

## ORIGINAL ARTICLE

# Relationship between QT and JT peak interval variability in prepubertal children

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**Background:** The QT variability index (QTVI) is a noninvasive index of repolarization lability that has been applied to subjects with cardiovascular disease. QTVI provides a ratio of normalized QT variability to normalized heart rate variability, and therefore includes an assessment of autonomic nervous activity. However, measurement of QT time is particularly difficult in children, who exhibit physiologically high heart rates compared with adults. In this study, we developed a set of standard values of J-point to Tpeak interval (JTp) for infants by age, and assessed the correlation of QTVI with the JTp variability index (JTpVI).

**Methods:** Subjects included 623 infants and children (0–7 years of age) without heart disease and 57 healthy university students. All subjects were divided into three groups by age. QTVI and JTpVI were calculated based on an electrocardiogram, and age-specific standard values, a gender-specific classification, and a standard growth curve were constructed.

**Results:** JTpVI markedly decreased in infancy and slowly decreased thereafter, reaching adult values by school age. There was also a strong correlation of JTpVI with QTVI ( $r = .856$ ).

**Conclusions:** JTp can be used to evaluate the variability of the repolarization time in healthy infants, and may be useful for detection of early repolarization abnormalities.

## KEYWORDS

autonomic nervous system, JT peak interval, QT interval, variability index

## 1 | INTRODUCTION

Body surface electrocardiography (ECG) can provide electrophysiological information on the myocardium, and is useful for evaluation of autonomic balance and arrhythmogenic substrates, and for prediction of patient prognosis. Heart rate variability is a measure of autonomic balance (Goldkorn et al., 2015; Akselrod et al., 1981) and the ventricular late potential (Simson, 1981; Malik et al., 1992), and was recently used to determine the delay and disturbance of myocardial depolarization

based on the QRS complex, the heterogeneity of transmural dispersion of repolarization (Antzelevitch, Yan, & Shimizu, 1999; Smetana et al., 2011; Antzelevitch, 2005), and QT dispersion, for evaluation of repolarization based on the potential differences between myocardial regions (Napolitano, Priori, & Schwartz, 2000).

The QT variability index (QTVI) (Berger et al., 1997) is a measure of temporal instability, and is used to evaluate heart rate variability-induced QT time variation by normalizing this variation using the mean and variance of heart rate. We previously reported standard

childhood values of QTVI (Kusuki et al., 2011) and evaluated the lability of repolarization in pathological states using QTVI (Kuriki et al., 2011). However, evaluation using the QT time does not reflect the pure repolarization process as it contains the QRS time. Furthermore, it was often difficult to measure the end of the QT time, due to the overlap in the T-wave endpoint and P wave of the next heartbeat in children, in whom baseline heart rate is physiologically high.

Several methods for analysis of the QT time using the subinterval between depolarization and repolarization have been reported. For example, the JT time is determined by excluding the QRS time (the depolarization time) from the QT time. JT time is then divided into the JTp time (from the end of the QRS complex [J-point] to the T-wave peak [Tpeak]) and the Tp-e time (from Tpeak to the end of the T wave [Tend]). The Tp-e time represents the late repolarization time, and arrhythmogenicity can be identified by analyzing the relationship between the Tp-e and QT time (Gupta et al., 2008). Using Tpeak allows accurate measurement of the JTp time, which can be measured in waveforms of infants with a high heart rate. In addition, JTp time can be measured in waveforms with bundle branch block, as the QRS complex (a depolarization waveform) is excluded. Thus, the repolarization process can be evaluated, at least in part, in ECG waveforms that are difficult to evaluate using the QT time.

The electrophysiological significance of the early repolarization time is not fully understood. The autonomic nervous system is thought to have limited influence on the inward rectifier current (IK1), which determines this early repolarization phase, but can have marked effects on the inward calcium current, resulting in changes in the duration of the action potential (Wetzel & Klitzner, 1996; Lopatin & Nichols, 2001). Moreover, variation of the repolarization time, including the JT peak, among the ECG lead sites is predicted due to the potential gradient between the endocardium and the epicardium, and the spatial potential gradient between the apex and base of the heart (Malik & Batchvarov, 2000).

In the present study, we developed a set of standard values of the early repolarization time (JTp) for infants by age, and assessed the correlation of clinical QTVI with JTpVI, a variability index of the early repolarization time.

## 2 | METHODS

The subjects were 646 neonates and children who had been determined to have no organic heart disease by electrocardiograph and cardiac ultrasonography and no systemic inflammatory disease by laboratory examinations, in Fujita Health University Hospital between April 2008 and November 2015. For the present analysis, eight patients were excluded because stable ECG recordings were not possible due to vigorous motion. An additional 15 patients were excluded because they showed extremely high heart rates (HRs > 180 bpm) with overlapping of T-wave terminal portion and P wave. Finally, enrolled 623 patients had sufficient records of electrocardiography, and the T-wave endpoint could be measured automatically. Fifty-seven

university students were also examined as healthy controls. Written informed consent was obtained from the subjects or their parents. The study was approved by the Epidemiological Clinical Study Ethics Committee of our university.

ECGs (single CM5 lead) were recorded using a polygraph device (MP-150; Biopac Systems Inc., Goleta, CA, USA) during echocardiography performed between 4:00 and 6:00 p.m., prior to dinner. Infants of 3 months to 1 year of age were premedicated with Tricloral syrup (0.7 ml/kg) for sedation. Records of 60 heartbeats with a stable baseline were subjected to automatic analysis of the interbeat (RR) interval using analytical software (Acqknowledge v3.9; Biopac Systems Inc.). First-derivative and absolute-value processing were applied to the ECG waveforms. The starting point and endpoint (J-point) of the QRS complex and Tend were determined, and the RR interval, the QT time for the same heartbeat, and the JTp time were measured. The QTc interval was calculated by using Fridericia's formula. The mean and variance of each time parameter of the analyzed heartbeat were also calculated.

Subsequently, QTVI, JTVI, and JTpVI were calculated using Berger's formula, as follows:  $QTVI = \log_{10} (QTv/QTm^2)/(HRv/HRm^2)$ ,  $JTVI = \log_{10} (JTv/JTm^2)/(HRv/HRm^2)$ ,  $JTpVI = \log_{10} (JTpv/JTp m^2)/(HRv/HRm^2)$ , where the numerator (QTVN, normalized QT variability; JTVI, normalized JT variability; JTpVI, normalized JTp variability) contains the variance of intervals (QTv, JTv, JTpV) divided by the square of the mean interval (QTm, JTm, JTp m). The denominator (HRVN, normalized HR variability) contains the variance of HR (HRv) divided by the squared mean HR (HRm). The logarithm is taken for statistical reasons to ensure a normal distribution of the otherwise skewed variability indexes distribution.

Subjects were divided into two groups to assess age-related changes in values obtained from the ECG waveforms, as follows: group I, age < 1 year ( $n = 309$ , boys:girls = 180:129); group II, 1–7 years ( $n = 314$ , 172:142); and group III, healthy university students (mean age:  $21.0 \pm 1.2$  years;  $n = 57$ , 30:27).

Statistical analysis was performed using JMP software (SAS Institute Inc., Cary, NC, USA). The correlation of QTVI with JTpVI was investigated using linear regression analysis. Comparisons of each age group with university students were performed by Dunnett's test, the Wilcoxon signed rank test was used for pairwise comparison in each age-specific group, with the significance level at  $p < .05$ .

## 3 | RESULTS

### 3.1 | Comparison of electrocardiography parameters

ECG parameters in each age group (groups I and II) were compared with those for the university students (group III) (Table 1). The mean heart rate decreased with age, reflecting physiological changes (Table 1). By contrast, the QRS time increased with age, and was significantly higher in group III compared with groups I and II. The corrected QT time was significantly higher in groups I and II compared with group III, while the corrected JT time was higher in groups I and II compared with group III. In groups I–II, the measured JTp time was

**TABLE 1** ECG characteristics

	I (n = 309)	II (n = 314)	III (n = 57)
HR (bpm)			
Mean ± SD	155.3 ± 25.3*	100.7 ± 15.8*	68.3 ± 8.7
Median	159.7	99.3	67.9
(2nd–98th)	101.8–198.1	73.1–140.0	48.8–86.3
RR (ms)			
Mean ± SD	397.7 ± 73.6*	612.5 ± 95.2*	900.1 ± 121.3
Median	375.3	606.7	899.7
(2nd–98th)	305.0–589.7	429.0–824.8	700.4–1236.6
QRS (ms)			
Mean ± SD	67.8 ± 8.7*	85.5 ± 9.2*	104.4 ± 8.8
Median	65.8	85.9	103.0
(2nd–98th)	56.1–91.5	66.4–102.4	83.0–130.6
QT (ms)			
Mean ± SD	258.1 ± 28.4*	323.4 ± 28.5*	380.9 ± 26.4
Median	252.9	323.1	381.2
(2nd–98th)	212.8–321.7	267.5–382.0	325.7–449.0
QTc (ms)			
Mean ± SD	410.5 ± 20.4*	414.5 ± 17.5*	403.0 ± 24.0
Median	411.4	414.8	406.9
(2nd–98th)	368.4–450.4	378.2–447.4	350.2–441.0
JT (ms)			
Mean ± SD	190.4 ± 23.6*	237.8 ± 26.3*	276.6 ± 27.1
Median	187.7	239.3	279.7
(2nd–98th)	149.6–242.8	182.4–294.6	218.2–345.6
JTc (ms)			
Mean ± SD	302.7 ± 21.1*	304.4 ± 19.2*	292.5 ± 25.4
Median	305.4	304.6	295.5
(2nd–98th)	254.7–341.2	262.6–337.2	236.8–335.3
JTp (ms)			
Mean ± SD	133.6 ± 21.3*	169.3 ± 24.2*	193.9 ± 26.9
Median	130.1	170.8	193.4
(2nd–98th)	96.4–179.7	117.8–217.2	134.8–261.0
JTpc (ms)			
Mean ± SD	212.2 ± 22.6*	216.4 ± 21.1*	204.8 ± 24.8
Median	213.0	216.3	207.5
(2nd–98th)	164.9–257.5	170.5–254.8	148.4–254.7

Each value is expressed as the mean ± SD.

\* $p < .05$  (vs. III) with Dunnett's test.

significantly lower, and in groups I and II, the corrected JTp time was higher, compared with group III.

### 3.2 | Variability indexes

QTVI, JTVI, and JTpVI in each age group (groups I–II) were compared with those for university students (group III) (Table 2). All the variation rates were significantly different in groups I compared with group

**TABLE 2** Comparison of variability indexes

	I (n = 309)	II (n = 314)	III (n = 57)
QTVI			
Mean ± SD	-0.41 ± 0.58*	-1.20 ± 0.48	-1.35 ± 0.45
Median	-0.39	-1.30	-1.29
(2nd–98th)	-1.49 to 0.81	-1.89 to 0.02	-2.36 to -0.61
JTVI			
Mean ± SD	-0.16 ± 0.56*	-0.94 ± 0.47	-1.06 ± 0.42
Median	-0.16	-1.02	-0.95
(2nd–98th)	-1.21 to 1.06	-1.62 to 0.24	-2.09 to -0.34
JTpVI			
Mean ± SD	0.07 ± 0.64*	0.80 ± 0.56	-0.89 ± 0.45
Median	0.04	-0.91	-0.83
(2nd–98th)	-1.15 to 1.36	-1.65 to 0.65	-1.85 to 0.03
QTVN × 1000			
Mean ± SD	0.46 ± 0.35*	0.21 ± 0.19	0.21 ± 0.21
Median	0.38	0.14	0.13
(2nd–98th)	0.03 to 1.38	0.03 to 0.65	0.02 to 1.05
JTVN × 1000			
Mean ± SD	0.80 ± 0.61*	0.36 ± 0.32	0.38 ± 0.34
Median	0.68	0.28	0.29
(2nd–98th)	0.07 to 2.37	0.07 to 1.20	0.04 to 1.72
JTpVN × 1000			
Mean ± SD	1.56 ± 1.58*	0.57 ± 0.89	0.52 ± 0.39
Median	1.14	0.34	0.44
(2nd–98th)	0.11 to 5.93	0.10 to 2.51	0.08 to 1.82
HRVN × 1000			
Mean ± SD	1.46 ± 1.64*	3.61 ± 3.48	3.97 ± 3.23
Median	0.86	2.63	3.17
(2nd–98th)	0.08 to 6.42	0.17 to 13.14	0.59 to 16.40

Each value is expressed as the mean ± SD.

\* $p < .05$  (vs. III) with Dunnett's test.

III, while there were no differences between group II and group III. Normalized variabilities (QTVN, JTVN, JTpVN, HRVN) were significantly different in groups I compared with group III, while there were no differences between group II and group III.

### 3.3 | Gender differences

There were no gender differences in JTpVI between any age groups (Table 3).

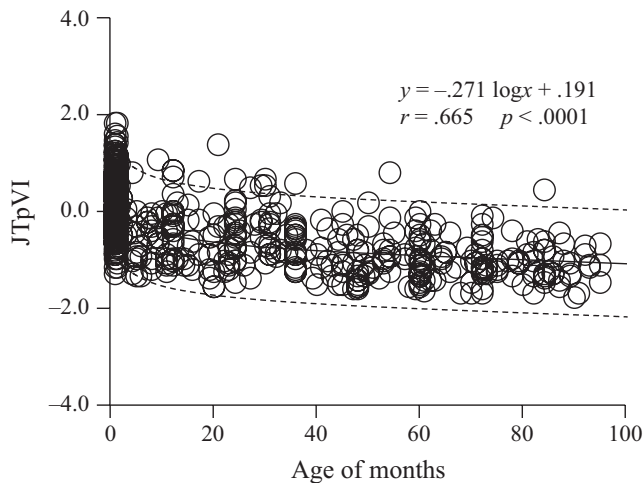
### 3.4 | Changes in JTpVI after birth

A scatter plot of the relationship between JTpVI and age in months is shown in Figure 1. The JTpVI value markedly decreased from the neonatal period to infancy, moderately decreased thereafter, and then stabilized by 3 years of age.

**TABLE 3** Gender differences in JTpVI in each group

	I (n = 309)	II (n = 314)	III (n = 57)
M/F	180/129	172/142	30/27
Age (month)			
Median	1	48	264
(2nd–98th)	0–11	12–91	233–289
Male	0.05 ± 0.65	−0.84 ± 0.58	−0.95 ± 0.56
Female	0.11 ± 0.64	−0.76 ± 0.54	−0.82 ± 0.26
p-value	.44	.09	.30

Each value is expressed as the mean ± SD. There is no significance with the Wilcoxon signed-rank test.

**FIGURE 1** Relationship between JTpVI and age in months. The JTpVI value decreased rapidly until 3 months after birth, decreased slowly during infancy, and then stabilized by elementary school age

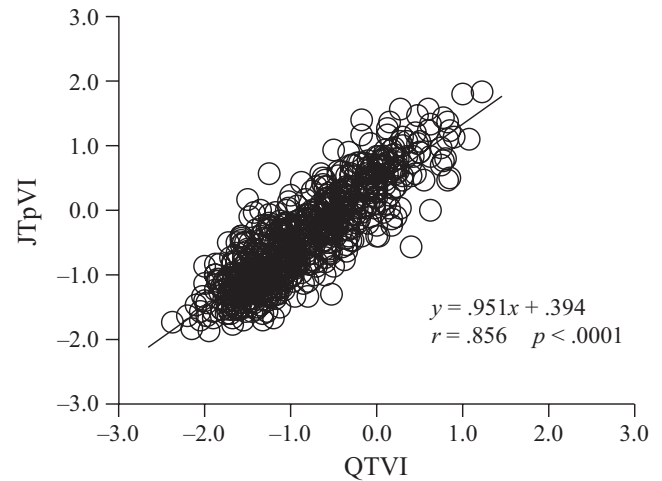
### 3.5 | Comparing QTVI to other ECG-based variability indexes

Correlation analysis showed a strong correlation ( $r = .856$ ,  $p < .0001$ ) of QTVI with JTpVI in children (Figure 2) and a significant relationship between JTVI and JTpVI ( $r = .897$ ,  $p < .0001$ ).

## 4 | DISCUSSION

In the present study, we used body surface electrocardiography to measure the early repolarization time, JTp, during childhood. The main finding was that the variability index (JTpVI) of the JTp time relative to the RR interval markedly decreased after birth, and then stabilized at 4–7 years of age. Furthermore, JTpVI was highly correlated with QTVI, which is used clinically to predict instability of myocardial repolarization.

Measurement of QT time is required for determining QTVI. However, as QT time includes the QRS complex time, false QT prolongation indicating QT extension is observed in cases with

**FIGURE 2** Relationship between QTVI and JTpVI

bundle branch block. Alternative methods have been developed to exclude the QRS complex when evaluating these waveforms, such as using the subinterval JT time from the J-point, which represents the QRS complex endpoint (QRS end) to the T-wave end. In a study of approximately 2,900 patients with bundle branch block, Zhou et al. (1992) reported that the JT time shortened with increasing QRS time. Furthermore, Berul, Hill, & Geggel (1997) measured the QRS, QT, and JT times in pediatric patients with long QT syndrome or right bundle branch block, and found QT prolongation in both groups, but JT prolongation only in patients with long QT syndrome. Thus, long QT syndrome and right bundle branch block can be differentiated by extraction and comparison of the JT time (Berul et al., 1997).

The ages of the subjects reported by Berul et al. (1997) ranged from 1 week to 18 years old, covering the neonatal period to school age and adolescence, suggesting that evaluation of repolarization time based on the JT time is useful in pediatric subjects. However, physiological heart rate is higher during infancy compared with in adulthood. Thus, the T-wave end and P wave can overlap, which prevents accurate measurement of the QT time. To overcome this problem, we used the time from Q, termed the early repolarization time, to the T-wave peak (QTp) in the repolarization process, or the time from the J-point to the T-wave peak (JTp). Although these are not complete substitutions for the QT time, we found a significant relationship between QTVI and JTpVI, indices of instability of myocardial repolarization.

Evaluation of arrhythmogenic substrates requires analysis of the time from Tpeak to Tend, which reflects “variation” of the duration of the action potential. This method is well established and is electrophysiologically valid (Antzelevitch et al., 1999; Smetana et al., 2011; Antzelevitch, 2005). However, patients with arrhythmogenicity characterized by short QT syndrome were recently reported (Bjerregaard & Gussak, 2005). Although there are no established diagnostic criteria for this syndrome, Gollob, Redpath, & Roberts (2011) proposed criteria for adults where shortening of the early repolarization time ( $JTp < 120$  ms) is scored as one point. Short QT syndrome

also develops in childhood, and separate diagnostic criteria may be needed. The utility of the measured or corrected value of the JTp time or variability index remains to be investigated in this context.

To our knowledge, there are no previous reports on JTpVI, and no large-scale studies on the repolarization time. The characteristics of the changes in JTpVI after birth (Figure 1) are similar to the age-related changes in QTVI reported by Kusuki et al. (2011). Furthermore, the age-related gradual changes in JTpVI closely resemble the frequency characteristic ratio (LF/HF) of heart rate variability described by Massin & Von Bernuth (1997). There is a progressive change in autonomic nervous system balance with growth after birth, with increased vagus nerve activity to match the predominant sympathetic nerve activity. LF/HF is a measure of autonomic nervous balance calculated from variation of the RR interval, and autonomic nervous input into the sinus node provides the basis for heart rate variability (De Rogalski et al., 2007; Longin et al., 2006). Thus, JTpVI might reflect the maturation of autonomic nervous control of the heart, similar to LF/HF and QTVI in healthy children.

Clinically, arrhythmia-associated cardiac events can be predicted from a high QTVI in adults with an impaired myocardium. However, QTVI shows diurnal variation, and its general use should be assessed in a randomized prospective study (Dobson, Kim, & Haigney, 2013). In the present study, we used healthy university students as controls to match the control groups used in previous studies (Dobson et al., 2013; Atiga et al., 1998; Myredal, Karlsson, & Johansson, 2008). We previously reported that variation of QTVI was dependent on development after birth in children (Kusuki et al., 2011). Furthermore, in a clinical study of children with systemic inflammation due to Kawasaki disease (studies were performed in the febrile and recovery stages), a high QTVI was observed in the febrile stage, but no patients developed arrhythmia, suggesting that fever increased sympathetic tension (Kuriki et al., 2011). These studies suggest that JTpVI and QTVI reflect autonomic nervous system balance in subjects with no myocardial impairment. JTpVI combines measure of both JTp interval and heart rate variability, and these factors can be evaluated independently to assess the relative contributions of electrical instability and autonomic nervous activity.

#### 4.1 | Limitations

This study had several limitations. First, the T-wave peak can vary among the 12-lead ECG sites, and the early repolarization time is not homogenous. To overcome this problem, we only analyzed the single CM5-lead ECG. Second, as the subjects were children with no organic heart disease and the QRS time did not exceed 120 ms in any subject, the influence of bundle branch block on JTpVI was not investigated. Future studies comparing the standard JTpVI values in cases with bundle branch block cases are required. Third, we administered sedative to infants who were 3–12 months. It is possible that the activity of sympathetic nervous system was decreased by the sedative. Fourth, we did not perform a comparison of subjects in the present study with excluded subjects that showed a T-wave end overlap in the ascending limb of the P wave.

## 5 | CONCLUSION

This study demonstrated that QTVI, which reflects instability of myocardial repolarization, and JTpVI determined by subinterval analysis, were positively correlated in healthy children, suggesting that JTpVI can be used to evaluate repolarization lability of the myocardium. Furthermore, JTpVI changed with age, reflecting fluctuations in the cardiac cycle and autonomic nervous input into repolarization (i.e., physiological development of the autonomic nervous system). Future studies are required to investigate the utility of JTpVI in subjects with organic heart pathology, with the goal of using this parameter for detection of early repolarization abnormalities.

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### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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