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ORIGINAL RESEARCH

Cardiac Mechanical Alterations and Genotype Specific Differences in Subjects With Long QT Syndrome

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ABSTRACT

OBJECTIVES This study aimed to explore systolic and diastolic function and to investigate genotype-specific differences in subjects with long QT syndrome (LQTS).

BACKGROUND LQTS is an arrhythmogenic cardiac ion channelopathy that traditionally has been considered a purely electrical disease. The most commonly affected ion channels are the slow potassium channel, I_{Ks} (KCNQ1 gene/LQT1), and the rapid potassium channel, I_{Kr} (KCNH2 gene/LQT2). Recent reports have indicated mechanical abnormalities in patients with LQTS.

METHODS We included 192 subjects with genotyped LQTS (139 LQT1, 53 LQT2). Healthy persons of similar age and sex as patients served as controls (n = 60). Using echocardiography, we assessed systolic function by left ventricular (LV) ejection fraction (EF), global longitudinal strain (GLS), and contraction duration (16 LV segments). Mechanical dispersion was calculated as standard deviation of contraction duration. Time difference between contraction duration and QT interval from electrocardiography (ECG) was defined as electromechanical time difference. We assessed diastolic function by transmitral filling velocities, early diastolic myocardial velocity (e′), and left atrial volume index (LAVI). Heart rate corrected QT interval (QTc) was assessed from 12-lead ECG.

RESULTS Systolic function by GLS was reduced in subjects with LQTS compared with healthy controls (−22.1 ± 2.1% vs. −23.0 ± 2.0%, p = 0.01), and GLS was worse in subjects with LQT2 compared with subjects with LQT1 (p = 0.01). Subjects with LQTS had longer contraction duration (426 ± 41 ms vs. 391 ± 36 ms, p < 0.001) and more dispersed contractions (33 ± 14 ms vs. 21 ± 7 ms, p < 0.001) compared with healthy controls. Diastolic function was also reduced in subjects with LQTS compared with healthy controls; e′ was lower (10.7 ± 2.7 cm/s vs. 12.5 ± 2.0 cm/s, p < 0.001), and LAVI was increased (30 ± 8 ml/m^2 vs. 26 ± 5 ml/m^2, p = 0.01), also when adjusted for age and other possible confounders.

CONCLUSIONS Subjects with LQTS had a consistent reduction in both systolic and diastolic function compared with healthy controls. Differences in myocardial function between subjects with LQT1 and subjects with LQT2 may indicate that mechanical alterations in LQTS are genotype specific. (J Am Coll Cardiol Img 2015;8:501-10) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

BSA = body surface area

CI = confidence interval

e' = early diastolic myocardial velocity

ECG = electrocardiography

EF = ejection fraction

GLS = global longitudinal strain

IVRT = isovolumic relaxation time

LAVI = left atrial volume index

LQTS = long QT syndrome

LV = left ventricular

QTc = QT interval corrected for heart rate

The congenital long QT syndrome (LQTS) is an inheritable ion channelopathy, predisposing to life-threatening ventricular arrhythmias. Congenital LQTS is most commonly caused by mutations in the genes encoding cardiac potassium channels (1,2). Dysfunction of the cardiac potassium channels results in prolonged cardiac action potential duration, which can be measured as a prolonged QT interval on electrocardiography (ECG). Prolonged and dispersed cardiac action potential durations are considered to be important mechanisms for the life-threatening torsade de pointes ventricular arrhythmia in patients with LQTS (3). LQTS has traditionally been considered to be purely electrical, but mechanical alterations in patients with LQTS were reported by M-mode echocardiography more than 40 years ago (4). We have previously shown, by novel echocardiographic techniques, that mechanical alterations including prolonged contraction durations were present in LQTS (5,6). A more recent multicenter study reported that differences in mechanical and electrical timing were present in LQTS (7). However, to the best of our knowledge, comprehensive and detailed assessments of systolic and diastolic function linked to specific ion channel dysfunction have not been performed in LQTS patients previously. Different types of LQTS exist; LQT1 is characterized by dysfunction of the slow potassium channel (I_{Ks}) (KCNQ1 mutations) (2), whereas LQT2 is characterized by dysfunction of the rapid potassium channel (I_{Kr}) (KCNH2 mutations) (1). The cardiac phenotypes in LQT1 and LQT2 are different, with typical exercise-triggered events in LQT1 and emotion- and postpartum-triggered events in LQT2 (8). To our knowledge, possible mechanical consequences of specific ion channel dysfunction have not previously been studied. Strain echocardiography is a sensitive method for detecting subtle myocardial changes when function is relatively preserved (6,9,10).

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We wanted to investigate genotype-specific differences between subjects with LQT1 and LQT2 as different potassium channels are affected. We hypothesized that there is a link between specific ion channel dysfunction and mechanical alterations. Furthermore, we wanted to explore detailed myocardial mechanics in a large LQTS population compared with healthy controls.

METHODS

STUDY POPULATION. In this cross-sectional study, LQTS mutation-positive subjects were included from our outpatient clinic. Index patients were genetically tested and mutation-positive family members were included by cascade genetic screening. Both single-mutation (n = 183) and double-mutation (n = 9) carriers were included. The exclusion criterion was concomitant cardiac disease of other origin. All participants underwent clinical examination, and LQTS related symptoms were recorded, defined as cardiac syncope or aborted cardiac arrest. Presence of hypertension, diabetes mellitus, or other comorbidities was recorded by interview or from medical records. Blood pressure and the use of beta blocker medication at the time of the echocardiographic examination were recorded. Because beta blocker therapy could influence the studied parameters, beta blocker- naïve subjects with LQTS were analyzed separately. Healthy persons of similar age, sex, and body surface area (BSA) as the patient population were recruited by invitation from hospital staff, medical school, and research laboratories and underwent clinical examination, 12-lead ECG, and echocardiographic examination. None of the healthy persons used QT-prolonging drugs or had cardiovascular disease.

ELECTROCARDIOGRAPHY. Twelve-lead ECG was obtained at time of the echocardiographic examination. The QT interval was measured by the tangent method and was corrected for heart rate (QTc) by Bazett's formula (11). Modified QT dispersion was calculated as the time difference between the longest and the shortest QT interval from the precordial leads (12). T-wave morphology was evaluated for notching (13) and the presence of U waves (14).

ECHOCARDIOGRAPHIC STUDIES. Two-dimensional echocardiographic studies were performed on Vivid 7 or 9 scanners (GE Healthcare, Horten, Norway). Data were analyzed with EchoPAC version 112 (GE Healthcare). Heart rate was recorded at the time of echocardiographic examination.

Systolic cardiac function. Cardiac volumes and left ventricular (LV) ejection fraction (EF) were measured by Simpson's biplane method. LV mass was calculated using the ASE equation (0.8 [1.04 ([LVIDD + PWTD + IVSTD]3 − [LVIDD]3)] + 0.6 g where LVIDD = left ventricular internal dimension in diastole, IVSTD = interventricular septal thickness in diastole, and PWTD = posterior wall thickness in diastole) (15). We assessed longitudinal strains by speckle tracking echocardiography from 3 apical views at a frame rate >50/s (10). The myocardium was traced in each view,

and speckles were tracked frame by frame during the cardiac cycle. The operator manually adjusted segments that failed to track, and segments that subsequently failed to track were excluded. Subjects with <9 accepted segments were excluded from strain analyses. Longitudinal strain curves from 16 LV segments were obtained. The value of the mathematical peak negative strain during the entire cardiac cycle and the time from Q/R on ECG to this time point were detected automatically for each curve by the software. LV global longitudinal strain (GLS) was defined as the average of peak negative strain from 16 LV segments. Contraction duration was calculated as the time from ECG onset of the Q/R-wave to peak negative strain in 16 LV segments (5,6,16). Mechanical dispersion was defined as the standard deviation of the contraction durations (5,6). Electromechanical time difference was defined as the time difference between average contraction duration as a mechanical measure and the QT interval from 12-lead ECG as an electrical measure.

Diastolic cardiac function. Patients with a diagnosis of hypertension or taking antihypertensive medication (n = 10) or patients with diabetes mellitus (n = 6) were excluded from diastolic measurements. We calculated left atrial volume by using the area length method corrected for BSA (left atrial volume index [LAVI]) (17,18). LAVI >28 ml/m^2 was considered increased (17). Using pulsed Doppler, we measured transmitral early (E) and atrial-induced (A) flow velocities, their ratio, and E velocity deceleration time. Isovolumic relaxation time (IVRT) was obtained by pulsed Doppler measurements showing both aortic outflow and mitral inflow. Using tissue Doppler, myocardial early diastolic velocity (e′) was measured at the septal and the lateral annulus by using the average value of 3 measurements. The average of septal and lateral e′ was used for E/e′ (11). Diastolic dysfunction was graded into grades 1, 2, and 3 (11). Because of the age dependency of diastolic function, subjects were grouped by age as <16 years, 16 to 20 years, 21 to 40 years, 41 to 60 years, and >60 years. In addition, findings in subjects with LQTS were compared with established values (11). All echocardiographic studies were de-identified and assigned a study number and stored by an independent study nurse. All measurements were obtained by personnel blinded to patients' status and clinical data.

FEASIBILITY AND VARIABILITY ANALYSES. Strain analyses could be performed in 158 of 192 (82%) patients and in 50 of 60 (83%) healthy controls; 90% of segments could be analyzed in patients, and 93% of segments could be analyzed in healthy controls. Intraobserver and interobserver intraclass correlation for GLS and mechanical dispersion by strain echocardiography were 0.98 (95% confidence interval [CI]: 0.94 to 1.0) and 0.98 (95% CI: 0.95 to 1.0) and 0.88 (95% CI: 0.54 to 0.97) and 0.88 (95% CI: 0.49 to 0.97), respectively.

GENETIC ANALYSES. Genetic testing was performed as part of the diagnostic work-up in patients with LQTS, and only subjects with a pathogenic mutation were included. Cascade genetic screening was performed in family members of mutation-positive index patients. DNA sequencing of the *KCNQ1* and *KCNH2* genes was performed using version 3.1 of BigDye-terminator cycle-sequencing kit and a GeneticAnalyzer 3730 (Applied Biosystems, Foster City, California).

STATISTICAL ANALYSES. Comparisons of proportions were performed by the chi-square test. Continuous data were presented as mean ± SD or as median (quartile 1, quartile 3). Comparisons of means between groups were performed by unpaired Student *t* test (SPSS version 21.0, SPSS Inc., Chicago, Illinois) or by analysis of variance (ANOVA) F test and Bonferroni post-hoc correction when >2 groups were compared. Echocardiographic parameters were adjusted for age, gender, heart rate, BSA, LV mass, blood pressure, and end-diastolic volume by multivariate logistic regression except when collinearity was observed. Correlations among continuous data were explored by linear regression analyses and Pearson's bivariate correlation. A sample size of 60 healthy persons was calculated by power analyses. Interobserver and intraobserver variabilities were expressed by intraclass correlation coefficients. Two-sided p values ≤0.05 were considered statistically significant.

All participants gave written informed consent. The study complied with the Declaration of Helsinki and was approved by the Regional Committees for Medical Research Ethics.

RESULTS

A total of 192 subjects with LQTS (age 36 ± 16 years, 117 [61%] female) were included in the study (**Table 1**). Of the 192, 139 (72%) subjects had LQT1 locus mutations and 53 (28%) had LQT2 locus mutations. Of the 139 subjects with a mutation in the LQT1 locus, 9 (6%) were double-mutation carriers (**Table 2**). Furthermore, 69 (36%) had LQTS-related symptoms (14 cardiac arrest, 55 syncope) and 123 (64%) were asymptomatic mutation-positive family members (**Table 3**). At the time of echocardiographic examination, 75 (39%) subjects with LQTS were taking beta blocker medication. Metoprolol succinate (100 [81,

TABLE 1 Clinical Characteristics and Echocardiographic Findings in 192 Subjects With LQTS and 60 Healthy Persons and Adjusted Odds Ratios for LQTS Patient Status Versus Healthy Persons

	Healthy (n = 60)	LQTS (n = 192)	p Value	OR (CI)*	Adjusted p Value*
Age, yrs	37 ± 10	36 ± 16	0.50		
Female	32 (53)	117 (61)	0.30		
QTc, ms	389 ± 25	467 ± 39	<0.001		
BSA, m^2	1.8 ± 0.2	1.8 ± 0.3	0.87		
Heart rate, beats/min	65 ± 10	64 ± 12	0.31		
Systolic blood pressure, mm Hg	124 ± 13	121 ± 17	0.28		
Diastolic blood pressure, mm Hg	75 ± 10	80 ± 14	0.07		
LV mass, g	129 ± 44	129 ± 45	0.99		
EDV, ml	111 ± 30	109 ± 29	0.60		
EF, %	61 ± 5	61 ± 5	0.98	0.90 (0.81–1.01)	0.07†
GLS, %	−23.0 ± 2.0	−22.1 ± 2.1	0.01	1.65 (1.20–2.26)	0.002
Mechanical dispersion, ms	21 ± 7	33 ± 14	<0.001	1.11 (1.05–1.17)	<0.001
Contraction duration, ms	391 ± 36	426 ± 41	<0.001	1.03 (1.01–1.05)	0.001
Electromechanical time difference, ms	8 ± 32	−32 ± 46	<0.001	0.97 (0.95–0.99)	0.03
Average e′, cm/s	12.5 ± 2.0	10.7 ± 2.7	<0.001	0.96 (0.93–0.99)	0.03
E deceleration time, ms	160 ± 30	185 ± 41	<0.001	1.01 (0.99–1.03)	0.27
IVRT, ms	72 ± 11	83 ± 14	<0.001	1.08 (1.02–1.13)	0.004
Left atrial volume, ml	48 ± 12	56 ± 17	0.002	1.08 (1.03–1.14)	0.003
LAVI, ml/m^2	26 ± 5	30 ± 8	0.01	1.11 (1.02–1.21)	0.02‡
Left atrial area, cm^2	16.9 ± 2.8	18.7 ± 3.3	0.001	1.59 (1.21–2.08)	0.001
E/A	1.9 ± 0.5	1.7 ± 0.7	0.09	0.47 (0.13–1.63)	0.23
E/e′	6.1 ± 1.3	7.1 ± 2.2	0.01	1.22 (0.85–1.76)	0.29

Values are mean ± SD or n (%). p values calculated by unpaired Student *t* test. Odds ratios (OR) and adjusted p values by multivariate logistic regression. *Adjusted for age, gender, heart rate, BSA, LV mass, blood pressure, and EDV. †Adjusted for the foregoing parameters (*), except EDV as a result of collinearity. ‡Adjusted for the foregoing parameters (*), except BSA as a result of collinearity.

BSA = body surface area; CI = confidence interval; e′ = early diastolic myocardial velocity; E/A = ratio between early and atrial transmitral flow velocities; EDV = end-diastolic volume; E/e′ = ratio between early transmitral filling velocity and early diastolic myocardial velocity; EF = ejection fraction; GLS = global longitudinal strain; IVRT = isovolumic relaxation time; LAVI = left atrial volume index; LQTS = long QT syndrome; QTc = QT interval corrected for heart rate.

100] mg) was given in 52 (27%) subjects, propranolol (155 [80, 320] mg) in 6 (3%) subjects, atenolol (50 [38, 81] mg) in 5 (2%) subjects, pindolol (15 [15, 15] mg) in 4 (2%) subjects, bisoprolol (3 [3, 10] mg) in 3 (2%) subjects, timolol (20 [10, 20] mg) in 3 (2%) subjects, nadolol (60 mg) in 1 (0.5%) subject, and metoprolol mixture (30 mg) in 1 (0.5%) subject.

In addition to beta blocker therapy, 19 (10%) patients with LQTS were treated with an implantable cardioverter-defibrillator, 7 (4%) with a single-chamber atrial pacemaker, and 1 (0.5%) with left sympathetic cardiac denervation.

We included 60 healthy persons (Table 1). As expected, QTc was longer in subjects with LQTS compared with the controls. QTc did not differ between LQT1 and LQT2; however, notched T waves/U waves were more common in LQT2 compared with LQT1 (41% vs. 19%, p = 0.01).

SYSTOLIC MYOCARDIAL FUNCTION IN SUBJECTS WITH LQTS. EF was similar in subjects with LQTS and in healthy controls (p = 0.98) (Table 1). Although GLS was within normal limits in the LQTS group, systolic function by GLS was lower in subjects with LQTS compared with healthy controls (p = 0.01) (Figure 1), also when adjusted for age, gender, heart rate, BSA, LV mass, blood pressure, and end-diastolic volume (Table 1) and in separate analyses of beta blocker-naïve subjects (Online Table 1). Importantly, this result was driven by reduced systolic function by GLS in LQT2. Subjects with LQT2 had worse GLS compared with subjects with LQT1 (p = 0.01) (Figure 2). This result remained significant also in analyses of only beta blocker-naïve subjects (n = 94) (LQT2: GLS −20.8 ± 1.8%, vs. LQT1: GLS −22.1 ± 2.1%, p = 0.02). GLS in subjects with LQT1 did not differ from GLS in healthy controls (p = 0.11) (Figure 2).

Contraction duration was longer in subjects with LQTS than in healthy controls (p < 0.001) (Table 1), and it was even longer in symptomatic compared with asymptomatic subjects with LQTS (p < 0.001) (Table 3). In subjects with LQTS, contraction duration was 32 ms shorter than the QT interval. In other words, the electromechanical time difference was −32 ± 46 ms, whereas healthy persons had a longer contraction duration than QT interval, thus giving a

time difference of 8 ± 32 ms ($p < 0.001$) (Table 1). The electromechanical time difference was more pronounced in the symptomatic subjects with LQTS compared with asymptomatic subjects ($p = 0.04$) (Table 3). Mechanical dispersion, reflecting heterogeneous contraction, was more pronounced in the subjects with LQTS compared with healthy controls ($p < 0.001$) (Table 1), and it was most pronounced in symptomatic patients with LQTS ($p < 0.001$) (Table 3). Results were similar for all systolic measures in beta blocker-naïve subjects (Online Table 1) and when adjusted for possible confounders (Table 1). Interestingly, mechanical dispersion was able to differentiate between patients with cardiac arrest (n = 14) and those with syncope (n = 55) (48 ± 16 ms vs. 38 ± 14 ms, $p = 0.02$), a finding indicating a continuum of risk assessed by this parameter.

DIASTOLIC MYOCARDIAL FUNCTION IN SUBJECTS WITH LQTS. After exclusion of patients with hypertension (n = 10) and diabetes mellitus (n = 6), 160 subjects with LQTS were available for diastolic measurements. Diastolic dysfunction was found in 45 (26%) subjects with LQTS. Seventeen (11%) patients had diastolic dysfunction grade 1, 25 (16%) had grade 2, and 3 (2%) had grade 3. The 3 LQTS subjects with diastolic dysfunction grade 3 were 16, 39, and 42 years old and had severe phenotypes, and 1 subject had survived 2 near-drowning accidents.

Average e′ was reduced in subjects with LQTS compared with healthy controls ($p < 0.001$) (Table 1, Figure 3). IVRT and E deceleration times were longer and LAVI was larger in subjects with LQTS (all $p < 0.01$). The diastolic parameters e′, IVRT, and LAVI were altered in LQTS also when adjusted for age, gender, heart rate, BSA, LV mass, blood pressure, and end-diastolic volume (Table 1). Age-grouped analyses showed that LAVI was increased only in age group 41 to 60 years ($p = 0.001$) (Table 4). Beta blocker-naïve subjects with LQTS showed similarly decreased diastolic function (Online Table 1). No differences in diastolic parameters were observed between LQT1 and LQT2.

ELECTROMECHANICAL CORRELATIONS. Electrical measures by QTc in tertiles and QT dispersion both correlated with mechanical measures in subjects with LQTS. QTc in tertiles correlated with contraction duration ($p = 0.006$), mechanical dispersion ($p = 0.01$), electromechanical time difference ($p < 0.001$), LAVI ($p = 0.01$), and E/A ratio ($p = 0.03$) (Figure 4). In addition, QT dispersion correlated with contraction duration ($R = 0.46$, $p < 0.001$), electromechanical time difference ($R = 0.35$, $p = 0.001$), and mechanical dispersion ($R = 0.32$, $p = 0.001$).

TABLE 2 Clinical Characteristics and Echocardiographic Findings in 130 Subjects With LQT1, 53 Subjects With LQT2, and 9 Double-Mutation Carriers

	LQT1 (n = 130)	LQT2 (n = 53)	Double-Mutation Carriers (n = 9)	p Value
Age, yrs	36 ± 15	36 ± 18	26 ± 20	0.14
Female	80 (62)	29 (55)	8 (89)	0.15
Heart rate, beats/min	64 ± 12	63 ± 11	67 ± 16	0.68
QTc, ms	462 ± 34	463 ± 30	561 ± 48*	<0.001
QT dispersion, ms	21 ± 15	20 ± 13	64 ± 34*	<0.001
Symptoms	39 (30)	21 (40)	9 (100)	<0.001
EF, %	61 ± 5	61 ± 6	64 ± 8	0.47
GLS, %	−22.4 ± 2.3	−21.4 ± 1.7†	−22.5 ± 2.5	0.04
Mechanical dispersion, ms	31 ± 13	32 ± 14	54 ± 13*	<0.001
Contraction duration, ms	425 ± 37	418 ± 41	469 ± 62*	0.002
Electromechanical time difference, ms	−24 ± 46	−39 ± 40	−86 ± 25*	0.001
LAVI, ml/m^2	29 ± 8	30 ± 8	35 ± 5	0.44

Values are mean ± SD or n (%). p values calculated by analysis of variance (ANOVA) F-test, or chi-square test. *$p < 0.05$ versus LQT1 and versus LQT2 by Bonferroni post-hoc correction. †$p < 0.05$ versus LQT1 by Bonferroni post-hoc correction. Nominal tests (gender and symptoms) were not post-hoc corrected.

Abbreviations as in Table 1.

DISCUSSION

This study showed that subjects with LQTS had alterations in both systolic and, even more pronounced, diastolic myocardial function. These new data support that mechanical consequences of I_{Ks} and I_{Kr} ion channel dysfunctions exist. Interestingly, genotype-specific differences were present showing lower systolic function in LQT2 and indicating more severe mechanical alterations in subjects with I_{Kr} channel dysfunction.

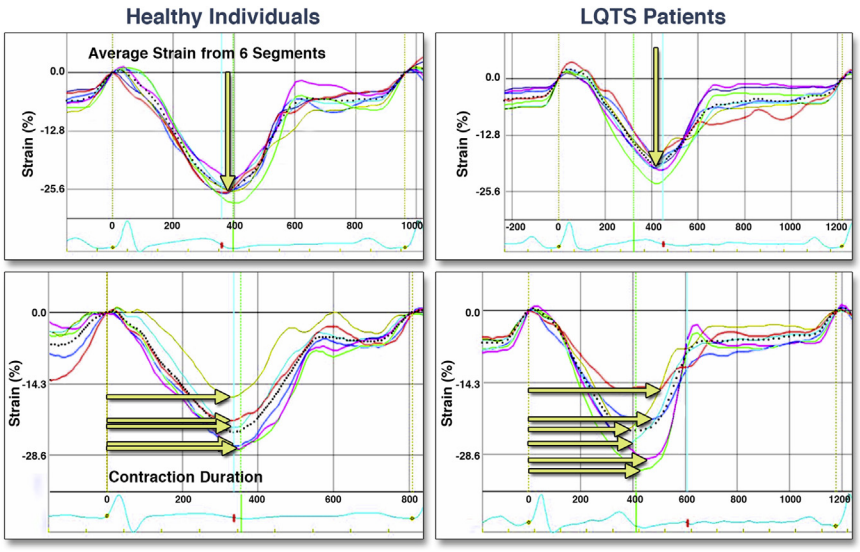
TABLE 3 Echocardiographic Findings in 123 Asymptomatic and 69 Symptomatic Subjects With LQTS

	Asymptomatic (n = 123)	Symptomatic (n = 69)	p Value
Age, yrs	38 ± 16	32 ± 16	0.008
Female	66 (54)	51 (74)	0.006
QTc, ms	456 ± 29	486 ± 47	<0.001
LQT1/LQT2/double-mutation carriers	91/32/0	39/21/9	<0.001*
Aborted cardiac arrest	0	14	<0.001
Heart rate, beats/min	65 ± 12	62 ± 11	0.14
Mechanical dispersion, ms	28 ± 12	40 ± 15	<0.001
Contraction duration, ms	414 ± 37	442 ± 40	<0.001
Electromechanical time difference, ms	−24 ± 42	−42 ± 49	0.04
E/e′	6.9 ± 2.0	7.5 ± 2.6	0.09
E/A	1.6 ± 0.6	1.9 ± 0.7	0.02
IVRT, ms	84 ± 12	82 ± 16	0.43
EF, %	60 ± 5	61 ± 6	0.31
GLS, %	−22.0 ± 2.3	−22.2 ± 2.0	0.65

Values are mean ± SD, n (%), or n. p values calculated by unpaired Student *t* test or chi-square test. *$p < 0.05$ for LQT1/2 versus double-mutation carriers.

Abbreviations as in Table 1.

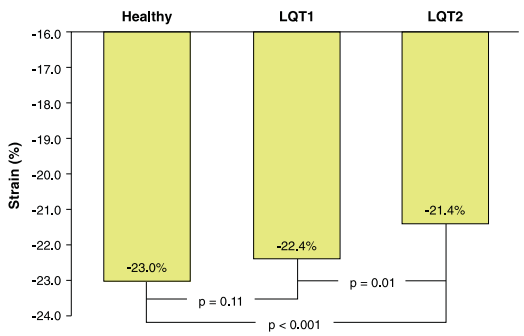
FIGURE 1 Strain Curves in Healthy Persons and in Subjects With LQTS



Strain curves from healthy persons **(left panels)** and subjects with long QT syndrome (LQTS) **(right panels)**. **(Upper) Dotted lines** indicate average longitudinal strain from 6 segments, and the **yellow vertical arrow** indicates the average peak strain. Global longitudinal strain was calculated as average from 16 left ventricular (LV) segments. **(Lower) Yellow horizontal arrows** indicate contraction duration, defined as time from Q/R on electrocardiography to peak strain. Mechanical dispersion was defined as the standard deviation of contraction duration from 16 LV segments. The subjects with LQTS show worse global longitudinal strain and more pronounced mechanical dispersion compared with the healthy persons.

SYSTOLIC MYOCARDIAL CHANGES IN LQTS. Systolic myocardial function by GLS was lower in subjects with LQTS compared with healthy controls, adjusted for possible confounders (19,20) and also in the subgroup of beta blocker-naïve subjects with LQTS. This study confirms and extends previous reports on altered systolic timing (4-7). The mechanisms for the reduced systolic function in LQTS are unclear and were specifically linked to subjects with LQT2. Myocardial function by strain echocardiography was lower in LQT2 compared with LQT1, despite a similar fraction of symptomatic patients and similar QTc values. Our results may suggest a greater impact of I_{Kr} than I_{Ks} channel dysfunction on systolic mechanics at rest. At rest, I_{Kr} channels (LQT2) are more important for normal repolarization (21), whereas I_{Ks} is more important during adrenergic stimulation and at exercise. I_{Ks} dysfunction causes the well-known QT prolongation during and after exercise and the typical exercise-triggered arrhythmias in LQT1 (8,22). Echocardiography was performed at rest, when I_{Kr} is most important for normal repolarization, and this could explain more overt myocardial alterations and lower function in LQT2 compared with LQT1. Future studies should explore myocardial function during and after exercise, to understand how activity level influences the mechanical consequences of ion channel dysfunction.

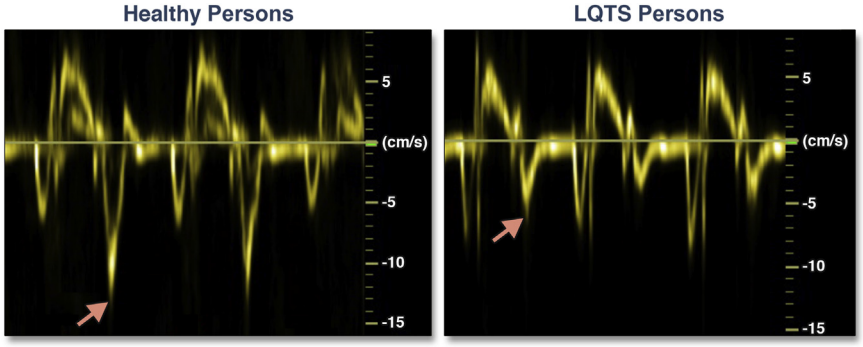
FIGURE 2 Bar Chart of Systolic Function in Healthy Persons and in LQT1 and LQT2 Mutation-Positive Subjects



Average systolic function was lower in long QT syndrome (LQTS) compared with healthy controls, and this difference was mainly the result of the changes in subjects with LQT2.

In the total LQTS population only parameters of myocardial timing were markers of arrhythmic

FIGURE 3 Diastolic Measurements in a Healthy Person and in a Subject With LQTS



Spectral Doppler imaging for measurements of septal early diastolic myocardial velocity from a healthy person **(left)** and a patient with long QT syndrome (LQTS) **(right)**. **Arrows** indicate early diastolic myocardial velocity and show lower value in the subject with LQTS.

events. We have previously reported on myocardial timing by tissue velocities in LQTS and have shown that mechanical systole was regionally prolonged and that onset of diastole was delayed (5). Mechanical dispersion was linked to arrhythmias and was particularly pronounced in subendocardial fibers (6). Mismatch between electrical and mechanical systole has previously been suggested as a mechanism for ventricular arrhythmias, in particular torsade de pointes (23,24). Ter Bekke et al. (7) recently reported a time difference between mechanical and electrical systole in subjects with LQTS. These investigators measured the systolic duration by Doppler flow from the LV outflow tract and found that the electromechanical mismatch was most pronounced in patients with LQTS who had arrhythmic events (7). The mismatch between electrical and mechanical systole was confirmed in this study by the even more accurate strain technique. The previous studies did not examine genotype-specific differences in function and did not present a detailed report on diastolic function.

A strong interaction between myocardial electrical and mechanical function was furthermore demonstrated in our study by the correlation of QTc in tertiles and QT dispersion from ECG with mechanical time measurements. In summary, the arrhythmogenic nature of LQTS may originate from the prolonged and dispersed electromechanics and specific ion channel behavior at rest.

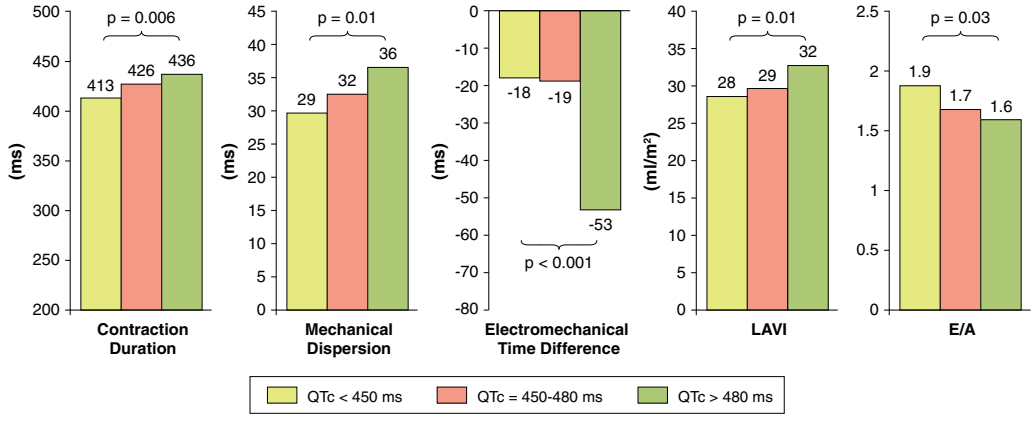
DIASTOLIC MYOCARDIAL CHANGES IN LQTS. In this comprehensive assessment of diastolic function in a large LQTS population, we could consistently demonstrate subtle impairments in diastolic parameters compared with healthy persons. These impairments remained when adjusted for confounders and compared with established values for normal diastolic function (11). In all, 45 patients had diastolic dysfunction by definition. The 3 patients with LQTS who had diastolic dysfunction grade 3 were young persons with severe phenotypes, a finding indicating a relationship between LQTS symptoms and diastolic cardiac function. Diastolic changes are clearly age dependent (25,26), and we therefore age grouped our diastolic results. Subjects with LQTS who were 21 to 40 years of age and 41 to 60 years of age had reduced e′, whereas only those who were 41 to 60 years of age had an enlarged left atrium. This suggests that the changes in e′ precede the changes in atrial size and that atrial enlargement may be a result of long-standing diastolic changes (27). The mechanisms for the observed diastolic alterations in

TABLE 4 Age-Adjusted Diastolic Parameters in LQTS Compared With Age-Adjusted Healthy Persons

	Age (yrs)	Healthy (n = 56)	LQTS (n = 160)	p Value
IVRT, ms	21–40	72 ± 11	85 ± 12	<0.001
	41–60	74 ± 9	83 ± 13	0.04
Average e′, cm/s	21–40	12.9 ± 1.9	11.1 ± 2.2	0.001
	41–60	11.2 ± 1.8	9.6 ± 2.2	0.02
LAVI, ml/m^2	21–40	27 ± 5	29 ± 8	0.15
	41–60	24 ± 3	31 ± 7	0.001
E deceleration time, ms	21–40	163 ± 24	191 ± 39	<0.001
	41–60	159 ± 41	187 ± 37	0.02

Values are range or mean ± SD. p values calculated by unpaired Student *t* test.
Abbreviations as in Table 1.

FIGURE 4 Electromechanical Correlations in Subjects With LQTS



Comparison of QT interval corrected for heart rate (QTc) tertiles; contraction duration, mechanical dispersion, electromechanical time difference, left atrial volume index (LAVI), and ratio between early and atrial transmitral flow velocities (E/A ratio). p value by Pearson's bivariate correlation. LQTS = long QT syndrome.

LQTS are unknown. The reduction of e′ and prolongation of E deceleration time may reflect regional differences in onset of myocardial relaxation resulting from heterogeneity in contraction duration (5). Similarly, the prolongation of IVRT may be attributed to regional differences in onset of relaxation resulting in slowing of LV isovolumic pressure decay and therefore delay in mitral valve opening (28). Potentially, this apparent impairment of LV relaxation in subjects with LQTS may cause elevation of LV early diastolic pressure with subsequent increase in left atrial pressure, leading to the mild atrial enlargement.

A subset of our patients fulfilled the echocardiographic diastolic criteria for heart failure with preserved EF. However, none of our patients had symptoms of heart failure. We believe that the diastolic alterations found in subjects with LQTS are caused by other mechanisms than the diastolic dysfunction in patients with hypertension, diabetes, or LV hypertrophy (29,30). Our findings add to current knowledge that patients with LQTS have impaired diastolic function and support a few previous LQTS case reports; Moss et al. (31) described prolonged IVRT and mitral E deceleration time in 5 patients with LQT3. In addition, a case report of a 2-month-old boy with extreme QT prolongation showed prolonged IVRT and decreased e′ (32).

A subset of subjects was treated with beta blocker medication at the time of echocardiographic examination. Therefore, all analyses were additionally adjusted for heart rate, and beta blocker-naïve subjects were analyzed separately with unchanged results. Therefore, our findings could not be attributed to the use of beta blocker medication.

CLINICAL IMPLICATIONS. The implications of reduced systolic and diastolic function in subjects with LQTS are not clear. None of our patients had overt symptoms of heart failure. Future studies should investigate how normal aging and age-related cardiac comorbidities (e.g., heart failure and coronary artery disease) will affect cardiac function in patients with congenital ion channel dysfunction.

STUDY LIMITATIONS. It could be speculated that the subtle reduction in systolic myocardial function in subjects with LQTS represents myocardial damage resulting from repeated cardiac arrhythmias, syncopes, or even aborted cardiac arrests. However, the frequency of LQTS-related symptoms was similar in LQT1 and LQT2 subjects and could therefore not explain the difference in function.

All echocardiographic measurements were performed in a blinded fashion. However, the presence of an implantable cardioverter-defibrillator lead (n = 19) and differences in the echocardiographic protocol may have revealed the subjects' status as patients versus healthy controls. Strain measurements depend on good image quality and operator experience, as do all echocardiographic measurements.

The observed alterations were subtle, and the importance for clinical outcome has not been elucidated. In addition, the correlation between mechanical and electrical parameters and the underlying mechanisms

should be explored and validated in experimental studies.

CONCLUSIONS

Subjects with LQTS had subtle but widespread changes in cardiac mechanics present during both systole and diastole. Systolic function was more reduced in subjects with LQT2 compared with subjects with LQT1, a finding indicating that specific ion channel dysfunction may have different consequences for cardiac mechanics.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: LQTS has been considered a purely electrical disease. This study indicates the presence of additional myocardial contraction abnormalities and altered systolic and diastolic function. Systolic alterations were most pronounced in symptomatic subjects with LQTS, and evaluation of cardiac mechanics may add information on risk stratification of arrhythmias.

TRANSLATIONAL OUTLOOK: Insight into electromechanical interactions in humans with isolated ion channel dysfunction, as in patients with LQTS, may be of importance for patients with other ion channel diseases and may contribute to future treatment strategies. Future studies should investigate how normal aging and age-related cardiac comorbidities (e.g., heart failure and coronary artery disease) will affect cardiac function in patients with congenital ion channel dysfunction.

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KEY WORDS genotyped, long QT syndrome, myocardial function, strain echocardiography, ventricular arrhythmia

APPENDIX For a supplemental table, please see the online version of this article.