Assessment of QT Intervals and Prevalence of Short QT Syndrome in Japan

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ABSTRACT

Background: Long QT syndrome causes ventricular tachyarrhythmias and sudden death. Recently, a short QT interval has also been shown to be associated with an increased risk of tachyarrhythmia and sudden death. However, the prevalence of short QT syndrome is not well-known.

Hypothesis: The aim of this study was to assess the distribution of corrected QT intervals (QTc) and prevalence of short QT syndrome.

Methods: This study comprised 12,149 consecutive subjects who received a consultation at Kanazawa University Hospital, Kanazawa, Japan, and had an electrocardiogram (ECG) between February 2003 and May 2004. Of these subjects, 1,165 subjects were excluded because of inappropriate ECGs, while the remaining 10,984 subjects had their last-recorded ECGs analyzed.

Results: The QTc values showed a nearly normal distribution (408 ± 25 msec$^{1/2}$), and were significantly longer in females (412 ± 24 msec$^{1/2}$) than in males (404 ± 25 msec$^{1/2}$) ($p<0.05$). Among 5,511 males, 69 subjects (1.25%) exhibited QTc <354 msec$^{1/2}$ (2 standard deviations [SDs] below the mean in males), and among 5,473 females, 89 subjects (1.63%) exhibited QTc <364 msec$^{1/2}$ (2 SDs below the mean in females). Only 3 subjects (0.03% in all subjects and 0.05% in males) exhibited QTc <300 msec$^{1/2}$, however, none had clinical symptoms of short QT syndrome.

Conclusions: Short QT syndrome may be very rare.

Key words: short QT interval, sex difference of QT intervals, electrocardiogram, sudden death, arrhythmia

Introduction

The QT interval on an electrocardiogram (ECG) represents ventricular depolarization and repolarization. It is well-known that a prolonged QT interval is associated with an increased risk of tachyarrhythmias and sudden cardiac death.[1–4] Furthermore, there have been recent reports of a similar association between a short QT interval and tachyarrhythmias and sudden cardiac death.[5] The short QT syndrome is a new clinical entity that was first reported by Gussak et al.[5] in 2000. It is characterized by short QT intervals on the ECG (corrected QT interval [QTc]: QTc <300 msec$^{1/2}$), a high incidence of ventricular tachycardia and fibrillation, the absence of structural heart disease, a familial history of sudden cardiac death, resuscitated cardiac arrest, and syncope. The familial nature of this syndrome was confirmed by Gaita et al. in 2003.[6] Until now, focus has been given to the predominant prolonged QT interval, and an upper limit of normal has been proposed for QTc.[7] Nevertheless, the lower limit of normal for QTc, the prevalence of short QT intervals in the population, and the frequency of short QT syndrome have not been determined. Accordingly, we assessed the distribution of QTc interval and the frequency of short QT syndrome.

Materials and Methods

Subjects and ECG Analysis

We analyzed 26,350 consecutive ECGs that had been recorded at Kanazawa University Hospital, Kanazawa, Japan, for cardiac examination between February 2003 and May 2004. These ECGs had been obtained from 12,149 subjects, with a mean age±standard deviation (SD) of 51±21 y (range, birth to 96 y); 6,286 were male and 5,863 were female. For individual subjects with several ECGs, the last recorded ECG was selected for the analysis. All ECGs were recorded with an FCP-4266L instrument (Fukuda Denshi Co., Tokyo, Japan). The RR interval and QT interval were automatically measured with the same instrument. The RR interval is the average value across all beats, excluding premature beats measured in a 10-sec period. The QT interval is the average value across averaged 12-lead waveforms, excluding premature beats according to the setup of the instrument. As in the method of recognizing the end point of a T-wave, the first point of the differentiated average waveform that reached the baseline from the peak (i.e., became lower than the noise level of baseline) was defined as the end point of the T-wave. The QTc was calculated using Bazett's formula:[8] $QTc=QT/RR^{1/2}$. The averaged values of the QT and RR intervals as described previously were used.

Regarding ECGs with QTc ≤360 msec$^{1/2}$ or ≥440 msec$^{1/2}$, the QT interval was remeasured manually and was adopted

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for the analysis. The QT intervals were measured manually from a 12-lead ECG recorded at a paper speed of 25 mm/sec. The QT interval was defined as the time between the beginning of the QRS complex and the point at which the line of the maximal downslope of the T-wave crossed the isoelectric line. Predicted QT interval (QTp) was calculated using Rautaharju's formula:[9] QTp (msec) = 656/(1 + heart rate/100).

The following ECGs, with inappropriate findings for QTc analysis, were excluded: (1) irregular rhythms such as atrial fibrillation, frequent premature ventricular, and/or supraventricular contractions; (2) conduction disturbances such as sick sinus syndrome, advanced atrioventricular block, or bundle-branch block; and (3) wide QRS complexes such as pacemaker rhythm, Wolff-Parkinson-White syndrome, or marked left ventricular hypertrophy. Consequently, a total of 1,165 subjects were excluded and the remaining 10,984 subjects were analyzed. We also investigated the distribution of QTc values according to the sex of the subject, in order to determine if there was a difference between males and females. This study was approved by the Bioethical Committee on Medical Researches, School of Medicine, Kanazawa University, Kanazawa, Japan.

Statistics

Values are expressed as the mean±SD; 95% confidence intervals (CIs) were calculated. A normal distribution test was carried out by using a normal probability plot. A p-value of <0.05 was considered statistically significant. Comparisons of data were performed using the unpaired Student *t*-tests and Mann-Whitney U-tests. Statistical analyses were carried out with the computer software StatView for Windows version 5.0 and JMP for Windows version 5.1 (SAS Institute Inc., Cary, NC, USA).

Results

Distributions of QTc

The distribution of QTc showed a nearly normal distribution (408±25 $msec^{1/2}$), and was not statistically significant (Figure 1). The 95% CI for QTc ranged from 358 to 458 $msec^{1/2}$.

The results of ECG analysis in males and females are shown in Table 1. The study population, with a mean age of 52±21 y, was evenly distributed between males and females: 5,511 (50.2%) versus 5,473 (49.8%), respectively. The QTc intervals of the female subjects (412±24 $msec^{1/2}$) were significantly longer than those of the males (404±25 $msec^{1/2}$), ($p<0.05$) (Table 1). Heart rates, QT intervals, and QTc values in the various age groups are shown in Table 2. In both males and females, the highest heart rate was observed in the youngest age group (0–10 y) and the lowest heart rate was observed in the 11–20 y age group in both males and females. The QTc values of females were significantly longer than those of males in all age groups from 11 to 80 y.

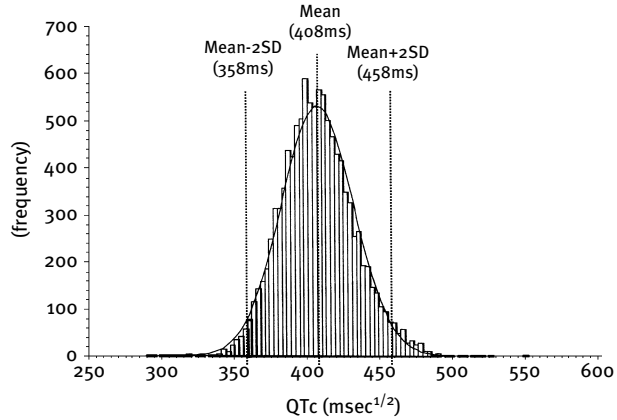

Figure 1: The QTc values show a nearly normal distribution (408±25 $msec^{1/2}$, mean±SD).

TABLE 1: Baseline characteristics of study subjects

Data	Male	Female	p-value
Number (%)	5,511 (50.2)	5,473 (49.8)	—
Age (y)	51.8±21.8	50.2±21.6	<0.001
ECG			
HR (bpm)	69.2±15.2	70.8±15.3	<0.001
QT (msec)	380±36	383±36	<0.001
QTc ($msec^{1/2}$)	404±25	412±24	<0.001

Data are shown as mean±SD. *Abbreviations*: ECG = electrocardiogram; HR = heart rate; QT = QT interval; QTc = corrected QT interval.

Short QT Interval

The minimum QTc recorded in this study was 290 $msec^{1/2}$. Among the 5,511 male subjects, 69 subjects (1.25%) exhibited QTc <354 $msec^{1/2}$ (2 SDs below the mean in males). Whereas, 89 (1.63%) of the 5,473 female subjects exhibited QTc <364 $msec^{1/2}$ (2 SDs below the mean in females) (Figure 2). The ECGs that showed the shortest QTc in male and female subjects are shown in Figures 3 and 4, respectively. Only 3 subjects, all males, exhibited QTc <300 $msec^{1/2}$ (0.03% in all subjects and 0.05% in male subjects). These were as follows: (1) 23-y-old male, QTc = 290 $msec^{1/2}$, 74% of QTp; (2) 53-y-old male, QTc = 295 $msec^{1/2}$, 81% of QTp; and (3) 25-y-old male, QTc = 299 $msec^{1/2}$, 78% of QTp. None had a history of syncope, ventricular tachyarrythmias, or a family history of sudden cardiac death.

Discussion

Long QT syndrome is associated with a risk of life-threatening events, but little has previously been known

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TABLE 2: Heart rates, QT intervals, and QTc values in various age groups

Age (y)	Males				Females				
	Heart rate				Heart rate				
	number	(bpm)	QT (msec)	QTc (msec$^{1/2}$)	number	(bmp)	QT (msec)	QTc (msec$^{1/2}$)	p-value[a]
0–10	258	95±24	338±39	417±20	212	100±29	332±47	417±22	0.9547
11–20	433	65±15	385±33	397±24	437	65±14	394±35	408±24	<0.0001
21–30	507	65±13	374±31	387±23	625	69±16	378±36	401±21	<0.0001
31–40	390	68±14	371±30	392±21	533	70±13	379±31	405±24	<0.0001
41–50	476	68±14	376±33	398±23	547	70±14	382±32	409±23	<0.0001
51–60	1028	68±13	381±33	403±24	991	70±13	385±34	412±23	<0.0001
61–70	1202	68±13	386±35	408±24	1021	70±12	388±33	416±24	<0.0001
71–80	1028	69±14	388±36	411±24	893	71±13	388±25	419±25	<0.0001
81–90	182	70±13	391±39	418±23	204	71±12	390±37	422±25	0.0738
<90	7	70±12	390±40	418±30	10	68±12	393±35	416±27	0.8579

Data are shown as mean±SD. [a]p-value of QTc values in males versus in females.

about the significance of a short QT interval. Short QT intervals may be related to an increase in heart rate, ionic changes (i.e., hypercalcemia, hyperkalemia), acidosis, autonomic nervous system imbalance, or the effect of a particular drugs (e.g., digitalis).[10–13] In 1933, with an analysis of 6,693 consecutive Holter recordings, Algra et al.[14] reported that an increased risk of sudden death was presented not only in patients with long QT interval but also in those with short QT interval (<400 msec). Both abnormalities were associated with a 2-fold increase in the risk of sudden death. Their report was the first to point out the risk associated with short QT intervals. Short QT is defined by an interval that is always <300 msec, with no display of significant dynamic changes during heart rate variations or on exertion.[6] That is, an individual is regarded as having a short QT when the intervals are consistently <300 msec.[6] On the other hand, Rautaharju et al.[9] investigated the QT intervals in 14,379 healthy subjects, and established a formula by which the QT interval could be predicted: QTp (msec) = 656/(1 + heart rate/100). In their study, the prevalence of a QT interval shorter than 88% of predictive value was 2.5% (360 out of 14,379). Since 2 SDs below the mean is 88% of QTp (with only 2.5% of the population having a shorter QT interval), this value could reasonably be set as the lower limit of normal QT interval.[5] In their study, a QT interval <80% of QTp occurred in only 0.03% of subjects (3 out of 14,379). Therefore, we tried to identify the patients with short QT syndrome using these 2 indices: QTc <300 msec and QTc <88% of QTp. Consequently, only 3 subjects (0.03% in all subjects and 0.05% in male subjects) exhibited QTc <300 msec$^{1/2}$ and QTc <88% of QTp. However, they had no clinical symptoms of short QT syndrome, such as palpitation or syncope, no family history of sudden death, and no distinctive ECG features, such as tall, peaked, and symmetrical T-waves. These results suggest that short QT syndrome may be very rare.

In this study, we investigated only subjects with normal sinus rhythm. However, there have been reports of short QT syndrome in patients presenting with other arrhythmias, such as atrial fibrillation.[5,6] Therefore, short QT syndrome might well exist in subjects who were excluded from our study. Although only a few cases have been reported until now, it is possible that its prevalence is underestimated because little attention has been focused to date on short QT interval. We need to pay more attention to the existence of short QT interval.

Gain of function mutations in the genes for outward potassium currents such as *KCNQ1, KCNH2*, and *KCNJ2* have been shown to underlie short QT syndrome.[15–17] In

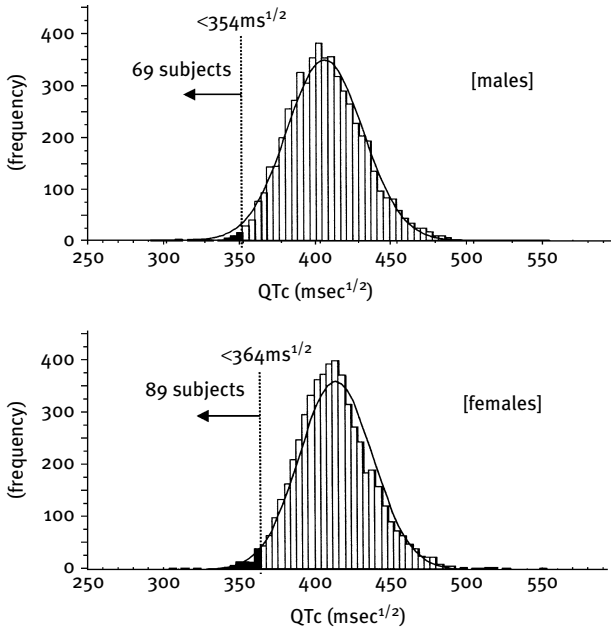

Figure 2: Distributions of QTc in males and females. Mean±SDs of QTc in males and females are $404\pm25^{1/2}$ and 412 ± 24 msec$^{1/2}$, respectively. The QTc intervals of females are significantly longer than those of males ($p<0.05$).

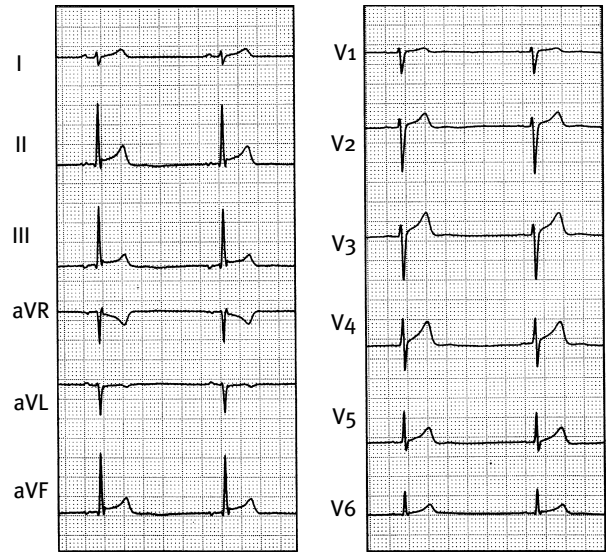

Figure 3: Electrocardiogram showing the shortest QTc interval in male subjects. The QTc is 290 msec$^{1/2}$.

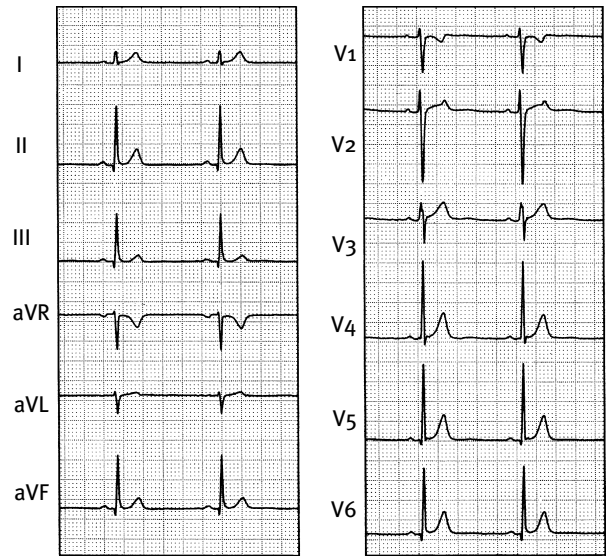

Figure 4: Electrocardiogram showing the shortest QTc interval in female subjects. The QTc is 304 msec$^{1/2}$.

contrast, loss of function mutations in these genes leads to long QT syndrome.[18] In an analysis of 2,008 individuals from the general population, Laetitia et al.[19] reported an interesting finding that subjects with borderline QTc prolongation were carriers of *KCNQ1* gene mutations that placed them at a potential risk of arrhythmia. Their report suggests that subjects with borderline short QTc values may be carriers of the gene mutation. With this in mind, studies should be carried out to investigate further this genetic involvement. In addition, it is desired that the genotype-phenotype correlation in short QT syndrome will be clarified in the future, as has been done in long QT syndrome.

It is known that the QTc values in females are generally longer than in males.[9] We confirmed this in our study, where the QTc values of females were significantly longer than that of males. This difference has been reported to be due to shortening in QTc values in adolescent males after puberty, whereas QTc values of females remain unchanged throughout the growth, maturation, and reproductive years.[9] The precise reasons for this difference are not well-known, and we should define the lower limits of QTc and the criteria of short QT syndrome in males and females separately. Unfortunately, until now there have been no reports that define short QT syndrome in males and females separately. Therefore, we introduced Gaita's criteria[6] of QTc <300 msec in the present study. All 3 subjects showing QTc <300 msec were male, and sex differences might affect the results. We should consider the difference in sex for diagnosing short QT syndrome as is done in long QT syndrome, and further investigations are necessary.

Study Limitations

This study had some limitations. First, subjects were selected from those who had come to the University Hospital for some medical advice; they did not include healthy individuals. The QTc distribution in the present

study was almost comparable with past reports.[20,21] Second, we did not take into account in our analysis, the effect of the concomitant medications being taken by our subjects or the presence of any underlying illnesses. So, it is possible that short QT intervals were concealed by such factors. Third, the QTc can vary within the same day, or from day to day even in the same subject, and we analyzed ECGs at a single moment in time. So there is the possibility that transient short QT intervals may have been overlooked. And in several subjects, especially among children, shortening of QT intervals independent of heart rate have probably been concealed by tachycardia. The existence, or the degree of, QT variation in patients with short QT syndrome is not well-known. In the future, further studies should include gene analysis as well as such factors.

Conclusion

QTc <300 $msec^{1/2}$ was found in 0.03% of the presently examined population. Our results suggest that short QT syndrome may be very rare.

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