Anisotropic Structural Complexities in the
Genesis of Reentrant Arrhythmias

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The paper by Brugada et al in this issue of Circulation adds importantly to mounting evidence that the anisotropic passive electrical properties of cardiac muscle play an important role in atrial and ventricular reentrant arrhythmias. The anisotropic properties involved are determined at a microscopic size scale (<200 μm) by the alignment of cardiac myocytes, their complex shapes, the distribution of their interconnections (gap junctions), and the geometry of interstitial (extracellular) space. These electrical properties are different in the atria and ventricles of normal adult hearts. For descriptive purposes, the different types of anisotropic properties have been characterized simply as "uniform" and "nonuniform" anisotropy. Normal ventricular muscle generally has uniform anisotropic properties due to the presence of frequent side-to-side electrical connections between cells and groups of cells; such bundles produce low amplitude smooth unipolar extracellular waveforms when propagation occurs across cells (transverse propagation). In many normal adult atrial bundles, however, the side-to-side connections are sparse, producing nonuniform anisotropic properties. During transverse conduction this results in small multiphasic (fragmented) extracellular waveforms due to asynchronous firing of adjacent cells or groups of cells. Additionally, the anisotropic properties of the same structure change from uniform to nonuniform during development following birth, with aging, and in the border zone of healed myocardial infarcts.

Functionally, the different anisotropic properties behave differently in response to the same intervention. For example, in human and canine atrial and ventricular bundles early premature stimuli and sodium channel-blocking drugs produce unidirectional longitudinal conduction disturbances in nonuniform anisotropic bundles but not in uniform anisotropic preparations. The surviving ventricular muscle of the outer ventricular wall in the rabbit ventricular experimental model used by Brugada et al has been shown to have normal action potentials and the anisotropic properties appear to be uniform in nature. A new feature provided by the results of Brugada et al, therefore, is the occurrence of unidirectional longitudinal conduction block of premature impulses in ventricular tissue with apparently uniform anisotropic properties. It is possible that the barrier they created (cut near the anterior descending coronary artery) plays a role. However, it seems more likely that the descriptive characterization of anisotropic electrical properties simply as uniform or nonuniform is insufficient. The considerable variation in the distribution of the gap junctions in different cardiac structures in normal and disease states likely produces a wide range of anisotropic electrical properties. Also, differences in the distribution of gap junctions of the same structure in different species remain to be clarified.

That there are anisotropic structural "mechanisms" (effects on the membrane depolarizing current) in conduction disturbances has become evident only during the past decade. These mechanisms are poorly understood at present and, in the absence of clinical data, there is a large gap between information obtained in the experimental laboratory and application of the data to patients. On the other hand, it now seems clear that anisotropic structural mechanisms can produce almost all of the conduction disturbances previously thought to be due solely to changes in the ionic properties of the sarcolemmal membrane. For example, "slow conduction" (<0.1 m/sec) was long considered to be due to depolarizations produced by the slow inward calcium current, which occurs in "depressed" tissue or in the atrio-ventricular node. It is now known that very slow conduction (<0.07 m/sec) occurs when normal action potentials propagate across fibers with sparse side-to-side electrical connections (nonuniform anisotropy) in human atrial bundles from geriatric patients and in the border zone of healed canine ventricular infarcts. Ursell et al showed that the intracellular action potentials have normal characteristics in the surviving epicardial tissue forming the border zone of healed infarcts. During transverse propagation in the
border zone, Dillon et al. found the effective conduction velocity to be so low that it appeared from isochrone maps that transverse conduction block had occurred. The common denominator of very slow transverse conduction in atrial bundles and in the border zone after infarction is the sparseness of side-to-side electrical connections. Morphologically both tissues demonstrate thin collagenous septa between groups of cells; the collagenous septa mark areas where there cannot be side-to-side connections between cells.

It seems appropriate to put the above considerations into perspective with regard to long-held ideas that mechanisms of cardiac conduction disturbances are limited to the sarcolemmal membrane ionic channels. Cardiac bundles have long been known to be anisotropic in nature due to the parallel alignment of the elongated cells; that is, the bundles exhibit properties with different values when measured along axes in different directions. Past ideas, however, have centered on the effects of the parallel alignment of cells on conduction. Because it was known that electrical transmission occurred from cell-to-cell through the low resistance of gap junctions, cardiac muscle was considered to behave electrically as a continuous medium; for example, similar to nerve axons. These ideas were consistent with the classical demonstration by Weidmann that changes in potential produced by injecting small currents into one cell extended over many cell lengths along small cardiac bundles. Also, the apparently smooth contour of unipolar waveforms of normal ventricular muscle appears consistent with a continuous medium. Thus, at the size scale of a few millimeters or greater the spread of excitation appears smooth in nature, consistent with the presence of an electrically continuous syncytium, even if the medium is anisotropic.

A decade ago, however, Spach et al. reported that the shape of the upstroke of the transmembrane action potential changed when the direction of propagation was altered with respect to the fiber orientation. $V_{\text{max}}$ is usually greater during slow conduction across fibers than during fast conduction along the fibers. This relationship is opposite to the classical one, such as in Purkinje strands, in which increases in $V_{\text{max}}$ are associated with increases in conduction velocity. The directional differences in $V_{\text{max}}$ were used to predict that the safety of propagation should be greater with slow transverse propagation than with fast longitudinal conduction when the sodium current is decreased. This was confirmed by the occurrence of longitudinal conduction block of premature impulses in atrial muscle bundles.

The above led to the hypothesis that at a microscopic level the distribution of the cellular connections produces recurrent discontinuities of axial resistance that, in turn, result in anisotropic propagation being discontinuous at a microscopic level. The term "discontinuous" seems appropriate at a cellular level because it provides a clear distinction from the well-known continuous conduction properties of nerve axons and the seemingly continuous nature of conduction at a larger size scale in many cardiac bundles. Specifically, discontinuous propagation is due to recurrent discontinuities of resistance related to the distribution of connections between myocytes and groups of myocytes. It does not imply that propagation actually stops at each discontinuity. Rather, it suggests that at recurrent sites where the resistance is higher than that of the cytoplasm, there are local delays in the propagation of the impulse while sufficient current continues to flow across each resistance discontinuity to depolarize the sarcolemmal membrane of the next cell or group of cells.

The significance of microscopic resistive discontinuities produced by the arrangement of the cellular connections is that wave fronts encounter a different distribution of discontinuities depending on the angle of propagation with respect to the fibers. In turn, this results in directional differences in electrical load on the sarcolemmal membrane and produces specific areas where conduction block can occur. For example, in the right atrium of dogs multiple disturbances of premature impulse conduction occur at localized sites due to anisotropic structural discontinuities and to inhomogeneities of repolarization (which are often related to anisotropic discontinuities in the atrium).

The multiple conduction abnormalities at localized sites interact to produce different types of atrial reentry circuits at a larger size scale (25 mm² to several cm²). Thus, as the events throughout a reentrant circuit are resolved at a smaller size scale, the picture becomes more complex than previously considered. The results of Brugada et al are noteworthy in this regard for noninfarcted ventricular muscle. A major implication of the localized events in both atrial and ventricular reentry circuits is that variations in the duration of the excitatory gap should be found from site to site, if the measurements are resolved at a sufficiently small size scale.

Although Brugada et al found conduction block of premature impulses to occur during longitudinal conduction almost every time, they did observe transverse conduction block to occur twice. These exceptions to unidirectional longitudinal block probably are important. Delgado et al. recently reported transverse conduction block of premature impulses in an "L-shaped" preparation of sheep ventricular epicardial muscle. Zuanetti et al. also recently reported conduction block in the transverse direction in epicardial tissue overlying canine infarcts.

Our recent measurements of normal excitation spread at sites 100 µm apart in canine ventricular epicardium indicate that the wave front is quite irregular or fragmented at a cellular level during transverse propagation. This contrasts to the smooth "plane-wave" appearance of isochrones derived from measurements at the larger macroscopic level. Also, the local direction of propagation was found to shift with respect to the myocytes as the
wave front progressed in the transverse direction in “normal” in vitro canine ventricular preparations (Spach, unpublished observations). At this point, it seems clear that more detailed information about propagation at a cellular level is needed. It may be an oversimplification to predict the angular dependence of conduction block without microscopic measurements of excitation speed and the arrangement of the connections between myocytes at specific sites. Janse et al22 have described the considerable difficulty of those correlations in nodal tissues, and these difficulties also exist in atrial and ventricular muscle. Structural analyses of the distribution of gap junctions localized by antibodies to connexin43 should provide an important method for such correlations.23-25

What are the clinical implications that anisotropic “mechanisms” may play an important role in reentrant arrhythmias? In the absence of clinical data one can only speculate. At first, clinical considerations of the increased complexity produced by anisotropy may seem too subtle or unduly cumbersome. On the contrary, the addition of anisotropic structural mechanisms2-4 to those of the leading circle concept26,27 adds remarkably to the ability to account for phenomenon that have defied reasonable explanation based solely on inhomogeneities of repolarization; for example, the occurrence of micro-reentry4 in areas less than 2 mm².

The major challenge presented by anisotropic mechanisms at present is the need to develop practical techniques that provide greater resolution of both temporal and spatial electrical events in patients, as well as in laboratory experiments. The results of Brugada et al in this issue of Circulation are especially noteworthy in this regard because they emphasize that the major events initiating and terminating the reentrant tachyarrhythmia occurred within small areas of the total reentrant circuit.

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