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Cardiac electrical dynamics: maximizing dynamical heterogeneity

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Abstract The relationships between key features of the cardiac electrical activity, such as electrical restitution, discordant alternans, wavebreak, and reentry, and the onset of ventricular tachyarrhythmias have been characterized extensively under the condition of constant rapid pacing. However, it is unlikely that this scenario applies directly to the clinical situation, where the induction of ventricular tachycardia (VT) typically is associated with the interruption of normal cardiac rhythm by several premature beats. To address this issue, we have developed a general theory to explain why specific patterns of premature stimuli increase dynamic heterogeneity of repolarization and precipitate conduction block. The theory predicts that conduction block is caused by (1) creation of a spatial gradient in diastolic interval (DI) by waves traveling at slightly different velocities (ie, conduction velocity dispersion) and (2) amplification of the spatial gradient in DI over subsequent action potentials, secondary to a strong dependence of action potential duration on the preceding DI (ie, a steep action potential duration restitution function). Tests of this theory have been conducted in computer models of homogeneous tissue, where increased spatial dispersion of repolarization during premature stimulation can be attributed solely to the development of dynamical heterogeneity, and in a canine model exhibiting spontaneously occurring VT and sudden death. Our results thus far indicate that the probability of inducing ventricular fibrillation (VF) in the animal model is highest for those sequences predicted to cause conduction block in the computer model. An understanding of the mechanisms underlying these observations will help to identify key electrical phenomena in the onset of VT and fibrillation. Drug and electrical therapies can then be improved by targeting these specific phenomena.

Keywords: Restitution; Alternans; Fibrillation; Heterogeneity

Electrical restitution and spatial dispersion of repolarization

Given that sudden cardiac death remains the leading cause of death in the United States, the mechanisms underlying the development of VF continue to be an area of intense scientific interest. Although several theories regarding the cellular electrophysiologic mechanism for VF currently are being evaluated,[1-3] substantial evidence has accumulated over the last few years to suggest that fibrillation is a state of spatiotemporal chaos consisting of the perpetual nucleation and disintegration of spiral waves,[1,3] in association with a period doubling bifurcation of local electrical properties.[4-6] Nucleation of the initiating spiral wave pair is caused by local conduction block (wavebreak) secondary to spatial heterogeneity of refractoriness in the ventricle.[7-9] Until recently, spatial heterogeneity was thought to result solely from regional variations of intrinsic cellular electrical properties [9,10] or from stimulation at more than one spatial location.[11,12] However, it is now appreciated that purely dynamical heterogeneity can be sufficient to cause conduction block during single-site stimulation in both homogeneous 1-dimensional models of canine heart tissue and in rapidly paced canine Purkinje fibers. A similar mechanism has been shown to precipitate conduction block and spiral breakup in models of homogeneous 2- and 3-dimensional tissues.[11,13-16]

The period doubling bifurcation implicated in the transition to conduction block is manifested as alternans, a beat-to-beat long-short alternation in the duration of the cardiac action potential.[4-6,17,18] Previous investigators have hypothesized that alternans can be accounted for by a simple unidimensional return map called the action potential duration (APD) restitution function.[18] This hypothesis

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assumes that the duration of an action potential (APD) depends only on its preceding diastolic interval (DI) through some function a(DI) that is measured experimentally. If the APD restitution function has a slope of 1 or higher, then a period doubling bifurcation occurs for some value of the pacing cycle (BCL), where BCL = APD + DI. The velocity at which an action potential propagates (CV) can also be described by a restitution function, where CV = v(DI). More recently, other potential modulators of restitution, such as memory and calcium cycling, have been incorporated into formulations for restitution.[13,19-21]

Dynamically induced spatial dispersion of repolarization

It has been shown previously that the combination of a steeply sloped APD restitution function and a monotonically increasing CV restitution function is sufficient to produce dynamics conduction block during sustained pacing at a short cycle length.[11,22] This observation may provide a generic mechanism for wavebreak and the onset of ventricular tachycardia (VT) and fibrillation. However, it is unlikely that the conditions used to demonstrate this phenomenon experimentally apply to the clinical situation, where the induction of ventricular tachyarrhythmias typically is associated with the interruption of normal cardiac rhythm by only a few premature beats.

Recently, we determined whether dynamical heterogeneity and conduction block occur in a computer model of canine heart fibers in which pacing at a slow rate is interrupted by 1 to 4 premature stimuli.[23] This protocol simulates the interruption of sinus rhythm by 1 to 4 premature ventricular complexes, a situation that can lead to the onset of ventricular fibrillation clinically. Furthermore, we determined whether the conduction block induced in this way can be accounted for by the same dynamics mechanism that underlies the development of conduction block during rapid pacing. A coupled map model of the heart tissue was used for the study, which allowed us to identify the roles that CV and APD restitution play in the development of dynamic heterogeneity. We also considered the additional contribution of cardiac memory to the development of dynamical heterogeneity and conduction block.

These studies indicated that a short-long-short-short coupling interval pattern of premature stimuli induced marked spatial dispersion of repolarization and conduction block. The dynamical mechanism for the development of block was the same as for the development of discordant alternans during sustained rapid pacing. This type of conduction block could lead to wavebreak and spiral wave initiation if it occurred in 2- and 3-dimensional tissue, provided the block was local. The development of local block would be facilitated in intact myocardium by twist anisotropy and intrinsic heterogeneity.

Other researchers also have examined certain aspects of this problem. Watanabe et al[12] demonstrated that a single premature beat is sufficient to cause spatial heterogeneity in the form of discordant alternans, whereas Comtois et al[24] have demonstrated that 2 properly timed stimuli after the passage of a propagating wave can produce unidirectional

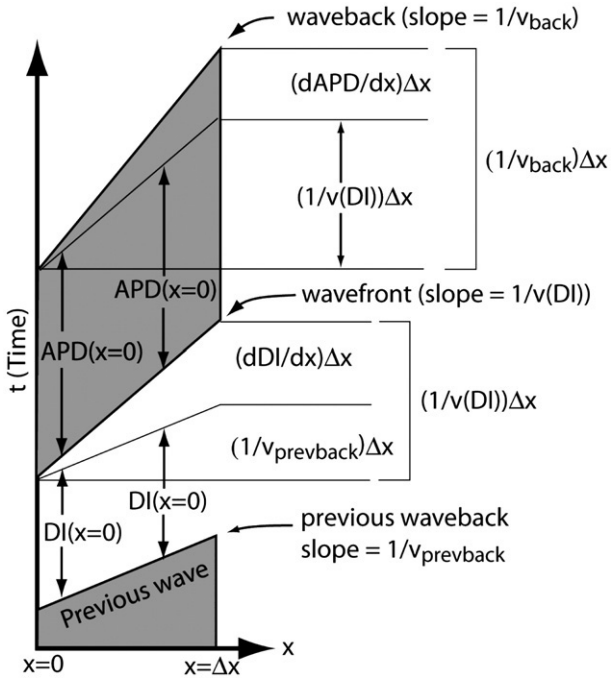

Fig. 1. Graphical derivation of Eqs (1) and (2) in x-t space for a short segment of tissue of length Δx. Stimuli are launched from $x = 0$. The lower portion of the figure shows dDI/dx as the difference in slopes between the inverse wavefront velocity, $1/v$(DI), and the inverse of the previous waveback velocity, $1/v_{\text{prevback}}$. The upper part of the figure shows dAPD/dx as the difference between the waveback and wavefront velocities, $1/v_{\text{back}}$ and $1/v$(DI).

block and spiral wave reentry with a large window of vulnerability. Qu et al[25,26] have conducted more extensive studies to determine how preexisting gradients in refractoriness interact with one or more premature stimuli to produce conduction block. However, general extension of these block mechanisms to 2 and 3 dimensions, their interaction with intrinsic and anatomical heterogeneity, and their relationship to the development of wavebreak, in either simulation or experiment, have yet to be extensively explored.

A theory for the development of conduction block after premature stimulation

Recently, Otani[27] developed a method that uses the APD and CV restitution relations to generate predictions regarding which sequences of premature stimuli are most likely to induce conduction block and reentry. This method relies on the fact that when $1/v_{\text{prevback}}$ is greater than $1/v(\text{DI}_{\text{min}})$ at the stimulus site, block will occur for some finite range of the interval between the preceding and current stimuli. Here, v_{prevback} is the velocity of the waveback of the preceding wave and $v(\text{DI}_{\text{min}})$ is the conduction velocity when the preceding DI is the smallest value that allows propagation. Thus, block occurs when the trailing edge of the preceding wave travels slower than the leading edge of the current wave, allowing the latter to encroach and terminate on the former.

To determine when this blocking condition will be satisfied at the stimulus site, we developed relationships