Is Long QT Syndrome a Disease of Abnormal Mechanical Contraction?

David S. Rosenbaum, MD

It is generally assumed that long QT syndrome (LQTS) is an arrhythmic disorder that occurs in patients with normal left ventricular systolic function. The present article by Haugaa et al challenges this assumption.1 One hundred and one patients with genetically documented LQTS were systematically compared to an age-matched unaffected control population for differences in regional contraction patterns assessed by the speckled tracking method. Among the LQTS population, 64 had LQT1, 26 had LQT2, 1 had LQT3, 1 had LQT5, and 9 had documented Jervell and Lange Nielsen Syndrome. About half of all patients with LQTS were symptomatic. Various metrics of regional left ventricular contraction and spatial inhomogeneity of contraction were assessed. In addition to global strain, mean contraction duration measured separately in the longitudinal and circumferential directions was assessed as a mechanical counterpart to action potential duration or QT interval, dispersion of longitudinal or circumferential contraction duration served as a mechanical counterpart to regional (eg, apex versus base) dispersion of repolarization, and differences between longitudinal and circumferential contraction duration within individual regions served as a mechanical counterpart to transmural dispersion of repolarization. The latter measure was based on the assumption that longitudinal and circumferential contraction arise selectively from endocardial and midmyocardial locations, respectively, across the transmural wall. This assumption, in turn, is based on the finding that subendocardium mainly consists of longitudinal fibers, whereas midmyocardium mainly consists of circumferentially oriented fibers.2

The principal findings were that, in comparison with normal controls, patients with LQTS exhibited, of course, longer QT interval, longer contraction duration, and, interestingly, higher degrees of spatially inhomogeneous contraction times. From these findings, the authors conclude that transmural mechanical dispersion is a feature of LQTS, which may correspond to previously described electrophysiological dispersions that are thought to contribute to arrhythmogenesis in this disorder. Interestingly, a retrospective receiver operator analysis of this population suggested that dispersion of mechanical contraction time is a better predictor of past cardiac events than the corrected QT interval (ie, the best available gold standard test for prognosticating outcomes in LQTS). Taken together, these findings challenge conventional wisdom that LQTS is associated with normal left ventricular mechanical contraction. Rather, it seems that patients with LQTS, and particularly patients with symptoms, manifest prolonged and regional dysynchronous contraction patterns compared with normal subjects. Moreover, the data presented put forward the intriguing possibility that regionally inhomogeneous contraction patterns as detected by the speckled tracking method might provide a much needed tool for improving our ability to predict outcomes in patients with LQTS.

LQTS represents a diverse group of heritable monogenetic disorders that arise from mutations of ion channels leading to a reduction of an outward K current or gain of function of inward current such as \( I_{Na} \).3 Either of these ionic mechanisms produces the characteristic hallmark of this disorder, manifested by prolongation of action potential duration at the myocyte level or the QT interval at the clinical level. These fundamental alterations of cardiac repolarization predispose to life-threatening ventricular arrhythmias, such as Torsade de Points, through several mechanisms. At the cellular level, a prolongation in action potential duration increases the probability for secondary depolarizations (early afterdepolarizations) provided that the action potential plateau is maintained for a sufficient time to allow recovery from inactivation of inward current \( I_{Na} \). When early afterdepolarizations exceed threshold potential, they can elicit ectopic triggering beats that initiate Torsade de Points. However, in addition to these triggering mechanisms, the sustenance of arrhythmia is thought to require a suitable myocardial substrate consisting of spatially inhomogeneous repolarization properties. In particular, prolongation in action potential duration of midmyocardial cells relative to neighboring epicardium produced spatial gradients of excitability of sufficient magnitude to cause conduction block of ectopic impulses at the epicardial–midmyocardial interface, leading to reentrant excitation.4 Therefore, the hypothesis put forward by Haugaa et al, that LQTS is associated with regionally inhomogeneous contraction, is well founded and compelling. A channelopathy that

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Heart and Vascular Research Center, MetroHealth Campus, Case Western Reserve University, Cleveland, Ohio.

Correspondence to David S. Rosenbaum, MD, Director, Heart and Vascular Research Center, MetroHealth Campus, Case Western Reserve University, 2500 MetroHealth Drive, Hamman 330, Cleveland, OH 44109. E-mail drosenbaum@metrohealth.org

(Circulation. 2010;122:1353-1354.)

© 2010 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.110.980706
prolongs cellular repolarization is expected to prolong contraction because the sustenance of the action potential plateau will allow persistence of Ica current and hence prolonged contraction via calcium-induced calcium release mechanisms. So it is not surprising and almost self-evident that Haugaa et al observed longer overall contraction duration in patients with LQTS compared with normal subjects, and even longer contraction duration in symptomatic patients with LQTS (who had longer QT intervals). However, an interpretation of their findings related to spatially inhomogeneous contraction patterns is not as straightforward. Although Haugaa et al report enhancement of essentially every metric of inhomogeneous contraction in patients with LQTS, they place greatest emphasis on their finding of greater longitudinal-circumferential (ie, transmural) heterogeneity of contraction. Whereas it is certainly appealing to make the connection between the novel findings of transmural contraction time heterogeneity with the aforementioned transmural electrophysiological heterogeneities, several factors are worth considering before definitive conclusions can be drawn from these data. First, the electrophysiological basis for transmural dispersion of repolarization presumably differs in LQT1 versus LQT2. In LQT2, the transmural gradient in repolarization is thought to arise from selective prolongation of action potential duration in midmyocardial relative to epicardial cells, owing to a weak Iks current in midmyocardial cells. In contrast, in LQT1, transmural dispersion of repolarization only occurs under the condition of exogenous catecholamine stimulation, where epicardial action potentials shortened out of proportion to midmyocardial cells, presumably because they contain greater density of the catecholamine-sensitive Iks current. Unexpectedly, Haugaa et al report relatively lower levels of transmural contraction heterogeneity in patients at rest (in the absence of sympathetic stimulation) with LQT2 than in patients with Jervell and Lange Neilsen Syndrome. Second, previous reports have suggested that the most significant transmural gradients of repolarization reside at the epicardial–midmyocardial interface, whereas the assessment of longitudinal versus circumferential contraction is thought to reflect midmyocardial to endocardial differences in contraction. Therefore, it is possible that these indices could have missed detecting even more substantial contraction heterogeneities occurring across the transmural wall. Also, it is important to emphasize that these metrics of transmural contraction heterogeneity do not directly measure contraction selectively in endocardium and midmyocardial layers, but rather are based entirely on the assumption that longitudinal and circumferential contraction arise selectively from these respective tissue layers. Finally, it is not clear why equally impressive heterogeneity in contraction times were observed between different left ventricular myocardial regions (“Delta contraction duration”) in patients with LQTS. As pointed out by the authors, it is possible that regional differences in ion channel density expression may produce heterogeneous action potential duration even with uniform reduction in the activity of the mutated ion channel. This finding requires further exploration.

Presently, our ability to identify patients with LQTS at greatest risk for life-threatening events is inadequate. This is particularly problematic in asymptomatic patients or when evaluating first-degree relatives of individuals with symptomatic LQTS. Marked prolongation of QT interval is a poor prognostic sign, but even individuals with genetically documented LQTS can have relatively normal QT intervals. Conversely, mutations known to cause LQTS cannot be detected in all patients with clinical signs of LQTS. Therefore, there remains a compelling need for better tools for risk stratifying patients with LQTS. Herein lies the rationale for the work of Haugaa et al. It is intriguing to speculate that a clinically available, noninvasive technique for assessing regional heterogeneity in ventricular contraction might be used to risk stratify patients with LQTS. Normally, a desirable next step would include a prospective evaluation of these mechanical parameters using predefined cut points for test positivity to determine whether speckled tracking can be applied to the LQTS population in general. However, this is not an easy undertaking in the case of a rare disease and would undoubtedly require a multicenter effort. Going forward, to predict events, better methods are required to improve our understanding of mechanisms that trigger lethal arrhythmias in patients with LQTS. The measurement of QT interval or QT dispersion fails to directly probe arrhythmia substrates in LQTS. A more complete understanding of the mutations, genetic modifiers, and environmental factors that trigger arrhythmic events is also required. Finally, more direct methods for assessing arrhythmia substrate, such as electrocardiographic imaging, may potentially lead to improved prediction and prevention of ventricular arrhythmias in LQTS.

Disclosures

None.

References


KEY WORDS: Editorials contractility torsade de pointes long QT syndrome
Is Long QT Syndrome a Disease of Abnormal Mechanical Contraction?
David S. Rosenbaum

*Circulation*. 2010;122:1353-1354; originally published online September 20, 2010;
doi: 10.1161/CIRCULATIONAHA.110.980706

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/122/14/1353

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/