Long QT syndrome, a purely electrical disease? Not anymore

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This editorial refers to 'Left ventricular mechanical dispersion by tissue Doppler imaging: a novel approach for identifying high risk individuals with long QT syndrome', by K.H. Haugaa et al. on page 330

The identification in 1995–1996 of the three major genes for the long QT syndrome (LQTS) has opened up the molecular era for arrhythmogenic disorders and has led to the frequent use of the term ‘channelopathies’ to define several diseases characterized by a high potential for life-threatening arrhythmias and by being caused by mutations on genes encoding ion channels involved in the control of the action potential. Another concept, developed in parallel, was that of ‘primary electrical diseases’ which is now regularly applied to disorders such as LQTS, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, and others. ‘Primary electrical diseases’ soon became equivalent to ‘purely electrical diseases’ and the consensus still is that in these diseases there are no mechanical dysfunctions. As far as LQTS is concerned, the idea that this was a purely electrical disease in an otherwise completely normal heart has been around since the early days. When in 1991 and 1994 we attempted to challenge this concept, the cardiological community gave us the cold shoulder. Now, the tide may have turned.

Kristina Hermann Haugaa, with the group led by Jan Amlie in Oslo, reports an interesting study that evaluated myocardial contraction duration by tissue Doppler imaging (TDI) in 73 patients with genetically confirmed LQTS. The group included nine subjects affected by the Jervell and Lange-Nielsen (JLN) syndrome,7 and 40 controls. Approximately half of the single mutation LQTS patients (RW-LQTS) and all JLN patients had a history of cardiac events (arrhythmias, syncope, or cardiac arrest). As expected, RW-LQTS patients had longer QT intervals compared with controls, and JLN patients had longer QT intervals compared with both controls and RW-LQTS patients. The duration of myocardial contraction was measured in the basal septal segment and defined as the time from the start of the R wave on ECG to the definitive zero-crossing of the decreasing velocity slope. The duration of contraction of the basal segment was assessed in all six traditional left ventricular wall positions and the standard deviation of these six values was calculated as an index of mechanical dispersion of contraction. A longer contraction duration was found between RW-LQTS patients and controls and, within LQTS patients, between those with and those without a previous cardiac event. Dispersion of contraction was also more pronounced in RW-LQTS patients with cardiac events compared with asymptomatic patients.

When we reported in 1991 the presence of an unsuspected abnormality in left ventricular contraction in 23 of 42 LQTS patients, we developed two quantitative indexes to quantify this phenomenon more efficiently. The most evident abnormality was the presence of a very slow contraction phase before rapid relaxation that appeared either as a plateau or as a double-peaked contraction. Subsequently, calcium channel blockade by intravenous verapamil was shown to normalize completely even the most severe patterns of abnormality such as those with a double-peak morphology.

Despite our pointing out that the contraction abnormality and, particularly, the double-peak morphology were the first clinical features found to be strongly associated with a history of syncope or cardiac arrest, these two reports were received with scepticism, more or less dismissed, and essentially ignored.

Seven years of silence passed until, in 1998, Nakayama, working in the group led by Tohru Ohe in Okayama, confirmed the presence of a phase of slow contraction (plateau) before rapid relaxation in patients with LQTS. They digitized two-dimensional short axis images performed at the basal and middle level of the left ventricle and reconstructed M mode echocardiograms in the corresponding 12 segments. They found that LQTS patients spent, on average, twice the amount of time in the plateau late systolic phase of contraction and that this plateau time, although abnormally prolonged in the whole left ventricle, was significantly more variable within the 12 analysed segments in LQTS patients.
The choice to use overall contraction duration as a parameter of risk also appears questionable. Since the goal of the study was to increase the predictive accuracy of current risk stratification strategies, the fact that the prolongation of action potential duration is intrinsically related to a prolongation of contraction certainly limits the independent predictive power provided by this parameter, once the QT interval duration is accounted for. Furthermore, Hermann Haugaa et al. provide no hypothesis for a prolongation of all phases of myocardial contraction in LQTS patients. We had suggested that LQTS patients tended to have a faster contraction in the early phase, a finding that was then confirmed. The echocardiographic pattern and related biological signal that characterizes LQTS patients and particularly the symptomatic ones is, in all likelihood, the very slow contraction in the late systolic phase, leading in some cases to a secondary contraction before rapid relaxation and thus resulting in a double-peak morphology. Hermann Haugaa et al. describe in several patients the presence of marked secondary peaks of myocardial velocity after aortic valve closure (post-ejection velocity), a pattern that mimics the one just mentioned, but the authors do not provide any correlation between this finding and symptoms.

We had observed a strong correlation with severe cardiac events (syncpe/cardiac arrest). We thought that this abnormal pattern might have been related to abnormal intracellular calcium handling with sustained or increased calcium concentration. These phenomena, in turn, could have been facilitated by early afterdepolarizations—a recognized cause of Torsades-de-Points in LQTS—not reaching threshold for the induction of arrhythmia, but causing an intracellular calcium increase. This hypothesis was reinforced by two findings. First, calcium channel blockade completely abolished the contraction abnormality in LQTS patients. Secondly, even a scarcely noticeable early afterdepolarization was shown to lead to a marked secondary intracellular calcium increase and consequent contraction in the isolated cardiomyocyte. The study by Hermann Haugaa et al. is important. It provides, in an adequate number of patients, what should be considered the final evidence that a contraction abnormality is an integral part of LQTS, which should no longer be regarded as a ‘purely electrical disease’. After almost 20 years it vindicates the validity of our original findings, thus showing that data carefully collected and carefully interpreted are eventually confirmed. This represents a rewarding and encouraging scientific message. Also the initial observation that this mechanical abnormality is more marked among symptomatic patients and has the potential to contribute to risk stratification has been confirmed. For this purpose, however, we believe that careful comparison of various echocardiographic measures is necessary to identify the single parameter that correlates best with symptoms and that may provide an independent contribution to risk stratification.

Conflict of interest: none declared.

References


