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Original Article

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

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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.

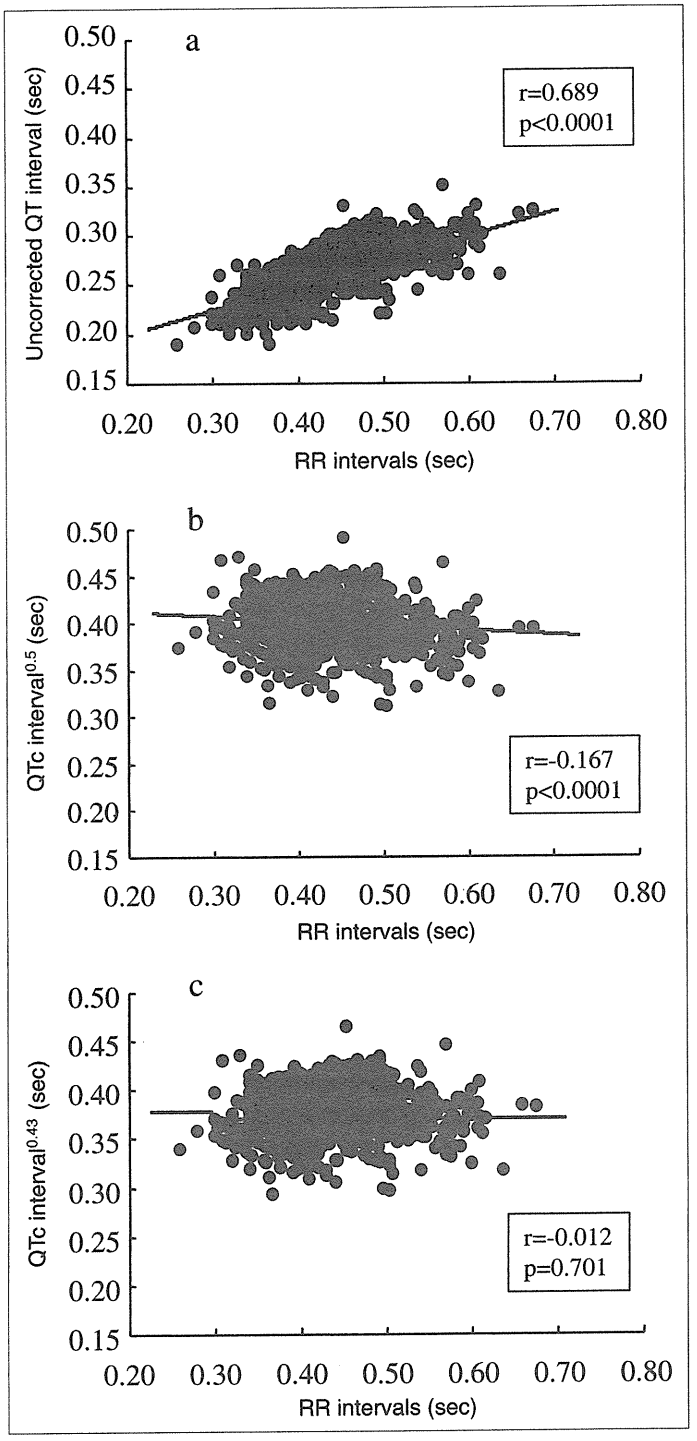

Figure 1 Association between RR intervals and the uncorrected QT intervals, QTc by Bazett's and the present formulas
The QT intervals are affected by the RR intervals, namely by heart rates (**a**). The QT intervals are corrected by the RR intervals to minimize the effect of heart rates usually by Bazett's 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

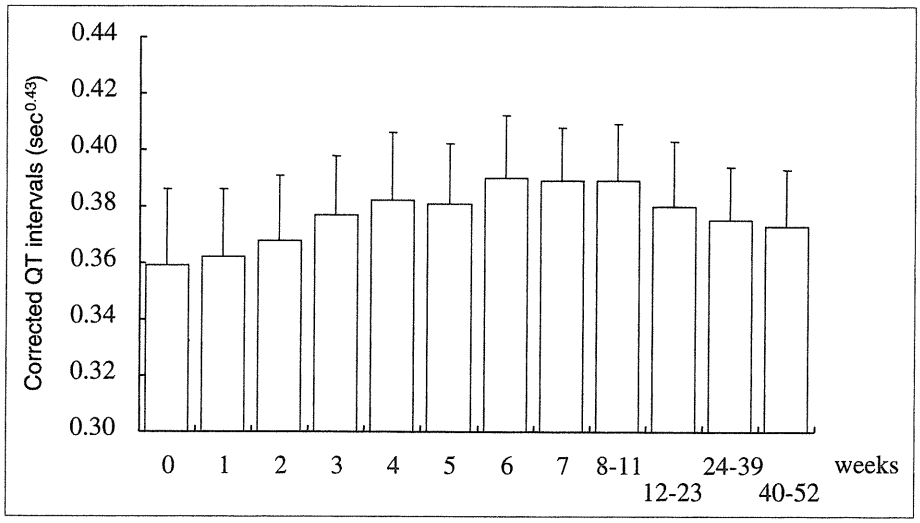

Figure 2 The QTc intervals from birth to 1 year of age
The QTc value showed a peak during 6 to 11 weeks of age. The Numbers of subjects in each group are shown in **Table 1**.

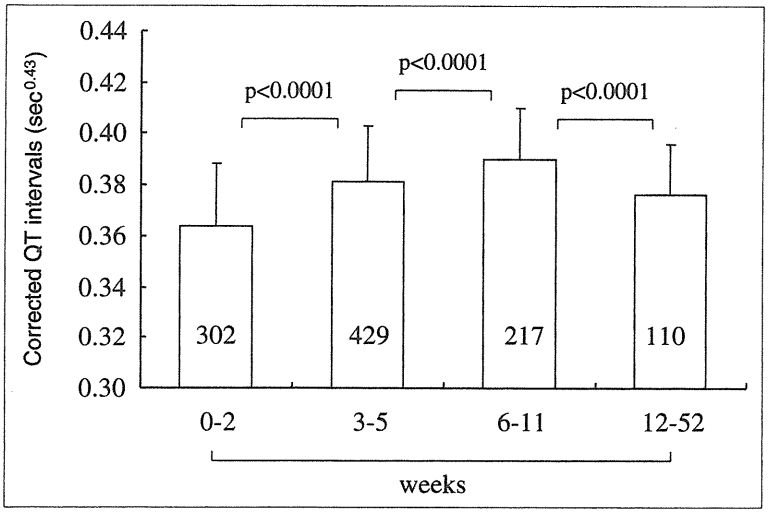

Figure 3 The QTc intervals at 0–2, 3–6, 6–11, and 12–52 weeks
Tukey's multiple comparison showed that the QTc intervals were significantly different between two successive groups with a peak value of 6–11 weeks. Numbers in the bars mean that of subjects in each group.

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.

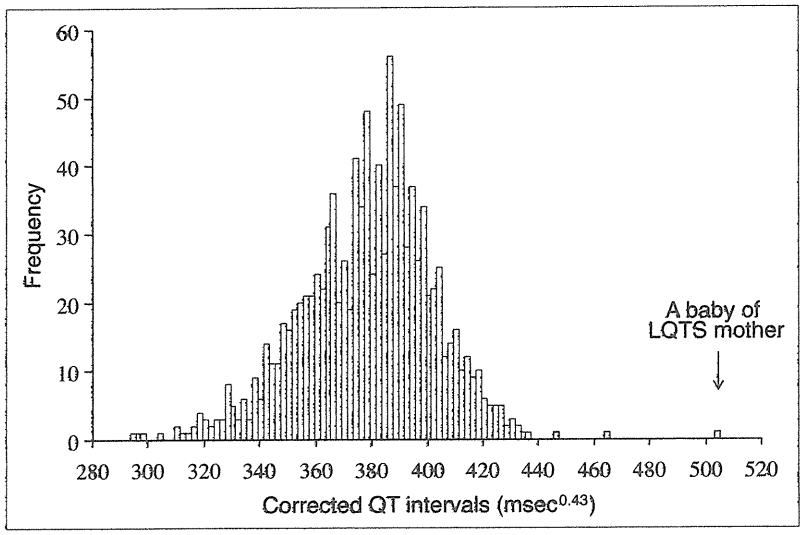

Figure 4 The frequency distribution of the QTc intervals
The frequency distribution showed a few cases with prominent QT intervals.

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 ($0.409 \pm 0.015\,sec^{0.50}$) 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 $0.409 \pm 0.022\,sec^{0.5}$, 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 $0.406 \pm 0.020\,sec^{0.5}$.[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

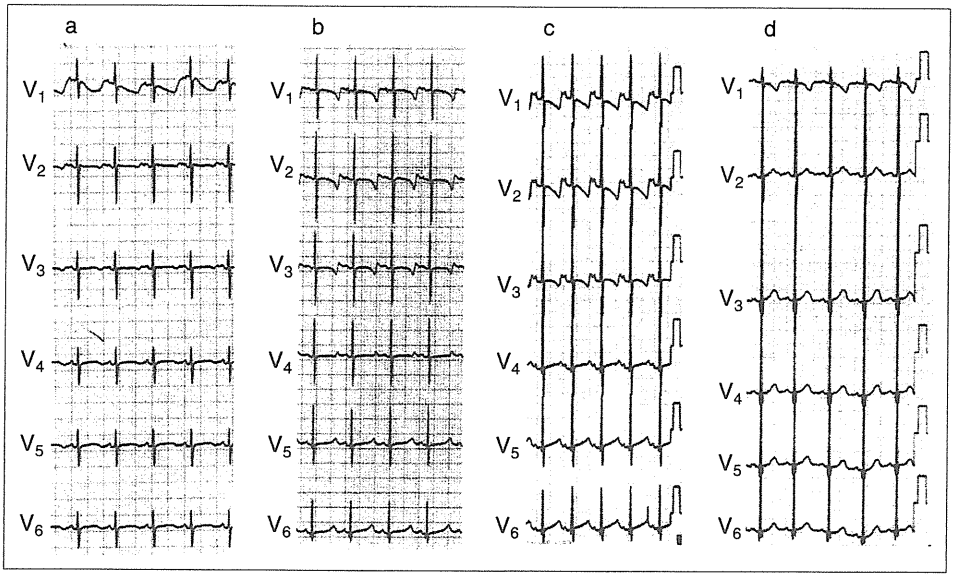

Figure 5 ECGs of infants with a high mean QTc value
The ECG (**Figure 5a**) on the first day of life before treatment showed biphasic T waves in leads V_1 to V_3, and the mean QTc interval in lead V_2 was 0.521 $sec^{0.43}$. He was diagnosed as having LQTS on the basis of family history and the findings 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.

Funding Sources

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Images in cardio-thoracic surgery

Isolated giant ascending aortic aneurysm in a child: a novel mutation of the ACTA2 gene

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Keywords: Isolated ascending aortic aneurysm; ACTA2 gene mutation; Child

An asymptomatic 8-year-old boy was referred with a giant isolated ascending aortic aneurysm (Fig. 1). Replacement of the ascending aorta was successfully performed (Fig. 2). DNA analysis revealed no mutation in *FBN1*, *FBN2*, *TGFBR1*, *TGFBR2*, or *SCL2A10*. However, analysis of the *ACTA2* gene showed a novel missense mutation (p.Arg39Cys (c.115C>T:ex2)).

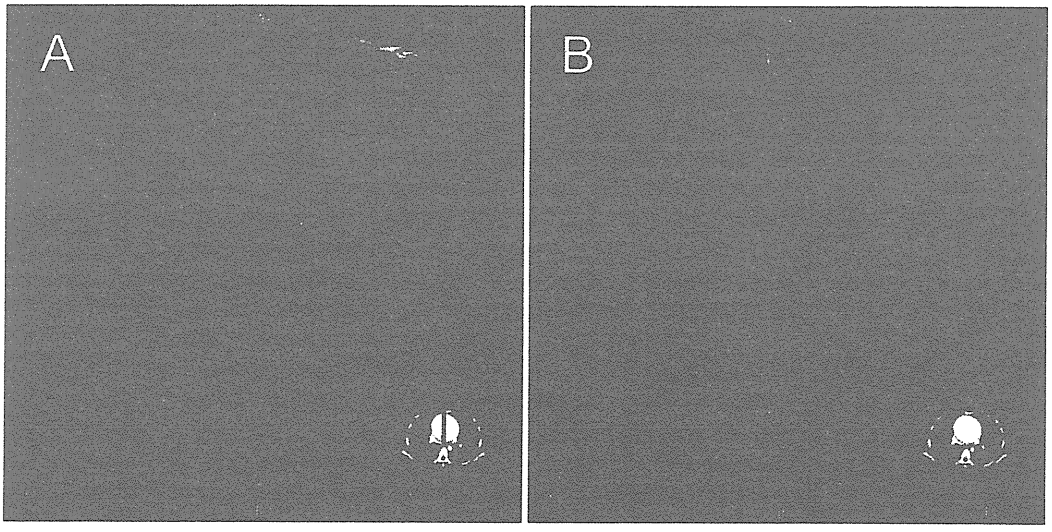

Fig. 1. Three-dimensional (3-D) computed tomographic scan showing a giant fusiform ascending aortic aneurysm with a maximal diameter of 87 mm. The patient exhibited hypertelorism and thick lips, but did not fulfill the criteria for known genetic connective tissue disorders (A). A right lateral 3-D view of the aneurysm. There was no compression on mediastinum structures such as the superior vena cava, pulmonary arteries or pulmonary veins (pulmonary arteries are not shown) (B).

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Fig. 2. Intraoperative picture shows a giant aneurysm originated 10 mm above the sinotubular junction and involved the entire ascending aorta. Replacement of the ascending aorta was performed under cardiopulmonary bypass with selective cerebral perfusion. The aortic valve was structurally normal, and the sinuses and annulus were uninvolved. Histological examination revealed cystic medial necrosis of the aortic wall with presence of type III collagen.

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Fatal pulmonary veno-occlusive disease after chemotherapy for Burkitt's lymphoma

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Key words Burkitt's lymphoma, chemotherapy, pulmonary hypertension, pulmonary veno-occlusive disease.

Pulmonary veno-occlusive disease (PVOD) is an uncommon cause of pulmonary hypertension (PH) and has poor prognosis. There are several case reports of PVOD developing after hematopoietic stem cell transplantation, but there are only a few cases reported of development after chemotherapy. We present here a boy with Burkitt's lymphoma complicated with fatal PVOD, which developed after complete remission of lymphoma following six courses of aggressive combination chemotherapy.

Case report

A previously healthy five-year-old boy was noticed to have abdominal distension seven days before admission. Neither fatigability nor weight loss was noted. Computed tomography of the abdomen revealed a perihepatic solid mass with skin invasion at the upper abdominal wall together with diffuse intestinal wall thickening. A biopsy specimen obtained from the abdominal wall showed typical histopathological features of Burkitt's lymphoma. No lymphoma cells were found in bone marrow or cerebrospinal fluid and a diagnosis of stage III non-Hodgkin's lymphoma was made. The patient already had tumor lysis syndrome (hyperphosphatemia, hypocalcemia, hyperkalemia, and hyperuricemia) including renal dysfunction, and continuous hemodialysis and filtration commenced soon after admission. Treatment for Burkitt's lymphoma was then started with time-intensive block chemotherapy according to the B cell type non-Hodgkin Lymphoma (B-NHL) protocol established by the Tokyo Children's Cancer Study Group.[1] Aggressive antitumor therapy (cyclophosphamide, methotrexate, epirubicin, etoposide, vincristine and cytosine arabinoside, prednisolone) was effective and continuous hemodialysis and filtration was stopped after 19 days of use. Toxic epidermolytic necrosis developed on day 10 of the initial course of chemotherapy, possibly due to the administration of allopurinol or trimethoprim/sulfamethoxazole. Soon after completion of the third chemotherapy course, the patient became dyspneic with arterial oxygen saturation (SaO_2) of 86% and chest X-ray examination revealed a moderate right-sided pleural effusion (Fig. 1a). No PH was noted on the electrocardiogram or echocardiogram at that time. The dyspnea improved following suspension of chemotherapy and administration of diuretics. The chemotherapy was resumed seven days after deterioration and was completed seven

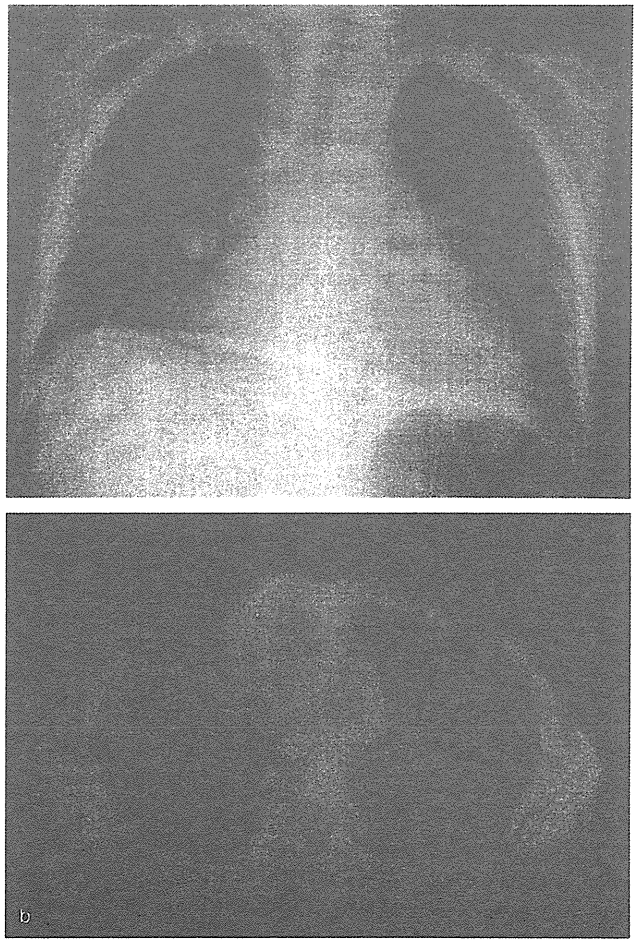

Fig. 1 (a) Chest X-ray film obtained in the first episode of dyspnea, showing bilateral pulmonary congestion and pleural effusion. (b) Computed tomography image of the lung base showing patchy foci of ground glass attenuation and septal thickening. Pulmonary arteries are enlarged.

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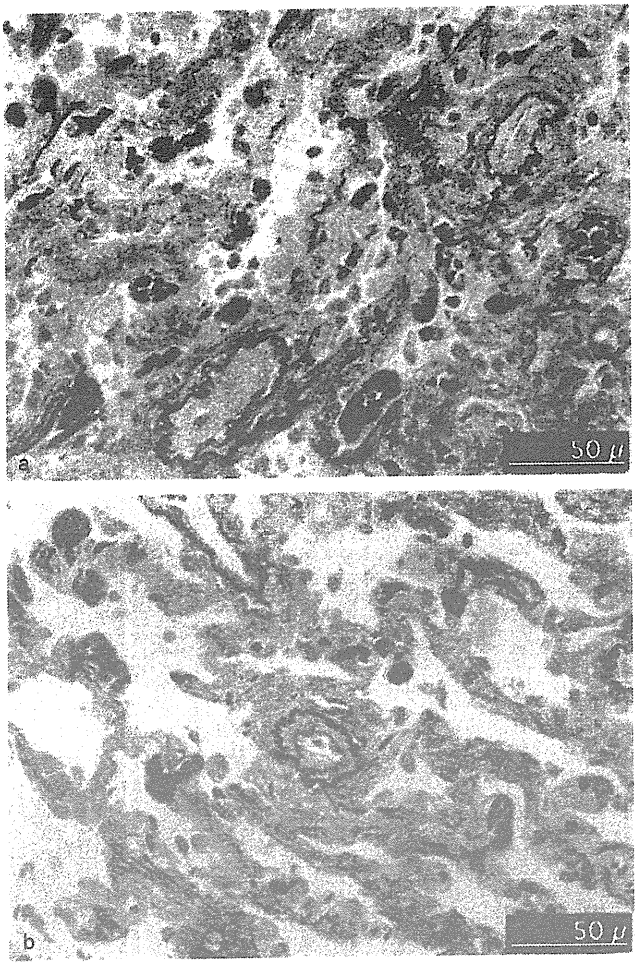

Fig. 2 (a)Postmortem examination of the right lung (Masson-trichrome stain) showing almost complete occlusion of small pulmonary veins (red arrow) and venules (30–50 μm in diameter) by fibrous proliferation of the intima. (b)Small pulmonary arteries (yellow arrow) show slightly thickened media without intimal lesions.

months later. The total doses of cyclophosphamide, methotrexate, epirubicin, etoposide, vincristine and cytosine arabinoside were 9 g/m^2, 6 g/m^2, 360 mg/m^2, 1.1 g/m^2, 3 mg/m^2 and 26 g/m^2, respectively. One week after completion of chemotherapy the patient became dyspneic again and SaO_2 decreased to 72% even though he had kept in complete remission. Electrocardiography revealed a right axis deviation and right ventricular hypertension. Echocardiography showed right atrial and ventricular enlargement and tricuspid regurgitation. Computed tomography of the chest demonstrated patchy reticulonodular interstitial opacities in the lungs and a right-sided pleural effusion without mediastinal abnormality (Fig. 1b). Right heart catheterization revealed PH with a mean pulmonary artery pressure of 50 mmHg. Pulmonary capillary wedge pressure could not be recorded and was abruptly increased after a saline infusion, followed by a gradual decrease. These findings allowed us to make a diagnosis of PVOD. Intravenous administration of prednisolone (2 mg/kg) was effective for relief of respiratory symptoms. After a few weeks, however, the dyspnea and hypoxemia recurred. Despite treatment with anticoagulants (75 units/kg of dalteparin sodium and 30 000 units of tisokinase) and diuretics (20 mg/day of furosemide), the patient died from refractory right heart failure one and a half months after the onset of respiratory symptoms. Postmortem examination of the right lung was performed. The pulmonary vein was completely occluded due to intimal fibrous tissue. Microscopically, the small pulmonary arteries showed almost no intimal proliferation but moderate medial thickening. In contrast, small pulmonary veins (<30–50 μm in diameter) showed severe luminal narrowing and occlusion by fibrous intimal hypertrophy. These findings of vascular remodeling in veins of small sizes and arteries, confirmed the diagnosis of PVOD (Fig. 2) with no evidence of relapse of the lymphoma.

Discussion

PVOD is a clinicopathological syndrome that accounts for a small number of cases of PH patients. Several risk factors for PVOD have been described including infection, genetic factors, autoimmune disorders, congenital heart disease and exposure to toxins.[2] PVOD has also been found in association with a variety of different tumors treated with chemotherapy protocols that most often contained mitomycin, bleomycin, gemcitabine or carmustine. Most of the published reports have followed hematopoietic stem cell transplantation however, with only a minority occurring after combined chemotherapy alone (Table 1a).[3–8] Whereas all of the patients with PVOD reported previously had at least one of the drugs mentioned above, our case did not receive any of these agents and had no other risk factors. We cannot confirm any association between the development of PVOD in our patient and other complications such as tumor-lysis syndrome, toxic epidermolytic necrosis or opportunistic infection. However, the protocol established by Tokyo Children's Cancer Study Group was aggressive antitumor therapy, so the high-dose combination chemotherapy itself should be recognized as a risk factor for PVOD.

Most patients with PVOD present with nonspecific complaints such as dyspnea on exertion and lethargy, making it difficult to diagnose the disease clinically.[2] If patients on anticancer chemotherapy show dyspnea of unknown cause, they should undergo electrocardiography, chest X-ray and echocardiography in order to rule out not only lung disease and myocardial dysfunction, but also PVOD. Further, if they show any findings suggestive of right heart overload or pulmonary hypertension with increasing pulmonary marking on chest X-ray, computed tomography of the chest would also be recommended. The characteristic tomographic findings of PVOD include smooth septal thickening, diffuse or mosaic ground glass opacities, multiple small nodules, pleural effusion and areas of alveolar consolidation, which can be gravitation-dependent.[2] We should keep in mind that PVOD is one of the differential diagnoses of dyspnea after combination chemotherapy, even though this combination chemotherapy might be just a trigger. We observed pulmonary intimal fibrosis in association with obstruction of the pulmonary veins.[2] Although the finding was typical of PVOD, the pathogenesis was unclear.

Table 1a Reported cases of pulmonary veno-occlusive disease (PVOD) following chemotherapy for malignant neoplasms

Neoplasm	Chemotherapy	Interval between chemotherapy and PVOD onset	Survival duration from PVOD onset	Clinical diagnosis	Pathological diagnosis	Reference
Lung adenocarcinoma	Gemcitabine, cis platinum, docetaxel	During chemotherapy	N.D.	N.D.	PVOD	3
Non-Hodgkin's lymphoma	Bleomycin, vincristine	3.5 mo	1 week	lung fibrosis	PVOD	4
Gastric adenocarcinoma	Doxorubicin, mitomycin C	15 mo	3 mo	N.D	PVOD	5
Glioma	BCNU	6 mo	2 mo	PVOD	PVOD	6
Squamous carcinoma uterine cervix	Bleomycin, mitomycin C, cis platinum	6 mo	3 mo	lung fibrosis	PVOD	7
Squamous carcinoma uterine cervix	Bleomycin, mitomycin C, cis platinum	N.D.	3 mo	N.D.	PVOD	8
Burkitt's lymphoma	Cyclophosphamide, vincristine, cytosine arabinoside, epirubicin, etoposide, methotrexate	During chemotherapy	1.5 mo	PVOD	PVOD	present case

BCNU, 1,3-Bis(2-chloroethyl)-1-nitrosourea (also known as carmustine); N.D., not described,;PVOD, Pulmonary veno-occlusive disease.

Various treatment options have been recommended for PVOD such as vasodilators, immunosuppressive medications, anticoagulant and antithrombotic agents, oxygen, and ultimately lung transplantation, but each of these modalities has been only in single case reports (Table 1b).[2,4,9,10] In our case, prednisolone was the most effective among all therapies tried, but the effect was only transient. The role of prednisolone as immunosuppressive medication in the treatment of PVOD remains undefined.[2] Prostacyclin has been widely used recently for PH but its application to PVOD is controversial. Prostacyclin dilates pulmonary arteries and arterioles, aggravating pulmonary congestion because the pulmonary venules ahead of the dilatation are largely obliterated. In fact, Palmer *et al.* reported a patient with PVOD who developed massive pulmonary edema leading to death after a low-dose prostacyclin infusion.[10] Lung transplantation is at present the only therapy that appears capable of significantly prolonging the lives of patients with PVOD.[2] Further research is required to establish a better therapy for PVOD.

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Table 1b Treatment of pulmonary veno-occlusive disease (PVOD) other than by prostaglandin-I_2 and nitrous oxide inhalation

Case	Age	Treatment	Clinical outcome	Reference no
T cell lymphoma	20	Steroid	Death	4
Adenocarcinoma	57	Steroid + diuretic therapy	Death	5
Interstitial pneumonitis	28	Steroid + oxygen + nifedipine	Death	9
ALL post-BMT	4	Steroid (2 mg/kg/day)	improved	10
ALL post-BMT	4	Steroid (2 mg/kg/day)	dyspnea → improved ALL relapse → death	10

ALL, acute lymphoblastic leukemia; BMT, bone marrow transplantation.

Detection of Extra Components of T Wave by Independent Component Analysis in Congenital Long-QT Syndrome

Hitoshi Horigome, MD, PhD; Yasuhiro Ishikawa, MD, PhD; Junko Shiono, MD, PhD; Mari Iwamoto, MD, PhD; Naokata Sumitomo, MD, PhD; Masao Yoshinaga, MD, PhD

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Detection of Extra Components of T Wave by Independent Component Analysis in Congenital Long-QT Syndrome

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Background—The main ECG criteria for the diagnosis of long-QT syndrome (LQTS) include abnormal T-wave morphology as well as prolonged QT interval. The T wave in LQTS probably includes additional components of the myocardial repolarization process, which are derived from aberrant ion currents. We investigated whether independent component analysis (ICA) can extract such abnormal repolarization components.

Methods and Results—Digital ECG data were obtained as a time series from 10 channels using 20 surface electrodes in 22 patients with genetically confirmed LQTS type 1 (LQT1) and 30 normal subjects. In each case, T-wave area was analyzed by radical ICA after noise reduction by the wavelet thresholding method. Furthermore, inverse ICA was applied to determine the origin of each independent component (IC). Radical ICA revealed that a T-wave consisted of 4 basic ICs in all control subjects, whereas ≥5 (mostly 6) ICs were identified in all 22 patients with LQT1. The extra ICs, which were not evident in normal subjects, were assumed to contribute to the formation of abnormal T-wave morphology. The extra ICs were identified even in patients with normal QTc values and in those taking β-blockers. Inverse ICA indicated that the additional ICs originate predominantly from the late phase of the T wave of the left ventricle.

Conclusions—Extra ICs appear during repolarization in all patients with LQT1 but not in normal subjects. ICA is a potentially useful multivariate statistical method to differentiate patients with LQT1 from normal subjects. (***Circ Arrhythm Electrophysiol.* 2011;4:456-464.**)

Key Words: electrocardiography ■ congenital ■ long QT syndrome ■ multivariate analysis

One of the main criteria used for the diagnosis of long-QT syndrome (LQTS) is QT-interval prolongation on the ECG. However, the end of the T wave sometimes is difficult to identify, and the QT interval fluctuates depending on the heart rate, status of the autonomic nervous system, and medications. The QT interval is not necessarily prolonged even in genotype-confirmed LQTS.[1,2] Another important diagnostic finding on ECG is aberrant T-wave morphology, although its analysis is largely qualitative.[2,3] The T wave represents the summation of the repolarization process of ventricular myocardial cells, and the presence of myocardial cells with malfunctional ion channels distorts the T-wave morphology.[4] We hypothesized that other components related to the abnormally long myocardial repolarization process are included in the T wave of LQTS. To investigate the nature of such T-wave components, we analyzed the T-wave area of digitized ECG in patients with LQTS type 1 (LQT1) by independent component analysis (ICA), and the results were compared with those of healthy control subjects.

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ICA is a recently developed multivariate statistical method capable of extracting source signals from the observed signals under the assumption that an observed signal is a linear mixture of non-Gaussian source components, which are independent of one another.[5,6] The ICA has been applied to analysis of complex phenomena in many scientific, social, and economic fields.[7] When ICA is applied to digitized ECG data, its merit is that multiple original signals of myocardial depolarization or repolarization can be extracted from the observed PQRST waveforms. On the other hand, one of the drawbacks of ICA is that the results tend to be influenced by the presence of noise, making it difficult to exclusively extract significant independent components (ICs).[8] On the

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*Drs Horigome and Ishikawa contributed equally to this work.

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Table. Clinical Characteristics and Results of Independent Component Analysis in Patients With Long-QT Syndrome

Pt No.	Age, y	Sex	Genotype	Syncope, ACA, or VT/TdP	QTc, ms	Pharmaco Therapy	No. ICs	Main Origin of ExT1†	Main Origin of ExT2†	Main Origin of ExT3†	Classification*
1	19	F	A226V	Syncope	482	BB	5	V2-V6, max-V4	V4-V6		d
2	46	F	A226V	...	478	...	5	V2-V6, max-V3	V3-V6, max-V6		d
3	15	F	D242N	...	473	...	5	V2-V6, max-V5	V3-V6		c
4	18	F	D242N	...	486	...	5	V2-V6, max-V3	V3-V6		c
5	10	M	V254M	Syncope	539	BB	5	V2-V6, max-V5	V3-V6, max-V5		d
6	15	M	V254M	Syncope, convulsion	478	BB	5	V1-V6, max-V2	V1-V6, max-V3		d
7	45	F	V254M	Convulsion	525	...	5	V1-V6, max-V2	V2-V5, max-V3		d
8	3	M	I313K	Syncope	528	BB, verap	6	V1-V4(n), V5-V6	V1(n), V5-V6	V1-V4, max-V3	a
9	13	M	I313K	Syncope	550	BB, verap	5	V2-V6, max-V4	V4-V6, max-V4		d?
10	34	F	I313K	Syncope	583	BB, mexil	6	V4-V6, max-V5	V2-V6, max-V4	V1, V3-V5	b
11	34	F	I313K	Syncope	590	BB, mexil	5	V2-V6, max-V5	V3-V6, max-V4		b
12	6	M	A341V	Syncope	580	BB	8	V1-V2, V3-V4(n)	V2, V4(n)	V2, V4	b
13	11	M	A344E	...	488	...	6	V1-V2(n), V4-V6	V2(n), V4-V6	V1-V3	d
14	20	F	L346V	...	492	BB	5	V1(n), V2-V6	V1(n), V3-V6		d
15	15	M	R366W	...	503	...	5	V1(n), V3-V6	V1(n), V5-V6		d?
16	12	M	P448R	...	428	...	6	V1-V2(n), V4-V6	V1(n), V4-V6	V1	c
17	20	F	P448R	Convulsion, TdP	543	BB	6	V1(n), V3-V6	V3-V6, max-V5	V1-V2	bifid
18	43	F	P448R	...	559	...	6	V1(n), V5-V6	V3-V6, max-V5	V1	bifid
19	17	M	R518G	Syncope	429	BB	5	V2-V5, max-V3	V3		c
20	18	M	R518G	Syncope	426	BB	5	V3-V5, max-V4	V3-V6		c
21	14	M	R555C	Syncope	508	BB	5	V1-V2(n), V5-V6	V1-V2(n), V4-V5		d
22	9	F	G643S	...	521	...	6	V2-V4(n), V6	V1-V4(n), V6	V1-V4(n), V6	bifid

ACA indicates aborted cardiac arrest; BB, β-blocker; IC, independent component; mexil, mexiletine; (n), negative wave; TdP, torsade de pointes; verap, verapamil; VT, ventricular tachycardia.

*T-wave type on original ECG according to the classification by Zhang et al[2] as follows: a indicates infantile type; b, broad-based type; bifid, bifid T wave usually observed in long-QT syndrome type 2; c, normal-appearing type; d, late-onset normal-appearing type; d?, type d is possible.

†Leads on original ECG from which each extra IC originated, with the maximum origin being presented as max.

ECG, some unavoidable noise exists, including that generated by respiratory movement and muscle contraction, in addition to extrinsic noise, such as that from electric waves. To filter these, we applied the wavelet thresholding method[9,10] to the digitized ECG before ICA to effectively reduce noises. Furthermore, inverse ICA (i-ICA), an algorithm originally developed by 1 of the authors (Y.I.),[11] was applied to the results of ICA to determine the origin of each IC extracted by the ICA that comes from the original surface. The i-ICA also was used to verify that each IC contributed significantly to the composition of the T wave and not derived from noise.

Methods

Subjects

We studied 22 patients (mean±SD age, 21.6±13.3 years) with genetically confirmed LQT1 (by *KCNQ1* gene mutation) and 30 age-matched healthy control subjects free from cardiovascular diseases. None of the subjects of the latter group were taking medications with electrophysiological effects. The study protocol was approved by the Ethics Committee of the University Hospital of Tsukuba (Ibaraki, Japan), and informed consent was obtained from each patient or parents if the patient was aged <15 years. Thirteen of the 22 patients with LQT1 had a history of syncope, convulsions, or previous demonstration of ventricular tachycardia on ECG, and 13 patients were being treated with oral β-blockers of whom 4 combined this with mexiletine or verapamil after the ECG recording (Table).

The T-wave morphology on the standard 12-lead ECG was classified according to the format proposed by Zhang et al.[2] They described 4 different T-wave morphologies characteristic for LQT1, including infantile type, broad-based type, normal-appearing type, and late-onset normal-appearing type.

Sampling of ECG Data

The ECG was recorded as time series data using an ECG amplifier (MA1000; TEAC; Tokyo, Japan). The time constant was set at 3.0 seconds. Signals were recorded from 10 channels using 20 silver-silver chloride surface electrodes. Channel 1 was set as lead I; channel 2 as lead II; channel 3 as lead III; channels 4 to 9 as bipolar leads from chest to left leg, each corresponding to C1 to C6 of conventional 12-lead ECG; and channel 10 as 4C9, representing a bipolar lead from the fourth intercostal space on the left spine border of the back to the fourth intercostal space at the left sternal border of the forechest. In each subject, the recorded data were digitized online with an A/D converter (EC-2360; Elmec; Tokyo, Japan) at a sampling rate of 1024 Hz and saved in a notebook computer as a data file for future analysis. The data of C1 to C6 were converted into V1 to V6 using the following formula to produce ECG images: $Vi=Ci+(II+III)/3$, where $i=1$ to 6.

ECG Data Analysis

The methods used for data analysis comprised the following 4 main steps: (1) noise reduction by wavelet thresholding method[9,10] (ie,

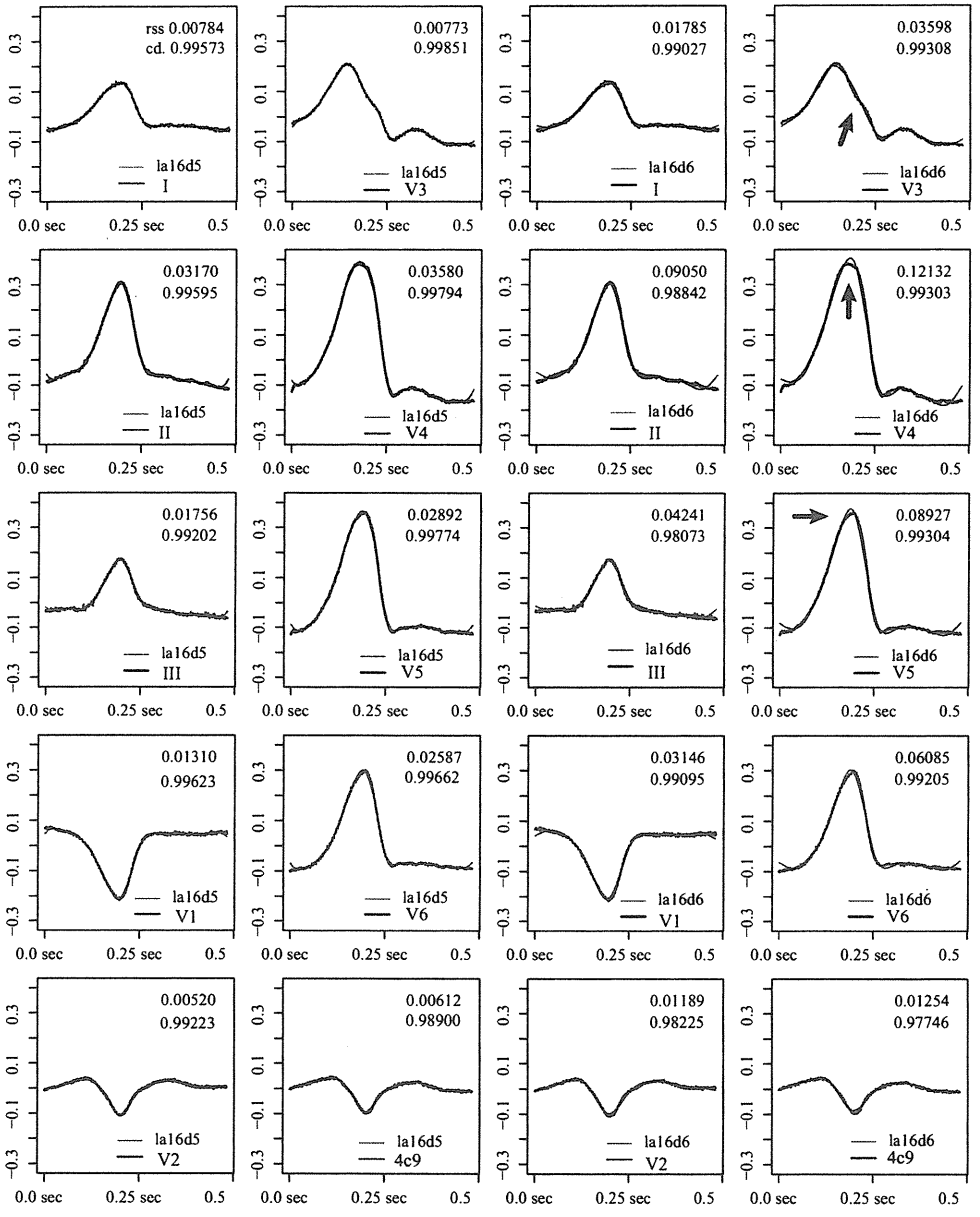

Figure 1. Noise reduction by wavelet thresholding method in a normal subject. Blue trace indicates original waveforms and red trace, approximated waveforms after noise reduction, indicating a good approximation (left 2 columns). However, when another level of wavelet was applied, there was dissociation between the peaks of the original T wave and the peaks of approximated T wave in V3 to V5 (right 2 columns, arrows), indicating inappropriate approximation. The unit for the vertical axis is mV.

approximation by wavelet), (2) radical ICA[8] with the additive random noise, (3) selection of the best model from the results of repeated ICAs, and (4) i-ICA for determination of the origin of each IC. The methods of these 4 steps used in the present study are described fully in the expanded Methods section in the online-only Data Supplement.

Noise Reduction by Wavelet Thresholding Method

To reduce noise before ICA, the hybrid threshold method (a combination of the universal threshold method and Stein unbiased risk estimate threshold method) was applied to the T-wave area (from the J point to the onset of the next P wave) of the digitized ECG. In this process, 4 types of wavelets were used, from which 1 with a maximum resolution level and best approximation to the original ECG was selected (online-only Data Supplement Figure 1). That the shape of the approximated data corresponded to the original data was confirmed by verifying each peak and flexion point of the T wave using the inverse wavelet transformation technique for each lead (Figure 1).

Radical ICA With the Additive Random Noise

The approximated data were analyzed by radical ICA. To improve the performance of ICA and, specifically, to avoid falling into the local extrema, we used the additive random noise, which was generated in multiples of the SD of the given data. The size of the additive noise had 10 values of SD, and radical ICA was repeated 16 times for each SD size, making the total times of ICA 160 for each case (online-only Data Supplement).

Selection of the Best Model From the Results of Repeated ICAs

To select the best model from the 160 results of ICA in each case, 3 indices of each ICA were calculated: Amari error,[12] relative mutual information, and the fourth-order cumulants.[13] We then used the