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Editorial

Diagnosis of Long QT Syndrome: Time to Stand Up!

Diagnóstico del síndrome de QT largo: valor del ortostatismo

Andrea Mazzanti[a] and Silvia G. Priori[a,b,c,*]

[a] Molecular Cardiology, IRCCS ICS Maugeri, Pavia, Italy
[b] Department of Molecular Medicine, University of Pavia, Pavia, Italy
[c] Fundación Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain

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In an original article recently published in *Revista Española de Cardiología*, Muñoz-Esparza et al.[1] report their observations on the value of the "stand-up" test in the diagnosis of long QT syndrome (LQTS) and its usefulness in guiding patient management. The topic is of interest, because in the clinical setting, the evaluation of patients with borderline prolongation of the corrected QT interval is one of the most common issues faced by the cardiologists when assessing family members of index cases affected by LQTS. However, even in the genetic era, with positive results of genetic testing for approximately 70% of the population, the accuracy of clinical diagnosis, ie, the identification of a prolonged QT interval, represents the mainstay of the diagnosis of LQTS, a potentially lethal disorder[2] for which there is effective therapy.[3] Furthermore, the correct and accurate measurement of the QT interval is of particular relevance to physicians, drug manufacturers, and regulatory agencies, because of the relationship between the degree of QT interval prolongation and the incidence of potentially lethal ventricular arrhythmias.[4]

Guidelines exist in the literature on which is the best method to measure QT interval and which lead(s) to choose,[4] but less is known on "when" it should be measured.

Traditionally, the QTc obtained from the ECG recorded in resting conditions during daytime hours has been used in clinical studies, even though it is known that these standards may not be ideal to detect QT prolongation in all cases. Indeed, the dynamic nature of the QT interval implies that it may appear normal (or at the upper limits of normality) for heart rates close to 60 to 70 bpm, ie, at rest, and become "long" only when the heart rate increases, for example during exercise, because it fails to adapt adequately to the progressive shortening of the cardiac cycle.

GENOTYPE-SPECIFIC RESPONSES OF THE QT INTERVAL TO CHANGES IN HEART RATE

Due to advances in the profiling of genotype-specific phenotype characteristics, we know that not all LQTS subtypes behave in the same way in response to changes in heart rate.

LQT1, the most frequent variant of LQTS (30%-35% of genotype-positive cases[5]), is due to mutations in the *KCNQ1* gene that induce a reduction of the I_{Ks} repolarizing current. Affected patients demonstrate a deficiency in their ability to adapt their QT interval in response to exercise-induced tachycardia and therefore the QTc interval becomes proportionally longer at faster heart rates. This behavior explains the increased risk of arrhythmias during exercise observed in LQT1 patients.

LQT2 affects 25% to 40% of genotype-positive LQTS patients[5] and is secondary to loss-of-function mutations in the *KCNH2* gene encoding for the I_{Kr} potassium repolarizing current. Patients typically exhibit a poor adaptation of the QT interval in response to abrupt changes in heart rate,[6] such as when standing or in response to sudden emotions, but overall they have good capacity to adapt their QT interval during prolonged exercise.

The much rarer LQT3 (5%-10% of genotype-positive patients[5]) depends on the increase of the depolarizing sodium current coded by the *SCN5A* gene. Patients show a more pronounced QT prolongation at rest, but demonstrate normal adaptation during exercise.

Finally, genotype-negative LQTS represents a melting pot of different genetic substrates that encompasses a spectrum of different diseases for which a unifying behavior is impossible to identify.

STRATEGIES TO DETECT QT PROLONGATION: STAND UP!

In all cases, when a prolonged QT is suspected, a careful evaluation of several ECGs recorded at different heart rates is mandatory, in order to avoid the problems related to both a missed diagnosis and to an overdiagnosis. Several ways to monitor the QT interval during "nonresting" conditions have been proposed over the years to aid physicians in the diagnosis of LQTS. Often, however, these additional tools have not entered the armamentarium used by cardiologists in their everyday practice, mostly because they lack validation in large sets of patients.

The infusion of low doses of epinephrine has been suggested as a diagnostic tool to distinguish controls from patients with concealed LQTS (especially LQT1) manifesting an equivocal QTc at rest.[7] The test, however, is invasive and no longer seems justified for the diagnosis of LQTS in current practice, except under very special conditions, such as survivors of idiopathic ventricular fibrillation lacking the ability to walk.

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* Corresponding author: Molecular Cardiology - IRCCS ICS Maugeri, Via Maugeri 10, 27100 Pavia, Italy.
E-mail address: silvia.priori@icsmaugeri.it (S.G. Priori).

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The exercise stress test and 24 hour-ECG holter[8] are probably the best ways to assess the dynamic of the QT interval during the day and night and to evaluate the influence of the autonomic nervous system on the heart.

Even simpler maneuvers, such as recording the ECGs in different positions, may actually be useful for the diagnosis of LQTS. It has been known for several years that most LQTS patients have an abnormal QT adaptation to sudden changes in heart rate provoked by brisk standing. This peculiar behavior was formalized by Viskin et al.[6] in 2010, when these authors proposed the performance of a bedside stand-up test to differentiate LQTS patients with an unclear diagnosis at baseline ECG from normal individuals. The protocol by Viskin et al. included the measurement of heart rates and QT intervals in the supine position and then in 3 stages during the 30 seconds after standing, to calculate the adaptations of the QTc interval over time. Viskin et al.[6] studied 68 LQTS patients and 82 control participants. In response to brisk standing, patients and control participants responded with a similar heart rate acceleration, while the response of the QT interval to tachycardia differed: on average, the QT interval of controls shortened by 21 ± 19 ms, whereas the QT interval of LQTS patients increased by 4 ± 34 ms ($P < .001$). Since the RR interval shortened more than the QT interval, the QTc interval increased by 50 ± 30 ms in the control group and by 89 ± 47 ms in the LQTS group ($P < .001$). Receiver-operating characteristic curves showed that the test added diagnostic value compared with the baseline supine QTc.

In the article by Muñoz-Esparza et al.[1] the authors propose a "simplified" version of the Viskin's protocol to evaluate the response of the QT interval to standing in 36 LQTS patients (81% of whom had genetic confirmation) compared with 41 age- and sex-matched controls. In this variant of the bedside stand-up test, only 2 measures of the QTc are performed, before standing (QTc supine) and within 10 seconds after standing (QTc standing). In their cohort, Muñoz-Esparza et al.[1] also found that QTc standing was significantly longer in the LQTS group than in controls (528 ± 46 *vs* 420 ± 15 ms; $P < .001$).

This simplified version of the bedside stand-up test was thus confirmed to have diagnostic utility and a cutoff of 475 ms for QTc standing demonstrated a 90% sensitivity and 100% specificity in differentiating LQTS cases from controls. Importantly, receiver-operating characteristic curves of QTc standing showed a significant 14% increase in diagnostic capability compared with QTc supine (area under the curve 0.99 vs 0.85; $P < .001$).

Besides helping in recognizing true LQTS cases, the bedside stand-up test may obviously play an important role in ruling out diagnoses in persons with a borderline normal QT interval at rest (eg, athletes) and a normal dynamic of the QT interval during exercise. It is interesting to note, in this regard, that a similar threshold of 474 ms for the QTc recorded in the first 15 seconds of standing was found by Viskin et al. to have 90% sensitivity, but only 75% specificity, in differentiating LQTS cases from controls.[6] The possible presence of false-positive results when the QTc is recorded within the first 10 to 15 seconds of standing needs to be evaluated further.

Another important step to validate the diagnostic strength of the bedside stand-up test would require a repeat of the study, with exclusion of patients with an obvious electrocardiographic diagnosis of LQTS and correlation of the findings with the results of genetic testing. In contrast with Viskin et al.,[6] the protocol by Muñoz-Esparza et al.[1] failed to identify significant differences in QTc standing and ΔQTc among LQ1 and LQT2 patients. This result, notwithstanding the uneven number of individuals in each genetic subgroup, might also depend on the brief interval that preceded the recording of the stand-up ECG and also requires further evaluation.

THE BEDSIDE STAND-UP TEST TO MONITOR TREATMENT RESPONSE

One of the innovative ideas in the study by Muñoz-Esparza et al.[1] was to evaluate, in a subgroup of their patients, whether the abnormal response to standing observed in LQTS patients may be ameliorated by the administration of beta-blockers, as previously suggested by Walker et al.[9]

In the present report, beta-blocker therapy attenuated the response to standing in LQTS patients, restoring values that are more similar to those recorded in controls (under therapy: QTc standing 440 ± 32 ms; $P < .0001$), thus supporting the hypothesis that QTc adaptation to sudden changes in heart rate becomes nearly normal when LQTS patients receive beta-blockers.

These results obviously require further confirmation, but they are intriguing for several reasons. First, they offer new insights in the understanding of the antiarrhythmic mechanisms of beta-blockers in LQTS. Second, they may contribute to explain why beta-blockers do not offer adequate protection in some LQTS patients. Third, but not least, they may offer a support to decide whether the dose of beta-blocker administered to an individual patient is satisfactory, at the same time allowing for comparisons among different molecules.

Overall, the study by Muñoz-Esparza et al.[1] is welcome because it underlines that, while the mainstay for the diagnosis of LQTS will remain measurement of the QT interval, the practice of measuring the QTc in resting supine conditions may need to be accompanied by the addition of other measurements.

It could be interesting, for instance, to combine the information obtained from the bedside stand-up test with other tools that could aid in the clinical diagnosis of LQTS, like the QTc duration measured at the fourth minute of recovery after exercise proposed by Sy et al.[10] The overall results of such a combined approach would possibly help to recognize true LQTS patients and to discharge borderline cases with normal behavior of the QTc to changes in posture or adaptation to exercise.

Furthermore, the possible usefulness for the monitoring of response to therapy and to assess the usefulness of beta blockade appears extremely appealing, though preliminary.

Muñoz-Esparza et al. should be congratulated for sharing their results that, if confirmed in larger studies, could contribute to a reshaping of the diagnosis, and possibly the management, of patients with LQTS.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Muñoz-Esparza C, Zorio E, Domingo Valero D, et al. Value of the "Standing Test" in the Diagnosis and Evaluation of Beta-blocker Therapy Response in Long QT Syndrome. *Rev Esp Cardiol.* 2017;70:907–914.
2. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *New Eng J Med.* 2003;348:1866–1874.
3. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). *Eur Heart J.* 2015;36:2793–2867.
4. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval. *J Am Coll Cardiol.* 2009;53:982–991.
5. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace.* 2011;13:1077–1109.

6. Viskin S, Postema PG, Bhuiyan ZA, et al. The response of the QT interval to the brief tachycardia provoked by standing: a bedside test for diagnosing long QT syndrome. *J Am Coll Cardiol.* 2010;55:1955–1961.
7. Ackerman MJ, Khositseth A, Tester DJ, Hejlik JB, Shen WK, Porter CB. Epinephrine-induced QT interval prolongation: a gene-specific paradoxical response in congenital long QT syndrome. *Mayo Clin Proc.* 2002;77:413–421.
8. Coumel P. From provocation tests to clinical practice: invasive and non-invasive electrophysiology. *Arch Mal Coeur Vaiss.* 2003;96:48–53.
9. Walker BD, Krahn AD, Klein GJ, et al. Effect of change in posture and exercise on repolarization in patients with long QT syndrome with HERG channel mutations. *Can J Cardiol.* 2005;21:33–38.
10. Sy RW, Gollob MH, Klein GJ, et al. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm.* 2011;8:864–871.