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Editorial Comment

Twisting of the Points*

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The aggregation of the defining electrocardiographic features of the long QT syndromes occupied a decade of observations collected by various observers scattered around the world. The first description of a congenital form of the syndrome by Jervell and Lange-Nielsen (1) highlighted the association of strikingly prolonged QT intervals and abnormal TU wave forms with sudden death but did not pinpoint the basis for sudden death. Later, ventricular tachyarrhythmias were identified as the mechanisms for sudden death in the congenital forms of the syndromes (2,3). Acquired forms of the syndromes with similar association of prolonged QT intervals and ventricular tachyarrhythmias were identified (4). It was left to Dessertenne (5) to point out the distinctive undulating pattern of sequential QRS complexes and T waves during ventricular tachycardia and to imprint the enduring phrase, torsade de pointes, twisting of the points. The intriguing association of features aroused curiosity and a search for the mechanisms for each of the features and for their linkage.

The ionic bases for the prolongation of the QT intervals have been clarified to a major extent. Most agents and conditions that induce the acquired long QT syndromes reduce outward K^+ currents that mediate repolarization, most commonly the I_{Kr} current, which is activated and increases during the action potential. The genetic defects and the corresponding disorders of ionic movements that delay repolarization in the congenital long QT syndromes have been elucidated at a dazzling pace in recent years (6). Defects in the genes *KVLQT1* (7) and *HERG* (8), which express the sarcolemmal channels transmitting the K^+ currents I_{Ks} and I_{Kr}, respectively, express abnormal channels and diminished currents. Retardation of repolarization results. A defect in the gene *SCN5A* (9) encoding the Na^+ channel interferes with inactivation of the current and causes persistent flow (during repolarization) of depolarizing Na^+ current, which also retards repolarization (10). Protracted repolarization can lead to surges of transient depolarizing inward current during repolarization manifesting as early afterdepolarizations (EADs) and triggered firing (11). The ionic mechanisms for EADs are not fully clarified, but there is persuasive evidence that the Ca^{2+} current ($I_{Ca\text{-}L}$) and Na^+:Ca^{2+} exchanger current are involved, depending on the conditions (6).

Thus, the abnormalities of ionic currents responsible for the prolonged QT intervals are well understood; the trigger for the arrhythmia generation has been identified as EADs, and substantial progress has accrued toward clarification of the ionic currents underlying EADs. However, the mechanisms for the maintenance of the ventricular tachycardia and its distinctive undulating pattern have remained mainly speculative.

Early on, "focal" mechanisms were proposed for torsade de pointes (5,12). Specifically, it has been suggested that two widely separated foci, firing at slightly different varying rates and protected from capture, could produce the pattern by generating QRS complexes with continuously varying degrees of fusion of activation sequences. Originally, the specific electrophysiologic generators at the putative foci were not specified, but with the acceptance of EADs as trigger mechanisms when repolarization is prolonged, it is plausible to postulate that the hypothetic foci could be sites of EAD generation. Thus, the trigger mechanism and the sustaining mechanism for torsade de pointes could be the same—EADs.

In contrast, prolonged repolarization could imply heterogeneous repolarization and refractoriness, which in turn provide a milieu for reentry recognized at the beginning of the century. Reentry in a background of exaggerated heterogeneity of repolarization has been advocated forcefully as the mechanism for torsade de pointes (13). Enhanced dispersion of repolarization and refractoriness have been demonstrated in the long QT syndromes (14,15).

Recent revelations have greatly expanded our understanding of heterogeneous repolarization in the ventricles. Midmyocardial layers are composed of so-called M cells, which have more prolonged repolarization than the myocardial cells of subendocardial or subepicardial layers because those cells have relatively less I_{Kr} (16). More important, from the standpoint of the long QT syndromes, factors that prolong repolarization accent the physiologic heterogeneity of repolarization by preferentially prolonging repolarization in the M cell layers. Under such conditions, premature excitation of regions of myocardium with refractory periods of shorter duration would allow the formation of macroreentrant pathways encircling regions of myocardium with more prolonged repolarization and refractoriness (16). A more recent modification of the reentry hypothesis proposed that drifting spiral waves of reentry could produce the pattern of torsade de pointes (17).

The pattern of macroreentrant activation differs fundamentally from the pattern of activation from a single focus; detailed activation mapping should distinguish these patterns readily. In this issue of the Journal, Asano et al. (18) utilized avant garde technology to map activation during torsade de pointes occurring in Langendorff-perfused rabbit hearts under conditions known to produce long QT syndromes in humans—bradycardia and treatment with the K^+ channel blocking agents quinidine and E4031. Intracellular potentials were monitored by means of optical recordings of light emission

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Abbreviations and Acronyms

EADs = early afterdepolarizations
I_{Kr} = rapidly activating delayed rectifier K^+ current
I_{Ks} = slowly activating delayed rectifier K^+ current

from a voltage-sensitive indicator at 400 sites over the ventricles with a resolution of ~0.15 mm. For comparison with the activation patterns during torsade de pointes, the investigators induced macroreentrant activation by rapid stimulation in untreated hearts without prolonged QT intervals. The results of the mapping indicate that torsade de pointes is sustained primarily by repetitive multifocal excitation with a lesser role for migratory spiral waves of reentrant activation. A caution in the interpretation of their findings is that their method does not allow three-dimensional mapping. Inferences concerning intramural activation must be made from activation maps of the endocardial and epicardial surfaces. However, the patterns reflected on those surfaces were convincingly different from patterns produced by known macroreentrant excitation in their model and persuasively suggested spread of activation in centrifugal concentric waves from focal sites of excitation. Monophasic action potential recordings from the endocardium verified the appearance of EADs in the hearts with torsade de pointes, indicating that the electrophysiologic mechanism for focal excitation was EADs.

A recently published study by El-Sherif et al. (19) also implicated EADs and macroreentry as major mechanisms for torsade de pointes, but the mechanism for sustaining torsade de pointes was almost exclusively macroreentry in their studies, and the role of EADs was largely confined to the initiation of the first beat of the tachycardia, which then initiated reentry. The model in those studies was the intact dog in which torsade de pointes was induced by anthopleurin-A, a neurotoxin that prolongs repolarization by interfering with Na^+ channel inactivation. This model has a counterpart in one of the genotypes of the congenital long QT syndromes (9). The differences in the two studies in the relative roles of the two major mechanisms may derive from differences in the models. M cell layers with prolonged repolarization are prominent in the dog; it is unclear that they have similar relative prominence in the rabbit. A greater prominence of M cells would favor greater heterogeneity of repolarization and macroreentrant activation. The findings in humans that torsade de pointes is not readily inducible by programmed stimulation fit better with the observations and conclusions of Asano et al. (18) than those of El-Sherif et al. (19). Were heterogeneity of repolarization an overriding characteristic of human hearts with prolonged QT syndrome, macroreentrant ventricular tachyarrhythmias should be easily inducible by premature stimulation of the ventricles. It is possible that the endocardial sites are not the most propitious sites for inducing macroreentrant excitation compared with epicardial sites, which have the most brief repolarization and refractoriness. However, the studies of El-Sherif et al. demonstrated that the initiating beats in their model originated near the endocardium, presumably from EADs generated in the Purkinje system. Consequently, endocardial excitation by other means should be equally effective in inducing macroreentrant excitation. Such has not been the case in humans.

Clarification of the mechanisms for initiating and sustaining torsade de pointes is more than an intellectual exercise for electrophysiologists. Continued enhancement of our understanding of the mechanisms for initiating and sustaining torsade de pointes is vital for devising means to avert and suppress this life-threatening tachycardia. In the case of the congenital long QT syndromes, or for acute treatment of the acquired long QT syndromes, therapy can be targeted at the prolonged QT interval. Normalization of repolarization would eliminate the tachyarrhythmia. In the long QT syndromes induced by antiarrhythmic drugs with class III action, it would be desirable to retain the prolongation of repolarization and refractoriness, a potent antiarrhythmic action, but to eliminate torsade de pointes. To achieve this end, the ionic currents underlying EADs must first be elucidated so that countermeasures can be contrived. Also, the role of heterogeneity of repolarization in humans must be clarified and means devised to minimize heterogeneity while prolonging repolarization. The achievement of these goals would allow full realization of the powerful antireentry action of prolongation of repolarization and rejuvenate the pharmacotherapy of arrhythmias.

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