T-Wave Morphology in Short QT Syndrome

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Background: Short QT syndrome (SQTS) is an inherited disorder characterized by a short QT interval and vulnerability to ventricular tachyarrhythmias. The diagnostic criteria for this syndrome are not well defined, since there is uncertainty about the lowest normal limits for the corrected QT (QTc) interval.

Objective: The aim of this study was to determine whether T-wave morphology parameters are abnormal in short QT subjects and whether those parameters can help in the diagnosis of SQTS.

Methods and Results: We describe three families (10 patients) with short QT intervals (QTc 310 ± 32 ms). Seven subjects had suffered serious arrhythmic events and three were asymptomatic. T-wave morphology was assessed using the principal component analysis (PCA). QTc was significantly shorter and T-wave amplitude in lead V_2 higher in the short QT subjects compared to healthy controls ($n = 149$), ($P < 0.001$ for both). The total cosine of the angle between the main vectors of the QRS and T-wave loops (TCRT) was markedly abnormal among the symptomatic patients with short QT syndrome ($n = 7$) (TCRT -0.14 ± 0.55 vs 0.36 ± 0.51, $P = 0.019$). None of the three asymptomatic patients with short QT but without a history of arrhythmic events had an abnormally low TCRT.

Conclusion: Our observations suggest that patients with a short QT interval and a history of arrhythmic events have abnormal T-wave loop parameters. These electrocardiogram (ECG) features may help in the diagnosis of SQTS in addition to the measurement of the duration of QT interval from the 12-lead ECG.

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short QT syndrome; diagnosis; electrocardiogram; computer-assisted analysis; T-wave morphology

Short QT syndrome (SQTS) is a novel inherited arrhythmogenic disorder characterized by an abnormally short QT interval and vulnerability to ventricular tachyarrhythmias.[1,2] In addition to the short QT interval, the ST segment is almost absent and another characteristic is the presence of tall, peaked T waves in the precordial leads.[1,2]

At present, there are relatively few recognized patients with abnormally short QT interval. Therefore, diagnostic criteria and risk stratification for these patients are not well defined, and many questions regarding the diagnosis and treatment remain open. There is a high incidence of atrial fibrillation (AF) in patients with the SQTS but they have also a high risk of sudden cardiac death. Therefore, it is crucial to identify those patients who are vulnerable to life-threatening cardiac arrhythmias.

Lately, there has been a growing interest on T-wave/QRS loop descriptors in the assessment of risk for ventricular tachyarrhythmias. For example, the total cosine of the angle between the main vectors of the QRS and T-wave loops (TCRT),

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which reflects the homogeneity between depolarization and repolarization, has been shown to predict outcome in several patient populations.[3,4] This study aimed to assess whether there are abnormalities in T-wave/QRS loop-based parameters in patients with SQTS by comparing these variables between short QT patients and healthy controls.

METHODS

Study Population

Ten patients with a short QT interval (SQTS subjects) from three different SQTS families were included in the study. Two families were from Italy (families F1 and F2, respectively) with a documented gain-of-function mutation of the human ether-a-go-go-related gene (HERG). One family was from Finland (family F3) without any detected gene mutation but exhibiting well-documented life-threatening arrhythmias (Table 1). SQTS was defined as a visibly short QT interval with peaked T waves in the right precordial leads and a family history of ventricular tachycardia (VT), ventricular fibrillation (VF), or syncope. All families had at least one family member who had SQTS-related severe symptoms, such as syncope events or documented VT/VF episodes. All subjects underwent extensive examinations including clinical examination, echocardiography, and 12-lead electrocardiogram (ECG). Programmed electrical stimulation (PES) was performed in all of the symptomatic subjects to estimate the inducibility of ventricular tachyarrhythmias. Demographic data, baseline ECG measurements, symptoms, and documented arrhythmias of the SQTS subjects are shown in Table 1. The control population consisted of 149 healthy subjects (age 51 $\pm$ 6 [mean $\pm$ SD] years, 72 males). These subjects underwent a thorough clinical examination, two-dimensional and M-mode echocardiography, and extensive laboratory tests in the Oulu University Hospital. The details of this population have been described earlier.[5,6]

ECG Analysis

T-wave/QRS loop descriptors were assessed to evaluate possible inhomogeneity of the depolarization and repolarization waveforms by using the principal component analysis (PCA) technique.

A standard 12-lead ECG was obtained from each study subject at a paper speed of 50 mm/s in the Finnish family and control population, and at a paper speed of 25mm/s in the Italian families. All subjects were in sinus rhythm during the ECG recording. Manual QT interval measurement was performed using routine tangential method and rate-corrected QT time was calculated by the Bazett's method. The ECGs were scanned and digitized using the UN-SCAN-IT Graph Digitizing System Version 6.0 (Silk Scientific Inc, Orem, UT). Several descriptors of T-wave morphology were automatically calculated from the 12-lead ECGs, using a custom-made software application described earlier.[7]

T-Wave/QRS Loop Descriptors

The software automatically creates T-wave and QRS loops in Frank's three-dimensional space using matrix modification and the singular value decomposition technique. The software calculates the plane where the loop has the maximum first and second dimensions. The loop is rotated until its longest axis is parallel to the x-axis. The longest axis of the loop is defined as the width of the loop (W), and the second longest axis perpendicular to the longest axis as the height of the loop (H). The ratio of H to W (H/W), which indicates the shape of the loop, is then calculated. Next, a rectangle is arranged around the loop. The rectangle is divided into 100 (10 $\times$ 10) subrectangles. T-wave loop dispersion (TWLD) is defined as the number of subrectangles traversed by the borderline of the corresponding loop. The cosine of the angle between the main vectors of the T-wave loop and the QRS loop in the 3-dimensional space (TCRT) is determined. It represents the relationship between the orientations of the repolarization and depolarization fronts.[3]

Genetic Screening

The HERG, KCNQ1, and KCNJ2 genes, which have been previously described in SQTS, were screened in all families.[8–11] Genomic DNA was isolated from peripheral blood leukocytes using a commercial kit (Puregene; Gentra System, Qiagen, Hilden, Germany). The exons of HERG, KCNQ1, and KCNJ2 genes were amplified and analyzed by direct sequencing using primers designed from the published gene sequences. Polymerase chain reaction products were purified with a commercial reagent (ExoSAPIT, USB, Cleveland, OH) and

Table 1. Individual Characteristics and T-wave Loop Parameters of the Short QT Syndrome Subjects and Controls

Parameters	F1-1	F1-2	F1-3	F2-4	F2-5	F2-6	F2-7	F3-8	F3-9	F3-10	Control Population
Age	35	31	6	51	39	49	21	19	50	82	51 ± 6 years
Sex	M	F	F	M	M	M	M	M	M	M	M: 48.3%
QT	320	240	240	300	320	320	320	280	310	280	—
QTc	292*	262*	279*	335*	345*	358*	330*	313*	307*	280*	405 (399.2–412.2)
Mutation	HERG	HERG	HERG	HERG	HERG	HERG	HERG	Not defined	Not defined	Not defined	
Symptoms	Syncope	Pre-syncope	Aborted SCD	Syncope	Syncope	——	——	Aborted SCD	VT	——	
T-wave amplitude V_2	1.89*	0.71*	0.39*	1.19*	1.03*	1.43*	1.11*	1.30*	1.05*	0.61*	0.50 (0.44–0.55)
TCRT	0.85*	−0.44*	−0.21*	0.15*	−0.22*	0.26	0.63*	−0.13*	−0.95*	0.84*	0.36 (0.25–0.47)
Width	1.48	0.59	0.39	0.73	0.54	0.87	0.61	0.75	0.56	0.57	3.98 (0–10.65)
Height	0.24*	0.30*	0.18*	0.44*	0.26*	0.26*	0.18*	0.23*	0.28*	0.22*	0.14 (0.13–0.16)
Ratio	0.16*	0.50	0.47	0.60*	0.48	0.30*	0.29*	0.30*	0.50	0.39	0.43 (0.32–0.53)
TWLD	36	35*	41*	36	35*	35*	36	33*	39*	34*	37 (36–38)

M = male; F = female; SCD = sudden cardiac death; VT = ventricular tachycardia; QT and QTc (ms); TCRT = total cosine R-to-T; Width = width of the T-wave loop; Height = height of the T-wave loop; Ratio = ratio of the T-wave loop height and width; TWLD = T-wave loop dispersion. * = Value outside of the control population 99% confidence interval.

Table 2. QTc, T-wave Amplitude and T-wave Loop Parameters in Short QT Syndrome Subjects versus Control Population

Parameters	All SQT Subjects (n = 10)	Symptomatic SQT Subjects (n = 7)	Control Population (n = 149)	P Value
T-wave amplitude V_2	1.07 ± 0.43* (0.39–1.89)	1.08 ± 0.47† (0.39–1.89)	0.50 ± 0.27 (−0.29–1.18)	*P < 0.001 †P = 0.001
TCRT	0.08 ± 0.58 (−0.94–0.85)	−0.14 ± 0.55† (−0.95–0.85)	0.36 ± 0.51 (−0.99–0.98)	†P = 0.019
Width	0.71 ± 0.30* (0.39–1.48)	0.72 ± 0.35† (0.39–1.48)	3.98 ± 31.2 (0.10–315.7)	*P < 0.001 †P = 0.004
Height	0.26 ± 0.07* (0.18–0.44)	0.27 ± 0.08† (0.18–0.44)	0.14 ± 0.07 (0.01–0.39)	*P < 0.001 †P < 0.001
Ratio	0.40 ± 0.13 (0.16–0.60)	0.43 ± 0.15 (0.16–0.60)	0.43 ± 0.50 (0.11–4.83)	N/A
TWLD	35.9 ± 2.38 (33–41)	36.3 ± 2.75 (33–41)	37.2 ± 5.62 (3–50)	N/A
QTc	309.8 ± 32.1* (262–358)	306.9 ± 38.2† (262–358)	405.7 ± 30.2 (297–503)	*P < 0.001 †P < 0.001

Numbers are presented as mean ± standard deviation and range in parenthesis; QTc (ms), TCRT = total cosine R-to-T; Width = width of the T-wave loop; Height = height of the T-wave loop; Ratio = ratio of the T-wave loop height and width; TWLD = T-wave loop dispersion; N/A = not significant, P > 0.05. *Significant difference between SQTS subjects vs. control population; †Significant difference between symptomatic SQTS subjects vs. control population.

were directly sequenced from both directions with the use of ABI PRISM 3100- Avant Automatic DNA Sequencer (Applied Biosystems, Foster City, CA).

Statistical Analysis

The data were analyzed using SPSS 10.1 software (SPSS Inc., Chicago, IL, USA). The results are expressed as means with standard deviation. A nonparametric Mann-Whitney test of independent samples was used to study the statistical significances of the differences of the variables between the study groups. P values less than 0.05 were considered statistically significant. T-wave loop parameters and corrected QT (QTc) values were considered abnormal when they outranged the 99% confidence interval (CI) boundaries of the control population.

RESULTS

Genetic Screening

A gain of function mutation in the HERG gene had been detected earlier in all of the SQTS subjects of the two Italian SQTS families.[9] In the Finnish SQTS family, HERG, KCNQ1, and KCNJ2 were screened but no mutations were found.

QTc Intervals and T-Wave Amplitude in SQTS Subjects

The QTc intervals of SQTS patients were significantly shorter and T-wave amplitudes in lead V2 significantly higher than those of the control subjects (Table 2). All SQTS subjects had shorter QT interval and nine out of 10 of the SQTS subjects had higher T-wave amplitude in lead V2 than the 99% CI boundaries of the control population (Table 1).

T-Wave Loop Parameters in SQTS Subjects

The SQTS patients had significantly narrower and higher T-wave loops than the healthy control subjects (Table 2). The families did not differ from each other in the T-wave loop parameters, even though they did differ from each other in terms of the gene mutation causing the SQTS.

QT/T-Wave/QRS-Based Parameters in Symptomatic SQTS Subjects

QTc interval, T-wave amplitude from lead V2, and the width and height of the T-wave loop were also significantly different among the seven symptomatic SQTS patients, that is, those who had documented VT/VF episodes or syncope, compared

with the control subjects (Table 2). The symptomatic patients with SQTS had significantly lower TCRT than the healthy control subjects (Table 2). Six out of seven symptomatic, but none of the asymptomatic patients with short QT, had abnormally low TCRT values, that is, values lower than the lower boundary of the 99% CI of TCRT in the healthy control population (Table 1). The mean QTc interval and T-wave amplitude in lead V2 did not differ significantly between the asymptomatic and symptomatic SQTS subjects (mean QTc 316.7 ms $\pm$ 11.9 ms in asymptomatic patients vs 306.9 ms $\pm$ 38.2 ms in symptomatic patients, ns, and mean T-wave amplitude in lead V2 1.05 mV $\pm$ 0.41 mV in asymptomatic vs 1.08 mV $\pm$ 0.47 mV in symptomatic patients, ns).

DISCUSSION

This study revealed that most of the symptomatic subjects with SQTS have abnormal T-wave/QRS loop parameters compared with healthy individuals. These findings suggest that an analysis of T-wave loop and QRS loop-based parameters could well be useful in SQTS diagnostics in supplementing the measurement of the length of the QT interval.

SQTS

The SQTS is a newly described inheritable arrhythmic entity associated with increased risk for arrhythmias. Incidence of either paroxysmal or permanent AF is high in these subjects. More than two thirds of the patients with SQTS are reported to experience AF and in 22% of these individuals, this is observed to be the first presenting arrhythmia.[8–12] Nevertheless, on many occasions, SQTS is diagnosed in a family only after a devastating episode of sudden cardiac death or syncope in one of the family members. The symptoms in SQTS patients can appear in all age groups including newborn babies.[2] In addition to typical ECG findings, programmed electrical stimulation usually reveals abnormally short atrial and ventricular refractory periods with a high incidence of inducible ventricular arrhythmias.

At present, genetic screening has identified three gain-of-function mutations in genes encoding for cardiac potassium-ion channels (HERG, KCNQ1, and KCNJ2). However, in a considerable number of patients, genetic testing has proved negative and also in our study, we encountered subjects without recognizable gene mutations. In the Finnish SQTS family, HERG, KCNQ1, and KCNJ2 were screened and no disease-explaining mutations were found.

The high incidence of sudden cardiac death makes this syndrome important. Although VF has been easily induced in most of the published patient cases, we still lack reliable noninvasive methods for identifying those patients at high risk of suffering serious ventricular arrhythmias. Until today, the only reliable treatment for these patients is an implantable cardioverter-defibrillator. However, in some cases, particularly in those with a mutation in the HERG gene (SQT-1), quinidine treatment may be useful.

T-Wave Morphology and SQTS

Previous studies by Extramiana and Antzelevitch have shown that in an experimental setting, the transmural dispersion of repolarization measured by Tpeak-Tend/QT is increased in SQTS wedge model and the increased Tpeak-Tend/QT index associated with inducibility of ventricular arrhythmias.[13] In our previous analysis, we have had similar results presenting that SQTS subjects have higher Tpeak-Tend/QT index and lesser capacity to change Tpeak-Tend intervals in an ambulatory ECG analysis.[14] Both of these studies suggest that the increased dispersion of repolarization in SQTS could partly explain the high vulnerability to ventricular arrhythmias.

PCA has already been used as a technique to study electrocardiographic repolarization in patients with long QT syndrome[4] and remote myocardial infarction.[3] T-wave loop-based parameters have been shown to yield prognostic and diagnostic information in both of these conditions. In a study done with long QT subjects by Priori et al., PCA of electrocardiographic repolarization was found to be beneficial in the diagnosis of long QT syndrome and in describing the dynamic nature of the disease.[4] Our study presents the first clinical data where PCA of electrocardiographic repolarization has been applied for SQTS diagnostics. In the PCA technique, T-wave and QRS loops are reconstructed from a standard 12-lead ECG. Of the T-wave/QRS loop-based parameters, TCRT describes the synchrony between depolarization and repolarization wavefronts in the myocardium. The synchrony of depolarization and repolarization is

crucial in the normal cardiac electrical activity. Negative TCRT values indicate that the angle between the main vectors of QRS loop and T-wave loop is between 90 and 180 degrees and positive values mean that the angle is between 0 and 90 degrees. In our control population, TCRT was almost uniformly positive since the mean TCRT was of the order or 0.40 and the variation of the 99% CI was strikingly narrow. Five out of seven of the symptomatic SQTS subjects exhibited clearly negative TCRT values. Other T-wave loop parameters, that is, the width and height of the loop and TWLD were also abnormal in a majority of SQTS subjects. Thus, the SQTS patients' cardiac repolarization pattern seems to be universally abnormal. We did not find any significant difference in the T-wave loop parameters between patients with a gain-of-function mutation in HERG gene and those patients who did not have any detected mutation (Table 1). Thus, unlike the situation in long QT syndrome, a gene mutation causing the SQTS does not seem to have any major influence on T-wave morphology.

CONCLUSION

Our analysis of 10 patients with SQTS and a large population of healthy subjects indicate that the determination of T-wave loop/QRS loop-based parameters does provide supplemental information for the diagnosis of symptomatic SQTS. Additional studies in larger populations with SQTS will be needed to assess the value of various ECG patterns in risk stratification of these patients, in particular, in estimating the suitability of the patient for implantable cardioverter-defibrillator therapy.

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