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EDITORIAL COMMENT

Strain Echocardiography and LQTS Subtypes

Mechanical Alterations in an Electrical Disorder*

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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 result from mutations in 3 genes coding for pore-forming subunits of 2 potassium channels (KCNQ1 and KCNH2 coding for the slow and rapid delayed rectifier potassium channels [I_{Ks} and I_{Kr}], respectively) and a sodium (SCN5a for Nav1.5) channel, thus 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 because members carrying the same mutation may present differently, from asymptomatic to a more malignant course with recurrent syncope or cardiac arrest (1). Genotype-phenotype studies have correlated functional effects of gene mutations on electrocardiographic parameters, clinical presentation, triggers for arrhythmogenesis, and responsiveness to therapy (2). Although spatial and temporal differences in repolarization resulting from individual ion channel defects and the heterogeneous distribution within the myocardium have been described (2), the impact on cardiac electrical and mechanical coupling has not been fully explored (3-6).

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In this issue of *iJACC,* Leren et al. (7) present their findings on the use of conventional and strain echocardiography in 192 patients with genotyped LQTS (139 with LQTS1, and 53 with LQTS2) compared with 60 age- and gender-matched healthy controls to identify abnormal myocardial mechanical parameters as a marker of arrhythmogenic risk. Not surprisingly, left ventricular (LV) ejection fraction was normal. In patients with LQTS, there were subtle differences in diastolic function with mildly reduced early diastolic myocardial velocity (but within normal range), prolonged isovolumic relaxation time, and an enlarged left atrium compared with 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 patients with LQTS versus healthy controls ($-22.1 \pm 2.1\%$ vs. $-23.0 \pm 2.0\%$). In addition, prolonged contraction duration and more dispersed contractions were present in patients with LQTS. Electromechanical time (EMT), defined by the difference between the QT interval and the Q-wave to aortic valve closure duration, was also abnormal. Patients with LQTS2, especially symptomatic patients, exhibited greater alterations than did patients with 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 an increase in QTc interval, a finding suggesting a direct relationship with QT prolongation, particularly in 9 patients with double mutations or a history of syncope or aborted sudden death. The study investigators therefore suggest that these parameters

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could be used as markers of high risk in patients with LQTS.

These findings add to the body of observational literature in this field (3-6), seeking to correlate electrical alterations in patients with LQTS with echocardiographically assessed mechanical abnormalities in ventricular function. Altered ventricular function initially was reported in patients with LQTS by using M-mode echocardiography (3). These findings demonstrated characteristic alterations in contractility with a rapid early contraction phase followed by an extended phase of LV wall thickening before relaxation, 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 because calcium-channel blockers can normalize some of the mechanical abnormalities (3,4). Strain imaging is a newer technique that characterizes global and regional ventricular function and offers outstanding temporal resolution. Strain analysis was used by the investigators in their previous studies that included patients with LQTS, and it is 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 represents a marker for increased arrhythmogenesis (5,6). The current study extends these findings to genotyped subgroups, with changes observed predominantly in patients with LQTS2, rather than in patients with LQTS1. These interesting observations will require additional studies to identify a mechanistic basis for selective impact of mutation in I_{Kr} on systolic and diastolic parameters when compared with I_{Ks}.

The strength of the study includes high intraobserver and interobserver reliability for GLS for a notoriously observer-dependent technique. The investigators were careful to exclude patients with hypertension and diabetes mellitus because these disorders have been shown to correlate independently 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 are 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 because EMT changes were previously shown to be caused by QT prolongation (9), with a fixed Q-wave aortic valve closure time not influenced by repolarization duration.

In addition, the connection between contractile strain and loss of function potassium channel mutations that result in LQTS1 and LQTS2 is still unclear. The reported finding that overall GLS is reduced in patients with I_{Kr} mutation is 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 sustains the action potential (AP) plateau and allows 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 cellular data on strain and its dispersion are limited. The possible explanation for the mechanical effect of acute AP prolongation in rat ventricular cardiomyocytes was provided by Bouchard et al. (11). These researchers demonstrated a positive inotropic effect of AP prolongation with an increase in the magnitude and duration of cell shortening, intracellular calcium transients, and 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 do not explain the differences in strain reported in this study.

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

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