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Reprint of 'Model of unidirectional block formation leading to reentrant ventricular tachycardia in the infarct border zone of postinfarction canine hearts'

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ABSTRACT

Background: When the infarct border zone is stimulated prematurely, a unidirectional block line (UBL) can form and lead to double-loop (figure-of-eight) reentrant ventricular tachycardia (VT) with a central isthmus. The isthmus is composed of an entrance, center, and exit. It was hypothesized that for certain stimulus site locations and coupling intervals, the UBL would coincide with the isthmus entrance boundary, where infarct border zone thickness changes from thin-to-thick in the travel direction of the premature stimulus wavefront.

Method: A quantitative model was developed to describe how thin-to-thick changes in the border zone result in critically convex wavefront curvature leading to conduction block, which is dependent upon coupling interval. The model was tested in 12 retrospectively analyzed postinfarction canine experiments. Electrical activation was mapped for premature stimulation and for the first reentrant VT cycle. The relationship of functional conduction block forming during premature stimulation to functional block during reentrant VT was quantified.

Results: For an appropriately placed stimulus, in accord with model predictions: 1. The UBL and reentrant VT isthmus lateral boundaries overlapped (error: 4.8 ± 5.7 mm). 2. The UBL leading edge coincided with the distal isthmus where the center-entrance boundary would be expected to occur. 3. The mean coupling interval was 164.6 ± 11.0 ms during premature stimulation and 190.7 ± 20.4 ms during the first reentrant VT cycle, in accord with model calculations, which resulted in critically convex wavefront curvature and functional conduction block, respectively, at the location of the isthmus entrance boundary and at the lateral isthmus edges.

Discussion: Reentrant VT onset following premature stimulation can be explained by the presence of critically convex wavefront curvature and unidirectional block at the isthmus entrance boundary when the premature stimulation interval is sufficiently short. The double-loop reentrant circuit pattern is a consequence of wavefront bifurcation around this UBL followed by coalescence, and then impulse propagation through the isthmus. The wavefront is blocked from propagating laterally away from the isthmus by sharp increases in border zone thickness, which results in critically convex wavefront curvature at VT cycle lengths.

1. Introduction

In postinfarction hearts, a reentrant circuit causing ventricular tachycardia (VT) can form within the infarct border zone, which is the thin region of remaining viable myocardium located between the infarct and the epicardial surface of the heart [1]. In canine postinfarction, a complete reentrant circuit is often apparent when the epicardial surface of the epicardial border zone is mapped with a multielectrode array [2]. In humans, post myocardial infarction reentrant VT circuits are mostly endocardial; however, epicardial circuits have also been described [3]. It has been shown that the isthmus, or diastolic pathway, present when the pattern of reentrant VT is that of a double-loop, coincides with the region of thinnest border zone [4–6]. Based in part on this observation, it

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was previously demonstrated that changes in activation wavefront curvature along the border zone *Z*-axis (thickness axis) likely result in very slow conduction or functional conduction block at the lateral isthmus boundaries during VT [6]. The wavefront becomes critically convex when it propagates in the outward direction at those locations due to the sharp spatial gradient from thinner to thicker border zone (lesser to greater volume of tissue activating), with a resulting source/sink mismatch. Because the current available forward to the propagation direction is insufficient to activate the larger volume of tissue downstream, the wavefront slows and blocks. Yet, block due to convex wavefront curvature is also activation rate dependent [7], and the relationship of activation rate to *Z*-axis thickness changes has not yet been considered.

More recently, it was shown that if the spatial change from thin to thick at the lateral isthmus boundaries has variable steepness, it can result in very slow and variable conduction across the lateral boundaries [8]. The resulting discontinuities in the laterally propagating electrical activation wavefront are a source of electrogram fractionation. Fractionation is defined as the presence of multiple variable deflections in the electrogram arising from asynchronous electrical activity. This compares with the normal condition in which a single activation wavefront is present, the source of the biphasic electrogram shape which is recorded from healthy myocardium. Because the geometric configuration of the conducting medium in postinfarction hearts is intransigent over time intervals of hours or more, electrogram fractionation can often be observed at the same recording location during normal sinus rhythm as well as during reentrant VT, depending on the wavefront direction [8] and the coupling interval for electrical activation.

Although the functional block lines forming at the lateral isthmus boundaries, and electrogram fractionation arising from those locations, can be explained on the basis of critically convex wavefront curvature, the cause of unidirectional block line (UBL) formation during premature stimulation, which leads to onset of reentrant VT with a double-loop reentrant circuit pattern, has not been entirely elucidated. It is possible that large spatial changes in refractoriness are partially responsible for UBL formation leading to reentrant VT, as was shown in some prior canine experiments [9,10]. However in canine postinfarction, the effective refractory period at the isthmus location (inner pathway), versus immediately outside the isthmus (outer pathway), may also have little or no difference [11,12]. A low safety factor associated with longitudinal propagation in a non-uniformly anisotropic substrate can also contribute to conduction block [13]. Alternatively, herein it is shown how critically convex wavefront curvature, caused by changes in infarct border zone thickness, can result in unidirectional conduction block during premature excitation, and lead to the formation of a double-loop reentrant circuit with central isthmus at VT onset. The model can be helpful for understanding reentrant circuit formation because wavefront curvature changes have an anatomical, i.e., structural basis, and do not require the presence of sharp spatial changes in molecular-level properties at locations where functional block lines arise.

2. Method

2.1. Canine data acquisition

From an archived retrospective database of canine postinfarction, experiments were selected for analysis in which monomorphic ventricular tachycardia with a stable double-loop reentrant circuit was inducible by premature stimulation. Of 20 experiments that were analyzed, 12 met the inclusion criteria for the study. In all experiments, mongrel canines weighing 20–40 kg were anesthetized using sodium pentobarbital (intravenous, 30 mg/kg). The left anterior descending coronary artery (LAD) was then ligated near its base [1,2]. A transmural anteroseptal myocardial infarction resulted, with an epicardial rim of muscle having variable thickness, termed the infarct border zone. Canines were prepared for electrophysiological analysis 3–5 days following ligation of the LAD, which is the interval during which the postinfarction canine heart is most likely to be arrhythmogenic [1,2,4,5,14]. Bipolar electrodes sutured onto the left ventricle, near the LAD artery, at the base of the heart (BASE), the center region, and the left lateral edge (LAT), were used to induce reentrant VT via programmed electrical stimulation. A train of 10 S1 pulses with an interval of 250–300 ms between pulses was followed by a premature stimulus. The pace train was repeated, shortening the last stimulus interval by 5–10 ms on each subsequent train, until reentry was initiated or until block occurred at the stimulus site. During the normal sinus rhythm, premature stimulation, and during any monomorphic VT that was induced, electrograms were simultaneously recorded from the epicardial surface of the left ventricle, where the border zone usually forms in postinfarction canine hearts after LAD ligation, from 196 to 312 bipolar electrodes configured as a multielectrode array. These methods were previously described in detail [2]. An image of the 312 bipolar multielectrode array taken during its construction is shown in Fig. 1. The array consists of silver disks 1 mm in diameter arranged on a square grid and embedded in polyurethane. Each silver disk was formed by melting the end of a thin solid silver wire. The 624 silver wires (two for each of 312 bipolar pairs) were attached to the data acquisition system via a zero insertion force (ZIF) connector. At the data acquisition system, a differential amplifier was used to form bipolar signals from pairs of leads, which were bandpass filtered at 0.5–500 Hz, digitized at 1 to 2 kHz per channel, and streamed to computer disk. Further details of the electronic configuration of the acquisition system and data throughput are described elsewhere [15], as are details of electrical activation mapping [2,4,5,14]. The quantitative methods for registration of the multielectrode array with respect to anatomical landmarks have also been described [16]. The canine experiments were approved by the Institutional Review Board of Columbia University Medical Center, and the experimental paradigm was in accord with institutional guidelines.

2.2. Model of unidirectional block leading to reentrant VT

In prior work, details concerning the relationship between infarct border zone thickness, wavefront curvature, and conduction velocity were provided [6]. In this section it is shown how the wavefront curvature model can be used to predict where functional electrical conduction block will form in the infarct border zone. The summary equation for thickness-induced changes in wavefront curvature in the border zone is given by [6]:

$$\theta \approx \theta_0 - \frac{D}{c}\cdot\frac{\Delta T}{T} \tag{1}$$

where θ is the conduction velocity of the propagating wavefront, θ_0 is the conduction velocity of the propagating wavefront when the geometry of the conducting medium along a particular distance is unchanged, resulting in a rectilinear (straight) leading edge ($\sim$0.4 mm/ms in ventricular myocardium), T is the border zone thickness, c the space step and D the diffusion coefficient are constants, and ΔT is the spatial change in thickness per unit space step c, taken as the absolute maximum ΔT in the vector field about the measurement point. For the present study, values of $c=1$ mm or unity (cia07) and $D=0.1$ mm^2/ms [17] were used. Based on Eq. (1), therefore, when $\Delta T/T \rightarrow 4.0$ (unitless), $\theta \rightarrow 0$ mm/ms, i.e.,