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Novel ECG markers for ventricular repolarization: Is the QT interval obsolete?

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The congenital long QT syndromes (LQTS) are a group of rare genetic disorders caused by mutations in genes that encode for cardiac ion channels; causing prolongation of ventricular action potential (APD), delayed repolarization and carry a high risk for the life-threatening polymorphic ventricular tachycardia, Torsades de Pointes (TdP).¹ Congenital LQTS may result from mutations that disrupt any number of ion currents, including I_{Ks} , I_{Kr} , and I_{Na} . In contrast, the mechanism by which drugs cause acquired LQTS is almost always block of the rapid component of the delayed rectifier potassium current, I_{Kr} . This $KCNH2$ channel is blocked by drugs with diverse structures encompassing many different drug classes, including antiarrhythmics, antipsychotics, antibiotics and antihistamines and can exhibit a phenotype similar to carriers of mutations in *KCNH2* (LQTS2).^{2,3} The Food and Drug Administration (FDA) in the “critical path initiative” report and later in “thorough QT/QTc studies (TQT)”, laid emphasis on the need to develop new methods of assessing QT-prolonging effect of new drugs.⁴ In recent years more than 50 prescriptions drugs have been identified that prolong QT interval and of these, more than 30 have been associated with TdP.⁵ As the QT interval is a surrogate marker of I_{Kr} -block, and the development of TdP is inevitably accompanied by QT interval prolongation, great attention has been focused on this marker. However, the QT interval characterizes only the total duration of repolarization, ignores any abnormalities of repolarization sequence and requires normalization for the patient’s heart rate due to inherent confounding phenomenon such as QT lag and hysteresis.^{6,7}

In recent years due to the availability of digital electrocardiograms (ECGs), T-wave morphology has gained importance both as a surrogate and as a predictor of adverse cardiac events in patients with congenital and acquired LQTS.⁸ Individuals with heterozygous mutations in the *KCNQ1* gene (LQTS1) exhibit a normal to generous amplitude of the T wave and a broad-based T wave pattern without a distinct T wave onset,⁹ whereas individuals with mutations in *KCNH2* (LQTS2) exhibit low amplitude T waves with a notched, double-hump and a distinct second protuberance above the apex of the T wave.¹⁰ Further, T wave heterogeneity is seen in individuals with LQTS3 (SCN5A mutations) and LQT7 (KCNJ2 mutations).¹¹ With the advent of the so-called principal component analysis (PCA) based on algebraic decomposition of multilead ECG signals, vectorcardiographic T-wave loop has been shown to be an important predictor of adverse cardiac events in patients with LQTS,¹² acute myocardial infarction,¹³ and in the general population.¹⁴

In this issue of *Heart Rhythm*, Couderc et al.¹⁶ asked the important question whether certain cardiac ventricular repolarization parameters, as quantified by ECG and used to generate eigenleads by applying PCA, could predict the acquired and congenital forms of LQTS and

if these abnormalities are association with adverse cardiac events in patients with *KCNH2* mutations. These parameters were first developed in a learning cohort and then validated in separate validation cohort. The study population composed of 411 healthy individuals exposed to moxifloxacin (I_{Kr} -blocker) in a cross-over design from seven TQT studies with a set of 4,784 digital ECGs available for analyses. A second set of ECG data composed of 1,674 paper ECGs from 622 subjects with genetically tested *KCNH2* mutations (321 non-carriers and 301 carriers). After digitization and quality control, 150 digital ECGs from non-carrier and 143 digital ECGs from LQTS2 mutation carriers were included in the final analysis. Quantification of cardiac ventricular repolarization included: QT apex (QT_a), T_{peak} to T_{end} (T_pT_e), the amplitude of the T wave (T_{amp}), and the left and right slopes of the T wave (α_L , α_R). PCA was used to generate early and late repolarization durations (ERD30%, ERD50%, LRD30% and LRD50%) by eigenleads (ev1 and ev2) to analyze the T loop by quantifying T roundness. In LQTS2 carriers, cardiac events were categorized as cardiac arrest, syncope, and sudden cardiac death.

QTc prolongation was seen in the healthy subset of patients after moxifloxacin administration as compared to placebo and in LQTS2 carriers compared to non-carrier family members. All scalar parameters, determined by lead II and vectorial parameters (lead ev1), were significantly different between LQTS2 mutation carriers and non-carriers. In a multivariate moxifloxacin prediction model, none of the scalar parameters contributed significantly and only ERD30% from the vectorial parameters contributed a 12% increased probability of being on moxifloxacin. In the LQTS2 prediction model, the left tangent of the T wave (α_L) corresponded to ~ 60% increased probability of carrying a *KCNH2* mutation for each 1.5 $\mu V/ms$ decrease in slope measured by either scalar or vectorial method. This model held true even when QTc was dichotomized to <500msec and <470msec. The same model dropped slightly in its power to predict LQTS2 mutation carriers with QTc <440 msec but remained significant. In Cox regression model for cardiac events, QTc duration and T wave roundness were associated with significant hazard ratios (HR). Even after adjusting for beta-blockers, 10% increased T wave roundness was associated with 15% increased probability of cardiac events in LQTS2 patients.

The authors have presented commendable data supporting their hypothesis that I_{Kr} impairment is associated with morphologic T wave changes that are complementary to QTc prolongation. However, before implementing such an approach, a number of issues might warrant further consideration. Are the presented prediction models generalizable to other subtypes of LQTS and across different ranges of I_{Kr} -related abnormalities? In the moxifloxacin multivariate prediction model, ERD30% conferred a 12% increased probability of being on moxifloxacin compared to 17% increased probability for every 1 msec increase in QTc. As the authors point out, ERD30% could not discriminate LQTS2 patients with and without cardiac events, which in part is explained by the region of repolarization covered by ERD30% being close to the T wave apex. In patients with LQTS, there is considerable T wave heterogeneity, which likely spreads to regions outside those covered by ERD30%. Here, assessing T-wave loop becomes more relevant and informative.^{12,13} In recent years T roundness has been used to quantify repolarization heterogeneity and several studies have shown it to be a reliably predictor of adverse cardiac events in multiple cohorts with distinct phenotypes.^{13,15} The authors were able to confirm this association strengthening the argument for assessing T wave loop dispersion in patients suspected of the LQTS especially those with near-normal QTc intervals. The incorporation of these additional parameters into future ECG software will also require considerable testing and real time validation.

In summary, Couderc et al.¹⁶ identified several novel parameters of T wave morphology in subjects exposed to an I_{Kr} -blocker and patients with *KCNH2* mutations. However, only T-

roundness complemented QTc in predicting cardiac events. Although this study suggests that the phenotypic expression of *KCNH2* mutations and I_{Kr} -blocking drugs on the surface ECG appears to be specific, whether T-wave roundness can be used clinically to risk stratify individuals or guide therapy remains to be determined.

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