HHS Public Access

Author manuscript

JACC Cardiovasc Imaging. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

JACC Cardiovasc Imaging. 2015 May ; 8(5): 511–513. doi:10.1016/j.jcmg.2015.03.001.

Strain Echocardiography and LQTS Subtypes — Mechanical Alterations in an Electrical Disorder

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Keywords

long QT syndrome; strain; echocardiography; LQTS1; LQTS2; diastolic dysfunction; arrhythmia; risk

Long QT syndrome (LQTS) is a heterogeneous disorder of prolonged repolarization that increases the risk for life-threatening arrhythmias. The diagnosis, based on a scoring system of clinical and electrocardiographic parameters is aided by genetic testing that allows classification into subtypes centered on mutations in genes coding for ion channel subunits or associated proteins (1). At least 15 different genes are implicated in LQTS, but the common subtypes are due to mutations in 3 genes coding for pore-forming subunits of 2 potassium (KCNQ1 and KCNH2 coding for I_{Ks} and I_{Kr}, respectively) and a sodium (SCN5a for Nav1.5) channel giving rise to what is known as LQTS1, LQTS2 and LQTS3, respectively. Despite advances in genotype characterization, it is difficult to predict the clinical presentation even within the same family, as members carrying the same mutation may present differently, from asymptomatic to more malignant course with recurrent syncope or cardiac arrest (1). Genotype-phenotype studies have correlated functional effects of gene mutations on ECG parameters, clinical presentation, triggers for arrhythmogenesis and responsiveness to therapy (2). Although spatial and temporal differences in repolarization due to individual ion channel defects and its heterogeneous distribution within the myocardium have been described (2), its impact on cardiac electrical and mechanical coupling has not been fully explored (3-6).

In this issue of the *Journal*, Leren and colleagues (7) present their findings on the use of conventional and strain echocardiography in 192 genotyped LQTS patients (139 with LQTS1, and 53 with LQTS2) compared to 60 age- and gender-matched healthy controls to

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Conflicts of Interest: The authors have no conflicts of interest to report.

identify abnormal myocardial mechanical parameters as a marker of arrhythmogenic risk. Not surprisingly, left ventricular (LV) ejection fraction was normal. In LQTS patients, there were subtle differences in diastolic function with mildly reduced e' (but within normal range), prolonged isovolumic relaxation time and an enlarged left atrium compared to healthy controls. All parameters were within the normal range on strain echocardiography, yet a statistically significant reduction in global longitudinal strain (GLS) was present in LQTS patients versus healthy controls (−22.1±2.1% vs -23.0±2.0%). In addition, prolonged contraction duration and more dispersed contractions were present in LQTS patients. Electro-mechanical time (EMT) defined by the difference between the QT interval and the Q-wave to aortic valve closure duration was also abnormal. LQTS2, especially symptomatic patients exhibited greater alterations than the LQTS1 or asymptomatic subjects. When adjusted for age and gender, these differences were still statistically significant. The magnitude of contraction duration, mechanical dispersion and EMT increased with increase in QTc interval, suggesting a direct relationship with QT prolongation, particularly in 9 patients with double-mutations or history of syncope or aborted sudden death. The authors therefore suggest that these parameters could be used as markers of high risk in LQTS patients.

These findings add to the body of observational literature in this field (3-6), seeking to correlate electrical alterations in LQTS patients with echocardiography-assessed mechanical abnormalities in ventricular function. Altered ventricular function initially was reported in patients with LQTS using M-mode echocardiography (3) demonstrating characteristic alterations in contractility with a rapid early contraction phase followed by an extended phase of LV wall thickening before relaxations, with more prominent changes in those with symptoms. Similar findings have also been reported using tissue Doppler imaging techniques (5). The underlying mechanism for these mechanical changes remains poorly defined, but intracellular calcium is suggested to play a role as calcium channel blockers can normalize some of the mechanical abnormalities (3,4). Strain imaging is a newer technique which characterizes global and regional ventricular function and offers outstanding temporal resolution. Strain analysis has been used by the authors in their previous studies that included LQTS patients also reported in the current study to describe regional differences in contraction duration and transmural mechanical dispersion in symptomatic LQTS mutation carriers, thus proposing that mechanical dispersion represented a marker for increased arrhythmogenesis (5,6). The current study extends these findings, to gentyped subgroups, with changes observed predominantly in LQTS2 than LQTS1 patients. These are interesting observations that will require additional studies to dissect out a mechanistic basis for selective impact of mutation in I_{Kr} on systolic and diastolic parameters when compared to I_{Ks}.

The strength of the study includes high intraobserver and interobserver reliability for GLS for a notoriously observer-dependent technique. The authors were careful to exclude patients with hypertension and diabetes mellitus, as they have been shown to independently correlate with strain parameters. However, what is not clear is the clinical significance of the minor changes in GLS (<1% between LQTS and healthy control) that is within the broad range (−15.9% to −22.1%) of strain values reported in normal subjects (8). The relevance of the negative EMT as a better marker of arrhythmogenesis than QT prolongation also needs to be

validated prospectively, as EMT changes were shown to be due to QT prolongation (9), with a fixed Q-aortic valve closure time not influenced by repolarization duration.

In addition, the connection between contractile strain and loss of function potassium channel mutations that results in LQTS1 and LQTS2 is still unclear. The reported findings that overall GLS is reduced in patients with I_{Kr} mutation are interesting in light of previous work demonstrating a positive inotropic effect of potassium channel inhibition (10). The mechanical abnormalities could be related to abnormal cellular repolarization that sustain action potential (AP) plateau and allow increased intracellular calcium through the L-type calcium channel or the sodium calcium exchanger facilitating secondary depolarization that may prolong mechanical contraction in a heterogeneous manner within myocardial layers (3,4,10,11). Although this hypothesis is attractive, experimental data on strain and its dispersion is limited. The possible explanation for mechanical effect of acute AP prolongation in rat ventricular cardiomyocytes was provided by Bouchard et al. (11), demonstrating a positive inotropic effect of AP prolongation with increase in the magnitude and duration of cell shortening, intracellular calcium transients, sarcoplasmic reticulum calcium loading and release with a delay in calcium extrusion during the slower repolarization. These results indicate a nonspecific effect of AP prolongation on contractility and are in agreement with reports that the magnitude of QT prolongation is important in promoting risk of arrhythmias, but does not explain the differences in strain reported in this study.

Although, the quest to identify high-risk LQTS patients has led to several hypotheses including work by the authors, the findings of the present study should be interpreted as encouraging but not yet definitive. The conclusions that LQTS patients have subtle systolic or diastolic dysfunction and that mechanical strain represents a prognostic marker for arrhythmogenesis needs further validation. We look forward to more prospective evaluation to define functional significance, before these echocardiography parameters can be added to the risk stratification algorithm.

Acknowledgments

Funding Source: Dr. Jahangir's effort is supported in part by National Heart, Lung, and Blood Institute grants [RO1 HL101240] and [R01 HL089542].

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