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Congenital Long QT Syndrome and Concomitant Early Repolarization Pattern: A Benign Association or An ICD-Worthy One?

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The seminal studies performed by Antzelevitch and colleagues have provided the fundamental basis for the current understanding of early repolarization/J wave syndromes [1–6]. The J wave is thought to reflect a transmural repolarization gradient resulting from early outward current, and dictated by a higher prominence of I_{to} in epicardial tissue compared to endocardium [3, 5]. Early Repolarization (ER) has been defined as an elevated J point, terminal slurring of the QRS, and possible ST segment elevation [1, 2, 7]. The substrate of ER involves altered potassium, calcium, and sodium channels resulting in faster repolarization [2, 3, 8]. The resultant dispersion of repolarization creates the potential for arrhythmogenesis via phase 2 re-entrant short-coupled extra-systoles [3, 6].

The new non-invasive marker of “badness” seems to be ER, with the latest target being the congenital long QT syndrome (LQTS) [9]. ER has been declared benign in studies involving young and healthy males, blacks, athletes, and on the contrary, malignant when found to be associated with sudden cardiac death and/or electrical storm [4, 6–8]. Two studies in particular have been pivotal in highlighting the arrhythmogenic potential associated with ER and its potential for risk stratification [7, 10]. Continued research has raised concerns regarding what constitutes a “high risk” individual with ER, as the lines between benign and malignant repolarization remain blurred [1, 8, 11].

Further complicating the ability for use in clinical prediction is that the signature ER pattern is mediated by multiple factors. ECG changes vary with heart rate, beta-adrenergic

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stimulation, autonomic tone, drugs, and hormones, all of which can alter the presence and/or pattern of ER [6, 12]. The dynamic presence of ER may lead to differences in accurate diagnosis, difficulty in assessing risk [11], and complicate clinical judgement, especially in those already at risk with LQTS.

In this issue of *Heart Rhythm*, Laksman and colleagues report the presence of ER in the inferior and/or lateral leads as a strong, independent predictor for increased syncope, polymorphic ventricular tachycardia, or resuscitated cardiac arrest in a cohort of patients with the two most common genetic subtypes of LQTS [9]. The impetus of the study was to determine the prevalence and utility of ER as a prognostic tool for LQT1 and LQT2. The authors speculated that the concomitant presence of ER might explain some of LQTS' variable expressivity. The authors found a relatively large percentage (44%) of ER (1 mm J point elevation) in their cohort, and found 27% of these patients were symptomatic with primarily LQTS-triggered syncope. An odds ratio of 5.97 was found in association of symptoms with "major" ER (2 mm J point elevation). This association persisted in a multivariate model which included univariate predictors such as QTc >500 msec (OR: 4.50), and female sex (OR: 5.21).

Should the presence of ER serve as a tie-breaker for the intensification of a patient's LQTS-directed treatment program with an implantable defibrillator (ICD)? Already the reflex from LQTS to ICD is fast in some areas of the world and before adding ER to our LQTS patient's prognostic scorecard, caution is well advised. Despite the strong association after multivariate analysis between "major" ER and symptoms in this LQTS cohort, some issues regarding the general applicability of these findings before invocation into the clinical realm remain.

First, the large number of patients with ER, especially those with "major" ER creates an initial pause for reflection. The extremely high prevalence found in this cohort begs the question of why this association has not become more readily apparent to clinicians involved in the care of patients with LQTS. Perhaps these findings merely have been overlooked or not examined systematically and therefore the abundance stemming from this study is reflective of increased scrutiny and rigorous analysis. Alternatively, another potential explanation would be an association bias, whereby LQTS patients are more likely to be symptomatic regardless of ER findings, and a high prevalence in this cohort is merely coincidental. Furthermore, the intermittent ER findings also complicate the use of this marker for risk prediction and may reflect discrepancies amongst reports of prevalence. For example, even in the "major" ER subgroup, a large amount of patients (42%) had at least one ECG without a J point elevation reaching a definition of ER.

Second, the findings of equivalency of "severe" ER regardless of whether patients under comparison had LQTS or were genotype-negative relatives creates concern about the "malignancy" of ER and its role in risk stratification. Because of the large prevalence in this cohort, the authors generated a comparison group to assess the number of ECGs and the likelihood of detecting ER. A curious finding was revealed, as the prevalence of "major" ER was similar in both LQTS and control groups. It remains unclear why ER, which is supposed to serve as a predictor for symptoms, would be seen at the same frequency in genotype

positive and negative patients. These findings put into context the inconsistency of this risk marker in LQTS.

Finally, the premise of using “major” ER as a predictive risk marker is strongly dependent on its detectability and/or persistence, and correlation to symptoms. These tenets are challenged in this study, especially with regards to the “spectrum” of significant ER. If “major” ER is indeed a marker for worse outcomes, it would be expected that a gradation of ER should follow along with a correlated incidence of symptoms. Contradictory to this expected finding, “no” ER was correlated with 24% of patients having symptoms versus 13% with “minor ER”. As “major” ER was correlated to 58% of patients having symptoms, it is unclear why a difference of 1mm in J point elevation would be associated with fewer symptomatic patients compared to those with “no” ER. Moreover, the absolute number and percentage of patients across syncope, polymorphic VT, SCD, and appropriate shocks were seen more commonly in the “no” ER group compared to the “minor” ER group. This should raise caution in interpretation of these findings, and puts strain on acceptance of any proposed mechanism, or even causality.

Further studies to decipher what ER means specifically in LQTS are needed to clarify any remaining doubt before discussion for clinical implications can begin. It is prudent to take into account the small numbers when assessing the applicability of these findings, especially in the setting of such high prevalence. This is appreciated on inspection of the extremely small difference of patients meeting the “major” ER criteria and correlation to symptoms; the symptomatic group had 11 patients with “major” ER (out of 30) versus the asymptomatic group with 8 (out of 83). Therefore, although the high percentage of ER in this cohort is intriguing, its clinical relevance requires further investigation. In addition, issues raised such as ER being a more common finding in this study because the ECGs were more closely scrutinized or an increased number of ECGs were performed thereby increasing the likelihood of identifying “major” ER will need to be tested.

Therefore, it must be cautioned that before LQTS joins a growing list of ER-modifiable conditions, additional testing and confirmation studies must be undertaken. A systematic assessment of ER involving other cohorts of LQTS is needed to validate or refute this translational discovery. Until then, please resist the temptation to consider the following formula: LQTS+ER=ICD.

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