New echocardiographic insights in short QT syndrome: More than a channelopathy?

Simone Frea, MD,[*] Carla Giustetto, MD,[*] Michele Capriolo, MD,[*] Chiara Scrocco, MD,[*] Cristina Fornengo, MD,[*] Sara Benedetto, MD,[*] Francesca Bianchi, MD,[†] Stefano Pidello, MD,[*] Mara Morello, MD,[*] Fiorenzo Gaita, MD[*]

From the [*]Division of Cardiology, University of Turin, Department of Medical Sciences, Città della Salute e della Scienza Hospital, Turin, Italy, and [†]Division of Cardiology, Mauriziano Hospital, Turin, Italy.

BACKGROUND Short QT syndrome (SQTS) is a congenital ion channel disease characterized by an increased risk of sudden cardiac death. Little is known about the possibility that accelerated repolarization alters mechanical function in SQTS.

OBJECTIVES The study investigated the presence of left ventricular dysfunction and mechanical dispersion, assessed by tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE), and their correlation with QT interval duration and genetics.

METHODS Fifteen SQTS patients (7 with HERG and 3 with KCNQ1 mutation) were studied. Electrocardiographic and echocardiographic parameters were compared with age- and sex-matched healthy controls.

RESULTS When compared to the control group, SQTS patients showed reduced left ventricular contraction (global longitudinal strain: $-16.0\% \pm 3.4\%$ vs $-22.6\% \pm 1.7\%$, $P < .001$; myocardial performance index 0.59 ± 0.17 vs 0.34 ± 0.08, $P < .001$) and a higher incidence of ejection fraction $<55\%$ (odds ratio 11, 95% confidence interval 1.045–374, $P = .04$). Mechanical dispersion assessed by TDI ($P < .01$) and STE ($P < .001$) was higher in the SQTS group than in controls; each parameter showed a significant inverse correlation with QT interval but not with QT dispersion.

CONCLUSION This study showed that in SQTS systolic function may also be affected. SQTS patients presented a significant dispersion of myocardial contraction. TDI and STE could become part of the evaluation of this rare disease.

KEYWORDS Short QT syndrome; Genetics; Arrhythmias; Tissue Doppler imaging; Speckle tracking echocardiography; Global longitudinal strain

ABBREVIATIONS **CD** = contraction duration; **ECG** = electrocardiography; **GCS** = global circumferential strain; **GLS** = global longitudinal strain; **HQ** = hydroquinidine; **ICD** = implantable cardioverter defibrillator; **LV** = left ventricular; **MPI** = myocardial performance index; **SD** = standard deviation; **SQTS** = short QT syndrome; **STE** = speckle tracking echocardiography; **TDI** = tissue Doppler imaging

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Introduction

Short QT syndrome (SQTS) is a primary cardiac electrical disease caused by autosomal dominant gain-of-function mutations in genes encoding for potassium channels, resulting in a substantial shortening of QT interval,[1–4] which predisposes to life-threatening arrhythmias. Left ventricular (LV) function has been assumed to be normal in SQTS patients and echocardiography has traditionally been performed only to exclude an additional heart disease. There are clues in support of the hypothesis that electrical changes may cause subtle mechanical dysfunction, as previously reported in long QT syndrome patients.[5,6] Moreover, recent strain studies revealed that patients with long QT syndrome have both prolonged and dispersed myocardial contraction,[7,8] which have been associated with a higher risk of cardiac arrhythmias.

In the setting of SQTS a different density of slow delayed rectifier potassium current (IKs) and inwardly rectifying potassium current (IKr) channels was shown in the ventricles. This could lead to a heterogeneous shortening of the action potential duration through different segments of the left ventricle and could be the substrate for ventricular arrhythmias in SQTS patients. Little is known about the possibility that accelerated repolarization resulting in a shorter action potential could alter the mechanical function in SQTS. A previous study that evaluated SQTS patients by conventional echocardiography did not show any significant alteration in LV function.[9] Tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) have been proven to be superior for assessment of global and regional LV function.[10] We hypothesized that contraction duration (CD) is inhomogeneously distributed through the left

Address reprint requests and correspondence: Dr Stefano Pidello, Division of Cardiology, University of Turin and A.O. Città della Salute e della Scienza, Turin, Italy. E-mail address: stefano.pidello@gmail.com.

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Table 1 Clinical and electrocardiographic characteristics of short QT syndrome patients

Family	Patient no.	Sex	Age	Involved gene	Basal ECG			Therapy			Clinical features			
					HR	QT interval (ms)	QTc interval (ms)	QTc interval on HQ (ms)	Daily HQ dosage (mg)	Implanted device	Family history of SD	First clinical manifestation	Events at follow-up
A	1	M	44	KCNH2	66	270	280*	390*	1000	ICD	Y	Syncope, AF	–
	2	F	41	KCNH2	78	260	300*	430	500	ICD	Y	–	AF
B	3	F	49	KCNH2	88	250	300*	340*	500	ICD	Y	Palpitations	–
	4	M	19	KCNH2	77	300	340*	370*	900	–	Y	–	–
C	5	F	58	Unknown	68	300	320*	380	500	ICD	Y	–	NSVT
	6	M	31	Unknown	67	310	330*	400*	500	ICD	Y	–	NSVT
D	7	M	18	KCNH2	66	260	270	310*	1000	ILR	Y	–	–
	8	F	23	KCNH2	65	300	310	400*	750	ILR	Y	–	NSVT
	9	F	48	KCNH2	77	300	340*	420*	750	ICD	Y	aSD	NSVT
E	10	M	36	KCNQ1	70	320	340*	360	450	–	–	Palpitations	–
	11	M	5	KCNQ1	95	280	350*	–	–	–	–	–	–
	12	F	10	KCNQ1	68	320	340*	–	–	–	–	–	–
F	13	M	22	Unknown	80	310	350*	–	–	ILR	Y	Syncope	–
G	14	M	22	Unknown	70	315	340*	390	600	ILR	–	Palpitations	–
H	15	M	27	Unknown	62	320	325*	–	–	ILR	Y	Syncope	–

AF = atrial fibrillation; aSD = aborted sudden death; HQ = hydroquinidine; ICD = implantable cardioverter-defibrillator; ILR = implantable loop recorder; nsVT = nonsustained ventricular tachycardia; Y = yes.
*QTc value at the time of echocardiogram index.

ventricle, leading to mechanical dispersion. Furthermore, we sought to evaluate whether echocardiographic mechanical dispersion is related to genotype and is affected by pharmacologic therapy.

Methods

Short QT syndrome patients

Fifteen patients with diagnosis of SQTS[11] were included in the study (Table 1). None had structural heart disease. All 15 patients underwent genetic analysis for SQTS: in 7 patients a mutation in KCNH2 (HERG) was found (SQTS1) and 3 patients had a mutation in KCNQ1 (SQTS2), whereas no known mutation was found in 5 patients. Six patients had an implantable cardioverter defibrillator (ICD) and 5 an implantable loop-recorder. One patient had a previous cardiac arrest, 3 patients had a probably arrhythmic syncope, 4 patients had nonsustained ventricular tachycardia documented with the ICD or loop-recorder, 1 patient had paroxysmal atrial fibrillation, and 3 had nondocumented palpitations. Eleven patients received hydroquinidine (HQ) treatment for primary prevention of ventricular arrhythmias, due to frequent nonsustained ventricular tachycardia, or for atrial fibrillation prophylaxis (Table 1).

Control group

Fifteen healthy age- and sex-matched individuals, recruited from hospital staff, served as a control group. All had normal clinical examination, electrocardiography (ECG), QT interval corrected for heart rate (QTc), and standard echocardiography.

The present study conforms with the principles outlined in the Declaration of Helsinki and was approved by the local institutional review board; patients and controls gave written informed consent.

Electrocardiography

A 12-lead ECG was obtained in all subjects at the time of echocardiographic examination. Figure 1 shows the ECG of Patient 2 in Table 1. Bazett's formula was used for QT correction.[12] QTc dispersion was measured as the standard deviation (SD) and as the difference between the longest and the shortest QTc intervals in any of the 12 ECG leads.[13] In SQTS patients on HQ therapy ECG findings were compared to ECG obtained before treatment.

Echocardiographic studies

The echocardiographic studies were performed using iE33 (Philips) and analyzed with the software CMQ 9 for QLAB Advanced Quantification Software version 9.0 (Philips, Eindhoven, NL). SQTS patients on chronic HQ did not discontinue treatment before echocardiographic evaluation.

Since this is, to the best of our knowledge, the first study to evaluate systolic and diastolic impairment in SQTS, we performed a comprehensive echocardiographic evaluation with standard echocardiography, TDI, and STE.

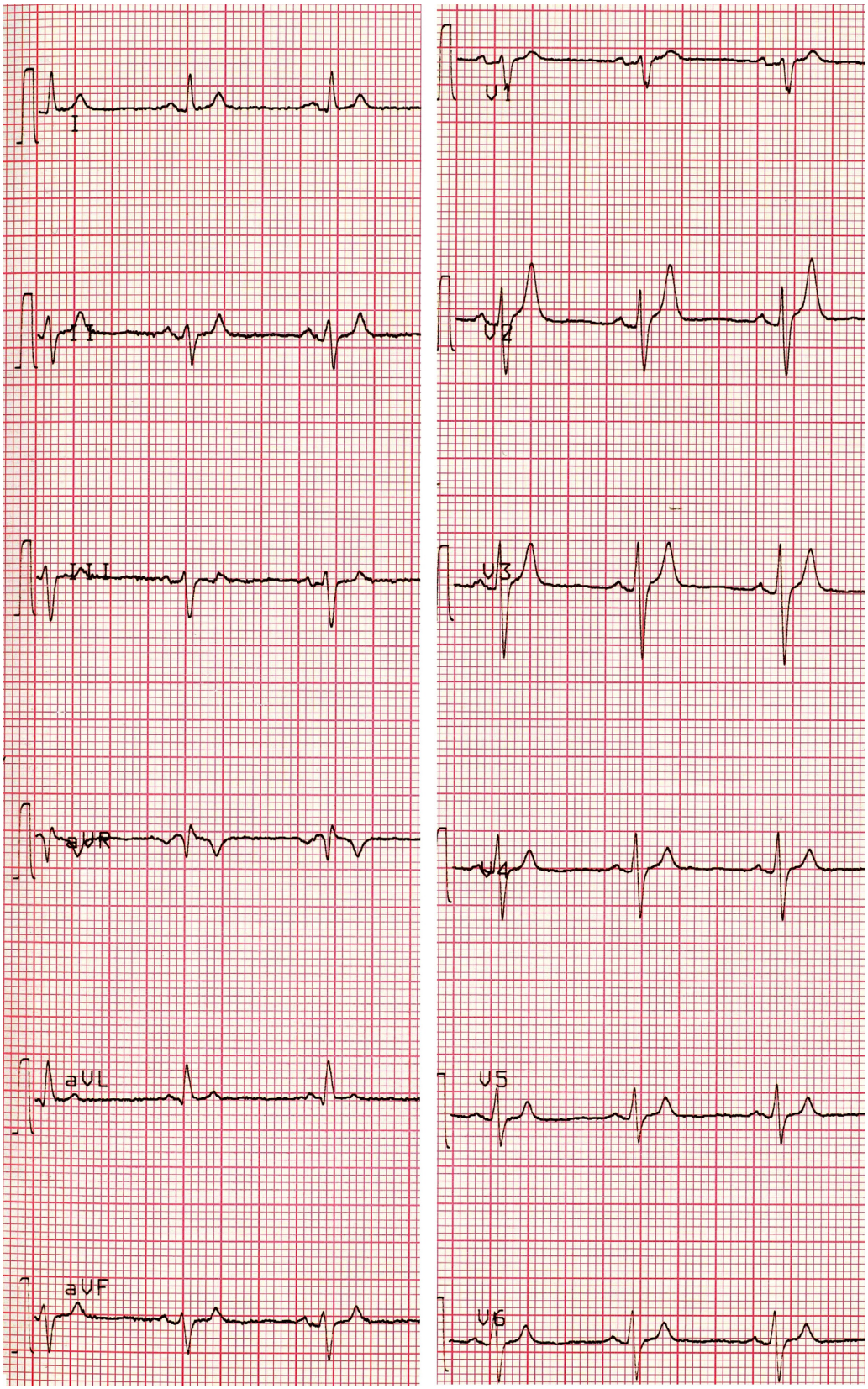

Figure 1 Electrocardiogram of Patient 2 in Table 1 at time of diagnosis. Heart rate 78 bpm, QT 260 ms, QT interval corrected for heart rate 300 ms.

Standard echocardiography

The following parameters were assessed: LV dimensions, systolic (ejection fraction, peak lateral S2 velocity, and myocardial performance index [MPI]) and diastolic function (E/A ratio, deceleration time, isovolumic contraction and relaxation times, septal and lateral e′ and a′, E/e′ ratio), atrial dimensions, right ventricular dimensions, and function. Predefined parameters of systolic dysfunction were as follows: EF $<$ 55%, peak lateral S2 velocity $<$ 8 cm/s,[14] and MPI $>$ 0.47.[15] Predefined parameters of diastolic dysfunction were as follows: septal e′ $<$ 8 cm/s, lateral e′ $<$ 10 cm/s, left atrial volume $\geq$ 34 mL/m^2.[16]

Moreover, the interval from the end of the T wave to aortic valve closure and the interval from the beginning of the Q wave to closure of the aortic valve were analyzed.

Segmentary CD and mechanical dispersion were analyzed by TDI and STE.

Tissue Doppler imaging

The following parameters from TDI were assessed (Figure 2):

(1) S1 or pre-ejection velocity.
(2) S2 or peak ejection velocity; lateral S2 velocity was used as a parameter of LV systolic function.
(3) S3, defined as peak myocardial velocity after aortic valve closure or postejection velocity. Maximum S3 in absolute value, negative or positive, was measured.
(4) Time to beginning of contraction, measured in the 6 basal segments as the time from start of the Q wave on ECG to the beginning of S2.
(5) CD, measured in the 6 basal segments in 3 different ways as the time from ECG onset of the Q wave to end of S2, to end of S3 (zero-crossing) if S3 was present, and to the peak of contraction detected with tissue color M-mode; and SD of these values, calculated as a parameter of mechanical dispersion of contraction.

Speckle tracking echocardiography

We assessed longitudinal and circumferential strains by the speckle tracking technique with a frame rate $>$ 70 frames per second. Three cardiac cycles were analyzed. We assessed the following parameters from myocardial strain:

(1) Global longitudinal strain (GLS), calculated as the average of longitudinal maximum myocardial shortening from 17 LV segments. A GLS value $<$ −18.9% was considered a marker of impaired systolic function.[17]
(2) Global circumferential strain (GCS), calculated as the average of circumferential maximum myocardial shortening from 6 LV medial segments. A GCS value $<$ −22.1% was considered a marker of impaired systolic function.[17]
(3) CD, defined as the time from ECG onset of the Q wave to maximum myocardial shortening of the 17 longitudinally measured and 6 circumferentially measured segments; SD of longitudinal (Figure 3A from a healthy control and Figure 3B from an SQTS patient) and circumferential CD was calculated as a parameter of mechanical dispersion.

Heart rate was recorded at the time of echocardiographic examination, and all echocardiographic time measurements were corrected for heart rate with Bazett's formula.[12]

Efforts were made to ensure good image quality in each patient. TDI parameters could be assessed in 100% of the myocardial segments in SQTS patients and in 100% of the subjects in the control group. Myocardial strain could be

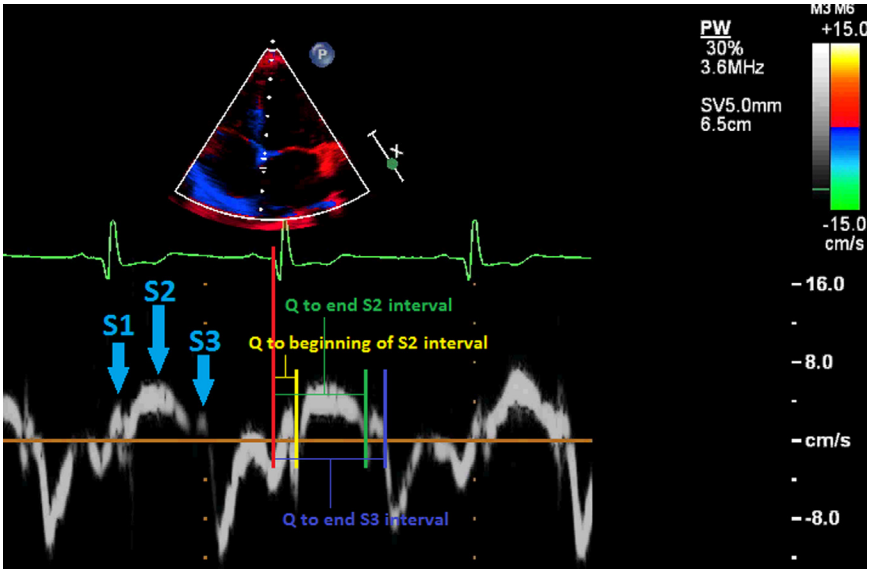

Figure 2 Septal mitral annulus tissue Doppler imaging (TDI) analysis from a patient with short QT syndrome (Patient 1 in Table 1) showing S1 or pre-ejection velocity (isovolumic systole), S2 or peak ejection velocity, and S3 or postejection velocity waves and the derived time intervals evaluating different phases of contraction (respectively, time to beginning of contraction, time to end of ejection contraction, and time to end of postejection contraction). This TDI analysis was performed for all 6 basal segments.

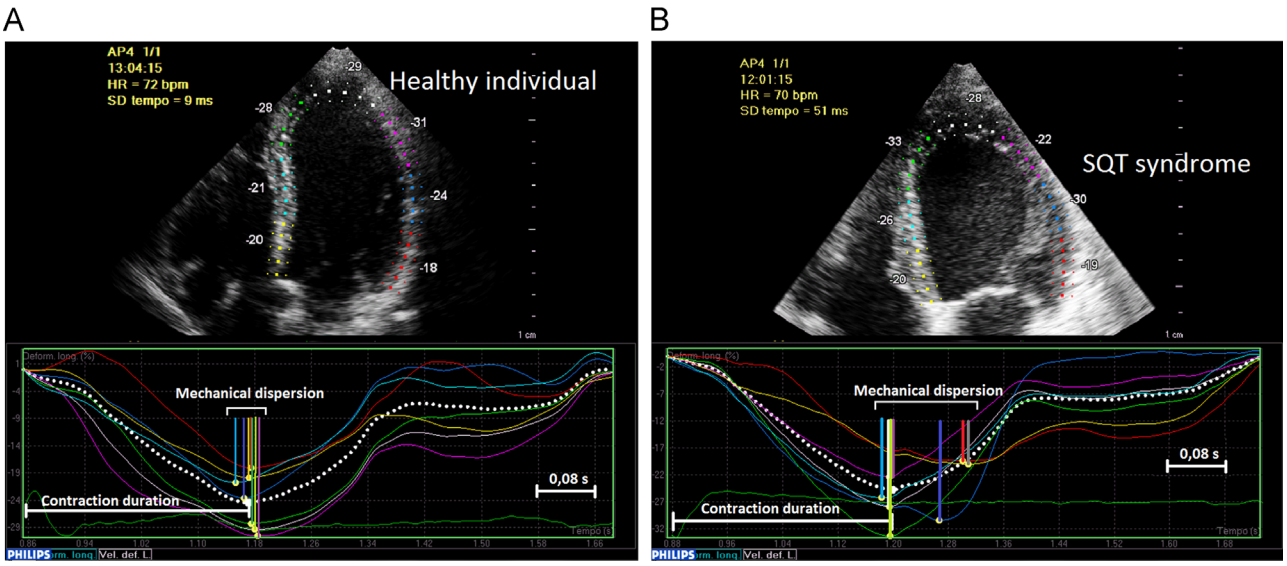

Figure 3 **A:** Mechanical dispersion assessed by speckle tracking echocardiography (STE). The panel shows longitudinal strain curves from 7 different segments (colored lines) and the average strain of the 7 segments (dotted line) from a 4-chamber view in a healthy control. White arrows indicate timing of maximum myocardial shortening. The standard deviation of contraction duration from these 7 segments is 9 ms. The global (from 17 segments) standard deviation of contraction duration is 17 ms. **B:** Mechanical dispersion assessed by STE. The panel shows longitudinal strain curves from 7 different segments (colored lines) and the average strain of the 7 segments (dotted line) from a 4-chamber view in a short QT syndrome (SQTS) patient (Patient 1 in Table 1) with gain-of-function mutation of HERG and previous cardiac syncope. White arrows indicate timing of maximum myocardial shortening. The SQTS patient shows pronounced mechanical dispersion compared to the healthy individual (respectively, standard deviation of contraction duration from the 7 segments by the 4-chamber analysis: 51 vs 9 ms and global standard deviation of contraction duration: 93 vs 17 ms).

assessed in 91% of the myocardial segments in SQTS patients and in 91% of the segments in the control group. The primary analysis was done by a single blinded observer and repeated in a blinded fashion 1 month later by the same operator and by another blinded imaging expert. The authors had full access to data and take responsibility for its integrity.

Statistical analysis

Data are presented as mean ± SD. Comparisons of means were carried out with analysis of variance. Categorical variables are expressed as count and percentage (%). Mid-P exact test was used to compare presence of systolic (any of the following prespecified parameters: EF $< 55\%$, S2 peak ejection velocity < 8 cm/s, MPI > 0.47, GLS $< -18.9\%$, GCS $< -22.1\%$) or diastolic dysfunction (any of the following prespecified parameters: septal e′ < 8 cm/s, lateral e′ < 10 cm/s, left atrial volume ≥ 34 mL/m^2). The normal distribution of mechanical dispersion (TDI parameters: SD of cCD, assessed as Q to end of S2, end of S3, and end of contraction at tissue color M-mode; STE parameters: SD of longitudinal and circumferential cCD [corrected CD–corrected with Bazett's formula]) and ECG dispersion (QTc dispersion, assessed as delta QTc and SD of QTc) was tested with Kolmogorov-Smirnov test and graphically with histograms and normal curve to appraise skewness (data not shown). According to normality testing, strength and direction of the correlation was evaluated with Pearson or Spearman rho tests for all patients: given the low number of patients, the one with the lower significance was reported. Reproducibility was expressed as intraclass correlation coefficient for single measures.

For all statistical analyses, *P* values were 2-sided, with results less than .05 considered significant.

Results

Electrocardiographic findings

Clinical and ECG findings are listed in Table 1. The SQTS group presented significantly ($P < .001$) shorter QT and QTc intervals both at diagnosis (QT 294 ± 25; QTc 322 ± 25 msec) and at the time of the echocardiographic examination (QT 345 ± 35 msec), when compared to the control group. QTc dispersion was significantly higher in SQTS patients (Table 2).

Table 2 Clinical and electrocardiographic findings in short QT syndrome vs control group at time of echocardiogram examination

	SQTS (n = 15)	Control (n = 15)	*P* value
Age (y)	33 ± 13	33 ± 13	1
Male sex (n)	9 (60%)	9 (60%)	1
Hypertension (n)	0 (0%)	0 (0%)	1
Heart rate (bpm)	79 ± 12	69 ± 12	.01
QT (ms)	305 ± 29	381 ± 28	<.001
QTc (ms)	345 ± 35	405 ± 25	<.001
QT dispersion:			
– delta QT	38.5 ± 19	18 ± 6.8	<.001
– delta QTc	44 ± 19.7	20.2 ± 7.9	.001
– SD of QT	12.3 ± 5.5	6.8 ± 1.8	<.001
– SD of QTc	13.9 ± 5.8	7.3 ± 2.2	<.001

Values are mean ± SD.

QTc = QT corrected for heart rate with the Bazett's formula; SD = standard deviation; SQTS = short QT syndrome.

Left ventricular function

Echocardiographic characteristics of SQTS patients and control group subjects are shown in Table 3. Average EF and peak lateral S2 velocity were normal in the SQTS group (EF 60% ± 8% and lateral S2 velocity 10.6 ± 1.8 cm/s). Nevertheless, SQTS patients had a significantly lower EF when compared to the control group and a higher probability to show a slightly reduced (<55%) EF (5 patients in the SQTS group, respectively 52%, 46%, 53%, 49%, and 50%, and no patient in the control group; odds ratio [OR] 11, 95% confidence interval [CI] 1.045–374, $P = .04$). Moreover, SQTS patients showed lower values of GLS (SQTS group −16.0% ± 3.4% vs control group −22.6% ± 1.7%, $P < .001$) and GCS (SQTS group 22.3% ± 7.5% vs control group 27.8% ± 4.8%). Particularly, SQTS patients showed a significantly higher risk to present reduced myocardial contraction (GLS < 18.9%) when compared to the control group (12 SQTS patients vs 1 patient in the control group, OR 45, $P < .001$). Besides, MPI was significantly higher in the SQTS group than in the control group (respectively, 0.59 ± 0.17 vs 0.34 ± 0.08, $P = .001$); 11 patients in the SQTS group and no patient in the control group showed an MPI >0.47 (OR 6.9, $P < .001$). Both GLS and MPI showed an excellent diagnostic accuracy (respectively, area under the curve [AUC] 0.94, 95% CI 0.84–1, $P < .001$ and AUC 0.90, 95% CI 0.76–1, $P < .05$) in detecting SQTS patients. No significant difference in parameters of diastolic function was detected between SQTS patients and control group.

Mechanical dispersion

The intraobserver variability for CD and mechanical dispersion assessed by TDI demonstrated an intraclass correlation coefficient of 0.97 (95% CI 0.99–0.94) and 0.98 (95% CI 0.99–0.96), respectively.

Table 3 Echo-Doppler parameters in short QT syndrome vs control group

	SQTS (n = 15)	Control (n = 15)	*P* value
Chamber quantification			
LVEDD (mm)	51 ± 6.1	49 ± 3.6	.30
LVESD (mm)	32 ± 7.2	27.5 ± 4	.02
dIVST (mm)	9.5 ± 1.6	9.6 ± 1.9	.56
dPWT (mm)	10.1 ± 2.1	9.8 ± 1.7	.77
LA volume (mL/m^2)	25.9 ± 7.4	25.1 ± 7.3	.76
RVEDD (mm)	37 ± 8	37 ± 7	.96
LV function analysis			
EF (%)	60 ± 8	66 ± 7	.05
EF < 55% (n)	5 (66.6%)	0 (0.0%)	.04
IVC time (ms)	89.8 ± 32.7	62.7 ± 18.6	.03
IVR time (ms)	89.9 ± 19.1	79.3 ± 14.9	.08
Ejection time (ms)	258 ± 22	306 ± 27	<.001
Pulsed Doppler MPI	0.59 ± 0.17	0.34 ± 0.08	<.001
Pulsed Doppler MPI < 0.47 (n)	11 (73.3%)	0 (0.0%)	<.001
cT_{end} –AV closure (ms)	70 ± 41	33 ± 15.9.3	.001
cQ-AV closure (ms)	406 ± 23.4	390 ± 30	.20
Average positive S1, pre-ejection velocity (cm/s)	5.81 ± 2.28	6.54 ± 2.18	.02
Average S1, pre-ejection velocity (cm/s)	2.57 ± 0.97	2.25 ± 0.98	.47
Peak lateral S2 velocity (cm/s)	10.6 ± 1.8	11.1 ± 1.4	.40
Peak lateral S2 velocity < 8 cm/s (n)	2 (13.3%)	0 (0.0%)	.12
Average positive S3, postejection velocity (cm/s)	4.42 ± 0.69	4.42 ± 1.23	.98
Average S3, postejection velocity (cm/s)	−0.51 ± 1.96	−1.4 ± 1.35	.28
Average TDI MPI	0.59 ± 0.06	0.51 ± 0.05	.01
Global longitudinal strain (%)	−16.0 ± 3.4	−22.6 ± 1.7	<.001
Global longitudinal strain < 18.9% (n)	12 (80.0%)	1 (6.7%)	<.001
Global circumferential strain (%)	22.3 ± 7.5	27.8 ± 4.8	.019
E/A ratio	1.4 ± 0.38	1.48 ± 0.53	.63
DT (ms)	162 ± 45	177 ± 61	.36
Septal e′ (cm/s)	10.5 ± 1.9	11.5 ± 2.3	.23
Lateral e′ (cm/s)	16.4 ± 3.2	15.9 ± 4.2	.74
Septal E/e′ ratio	8 ± 1.9	7.7 ± 1.8	.87
Lateral E/e′ ratio	5.9 ± 1.9	5 ± 1.5	.25
RV function analysis			
TAPSE (mm)	24.8 ± 4.6	27.2 ± 4.1	.14
Peak RV S2 velocity (cm/s)	13.5 ± 4.5	15 ± 2.5	.26
sPAP (mm Hg)	26.3 ± 5	25.8 ± 3.6	.77

Values are mean ± SD.

dIVST = diastolic interventricular septum thickness; dPWT = diastolic posterior wall thickness; DT = deceleration time; DTI = tissue Doppler imaging; EDD = end diastolic diameter; EF = ejection fraction; ESD = end systolic diameter; IVC = isovolumic contraction; IVR = isovolumic relaxation; LA = left atrial; LVEDV = left ventricular end diastolic volume; LVESV = left ventricular end systolic volume; MPI = myocardial performance index; Tend–AV closure = interval from end of T wave to aortic valve closure; Q–AV closure = interval from Q wave to aortic valve closure; RVEDD = right ventricular end diastolic diameter; sPAP = systolic pulmonary artery pressure; SQTS = short QT syndrome; TAPSE = tricuspid annular plane systolic excursion.

No significant difference was detected in mean CD between the 2 groups by TDI and STE analysis (Table 4).

In contrast to healthy individuals, SQTS patients showed mechanical dispersion, assessed as standard deviation of CD (Q wave to end of contraction) at TDI (Q to end of S3: 22.4 ± 10.1 ms vs 14.2 ± 5.2 ms, $P = .01$; color M-mode: 30.8 ± 14 ms vs 16.2 ± 9.5 ms, $P < .01$) and at STE evaluation (SD of corrected longitudinal CD: 63 ± 13.6 ms vs 37 ± 9.6 ms, $P < .001$). Besides, TDI analysis did not show any difference in the first phases of contraction (Q wave to beginning of S1 and S2 as absolute values and SD of CD) between the 2 groups. Thus TDI showed that mechanical dispersion affects only the final part of contraction, as Q to end of S3 showed significant difference while Q to end of S2 did not. No significant difference in mechanical dispersion was appreciated between patients with and without HERG mutation. Interestingly, patients with a history of cardiac events (1 patient with previous aborted sudden death and 3 patients with previous probable arrhythmic syncope) showed a higher mechanical dispersion when compared with patients without events (SD of corrected longitudinal CD: 74.9 ± 13.5 ms vs 60.4 ± 8.4 ms, $P = .025$; SD of contraction deviation assessed by color M-mode: 40.7 ± 6 vs 26 ± 14.5, $P = .08$).

Influence of hydroquinidine on electrocardiographic and echocardiographic findings

Patients on HQ therapy showed significantly longer values of QT and QTc (respectively, 338 ± 24 ms vs 296 ± 32.4 ms, $P = .02$; 380 ± 39 ms vs 335 ± 29 ms, $P = .03$) and lower QTc dispersion (delta QTc 25.2 ± 9.5 ms vs 48.5 ± 15.1 ms, $P < .01$; SD of QTc 9.2 ± 2.5 ms vs 15.8 ± 4.6 ms, $P < .01$) when compared to ECG findings before treatment.

No significant difference in LV function was appreciated between patients on HQ and those who were not. Patients on HQ treatment showed a nonsignificant trend towards a lower mechanical dispersion (SD of CD assessed by Q to end of S3: 17.3 ± 9.5 ms vs 24.6 ± 10.6 ms, $P = .37$; by color M-mode: 22.5 ± 12.9 ms vs 35.3 ± 14.1 ms, $P = .19$; by longitudinal strain: 55 ± 17 ms vs 62 ± 9 ms, $P = .32$).

Correlations between left ventricular function, mechanical dispersion, and electrocardiogram

A direct correlation was appraised between systolic function assessed by GLS and average peak S2 velocity and QT duration (respectively, $r = -0.519$, $P < .01$ and $r = -0.33$, $P = .07$) (Figure 4A).

Mechanical dispersion assessed by TDI (end-S3 and color M-mode) and STE showed a significant inverse correlation with QT duration (respectively, $r = -0.487$, $P < .01$; $r = -0.448$, $P < .05$; and $r = -0.404$, $P < .05$) (Figure 4B) but not with QT dispersion. Finally, greater mechanical dispersion at TDI (end-S3 and color M-mode) and STE correlated with lower GLS (respectively, $r = 0.468$, 0.648, and 0.493, $P < .01$ for each parameter, Figure 4C).

Discussion

Short QT syndrome and left ventricular function

SQTS is a channelopathy; therefore, LV function is assumed to be normal. The present study for the first time calls this axiom into question. SQTS patients have slight but significant systolic dysfunction in presence of normal (or near-normal) ejection fraction. MPI was significantly prolonged, even when compared to normal values (0.37 ± 0.05 and 0.39 ± 0.05) reported in previous studies.[18,19] MPI was previously studied as a diagnostic and prognostic tool in idiopathic dilated cardiomyopathy[18] and other structural cardiac diseases such as amyloidosis and heart transplantation.[20] As we did not observe a significant change in isovolumic contraction and relaxation times, the higher MPI must be driven by the reduced ejection time. Whether

Table 4 Contraction duration and mechanical dispersion in short QT syndrome and control group

	SQTS (n = 15)	Control group (n = 15)	*P* value
Contraction duration:			
– TDI analysis			
Time to contraction, Q to begin of S2 (ms)	21 ± 10.9	15.7 ± 5.1	0.18
Mean cCD, Q to end of S2 (ms)	397 ± 26	399 ± 23	0.86
Mean cCD, Q to end of S3 (ms)	466 ± 37	465 ± 32	0.94
Mean cCD, tissue color M-mode (ms)	458 ± 44	441 ± 44	0.3
– STE analysis			
Mean cCD, longitudinal (ms)	378 ± 64	359 ± 42	0.48
Mean cCD, circumferential (ms)	381.4 ± 18.7	376.8 ± 27.6	0.67
Mechanical dispersion:			
– TDI analysis			
SD of cCD, Q to end of S2 (ms)	16.2 ± 7.7	14.4 ± 11.6	0.62
SD of cCD, Q to end of S3 (ms)	22.4 ± 10.1	14.2 ± 5.2	0.01
SD of cCD, tissue color M-mode (ms)	30.8 ± 14	16.2 ± 9.5	0.002
– STE analysis			
SD of longitudinal cCD (ms)	63 ± 13.6	37 ± 9.6	<.001
SD of circumferential cCD (ms)	61 ± 20.6	43.4 ± 20.9	0.08

Values are mean ± SD.

cCD = contraction duration corrected for heart rate with Bazett's formula; SD = standard deviation; TDI = tissue Doppler imaging.

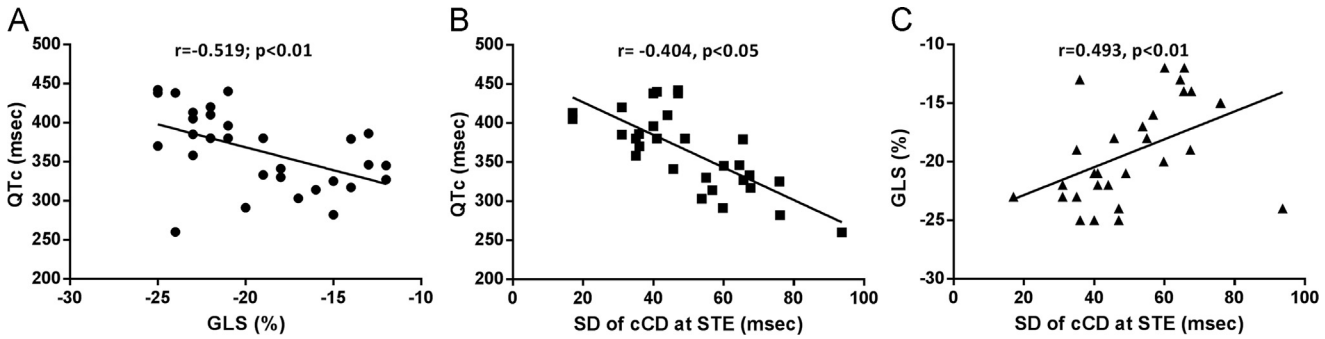

Figure 4 **A:** Correlation between global longitudinal strain (GLS) and corrected QT interval (QTc). **B:** Correlation between mechanical dispersion assessed by speckle tracking echocardiography (STE) (as standard deviation of corrected contraction duration) and QTc. **C:** Correlation between mechanical dispersion assessed by STE (as standard deviation of corrected contraction duration) and GLS.

the impaired MPI is a mere numerical result of the accelerated repolarization or a marker of reduced contractility is a challenging question. Still, this is an interesting result that highlights the electromechanical consequences of this channelopathy. These data are partially in contrast with previous findings by Schimpf et al[9]: comparing 5 SQTS patients with a control group, they did not find any statistical difference in ejection times, isovolumic contraction, and relaxation. Nevertheless, they did not calculate MPI, a ratio of isovolumic times to ejection time; obtaining average MPI from their data, we could appreciate a difference between SQTS patients and controls (0.49 vs 0.39).

In addition, strain echocardiography confirmed the surprising results on systolic dysfunction in SQTS. GLS is a strong diagnostic tool for the diagnosis of suspected cardiomyopathies and it has been recently demonstrated to be a prognostic marker even in the presence of preserved ejection fraction. Interestingly, more than half of the SQTS population showed pathologic values of GLS. We did not report any difference in GLS between SQTS patients with or without HQ treatment. This fact seems to suggest that lower GLS is not linked to HQ treatment. On the other hand, we observed that the shorter the QTc interval, the lower the GLS. The association with QTc strengthens our hypothesis about the possible impact of electrical changes on mechanical function. Moreover, TDI analysis, although a less robust tool for LV function assessment, gave comparable results. These results lead to the unexpected hypothesis that the time course of the calcium transient might be altered by the marked abbreviation of the ventricular action potential. In fact, a recent study on electromechanically coupled human ventricle models effectively showed that accelerated repolarization, without compensatory changes, might result in altered calcium loading and a reduction in contractile activity.[21]

Short QT syndrome and left ventricular mechanical dispersion

SQTS patients showed a greater mechanical dispersion than a control group matched for age and sex. This reflects electrical dispersion of repolarization. TDI demonstrated mechanical dispersion at the end but not at the beginning of contraction. The explanation might be that accelerated repolarization affects the end but not the beginning of contraction. For this reason we preferred to use the term "mechanical dispersion" rather than "dyssynchrony." The low number of patients with aborted sudden death or syncope did not allow us to demonstrate whether the dispersion of mechanical contraction assessed by TDI and STE might help in identifying high-risk patients. Further studies are needed to confirm echocardiographic mechanical dispersion as an additional risk stratification tool in SQTS patients.

Possible mechanisms

Shortening of action potential duration and electrical dispersion may cause wall motion abnormalities, which can be assessed by echocardiography.[5,6] Dispersion of repolarization,[22] detected as mechanical dispersion by TDI or STE, has been recently proposed as the substrate of arrhythmias in patients with myocardial infarction,[23] arrhythmogenic right ventricular cardiomyopathy,[24] and long QT syndrome.[7,8] In the context of SQTS, dispersion of repolarization could facilitate the occurrence and maintenance of ventricular (and atrial) fibrillation by fragmentation of wavefronts and wavelet formation secondary to functional tissue heterogeneity.[25,26] A heterogeneous shortening of the action potential duration, both in the different layers of the left ventricle wall[26] and through the different segments, could be the substrate for re-entry responsible for tachycardia/fibrillation in SQTS patients. Spatial heterogeneity of ventricular repolarization may be due to the different densities of IKs and IKr channels.[27,28] Pharmacologic approaches blocking IKr and IKs, such as HQ, may reduce the vulnerability to tachyarrhythmias.[29,11]

Clinical implications and limitations

Mechanical dispersion is relatively simple to obtain and has excellent reproducibility in expert hands. We propose that TDI and STE echocardiography should become part of the routine clinical evaluation for SQTS patients. However, SQTS is a rare disease and the small sample size is a major limitation of the study. An external validation of these parameters is required to test their accuracy in a larger

population study. Owing to the low number of arrhythmic events, our study could not provide data to demonstrate that SQTS patients with greater mechanical dispersion assessed by echocardiography are more likely to develop arrhythmias than those without.

Since HQ treatment could not be discontinued before echocardiographic evaluation, we could not evaluate the impact of therapy on mechanical dispersion. As a significant inverse correlation between mechanical dispersion and QT interval was appreciated, we can suppose that the prolongation of QT interval obtained after HQ treatment may lead to a reduction of mechanical dispersion. Further studies are needed to demonstrate this hypothesis and to test the ability of echocardiography in the detection of response to HQ.

Conclusion

This study showed for the first time that SQTS, a primary electrical disease, may affect systolic function. SQTS patients showed a slight but significant reduction of LV systolic function and a high degree of mechanical dispersion assessed by TDI and STE. Therefore, we propose to include TDI and STE evaluation of systolic function and mechanical dispersion in the evaluation of STQS patients. Further studies are needed to validate the diagnostic and prognostic role of these data.

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CLINICAL PERSPECTIVES

This study shows for the first time that short QT syndrome (SQTS), a primary electrical disease, may affect left ventricular (LV) systolic function. Shortening of action potential duration and electrical dispersion may cause wall motion abnormalities, which can be assessed by echocardiography SQTS patients showed a slight but significant reduction of LV systolic function and a higher degree of mechanical dispersion assessed by tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE), when compared with a control group matched for age and sex. These techniques have been proven to be superior to conventional echocardiography for assessment of global and regional LV function.

Mechanical dispersion is relatively simple to obtain and has excellent reproducibility in expert hands. Mechanical dispersion showed a significant inverse correlation with QT duration. We propose that TDI and STE echocardiography become part of the routine diagnostic clinical evaluation for SQTS.

Independently from the pathologic substrate, above a critical degree, mechanical dispersion may represent an independent additional mechanism of ventricular arrhythmias. The low number of patients with aborted sudden death or syncope did not allow us to demonstrate whether the dispersion of mechanical contraction might help in identifying high-risk patients. Nevertheless, patients with events showed higher mechanical dispersion when compared with patients without history of cardiac events. Further studies are needed to confirm whether echocardiographic mechanical dispersion may become an additional risk stratification tool in SQTS patients.