New Insights into the Arrhythmogenic Substrate of the Long QT Syndrome

Running title: Moss; Long QT Syndrome

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A lot has transpired in our understanding of the inherited Long QT syndrome (LQTS) since the first description of a family with prolonged QT interval, deafness, and sudden death by Jervell and Lange-Nielsen in 1957\(^1\) and a similar family reported in 1958 by Levine, et al.\(^2\) Several children with LQTS and sudden death without deafness were reported by Romano, et al. in 1963\(^3\) and Ward in 1964.\(^4\) Numerous LQTS case reports were published during the next several years, and the first specific therapy for this disorder involving antiadrenergic left cervico-thoracic sympathetic ganglionectomy was reported in 1971,\(^5\) with beta-blocker therapy introduced a few years thereafter. The Rochester-based International LQTS Registry was initiated in 1979. Using some patients from the LQTS Registry, Keating, et al., reported linkage of LQTS to the Harvey ras-1 locus on chromosome 11 in 1991,\(^6\) and within a few years Keating and associates identified the genes for LQT1, 2, and 3 that ushered in the extensive LQTS genotype-phenotype studies during the last 20 years. Various clinical studies identified the duration of the QT interval corrected for heart rate (QTc) as a major risk factor for syncope, aborted cardiac arrest, and sudden death,\(^7\)-\(^10\) and several recent studies highlighted the cardiac risk associated with mutation type and location on the cardiac ion channel membranes.\(^11,12\) Various electrophysiologic studies have suggested the role of action potential prolongation, early after depolarizations, and spatial dispersion of repolarization as the substrate for ventricular tachyarrhythmias and torsade de pointes in this disorder.

In the current issue of *Circulation*, Vijayakumar, et al., from Yoram Rudy’s Cardiac Bioelectricity and Arrhythmia Center at Washington University in St. Louis, together with an international group of investigators used noninvasive ECG imaging to map the cardiac electrophysiologic substrate in order to evaluate the role of regional heterogeneities of repolarization in promoting arrhythmogenesis in 25 LQTS subjects, with 7 normal subjects as
controls. The non-invasive ECG imaging technique utilized to map the electrophysiologic substrate is quite involved and was developed by the Rudy group in canine experiments in 2001, and applied to the human heart in 2006. In brief, the approach permits mapping of the epicardium of the ventricular myocardium to identify regions with delayed repolarization and steep spatial dispersion of repolarization. The technique records 256 body-surface ECGs together with a thoracic CT scan gated to the R-R interval to noninvasively construct epicardial maps of recovery times, activation-recovery intervals (ARI – a surrogate for local action potential duration), and repolarization dispersion. All these intervals were prolonged in LQTS patients relative to controls, and ARI prolongation was spatially heterogeneous with repolarization gradients much steeper than in controls and in symptomatic than asymptomatic LQTS patients.

In this study, the authors showed that LQTS patients display regions with steep repolarization dispersion in the epicardial layer of the ventricular myocardium caused by localized action potential duration heterogeneities, a substrate not detectable by the surface ECG. Of interest, the steepness of the repolarization gradients did not correlate with the patients QTc determined from the standard 12-lead ECG. This new, patient-specific information is an important non-invasive marker of the disordered electrophysiology in intact hearts of LQTS patients that cannot be determined by any current non-invasive techniques.

We know from basic science studies that transmural repolarization heterogeneity can be recorded under certain conditions in invasive animal studies, with cells in the mid-myocardium (M cells) appearing to have a longer action potential duration. To date, presence of M cells have not been detected in the intact human heart in patients with or without heart disease. Thus, the current findings by Vijayakumar, et al., take on added meaning as it is the first study to document significant regional heterogeneities of the epicardium of patients with LQTS, an
inherited prolonged repolarization disorder. This study provides new insights into the
arrhythmogenic substrate for LQTS involving the epicardial cell layer of the intact heart. The
regional heterogeneities are thus two dimensional and multidimensional transmural gradients
cannot be measured by this ECG imaging technique.

One unexpected finding was the poor correlation between the steepness of the
repolarization gradients with the duration of the QTc, the latter being the dominant clinical risk
factor in the LQT1, 2, and 3 genotypes.7-10 I suspect the poor correlation may be a power issue
due the small number of patients studied by the ECG imaging technique. Additional
investigations are needed to clarify this issue.

This ECG imaging technique has provided new insights into the arrhythmogenic
substrate of LQTS, and it should have applicability in other genetic and acquired cardiac
arrhythmogenic conditions. The present methodology is complex, requires considerable
sophistication in its use, and is unlikely to be utilized clinically on a day-to-day basis at this time
or in the near future. However, we can expect improvement and simplification of the ECG
imaging technique with time, and when that occurs, we can anticipate substantial new advances
in our understanding and prevention of potentially malignant ventricular tachyarrhythmias in a
spectrum of cardiac disorders.

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