Spatiotemporal Dynamics of Damped Propagation in Excitable Cardiac Tissue

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Compared to steadily propagating waves (SPW), damped waves (DW), another solution to the nonlinear wave equation, are seldom studied. In cardiac tissue after electrical stimulation in an SPW wake, we observe DW with diminished amplitude and velocity that either gradually decrease as the DW dies, or exhibit a sharp amplitude increase after a delay to become an SPW. The cardiac DW-SPW transition is a key link in understanding defibrillation and stimulation close to the refractory period, and is ideal for a general study of DW dynamics.

Introduction.—The physics of the propagation of continuous waves in passive (linear) media has been studied exhaustively and exhibit reflection, refraction, and interference. In the classic example of electromagnetic (EM) waves in vacuum, waves of all frequencies propagate with the same phase velocity, so that a solitary EM pulse can propagate without distortion and can pass through another pulse unchanged. In lossy media, where energy is dissipated, wave amplitude decays as it propagates. In dispersive media, where wavelength depends upon propagation velocity, the wave shape can change with time and anomalous dispersion can occur.

In active (nonlinear) media, for which losses in the media are accompanied by the release of stored energy, solitary waves of a particular shape can propagate without distortion. The wave shape is determined by the governing nonlinear differential equations. Propagating nerve and cardiac action potentials (APs) are examples of solitary waves for which nonlinearities determine biologically important phenomena [1]: AP initiation requires a suprathreshold electrical stimulus, which in turn depends upon both the stimulus duration and the elapsed time since the previous AP. A minimum time interval, termed the absolute refractory period (ARP), must separate the leading edges of sequential APs, regardless of stimulus strength. Because of the ARP, upon collision APs will annihilate each other. Despite the common assumption that the AP has a constant shape and a uniform conduction velocity, experiments reveal that an AP following immediately after another AP will have a deformed shape (termed restitution) and reduced propagation velocity (termed dispersion) as compared to one after a longer separation in time [2]. Most of these phenomena are evident, for example, in reentrant cardiac arrhythmias [3]. Reduction of the threshold can increase the sensitivity to extraneous electrical activity and can lead to the spontaneous generation of waves that form expanding target patterns. AP annihilation upon collision results in a volume of tissue being refractory, so that any conduction through that region is blocked for a time longer than the ARP. Conduction block can lead to an AP that propagates over a closed path to form a vortex or more complex reentrant patterns [4]. A reduction in the ARP can lead to higher reentry frequencies, as seen in fibrillation, the most dangerous pattern of all cardiac reentries. Finally, there is an ongoing controversy as to whether reexcitation following an unsuccessful defibrillation shock arises from an unstable point focus (triggered activity), an intramural reentry not visible from the epicardium, or slow propagation in the electrically altered postshock tissue [5,6].

In this Letter, we demonstrate experimentally that nonuniform propagation and AP amplitude decay can play an important role in both conduction block and delayed activation. We used isolated rabbit hearts and applied a conditioning electrical stimulus (S1), which produced a solitary AP propagating with constant shape and amplitude. Following a specified interval, we applied a second stimulus (S2), which launches another wave into the wake of the initial one. This protocol is of special interest to the study of the vulnerability of the heart to the initiation of self-maintained, high frequency wave sources that have long been regarded as a precursor to dangerous cardiac arrhythmias [7–9]. A widely accepted mathematical description of vulnerability assumes that the effect of stimulation depends on the S2 timing: an S2 soon after S1 dies out, because it is applied to absolutely refractory tissue; an S2 long after S1 freely propagates, because it is applied to resting tissue; an S2 applied close to the boundary of absolute refractoriness may result in a discontinuous front that evolves into reentry (see Ref. [8] for details). This description bears its roots in the simple cellular automata model by Wiener and Rosenblueth [9], which assumes only discrete states of the medium occur; i.e., a wave either has a constant shape and propagates steadily, or it disappears. However, as mentioned above, theoretical and experimental observations indicate that the shape, amplitude, and velocity of a
propagating wave are not always constant. Our experiments were designed to test quantitatively in cardiac tissue theoretical predictions regarding the spatiotemporal effects of S₁ stimulation in the wake of the previous conditioning wave, particularly those by Aliev and Panfilov in the Belousov-Zhabotinsky reaction [10].

Experimental procedures.—We used cryoablation to obtain a 1 mm thick, quasi-2D layer of left ventricular epicardium [11] from 2–3 kg New Zealand white rabbits (n = 10). We visualized the distribution of the transmembrane potential using a standard fluorescence mapping system, and we voltage calibrated the fluorescence images with microelectrode measurements [12]. We used the important pinwheel stimulation protocol [13]: to initiate planar conditioning S₁ waves propagating across the left ventricle, we placed a linear wire electrode, oriented perpendicular to the fibers, on the lower part of the left ventricular wall, and paced the heart at a cycle length of 300 ms. S₂ was applied with a point electrode approximately at the center of the imaging area. The current used for S₁ pacing was just above the threshold, whereas the current for the S₂ was 2 mA (about 20× diastolic threshold). The stimulus duration was 2 ms for S₁ and 10 ms for S₂ pulses. During each experiment, the S₁-S₂ interval was progressively shortened in 5–10 ms steps starting from 250 ms down to the ARP, when S₂ no longer produced a propagating wave. The slow-wave dynamics described below were observed in all ten hearts when S₂ was applied near the refractory tail of the S₁ response.

Results.—The results displayed in Figs. 1 and 2 depict the analysis for one typical recording using an S₁-S₂ interval of 180 ms and a 2 mA cathodal S₂. Figure 1 demonstrates the dynamics observed after application of S₂ close to the refractory period. The frames of the false color voltage movie in Fig. 1(a) show the response of the heart following S₂ termination. The movie starts at the end of S₂, which was applied when the preceding S₁ wave produced a gradient of repolarization in the vicinity of the S₂ electrode location. The S₁-induced planar wave had already propagated along the fiber direction from the lower right to the upper left of the image area, with the tail of the S₁ steadily propagating wave (SPW) disappearing in the upper-left corner of the 0 and 8 ms frames. As a result of S₂, two low-amplitude waves appear to propagate in opposite directions (arrows in the 16 ms frame). The wave moving left and upward dies out by 28 ms, while the wave propagating right and downward becomes a full amplitude response, which starts to propagate in all directions (last frame). A time lag of approximately 40 ms exists between the termination of S₂ and the appearance of the full amplitude response.

Figure 1(b) shows two damped waves (DW) forming following S₂ stimulation, which was applied to the refractory tail of the SPW from S₁, but only one DW causes a fully propagating wave front (S₂ SPW). More detailed spatiotemporal characteristics of the dynamics are illustrated in the time-space plot of Fig. 1(c), for which the data movie was sliced along the dashed α axis in panel (b). From this plot, one clearly sees that the left wave dies, while the wave on the right results in a full amplitude response.

Figures 2(a) and 2(b) show the DW dynamics in terms of signal upstroke (dVₘ/dt). Figure 2(a) elucidates the wave front dynamics following S₂ stimulation (S₁ activity has been removed from the plot). The two waves propagate in opposite directions (white and black arrows) from the dog-bone shaped polarization [14] located at the center of the (x, y) plane. One of the waves decays, and the other transforms into a wave similar to the S₁-induced, high-amplitude SPW. Figure 2(b) demonstrates dVₘ/dt amplitude for the two waves as a function of time along
the dashed $\alpha$ axis in (a). The decaying wave, $A-A'$, exhibits very small $dV_m/dt$ until it finally dies, while for the other wave, $B-B'$, $dV_m/dt$ eventually increases. The crest position of the waves reflects the dynamics of the propagation velocity: $A-A'$ has slower velocity ($16.1 \pm 0.5$ cm/s) which approaches zero around 25 ms after $S_2$ termination, while $B-B'$ exhibits a higher, fairly stable velocity for the interval shown ($21.4 \pm 0.4$ cm/s). The two types of DW dynamics are clearly seen in Fig. 2(c). For $A-A'$ the amplitude of the wave decreases with time until it disappears almost 25 ms after $S_2$ cessation (filled circles). $B-B'$ (open circles) initially has similar dynamics, but instead of disappearing, eventually gains amplitude to produce a full-scale SPW.

The distance of low-amplitude DW propagation and the time delay between $S_2$ application and the transition of the DW into an SPW depends on the $S_1$-$S_2$ interval. Figure 3 illustrates the DW propagation distance and time delay, as well as the $S_1$-$S_2$ interval. The data presented in this figure were acquired from a different heart than the data shown in Figs. 1 and 2. Two phases are distinguishable in this curve: as the $S_1$-$S_2$ interval is decreased toward refractoriness, the character of the curve changes dramatically, with the distance and delay rising dramatically below 180 ms. This sharp change is caused by the transition of the stimulation mechanism from make to break [12,14]. In addition, the $X-Z$ projection demonstrates approximately linear distance-delay dependence for $S_1$-$S_2$ intervals between 180 and 150 ms, indicating only a slight influence of the $S_1$-$S_2$ interval shortening on DW velocity ($18.2 \pm 2$ cm/s). The minimal $S_1$-$S_2$ interval for response was 135 ms.

Discussion.—The “$S_1$-$S_2$” stimulation protocol has been widely used to study the cardiac response to premature stimulation. The dynamics are of special interest when the $S_1$-$S_2$ interval is close to the refractory period. We show damped propagating waves that either die out or evolve into a full-scale SPW. These dynamics are unusual from the point of view of classical theory [8] and, in our opinion, have received too little attention in either the theoretical or experimental literature.

Previously, the appearance of DW, sometimes referred to as decaying propagation, has been shown near the vulnerable window boundaries in both FitzHugh-Nagumo and Beeler-Reuter models of excitable media [8,15,16]. In a stimulated nerve fiber using the 1D FitzHugh-Nagumo model under temperature gradient conditions, a slow-velocity, unstable wave and a fast-velocity, stable wave originating from the same point and traveling in opposite directions have also been demonstrated [17]. Recent findings show that multiple responses exist after a single stimulation near the boundary of a vulnerable window and are the result of propagation and conversion of DW into normal pulses [10]. Similar patterns were observed in a theoretical study of an inhomogeneous medium [18], where the patterns occurred near the boundary of an inhomogeneity. An interesting insight to the problem was recently suggested by Biktashev [19], who reformulated the classical Hodgkin-Huxley approach to excitable systems to include two equations describing the front of the pulse. He found that under proper conditions, propagation loses stability and becomes dissipative.

In experimental cardiac studies, responses different than all-or-none activity were initially reported by Kao and Hoffman [20]. They used isolated papillary muscles and Purkinje fibers to produce graded and decremental responses by varying the $S_2$ strength applied at a fixed time during repolarization or by varying the $S_1$-$S_2$ interval using a fixed $S_2$ strength. Additionally, the differences between the experimental study by Jalife and Moe, examining the role of passive tissue properties in conduction delay and impulse reflection [21], and the present work, describing an active response to stimulation in the repolarization phase, should be emphasized. They used an isotonic sucrose solution as an isolator to produce an unexcitable gap between the proximal and distal sections of a Purkinje strand preparation, such that the
transmission of the excitation between the two excitable segments is accomplished electrotonically by a passive response, in contrast to the active mechanism in our DW study.

It is important to note that, until now, DW dynamics have been experimentally studied only for chemical media in the Belousov-Zhabotinsky reaction [10]. Cardiac research has begun to address this subject in terms of a “graded response” [22]. Gotoh et al. [23] used a stimulation protocol similar to ours to investigate the induction of reentry and observed that a propagating lower-amplitude response could initiate normal gate the induction of reentry and examined that a propagation mechanism from make to break.

Our work along with theoretical findings show that either functional inhomogeneity, which exists in the refractory tail [10], or an anatomical inhomogeneity [18] can result in damped propagation and, hence, demand a substantial revision of the classical explanation of vulnerability of cardiac tissue. Damped propagation must be examined in the context of apparent focal activity after a defibrillation shock [5]. We also conclude that cardiac tissue can serve as an ideal excitable medium to refine the measurement and understanding of the physics of damped propagation of waves in nonlinear, active media, particularly for reentrant, vortexlike excitation.

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FIG. 3. The delay between $S_2$ and SPW appearance versus the distance between electrode position and location of SPW origination as a function of the $S_1$-$S_2$ interval. The threshold of 95 mV amplitude was used to locate the earliest conversion of DW to SPW. The delay was calculated as the period between $S_2$ onset and full amplitude response activation time $[(dV_m/dt)_{max}]$. Projections of the curve onto the three axes are in gray. The sharp change in the curve corresponds to the transition of the stimulation mechanism from make to break.

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6. I.R. Efimov et al., Circ. Res. 82, 918 (1998).