The Modulated Dispersion Hypothesis Confirmed in Humans

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Conventional teaching suggests that the initiation of arrhythmias requires an initiating “trigger” and a suitable “substrate.” Moreover, the hallmark of electro-anatomic substrates for reentrant arrhythmias is spatially heterogeneous structural or electrophysiological properties. The fundamental requirement of heterogeneous refractory properties is not a new concept and was recognized by the early pioneers of cardiac electrophysiology. Under these conditions, an appropriately timed triggering beat will fail to propagate into the most refractory zones, leading to unidirectional block and reentry. One common form of spatially inhomogeneous electric properties is often referred to as “dispersion of repolarization,” in which action potential duration (APD) between neighboring myocytes spanning the epicardial surface or across the transmural wall vary to form spatial gradients of repolarization. It is the differences in ion channel composition and density between myocytes that presumably underlie spatial dispersion of repolarization.

Although the “trigger” and “substrate” for arrhythmias are often considered independent phenomena, Laurita et al previously demonstrated that a premature trigger can interact with and actively modulate spatial dispersion of repolarization through a process referred to as “modulated dispersion.” According to modulated dispersion, progressive shortening of premature coupling interval will, in turn, progressively reduce dispersion of repolarization, but at very short coupling intervals dispersion of repolarization will again rise sharply. Importantly, the coupling interval–dependent modulation of repolarization gradients directly impacted vulnerability to ventricular arrhythmias, with the heart becoming relatively resistant to arrhythmia when repolarization homogenized (at intermediate coupling intervals). Subsequently, the heart became more susceptible to arrhythmias when repolarization gradients increased again with the introduction of premature beats at very short coupling intervals. Modulation of repolarization gradients directly influence susceptibility to arrhythmias because the development of conduction block requires the presence of critical gradients of repolarization, typically exceeding 10 ms/mm in ventricle and 4 ms/mm in atria. Therefore, through the process of modulated dispersion, it is evident that a premature trigger is not independent of, but rather actively modulates, arrhythmia substrates in a predictable and coupling interval–dependent manner.

The mechanism underlying modulated dispersion of repolarization is inhomogeneous restitution properties between myocytes that comprise all ventricular regions. As the premature coupling interval is progressively shortened, APD decreases according to a well-established relationship referred to as APD restitution. Because restitution kinetics differ between myocytes, the extent to which APD shortens in one myocyte in response to a prematurely stimulated beat will differ from the extent to which APD shortens in other myocytes. Specifically, myocytes with the longest APDs have the fastest time constants of restitution, such that in response to a premature stimulus there is greater APD shortening for the longer APD myocytes than the shorter APD myocytes. This heterogeneous restitution response between cells with long and short APDs reduces dispersion of repolarization in the wake of a premature beat. As the coupling interval is further shortened, myocytes initially exhibiting the longest APD can actually manifest the shortest APD, resulting in restoration of a repolarization gradient. However, now the gradient of APD dispersion is oriented in the opposite direction. Modulated dispersion refers to the coupling interval–dependent eradication of the repolarization gradient followed by reestablishment of the repolarization gradient, with corresponding modulation of susceptibility to conduction block and reentrant excitation.

In this issue of Circulation: Arrhythmia and Electrophysiology, Hanson et al provide compelling data which in many respects confirm that the modulated dispersion hypothesis is operative in the human heart. These authors used noncontact mapping with a left ventricular endocardial probe to calculate endocardial unipolar electrograms in patients (essentially with structurally normal hearts) undergoing electrophysiological testing. Calculated unipolar electrograms were used to derive activation recovery intervals (ARIs) from numerous simultaneous ventricular sites, as a surrogate for the measurement of APD. The authors found that the introduction of a single progressively premature S2 stimulus did indeed produce APD shortening which varied between ventricular sites, depending on the restitution properties of myocytes at those sites. Specifically, the authors demonstrate that sites with longest ARI shorten more in response to a premature stimulus than sites with the shortest ARI. The net result was that...
ARI dispersion is reduced after a premature stimulus, nicely illustrating modulated dispersion of repolarization hypothesis.

The authors acknowledge a few differences between their study and the modulated dispersion response observed in animal models. Firstly, they did not fully illustrate the biphasic nature of the modulated dispersion response because of understandable safety concerns associated with the introduction of very tightly coupled premature stimuli. Specifically, by restricting their protocol to a range of intermediate to long S1S2 coupling intervals, they were able to demonstrate that ARI gradients shortens with increasingly premature stimuli, but they did not observe the reversal and amplification of ARI gradients predicted to occur at very short coupling intervals. Secondly, they did not determine whether modulated dispersion in their patients actually modulated susceptibility to arrhythmias as one might predict. Obviously, there are safety reasons that preclude this assessment in humans. One might also expect, however, that in the normal heart, the dispersion gradients induced in this study were not of sufficient magnitude to induce conduction block, consistent with the observation that single and double extrastimuli rarely induce sustained arrhythmias in normal human hearts. However, in experimental models that simulated myocardial disease by introducing source-sink mismatches with structural discontinuities in myocardium, modulated dispersion actively influenced susceptibility to reentry induced by extrastimuli. Lastly, the authors show what appears to be uniform activation sequences. However, without maps of activation or ARI, the orientation and topology of repolarization gradients cannot be determined with certainty from the data provided.

Hanson et al also found that APD progressively shorten in the direction of propagation, leading to an inverse relationship between activation time and APD. From this observation, the authors conclude that APD follows activation sequence in general and, specifically, necessarily shortens in the direction of propagation. However, it is well established that in human and other mammalian ventricles, the pattern of APD between myocytes is, in fact, resistant to change irrespective of activation sequence. It is only after several hours or days of altering activation, when myocytes recover from the so-called long-lasting "memory effect," that APD begins to shorten in the direction of propagation. Therefore, the apparent dependence of APD on activation sequence reported in this article could possibly be explained by the fact that the only pacing protocol tested closely simulated the apex to base activation sequence present during normal Purkinje activation of the ventricle before these patients were paced. It would have been interesting, therefore, to evaluate pacing protocols from different sites of the left or right ventricle.

The observations of Hanson et al provide an important framework for future study. For example, it will be very interesting to determine the role of modulated dispersion in diseased myocardium and its modulation by antiarrhythmic drugs. It will also be interesting and relevant to ascertain how desynchronized cardiac activation and, conversely, resynchronization therapies influence these highly dynamic properties of repolarization. Such studies could greatly improve our understanding of the functional organization and synchronization of cardiac repolarization in response to triggers of arrhythmias.

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References

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