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Vulnerability to Unidirectional Conduction Block and Reentry in Rabbit Left Ventricular Wedge Preparation: Effects of Stimulation Sequence and Location

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Abstract

Many factors influence the initiation of unidirectional conduction block and reentry. To explore the influential factors on the temporal vulnerable window of the unidirectional conduction block, we investigated the effect of stimulation sequence and location on the temporal vulnerability in epicardial and endocardial sites in an arterially perfused rabbit left ventricular wedge preparation at three basic cycle lengths (BCL) of 2,000, 1,000 and 500 ms. An extrastimulus (S_2) was introduced at coupling intervals incremented by 1 ms to scan the entire diastolic interval. The results showed that the vulnerable window increased with the lengthening of BCL, which ranged from 48.55 ± 18.04 ms at BCL of 500 ms to 92.50 ± 25.59 ms at BCL of 2,000 ms for endocardial, and is a similar style for epicardial from 21.00 ± 14.02 ms at BCL of 500 ms to 75.71 ± 16.34 ms at BCL of 2,000 ms ($P < 0.05$). The vulnerable window of endocardial was wider than that of epicardial ($P < 0.05$). Furthermore, the window size for reentry was about 39% smaller than that for unidirectional conduction block. Meanwhile, we found that increasing the number of premature beats enlarged the vulnerable window markedly due to enhanced transmural dispersion of repolarization (TDR) of ventricle. The vulnerable window is an effective index to evaluate the increased risk for unidirectional conduction block. Therefore, the factors that increase the vulnerable window are associated with the higher incidence of ventricular arrhythmias.

Key Words: vulnerable window, unidirectional conduction block, reentry

Introduction

Sudden cardiac death is most commonly due to ventricular fibrillation, which is characterized by multiple wavelets arising from an initial single or figure-of-eight reentrant circuit (18). Currently, it is held that the mechanism of ventricular arrhythmias is associated with spatial dispersion of repolarization (1, 8) and

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dynamic factors (9, 19). The steeper restitution curve is reported to exist in the normal heart to show dynamic instability, which reflects temporal heterogeneity of cardiac ionic channel recovery. Computer simulation study demonstrate that the interaction between the pre-existing spatial dispersion of repolarization and dynamic instability influences the genesis and maintenance of the reentry and ventricular tachycardia (10, 11, 18). Ventricular tachycardia can also degenerate to ventricular fibrillation due to dynamic instability caused by increased spatial dispersion of repolarization (18). Dispersion and dynamic instability form the substrate for unidirectional conduction block, which is required for the initiation of reentry by critically timed extrasystoles from a given spatial location.

Vulnerable window describes the temporal window within which unidirectional conduction block or reentrant excitation can be induced. In this study, The authors used the arterially perfused rabbit left ventricular wedge preparation to investigate how pre-existing gradients in refractoriness affect the vulnerability for unidirectional conduction block and reentry. First, the authors observed the characteristics of arrhythmogenicity of extrasystoles delivered from endocardium and epicardium layer with different basic cycle lengths (BCL). Then the relationship of the size of vulnerable window of unidirectional conduction block or reentry with the spatial dispersion of repolarization was examined. The authors also observed briefly how the first extrasystole modulated the existing dispersion of refractoriness, and thereby affected the vulnerable window of subsequent extrasystole.

Materials and Methods

Arterially Perfused Rabbit Left Ventricular Wedge Preparations

Fourteen hybrid male rabbits weighing 2.5 to 3 kg (supplied by Animal Center of Xi'an Jiao Tong University) were used in this study. The methods for the rabbit wedge preparation, described in detail in previous publications (15, 16, 21), are as follows: The rabbits were anticoagulated with heparin (200 IU/kg) and anesthetized with 20% urethane (5 ml/kg). The chest was opened *via* a left thoracostomy and the heart was excised and placed in a cold (4°C) high K^+ cardioplegic Tyrode's solution. The left circumflex branch of the coronary artery was cannulated and perfused with the cardioplegic solution. Unperfused areas of both atria, right ventricle, and septum were removed. The preparation was then placed in a small tissue bath and arterially perfused with normal K^+ Tyrode's solution buffered with 95% O_2 and 5% CO_2 at 35.7 ± 0.1°C. The left ventricular wedge was allowed to equilibrate in tissue bath for one hour prior to electrical recordings. The experiments were divided into two groups based on the position of premature stimulus (S2) delivered from the epicardial or endocardial sites following three different BCLs (2,000, 1,000 and 500 ms) of S1 stimulus delivered from the endocardium respectively (n = 14).

Electrophysiological Recordings

Transmembrane action potentials were recorded simultaneously from epicardial and endocardial sites using intracellular floating microelectrodes. In the meantime, a transmural electrocardiogram (ECG) was recorded concurrently in all experiments using extra cellular Ag/AgCl electrodes placed in the Tyrode's solution bathing the preparation 1.0 to 1.5 cm from the epicardial and endocardial surfaces.

The QT interval of transmural ECG was defined as the time from the onset of the QRS complex to the point at which the final descending branch of the T wave crosses the isoelectric line. The Tp-e interval, which stands for the time from the peak to the end of T wave, closely approximated transmural dispersion of repolarization (TDR) (7, 22, 23). The Tp-e interval was measured manually in three consecutive beats within the last minute of the recording, and the values were then averaged before premature beats.

Double diastolic threshold currents were delivered with BCL of 2,000, 1,000 and 500 ms (S1), respectively, to record transmembrane action potentials and transmural ECG (Fig. 1).

Measurement of the Temporal Vulnerable Window

Each driving train of S1 consisted of 10 beats. To determine temporal vulnerable window, the programmed stimuli (S2) were delivered at the cardiac apex either at endocardial or epicardial site. The S1-S2 coupling interval progressively increased with 1ms increment. Premature stimuli that occur early in the diastolic period elicit excitatory responses that diminish with increasing degree of prematurity. If the carefully timed stimulus, no matter the extra stimulus was delivered from epicardial or endocardial site, encountered directional differences in excitability due to different degrees of recovery from the previous action potential, the development of excitatory responses with a wider and opposite polarity QRS complex in ECG compared with the one induced by S1 was identified unidirectional conduction block. The development of excitatory responses with the same polarity as the one induced by S1, regardless of magnitude, was referred to as bidirectional conduction (14). The authors defined the temporal vulnerable window as the period between the onset of unidirectional block and the onset of bidirectional conduction (14). The first unidirec-

Table 1. Characteristics of vulnerable window when S2 was located at endocardium or epicardium

BCL (ms)	n	Endocardium			Epicardium		
		Upper limit (ms)	Lower limit (ms)	VW (ms)	Upper limit (ms)	Lower limit (ms)	VW (ms)
2,000	14	213.36 ± 39.44	299.71 ± 47.70	92.50 ± 25.59	221.50 ± 33.12	296.93 ± 37.19	75.71 ± 16.34*
1,000	14	196.43 ± 23.32	268.79 ± 30.28	73.21 ± 19.96$^{\#}$	195.00 ± 27.41	251.50 ± 28.41	59.50 ± 18.80*
500	11	160.73 ± 17.02	209.27 ± 26.19	48.55 ± 18.04^{+}	168.11 ± 9.17	193.56 ± 13.22	21.00 ± 14.02*$^{\#+}$

BCL = basic cycle length.

*, $P < 0.05$, the comparison of vulnerable window between S2 located at epicardium and S2 at endocardium with the same BCL.

#, $P < 0.05$ *vs*. 2,000 ms; +, $P < 0.05$ *vs*. 1,000 ms comparisons of vulnerable windows in the same group at different BCLs.

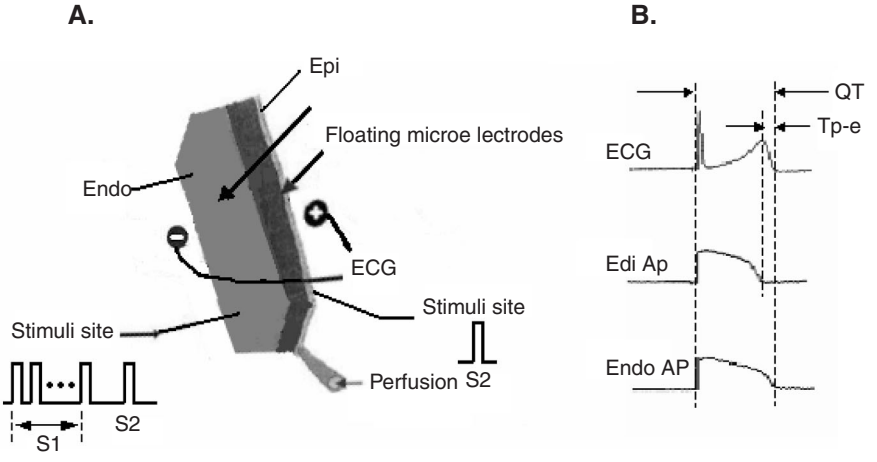

Fig. 1. (A) Schematic diagram of the wedge preparation anatomy, the location of simulator S1 and S2, and pulse sequences. (B) The recording of transmural ECG and transmembrane action potentials from epicardial (Epi AP) and endocardial (Endo AP) sites and the way to measure QT interval and Tp-e interval.

tional block generated by S2 were then identified as the upper limit, and the first bidirectional conduction as the lower limit of the vulnerable window as shown in table1. The vulnerable window of the reentrant excitation was the time course within which the ventricular tachycardia could be induced.

Data Analysis and Statistics

Data were collected and measured with RM6240B/C software (Cheng Du Instruments, Cheng Du, Sichuan, PRC) and presented as mean ± SD. Data analysis was performed using SPSS 13.0 software. Paired *t*-test was used to determine statistical significance of paired data of vulnerable window obtained from epicardial and endocardial sides of each preparation at the same BCL. Student's *t*-test was used for comparison of vulnerable window in the same group at different BCL. Significance was defined as a value of $P < 0.05$.

Results

Basic Cycle Length and Location of Extrastimulus with Temporal Vulnerable Window

We observed the changes of vulnerable window at BCL of 2,000, 1,000, and 500 ms, respectively. Table 1 illustrates the variation of vulnerable window when premature stimulus S2 was located at epicardial sites and endocardial sites. First, we found that vulnerable window for unidirectional conduction block increased dramatically with the BCL prolongation, regardless of the location of the S2 ($P < 0.05$), which ranged from 48.55 ± 18.04 ms at BCL of 500 ms to 92.50 ± 25.59 ms at BCL of 2,000 ms for endocardial (about 90.5% increment), similar style for epicardial from 21.00 ± 14.02 ms at BCL of 500 ms to 75.71 ± 16.34 ms at BCL of 2,000 ms (about 260.5% enlargement). We also found that the vulnerable window was associated with the location of the premature beats. The vulnerable window was wider when S2 were located at endocardial than that at epicardial site with the same basic cycle length ($P < 0.05$). The premature

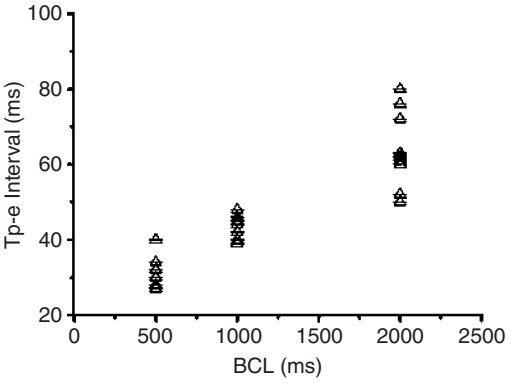

Fig. 2. The relationship between Tp-e interval and different BCLs.

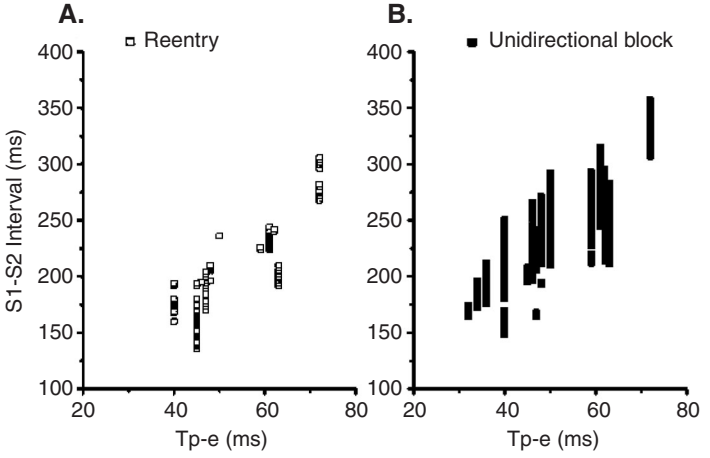

Fig. 3. The vulnerable period of S1-S2 interval with Tp-e interval. In Y-axis, S1-S2 interval reflects vulnerable window of unidirectional block and reentry. In X-axis, Tp-e represents transmural dispersion of repolarization. (A) Empty squares indicate initiation of reentry, while (B) solid squares refer to unidirectional conduction block induced by S2.

beats from endocardium were more likely to induce ventricular tachycardia (data not shown).

Transmural Dispersion of Repolarization and Vulnerable Window

We also measured the Tp-e interval at three different BCL. We found that under our experimental conditions, the longer the BCL, the larger the Tp-e interval (Fig. 2). Tp-e interval reflects the transmural dispersion of repolarization (TDR), which was demonstrated by Antzelevitch and Yan (7, 21). Our results showed that no matter the S2 was delivered from endocardial or epicardial site, the relationship between vulnerable window and TDR exhibited the same tendency, which illustrated that vulnerable window for unidirectional conduction block and reentry was proportional to the TDR and BCL. With the increase of the TDR, the vulnerable window of unidirectional conduction block and reentry increased dramatically.

However, the initiation of unidirectional conduction block by S2 is earlier than that of reentry, which means that S1-S2 intervals were longer for inducing unidirectional conduction block (Fig. 3B) than that for inducing reentry (Fig. 3A). The S1-S2 interval stands for the size of vulnerable window of unidirectional block and reentry. Compared with the vulnerable window for inducing unidirectional conduction block at the same interval of Tp-e, the vulnerable window for initiation of reentry appeared smaller. The window size for reentry was about 39% smaller than that for unidirectional conduction block. In other words, at the same S1-S2 interval, a large Tp-e was needed for inducing reentry, which suggesting that the augmentation of TDR profited recovery of part of cardiac excitability and provided the condition for the creation of the unidirectional block together with reentry.

Numbers of the Extrastimuli and Vulnerable Window

We observed briefly from three experiments how

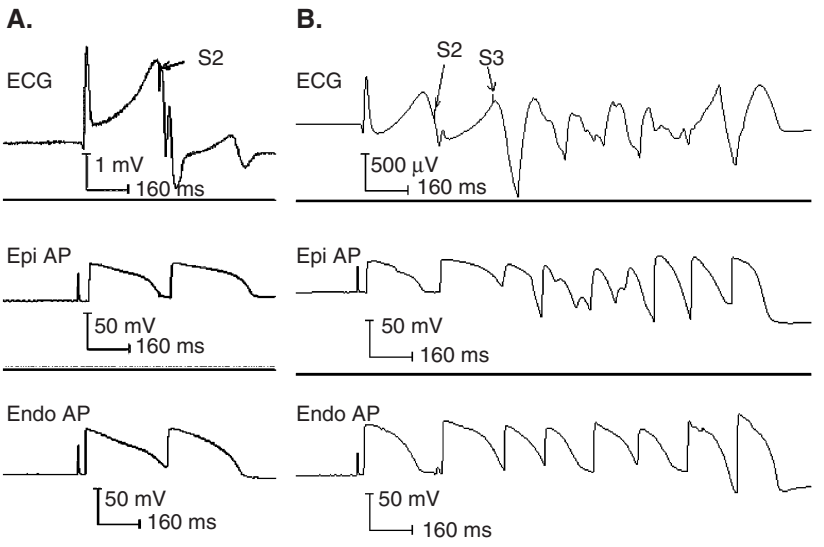

Fig. 4. Comparison of vulnerable window induced by single S2 and S2 plus S3. ECG and AP of endocardial and epicardial cells simultaneously recorded from arterially perfused rabbit left wedge preparations. (A) shows that when a single premature beat S2 was delivered at the descending branch of T wave, no polymorphic ventricular tachycardia would be generated at all. (B) shows that when another premature beat S3 was delivered at a right time following S2 which were still delivered at the descending branch of T wave, a train of polymorphic ventricular tachycardia would be induced by it.

the two premature extrasystoles influence the electrical heterogeneity, and also surveyed the effects of cardiac heterogeneity variation of repolarization on the vulnerable window progressively. The programmed S1-S2 coupling interval increased by 1ms increment, while the interval of S2-S3 was held invariably. We found that if a single S2 was delivered at the descending branch of T wave, there was no polymorphic ventricular tachycardia generated at all (Fig. 4A). However, if the second premature beat S3 was added at the right moment following this S2, a train of polymorphic ventricular tachycardia could be induced very easily (Fig. 4B). This finding implied that the first extrasystole interfered with the repolarization process and enlarged the cardiac pre-existing heterogeneity, thereby affected the vulnerable window of subsequent extrasystole. The results were associated with the wider vulnerable window generated by S2-S3 than that by a single S2.

Discussion

Unidirectional conduction block caused by dispersion of refractoriness is a necessary condition required to induce reentry (22, 23). In this study, we used the arterially perfused rabbit left ventricular wedge preparations to investigate how pre-existing dispersion in refractoriness affect the vulnerability for unidirectional conduction block and reentry.

Electrical heterogeneities is an intrinsic property which exists in the normal heart and can be modified in diseased heart by electrical and structural remodeling. Both fast and slow heart rate can modulate this property through different mechanisms. The spatial dispersion of refractoriness could be amplified by dynamically-induced discordant alternant at fast heart rates and reentry can be initiated, because of the steeper action potential duration restitution and broader conduction velocity restitution (20). However, under the condition of slow heart rate, a prominent increase in TDR accompanying the prolongation of QT interval is the most crucial factor for the development of Torsade de Pointes (TdP) and polymorphic tachycardia occurrence.

It has been estimated that TDR is related to spatial heterogeneities of ionic channels in myocytes. The rapidly activating delayed rectifier current (I_{kr}) appears to be homogeneously distributed across the ventricular wall. Because of the relatively weak slowly activating delayed rectifier current (I_{ks}), a larger late sodium current (late I_{Na}) and a larger sodium-calcium exchange current density, midmyocardial cells (M cells) in canine and human beings are distinguished by the ability of their action potentials to prolong more than those of epicardium and endocardium in response to a slowing heart rate and are more sensitive to many APD prolonging conditions than epicardial and endocardial cells (7, 24). Yan *et al.* have demonstrated that the electrophysiological characteristic of rabbit endocardium and subendocardium are consistent with canine M cells (22). Therefore, the TDR increased under the circumstance mentioned above. This may be the mechanism for the vulnerable window increase with the BCL prolongation in our study. This is consistent with the result observed by Henry and Rappel who reported a simulation study in which the tem-

poral vulnerable window was bound to increase at slow heart rate and under LQT2 conditions in one dimension and two dimension cardiac models (5).

Stimulus-induced changes could influence the electrophysiological properties and reach critical repolarization heterogeneity, which could provide the substrate for reentrant ventricular arrhythmias. Many results from experimental study have been achieved. A minimum repolarization gradient of 3.2 ms/mm was a necessary gradient at the isthmus of normal guinea pig heart for unidirectional block (6). Moreover, enhanced gradients, which was higher than 12 ms/mm, were responsible for the development of polymorphic ventricular tachycardia in dog with heart failure (12).

However, the propagation direction of a premature extrasystole has a significant influence on the critical gradient required for unidirectional conduction block. We found that in our experiment the vulnerable window was wider if the premature beat S2 was delivered from endocardial site and propagated in the same direction as the basic beat S1 than the S2 delivered from epicardial site and propagated in the opposite direction as the S1. The results illustrated that the activation sequence of a premature beat traveling in the same or opposite direction during sinus rhythm in real heart could produce different repolarization gradients and cause a different vulnerability. Qu and his colleagues' previous theoretical study also demonstrated that the critical gradient is higher for an extrasystole traveling in the opposite direction as the primary beat, like an epicardial extrasystole (10, 11). Once the critical refractory gradient is exceeded, the vulnerable window increases proportionately.

The vulnerable window for unidirectional conduction block is not equivalent to that of initiation of reentry in real hearts. In this study, as shown in Fig. 3, we found that the window size for reentry was about 39% smaller than that of the unidirectional block. And a great refractory barrier was needed for initiation of reentrant ventricular tachycardia. That is to say, a critical spatial dispersion of tissue heterogeneity is required in order for unidirectional conduction block to initiate reentry (3). The computor simulation study showed some convincing explanations for this phenomenon. As the unidirectional block leads to wavebreak, tissue that is excitable must be available for the broken tips of the waves and allow them to complete a full rotation (17). The results implied clinically that if the spatial heterogeneity of heart is decreased, the single or figure-of-eight reentrant circuit may be prevented.

Dynamic factors refer to cellular properties of the membrane voltage (including action potential duration, APD and conduction velocity, CV and Cai cycling, which dynamically generate wave instability and wavebreak (2, 18). A single premature beat might be strong enough to interfere the dynamic stability of the cardiac tissue or myocytes. In this study, we briefly observed the effect of two premature beats arising from the same location on the vulnerable window for reentry, which might correspond to a couplet in clinic and is common in diseased hearts. The dual premature activations could be a very effective way to generate reentry with a large vulnerable window (4). Our results showed as premature beat S2 was delivered on the descending branch of T wave and this one could not induce reentry by itself at all. However, the first premature stimulus that occurred lately in the diastolic period could cause bidirectional conduction and elicit two propagating waves in opposite directions, which might interfere the original pre-existing heterogeneity dynamically by changing the APD and CV restitution property (2, 11). This allowed a properly-timed second extrasystole (S3) encountering the dynamically heterogeneous substrate generated by the first extrasystole (S2) and further enlarging the vulnerable window (13) and the S3 could initiate a train of polymorphic tachycardia.

We only observed small amount of data for two premature extrasystoles interfering with the vulnerable window. However, the main goal of this study was created for understanding the relation between high incidence of ventricular tachycardia with wider vulnerable window of reentrant excitability and a pair of extrasystoles in clinical situations. Based on this part of preliminary data, we will use the voltage sensitive optical mapping technique to investigate the relationship between the number of extrasystoles and the vulnerable window systematically, and furthermore to analyze the characteristic of the cardiac dynamic properties.

In conclusion, spatial dispersion of refractoriness forms the substrate for unidirectional conduction block, which is required for the initiation of reentry by extrasystoles. In this study, we used the arterially perfused left ventricular wedge preparation to investigate the effect of stimulation sequence and location on the vulnerability to unidirectional conduction block and reentry. The results demonstrated that compared with premature beats at epicardial site, the vulnerable window induced by S2 located at endocardial site was wider and more likely to induce ventricular arrhythmias. The vulnerable window for initiation of reentry was smaller than for unidirectional conduction block. However, a large TDR was needed for inducing reentry. Meanwhile, we found that increasing the number of premature beats might enlarge the vulnerable window markedly due to the modification of the dynamic property of ventricle. The vulnerable window is an effective index to evaluate the increased risk for unidirectional conduction block. Therefore, the factors above which have increased the vulnerable window leads to the increase of incidence of ventricular arrhythmias.

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