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, and a similar family reported in 1958 by Levine and Woodworth. Several children with LQTS and sudden death without deafness were reported by Romano et al in 1963 and Ward in 1964. Numerous LQTS case reports were published during the next several years, and the first specific therapy for this disorder involving antiadrenergic left cervicothoracic sympathetic ganglionectomy was reported in 1971, with β-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, and within a few years Keating and associates identified the genes for LQT1, 2, and 3, which 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, and several recent studies highlighted the cardiac risk associated with mutation type and location on the cardiac ion channel membranes.

Various electrophysiological 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 electrophysiological substrate to evaluate the role of regional heterogeneities of repolarization in promoting arrhythmogenesis in 25 LQTS subjects, with 7 normal subjects as controls. The noninvasive ECG imaging technique used to map the electrophysiological 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 (a surrogate for local action potential duration), and repolarization dispersion. All these intervals were prolonged in LQTS patients relative to controls, and activation–recovery interval 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 noninvasive marker of the disordered electrophysiology in intact hearts of LQTS patients that cannot be determined by any current noninvasive 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 midmyocardium (M cells) appearing to have a longer action potential duration (QTc) than in controls and in symptomatic than asymptomatic LQTS patients. The regional heterogeneities are thus 2-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. I suspect the poor correlation may be a power issue resulting from 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 used 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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References

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