Original Article

The QT Intervals in Infancy and Time for Infantile ECG Screening for Long QT Syndrome

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Background: Electrocardiographic and molecular studies have clarified an association between sudden infant death syndrome (SIDS) and long QT syndrome (LQTS), and few data are available for the QT interval in infancy from birth to 1 year of age. Appropriate time of electrocardiographic screening is not clarified. Medical examinations during infancy are mandatory in Japan.

Methods and Results: The study population included 1,058 infants. Electrocardiograms were collected with information of infants at birth and at examination. The QT intervals of three consecutive beats were measured in lead V_5. Statistical analysis revealed that the following formula was appropriate to minimize the effect of heart rate for infants: corrected QT interval; QTc = QT interval/RR interval$^{0.43}$. Subjects were divided into four groups as follows: 0–2, 3–6, 6–11, and 12–52 weeks of age. Tukey's multiple comparison showed that the QTc intervals were longest ($p < 0.0001$) in subjects who were 6–11 weeks of age.

Conclusions: The QTc interval showed the highest peak at 6–11 weeks of age in infancy. The peak period of occurrence of SIDS is at approximately 2 months of age. An appropriate time of electrocardiographic screening for QT prolongation will be one month of age, and follow-up studies are needed.
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Introduction

Long QT syndrome (LQTS) is characterized by prolonged ventricular repolarization with a prolonged QT interval on the surface electrocardiogram (ECG) and the clinical presentation is the occurrence of syncope or cardiac arrest in children and young adults.[1,2] Patients with LQTS who experience aborted cardiac arrest during infancy are at very high risk for subsequent aborted cardiac arrest or death during their next 10 years,[3] indicating that these patients are an extremely high risk subset.

Sudden infant death syndrome (SIDS) is defined as sudden death of an infant that is unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause of death.[4] SIDS is one of the major causes of death in infancy with the highest prevalence at approximately 2 months of age.[5,6] SIDS is multi-factorial in origin; however, electrocardiographic and molecular studies have clarified an association between SIDS and LQTS.[7–10] Recent studies have shown that approximately 10% of cases diagnosed as SIDS carry functionally significant genetic mutations in LQTS genes.[11–13]

Electrocardiographic screening in infancy may permit the early detection of a substantial percentage of patients at risk for SIDS;[7] however, the change in the QT interval in the infantile period had been determined only in Italy.[14,15] In Japan, medical examinations during infancy are mandatory and medical examinations at one month of age are currently being performed for all infants. Therefore, the aims of the present study were to determine the QT intervals from birth to 1 year of age of infants and to determine an appropriate time for electrocardiographic screening to prevent sudden infant death due to LQTS.

Methods

Subjects

The study population included infants less than 12 months of age. A questionnaire was sent to the councilors of the Japanese Society of Pediatric Electrocardiology, and infant ECGs were obtained retrospectively. Information in the questionnaire included the following: date of birth, gestational age, birth weight, and Apgar scores of 1 and 5 minutes at birth, date, body weight, and body height at examination, aim of the ECG examination, and final diagnosis. Apgar scores are used in the obstetric and pediatric fields as a practical method of systematically assessing newborn infants immediately after birth to help identify those requiring resuscitation and predict survival in the neonatal period.[16] Inclusion criteria in the present study were infants whose findings of echocardiography were normal. Infants with underlying heart diseases were excluded with a few exceptions: physiological stenosis at the bifurcation of the main pulmonary artery in neonates and young infants, patent foramen ovale, and a hemodynamically insignificant muscular type of ventricular septal defect or patent ductus arteriosus. Infants with rare atrial or ventricular ectopy and those with prolonged QT intervals were also included. Infants with AV block were excluded. We obtained permission to use and analyze these data from the Ethics Committee of the National Hospital Organization Kagoshima Medical Center under the condition that the confidentiality of all personal data would be maintained.

Measurement and correction of QT intervals

All ECGs were recorded at a speed of 25 mm/s at each institution. The QT intervals of three consecutive beats were measured from the onset of the Q wave to the end of the T wave in lead V_5.[17–19] When the QT interval could not be measured because of instability of isoelectric levels in lead V_5, the QT intervals in lead II were measured. When the notch was present in more than 3 leads[20,21] and the notch appeared at the same timing,[22] the T wave was defined as the bifid T wave. The QT/RR data were measured by one author (MY) in the present study. The QT/RR data for each of three consecutive beats were corrected using the formula in the present study and the mean values for the three consecutive QTc were used.

Formula for the correction of QT intervals

Published diagnostic criteria using the corrected QT interval (QTc) by Bazett's formula recommend additional diagnostic caution when scaling with tachycardic patients.[20] Infants normally show a high heart rate. To determine the formula for the correction of the QT interval to minimize the effect of heart rate in infants, the following exponential model was used: $QTc = QT\ interval/RR\ interval^k$, where k is the parameter of the exponent. The value k was calculated by simple regression analysis using the log-transformed QT interval as the dependent variable and the log-transformed RR interval as the independent variable. All three QT/RR data of the subjects were used in the calculation.

Comparison of QTc by Bazett's formula with that by the formula in the present study

To assess the effectiveness of the present formula, association between the RR intervals and the uncorrected QT intervals, QTc by Bazett's formula, and that by the formula in the present study were determined using data of the present study.

Statistical analysis

Infants were arbitrarily grouped as 0, 1, 2, 3, 4, 5, 6, 7, 8–11, 12–23, 24–39, and 40–52 weeks depending on the number of subjects. The QTc intervals increased during the first few months and decreased thereafter with a peak value between 6 to 11 weeks (refer to the text). The subjects were then divided into four groups as follows: 0–2, 3–5, 6–11, and 12–52 weeks. Tukey's multiple comparison was carried out for the difference in the mean QTc values between two successive groups. To determine the effect of confounders at birth and at ECG examination on the QTc intervals, multivariate regression analysis was performed using the QTc interval as the dependent variable and the confounders that were significant in simple regression analysis as the independent variables. The QTc intervals showed peak values at 6–11 weeks; therefore, the analysis was performed after dividing the groups into two groups to conform to the linear regression models so that both groups contained the subjects with the peak periods of 6–11 weeks; the group with the increase in QTc values (from 0 to 11 weeks) and the group with the decrease in the QTc values (from 6 to 52 weeks). Statistical analysis was performed with PASW® Statistics 18 software (SPSS Inc, Tokyo, Japan). A p value of less than 0.05 was considered to indicate statistical significance.

Results

Study population

A total of 1,138 ECGs from 1,082 infants (540 males and 542 females) were obtained retrospectively between 2000 and 2009 from eight institutions. Of these ECGs, 58 were excluded as they were duplicated in children with more than 1 ECG and only the initial ECG was used. Two ECGs were excluded because of the presence of underlying heart diseases. QT/RR data could not be determined because of the instability of isoelectric levels in both leads V_5 and II in 22 infants (7 males and 15 females; median, 2.1 weeks; range, 0 days to 7 weeks). A final total of 1,058 infants were included as subjects. Of these final subjects, QT/RR data were obtained from lead V5 in 1,005 infants (93%). The aim for performing the ECG was to determine the presence or absence of heart diseases because of the presence of heart murmur (76%), preoperative examination for non-cardiac diseases (12%), presence of arrhythmia (7%) and miscellaneous (5%). Characteristics of subjects are shown in **Table 1**.

Formula for the correction of QT intervals

Simple regression analysis using the log-transformed QT intervals as the dependent variable and the log-transformed RR intervals as the independent variable revealed that the k value of 0.43 was appropriate. Therefore, the formula of (QT interval)/(RR interval)$^{0.43}$ was used to determine the QTc values.

Comparison of QTc by Bazett's formula with that by the present formula

Association between RR intervals and the uncorrected QT intervals, QTc by Bazett's and the present formulas were determined using the data of subjects in the present study. Because the QT intervals are affected by the RR intervals, namely by heart rates (**Figure 1a**), the QT intervals are corrected by the RR intervals to minimize the effect of heart rates usually by the Bazett's formula; however, the QTc intervals by Bazett's formula were still affected by the RR intervals ($r = -0.167$, $p < 0.0001$) (**Figure 1b**). On the other hand, the QTc intervals by the formula of the present study were not affected by the RR intervals (**Figure 1c**). Therefore, the QTc intervals by the formula of QT interval/RR interval$^{0.43}$ was used in the present study; however, the QTc values by Bazett formula were also shown in the case of ECG presentation for a better understanding for researchers who usually use the QTc values by Bazett formula.

Mean QTc values during infancy

The QTc intervals increased during the first few months and decreased thereafter with a peak value between 6 to 11 weeks (**Figure 2**). Subjects were then divided into four groups as follows: 0–2, 3–5, 6–11, and 12–52 weeks. The numbers of infants in each group were 302, 429, 217, and 110, respectively. The QTc intervals were longest in subjects who were 6–11 weeks of age, and Tukey's multiple comparison revealed that the QTc values were significantly different between two successive groups. (**Figure 3**)

Clinical status that may affect QTc intervals in infancy

The result of clinical status that may affect QTc intervals by simple regression analysis was shown in **Table 2**. Multivariate regression analysis showed that

Table 1 Characteristics of the subjects

Groups (weeks)	No of subjects	At birth				At examination			
		GA (weeks)	Weight (kg)	Apgar score 1 min	Apgar score 5 min	Age (weeks)	Height (cm)	Weight (kg)	BMI (kg/m^2)
0	30	(20) 39.6 ± 1.0	(26) 3.05 ± 0.34	(26) 8.9 ± 0.5	(26) 9.7 ± 0.5	(30) 0.7 ± 0.3	(24) 50 ± 1	(25) 3.07 ± 0.30	(24) 12.4 ± 1.0
1	155	(132) 39.2 ± 1.4	(135) 3.05 ± 0.40	(122) 8.8 ± 0.6	(122) 9.8 ± 0.5	(155) 1.4 ± 0.3	(134) 50 ± 2	(134) 3.15 ± 0.40	(134) 12.6 ± 1.1
2	117	(96) 39.3 ± 1.4	(97) 2.99 ± 0.43	(81) 8.8 ± 0.5	(81) 9.7 ± 0.5	(117) 2.4 ± 0.3	(94) 51 ± 2	(96) 3.42 ± 0.50	(94) 13.1 ± 1.1
3	70	(50) 38.6 ± 1.5	(50) 2.80 ± 0.54	(43) 8.8 ± 0.7	(43) 9.7 ± 0.5	(70) 3.4 ± 0.3	(52) 51 ± 3	(52) 3.46 ± 0.64	(52) 13.0 ± 1.4
4	141	(88) 39.0 ± 1.6	(94) 2.83 ± 0.52	(70) 8.7 ± 0.7	(70) 9.5 ± 0.5	(141) 4.6 ± 0.3	(99) 53 ± 3	(100) 3.98 ± 0.62	(99) 14.0 ± 1.2
5	218	(148) 39.1 ± 1.5	(153) 2.99 ± 0.42	(107) 8.8 ± 0.7	(107) 9.6 ± 0.6	(218) 5.4 ± 0.3	(161) 54 ± 2	(162) 4.29 ± 0.54	(161) 14.8 ± 1.5
6	94	(61) 38.7 ± 2.0	(64) 2.84 ± 0.52	(40) 8.5 ± 0.7	(40) 9.4 ± 0.6	(94) 6.3 ± 0.3	(67) 54 ± 3	(67) 4.31 ± 0.74	(67) 14.7 ± 1.7
7	43	(19) 38.5 ± 2.6	(20) 2.93 ± 0.61	(12) 8.0 ± 2.2	(12) 8.9 ± 1.4	(43) 7.4 ± 0.3	(20) 56 ± 4	(21) 4.97 ± 0.97	(20) 15.6 ± 1.5
8–11	80	(37) 38.2 ± 3.0	(51) 2.88 ± 0.66	(29) 8.6 ± 0.8	(29) 9.4 ± 0.7	(80) 9.1 ± 0.9	(41) 56 ± 4	(44) 4.94 ± 1.13	(41) 15.5 ± 1.8
12–23	33	(12) 37.7 ± 2.9	(15) 2.50 ± 0.61	(8) 8.6 ± 0.5	(8) 9.0 ± 0.5	(33) 16.6 ± 3.6	(18) 59 ± 5	(18) 5.71 ± 1.49	(18) 16.0 ± 2.1
24–39	34	(5) 39.7 ± 1.1	(7) 2.92 ± 0.28	(3) 8.9 ± 0.6	(3) 9.7 ± 0.5	(34) 31.7 ± 5.1	(7) 68 ± 3	(7) 7.73 ± 1.24	(7) 16.9 ± 1.3
40–52	43	(2) 40.6 ± 2.4	(7) 2.86 ± 0.52	(5) 8.8 ± 0.4	(5) 9.4 ± 0.5	(43) 46.4 ± 3.8	(8) 72 ± 4	(8) 8.48 ± 1.45	(8) 16.6 ± 2.4
Total	1,058	(669) 39.0 ± 1.7	(706) 2.94 ± 0.48	(545) 8.7 ± 0.7	(545) 9.6 ± 0.6	(1,058) 5.0 (0–52)	(708) 52 (43–78)	(717) 3.86 (2.12–11.1)	(708) 13.9 (9.5–22.7)

Data are expressed as the number of data obtained in parentheses and the mean ± standard deviation. Data for age, height, weight, and BMI at examination of the total cases were skewed; the data are expressed as the median value and the range in parentheses.

BMI, body mass index; GA, gestational age.

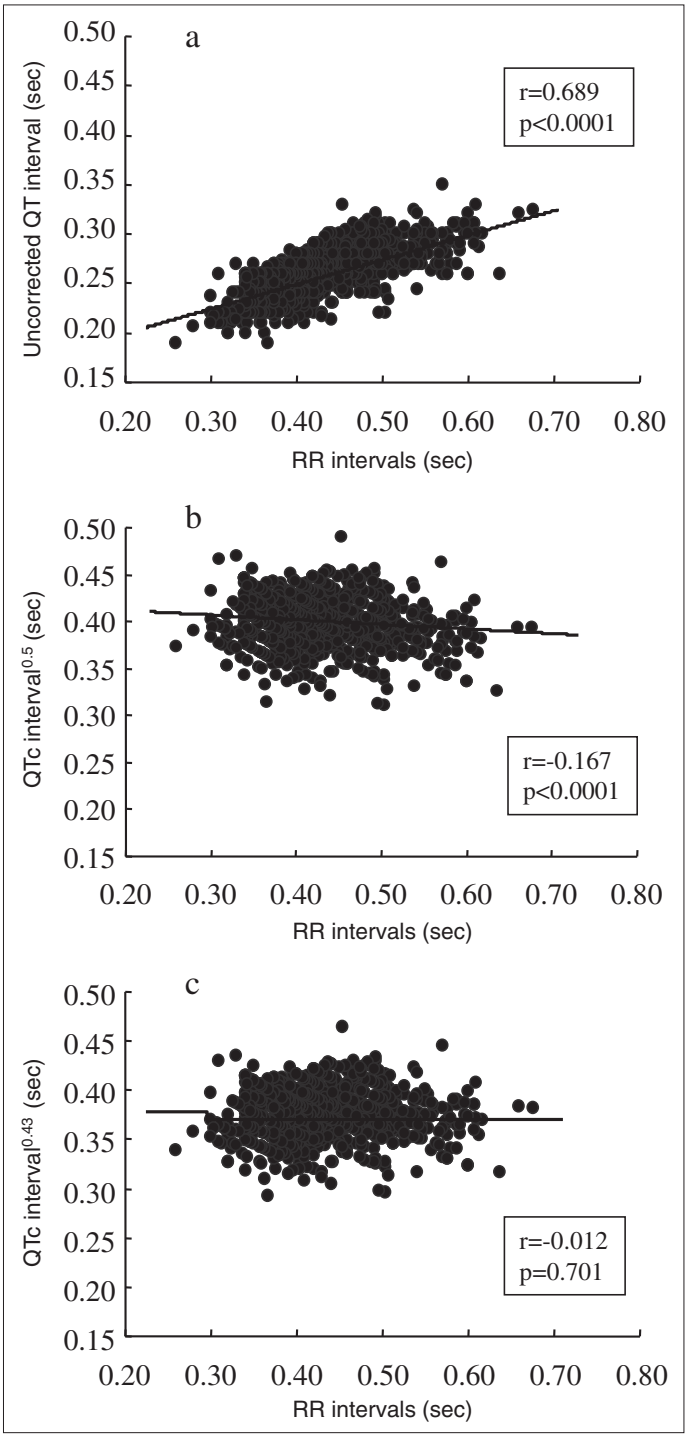

Figure 1 Association between RR intervals and the uncorrected QT intervals, QTc by Bazett's and the present formulas
The QT intervals are affected by the RR intervals, namely by heart rates (**a**). The QT intervals are corrected by the RR intervals to minimize the effect of heart rates usually by Bazett's formula; however, the QTc intervals by Bazett's formula were still affected by the RR intervals (**b**). The QTc intervals by the formula of the present study were not affected by the RR intervals (**c**).

age at examination was the sole strong significant predictor for QTc intervals in infants of both 0–11 weeks (t value; 7.60, $p < 0.0001$) and 6–52 weeks (t value; 5.52, $p < 0.0001$). In the analysis for infants of 6–52 weeks of age, sex and age at ECG examination were used as the independent variable among the significant parameters by single regression analysis, because the number of infants with all information for gestational age and birth weight was only 133 out of 326 subjects.

Frequency distribution of the QTc interval in infancy

Figure 4 shows the frequency distribution of the QTc interval of infancy. The infant with the longest

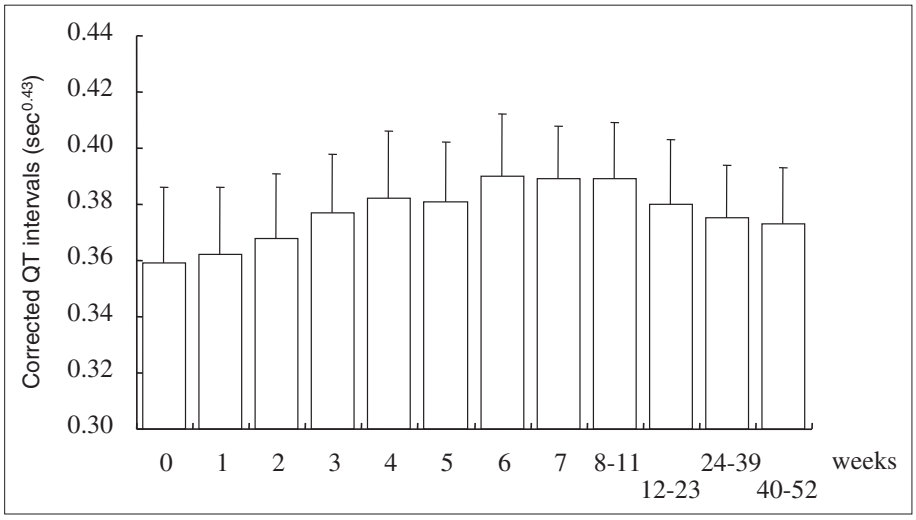

Figure 2 The QTc intervals from birth to 1 year of age
The QTc value showed a peak during 6 to 11 weeks of age. The Numbers of subjects in each group are shown in **Table 1**.

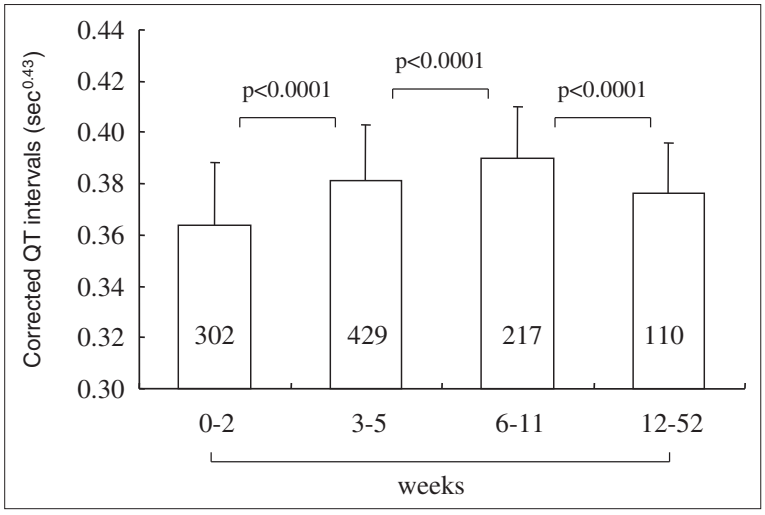

Figure 3 The QTc intervals at 0–2, 3–6, 6–11, and 12–52 weeks
Tukey's multiple comparison showed that the QTc intervals were significantly different between two successive groups with a peak value of 6–11 weeks. Numbers in the bars mean that of subjects in each group.

QTc value (mean QTc: 0.521 $sec^{0.43}$ by the present formula, 0.548 $sec^{0.5}$ by Bazett formula) was a baby of a LQTS mother (**Figure 5a**). He was diagnosed as LQTS on the basis of family history and the findings of ECG on the first day of life. Genetic diagnosis was not carried out in his family. His ECG recorded at 6 weeks still showed a prolonged QTc value (mean QTc: 0.503 $sec^{0.43}$, 0.527 $sec^{0.5}$ by Bazett formula) (**Figure 5b**), although this recoding was 4 weeks after the initiation of carteolol (0.2 mg/kg/day). Another two infants with prolonged mean QTc values of 0.464 $sec^{0.43}$ (0.490 $sec^{0.5}$ by Bazett formula) (**Figure 5c**) and 0.446 $sec^{0.43}$ (0.464 $sec^{0.5}$ by Bazett formula) (Figure not shown) visited a hospital because of heart murmur at 6 weeks and arrhythmia at 9 weeks, respectively. Their mean QTc values decreased to 0.391 $sec^{0.43}$ (0.409 $sec^{0.5}$ by Bazett formula) (**Figure 5d**) and 0.374 $sec^{0.43}$ (0.387 $sec^{0.5}$ by Bazett formula) (Figure not shown) at age 3.

Discussion

The present study showed that the QTc interval maximally prolonged at 6–11 weeks of age in infancy.

Some of the SIDS victims were reported to have strong relations to LQTS by electrocardiographic and molecular studies.[7–10] The change in the QT interval in the infantile period had been determined only in Italy.[14,15] The present study showed that the peak QTc values during infancy appeared at 6–11 weeks of age with a mean value of 0.390 ± 0.020 $sec^{0.43}$. Schwartz et al[14] reported the QT intervals corrected by Bazett's formula of the same

Table 2 The result of clinical status that may affect QTc intervals by simple regression analysis

	All subjects (n = 1,058)			0–11 weeks (n = 948)			6–52 weeks (n = 327)		
	No.*	t value	p value	No.	t value	p value	No.	t value	p value
Sex	1,058	0.67	0.50	948	0.11	0.91	327	2.02	0.045
At birth									
Gestational age	669	−0.64	0.52	650	−1.09	0.28	136	2.00	0.048
Birth weight	706	1.63	0.10	677	1.53	0.13	151	2.70	0.008
Apgar score at 1 min	545	−1.01	0.31	529	−1.13	0.26	97	1.38	0.17
Apgar score at 5 min	545	−0.85	0.40	529	−1.14	0.26	97	3.39	0.001
At ECG examination									
Age	1,058	1.54	0.12	948	13.0	<0.0001	327	−5.77	<0.0001
Height	708	6.17	0.50	675	8.09	<0.0001	156	−0.54	0.59
Weight	717	7.10	<0.0001	684	9.38	<0.0001	160	−0.17	0.86
BMI	708	7.52	<0.0001	675	7.99	<0.0001	156	0.89	0.38
Heart rate	1,060	−0.99	0.32	950	−1.81	0.07	327	0.21	0.84

*Numbers of subjects who had information obtained.

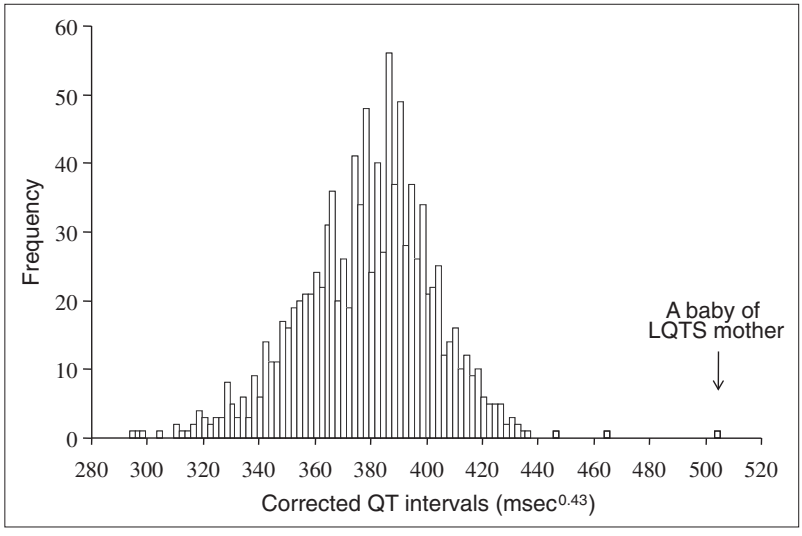

Figure 4 The frequency distribution of the QTc intervals
The frequency distribution showed a few cases with prominent QT intervals.

cohort of healthy infants in their fourth day of life and at 2, 4 and 6 months. They showed that healthy infants had the longest mean QTc values ($0.409 \pm 0.015\,\text{sec}^{0.50}$) at the second month (n = 2,418). The mean QT intervals of 2-month-old infants in the present study (61–90 days of age, n = 54) was $0.409 \pm 0.022\,\text{sec}^{0.5}$, if corrected by Bazett's formula, which was the same mean value as in the previous study.[14] Recently Schwartz et al have reported that 44,596 infants with the age of 15 to 25 days old showed the mean QTc interval of $0.406 \pm 0.020\,\text{sec}^{0.5}$.[15] The present study showed that the time of the maximal prolongation of the QTc intervals was not only at the second month, namely from 8 to 11 weeks, but it started as early as the 6th week of age (**Figure 2**).

Reasons of prolongation of the QT interval during early infancy have not been fully clarified. Schwartz et al suggested that abnormal development of cardiac sympathetic innervation could occur with a difference in the timing of maturation between left and right cardiac sympathetic innervation during the first months of life.[23] Neonatal rats treated with nerve growth factor show abnormal innervation patterns and abnormally prolonged QT intervals.[24] Another study showed that cardiac repolarization instability is present during normal postnatal development.[25] These electrophysiological characteristics during early infancy may be exaggerated when infants have genetic abnormalities. Franco et al reported that 18 future SIDS infants with a mean age of 8 weeks had significantly longer QTc values than those of 18

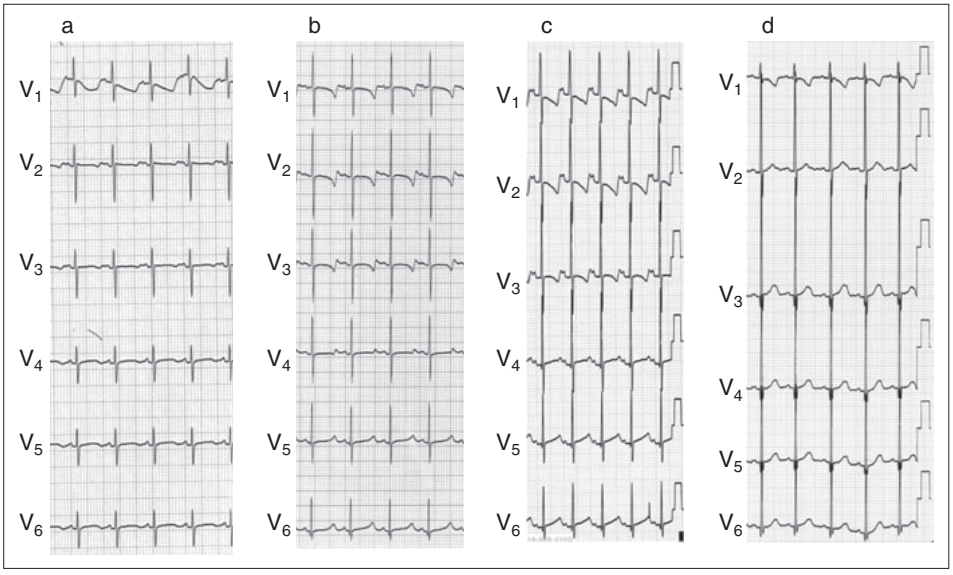

Figure 5 ECGs of infants with a high mean QTc value
The ECG (**Figure 5a**) on the first day of life before treatment showed biphasic T waves in leads V_1 to V_3, and the mean QTc interval in lead V_2 was 0.521 $sec^{0.43}$. He was diagnosed as having LQTS on the basis of family history and the findings of ECG, although the mean QTc interval in lead V_5 was 0.419 $sec^{0.43}$. His ECG recorded at 6 weeks still showed a prolonged QTc value (**Figure 5b**; mean QTc: 0.503 $sec^{0.43}$ in lead V_5), although this recoding was 4 weeks after the initiation of carteolol (0.2 mg/kg/day). A high mean QTc value of 0.464 $sec^{0.43}$ at 6 weeks of age in an infant (**Figure 5c**) decreased to that of 0.391 $sec^{0.43}$ (**Figure 5d**) at age 3. Refer to the text for the QTc values by Bazett formula.

control infants, and that median and maximal QTc values were associated with decreased parasympathetic activity and increased sympathovagal imbalance.[26] Prolongation of the QT interval favors the occurrence of lethal arrhythmias and is associated with an increased risk of sudden death.[7] These clinical and experimental studies including the present study suggest that both healthy and LQTS infants in around their 2nd month are more susceptible to increased QT intervals and arrhythmogenic properties.

Appropriate time of electrocardiographic screening for LQTS to prevent sudden death in infancy is not clarified. The highest prevalence of SIDS was at approximately 2 months of age.[5,6] In more detail, the first, second, the third peaks of occurrence were around the 75th, 44th, and 105th days of age, respectively.[4] In the current study, multivariate regression analysis showed that age at examination was the sole strong significant predictor for QTc interval in the subjects 0 to 11 weeks of age. Weight, gestational age, and Apgar scores at birth, and height and weight at examination did not affect the QTc interval. These data suggest that QTc values are applicable for all infants between 0 to 11 weeks of age, irrespective of birth weight, gestational age, and body status at examination from the data of the present study. On the other hand, Jedeikin et al reported the serial ECG findings from 5 to 96 hours after birth in 17 stressed neonates who had birth asphyxia or respiratory distress, and in 44 healthy term neonates.[27] They found that the changes in T-wave amplitude and ECG findings of myocardial ischemia were present until 96 hours after birth in both stressed and normal neonates, suggesting the ECG recording during very early neonatal periods after birth is not an appropriate time for screening. Considering the maximal prolongation of QT interval in normal infants at 6–11 weeks of age, the presence of ECG changes during very early neonatal periods, the presence of the second SIDS peak of 44th days of age, and finally infantile medical check-up was usually carried out at 1-month-old (around 30th day of age) in Japan, we suggest the appropriate timing of electrocardiographic screening for QT prolongation may be at the 1 month infantile medical check-up.

There are several limitations in the present study. First, the numbers of infants, especially those in the late infantile periods, were small when compared with a previous study.[14,15] Information of infants at birth and at examination in late infantile periods was extremely limited. Because the present study was retrospective, we were unable to perform

appropriate analysis for the association between the QTc intervals and confounders for the late infantile periods. Second, no genetic background was identified in the present study. These limitations should be investigated in the near future.

Conclusion

The QTc interval showed the highest peak at 6–11 weeks of age in infancy. The period was identical to the peak period of occurrence of SIDS. If the ECG screening for QT prolongation is set in the future, an appropriate time will be the medical examinations at one month of age. Examination of ECGs at that time and follow-up studies are needed.

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