Dynamic Changes in the QT-R-R Relationship during Head-Up Tilt Test in Patients with Vasovagal Syncope

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Background: QT interval is influenced by preceding R-R intervals and autonomic nervous tone. Changes in QT intervals during vasovagal reflex might reflect autonomic modulation of ventricular repolarization; however, this issue has not been fully elucidated. This study aimed to evaluate dynamic response of QT interval to transient changes in R-R interval during vasovagal syncope (VVS) induced by head-up tilt test.

Methods: Eighteen patients with VVS and 18 age- and sex-matched controls were studied. All patients with VVS had a positive mixed-type response to head-up tilt and all controls had a negative response. CM5-lead digital electrocardiogram (ECG) was recorded and QT intervals were analyzed using Holter ECG analyzer. Using scatter plots of consecutive QT and the preceding R-R intervals, QT-R-R relations during tilt-up and tilt-back or during vasovagal reflex were independently fitted to an exponential curve: $QT \text{ (second)} = A + B \times \exp[k \times R-R \text{ (second)}]$.

Results: During the tilt-up, A, B, and k did not differ between patients with VVS and controls. During the tilt back, k showed equivalent positive value compared to the tilt-up (4.1 ± 1.3 vs -4.6 ± 0.9) in controls. However, k remained negative (-1.3 ± 1.5) during vasovagal reflex in patients with VVS. In six patients, in whom metoprolol was effective in eliminating VVS, QT-R-R relationship during the tilt-back became similar to that in controls.

Conclusions: In patients with VVS, hysteresis of the QT-R-R relation is similarly shown during tilt-up as in controls, whereas this hysteresis is no longer evident and failure of QT prolongation is observed during VVS.

A.N.E. 2005;10(1):16-24

syncope; QT interval; head-up tilt; autonomic nervous system

Vasovagal syncope (VVS), or neurally mediated syncope, is the most frequent cause of unexplained syncope, especially in patients without apparent structural cardiovascular diseases.¹⁻³ Recently, a head-up tilt test is proven as a useful tool for the diagnosis of unexplained syncope.²⁻⁵ Several observations suggest that the hypotension-bradycardia induced by head-up tilt test is essentially equivalent to the spontaneous episodes of VVS.²⁻⁵ Initial descriptions of the mechanisms responsible for such syncope emphasized the role of a sudden vagal discharge.⁶ However, previous studies suggested the sympathovagal balance was altered resulting in sympathetic predominance just before VVS.^{4,7-9}

QT interval reflects the time course of ventricular repolarization and is influenced by preceding

R-R intervals and autonomic tone.¹⁰⁻¹⁶ Changes in QT intervals during vasovagal reflex may also reflect autonomic modulation of ventricular repolarization;¹⁶⁻¹⁸ however, this issue has not been fully elucidated. The aim of this study was therefore to determine response of QT interval to transient changes in R-R interval during VVS.

METHODS

Study Population

The VVS group consisted of 18 patients who had unexplained syncope, a positive response to the head-up tilt test (without isoproterenol), and the following characteristics: (1) normal QRS

complexes; (2) stable electrocardiogram (ECG) recordings throughout the head-up tilt test; (3) absence of baseline QT prolongation and drug use that could affect QT interval or heart rate; and (4) no evidence of organic heart disease. Eighteen age and sex-matched subjects without evidence of cardiovascular disease, QT prolongation, syncope, and a positive response to the head-up tilt during both the baseline and isoproterenol infusion served as controls. Patients with flat T-wave were not included in the present study because of technical feasibility using automatic measurement of QT interval. The study protocol was approved by our institutional review board and written informed consent was obtained from all subjects before participation.

Study Protocol

Study protocol was described elsewhere.⁴ Briefly, all subjects were studied in the fasting state at rest. Lead-II ECG and arterial blood pressure using tonometry (Jentow-7700, Nihon Colin, Komaki, Japan) at the level of the left radial artery were monitored continuously. An intravenous catheter was placed in the right median cephalic vein for saline infusion (60 ml/h). Two-channel Holter ECG recordings (FM-100, Fukuda Denshi, Tokyo, Japan) were obtained throughout the head-up tilt test. Head-up tilt test was started after 10-minute rest in the supine position. Each patient was tilted to a 60-degree upright position for 30 minutes with a footboard. A positive response was defined as a decrease in mean blood pressure over 20 mmHg from the value at 1 minute of tilt or a trough systolic blood pressure under 70 mmHg associated with syncope or presyncopal symptoms. During baseline head-up tilt without any provocative drugs, all patients in VVS group showed a positive mixed-type response as previously described.⁵ Mixed response was defined by symptoms in association with hypotension and decrease in heart rate, but without fall to <40 beats/min or falls to <40 beats/min for <10 seconds with or without asystole for <3 seconds.⁵ In all control subjects with a negative response to baseline head-up tilt, isoproterenol was infused intravenously at rates of 0.01–0.03 $\mu\text{g/kg}$ per minute and the test was repeated as in our previous study.⁴ All control subjects also showed a negative response during head-up tilt with isoproterenol.

CM5-lead digital ECGs during only baseline head-up tilt without isoproterenol were sampled at a sampling interval of 8 ms and analyzed by Holter ECG analyzing system (SCM 6000, Fukuda Denshi). We did not measure QT interval during isoproterenol infusion because isoproterenol could have direct effects on QT interval.

QT intervals were automatically measured by determining the end point of T-wave as the intersection of the steepest slope of descending T-wave and the isoelectric line, using a software for the waveform analyzing algorithm [HPS-QTM(I)]. To improve accuracy of the automatic measurement of QT intervals, two cardiologists ascertained and adjusted the end point of the T-wave on the monitor screen without any information about the subjects. Adjusted QT intervals showed no significant difference between these two cardiologists. The average difference between them was 9 ± 7 ms (mean $\pm$ standard deviation). Time series of the consecutive 100–150 sets of the QT and preceding R-R intervals were selected during tilt-up and vasovagal reflex in VVS group, and tilt-up and tilt-back in controls. Scatter plots of the QT-R-R relations were made and QT-R-R relations were fitted to an exponential curve as follows.

$$\text{QT (second)} = A + B \times \exp[k \times \text{R-R (second)}].$$

The QT-R-R relation during various physiologic conditions has been recognized to be well fitted to this exponential formula.^{13,19} We confirmed that the most commonly used Bazett's formula could not make a better fit than this formula in all study subjects. A correlation coefficient (r) was always higher when using this formula rather than the Bazett's formula. In six patients in VVS group, who showed negative response to head-up tilt during administration of oral metoprolol (60 mg, daily), the QT-R-R relation during head-up tilt was also determined.

Statistical Analysis

The values are presented as mean $\pm$ standard deviation. The 2-tailed unpaired Student's t -test was used for statistical comparison between two groups. The chi-square test was used to evaluate differences in gender between the two groups. A P value <0.05 was taken as significant.

Table 1. Clinical Characteristics and Hemodynamic Measurements (Mean $\pm$ SD)

	Control	VVS	P Value
Age (years)	35 $\pm$ 19	39 $\pm$ 21	NS
Men/women	11/7	12/6	NS
Baseline QT intervals (minute)	0.39 $\pm$ 0.05	0.40 $\pm$ 0.03	NS
Tilt duration (minute)		18 $\pm$ 8	
HR (beats/min)			
Supine	63 $\pm$ 11	63 $\pm$ 11	NS
Tilt 1 minute	77 $\pm$ 12	80 $\pm$ 12	NS
Tilt end or syncope	83 $\pm$ 14	66 $\pm$ 27	P < 0.05
Mean BP (mmHg)			
Supine	85 $\pm$ 12	80 $\pm$ 13	NS
Tilt 1 minute	94 $\pm$ 15	90 $\pm$ 12	NS
Tilt end or syncope	87 $\pm$ 15	46 $\pm$ 19	P < 0.001

BP = blood pressure, HR = heart rate, VVS = vasovagal syncope.

RESULTS

Subject Characteristics

The clinical characteristics of both the control group and the VVS group are summarized in Table 1. There was no significant difference in mean age, gender, and baseline QT intervals between the two groups. Both heart rate and the mean blood pressure were not significantly different between the two groups during supine and at 1 minute of the tilt. However, these hemodynamic indices at the time of syncope in the VVS group were significantly lower than those at the end of the tilt in control group. The mean duration of the tilt was 18 ± 8 min in the VVS group.

QT-R-R Relation During Head-Up Tilt

Relations between QT intervals and the preceding R-R intervals during baseline head-up tilt in a representative control subject are shown in Figure 1. The QT-R-R relations during tilt-up and back were independently fitted to exponential curves. The two regressions were point-symmetric to each other, and the QT-R-R relation consequently showed hysteresis between tilt-up and tilt-back. Changes in BP, R-R, and QT during baseline head-up tilt in a 39-year-old male patient with VVS are shown in Figure 2. ECG and scatter plots of QT-R-R relations during tilt-up and vasovagal reflex in this patient are shown in Figures 3 and 4. As compared with the QT-R-R relation in the control subject, the QT-R-R relation showed a similar pattern during tilt-up, but a different pattern during VVS. QT prolongation was obscured dur-

ing progressive prolongation of R-R interval due to VVS.

Figure 5 shows mean regression exponential curves of the QT-R-R relation during tilt-up and tilt-back in controls, and tilt-up and vasovagal reflex in VVS group. In controls, the QT-R-R relation showed hysteresis in directions of the changes in the R-R intervals. In VVS group, the QT-R-R relation during tilt-up showed the same pattern with the controls. However, the relation became different during vasovagal reflex from that of the tilt-back in the controls, although R-R intervals prolonged similarly in both study groups. The regression parameters A and B during tilt-up and tilt-back or vasovagal reflex were not different between the two groups (Table 2). Regression parameter k during tilt-up did not differ between VVS group and controls. The absolute value of k was essentially the same between tilt-up and tilt-back in the controls, but was not between tilt-up and vasovagal reflex in VVS group. The k showed a negative value during vasovagal reflex (Table 2).

Effects of Metoprolol on the QT-R-R Relation in Patients with VVS

In six patients in VVS group, who showed negative response to head-up tilt during administration of oral metoprolol, the QT-R-R relation during head-up tilt were compared between before and during the treatment. The QT-R-R relation during a negative response to head-up tilt test with metoprolol became similar to the controls. Consequently, regression parameter k during tilt-back was not different between controls and these six patients (Table 2).

Figure 1. Representative scatter plot of QT-R-R relations during transient changes in R-R interval caused by tilt-up (closed diamonds) and back (open triangles) in a 43-year-old female control subject. The QT-R-R relations during tilt-up and back were independently fitted to exponential curves. The two regressions were point-symmetric to each other, and the QT-R-R relation consequently showed hysteresis between tilt-up and tilt-back.

DISCUSSION

Major Findings

This study elucidated the dynamic response of QT interval to transient changes in R-R interval dur-

ing VVS and major findings were as follows. In patients with VVS, QT-R-R relation was the same during tilt-up as in controls, whereas the relation became different and QT prolongation was obscured during progressive R-R prolongation due to VVS.

Figure 2. Representative changes in BP, R-R, and QT during baseline head-up tilt in a 39-year-old male patient with VVS. At 13 minute of tilt, BP dropped gradually followed by prolongation of the R-R interval, and the patient had presyncopal symptoms. Then, he was returned to the supine position.

Figure 3. ECG changes during tilt-up (A) and vasovagal reflex (B) in the same patient as in Figure 2. An example of typical QT interval preservation despite marked bradycardia during vasovagal reflex is shown in panel B. QT and R-R intervals are in milliseconds.

In six patients with VVS in whom the response to head-up tilt test became negative during metoprolol therapy, QT-R-R relationship during both tilt-up and tilt-back became similar to that of controls.

The Postural Response of the QT-R-R Relation in Controls

In controls, QT interval slowly adapted to both shortening and lengthening of R-R interval, and

the QT-R-R relation consequently showed hysteresis along with changes in the R-R interval.

Effects of head-up tilt on QT interval have not been fully elucidated. During head-up tilt enhancement of sympathetic tone or withdrawal of parasympathetic tone has been shown with analysis of heart rate variability,⁴ changes in circulating catecholamines^{8,9} or muscle sympathetic nerve activities.⁷ These changes in autonomic nervous activities could influence QT intervals directly by

Figure 4. Scatter plot of QT-R-R relations during tilt-up (closed diamonds) and vasovagal reflex (open triangles) in the same patient as in Figure 2. The QT-R-R relation showed the same pattern during tilt-up as in controls, but became different from the control pattern during prolongation of R-R interval due to vasovagal reflex. Prolongation QT interval was obscured.

Figure 5. Averaged regression exponential curves of the QT-R-R relation during tilt-up and tilt-back in controls (left), and tilt-up and vasovagal reflex in VVS group (right). In controls, the QT-R-R relation showed hysteresis in directions of the changes in the R-R intervals. In VVS group, the QT-R-R relation during tilt-up showed the same pattern with that in the control. However, the QT-R-R relation along with R-R prolongation due to VVS was quite different from that seen along with similar R-R prolongation due to tilt-back in the control. QT prolongation was obscured in VVS group.

affecting the action potential duration (APD) of ventricular myocardium and indirectly by modulating R-R interval.¹⁰⁻¹⁶ Huang et al.²⁰ studied the postural response of the QT-R-R relation and reported the absence of a consistent relation between heart rate and QT interval during circulatory adjustment to the erect posture. However, they manually measured QT interval only of 5 adjacent beats during the first 13 seconds after standing and during continuous standing.²⁰ Their method seemed impractical for analyzing the dynamic responses of QT interval to postural changes. In the present study, the beat-to-beat changes in QT interval were automatically measured with a software for the wave-form analyzing algorithm.

In controls, QT interval slowly adapted to changes in R-R interval during tilt-up and tilt-back, and the QT-R-R relation showed hysteresis in direction of the changes in the R-R interval. This was consistent with the earlier study reported by Yamada et al.²¹ and hysteresis in the QT-R-R relation during transient changes in heart rate has been reported by other investigators.²²⁻²⁴ Despite differing physiologic conditions and thus differing autonomic status, all of these reports showed that changes in QT interval lagged behind the rapid and sustained changes in heart rate. Moreover, the findings of the point-symmetric response of QT interval between increase and decrease in heart rate were also reported by Yamada et al.²¹ These responses

Table 2. Exponential Regression of the QT-R-R Relation during Head-Up Tilt (Mean $\pm$ SD)

	Control		VVS		VVS (Met) (n = 6)	
	Tilt-Up	Tilt-Back	Tilt-Up	Vasovagal	Tilt-Up	Tilt-Back
A	0.40 $\pm$ 0.05	0.32 $\pm$ 0.06	0.42 $\pm$ 0.06	0.37 $\pm$ 0.12	0.40 $\pm$ 0.04	0.32 $\pm$ 0.05
B	-2.59 $\pm$ 3.05	0.05 $\pm$ 0.12	-3.93 $\pm$ 10.4	-4.27 $\pm$ 16.75	-2.15 $\pm$ 1.61	0.02 $\pm$ 0.02
k	-4.32 $\pm$ 2.47	4.18 $\pm$ 2.24	-4.42 $\pm$ 3.37	-1.51 $\pm$ 2.47 ^a	-4.34 $\pm$ 1.87	3.32 $\pm$ 2.32
r	0.74 $\pm$ 0.17	0.76 $\pm$ 0.13	0.77 $\pm$ 0.11	0.77 $\pm$ 0.15	0.85 $\pm$ 0.06	0.83 $\pm$ 0.11

A, B, and k = regression parameters of exponential model; QT (second) = A + B $\times$ exp[k $\times$ R-R (second)], r = correlation coefficient, Met = during oral metoprolol (60 mg, daily) therapy.

^aP < 0.001 versus tilt-back in control.

of QT interval might reflect mainly slow responses of the action potential duration to rapid changes in cycle length.^{21,25,26}

Changes in the QT-R-R Relation During Vasovagal Reflex

Our previous study and some earlier studies suggested the sympathovagal balance was altered to lead to sympathetic predominance just before sudden vagal discharge during VVS.^{4,7-9} Changes in QT intervals during vasovagal reflex could reflect autonomic modulation of ventricular repolarization.^{17,18} Jaeger et al.¹⁷ reported that QT intervals remained short in the presence of profound bradycardia during VVS, a finding consistent with the present study. However, they did not evaluate the beat-to-beat changes in the QT interval during VVS. In the present study, analyses of the beat-to-beat changes in the QT-R-R relation during head-up tilt clearly indicated the QT-R-R relation was different between tilt-back in controls and VVS, although both situations induced bradycardia. QT prolongation along with R-R prolongation was obscured during VVS.

In normal subjects, vagal stimulation causes a rate-independent prolongation of QT interval, whereas the exercise-induced increase in sympathetic tone causes a rate-independent shortening.^{10-12,14,18} QT interval shortens in response to exercise and atropine,^{11,13,16} therefore, and vagal inhibition with or without concomitant sympathetic excitation was therefore important in facilitating QT shortening.¹⁶ The QT-R-R relationship during recovery from exercise was also studied previously.¹¹ According to these earlier studies, QT interval could be prolonged under heightened vagal tone during VVS. However, the present study showed that that was not the case.

Two possible mechanisms could account for these findings. First, residual cardiac sympathetic stimulation on ventricular myocardium despite marked vagal influence on the sinus node and withdrawal of sympathetic effect on peripheral vasculature may contribute to failure of QT prolongation during bradycardia induced by VVS.¹⁷ A dissociation between sinus rate and ventricular repolarization has been demonstrated in experimental models using simultaneous activation of both limbs of the autonomic nervous system.²⁷

Second, paradoxical shortening of QT interval after a prolonged pause was reported in patients

with bradycardia due to sick sinus syndrome or atrioventricular block.^{28,29} The paradoxically shortened QT interval in these cases may indicate an unusual adaptation of repolarization time to abrupt increase in the preceding R-R interval.^{28,29} Castellanos et al.³⁰ reported QT intervals at the end of vagal-induced R-R pauses initially showed no prolongation as the pauses lengthened to 2450 ms, thereafter followed by gradual increases as the R-R intervals prolonged. They suggested the QT intervals in young patients without structural heart disease is determined by a complex interaction between the cumulative effects of previous cycle length (memory effect³¹) and the autonomic (mainly parasympathetic) nervous system.³⁰ Earlier studies reported the action potential duration of ventricular myocardium was shortened after a rest period.³² Slower recovery from inactivation of the transient outward current (I_{to}) could play a role in paradoxically shortened QT intervals at longer R-R intervals.³²

Effects of Metoprolol on the QT-R-R Relation in Patients with Vasovagal Syncope

Because increased sympathetic nervous activities precedes or triggers vasovagal reflex,^{5,6,9-11} β -adrenergic receptor blockade has been proposed as a prophylactic drug for prevention of VVS.^{33,34} In this study, metoprolol (60 mg, daily) successfully prevented VVS in six patients with VVS. In these patients, the QT-R-R relation during head-up tilt with metoprolol therapy became similar to that in control subjects.

Lecocq et al.¹³ observed no significant changes in the QT-R-R relation after β -blockade evaluated by the same exponential formula as we used. Other investigators¹⁴ also showed failure of β -blockade to modify the regression curve of QT-R-R relation. However, effect of β -blockade on dynamic changes in QT-R-R relation or QT hysteresis during postural change especially in patients with VVS remains to be elucidated. We observed patients with VVS showed a negative response to head-up tilt test and similar QT-R-R relation during tilt-up and tilt-back to that in controls during metoprolol therapy. Depending on the earlier observation that β -blockade did not modify QT-R-R relation,^{13,14} these changes may be mainly explained by the prophylactic effects of β -blockade on VVS.^{33,34}

Methodological Considerations and Study Limitations

There are several limitations in the present study. First, the methods used in measuring QT are critically important to ensure accuracy and reproducibility. In this study, CM5-lead digital ECGs were analyzed and QT intervals were measured automatically using a software for the waveform analyzing algorithm. To improve accuracy of the automatic QT-interval measurement, two cardiologists adjusted the end point of the T-wave on the monitor screen and adjusted QT intervals showed no significant difference between these two cardiologists. In this study, only CM-5 lead was utilized and subjects with flat T were excluded. These could hamper the present result.

Second, we selected time series of the consecutive 100–150 sets of the QT and preceding R-R intervals during tilt-up and tilt-back or vasovagal reflex to determine the dynamic changes in QT-R-R relation. For this purpose, only patients with a mixed-type response⁴ to head-up tilt test with gradual prolongation of R-R intervals were included in this study. Subjects with a pure cardioinhibitory response or vasodepressor response could show a different dynamic QT-R-R relation during head-up tilt test.

Finally, we did not evaluate changes in autonomic nervous activities during head-up tilt test in the present study. Using analysis of heart rate variability, our previous study and some earlier studies reported sympathetic predominance just before, and subsequent increase in vagal tone during VVS.^{7–9} These changes in autonomic nervous activities might explain, at least in part, the dynamic changes in QT-R-R relation observed during VVS in the present study.

CONCLUSION

In patients with VVS, QT prolongation along with R-R prolongation was obscured during VVS. This finding would provide an insight into the dynamic alteration in the autonomic nervous tone during VVS.

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