Electrocardiographic Transmural Dispersion of Repolarization in Patients with Inherited Short QT Syndrome

Olli Anttonen, M.D.,* Heikki Väänänen, M.Sc.,† Juhani Junttila, M.D.,‡
Heikki V. Huikuri, M.D.,‡ and Matti Viitasalo, M.D.§

From the *Department of Medicine, Päijät-Häme Central Hospital, Lahti, Finland; †Laboratory of Biomedical Engineering, Helsinki University of Technology, Espoo, Finland; ‡Department of Internal Medicine, University of Oulu, Oulu, Finland; and §Department of Cardiology, University of Helsinki, Helsinki, Finland

Background: Short QT syndrome (SQTs) carries an increased risk for sudden cardiac death. However, only a short QT interval does not express the risk of ventricular arrhythmias. Thus, additional evaluation of the repolarization abnormality in SQTs patients is essential. In experimental models of SQTs, increased transmural dispersion of repolarization (TDR) and its electrocardiographic counterpart T-wave peak to T-wave end interval (TPE) appeared critical for induction of polymorphic ventricular tachycardia (PMVT). In a clinical study with acquired long QT syndrome patients, TPE/QT ratio > 0.28 indicated arrhythmia risk. We hypothesized that the TPE/QT ratio would be greater in SQTs patients than in control subjects.

Methods and Results: We compared the behavior of the electrocardiographic TDR in three seriously symptomatic SQTs patients of unknown genotype presenting baseline QTc values <320 ms and in nine healthy age-matched control subjects. We determined QT and TPE intervals as well as TPE/QT ratio from 24-hour ECG recordings using a computer-assisted program. Diurnal average of TPE/QT ratio was 0.28 ± 0.03 in SQTs patients and 0.21 ± 0.02 in control subjects ($P = 0.01$). SQTs patients had also lesser capacity to change TPE intervals from steady-state conditions to abrupt maximal values than control subjects.

Conclusion: SQTs patients have increased and autonomically uncontrolled electrocardiographic TDR. According to experimental SQTs models, the present results may in part explain increased vulnerability of SQTs patients to ventricular arrhythmias.

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Short QT syndrome (SQTs) is a novel inherited syndrome characterized by a short QT interval, nearly absent ST segment, and tall, peaked T waves in the electrocardiogram, and a high risk of sudden cardiac death.¹ For the present time, genetic screening has revealed mutations in *HERG*, *KCNQ1*, and *KCNJ2* genes leading to short QT syndrome. There are no unanimously accepted cutoff values of QT intervals for SQTs but in a recent European review, all affected SQTs patients exhibited a QT interval less than 320 ms and a QTc value less than 340 ms.²

A short QT interval is a physiological response to increases in the heart rate. In patients with SQTs, the QT interval seems to be relatively normal at high heart rates whereas at low heart rates the QT interval is abnormally short.³ In addition, Gussak et al. have reported a 4-year-old girl with several episodes of cardiac arrest showing paradoxical shortening of the QT interval with a decrease in the heart rate.⁴ After initial reports of dire prognosis of SQTs, it has become obvious that simply the presence of a shorter-than-normal QT interval in

Address for reprints: Olli Anttonen, M.D., Department of Medicine, Päijät-Häme Central Hospital, Lahti, Finland. Fax: 358-3-8192608; E-mail: olli.anttonen@phsotey.fi

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the ECG does not justify the diagnosis of the SQTs. Furthermore, not all subjects with a short QT interval in the ECG are at increased risk of sudden cardiac death or other arrhythmias.^{5–7} At the present time, there are no reliable noninvasive methods for risk evaluation in patients exhibiting a short QT interval.

In their experimental SQTs model, Extramiana and Anzelevitch showed that short action potentials locate heterogeneously in different regions of the left ventricle wall increasing transmural dispersion of repolarization (TDR) and this facilitates induction of polymorphic ventricular tachycardia (PMVT).⁸ They reported also that smaller TDR is critical for the initiation of PMVT in SQTs than in the long QT syndrome. In electrocardiographic terms one may suppose, therefore, that the ratio between the electrocardiographic counterpart of TDR, T-wave peak to T-wave end (TPE) interval, and the QT interval (TPE/QT ratio) might serve as an index of the risk of PMVT also in the SQTs as has been shown in the acquired long QT syndrome.⁹

In this study, we compared the behavior of the electrocardiographic analogue of TDR in three

symptomatic SQTs patients and in their nine healthy controls. We hypothesized that the TPE/QT ratio would be greater in SQTs patients than in control subjects.

METHODS

Study Population

We reviewed Holter recordings in three individuals from one family with a short QT syndrome.² These three patients are at the present time the first and only individuals who have been found to have short QT syndrome in Finland. The proband subject was an 18-year-old male who had experienced aborted sudden cardiac death while playing computer game (Fig. 1). His father (53 years) complained palpitations during exercise and presented runs of PMVT on a treadmill exercise test. His coronary angiogram was normal without signs of coronary artery disease. The grandfather (80 years) had complained of disturbing palpitations when young but now was asymptomatic except paroxysmal atrial fibrillation. Abovementioned gene mutations known to cause SQTs were tested and found

Figure 1. Baseline ECG recording (leads V₁ to V₆, paper speed 25 mm/s) of an 18-year-old male with short QT syndrome. Note the short QT interval, tall, peaked T waves, and nearly absent ST segments.

Table 1. ECG Characteristics of Study Subjects

Measure	SQTS Patients (n = 3)	Control Subjects (n = 9)	P Value
Heart rate (beats/min)	68 ± 15	61 ± 10	0.3
QT interval (ms)	287 ± 23	408 ± 27	0.01
QTc (ms)	304 ± 11	407 ± 17	0.01
TPE interval in lead V ₅ (ms)	82 ± 13	79 ± 14	0.77
Maximal TPE interval in any lead (ms)	90 ± 20	92 ± 13	0.85
TPE/QT in lead V ₅ (%)	0.29 ± 0.05	0.2 ± 0.05	0.03
Maximal TPE/QT in any lead (%)	0.32 ± 0.08	0.23 ± 0.04	0.1
T-wave amplitude in lead V ₅ (mV)	0.5 ± 0.1	0.5 ± 0.2	0.78
T-wave amplitude in lead V ₂ (mV)	1.1 ± 0.2	0.7 ± 0.3	0.09

SQTS = short QT syndrome; TPE = T-wave peak to T-wave end interval.

negative. All three patients had abnormal short QTc intervals <320 ms in baseline ECG (Table 1). Thorough clinical cardiac examinations including echocardiography were normal in each case. The baseline ECG and 24-hour recording were obtained off drug.

For control subjects, we reviewed our database of genotyped unaffected family members with symptomatic long QT syndrome patients with available Holter recordings. From these unaffected family members we took three male patients with the closest age match for each SQTS patient as the control subjects. These nine family members with the mean age of 41 ± 15 years and with normal baseline QTc intervals were tested not to have the known long QT syndrome causing mutation of the family. Table 1 shows the ECG characteristics of the study subjects. None of the subjects took β -blockers or any other medication known to influence cardiac repolarization. All subjects were in sinus rhythm and did not show bundle branch block. Normal daily activities were encouraged during the recordings. The Ethical Review Committees of the responsible institutes approved the study and informed consent was obtained from all participants.

Holter Recordings and Analyses

SQTS patients and control subjects underwent one 24-hour ECG recording (model 8500; Marquette Electronics Inc., Milwaukee, WI, USA). The tapes were initially analyzed with a Marquette 8000 Holter Analysis system (version 5.8 software) to label the QRS complexes to normal, ventricular extrasystoles, or aberrant complexes. The ECG data were then transferred to a personal computer for further analysis of the QT and TPE intervals.

Measurement of the QT and TPE Intervals

To measure the QT and TPE interval durations from the 24-hour ECG recordings, we used previously described methods for determination of T-wave fiducial points¹⁰ and for measurement of QT¹¹ and TPE intervals.¹² Only upright monophasic T waves with amplitude of ≥ 0.1 mV were included in the measurements. All measurements were done with modified lead V₅.

Data Analyses and Definitions

The measured QT and TPE intervals as well as computed TPE/QT index values were analyzed by plotting all the QT, TPE, and TPE/QT values recorded during 24 hours against the preceding respective RR intervals as described previously.^{11,12} We first determined diurnal maximal QT peak, QT end, and TPE intervals. QT end intervals were recorded also at stable heart rates (the rate-adapted QT end interval).¹¹ We computed the median values of the QT end and TPE intervals as well as TPE/QT end index values against RR intervals in RR steps of 10 ms. We present maximal QT peak, QT end, and TPE intervals at different RR intervals with RR steps of 100 ms (from 500 to 1100 ms). We also present the difference between maximal QT end and rate-adapted QT end intervals and the difference between maximal and median TPE intervals at different RR intervals representing each patient's capacity to change QT end and TPE intervals, respectively, from steady-state conditions to maximal values. To analyze the rate dependence of the QT end intervals, we calculated the slopes for each subject's QT/RR curve using successive RR intervals of 100 ms (interval slope).¹¹ We calculated

Table 2. Heart Rates, T-Wave Amplitudes, and Durations and Rate Dependences of QT Intervals of the Study Subjects during 24-hour Electrocardiographic Recordings

Measure	SQTS Patients (n = 3)	Control Subjects (n = 9)	P Value
Minimal heart rate (beats/min)	48 ± 2	46 ± 9	0.27
Mean heart rate (beats/min)	75 ± 4	73 ± 10	0.52
Maximal heart rate (beats/min)	121 ± 8	140 ± 22	0.3
Average of T-wave amplitude (mV)	0.85 ± 0.23	0.68 ± 0.18	0.31
Maximal QT peak interval (ms)	258 ± 25	391 ± 32	0.01
Maximal QT end interval (ms)	349 ± 43	477 ± 33	0.01
Median QT end interval at stable heart rates of 60 beats/min (ms)	326 ± 34	422 ± 15	0.01
Average slope of QT/RR curve	0.11 ± 0.03	0.2 ± 0.04	0.01
Maximal slope of QT/RR curve	0.22 ± 0.04	0.4 ± 0.09	0.02
Maximal TPE interval (ms)	100 ± 21	151 ± 33	0.03
Median TPE interval (ms)	86 ± 18	85 ± 6	0.58
Average of TPE/QT end (%)	0.28 ± 0.03	0.21 ± 0.02	0.01

SQTS = short QT syndrome; TPE = T-wave peak to T-wave end interval.

the maximal interval slope at RR intervals >600 ms and the mean interval slope at RR intervals from 600 to 1000 ms in the 24-hour data. The mean amplitude of T-waves was calculated from the 24-hour data. The baseline QT interval was measured in lead II from 12-lead ECG and adjusted for heart rate using the Bazett formula.

Statistical Analyses

Data are presented as mean ± SD. Comparisons between the two study groups were performed by Mann-Whitney *U* test. Two-tailed *P* < 0.05 was considered statistically significant.

RESULTS

During the 24-hour ECG recordings heart rates were similar in the study groups (Table 2). Patients with the short QT syndrome showed T waves of similar amplitudes as control subjects (Table 2). Figure 2 highlights the impaired lengthening of QT intervals with decreasing heart rates in short QT syndrome patients. Both the average and maximal slope values of the QT/RR curve were smaller among SQTS patients than in the control group (Table 2). Figure 2 also shows that the difference between the maximal QT interval and the rate-adapted QT interval (exhibiting a patient's capacity to change the QT interval in relation to the RR interval) was smaller in SQTS patients. During night, average QT intervals prolonged 19 ± 5 ms in SQTS patients and 55 ± 20 ms in control subjects (*P* < 0.001).

Maximal TPE intervals were significantly longer in control subjects than in SQTS patients whereas corresponding median values in the study groups were similar (Table 2). Figure 3 shows a great difference between the study groups in the capacity to change the TPE intervals from median to abrupt maximal values.

Diurnal average of TPE/QT ratio was 0.28 ± 0.03 in SQTS patients and 0.21 ± 0.02 in control subjects (*P* = 0.01). Figure 4 shows median TPE intervals divided by the corresponding QT end intervals at specified heart rates. With a decrease in the heart rate the value of the TPE/QT ratio decreased in

Figure 2. Maximal QT end intervals (triangles, mean ± SEM) and median QT end intervals at stable heart rates (squares, mean ± SEM) at specified heart rates in control subjects (broken lines) and in short QT syndrome patients (solid lines) during 24-hour daily activities.

Figure 3. Maximal T-wave peak to T-wave end (TPE) intervals (triangles, mean $\pm$ SEM) and median TPE intervals (squares) at specified heart rates in control subjects (broken lines) and in short QT syndrome patients (solid lines) during 24-hour daily activities.

control subjects whereas it remained at high level also during slow heart rates in the SQTs patients.

DISCUSSION

Main Findings

The present results show abnormally high TDR, measured as TPE/QT, in symptomatic SQTs patients. Our SQTs patients also had lesser capacity to change QT and TPE intervals than control subjects.

Figure 4. Median T-wave peak to T-wave end (TPE) interval divided by the corresponding QT end interval (mean $\pm$ SEM) at specified heart rates in short QT syndrome patients (closed symbols) and in control subjects (open symbols).

TDR in Experimental SQTs Models and TPE/QT Index as a Measure of TDR

In an experimental SQTs model, abbreviation of ventricular action potential duration by a potassium current activator amplified TDR and increased the likelihood of PMVT.⁸ The same authors reported also that under conditions associated with short QT intervals, the threshold at which TDR can permit PMVT is less than the corresponding threshold under long QT conditions.⁸ Using electrocardiographic measures, the value of TPE/QT index was 0.13 under baseline conditions and 0.21 under short QT conditions associated with inducibility of PMVT in this SQTs model.⁸

TPE/QT Index in SQTs

We found that median TPE values were almost identical between SQTs patients and control subjects at whole range of heart rates. Because SQTs patients have much shorter QT end intervals, it follows that SQTs patients showed abnormal high values of TPE/QT index compared with controls subjects. Of note is also that SQTs patients failed the normal response to shorten this index during slow heart rates. Previously, Yamaguchi et al. reported that among patients with an acquired long QT syndrome, a TPE/QT threshold value of 0.28 appeared to discriminate between patients who developed Torsade de Pointes tachycardia and those who did not.⁹ In our SQTs patients, the TPE/QT index was close to the level of 0.28 at heart rates higher than 75 beats per minute. Therefore, the high level of TDR may increase SQTs patients' susceptibility to PMVT at elevated heart rates. At low heart rates the normal response of the index is a decrease under the level of 0.20 as shown in our control subjects and previously observed in healthy children.¹³ On the other hand, in a previous study among patients with the long QT syndrome the minimal value of the TPE/QT index was 0.19 in LQT1 and 0.23 in LQT2 patients.¹¹ Thus, the continuous high level of TDR in SQTs patients differs also from the behavior of TDR in patients with the long QT syndrome.

The Changing Capacity of Electrocardiographic Ventricular Repolarization in SQTs

We observed that SQTs patients had a lesser capacity to change both QT and TPE intervals from steady-state conditions to abrupt maximal values

than control subjects. In addition, according to previous observations, our SQTs patients exhibited diminished heart rate dependence of QT intervals.³ Our SQTs patients also failed to prolong QT intervals during sleep. These observations suggest that responses of the ventricular repolarization both to abrupt autonomic impulses, heart rate changes as well as changes in the autonomic tone, respectively, are impaired in SQTs patients. Although both blunted autonomic control^{14,15} and impaired rate adaptation of electrocardiographic ventricular repolarization¹⁶ have been related to susceptibility to sudden cardiac death after myocardial infarction, the arrhythmogenic significance of these parameters in SQTs remains unclear.

Study Limitations

We studied three symptomatic SQTs patients with an unknown genotype. Therefore, one cannot generalize the findings to all subjects presenting a SQTs. Although the present finding of high level of electrocardiographic TDR may indicate a typical characteristic in the SQTs, the usefulness of this measure in clinical arrhythmia risk evaluation remains unknown.

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