blockade slightly or considerably shifted the left border of the VW rightwards (to the later phase) rather than leftwards.

On the other hand, regardless of the type of RG, the reentry induced by electric shock delivered near the right border of the VW depended on whether the cathode-break excitation wavefront(s) could reenter the repolarized region in the vicinity of the shock electrode (refer Figs 4C,5C and 6C). Because the cathode-break excitation wavefront(s) initially propagated along the periphery of the virtual cathode until the virtual cathode was fully repolarized, the cycle length of the first revolution of the excitation wavefront(s) was significantly longer than that of the following revolutions (83±6 vs 54±4 ms in all cases, mean±SD; p<0.01 by Student’s t-test). For this reason, the reentry induction mechanism was not largely affected by the changes in CV and APD, and thus sodium channel blockade did not greatly shift the right border of the VW. Consequently, in the case of NRG, the VW was not increased even under sodium channel blockade.

**Comparison With Previous Studies**

Previous studies have reported that pure sodium channel blockers reduced the CV and shortened the APD of excitation propagation in ventricles during point pacing stimuli, which might produce non-physiological RG. Those results are compatible with our finding that sodium channel blockade shortened the APD in the case of LRG or TRG. However, based on our results for NRG, we conjecture that if the APD was recorded during sinus rhythm with a relatively flat RG, the degree of APD shortening would be comparatively small.

Cheng et al and Roth have suggested that the preshock RG does not affect the mechanisms of reentry induction because reentry is induced by VEIPS; however, other studies have shown that the shock outcome depends on the shock timing and shock RG type. They showed that the CV slowing and the APD prolongation resulting from the CV slowing and the APD prolongation or shortening under sodium channel blockade.

In addition, Li et al investigated the mechanism of the adverse effects of the pure sodium channel blocker, lidocaine, on VEIPS-mediated ventricular vulnerability using both monophasic and biphasic shocks. They showed that ventricular vulnerability was considerably increased by sodium channel blockade using monophasic shock rather than biphasic shock, and concluded that slowing the CV of the monophasic shock-induced break excitation propagation is one of the important mechanisms of the deterioration of ventricular vulnerability. However, they used only 1 type of preshock RG, which was non-physiologically produced by constant pacing stimuli at the epicardial ventricular apex, and thus did not examine the influence of preshock RG on the mechanism of the increase in ventricular vulnerability under sodium channel blockade. In the present study, we focused on the influence of preshock RG on ventricular vulnerability and found that the type of preshock RG is another important factor in the increase in ventricular vulnerability under sodium channel blockade.

**Clinical Implications**

Sodium channel blockade increases the vulnerability for the induction of ventricular arrhythmias and increases the upper limit of vulnerability and the defibrillation threshold in hearts with a large RG, such as with the Brugada
syndrome and the pacing electrode configurations producing non-physiological RG. The results of the present bidomain model study suggest that appropriate resynchronization of repolarization in ventricles by biventricular pacing nullifies the adverse effect of sodium channel blockade on ventricular vulnerability.

Study Limitations
The limitations associated with the LR-A model were discussed in a previous article. Moreover, the modification for reproducing a negative bias in the asymmetry of transmembrane potential changes induced by shocks delivered during the action potential plateau was not included in this model. We did not consider other configurations of the shock and grounding electrodes, or other shock waveforms. Actually, it is known that electric shock with reversed polarity (anodal shock) alters ventricular vulnerability.13,33 Thus, in the present study, we focused on the change of repolarization in ventricles by biventricular pacing and the preshock RG under sodium channel blockade. However, we believe that the results of the present study contain all the fundamental mechanisms with regard to the change of interaction between the VEP induced by the shock and the preshock RG under sodium channel blockade. Based on the results of the present study, the mechanisms of the deterioration of ventricular vulnerability under sodium channel blockade include VEP; therefore, consistent with previous experimental data, it is probable that the weaker VEP in the case of a biphasic shock waveform attenuates the increase in the vulnerability. From a structural point of view, we used parallel fibers oriented horizontally in the myocardial sheet. The fiber curvature in the sheet affects the shape of the VEP, and it is possible that the VW is altered by different fiber orientations. In addition, we did not take into account the effects of either the complex 3-dimensional tissue structures or the dispersion of repolarization both of which might affect ventricular vulnerability for intramural reentries. Further computer simulations and experimental studies are required to elucidate the exact contribution of the RG to the change in ventricular vulnerability under sodium channel blockade. Despite these limitations, we speculate that the preshock RG may be strongly related to the mechanisms of deterioration of ventricular vulnerability under sodium channel blockade.

Conclusions
Our findings suggest that the type of preshock RG alters the degree of the increase in ventricular vulnerability under sodium channel blockade. Thus, this study provides new insights into the mechanisms of the proarrhythmic effects of sodium channel blockers.

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Mechanism of Arrhythmogenesis Under INa Blockade


