QT Intervals at Heart Rates From 50 to 120 Beats per Minute During 24-Hour Electrocardiographic Recordings in 100 Healthy Men

Effects of Atenolol

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Background. Conflicting reports about changes in QT intervals suggest that QT values should be compared at similar heart rates.

Methods and Results. Relations between QT and RR intervals were determined after measurement of QT values by Holter recording at heart rates of 50, 60, 70, 80, 90, 100, 110, and 120 beats per minute in 100 healthy young men. Fifteen men underwent a second recording during acute treatment with the \( \beta \)-blocking agent atenolol. At heart rates between 80 and 120 beats per minute, the QT interval was significantly longer (from 9 to 16 msec), and at a heart rate of 50 beats per minute significantly shorter (26 msec), than values calculated from Bazett’s formula. Sleep prolonged QT values by 18 msec at a heart rate of 60 beats per minute and by 21 msec at a heart rate of 50 beats per minute compared with the waking state. Atenolol lengthened QT intervals significantly (by 11–14 msec) at heart rates between 90 and 110 beats per minute and shortened them (by 12 msec) at a heart rate of 60 beats per minute. During sleep, QT intervals were the same before and after atenolol.

Conclusions. The method of plotting QT against RR intervals after measurement of QT values at similar stable spontaneous heart rates before and after intervention allows changes in autonomic state and heart rate to be taken into account. By this method, QT values can be compared without distortion effects caused by correction formulas. (Circulation 1992;86:1439–1442)

KEY WORDS • electrocardiography • receptors, \( \beta \)-adrenergic blockers • electrophysiology

Prolongation of the QT interval has been found to correlate with the development of malignant arrhythmias in patients after acute myocardial infarction,\(^1\) in association with mitral valve prolapse syndrome,\(^2\) and in patients with congenital and acquired long-QT syndrome.\(^3,4\) It is well known that heart rate, autonomic tone, electrolyte levels, and many drugs influence QT intervals. QT values should be compared only after differences in heart rate have been taken into account. Numerous attempts have been made to allow for the effect of heart rate on QT interval.\(^5\) Studies of the effects of drugs on QT intervals have given conflicting results, presumably because the changing autonomic tone affects the relation between the QT and RR intervals.\(^6\)

Previous formulas to correct QT intervals for heart rate have been based on one QT interval value and one RR interval value from each individual.\(^7–10\) Recently, data from continuous ECG recordings have been used, but the data were obtained over set intervals of time, not at particular heart rates.\(^11–13\) The data therefore reflect the predominant heart rates in the groups studied.\(^11\) One way to overcome these effects would be to use atrial pacing in intervention studies. There would still be major problems, however: paced cycle lengths would be shorter than most spontaneous sinus cycle lengths, and thus, important information would be missed. Pacing would not control the autonomic state. Pacing is an invasive procedure and unsuitable for use in population studies.

The purpose of this study was to determine relations between QT intervals and heart rates at spontaneous stable sinus rates of 50, 60, 70, 80, 90, 100, 110, and 120 beats per minute and to determine the effects of the \( \beta \)-selective \( \beta \)-blocking agent atenolol on QT intervals at similar heart rates in healthy men. The reliability of Bazett’s equation to predict QT values at different heart rates was evaluated.

Methods

Characteristics of Subjects

The subjects were 100 healthy men 18–30 years old (mean±SD, 21.5±3.8 years). No subject exhibited any evidence of heart disease on the basis of history, physical examination, chest x-ray findings, or resting ECG. ECGs had to meet the following criteria: PR interval during normal sinus rhythm no more than 200 msec and no delta
TABLE 1. QT Intervals and 99% Confidence Limits for Measured QT Values* and Corresponding QT Values Calculated From Bazett’s Equation

<table>
<thead>
<tr>
<th>Heart rate (bpm)</th>
<th>No. of subjects</th>
<th>Measured QT (msec) (mean±SD)</th>
<th>99% Confidence interval</th>
<th>Calculated QT (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>29</td>
<td>406±23</td>
<td>394–417</td>
<td>431</td>
</tr>
<tr>
<td>60</td>
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<td>82</td>
<td>368±16</td>
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<td>100</td>
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<td>88</td>
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<td>290</td>
</tr>
<tr>
<td>120</td>
<td>89</td>
<td>289±15</td>
<td>285–293</td>
<td>278</td>
</tr>
</tbody>
</table>

*At stable heart rates of 50, 60, 70, 80, 90, 100, 110, and 120 beats per minute in 100 individuals.

wave, QRS duration <100 msec, corrected QT interval (Bazett’s equation) <440 msec, no U wave interfering with the definition of the T wave (one subject was excluded because of a long QTU complex), and <100 ventricular premature beats per 24 hours. No subject was a trained athlete or was taking any medication.

All subjects gave informed consent. The study protocol was approved by the local ethical committee.

ECG Recording Protocol

All 100 participants were subjected to 24-hour ECG recording (Model 445, Avionics). The next day, 15 of the participants, 19–27 years old (mean, 20.3±2.1 years), were subjected to a second 24-hour recording after treatment with the β₁-selective β-blocking agent atenolol, 100 mg of which was taken by mouth at 8 AM. Recording started at 10 AM. A second dose of 100 mg was taken at 8 PM. The sleeping period was considered to be the period the subjects recorded themselves in their diaries as having slept.

QT Analyzing System

The recordings were analyzed with an Avionics Electrocardioscanner model 660A. The frequency response of the entire recording and playback system is 0.09–27 Hz. Heart rates of 50, 60, 70, 80, 90, 100, 110, and 120 beats per minute were sought by observing a display of RR intervals indicating heart rate. Heart rate had to be stable for at least 60 seconds. A variation of ±5 beats per minute was allowed (e.g., heart rate could have been between 45 and 55 beats per minute to be accepted as a heart rate of 50 beats per minute). The samples were printed on chart paper at a speed of 25 mm/sec, and the final desired heart rates were sought on these strips, taking 10 successive RR intervals. A variation of ±2 beats per minute was allowed (e.g., heart rates between 48 and 52 beats per minute were accepted as rates of 50 beats per minute). The duration of the QT interval was then measured from these samples with a digitizing board (Microgrid MGRX 12, Sphynxographics Corp.) interfaced with a PDP 11/34 DEC computer. Ten complexes were measured from each trace, and arithmetic means were determined. The duration of each QT interval was measured from the beginning of the Q or R wave to the termination of the T wave at the point of its merger with the TP segment. In those few measurements in which a separate U wave interrupted the T wave before return to the TP segment, the QT interval was measured to the nadir of the curve between T and U waves in the lead corresponding to V₅. Measured QT values were compared with values calculated from Bazett’s equation (QT=k×√RR). The constant k is the QT interval at a heart rate of 60 beats per minute. It was 0.393 seconds in this study.

To determine speed errors of the recording and analyzing systems, pulses were fed to the recorder tape from a pulse generator (Interstate P 24), and their frequencies were checked with a Universal Counter Timer (Racal 9903). The tape was analyzed with the Electrocardioscanner, and errors were calculated. The mean speed error in relation to the whole system was 1%. The SD of the speed jitter was 2% of the pulse interval.

Statistical Analysis

To test significances of intraindividual changes caused by β-blockade or sleep, the paired t test was used. To evaluate the reliability of Bazett’s equation in predicting QT values at different heart rates, 99% confidence limits were calculated for measured QT intervals for the whole group.

Results

QT Versus Heart Rate

The measured values of QT intervals at waking heart rates of 50, 60, 70, 80, 90, 100, 110, and 120 beats per minute and corresponding values derived from Bazett’s equation are shown in Table 1. At heart rates of 80, 90, 100, 110, and 120 beats per minute, measured QT intervals were longer than those predicted with Bazett’s equation, and at a heart rate of 50 beats per minute, they were significantly shorter (Figure 1).

Effect of Sleep

In 23 subjects, QT intervals could be measured when subjects were awake and asleep at stable heart rates of 50 and 60 beats per minute. At a heart rate of 50 beats per minute, the QT interval was 405±17 msec (mean±SD) while awake and 426±15 msec while asleep (p<0.01). At a heart rate of 60 beats per minute, the corresponding values were 388±16 and 406±17 msec, respectively (p<0.01) (Figure 1).

Effects of Atenolol

The mean waking heart rate before atenolol administration was 77±6 beats per minute. After atenolol administration, it was 66±4 beats per minute.
(p<0.001). During sleep, the corresponding values of mean heart rates were 56±6 and 51±3 beats per minute, respectively (p<0.001) (Figure 2). Values of QT intervals before and after atenolol treatment are shown in Table 2. After β-blockade, QT intervals were significantly longer at heart rates of 90, 100, and 110 beats per minute and significantly shorter at a heart rate of 60 beats per minute than before β-blockade (Figure 3). At heart rates of 50 and 120 beats per minute, the effects of atenolol on QT intervals were not analyzed because too few observations were available. While the subjects were asleep, at a heart rate of 60 beats per minute, the QT interval was 408±13 msec before β-blockade and 408±18 msec after β-blockade.

Discussion

Measured Versus Calculated QT Interval

The results show the relations between QT and RR intervals during normal daily activities in healthy men when momentary changes are excluded. As Figure 1 shows, the slope of the line relating QT and RR intervals is less than would be expected on the basis of Bazett’s equation. Bazett’s formula seems to work best at sinus cycle lengths from 1,000 to 860 msec (from 60 to 70 beats per minute). At a sinus cycle length of 1,200 msec as well as at sinus cycle lengths from 750 to 500 msec, skewing is significant.

Sleep and QT Interval

Sleep prolongs the QT interval, as Browne et al., using a complex calculation method, and Bexton et al., after studies in pacemaker patients, have noted. Our data confirmed this. The magnitudes of the prolongation were almost identical: the difference in QT interval between the waking and sleeping states at a heart rate of 60 beats per minute was 19 msec in the study of Browne et al. and 18 msec in the study reported here. At a heart rate of 50 beats per minute, the prolongation was 21 msec in the present study. With a ventricular pacing rate of 70 beats per minute, the difference was 23 msec. Allowing the heart rate to vary by no more than ±5 beats per minute during sampling seems to exclude errors caused by short-term reflex changes in QT intervals, and thus, the present method gives reliable results. It has been suggested that prolongation of the QT interval during sleep may be a result of heightened parasympathetic tone and decrease in levels of circulating catecholamines.

Effects of β-Blockade

Increases in steady-state pacing frequencies cause QT intervals to decrease. On the other hand, autonomic tone has direct effects on QT intervals, independent of

<table>
<thead>
<tr>
<th>Heart rate (bpm)</th>
<th>No. of subjects</th>
<th>Baseline (mean±SD)</th>
<th>After atenolol (mean±SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>13</td>
<td>395±12</td>
<td>383±19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>70</td>
<td>15</td>
<td>367±17</td>
<td>366±15</td>
<td>NS</td>
</tr>
<tr>
<td>80</td>
<td>15</td>
<td>347±15</td>
<td>350±16</td>
<td>NS</td>
</tr>
<tr>
<td>90</td>
<td>15</td>
<td>326±14</td>
<td>339±13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>100</td>
<td>15</td>
<td>311±12</td>
<td>325±13</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>110</td>
<td>12</td>
<td>304±16</td>
<td>315±17</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

bpm, Beats per minute.

*At stable heart rates of 60, 70, 80, 90, 100, and 110 beats per minute.

FIGURE 1. Graph showing relation between QT and RR interval in 100 healthy young men at stable waking heart rates of 50, 60, 70, 80, 90, 100, 110, and 120 beats per minute (△) compared with values derived with Bazett’s equation (●). Asterisks indicate where the values derived with Bazett’s equation remain out of the 99% confidence intervals of the measured values. Dotted line indicates QT values during sleep in 23 men.

FIGURE 2. Graph showing mean hourly heart rates in 15 men before (▲) and after (●) atenolol administration.

FIGURE 3. Graph showing relation between QT and RR intervals in 15 men before (▲) and after (●) atenolol administration at stable waking heart rates of 60, 70, 80, 90, 100, and 110 beats per minute (*p<0.05).
heart rates. Accordingly, in the natural state, the QT interval is modified by heart rate per se and by autonomic tone. It has been shown that β-blockade with propranolol causes no significant changes in QT intervals when heart rate is held constant by pacing.\(^{18}\) If β-blockade changes the normal relation between QT and RR intervals, this could be mediated by changes in effects of autonomic tone on QT intervals. In the study reported here, acute treatment with the β-selective β-blocking agent atenolol changed the dependence of the QT on the RR interval (Figure 3). The slope of the curve relating QT to RR intervals was less after β-blockade than before such blockade. The difference was greatest at heart rates between 90 and 110 beats per minute, when atenolol lengthened the QT interval. This may reflect blockade of the sympathetically shortening effect on QT intervals as heart rate increases, because it has been shown that prolonged sympathetic stimulation shortens QT intervals.\(^{19}\) At a waking heart rate of 60 beats per minute, the QT interval was shorter after atenolol treatment than before such treatment. During β-blockade, the heart rate slowed to 60 beats per minute, with a relatively smaller parasympathetic influence than before atenolol; i.e., the effect of parasympathetic tone on the QT interval became weaker, and the QT interval at a heart rate of 60 beats per minute declined. During sleep, the QT interval was the same before and after atenolol administration at the same heart rates, as would be expected, because sympathetic activity is less and secretion of circulating catecholamines decreases during sleep, and thus, the sympathetically shortening effect on QT intervals remains weak.

In this study, a high dose of atenolol was used to produce nearly complete β-blockade. As a result, the induced bradycardia was marked at 2 hours after the first dose of atenolol and did not increase during the monitoring period (Figure 2). It is therefore unlikely that theoretically more complete β-blockade during the latter portion of the 24-hour recording could have significantly different effects on the QT interval compared with the initial portion of the monitoring period.

The results of the study reported here show that the slope of the normal line relating QT and RR intervals is less than would be expected on the basis of Bazett’s equation and even less after β-blockade with atenolol. Thus, use of Bazett’s equation in studies with β-blocking agents gives incorrect results.

### Limitations of the Study

The relation between QT and RR intervals has been shown to depend on sex and age. In the study reported here, all of the subjects were young men. Therefore, the QT values in this study cannot be used as reference values for women or older men. In addition, measurement of the QT intervals was possible with only one ECG lead. In normal 12-lead ECGs, values should be somewhat longer. The method presented in this study is applicable to determine the effect of a particular intervention to the QT interval, whereas evaluating the QT interval in a particular ECG still needs the use of reference values.

### Implications

In studies in ambulant subjects, use of coefficients reflecting for changes in heart rates may result in misleading QT values, because any intervention may change the coefficients, and the effects of possible autonomic changes may be excluded. When QT values are compared, the curves relating QT to RR intervals give more information than single values. The method described in this article of plotting QT against RR intervals after measurement of QT values at similar stable spontaneous heart rates before and after intervention allows changes in autonomic state and heart rate to be taken into account. For patient care, this method can be used in observing the possible effects of disease processes or medications on the QT interval. For research purposes, the method is applicable to evaluating the QT interval during interventions. Previously reported changes in QT intervals in ambulatory patients based on heart rate correcting coefficients should be reevaluated by use of the principle of the present method.

### References

QT intervals at heart rates from 50 to 120 beats per minute during 24-hour electrocardiographic recordings in 100 healthy men. Effects of atenolol.
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