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Na^+ Channel Blockade Causes a Prolongation of Electrical Diastole during Spiral-type Reentry in the Ventricle

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Abstract: Spiral-type reentry is crucial for genesis and maintenance of the life-threatening ventricular tachyarrhythmia, but little information is available for its pharmacological control. We examined the effects of pilsicainide (Pil), an antiarrhythmic drug having a specific Na^+ channel blocking action, on the spiral dynamics during ventricular tachycardia (VT). Optical action potential signals were recorded with the aid of a voltage-sensitive dye from the epicardial ventricular surface of rabbit heart perfused in-vitro. The endocardial side of the left ventricule was cryoablated to prepare 2-D subepicardial ventricular muscle layers. A high-resolution video-imaging system combined with fiber optic probes was employed for signal recordings. Pil (3 μM) caused a significant reduction of conduction velocity under basal stimulation (S1, 2.5 Hz) without affecting action potential duration. Ventricular tachycardia (VT) induced by cross-field stimulation (S2, 20 V) in the presence of Pil were characterized by slower cycle length (by 22.7 %) and longer electrical diastole (by 107.2 %) compared with controls. Pil also caused an enlargement of core area in stational spiral-type excitation. Possible mechanisms involved in the modulation of spiral-type reentry in the ventricle are discussed.

Key words: arrhythmia, spiral-reentry, sodium channel

Spiral-type reentry plays an important role in the genesis and maintenance of the life-threatening VT.[1)] Available information on the regulation of the spiral-type reentry by ion channel blockade is still limited. Pilsicainide (Pil) is a novel class I antiarrhythmic agent developed in Japan. This drug is indicated for supraventricular and ventricular tachyarrhythmias, and is considered highly effective and safe.[2)] Recently we developed a new optical mapping system using a high-speed video camera combined with light-emitting diodes (LEDs) and it has an advantage in terms of high spatio-temporal resolution as well as signal quality.[3)] In the present study, we investigated the effects of Pil on spiral-type reentry induced in the ventricles of rabbit heart by using our high-resolution optical action potential mapping system.

Materials and Methods

Isolated rabbit hearts for optical signal recording were prepared as discussed previously.[3-6)] In brief, Japanese white rabbits weighing 1.5~2.0 kg were heparinized and anesthetized with pentobarbital sodium (30~40 mg/kg, i.v.). Then the hearts were removed and perfused in a Langendorff-apparatus. After producing complete atrio-ventricular block by ligating the proximal portion of the His-bundle, the heart was stained with voltage sensitive dye, di-4-ANEPPS (Molecular Probes, Inc. Eugene, OR, 2 μM). Diacetyl monoxiame (15 mM) was added into the perfusate to minimize mechanical movement because mechanical movement of the heart makes it difficult to analyze optical signal precisely. In order to prevent the intramural wave propagation, we produced a two-dimensional subepicardial sheet preparation by endocardial cryoablation.[3)] A thin (~1 mm) subepicardial myocardial layers were preserved viable after the procedure.

Optical probe recording system and high-speed digital video camera system were employed for detecting the changes of the membrane action potential. Details about the experimental setup have been described previously.[3-6)] Optical action potential signals were monitored simultaneously from the base

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and apex of the left ventricle by using fiber optic probes during basal stimulation (S1, 1 or 2.5 Hz) applied at the apex of heart, and during VT induced by cross-field stimulation (S2, 20 V) applied through a pair of electrodes on the lateral side of both ventricles. The action potential duration (APD) was measured at 90 % repolarization level. Diastolic interval, which plays an important role on the wave break of spiral-type reentry[7], was defined as the difference between cycle length and APD. In some experiments, fluorescence images of the anterior wall of the left ventricle were recorded by a high-speed digital video camera (Fastcam-Ultima 40K, Photoron) to analyze epicardial activation patterns. The spatial and temporal resolution of this video-imaging system was 0.12 mm/pixel and 1.3 ms/frame, respectively. Pil was added to the perfusate at final concentration of 3 or 5 μM. Data were expressed as mean ± SE. Student's paired *t*-test was employed for statistical analysis and the results were considered significant when $P<0.05$.

Results

During S1 stimulation, epicardial activation pattern analyzed by the high-speed digital video camera system revealed that the activation front was almost planner and was propagating from the stimulation site at the apex towards the base of the ventricle under control condition. After the application of Pil (3 μM), the planner pattern of activation front was well preserved but propagating speed of activation front (i.e. conduction velocity) was significantly decreased (from 57.6 ± 6.0 to 39.9 ± 5.6 cm/s at 1 Hz and from 56.5 ± 5.8 to 36.7 ± 5.0 cm/s at 2.5 Hz, n=7, $p<0.05$). There was no significant change in APD before and after the application of Pil (3 μM).

Fig. 1 shows representative signal records obtained by fiber optic probe system before and after the application of Pil (3 μM). S2 with appropriate coupling intervals for a vulnerable period of the S1 action potential initiated monomorphic sustained VT before and after the application of Pil. VT cycle length (CL_{VT}) was longer in the presence of Pil than in its absence. In seven preparations, there was a significant increase in CL_{VT} (by 22.7 % in average, Fig. 2A). The increase in CL_{VT} was the result of marked increase in the electrical diastolic interval (DI_{VT}, by 107.2 %, Fig. 2C) combined with significant but minimum increase in APD (APD_{VT}, by 12.2%, Fig. 2B).

Fig. 3 illustrates an example of spiral-type reentry with stationary core during VT before and after the application of Pil (5 μM). Isochrones of the wavefront were drawn every 10.7 ms (8 frames), and the central area encircled by the trajectory of pivoting points of the wavefront during a full rotation was defined as a core. After application of Pil, there was a prolongation of spiral rotation period (equivalent to CL_{VT}) from 145 to 220 ms, and this was accompanied with an enlargement of

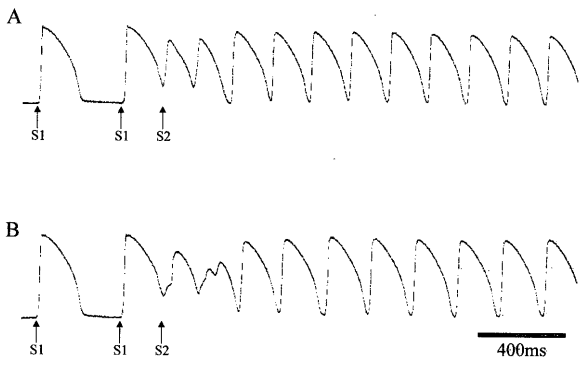

Fig. 1 Representative optical signal records during induction of VT by S2 stimulation in control condition (A) and Pil (3 μM) application (B). CL_{VT} was elongated by Pil application.

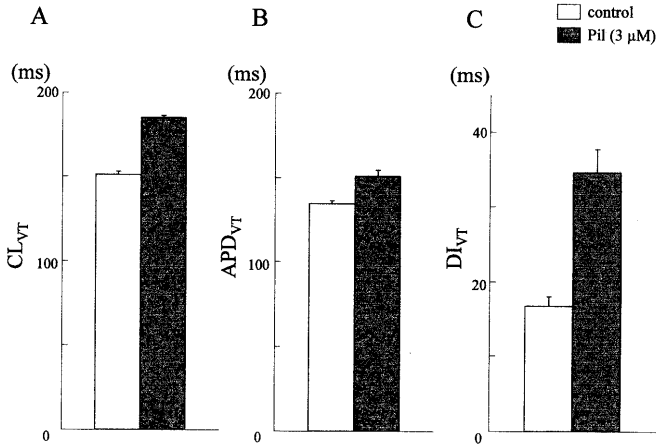

Fig. 2 Effects of Pil on CL_{VT} (A), APD_{VT} (B) and DI_{VT} (C) of the rabbit heart.
There was significant increase in CL_{VT} (A: 151.2 ± 5.2 vs 185.5 ± 3.0 ms, $p<0.01$) by 22.7 %. Pil induced slight but significant prolongation of APD_{VT} (B: 134.5 ± 4.1 vs 150.8 ± 9.9 ms, $p<0.01$) by 12.2 %. DI_{VT} was doubled by Pil(C: 16.7 ± 3.4 vs 34.6 ± 8.4 ms, $p<0.01$). □: controls, ■: Pil (3 μM), mean ± SE.

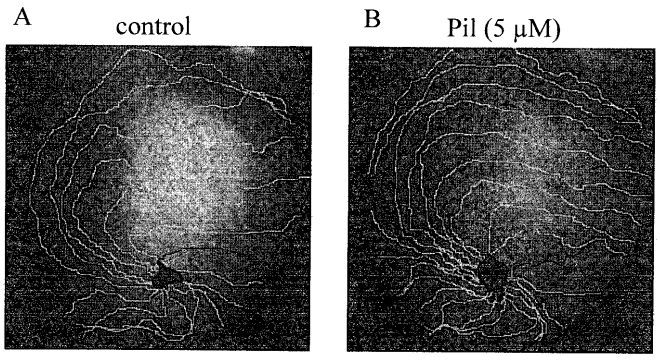

Fig. 3 Isochronal maps during VT.
A; Spiral type reentry under control condition.
B; Spiral type reentry after application of Pil (5 μM).
The interval of every isochrone is 10.67 ms. Shaded area marked with * indicates core area. Note that the core area of the Pil is larger than that of control.

the core and with an equal crowding of isochrones during the whole rotation showing homogeneous slowing of conduction velocity (Fig. 3).

Discussion

In the present study, we demonstrated that Pil caused a significant decrease in conduction velocity during basal stimulation without affecting APD. This was a consequence of reduced membrane excitability. During VT, the application of Pil resulted in a significant slowing the rotation of spiral reentry (equivalent to increase in CL_{VT}) and an enlargement of the core area. These changes in spiral reentry were associated with a marked increase in DI_{VT} and a minimal increase in APD_{VT}.

The complicated modulation of spiral-type reentry by Na^+ channel blockade can be explained on the basis of the theory of wave propagation in excitable media, which considers wave front curvature a major determinant of conduction velocity. [8,9] The theory suggests that there is a critical radius of the curvature at which propagation ceases. Under control condition in normal myocardium having high excitability, the critical radius is small and therefore, the tip of the wave front may undergo sharp turns, leading to a small core area. Under conditions of decreased excitability, where Na^+ channel are partially blocked, the critical radius of curvature becomes larger, and consequently, the trajectory of the spiral tip also increases; thereby the path taken by the wave front to complete a full rotation is longer, resulting in an increase in the size of the core and a prolongation of the rotation period.

There was a slight increase in APD_{VT} after Na^+ channel blockade, and this is secondary to increase in CL_{VT}. Because the increase in APD_{VT} induced by Na^+ channel blockade was less than that in CL_{VT}, there was marked increase in electrical diastole (i.e. DI_{VT}). In another words, Na^+ channel blockade causes a widening of excitable gap between action potentials in spiral-type reentry.

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