Anisotropic Effects of Sodium Channel Blockers on the Wavelength for Ventricular Excitation in Dogs

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The purpose of this study was to determine the anisotropic effects of sodium channel blockers on wavelength (WL) and proarrhythmia. In 18 anesthetized, open chest dogs, a 64-electrode array was placed on the left ventricle and the ventricle was constantly paced. Disopyramide, lidocaine or flecainide was intracoronarily administered. Conduction velocity (θ) and activation–recovery interval (ARI) were measured in the longitudinal (L) and transverse (T) directions. Flecainide markedly decreased θL, but did not alter θT or ARIs in either direction. As a result, the wavelength was significantly shortened only in the L direction. Disopyramide or lidocaine did not show direction-dependent effects on θ or WL. In 3 of 6 dogs with flecainide exposure, ventricular fibrillation (VF) developed. However, no VF occurred with disopyramide or lidocaine. Accordingly, the WL is dependent on the fiber orientation of myocardium. The anisotropic shortening of the WL may explain the character of the proarrhythmia observed with flecainide. (Jpn Circ J 2000; 64: 689–694)

Key Words: Anisotropy; Proarrhythmia; Wavelength

The wavelength (WL) of cardiac excitation implies the distance traveled by the depolarization wave for the duration of the refractory period on the reentrant circuits in the leading circle concept. When the WL is reduced by depressed conduction and/or shortened refractoriness, small areas of conductive block may suffice to form reentrant circuits. Therefore, the WL has been suggested as an index for estimating the susceptibility to reentrant arrhythmias and applied to the evaluation of the effects of antiarrhythmic agents. It is also widely known that excitation conduction is dependent on myocardial fiber direction. Anisotropic properties of cardiac muscle block electric excitation and contribute to the induction of reentrant activity as a component of the reentry circuit. However, the fiber direction is rarely considered, when measuring the WL.

Sodium channel blockers suppress electric conductivity and are used as an antiarrhythmic strategy. They are traditionally subclassified by their effects on action potential duration (APD). Each sodium channel blocker has different use- and state-dependency (activation or inactivation) of sodium blocking action. Such heterogeneity in the sodium channel blockers possibly affects anisotropic electric propagation. Changes in the WL should be influenced by myocardial anisotropy. The purpose of the present study was to determine the effects of sodium channel blockers on the WL of cardiac impulse and ventricular arrhythmias.

Methods

Instrumentation

Eighteen adult mongrel dogs (weight, 18±1.1kg) were anesthetized with sodium pentobarbital (30mg/kg, iv) and received supplemental doses as needed. Dogs were ventilated with room air supplemented with oxygen (3–5L/min). The thorax was opened in the fifth intercostal space and a pericardial cradle was made to support the heart in an appropriate position. After an intravenous bolus of heparin (10,000IU), a 24-gauge plastic cannula was inserted into the left anterior descending artery (LAD) at the distal site of the second diagonal branch. The cannula was kept open by continuous infusion of saline at 1 ml/min. An array of 64 epicardial electrodes was placed on the anterior surface of the ventricle (Fig 1). Complete atrioventricular block was induced and the left ventricle was constantly paced.

![Fig 1](image-url)
using a model SEN-7203 stimulator (Nihon Koden, Tokyo, Japan) on one corner of the electrode-array (Fig 1). At baseline measurement, the left ventricle was paced at cycle lengths of 600, 500, 400 or 300 ms. During administration of each sodium channel blocker, the left ventricle was constantly paced at a cycle length of 500 ms. Each unipolar electrode consisted of fine silver wire (0.2-mm diameter) sutured to the plaque. Columns (A–H) and rows (1–8) of the epicardial electrodes were 2 mm apart. All recording electrodes were referenced to the Wilson’s central terminal, and multicellular electrogams were digitized every millisecond using a multiplexed data processing system (CD-G015, Chunichi Denshi, Nagoya, Japan) as described in previous studies.16–18 The recorded signals were filtered with band-pass filter range of 0.05–500 Hz. The thoracic cavity was covered with a plastic wrap to prevent cooling and dehumidifying, and body temperature was maintained at 37–38°C. An arterial line was inserted into the right femoral artery to continuously monitor mean arterial pressure. Lead II of electrocardiogram and blood pressure were recorded simultaneously throughout the study on a model 2666 recorder (NEC San-ei, Tokyo, Japan). This study conformed to the ‘Guide for the Care and Use of Laboratory Animals’.

Experimental Protocol
Flecainide (low dose: 10 μg·kg⁻¹·min⁻¹; high dose: 100 μg·kg⁻¹·min⁻¹; n=6), lidocaine (low dose: 0.12 mg·kg⁻¹·min⁻¹; high dose: 0.6 mg·kg⁻¹·min⁻¹; n=6) or disopyramide (low dose: 20 μg·kg⁻¹·min⁻¹; high dose: 200 μg·kg⁻¹·min⁻¹; n=6), was intracoronarily infused using an infusion pump (model SP-100, JMS, Hiroshima, Japan). The lower dose of flecainide, disopyramide or lidocaine was 1% of that used intravenously in an experimental study and the higher dose was 5–10%.15,17,18 After baseline measurements, the low-dose protocol was performed during the first 20 min and the high one was continued for the next 20 min. Epicardial electrograms were recorded every 5 min after the beginning of the low-dose infusion. When spontaneous ventricular tachyarrhythmias began, epicardial electrograms were immediately recorded.

Analysis of Multichannel Epicardial Electrograms
Multichannel epicardial electrograms were processed on an off-line microcomputer: SUN 4/2 (SUN Microsystems, Mountain View, CA, USA). Epicardial activation of each electrogram was defined as the time at the minimum derivative of the QRS signal. The earliest activation was assigned to the time zero and the activation time (AT) was determined as the interval between the time zero and each activation. Activation–recovery intervals (ARI), which were defined as the time between AT and the time at the maximum derivative in T wave, were also measured.19 ARI is known to be well correlated to the APD and effective refractory periods.20,21 The conduction velocities (θ) along the longitudinal (L) and transverse (T) directions were derived from the inter-electrode distance divided by AT. The WL was also calculated by conduction velocity multiplied by ARI.

Statistical Analysis
Quantitative data are reported as mean ± SEM. Statistical analysis was performed with one-way ANOVA. A confidence level of 95% was considered statistically significant.

Results
Effects of Basic Cycle Lengths on Wavelength
Fig 2 indicates the effects of basic cycle length (BCL) on θ, ARI or WL. The θr was significantly greater than θ (Fig 2A). The conduction velocity in the L direction was about 2-fold faster. However, there was no directional difference in ARIs (Fig 2B). Therefore, the WL in the L direction was about 2-fold longer than in the T direction (Fig 2C). ARIs shortened proportionally to BCL shortening (L; r=0.78, p<0.0001; T; r=0.74, p<0.0001). However, it did not alter θr or θT. Therefore, WL estimated by the formula of θ×ARI, shortened with BCL shortening.

Anisotropic Effects of Flecainide and Ventricular Arrhythmias
Fig 3 illustrates the cardiac surface distribution of ATs and ARIs before and during flecainide administration in a representative experiment. Excitation propagation was faster in the L direction than in the T direction (Fig 3A). After flecainide infusion, line density shown in isochronal maps increased mainly in the L direction, which was further exaggerated with the high dose. Slowed conduction appeared mostly in the L direction. In ARI maps (Fig 3B),
Fig 3. Activation time (AT) and activation-recovery interval (ARI) before and during flecainide administration in a representative experiment. The left ventricle was constantly paced at a basic cycle length (BCL) of 500 ms (asterisk). (A) AT in the L direction was smaller than in the T direction. After flecainide infusion, line density crowded mainly along the L axis. (B) The ARI map in control shows proportional propagation. High-dose flecainide slightly decreased the ARI in the L direction. L, longitudinal; T, transverse.

Fig 4. Activation sequences of first 3 beats (VT1, VT2 and VT3) of ventricular tachycardia (VT) and the previous beat (A). Ventricular fibrillation (VF) followed several VT beats (upper-right electrogram).
the directional difference was not seen during control or during low-dose flecainide. ARI in the L direction tended to shorten during high-dose infusion. Because conduction block occurred in the L direction, the excitation impulse rotated around block line as shown in Fig.4. Then, reentrant ventricular tachycardia (VT) ensued. Ventricular fibrillation (VF) followed several beats of VT. In 3 of 6 dogs, VF developed after flecainide exposure. In contrast, ventricular arrhythmias did not occur in the other 12 dogs to which disopyramide or lidocaine was given.

Three Types of Sodium Channel Blockers and Wavelength
The anisotropic differences in conduction velocity among the 3 types of sodium channel blockers were examined (Fig 5). The directional difference was observed only during high-dose flecainide, which markedly decreased $\theta_L$, compared with $\theta_T$. However, with lidocaine or disopyramide, such anisotropic difference was not observed. The ARIIs were not significantly altered by any of the sodium channel blockers in either direction (Fig 6). As a result, the WL shortened uniquely in the L direction during high-dose flecainide (Fig 7). Disopyramide or lidocaine did not alter the WL in either direction.

Discussion
In the present study, we verified that flecainide preferentially suppressed longitudinal conduction and induced ventricular arrhythmia. Our results suggested that the anisotropic shortening of the WL may reflect the proarrhythmic character of flecainide.

The WL has been used as an indicator for estimating the susceptibility to reentrant tachyarrhythmias and estimating the preventive effects of drugs on arrhythmia. Girouard et al. applied optical action potential mapping and measured the WL in the rabbit ventricle, which demonstrated that the WL was not homogeneous even in a fixed reentrant ventricular tachycardia circuit.

The possible proarrhythmic effect of sodium channel blockers was discussed in the CAST study. Recently, a genetically induced disturbance in the sodium channel was found in patients with the Brugada form of idiopathic VF. Increased attention has been given to the relationship between sodium channel suppression and arrhythmia. Electrophysiological mechanisms of their proarrhythmic effect probably relate to prolongation of repolarization, the development of early afterdepolarizations, and exacerbation of regional myocardial conduction delay. However, few reports have documented the effect of sodium channel blockers on myocardial anisotropy and the WL, which may lead to proarrhythmia.

In the present study, with high-dose flecainide, the WL was significantly shortened in the L direction, which may be related to the occurrence of reentrant VT. Lidocaine or disopyramide did not alter the WL and did not evoke ventricular arrhythmia. The response of the WL may explain...
Fig. 7. Effect of each sodium channel blocker on the wavelength (WL). The WL-shortening resulting from flecainide administration occurred only in the L direction. Disopyramide, which increased the activation–recovery interval (ARI) and decreased conduction velocity (θ) did not change the WL. Lidocaine did not decrease θ so much that WL could not be significantly shortened. L, longitudinal; T, transverse.

the different proarrhythmic effects among the subclasses of sodium channel blockers. It is known that the L conduction is fragile, although the conduction velocity is faster. We previously reported that flecainide preferentially suppressed the L conduction in an intact canine heart and in the present study, only flecainide caused L conduction suppression and WL shortening. The mechanism of this flecainide-specific phenomenon is unclear. One possible explanation is the binding kinetics to the sodium channel. Lidocaine, disopyramide and flecainide are classified as a fast, intermediate or slow kinetic drug, respectively. With the examined BCL of 500 ms, the blocking action of flecainide would be greater than lidocaine or disopyramide. Another possible mechanism is the open-state blocking action of flecainide. Because the open time of sodium channels is prolonged more during L propagation than T propagation, conduction suppression by an open-state sodium channel blocker should be more prominent during L propagation than T propagation. These may explain the L suppression observed with flecainide. We conjecture that the doses of sodium channel blockers used in these studies might be higher than those in therapeutic use in humans, even the low doses, so this result can not be directly extend to clinical use. However, the present study provided evidence that only flecainide potentially caused WL shortening and evoked ventricular arrhythmias.

In conclusion, the present study demonstrated that the WL is dependent on the fiber orientation of the myocardium. The anisotropic difference in the WL may explain the proarrhythmic character of flecainide.

Acknowledgments
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