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Original article

Value of the "Standing Test" in the Diagnosis and Evaluation of Beta-blocker Therapy Response in Long QT Syndrome

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ABSTRACT

Introduction and objectives: Patients with congenital long QT syndrome (LQTS) have an abnormal QT adaptation to sudden changes in heart rate provoked by standing. The present study sought to evaluate the standing test in a cohort of LQTS patients and to assess if this QT maladaptation phenomenon is ameliorated by beta-blocker therapy.

Methods: Electrographic assessments were performed at baseline and immediately after standing in 36 LQTS patients (6 LQT1 [17%], 20 LQT2 [56%], 3 LQT7 [8%], 7 unidentified-genotype patients [19%]) and 41 controls. The corrected QT interval (QTc) was measured at baseline (QTc_{supine}) and immediately after standing ($QTc_{standing}$); the QTc change from baseline (ΔQTc) was calculated as $QTc_{standing} - QTc_{supine}$. The test was repeated in 26 patients receiving beta-blocker therapy.

Results: Both $QTc_{standing}$ and ΔQTc were significantly higher in the LQTS group than in controls ($QTc_{standing}$, 528 ± 46 ms vs 420 ± 15 ms, $P < .0001$; ΔQTc, 78 ± 40 ms vs 8 ± 13 ms, $P < .0001$). No significant differences were noted between LQT1 and LQT2 patients. Typical ST-T wave patterns appeared after standing in LQTS patients. Receiver operating characteristic curves of $QTc_{standing}$ and ΔQTc showed a significant increase in diagnostic value compared with the QTc_{supine} (area under the curve for both, 0.99 vs 0.85; $P < .001$). Beta-blockers attenuated the response to standing in LQTS patients ($QTc_{standing}$, 440 ± 32 ms, $P < .0001$; ΔQTc, 14 ± 16 ms, $P < .0001$).

Conclusions: Evaluation of the QTc after the simple maneuver of standing shows a high diagnostic performance and could be important for monitoring the effects of beta-blocker therapy in LQTS patients.

Valor del «test de bipedestación» en el diagnóstico y la evaluación de la respuesta al tratamiento con bloqueadores beta en el síndrome de QT largo

Palabras clave:
Síndrome de QT largo
Test de bipedestación
Intervalo QT corregido
Morfología de la onda T
Tratamiento con bloqueadores beta

RESUMEN

Introducción y objetivos: Los pacientes con síndrome de QT largo (SQTL) tienen una adaptación anormal del QT a los cambios bruscos de la frecuencia cardiaca producidos con la bipedestación. Este trabajo estudia la utilidad del test de bipedestación en una cohorte de pacientes con SQTL y evalúa si el fenómeno de «mala adaptación» del QT se normaliza con el tratamiento con bloqueadores beta.

Métodos: Se realizó un electrocardiograma basal y otro inmediatamente tras la bipedestación a 36 pacientes con SQTL (6 [17%] con QTL1, 20 [56%] con QTL2, 3 [8%] con QTL7 y 7 [19%] con genotipo no identificado) y 41 controles. Se midió el intervalo QT corregido (QTc) basal ($QTc_{decúbito}$) y tras la bipedestación ($QTc_{bipedestación}$) y el incremento del QTc ($\Delta QTc = QTc_{bipedestación} - QTc_{decúbito}$). Se repitió el test en 26 de los pacientes bajo tratamiento con bloqueadores beta.

Resultados: El $QTc_{bipedestación}$ y el ΔQTc fueron mayores en el grupo de SQTL que en el grupo control ($QTc_{bipedestación}$, 528 ± 46 frente a 420 ± 15 ms; $p < 0,0001$; ΔQTc, 78 ± 40 frente a 8 ± 13 ms; $p < 0,0001$). No hubo diferencias significativas entre los pacientes con QTL1 y QTL2. Los pacientes con SQTL presentaron patrones típicos del segmento ST-onda T tras la bipedestación. Las curvas *receiver operating characteristic* del

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$QTc_{bipedestación}$ y ΔQTc mostraron un incremento significativo del valor diagnóstico comparadas con la del $QTc_{decúbito}$ (área bajo la curva de ambos, 0,99 frente a 0,85; $p < 0,001$). El tratamiento con bloqueadores beta atenuó la respuesta a la bipedestación de los pacientes con SQTL (en tratamiento, $QTc_{bipedestación}$, 440 ± 32 ms [$p < 0,0001$] y ΔQTc, 14 ± 16 ms [$p < 0,0001$]).

Conclusiones: La evaluación del intervalo QTc tras la bipedestación proporciona un alto rendimiento diagnóstico y podría ser de gran utilidad en la monitorización del tratamiento con bloqueadores beta en los pacientes con SQTL.

Abbreviations

ΔQTc: corrected QT interval change from baseline
BB: beta-blocker
ECG: electrocardiogram
LQTS: long QT syndrome

INTRODUCTION

Although long QT syndrome (LQTS) is a highly treatable channelopathy, its diagnosis remains a challenge for clinicians for a number of reasons: first, there is considerable overlap in the QT interval distribution between otherwise healthy individuals and patients with genetically confirmed LQTS[1,2]; second, arrhythmic episodes are uncommon and usually occur in unmonitored settings; and third, a negative genetic test cannot unequivocally exclude the diagnosis of LQTS by itself and it is sometimes difficult to distinguish pathogenic mutations from innocuous rare variants.[3]

Patients with suspected LQTS are often subjected to additional diagnostic studies such as exercise stress testing, 24-hour Holter monitoring, and epinephrine tests.[4] The ideal diagnostic tool for this life-threatening disease should be simple to perform and interpret so that treatment can be started immediately without diagnostic delays. Long QT syndrome patients have recently been described[5,6] to have an insufficient QT interval shortening to the tachycardia provoked by standing because they have an abnormal response to heart rate (HR) acceleration and because standing produces sudden changes in autonomic nervous system tone. Thus, beta-adrenergic stimulation fails to increase the net outward repolarizing current in LQTS patients with a defect in currents that are sensitive to sympathetic stimulation (I_{Ks}, I_{Kr}, and I_{K1}).[7–9]

The objectives of this study were to *a)* corroborate the previous results of the standing test in our cohort of LQTS patients and controls, *b)* describe changes in ST-T wave patterns that could be used to identify genotypes, and *c)* evaluate whether beta-blocker (BB) treatment of LQTS patients improves the corrected QT interval (QTc) shortening response to abrupt standing.

METHODS

Study Population

We consecutively enrolled 36 newly diagnosed LQTS patients from Arrixaca University Hospital (Murcia, Spain) and La Fe Polytechnic and University Hospital (Valencia, Spain). Diagnosis of LQTS was based on the presence of a Schwartz score punctuation[10] ≥ 4 and/or a pathogenic mutation in LQTS genes.

A causal mutation was found in 29 patients (80.5%). The remaining 7 patients had congenital deafness (n = 2), syncope (n = 4), QTc 4th minute of recovery from exercise stress test ≥ 480 ms (n = 5), notched T waves (n = 5), and unexplained sudden cardiac death younger than age 30 among immediate family members (n = 2).

The control group consisted of 41 healthy asymptomatic relatives of patients with LQTS not carrying the familial mutation. Control individuals with electrocardiogram (ECG) abnormalities were excluded. The protocol was performed in all LQTS patients before treatment initiation with BBs and after the optimal BB dose in 26 patients. The study was approved by the Human Research Ethics Committees of the participating centers and was conducted in compliance with the Declaration of Helsinki. All patients provided written informed consent.

Protocol and Measurements

Standard 12-lead-ECG was recorded at a paper speed of 25 mm/s with a gain of 10 mm/mV. We used the "bedside stand-up test" previously described by Viskin et al.[5] Patients and controls underwent baseline ECG after resting supine for 10 minutes; during continuous ECG recording, they were then asked to get up quickly. We simplified the "Viskin protocol": QTc measurements were only performed *a)* before standing (QTc_{supine}), and *b)* immediately after standing-related artifacts disappeared ($QTc_{standing}$). Electrocardiograms recorded more than 10 seconds after standing were excluded. The QTc change from baseline (ΔQTc) was obtained by subtracting the QTc_{supine} from the $QTc_{standing}$. QT intervals were manually measured from the onset of the QRS complex to the end of the T wave, and the end of the T wave was defined as the intersection point of the tangent line of the maximal slope on the terminal T wave and the isoelectric line. The QT interval was measured in II and V_5 and was corrected by using Bazett's and Fridericia's formulae. Measurements of the QT interval were performed by an investigator who was blinded to the genetic and clinical information. ECG measurements were repeated 3 times and the average value was used in the statistical analysis.

In the protocol described by Viskin et al.,[5] electrocardiographic recording was performed within a 30-second period after standing to calculate the QTc in 3 stages: maximal HR, maximal QT interval, and maximal QT interval stretching. In our study, we propose a new way to measure the QTc. This method involves a single measurement, is easier, faster, and accessible to any professional, and solves the difficulty of accurately measuring the maximal QT stretching and the shortest RR interval outside an electrophysiology laboratory.

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