

Variability of the QT Measurement in Healthy Men, with Implications for Selection of an Abnormal QT Value to Predict Drug Toxicity and Proarrhythmia

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Torsades de pointes is the form of polymorphic ventricular tachycardia associated with prolongation of the QT interval that can occur as a proarrhythmic adverse response to a variety of drug treatments.^{1,2} However, the degree of QT prolongation at rest^{3,4} or during exercise⁵ is not necessarily a good predictor of the occurrence of torsades de pointes. Prolongation of the QT interval duration is seen during therapy with many different types of drugs including class IA antiarrhythmic agents as well as ketanserin, amiodarone, bepridil, sotalol, antidepressants, phenothiazines, erythromycin, antihistamines and liquid protein diets. Quinidine is the drug most frequently implicated in this syndrome with a calculated incidence of 1 to 8%.⁴ However, plasma drug level, absolute QT interval prolongation and the absolute QT_c have not been found to be very good predictors of the development of torsades de pointes.^{3,4}

Data on the spontaneous variability of the QT interval over time in normal subjects have not been established. Thus, we determined the magnitude of spontaneous QT interval variability over just 1 day using ambulatory long-term electrocardiographic (Holter) monitoring. Knowledge of normal variability of the QT interval is important in that prolongation of the QT interval during drug therapy is considered to be a risk factor for the development of a potential proarrhythmic effect. However, knowledge of the daily spontaneous variability of the QT interval makes it possible to determine the magnitude of QT interval prolongation, which is clinically important with

respect to its potential as a marker for risk of proarrhythmia.

Twenty healthy men (mean age ± standard deviation 40 ± 8 years [range 25 to 53]) were studied. All subjects had a normal history, physical examination, resting electrocardiogram, normal exercise treadmill test and normal echocardiogram. No subjects were taking drug therapy. We chose this group of volunteers to be more similar in age to patients seen in the usual adult cardiology practice who might be treated with drugs.

Subjects were studied in an inpatient unit to ensure a controlled stable state. The patients underwent 24 hours of Holter monitoring with an Avionics recorder (Delmar Avionics Corp., Irvine, California) with a reel-to-reel recorder that monitored leads V₁ and V₅. The QT interval of lead V₅ was measured 3 times per hour when the heart rate was <100 beats/min by a digitization procedure (Jandel's Sigma Scan software, Sunnyvale, California). This yielded 870 separate QT interval measurements. The QT_c was subsequently computed using Bazett's formula.⁶ Clinical judgment was used to define the junction between the T and U waves.

Statistical analysis was performed using a t test with significance at p < 0.05. All values given in the text are mean ± standard deviation.

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TABLE I QT_c Variability Over 24 Hours of Holter Monitoring

| Time Segment | Range of RR Intervals (ms) | Average QT _c (ms) | SD (ms) | No. of Intervals |
|----------------|----------------------------|------------------------------|---------|------------------|
| 8 a.m.–4 p.m. | 552–1,284 | 401 | 34 | 264 |
| 4 p.m.–12 a.m. | 597–1,328 | 407 | 35 | 324 |
| 12 a.m.–8 a.m. | 670–1,451 | 403 | 11 | 282 |

SD = standard deviation.

In this group of normal men, the QT_c averaged $404 \pm ms$ ($n = 870$; $QT = 368 \pm 41 ms$, $RR = 840 \pm 161$). When the day was divided into three 8-hour segments, the average calculated QT_c varied by 6 ms (Table I). The average pooled QT_c was relatively constant over the day and was not greatly influenced by circadian rhythm.

For individual subjects, the QT_c showed a large degree of daily variability ($p < 0.05$); the QT_c varied over 24 hours of Holter monitoring by an average of $76 \pm ms$ (range 35 to 108 ms, Table II). This large magnitude of QT_c variability was present during each of the three 8-hour segments of the 24-hour Holter monitoring period, indicating that the QT_c varied by a large magnitude not only over the entire day, but also throughout each of the 8-hour segments of the day. In individual subjects, the QT_c changed from normal ($< 440 ms$) to abnormal ($\geq 440 ms$) in 11 of the 20 subjects (55%), and exceeded 500 ms in 1 of the 20 subjects (5%) (Table II).

The subjects were then subdivided into groups. First, subjects with QT_c s that varied by $< 76 ms$ were compared with subjects whose QT_c s varied by $\geq 76 ms$. Five (5%) of the 9 subjects with QT_c variability less than the average (76 ms) had ≥ 1 abnormal QT_c value ($\geq 440 ms$), compared with 6 of the 11 patients (55%) with greater than average QT_c variability (difference not significant). Next, the subjects ($n = 9$) whose QT_c values varied only within the normal range ($< 440 ms$) were compared with those who had ≥ 1 abnormal QT_c value ($n = 11$). The QT_c varied by $73.4 \pm 18.3 ms$ in patients in whom all measured values of the QT_c were normal compared with those with ≥ 1 abnormal QT_c in which the QT_c varied by $77.3 \pm 20.8 ms$ (difference not significant). Thus, prolongation of the QT_c to abnormal values ($\geq 440 ms$) and the absolute magnitude of the variability of the QT_c were independent of one another in these normal men.

This study using ambulatory Holter monitoring as a surrogate of the supine resting electrocardiogram demonstrates that in normal men the QT_c has a high degree of spontaneous variability even over a single day under stationary conditions, and the magnitude of that variability was $\pm 19 ms$. In these normal subjects, 55% had QT_c values $> 440 ms$ and 5% had QT_c values $> 500 ms$ over a 24-hour period.

The normal QT_c is often stated to be $< 440 ms$.^{7,8} However, strong evidence that the upper limit of normal QT_c is 440 ms does not exist. Originally this range was supported by only 3 references, 2 of which were studies in children.⁷ Reviewing a 1,300 electrocardiographic database of healthy subjects, it was found that the normal QT_c ranged from 463 to 506 ms,⁹ which is similar to the range of QT intervals (336 to 487 ms) reported in 50 normal subjects by Mirvis.¹⁰ In agreement with our results, these studies demonstrate that the normal QT_c is highly variable.

Several studies have found that the development of torsades de pointes form of ventricular tachycardia is most frequently seen after a postectopic or post-tachycardia compensatory pause¹ and some investigators⁴ have suggested that a risk of a torsades de pointes increases greatly when the QT interval increases > 500 to 550 ms.

TABLE II QT_c Variability for Individual Subjects

| Subject No. | Age (yr) | QT_c Variability* (ms) | $QT_c > 440 ms$ † (%) |
|-------------|------------|--------------------------|-----------------------|
| 1 | 49 | 91 | 49 |
| 2 | 50 | 93 | 8 |
| 3 | 34 | 86 | 0 |
| 4 | 40 | 66 | 17 |
| 5 | 36 | 61 | 6 |
| 6 | 49 | 76 | 61 |
| 7 | 29 | 56 | 0 |
| 8‡ | 53 | 84 | 74 |
| 9 | 43 | 63 | 16 |
| 10 | 40 | 74 | 3 |
| 11 | 44 | 35 | 24 |
| 12 | 39 | 77 | 0 |
| 13 | 43 | 62 | 0 |
| 14 | 37 | 108 | 3 |
| 15 | 33 | 100 | 2 |
| 16 | 28 | 86 | 0 |
| 17 | 43 | 102 | 0 |
| 18 | 40 | 82 | 0 |
| 19 | 25 | 42 | 0 |
| 20 | 49 | 68 | 0 |
| Mean | 40 ± 8 | 76 ± 19 | 13 ± 22 |

* Defined as longest QT_c - shortest QT_c measured in each subject.
† Defined as the number of abnormal QT_c values/total number of measured QT_c values measured in each subject.
‡ Subject no. 8 had 3 QT_c values $> 500 ms$.

Kay et al¹¹ reported on 32 patients who developed torsades de pointes as a result of antiarrhythmic therapy; before initiating therapy, 88% of these patients had a $QT_c > 440 ms$ and 9% had a $QT_c > 500 ms$ on baseline electrocardiogram. These findings are similar to results from our study of normal persons. We may expect that at baseline, QT_c values would exceed 500 ms in 5% of the patients and the QT_c values would be $\geq 440 ms$ in 55% of patients. Kay et al¹¹ reported that, after quinidine therapy, the QT_c was abnormal ($\geq 440 ms$) in 100% of the patients, the QT_c exceeded 500 ms in 84% of the patients and the average QT_c increased by 131 ms (from 463 ± 59 to $594 \pm 84 ms$). This is in general agreement with the results reported by others^{1,12} and consistent with our recommendations. Namely, we suggest that for a clinically important marker of a proarrhythmic drug effect that could lead to polymorphic ventricular tachycardia, syncope or sudden death rather than just a $QT_c > 440 ms$, a clinically significant change in the QT_c occurs when $> 5%$ of treated subjects have QT_c values $> 500 ms$ or when an individual patient has a change in the QT_c of $> 75 ms$.

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