Tissue Doppler Echocardiography in Patients with Long QT Syndrome

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Background: Congenital long QT syndrome (LQTS) is a well-defined clinical entity associated with a high mortality among untreated patients. Tissue Doppler (TD) echocardiography that has been recently introduced, facilitates wall motion analysis. Therefore, to further characterize myocardial velocity abnormalities associated with LQTS, using TD and conventional echocardiography, we compared control subjects and LQTS patients.

Methods and results: Ten patients with mild LQTS and 14 control subjects were examined with standard and TD echocardiography. We studied myocardial velocities in basal and mid-segments of the septal, lateral, inferior and anterior walls. Peak velocity and time intervals were measured in each segment. We confirmed previously described M-mode abnormalities, demonstrated by an increase of the wall thickening time index. TD analysis demonstrated increased systolic and diastolic peak velocities for all segments in LQTS patients. Regional isovolumic relaxation time and systolic velocity half time (VHT) were significantly longer in LQTS group associated with a prolonged late systolic phase, resulting in a plateau morphology.

Conclusion: We demonstrated that TD allows the characterization of myocardial velocity abnormalities in LQTS patients. TD measurements could become part of the routine clinical evaluation for patients potentially affected by the LQTS as a new phenotypic marker.


Key Words: Tissue Doppler; echocardiography; long QT syndrome.

Introduction

Congenital long QT syndrome (LQTS) is a well-defined clinical entity associated with a high mortality among untreated patients[1–3]. Previous studies have shown electrocardiographic abnormalities such as prolongation and dispersion of ventricular repolarization with occurrence of polymorphic ventricular tachycardia (torsade de pointe). Mutations in cardiac potassium channel genes and in the sodium channel gene have been confirmed in LQTS patients[4,5] but all LQTS genotypes have not yet been found. Because the penetrance of the LQTS is low, reliable phenotypic markers are needed. Recently, several studies have shown ventricular wall motion abnormality. Firstly, using M-mode echocardiography, Nador et al. have demonstrated that the early contraction phase was more rapid in severe LQTS patients with the presence of slow contraction in the late thickening phase[6]. These abnormalities were confirmed by later studies[7,8]. Tissue Doppler (TD) echocardiography that has been recently introduced, facilitates wall motion analysis and quantification of myocardial velocities[9–12] and could be a new sensible phenotypic tool for LQTS. Therefore, using conventional echocardiography and TD echocardiography, we compared control subjects and asymptomatic mild LQTS patients.
patients to further characterize myocardial velocity abnormalities associated with LQTS.

**Methods**

**Study Population**

This prospective study involved 10 LQTS patients (seven females and three males; mean (SD) age: 35.7 (12) years) from eight families referred to our institute for familial evaluation after identification of a symptomatic LQTS patient in the family. The reasons for exclusion were as follows: children (cut-off age of ≥16 years), patients with pacemaker, valvular or myocardial diseases. Only two patients had a history of syncope. Mean rate corrected QT interval was mildly prolonged (QTc: 454 (37) ms 1/2). Among these patients, four patients have QTc <440 ms 1/2. Three of them were asymptomatic gene carriers. Definitive diagnosis of LQTS was based on results of the genetic study with LQT1 found in three patients and LQT2 in five patients. Two patients (QTc: 430 and 460 ms 1/2) refused the genetic study, they had a typical electrocardiogram (ECG) with abnormal T wave pattern and both belonged to two LQTS families. Moreover, the patient with normal QTc (430 ms 1/2), during the echocardiographic examination, had previously presented prolonged repolarization (QTc = 452 ms 1/2). In these families, at least one subject, the proband had a long QTc interval >440 ms 1/2, an abnormal T wave pattern and was symptomatic.

We systematically proposed beta-blockade therapy in asymptomatic LQTS patients. At the time of the echocardiographic study, treatment was as follows: six received beta-blockade therapy, four patients refused any treatment.

Fourteen age-matched healthy subjects (seven females and seven males; mean age, 33.6 (9.4) years) without a history of heart disease and having normal electrocardiograms (normal QT interval: QTc: 363 (29) ms 1/2) and echocardiograms served as controls.

**Echocardiographic Study**

The echocardiographic studies (conventional and TD echocardiography) were performed by one observer (C.S.) using an HDI 5000 echocardiograph (Philips Ultrasound, Bellevue, Washington) equipped with a 2.5 MHz probe. Two-dimensional, M-Mode and Doppler blood flow studies were recorded in a conventional manner. Measurements were done for peak mitral E and A wave velocities, systolic aortic velocity and isovolumic relaxation time (IVRT). M-mode echocardiograms of mid-septum wall, in a parasternal view, were digitalized. We assessed wall motion abnormality with the wall thickening time index (ThT) as previously described. ThT was defined as the period in which the wall thickness exceeded 90% of the maximum wall thickness.

**Tissue Doppler Echocardiography**

We recorded color TD signal in the apical view on septal, lateral, inferior and anterior walls of the left ventricle. For each wall, the basal and mid-segments were recorded. Special attention was paid to the Doppler velocity range to avoid aliasing (Nyquist limit 15 cm/s). Acquisitions were stored in digital format. Using off-line software (HDI Lab, Philips Ultrasound) we analyzed the digital cine-loops. For each image, this off-line software allowed us to correct the position of the sample volume and to place it in the middle of the basal and the mid-segment of each wall, and thus to avoid artifact caused by translational motion of the heart or by breathing. Doppler profiles were built with good resolution near 100 images/s.

Based on the wall motion velocity pattern, peak myocardial velocities were measured in pre-ejection (peak PE), in systole (peak S), in early diastole (peak E) and in late diastole (peak A). We also determined RR interval, ejection time, systolic deceleration time, regional IVRT, peak E acceleration time and peak E deceleration time. Deceleration time to reach half of maximal systolic velocity (VHT) was also measured and was an index of the late thickening systolic phase. Values of all echocardiographic parameters were averaged over five cardiac cycles. All measurements were blinded. Time values were presented as percentages of the cardiac cycle because of the possibility that different heart rates might influence the comparability of these indexes.

**Statistical Analysis**

Data are expressed as mean (SD). Unpaired Student’s t-test was used for mean comparison. A value of P < 0.05 was considered statistically significant.

**Results**

**General Characteristics**

LQTS and control groups were similar for age (35.7 (12) vs 33.6 (9) years, respectively) and heart rate (RR; 962 (141) vs 941 (186) ms, respectively). As expected, QT interval and QTc were markedly longer in LQTS patients (442 (35) vs 356 (32) ms; P < 0.001; 454 (37) vs 363 (29) ms 1/2; P < 0.001; respectively).

**Echocardiographic Analysis**

No abnormality was found in LQTS patients for ventricular size, wall thickness and conventional Doppler examination (Table 1). There was no significant difference for mitral inflow velocities (peak E: 0.83 (0.19) vs 0.86 (0.17) m/s; peak A: 0.48 (0.15) vs 0.50 (0.11) m/s) and aortic velocities (1.00 (0.19) vs
1.09 (0.2) m/s) between LQTS and control subjects, respectively. IVRT measured, using conventional Doppler, was similar in LQTS patients and in controls (88.6 (11) vs 89.4 (11.4) ms and 88 (21) vs 97 (16)% of the cardiac cycle; respectively; NS).

All LQTS patients had a wall motion abnormality, as demonstrated by an increased ThT index in LQTS patients compared with control subjects (130 (24) vs 78 (19) ms; \( P < 0.0001 \), respectively).

### Tissue Doppler Echocardiography

Anterior wall motion study was possible only in four patients and so was not used for analysis.

The profile of TD velocities was different between LQTS patients and control subjects. In LQTS patients, the S wave pattern was found to be morphologically different with a rapid early contraction phase and a late systolic plateau, in each segment (Fig. 1).

Systolic and diastolic peak velocities were increased in all segments in LQTS group compared with control group (Fig. 2). Peak S was significantly different in basal and mid-septal wall (7.2 (2.1) vs 4.6 (1.4) cm/s; \( P < 0.05 \) and 4.7 (2.2) vs 3.2 (0.8) cm/s; \( P < 0.05 \), respectively). Peak E was significantly different in basal and mid-septal wall, in basal and mid-lateral wall and in basal inferior wall. Peak A was significantly different in mid-septal wall and basal inferior wall. In contrast to IVRT measured using conventional Doppler, regional IVRT measured using TD, in percentage of the cardiac cycle, was increased in each segment in LQTS patients. The increase of regional IVRT was statistically significant in mid-septum, basal and mid-inferior and basal and mid-lateral walls (Fig. 3).

### Discussion

The present data confirm that LQTS is associated with several wall motion abnormalities that can be assessed using TD. The first one was a modification of the peak S velocity profile. This was in concordance with the results of Nador et al.\([6]\) who found, using M-mode on the left ventricle posterior wall, that both early contraction and late phase of wall thickening were affected. Similarly, using TD, we found an increase in peak S velocity indicating that LQTS patients reach maximal systolic contraction more rapidly than controls. Similarly, using TD, we found an increase in peak S velocity indicating that LQTS patients reach maximal systolic contraction more rapidly than controls. Similarly, using TD, we found an increase in peak S velocity indicating that LQTS patients reach maximal systolic contraction more rapidly than controls. 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As previously described\([7,8]\), the ThT index, assessing also this late systolic abnormality, was significantly prolonged in our LQTS patients.

Additionally, we found other wall motion abnormalities demonstrated by an increase in peak E and A velocities and a prolongation of the regional IVRT. Moreover, these different wall motion abnormalities were found in the entire ventricle. This is in con-
cordance with Nakayama et al. who found modifications on the entire ventricle but only of the late systolic contraction phase. TD echocardiography, which has been recently introduced, offers several potential benefits over conventional echocardiography. TD enables one to quantify precisely myocardial velocities and to perform regional measurements[10–12]. Moreover, digital acquisitions allow the sample volume to be repositioned at the same place throughout the cardiac cycle; so this technique is subject to less error with respect to translational motion of the heart. Of note, M-mode analysis, as previously described[6–8], assess radial wall thickness. In contrast, using DT in apical view, we assessed longitudinal myocardial velocities.

The increased regional IVRT may be explained by the longer repolarization and so the longer relaxation observed in LQTS patients. Prolongation of the repolarization, due to mutations in potassium channels genes, is observed in LQT1 and LQT2 patients. During the delayed repolarization, the inward Ca²⁺ current may be increased and induces a higher intracellular calcium concentration. This higher intracellular influx of calcium results in a prolonged contraction[13–16]. The elevated intracellular calcium concentration is probably supported by the presence of early after depolarization (EAD) in LQTS, several studies having demonstrated that EAD are linked to intracellular calcium concentration[17–19]. Moreover, De Ferrari and colleagues[20] have demonstrated that wall motion abnormality in LQTS was completely abolished by a calcium channel blocker.

In our study, beta-blockade therapy rather than the LQT syndrome could have induced the wall motion abnormalities. However, in our series, both groups had similar heart rates, ruling out the heart rate dependent effect of beta-blockade therapy. The wall motion abnormalities were also found in the four LQTS patients without beta-blockade therapy. Additionally, peak S velocity was not correlated with RR interval (r = 0.43, P = 0.98). Lastly, in Nador’s study, beta-blockade (seven patients) did not significantly influence indexes of wall motion analysis[6].

Nador et al. found that the presence of movement abnormalities carried a significantly greater probability of syncope or cardiac arrest. In their
population, 43% of the patients were asymptomatic, the mean QTc interval was markedly prolonged (504 (54 ms)) even in the asymptomatic patients (487 (18 ms)). The described abnormalities were more frequent in symptomatic than in asymptomatic patients (77 vs 19%). In contrast, Nakayama et al. did not find any difference between the six symptomatic and the two asymptomatic patients. In our series, QT intervals were mildly prolonged and only 20% of the patients were symptomatic. Using TD echocardiography, we were able to find wall motion abnormalities in all LQTS patients.

TD analysis demonstrates abnormalities even in LQTS patients with mild prolonged QTc. These TD abnormalities are not markers of increased risk in LQTS but they should become part of the routine clinical evaluation for patients potentially affected by LQTS with mild prolonged QTc. These TD abnormalities in all LQTS patients.

**Study Limitations**

The number of patients was small and genetic analysis disclosed the two main LQTS genotypes (LQT1, LQT2) but the sample in each group was too small to make comparisons. Moreover, our population was too small to determine cut-off values. Thus our results may only reflect a part of the wide spectrum of LQTS. We only evaluated the segments in the basal and mid-left ventricular regions. We could not record apical images by Doppler echocardiography because the angle dependence restricted accurate measurement in this region. Anterior wall motion could not be recorded precisely in almost all patients.

**Conclusion**

In this study, using TD, we confirmed in LQTS the presence of regional wall motion abnormalities of the left ventricle in systole. We have disclosed other abnormalities as an increase in regional IVRT and in diastolic velocities. These abnormalities were present in patients with mild QT prolongation and even in patients with normal QTc. The role of this new echocardiographic technique, in the evaluation of LQTS patients, merits further larger studies.

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**References**


