Relation between Beat-to-Beat QT Interval Variability and T-Wave Amplitude in Healthy Subjects

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Objectives: Elevated beat-to-beat QT interval variability (QTV) has been associated with increased cardiovascular morbidity and mortality. The aim of this study was to investigate interlead differences in beat-to-beat QTV of 12-lead ECGs and its relationship with the T wave amplitude.

Methods: Short-term 12-lead ECGs of 72 healthy subjects (17 f, 38 ± 14 years; 55 m, 39 ± 13 years) were studied. Beat-to-beat QT intervals were extracted separately for each lead using a template matching algorithm. We calculated the standard deviation of beat-to-beat QT intervals as a marker of QTV as well as interlead correlation coefficients. In addition, we measured the median T-wave amplitude in each lead.

Results: There was a significant difference in the standard deviation of beat-to-beat QT intervals between leads (minimum: lead V₃ (2.58 ± 1.36 ms), maximum: lead III (7.2 ± 6.4 ms), ANOVA: $P < 0.0001$). Single measure intraclass correlation coefficients of beat-to-beat QT intervals were 0.27 ± 0.18 . Interlead correlation coefficients varied between 0.08 ± 0.33 for lead III and lead V₁ and 0.88 ± 0.09 for lead II and lead aVR. QTV was negatively correlated with the T-wave amplitude ($r = -0.62$, $P < 0.0001$). There was no significant affect of mean heart rate, age or gender on QT variability (ANOVA: $P > 0.05$).

Conclusions: QTV varies considerably between leads in magnitude as well as temporal patterns. QTV is increased when the T wave is small.

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The QT interval of body surface ECG reflects depolarization and repolarization of the ventricular myocardium. Abnormal prolongation as well as shortening of the QT interval has been associated with increased propensity of malignant ventricular arrhythmia.¹ Beat-to-beat variability of the QT interval reflects lability in ventricular repolarization; elevated beat-to-beat QT interval variability (QTV) has been associated with cardiac disease and increased risk for experiencing ventricular tachycardia and ventricular fibrillation, leading to sudden cardiac death.² In particular, elevated QTV has been reported in patients with dilated cardiomyopathy,³ coronary artery disease,⁴

congestive cardiac failure⁵ and during acute myocardial ischemia.⁶ In addition, elevated beat-to-beat QTV has also been demonstrated in patients with obstructive sleep apnea⁷ and mental disorders.⁸

However, the mechanisms underlying QTV are incompletely understood. Reduction in repolarisation reserve has been suggested to increase QTV.^{9,10} Furthermore, the autonomic nervous system has been implicated in the generation of beat-to-beat QTV. More specifically, it has been debated whether elevated beat-to-beat QT interval variability is a marker of sympathetic activation. Pharmacologic sympathetic activation/block and

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Figure 1. Example of beat-to-beat-QT intervals in the standard 12-lead ECG of a healthy subject recorded over 150 seconds.

orthostatic challenge have shown to affect QT variability.^{11,12} Spontaneous QTV appears to be reflective of sympathetic activation, but only when a cardiovascular morbidity exists.^{13,15}

In most previous studies, QTV has been reported only for a single lead. The aim of this study was to systematically compare QTV across the 12 standard leads and its association with the T-wave

amplitude, using short-term ECG recordings of healthy subjects.

METHODS

Subjects

Standard resting 12-lead ECGs of 72 healthy control subjects (17 females, mean age 38 ± 14 yrs and 55 males, mean age 39 ± 13 yrs) were investigated. The data have been obtained from the PTB diagnostic database (<http://www.physionet.org/physiobank/database/ptbdb/>). The ECGs were recorded for approximately two minutes at a sampling frequency of 1000 Hz and at 16-bit resolution over a range of ± 16.384 mV.

QT Variability Analysis

To analyse beat-to-beat QTV, the correct identification of the Q wave onset and T wave terminus are crucial, especially in the presence of noise and artefacts, which all ECG recordings typically contain to some extent. In this study, we used the algorithm proposed by Berger and coworkers.³ Here, the operator defines a template of the QT interval by selecting the onset of Q wave and offset of T wave for one beat in a particular lead. The algorithm then finds the QT interval of all other beats in that particular lead by determining how much each T wave must be stretched or compressed in time to best match with the template.³ If the operator selects a longer/shorter QT template, all of the QT intervals will be biased accordingly. In this way, a relatively robust estimation of QT interval is achieved by considering the whole T wave instead of commonly applied threshold techniques that are based on determining the end of the T wave and are prone to artefacts and noise sources.³ We identified the QT interval in lead I and used the same time interval for extracting QTV in all other leads. To quantify QTV, we calculated the standard deviation of QT intervals as well as the QT variability index, QTVI, according to the equation given by Berger and coworkers³:

$$QTVI = \log \frac{\frac{QTvar}{\text{meanQT}^2}}{\text{meanHR}^2},$$

Figure 2. Median and interquartile ranges of standard deviations of beat-to-beat QT interval (A) and QTVI (B) in the standard 12-lead ECG of 72 healthy subjects.

where QTvar and HRvar represent the variance of beat-to-beat QT intervals and heart rate, respectively.

In addition, we measured the amplitude of the T wave for each beat by obtaining the peak of the voltage deflection within the ST segment. For further analysis we considered the median of absolute values of the T-wave amplitudes of each lead.

As a measure of heart rate variability we computed the standard deviation of normal RR intervals (sdNN).

Statistics

For the statistical analysis, we used PASW Statistics 18 (IBM SPSS, Inc., Somers, NY, USA), GraphPad Prism 5 (GraphPad Software, Inc., La Jolla, CA, USA) and Microsoft Excel version 2007 (Microsoft Corp., Redmond, WA, USA). Overall beat-to-beat QTV was calculated for each lead as standard deviation of QT intervals and QTVI and compared using one-way ANOVA. Further,

Table 1. Post Hoc Test for Significant Differences in the Magnitude of Beat-to-Beat QT Variability in 12-Lead ECG

Lead	II	III	aVR	aVL	aVF	V ₁	V ₂	V ₃	V ₄	V ₅	V ₆
I	n.S.	***	n.S.	***	n.S.	*	n.S.	n.S.	n.S.	n.S.	n.S.
II		***	n.S.	***	n.S.	*	n.S.	n.S.	n.S.	n.S.	n.S.
III			***	n.S.	***	***	***	***	***	***	***
aVR				***	n.S.	**	n.S.	n.S.	n.S.	n.S.	n.S.
aVL					**	n.S.	***	***	***	***	***
aVF						n.S.	n.S.	*	*	*	*
V ₁							**	***	***	***	***
V ₂								n.S.	n.S.	n.S.	n.S.
V ₃									n.S.	n.S.	n.S.
V ₄										n.S.	n.S.
V ₅											n.S.

*** -P < 0.001.

** -P < 0.01.

* -P < 0.05.

n.s. = not statistically significant.

Figure 3. Single measure intraclass correlation coefficient of beat-to-beat QT intervals in the 12-lead ECG.

beat-to-beat QTV was compared between different leads using single measure intraclass correlation coefficient (ICC) and Pearson's correlation coefficients. One-way ANOVA was applied to test for lead differences in T-wave magnitude. Pearson's linear correlation coefficient was computed to test the relation between QTV and T-wave amplitude. Prior to correlation analysis, QTV and T-wave amplitude values were log-transformed to obtain normal distributed data. The two-way ANOVA was applied to test for gender and age differences in interlead QTV. The unpaired Student t-test was used to investigate age and gender differences in mean heart rate, heart rate variability and ICC values of QTV. All values were expressed as mean $\pm$ standard deviation. Test results were considered statistically significant when $P < 0.05$.

Figure 4. Median and interquartile ranges of T-wave amplitudes of standard 12-lead ECG of 72 healthy subjects.

RESULTS

Beat-to-beat QT interval variability in the 12 standard leads of a typical subject is shown in Figure 1. The standard deviations of beat-to-beat QT intervals vary between 2.7 ms and 6.4 ms in this recording.

Median and interquartile ranges of the standard deviation of beat-to-beat QT intervals in the 12 standard leads for the whole study group are shown in Figure 2A. There were a significant difference in QTV ($F = 18.93$, $P < 0.0001$) and QTVI ($F = 21.27$, $P < 0.0001$) between leads. Post hoc test results (Tukey's multiple comparison) are summarized in Table 1. Prominent deviations in QTV were observed in leads III (38 ms, [interquartile

Table 2. Group Means and Standard Deviations of Pearson's Correlation Coefficients Calculated for Beat-to-Beat QT Intervals in the Standard 12-Lead ECG

Lead	II	III	aVR	aVL	aVF	V ₁	V ₂	V ₃	V ₄	V ₅	V ₆
I	0.67 ± 0.22	0.15 ± 0.32	0.84 ± 0.16	0.58 ± 0.33	0.41 ± 0.30	0.36 ± 0.31	0.49 ± 0.28	0.65 ± 0.16	0.67 ± 0.18	0.72 ± 0.17	0.70 ± 0.18
II		0.34 ± 0.33	0.88 ± 0.09	0.27 ± 0.28	0.84 ± 0.16	0.27 ± 0.30	0.39 ± 0.30	0.49 ± 0.28	0.52 ± 0.27	0.55 ± 0.26	0.54 ± 0.26
III			0.27 ± 0.30	0.16 ± 0.43	0.47 ± 0.39	0.08 ± 0.33	0.21 ± 0.32	0.26 ± 0.30	0.28 ± 0.30	0.24 ± 0.33	0.217 ± 0.33
aVR				0.44 ± 0.27	0.69 ± 0.21	0.34 ± 0.31	0.47 ± 0.27	0.59 ± 0.21	0.63 ± 0.22	0.66 ± 0.21	0.66 ± 0.21
aVL					0.07 ± 0.31	0.21 ± 0.31	0.34 ± 0.33	0.41 ± 0.28	0.44 ± 0.26	0.46 ± 0.27	0.44 ± 0.29
aVF						0.18 ± 0.31	0.28 ± 0.31	0.34 ± 0.30	0.37 ± 0.31	0.37 ± 0.31	0.36 ± 0.32
V ₁							0.30 ± 0.31	0.41 ± 0.24	0.41 ± 0.27	0.46 ± 0.27	0.47 ± 0.26
V ₂								0.67 ± 0.30	0.60 ± 0.32	0.57 ± 0.32	0.54 ± 0.31
V ₃									0.83 ± 0.12	0.78 ± 0.15	0.73 ± 0.17
V ₄										0.84 ± 0.12	0.79 ± 0.14
V ₅											0.87 ± 0.09

Figure 5. Correlation between QTV and T-wave amplitude of the standard 12-lead ECG of 72 healthy subject before (A) and after log-transformation (B).

range, 4–8]), aVL (32 ms, [interquartile range, 3–7]) and aVF (33 ms, [interquartile range, 2.5–4.5]) compared to the majority of leads, in which QTV were below 11 ms in all subjects (I, II, aVR, V₂–V₆). The QTVI showed a similar pattern, see Figure 2B.

The single measure ICC of beat-to-beat QT intervals in the 12 leads was 0.27 ± 0.18 (see Figure 3), indicating a relatively low level of interlead consistency on beat-to-beat QT interval variability. The means and standard deviations of Pearson's correlation coefficients of QT intervals between the 12 leads are summarized in Table 2.

High correlations (i.e. $r > 0.8$) were observed between leads II and aVR (0.88 ± 0.095), leads V₅ and V₆ (0.87 ± 0.093), leads I and aVR (0.84 ± 0.16), leads V₄ and V₅ (0.84 ± 0.12) and leads II and aVF (0.84 ± 0.17). The lowest correlations were found

Figure 6. Median and interquartile ranges of standard deviations of beat-to-beat QT intervals in the standard 12-lead ECG of 14 males and 14 females.

Figure 7. Median and interquartile ranges of standard deviations of beat-to-beat QT intervals in the standard 12-lead ECG of healthy younger and older males.

in lead III, in particular, with lead V₁ (0.079 ± 0.33) and aVL (0.16 ± 0.43).

Relation Between QTV and T-wave Amplitude

The medians and interquartile ranges of the T-wave amplitude for each lead are shown in Figure 4. One-way ANOVA demonstrated significant T-wave amplitude differences between leads ($F = 105.7$, $P < 0.0001$). The maximum T-wave amplitude was measured in lead V₃ (0.53 ± 0.22 mV) and the minimum was observed in lead III (0.08 ± 0.059 mV).

We observed an inverse relation between QTV and T-wave amplitude (Figure 5A). To obtain normal distributed variables we log-transformed QTV and T-wave amplitude (Figure 5B). Subsequently,

a significant linear negative correlation was found ($r = -0.62$, $P < 0.0001$).

Relation Between QTV and Mean Heart Rate

To investigate the relationship between mean heart rate and QTV in different leads, we calculated Pearson's correlation coefficients. With the exception of lead aVF, which showed a marginal, but significant correlation between heart rate and QTV ($r^2 = 0.06$ and $P < 0.05$), no linear associations were found.

Gender Comparison of QTV

To investigate the role of gender on QTV, we compared 14 age-matched males with the 14 female subjects of our data set. Mean heart rate as well as heart rate variability were comparable between males and females (67 ± 11 bpm vs 65 ± 15 bpm, $P = 0.6$; 51 ± 29 ms vs 47 ± 21 ms, $P = 0.7$). Group medians and interquartile ranges of the standard deviation of beat-to-beat QT intervals for the 12 standard leads (in male and female subjects) are shown in Figure 6. The maximum value of QTV was measured in lead aVL for females (8.56 ± 7.32 ms) and in lead III for males (8.08 ± 6.78 ms). Two-way ANOVA identified lead difference ($F = 10.01$, $P < 0.0001$), but not gender as a significant factor. The single measure ICC for male and female subjects were 0.25 ± 0.17 versus 0.25 ± 0.16 , $P > 0.05$, indicating a similarly low level of interlead consistency of QTV.

Age Effect

To investigate the effect of age on QTV we excluded females and dichotomized the remaining data based on the median age to groups of younger men (17–37 years) and older men (37–69 years). Mean heart rate was not significantly different between groups (68 ± 11 bpm vs 68 ± 6 bpm, $P = 0.8$), but heart rate variability was significantly reduced in older subjects (54 ± 27 ms vs 36 ± 17 ms, $P = 0.008$). Group medians and interquartile ranges of the standard deviation of beat-to-beat QT intervals of young and old men are shown in Figure 7. The maximum values of QTV in younger and older men were both observed in lead III (6.76 ± 5.36 ms and 9.33 ± 9.46 ms). Two-way ANOVA identified lead difference ($F = 17.98$, $P < 0.0001$), but not age as a significant factor contributing to QTV. The single

measure ICC of beat-to-beat QTV for younger and older males were similarly low (0.34 ± 0.19 vs 0.20 ± 0.16 , $P < 0.05$).

DISCUSSION

The main findings of our study are as follows: (i) the magnitude of beat-to-beat QTV varied between the 12 standard leads and (ii) the interlead correlation of QTV was lead dependent; (iii) there was a negative correlation between QTV and T-wave amplitude; and (iv) there was no significant effect of mean heart rate, age and gender on QTV in 12-lead resting ECG of healthy subjects.

The QT interval of body surface ECG varies among leads¹⁶ and it has been previously suggested that QTV may be lead-dependent.¹⁷ However, most previous studies quantified QTV based on a single ECG lead with varying electrode placements.^{18–21} For practical reasons, leads with big T waves have been typically chosen, aiming for a good signal-to-noise ratio.

Our systematic investigation of the 12-lead ECG in healthy subjects confirms that QTV and QTVI, respectively, differ notably between leads and caution should be taken when comparing QTV obtained from different leads across studies. The QTV appears to be significantly pronounced in lead III compared to all other leads, except from lead aVL, which is in the same plane and in close proximity. No significant differences were observed between leads V₅ and V₆, leads V₄ and V₅, and V₃ and V₄, respectively, which might also be due the close proximity of electrodes. The latter finding is in contrast to those of Yeragani et al.,²² who compared QTV in leads V₁, V₃, and V₅ and found significant differences in V₅ and V₁ versus V₃. When taking into account the T-wave amplitudes across leads, our observations suggest that augmented QTV is measured in leads with a small T waves, vice versa. There appear to be exceptions to that rules, however, as observed in leads I and II, which are characterized by relatively low QTV despite small T-waves. The mean heart rate does not seem to affect QTV, despite its well-known effect on the T-wave amplitude. As we investigated ECGs recorded during rest, this association might have been masked by relatively low heart rates.

Considering temporal correlations in beat-to-beat QT variations across leads, rather than magnitudes, we found very high correlations ($r > 0.8$) between several adjacent leads (II and aVR, V₅ and V₆, I

and aVR) and low correlations ($r < 0.2$) between leads III and V₁ and leads III and aVL, respectively. The lack of correlation between lead III and aVL was initially unexpected, given that both leads capture similar projections of the vector angle and had similar magnitudes of QTV. However, the T waves were small in both leads and QTV augmented, which might indicate increased sensitivity to noise.²³ In a previous study, Berger et al. addressed the question of temporal correlations of QTV among a subset of leads (I, aVF, V₂) and reported correlation values between 0.6 and 0.7, which were partly confirmed by our results.¹⁸

In agreement with the finding of other authors,^{3,24–26} our analysis suggests that there is no significant overall gender difference in the QTV of the standard 12-lead ECG of healthy subjects (ANOVA, $P < 0.05$). A closer look at the single leads, however, indicates that QTV was higher in females in most of the leads (I, II, aVR, aVL, aVF, V₂–V₆) compared to males (Figure 5), despite similar mean heart rates and heart rate variability. Given that gender differences in the average rate-corrected QT interval and T-wave morphology are well known²⁷ this difference might possibly affect QTV in certain leads. In line with the overall group analysis, QTV was highest in lead III for males and lead aVL for females.

In this study, we did not find a significant difference in the overall QTV of the 12-lead ECG in older males compared to younger males. This finding is in agreement with two previous studies that did not observe age-dependent QTV differences in adults,^{26,28} and somewhat in contrast with one study, in which QTV differences were observed in children (6–14 years) compared to adults (22–55 years) in lead II.²⁹ Although overall QTV across all leads was not significantly different between younger and older males in our study, QTV appeared to be higher in younger than older men in most of the leads (I, II, aVR, aVF, V₁–V₆). Leads III and aVL did not follow that general pattern. The reason for the discrepancy in these two leads might be the relatively low T-wave amplitudes, which might be prone to noise. The elevation in QTV of young men may be partly explained by higher heart rate variability in young men and the rate-dependence of the QT interval. Although the relationship between RR and QT interval is intricate, spectral analysis of RR and QT time series demonstrated similar oscillatory components in both time series.³⁰

The main limitation of this study lies in its focus on healthy subjects. Although our findings on interlead correlations might not directly translate to cardiac patients that are characterized by altered substrate and repolarization heterogeneity, our data suggest that the choice of lead may influence temporal analyses such as power spectrum or entropy.^{30,31} The correlation between QTV and T-wave amplitude, on the other hand, may be generally valid, as it is presumably driven by technical limitations of the measurement algorithm. In fact, one might speculate whether the utility of QTV for cardiac risk stratification is partly due to flatter T waves that have been observed in high risk patients.³² An important limitation of the gender analysis in this study is the relatively small number of subjects. We cannot exclude the possibility of an overall gender difference in QTV due to the limited statistical power of our sample. Another limitation of our study is the relatively short duration of ECG recordings. Possibly, longer recordings might reduce the interlead difference in QT variability to some degree. Lastly, the information on the subjects included in the PTB database used for this study is limited and, for example, does not contain BMI values.

In conclusion, the magnitude and temporal pattern of beat-to-beat QT interval variability varies between leads. There is an inverse relation between QTV and T-wave amplitude. In general, caution should be paid when comparing QT variability results obtained from different leads across studies.

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