Repolarization Alternans
Toward a Unifying Theory of Reentrant Arrhythmia Induction

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The appearance of electrocardiographic T-wave alternans with elevated heart rate or metabolic insult has been observed for nearly a century.1 Macroscopic T-wave alternans is often noted as a harbinger of sudden arrhythmic death.2 Efforts to quantify the magnitude of more subtle repolarization alternans and relate these measurements to arrhythmia susceptibility have been pursued since the 1980s.3,4 Only in the last few years, however, have the mechanisms underlying repolarization alternans and their role in the genesis of arrhythmias been addressed.

Several investigators have described alternations in action potential duration and morphology coinciding with T-wave alternans in the surface ECG in a variety of proarrhythmic settings.5–7 The ionic basis for these beat-to-beat changes in action potential has only recently been explored. Shimizu and Antzelevitch8 found that under conditions mimicking congenital long-QT syndrome physiology in a ventricular wedge preparation, alternans of T-wave and action potential duration were elicited during rapid pacing and abolished by ryanodine and low extracellular calcium, implicating intracellular calcium cycling in the maintenance of T-wave alternans.

Pastore et al9 showed that alternations in action potential duration induced by rapid pacing are not uniform across the myocardium. Much of the ventricle exhibits sequential lengthening and shortening of the action potential, but fluctuations in some regions are 180 degrees out of phase with those in other regions, constituting a phenomenon known as discordant alternans. The resulting spatial gradients in transmembrane potential during the repolarization phase alternate in magnitude and direction from beat to beat, providing the basis for T-wave alternans in the surface ECG. Pastore et al9 additionally showed that discordant alternans can lead to sufficiently steep spatial repolarization gradients so as to produce unidirectional conduction block and functional reentry, resulting in ventricular fibrillation. Interestingly, Qu et al10 reproduced these findings in a simulated 2-dimensional sheet of cardiac tissue based on the Luo-Rudy11 model of the cardiac action potential with modified electrical restitution properties.

In this issue of Circulation Research, Pastore and Rosenbaum12 extend their previous work by examining the effects of induced repolarization alternans in the setting of a fixed structural barrier. In this elegant work, the authors used a Langendorff-perfused guinea pig heart preparation as before9 but added a 2×10-mm insulating structural barrier produced by a computer-driven laser. Electrical activity was assessed simultaneously at 128 ventricular sites using optical mapping techniques. The presence of the structural barrier led to a significant reduction in the critical heart rate at which discordant alternans appeared. It also served as an anchor for stable reentry, so that monomorphic ventricular tachycardia (VT) was induced more readily than ventricular fibrillation (VF). Importantly, neither VT nor VF occurred in this model unless discordant alternans was present.

These new findings suggest that a common mechanism may link the presence of discordant repolarization alternans to the initiation of diverse reentrant arrhythmias, depending on the anatomic nature of the substrate. This unifying hypothesis may explain what has been somewhat of a clinical enigma. In 1994, Rosenbaum et al13 reported a close concordance between inducibility of T-wave alternans with atrial pacing and inducibility of VT or VF with programmed stimulation in the electrophysiology laboratory. Similarly, Hohnloser et al14 showed that inducibility of T-wave alternans was predictive of subsequent arrhythmias detected by an implantable cardioverter defibrillator, 83% of which were VT, whereas VF constituted the remaining minority of cases. The association between T-wave alternans and vulnerability for VF or polymorphic VT was easy to understand. Abnormalities of repolarization are commonly associated with polymorphic arrhythmias or fibrillation, particularly in the setting of heart disease.15 But a mechanistic link between T-wave alternans and monomorphic VT was lacking until now.

Monomorphic VT is typically mediated by an anatomic ally fixed reentrant circuit.16 The arrhythmia is initiated by the development of unidirectional block on one side of the circuit, allowing propagation of the impulse on the other. Unidirectional block, in turn, has traditionally been attributed to conduction anisotropy, that is, directional differences in conduction velocity that lead to reduced safety factor for impulse transmission.17 Thus, monomorphic VT would seem to represent a consequence of altered activation rather than repolarization. However, as Pastore et al9 showed in their previous work, unidirectional block can occur as the result of discordant repolarization alternans. Therefore, it seems quite logical that the combination of an anatomic ally fixed structural barrier and discordant alternans should be sufficient to produce monomorphic VT. Their new findings12 are intriguing in that the presence of the structural barrier actually

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Circulation Research is available at http://www.circresaha.org

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promotes discordant alternans, thus additionally enhancing the likelihood of VT initiation.

Is discordant alternans necessary for initiation of reentry? In the model by Pastore and Rosenbaum, yes. But, as the authors point out, this may not be the case clinically. Spontaneous VT and VF are typically initiated by a single premature beat or a short-long-short interval sequence without the degree of antecedent heart-rate elevation required for elicitation of even microvolt-level T-wave alternans. As noted above, unidirectional block can result simply from anisotropic propagation. Furthermore, nonuniform recovery of excitability of any cause provides a substrate for unidirectional block and the initiation of reentry. In fact, the same authors point out, this may not be the case clinically.

It seems likely that discordant alternans is sufficient but not necessary for initiation of reentrant arrhythmias and that a structural barrier is necessary but not sufficient for the development of stable monomorphic reentry. The diseased ventricle may contain multiple effective structural barriers. Some of these barriers may promote discordant repolarization alternans, some may provide the substrate for stable reentry, and some may actually serve to preclude reentry by creating dead ends for impulse propagation. The barriers that enhance discordant alternans may or may not be the same ones that define the circuits for reentry, although the two are likely to coexist in the diseased ventricle. Elicited T-wave alternans, therefore, may be a marker for arrhythmia susceptibility without necessarily being causally linked.

The new findings by Pastore and Rosenbaum add a critical piece to the alternans puzzle. When combined with this group’s previous work in the field, a consistent and appealing story emerges. Under chronotropic or metabolic stress, the repolarization phase of the myocardial action potential develops an alternation in morphology and duration. With additional stress or in the presence of structural barriers, repolarization alternans becomes spatially discordant. Discordant alternans leads to sufficiently large repolarization gradients to produce unidirectional block and reentry. Without a structural barrier, reentry is functional and manifests as VF or polymorphic VT. In the setting of a structural barrier, reentry can become anatomically fixed, resulting in monomorphic VT.

The theory does not take into account some aspects of repolarization and arrhythmogenesis, such as the role of early afterdepolarizations in the initiation of torsade de pointes and similar polymorphic arrhythmias. However, it does provide a parsimonious explanation for a variety of electrophysiologic behaviors.

References

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_Circ Res._ 2000;87:1083-1084
doi: 10.1161/01.RES.87.12.1083

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/87/12/1083

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