Modulation of Spiral Wave Reentry by K\(^+\) Channel Blockade

Haruo Honjo, MD; Masatoshi Yamazaki, MD; Kaichiro Kamiya, MD; Itsuo Kodama, MD

It is well established that spiral wave reentry is the primary mechanism of ventricular tachyarrhythmias (ventricular fibrillation/tachycardia, VF/VT), but information is still limited concerning pharmacological modification of spiral waves by ion channel blockers. In this brief review, the antiarrhythmic and proarrhythmic actions of K\(^+\)-channel blockade (\(I_{\text{Ks}}\) and \(I_{\text{K1}}\)) are discussed in terms of spiral wave dynamics, primarily based on recent experimental findings in ventricular preparations perfused in vitro with the aid of high-resolution optical mapping, as well as their related theoretical studies using computer simulation. (Circ J 2007; Suppl A: A-26–A-31)

Key Words: Antiarrhythmic drugs; K\(^+\) channel; Spiral wave reentry; Ventricular fibrillation/tachycardia

Ventricular tachyarrhythmias, including ventricular fibrillation (VF) and polymorphic ventricular tachycardia (VT), are the leading causes of sudden cardiac death. Recent theoretical studies using computer simulation on nonlinear excitable media and experimental studies using high-resolution optical mapping have revealed that spiral wave reentry rotating around a functional obstacle is the major mechanism underlying most of these tachyarrhythmias. In order to establish reliable therapeutic methods of effective prevention and termination of these tachyarrhythmias, better understanding of spiral waves in cardiac tissues is essential. However, information obtained from real hearts of animals or human patients is still limited, especially concerning pharmacological modulation of spiral wave dynamics, and findings provided by computer simulation studies remain to be validated.

Recently, the effects of nifekalant, a selective blocker of the rapid component of the delayed rectifier K\(^+\) current \((I_{\text{Ks}})\), have been investigated in a 2-dimensional (2-D) layer of rabbit ventricular myocardium, using an original high-resolution video imaging system. It was found that nifekalant promotes self-termination of ventricular tachyarrhythmias through destabilization of spiral waves. In clinical practice, intravenous nifekalant is reported to be highly effective in terminating and preventing VF/VT that is resistant to other antiarrhythmic drugs and DC shocks. On the other hand, it is well known that excessive prolongation of ventricular action potentials by K\(^+\)-channel blockers (drug-induced QT prolongation) leads to an induction of torsades de pointes (TdP)-type polymorphic VT. In this brief review, such bimodal actions, antiarrhythmic and proarrhythmic, of K\(^+\)-channel blockers are discussed in terms of modulation of the spiral wave dynamics.

Spiral Wave Reentry in Ventricles

The concept of spiral waves appeared in the generic theory of excitable media to describe rotating waves of excitation in a variety of nonlinear excitable systems of chemical, physical and biological origin. Winfree is a pioneer who introduced the notion of spiral waves to cardiac electrophysiology to explain the mechanism of functional reentry. In the center of the rotating wave of excitation, the tip of the wave moves along a complex trajectory and waves emanate from the organizing center into the surrounding medium. Because the propagation velocity of a convex wavefront is lower than that of a flat wavefront, as the result of decreased local excitatory current distributing over a relatively larger membrane area downstream (source–sink mismatch), the rotating wave has to acquire the shape of a spiral. Spiral waves can be initiated when a disruption (wavebreak) of a propagating wave is formed in the excitable medium. Interaction of the propagating wavefront with an unexcitable obstacle, which is either an anatomical structure or functionally refractory tissue, results in wavefront fragmentation. The propagation dynamics of a broken wave differ qualitatively from those of planar or circular waves. During normal propagation initiated by a linear source (planar wave) or a point source (circular wave), the wavefront of depolarization and the wavetail of repolarization never meet; the distance between them corresponds to the wavelength of excitation. In contrast, in spiral waves, the front and the tail of a propagating wave touch each other at the wavebreak. In this situation, propagation velocity decreases toward the wavebreak (the broken end of the wave), as the result of pronounced source–sink mismatch of local excitatory current, and the wavefront starts to curl. Consequently, the wavebreak serves as a pivot point and the broken wave rotates around this organizing center.

The dynamics and stability of spiral waves in the heart depend on the underlying electrophysiological properties and anatomical structure of the myocardium, and therefore spiral waves can exhibit a variety of phenotypes. It is obvious that stationary spiral waves produce a regular
Spiral Wave Reentry and K⁺ Channel

Spiral waves are often anchored to small structural discontinuities, such as vessels, patches of fibrosis tissue, and in these cases, the stationary spiral waves pinned to anatomical structures give rise to long-lasting episodes of monomorphic tachycardia. In contrast, beat-to-beat changes in the organizing center of spiral waves may give rise to a complex pattern of activation, because a drifting spiral wave, like any other moving source of oscillation, produces a Doppler shift in the excitation frequency: the frequency is higher ahead of the moving center and lower behind it. Consequently, when meandering of spiral waves is quasiperiodic, coexisting different excitation frequencies produces the characteristic ECG pattern of TdP, showing waxing and waning modulation. When an organizing center moves at higher speed and in a more irregular and chaotic manner, the ECG pattern becomes more disorganized and loses periodic modulation (characteristic ECG pattern of polymorphic tachycardia or coarse fibrillation). Fibrillation is characterized by a complex spatiotemporal pattern in excitation, which results from spiral wave breakup8–11,14 (mechanisms of fibrillation maintenance will be described in detail later).

**Effects of IKr Blockade on Spiral Wave Reentry**

*Spiral Wave Reentry in 2-D Ventricular Myocardium*

In the intact ventricular myocardium having considerable wall thickness, functional reentry underlying VT/VF may be represented by scroll waves with a complex 3-dimensional (3-D) appearance rather than 2-D spiral waves35–37. However, no experimental methods are currently available for the analysis of wave propagation dynamics in 3-D ventricular myocardium with sufficient detail. Therefore, we created a thin epicardial layer of ventricular muscle preparations (≈1 mm thick) of Langendorff-perfused rabbit hearts by an endocardial cyoablation method originally described by Allessie’s group28,38,39 and propagation of action potentials in a quasi 2-D sheet of the left ventricular free wall was visualized by means of an optical mapping system equipped with a high-speed digital video camera15–17 (spatial and temporal resolution of the system, 0.1 mm and 1 ms, respectively). In those experiments, motion artifacts were minimized by infusion of an excitation–contraction uncoupler, BDM. The pattern of activation during constant pacing applied around the center of the anterior surface of the left ventricle (LV) exhibited uniform anisotropy: the activation isochromes showed a smooth ellipsoidal pattern with a long
axis almost parallel to the myocardial fiber orientation. The anisotropic ratio of conduction velocity estimated around the central area of the LV free wall was 2.4–2.6. A pair of paddle electrodes was placed on the lateral surface of both ventricles, and a single monophasic DC pulse (20 V, 10 ms) was applied to the heart during a vulnerable period of preceding constant stimuli from the apex. This “modified cross-field” stimulation consistently induced self-terminating or sustained VT. In approximately 60% of these VT episodes, a single-loop or figure-of-eight pattern of spiral wave reentry was documented and, in the remaining VTs, one-way propagation of excitation waves was observed. There was no breakthrough pattern of activation during any of the VT episodes induced by modified cross-field stimulation, suggesting that neither focal activity (enhanced automaticity and triggered activity) nor transmural reentry is responsible for the occurrence of VT in the quasi-2D ventricular preparations.

**Effects of Nifekalant on Spiral Wave Dynamics**

The effects of nifekalant (0.1 μmol/L) on the action potential and conduction have been characterized during constant pacing at a cycle length of 200–800 ms. Nifekalant prolongs the action potential duration (APD) in a reverse-frequency dependent manner (by 7–25%) without affecting conduction velocity. The APD prolongation was spatially homogeneous in the LV, but APD alternans during rapid pacing was enhanced after nifekalant. Nifekalant increased the maximum slope of APD restitution curves (from 0.48 to 0.70), but the values did not exceed 1 even after nifekalant administration. This suggests that factors other than restitution properties, such as unstable Ca\(^{2+}\) dynamics, electrotonic currents and short-term memory, may be also involved in the increased dynamic instability (APD alternans) induced by nifekalant. Cross-field stimulation induced VT in the presence of nifekalant, as in the control group, but the VT duration was significantly shorter after nifekalant: the percentage of sustained VT (>30 s) in the total VT episodes was approximately 20% under control conditions and was decreased to approximately 4% after nifekalant, and most VTs (>80%) self-terminated within 5 s after induction in the presence of nifekalant.

Fig 1A is a representative record of spiral wave reentry during a VT episode under control conditions: a spiral wave is rotating around a short line of functional block (≈ 7 mm in length) and this pattern of activation was stable for more than 10 s. The distant bipolar electrogram of ventricular excitation during this VT episode shows a monomorphic
pattern. Optical membrane potential signals recorded from the line of block show a double-potential pattern, which is characteristic of electrotonic interaction of excitation waves with a large phase shift across the line. This suggests that the line of block is a result of a refractory wake of a single wave moving back and forth after a full turn at the end of the line. According to the original theoretical concept of spiral wave reentry in an excitable media, the core of the spiral is excitable but unexcited. However, this is not the case in the real 2-D ventricular myocardium. Instead, the wave is rotating around a line of block equivalent to the “inactive core”, as proposed by the “leading circle” concept. Action potential signals close to the pivot point are characterized by a prolonged upstroke phase, sometimes with a notch, which may reflect a localized reduction in the excitatory current at the pronounced convex wavefront close to the pivot point.

Spiral wave reentry induced after application of nifekalant is not stationary but shows irregular meandering along remarkably prolonged complex lines of functional block (Fig 1B).17 Most lines of functional block are the result of a refractory wake of preceding excitations, similar to those under control conditions but, when multiple waves coexist (see the next section), head-on collision of wavefronts also produces lines of functional block. The electrogram shows a polymorphic pattern of VT with varying cycle length. Optical action potential signals also show a large beat-to-beat change in morphology. Such disorganized spiral wave reentry in the presence of nifekalant could not be sustained and self-terminated.

**Interactions Between Wavefront and Wavetail**

The nifekalant-induced modification of spiral wave reentry can be further characterized in terms of the wavefront—wavetail interaction and the phase singularity dynamics (Fig 2).17 In spiral wave reentry under control conditions, the wavefront of depolarization is always chasing its own tail at the tip of the wave. Therefore, the number of phase singularities (the organizing center of a spiral wave) recognized in the phase map is normally 1 (a single rotor) and only transiently increases to 2. After administration of nifekalant, the wavefront frequently encounters its own tail at the spiral arm distant from the tip of the wavefront. Such interactions of the wavefront and the wavetail result in either breakup of the original wave or a sudden movement of the organizing center of the spiral wave. In the phase map, the former is recognized as the appearance of a pair of new phase singularities with opposite chirality and the latter as a sudden spatial jump of the original phase singularity. Both of these events result in a remarkable enhancement of the disorganization of the spiral wave dynamics and prevention of their pinning to anatomical structures.

Theoretical studies have proposed 2 different mechanisms of spiral wave breakup in homogenous tissue:27,33; one is the result of large meandering of the spiral tip, producing prominent dispersion of the wavelength, leading to complex spatiotemporal chaos; the other type of breakup occurs in response to enhanced alternans of the wavelength in the spiral arm at a certain distance from a relatively stable organizing center. In the latter case, the dominant periodicity of excitation is kept constant. The spiral wave breakup in the presence of nifekalant may be attributable mainly to the former mechanism, because the breakup is associated with large meandering and marked variation of excitation cycle length.

**Self-Termination of Spiral Wave Reentry**

Computer simulation studies and theoretical considerations have suggested that there are 3 different modes of termination of spiral wave reentry:40; (1) a pair of counter-rotating spiral waves can mutually annihilate via collision of their rotation centers; (2) a spiral wave can run off a nonexcitable tissue boundary and terminate; and (3) a spiral wave tip is trapped in a region entirely surrounded by refractory tissue, leading to its own extinction. We have demonstrated these 3 patterns of spiral wave termination in experiments using 2-D ventricular tissue of rabbit hearts with the aid of phase mapping analysis.37 In the control conditions, type 1 (mutual annihilation of counter-rotating spiral waves) was the major mode of spontaneous termination of spiral waves. In contrast, in the presence of nifekalant, type 2 (collision of a phase singularity with nonexcitable tissue in the atrioventricular groove) and type 3 (trapping of a phase singularity in a region surrounded by refractory tissue) modes are predominant in spiral wave self-termination. The former may be the result of enhanced meandering and unpinning of the spiral tip and the latter may be a consequence of repolarization delay and its beat-to-beat variation.

**Inward Rectifier K+ Current (I\(K_1\)) and Spiral Wave Stabilization**

In working cardiomyocytes, action potential repolarization depends on coordinated activation of multiple types of K+ currents: delayed rectifier K+ currents (I\(K_s\), I\(K_h\)), transient outward current (I\(O_1\)), and I\(K_1\). During spiral wave propagation, the contribution of respective K+ currents is considered to be spatially heterogeneous, depending on their vicinity to the spiral tip.41-43 The results of our optical mapping study have suggested that I\(O_1\) plays a significant role in action potential repolarization close to the spiral tip, because the selective blockade of this current by nifekalant enhances meandering of the spiral tip. Such destabilization of spiral waves promotes their self-termination. A recent computer simulation study, using the Luo-Rudy action potential model, has also demonstrated that blockade of the delayed rectifier K+ channel increases dynamic instability and promotes spiral wave extinction through mutual annihilation and collision with an anatomical boundary in a finite-sized 2-D sheet.44 In contrast, Jalife et al41-43 have proposed that instantaneous I\(K_1\), rather than time-dependent I\(K_s\), is the major repolarizing current responsible for the prematurely abbreviated wavetail close to the spiral tip. In their studies using guinea-pig hearts, spatiotemporal periodicities with a domain-like distribution of excitation frequency always exist during VF and a persistent stable rotor that provides exceedingly high-frequency excitation and fibrillatory conduction is consistently located in the LV where the outward component of I\(K_1\) is larger than that in the right ventricle.42,43 Selective blockade of I\(K_1\) by Ba\(^2+\) was shown to abolish the high-frequency excitation in the LV and facilitate self-termination of VF.45 They have also demonstrated recently that genetic overexpression of Kir2.1, a major pore-forming unit of the I\(K_1\) channel, in the mouse heart results in a remarkable increase in the VF/VT frequency and a significant prolongation of VF/VT duration.46 Based on those findings, they have argued that I\(K_1\) plays a key role in action potential repolarization close to the spiral tip, allowing high-frequency rotors to stabilize.
VF and K⁺-Channel Blockade

As for the role of spiral-wave reentry in the maintenance of VF, there are 2 major working hypotheses: a “multiple-wavelet” hypothesis and a “mother rotor” hypothesis, in which the role of spiral wave breakup differs.7-10,42,43,47-50 According to the multiple-wavelet hypothesis, continuously generated wavebreak is the engine maintaining VF. In this hypothesis, wave breakup is originally thought to be the result of structural and/or functional heterogeneity of the myocardium, but it has been recently emphasized that dynamic factors, such as restitution properties, play synergistic roles with preexisting heterogeneity in amplifying the wave instability leading to spiral wave breakup (“dynamic wavebreak hypothesis”).14,48,49 On the other hand, Jalife et al have proposed that a fairly stable mother rotor serves as a source of high-frequency excitation and, because of its high frequency rate, waves of excitation emanating from the rotor develop intermittent conduction block at the periphery (fibrillatory conduction), which gives rise to the characteristic complex pattern of QRS on the ECG.10,42,43,50 Therefore, in this theory, wavebreak is just an epiphenomenon and not essential for the maintenance of VF. Recent studies have shown that these 2 mechanisms are interchangeable, depending on underlying conditions.51-53

Mother-rotor-type VF will not self-terminate as long as the mother rotor is anchored to small structural discontinuities. Blockade of Kᵢc promotes meandering and breakup of spiral waves through an increase in dynamic instability, and this facilitates unpinning of the spiral waves from anatomical structures.17,53,56 Unstable spiral waves showing chaotic meandering tend to self-terminate as a result of collision of the spiral tip with the nonexcitable boundary of a limited area of tissue. These processes may explain, in part, the arrhythmic actions of Kᵢc blockers. Blockade of Kᵢc may have similar actions. In contrast, the increased spiral wave breakup by Kᵢc blockade, as a result of increased wavefront–wavelike interactions in the spiral arm, promotes degeneration of stable VT to complex multiple wavelet-type VF, and this may be involved in the proarrhythmic actions of Kᵢc blockers. Such actions might be less with Kᵢc blockade, if the relative contribution of Kᵢc to action potential repolarization is much greater in the vicinity of the spiral tip than in the spiral arm. As for the modification of spiral wave reentry dynamics by K⁺-channel blockade, information available to date is mainly from 2-D cardiac tissues in computer simulation or in real hearts of small animals. Extending these results to 3-D hearts, especially in larger animals including humans, is not straightforward. An increase in the tissue mass (surface area and wall thickness) would reduce the chance of spontaneous termination of spiral wave reentry by rotor collision or trapping, and it would enhance rotor meandering and wave instability through complex 3-D dynamics in favor of the transition from VT to VF. The greater structural discontinuities and functional heterogeneities in diseased hearts would also alter the spatial requirements of spontaneous rotor termination. Further experimental and theoretical studies are required to shed light on these issues.

Acknowledgments

This study was supported, in part, by a Grant-in-Aid for Scientific Research (C) from the Ministry of Health, Labour and Welfare and from the Suzuken Memorial Foundation.

References


