Influence of Heart Rate and Inhibition of Autonomic Tone on the QT Interval

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SUMMARY To evaluate whether heart-rate-induced changes of the QT interval are dependent on autonomic tone, we studied 13 healthy subjects, mean age 67.5 years. The maximal uncorrected QT from leads I, II, V1, and V6 was determined during atrial pacing at 90 beats/min and 130 beats/min and after i.v. administration of propranolol, 0.1 mg/kg, and atropine, 0.02 mg/kg.

Significant reductions ($p < 0.01$) of QT were induced by the paced increases in heart rate before drugs (10%), after propranolol (10%) and after the combination of atropine and propranolol (9%). Propranolol caused no significant change in the QT interval when heart rate was held constant by pacing. In contrast, atropine produced rate-independent reductions of QT interval (5%) in subjects with β-adrenergic blockade ($p < 0.05$). Bazett's formula for heart-rate correction of the QT interval ($QT_C$) was not applicable for atrial overdrive pacing, as it gave proportionately longer $QT_C$ values at higher heart rates.

These results show that heart rate is a major determinant of the duration of the QT interval and that paced changes in heart rate induce QT-interval responses that are essentially uninfluenced by autonomic tone. The rate-independent effect of the QT interval produced by elimination of cholinergic tone suggests a direct influence of cholinergic activity on the repolarization of ventricular myocardium.

INTEREST in obtaining clinical information from the QT interval of the ECG has recently increased. One reason for this is the reported association between prolonged QT intervals and serious ventricular arrhythmias and the identification of QT prolongation as a prognostic factor for sudden death. Several factors influence the QT interval, including electrolyte disturbances and drugs. The effect of sympathetic nervous activity on the QT interval is well established. In addition, the autonomic nervous system affects the ventricular fibrillation threshold. Although cholinergic activity has been found to enhance ventricular electrical stability in dog experiments and the presence of cholinergic nerve fiber supplying the ventricular conducting system has been demonstrated in man, an effect of cholinergic activity on the QT interval has not been reported before.

Heart rate is a major determinant of the duration of the QT interval and this relation has been studied by many workers. In those studies, data were collected and the QT interval was measured at the spontaneous heart rate of each subject. Consequently, the data probably include individual differences both in intrinsic properties of the ventricular myocardium and in the autonomic balance at the time of measurement and thus do not clarify whether QT is strictly rate-dependent or whether it is also directly influenced by autonomic tone.

We undertook the present study to determine the variation of the QT interval in the same subjects (1) at spontaneous and atrially paced heart rates; (2) before and after inhibition of autonomic activity by propranolol and atropine; (3) to evaluate to what extent rate-related QT changes are dependent on autonomic neural tone; and (4) to determine whether Bazett's formula is applicable to changes in heart rate produced by atrial pacing.

Material and Methods

Thirteen healthy volunteers, mean age 67.5 years (range 54–76 years), were included in the study, which was part of an electrophysiologic investigation to define reference values for sinus node and atrioventricular (AV) node function. Requirements for participation were absence of a history of heart disease and absence of previous or present therapy with cardioactive drugs. Other exclusion criteria were signs of functionally relevant cardiac disease, ECG findings suggesting cardiac conduction disturbances and cardiac enlargement by chest x-ray. Five patients in the original group were excluded from the present study because clearly defined T waves were not present in all parts of the investigation protocol or 1:1 AV conduction or 2:1 AV block occurred after propranolol during pacing at 130 beats/min. Patients gave informed consent after the study was approved by the local ethics committee.

The electrophysiologic investigation was performed with patients in a nonedated, postabsorptive state. For atrial pacing, an electrode catheter was introduced through a femoral vein and advanced to the superior lateral part of the right atrium. ECG leads I, II, V1, and V6 were recorded on an ink-jet recorder (Siemens-Elema) at a paper speed of 100 mm/sec during spontaneous heart rate and at the end of 30 seconds of atrial pacing at 90 and 130 beats/min. This protocol was repeated 4 minutes after the administration of i.v. propranolol, 0.1 mg/kg, over 30 seconds and again 5 minutes after i.v. atropine, 0.02 mg/kg, over 30 seconds. Each repetition of the protocol was completed within 15 minutes. Thus, during the last
part of the study both propranolol and atropine were active and dual autonomic inhibition was achieved.

QT and RR intervals were measured from five consecutive beats when possible. However, during atrial pacing at 130 beats/min, the pacing stimulus sometimes fell at the end of the preceding T wave and a QT interval could be determined only in the last paced beat. The corrected QT interval (QTc) was calculated according to Bazett's formula. Measurements were made in the four recorded leads and the longest QT interval was chosen. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. No U waves were present in these subjects. The QT-interval measurements were made without knowledge of whether drugs had been given.

Statistical Methods
Conventional statistical methods were applied. The t test for paired data was used to compare QT values at different heart rates during the same treatment, and vice versa. Rate-induced QT differences between the various treatments were compared by applying Scheffé's procedure for linear contrast, which takes individual covariation into account when defining confidence intervals. The 5% confidence level was chosen to indicate a statistically significant difference.

Results
Uncorrected QT Interval in Relation to Heart Rate
The QT interval was significantly shorter during atrial pacing at 90 beats/min than at spontaneous heart rate (p < 0.01). A significant additional reduction in QT resulted when heart rate was further increased by pacing at 130 beats/min (p < 0.01). Significant decreases of the QT interval were also seen after administration of propranolol and again after the combination of atropine and propranolol (fig. 1, table 1).

Drug Effect on QT Interval
No significant change in the QT interval was recorded after propranolol when heart rate was kept constant at 90 and 130 beats/min by atrial pacing. In contrast, when atropine was added, the QT interval shortened significantly at both paced heart rates. It was also shorter than the value before both drugs at 90 beats/min, while a lesser, nonsignificant difference was present at a paced heart rate of 130 beats/min (fig. 1, table 1).

Influence of Autonomic Tone on Rate-related QT Changes
The difference between the QT interval at the two paced rates was 10% before drugs, 10% after propranolol and 9% after both propranolol and atropine administration. Thus, the magnitude of the changes was uninfluenced by autonomic tone (fig. 1, table 1).

Changes in Heart Rate and QTc Interval in Relation to Heart Rate and Drugs
Propranolol caused no significant change in heart rate, in contrast to the effect of atropine (p < 0.01). During pacing, heart rate correction of QT (QTc) ac-

Discussion
The relation between heart rate and the duration of the QT interval is well recognized. Higher heart rates are associated with shorter QT intervals. The mathematical definition of this relationship has been derived from population studies with each individual contributing one pair of values (i.e., the QT interval recorded at the spontaneous heart rate). However, this relationship is not necessarily the same under different physiologic conditions and at different heart rates in the same subject. Studies of exercise-induced changes in the QT interval indicated that the work-induced increase in heart rate was generally paralleled by a shortening of the QT interval. The purpose of these studies was to assess whether QT intervals are useful in predicting the presence of coronary artery disease. Some authors found that QT interval measurement may be useful in this respect, while others reported a lack of specificity. Further, in patients with long-QT syndromes, exercise may produce prolongation of the QT interval and alterations of the T wave, which may trigger syncopal attacks. Corresponding changes can also be produced by
asymmetric alterations of sympathetic nervous tone. Yanowitz et al.28 lengthened the QT interval in dogs either by stimulating the left stellate ganglion or by ablating the right stellate ganglion. Both prolongation and shortening of the QT interval can be produced by catecholamine administration. Abildskov18 found that brief nerve stimulation or rapid catecholamine injection in dogs was followed by transient prolongation of the QT interval, whereas slow catecholamine infusion or prolonged sympathetic nerve stimulation resulted in no alterations or a reduction of the QT interval. Sympathomimetic drugs have also been used therapeutically to decrease liability for ventricular arrhythmias and to shorten a prolonged QT interval produced by toxic quinidine treatment.4 Whether this beneficial effect is mainly a result of the acceleration of heart rate or a direct action on the repolarization of ventricular myocardium is not known.

Thus, both heart rate and adrenergic activity affect the duration of the QT interval, but it is not clear to what extent these effects are interrelated or whether the heart rate effects are independent of autonomic tone. Nor, to our knowledge, has the importance of a direct effect of cholinergic activity been demonstrated.

Rate-related Changes in QT

We used atrial pacing to achieve changes in heart rate independent of autonomic tone. The heart rate was increased in two steps, first to 90 and then to 130 beats/min, each associated with significant shortening of the QT interval. These reductions in QT were mainly rate-dependent and not significantly influenced by possible secondary reflex changes in autonomic tone, because the magnitudes were of the same after β-adrenergic blockade with propranolol and after combined autonomic inhibition by propranolol and atropine. Thus, the dependence of the QT interval on heart rate appears to be an intrinsic electrophysiologic property of the ventricular myocardium; the shortening is directly related to the reduction in ventricular cycle length.

A covariation between the duration of the QT interval and the refractoriness of ventricular myocardium is well established. The present findings agree with a shortening of the action potential at higher driving rates.6 In addition, a reduction of the effective refractory period of the human ventricular myocardium at higher heart rates has been shown.60, 81 In the study of Guss et al.,80 who also determined QT intervals, higher pacing rates gave a shortening of the same magnitude as in the present investigation.

Our data allow us to evaluate whether the relation between spontaneous heart rate and QT is also valid for artificially increased heart rates produced by atrial pacing. A lack of agreement is evident from our finding that calculating QTc values did not abolish heart-rate-dependent differences in QT during atrial pacing (table 2). Instead, correction produced an overadjustment and in fact reversed the differences between the uncorrected values. Thus, Bazett’s formula cannot be applied when heart rate is increased by short-term pacing. Corresponding results were obtained in a recent study by Milne et al.82 One reason for the overcorrection may lie in the short-term nature of the

TABLE 1. Mean Uncorrected QT in Relation to Heart Rate and Drugs Administered

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean heart rate (beats/min)</th>
<th>Mean QT (sec)</th>
<th>Rate-induced difference (p)</th>
<th>Drug-induced difference (p)</th>
<th>Drug influence on rate-dependent difference (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No drug</td>
<td>65 ± 5*</td>
<td>0.386 ± 0.023*</td>
<td>0.01</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Pacing</td>
<td>90</td>
<td>0.356 ± 0.019</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacing (Diff 90-130)</td>
<td>130</td>
<td>0.322 ± 0.024</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propr</td>
<td>62 ± 7*</td>
<td>0.392 ± 0.021</td>
<td>0.01</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Propr/pacing</td>
<td>90</td>
<td>0.365 ± 0.021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propr/pacing (Diff 90-130)</td>
<td>130</td>
<td>0.328 ± 0.010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propr + Atrop</td>
<td>77 ± 5*</td>
<td>0.368 ± 0.020</td>
<td>0.01</td>
<td>0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Propr + Atrop/pacing</td>
<td>90</td>
<td>0.343 ± 0.019</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propr + Atrop/pacing (Diff 90-130)</td>
<td>130</td>
<td>0.312 ± 0.020</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean ± SD.
Abbreviations: Propr = propranolol; Atrop = atropine.
Table 2. Mean Corrected QT (QTc) in Relation to Heart Rate and Drugs Administered

<table>
<thead>
<tr>
<th>Drug Treatment</th>
<th>Mean heart rate (beats/min)</th>
<th>Mean QTc (sec)</th>
<th>Rate-induced difference</th>
<th>Drug-induced difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous rhythm</td>
<td>65 ± 5*</td>
<td>0.402 ± 0.022*</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Pacing</td>
<td>90</td>
<td>0.439 ± 0.023</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Pacing</td>
<td>130</td>
<td>0.476 ± 0.034</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>(Diff 90–130)</td>
<td></td>
<td>0.037 ± 0.036</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propr</td>
<td>62 ± 7*</td>
<td>0.399 ± 0.026</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Propr/pacing</td>
<td>90</td>
<td>0.450 ± 0.028</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Propr/pacing</td>
<td>130</td>
<td>0.486 ± 0.016</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>(Diff 90–130)</td>
<td></td>
<td>0.035 ± 0.031</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propr + Atrop</td>
<td>77 ± 5*</td>
<td>0.415 ± 0.021</td>
<td>0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Propr + Atrop/pacing</td>
<td>90</td>
<td>0.423 ± 0.022</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Propr + Atrop/pacing</td>
<td>130</td>
<td>0.462 ± 0.032</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>(Diff 90–130)</td>
<td></td>
<td>0.039 ± 0.026</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean ± SD.
Abbreviations: See Table 1.

Effects, as pacing was applied for only 30 seconds. It is possible that long- and short-term effects do differ, in keeping with the influence of catecholamine infusion on the QT interval reported by Abildskov,16 but an alternative explanation seems more likely. The normal relation between the RR and QT intervals is dependent on the parallel influence of autonomic tone on heart rate and ventricular repolarization. An artificial increase in heart rate by atrial pacing abolishes this natural relationship.

Effect of β-adrenergic Blockage

In the present study, no significant change in either QT or QTc occurred after propranolol when heart rate was held constant at 90 or 130 beats/min. This absence of a significant change in QT is in agreement with other studies using acute administration of β-adrenergic blockade66, 67 as well as long-term therapy.68 Milne et al.32 investigated the effect of propranolol at various constant heart rates (atrial pacing). QT was increased in 10 of 15 subjects. In the present investigation, QT interval tended to be prolonged, but not significantly. This alteration of the QT interval by propranolol administration is probably explained by low initial sympathetic tone. In a study on the effect of long-term β-blockade therapy (metoprolol) in myocardial infarct patients,69 heart rate showed a significant change and the QTc interval was significantly shortened.

Effect of Cholinergic Drug Inhibition

With the heart rate held constant at 90 or 130 beats/min, atropine caused a significant shortening of the QT interval. This effect was seen when β-adrenergic blockade had already been instituted. At the lower paced heart rate, the autonomic inhibition of QT also differed significantly from that before drugs. At the higher paced heart rate there was a lesser, nonsignificant change in the same direction. Thus, cholinergic inhibition produced a rate-independent effect on the QT interval, suggesting a direct influence on the duration of the combined depolarization and repolarization of the ventricular myocardium. These findings support reports that cholinergic receptors are not limited to the sinus node, AV node and atrial myocardium, but may also be found in the human ventricular myocardium.18, 57 The former report also included a demonstration of enhanced ventricular electrical stability, an increase in the fibrillation threshold, mediated by cholinergic fibers in dogs. The reason why a rate-independent effect on QT was produced by atropine but not by propranolol in the present study probably mainly reflects the autonomic balance at rest, with cholinergic activity dominating over sympathetic tone.56, 57

We conclude that in healthy subjects, the relation between the RR interval and the QT interval is dependent on the integrated action of several factors. Alterations in heart rate and inhibition of cholinergic tone independently affected the duration of the QT interval, but no rate-independent effect of β-adrenergic blockade could be demonstrated. Atrial pacing at constant driving rates provides a sensitive method for demonstrating direct drug effects on the combined ventricular depolarization and repolarization time. The results also confirm that atrial overdrive pacing is
an efficient way to shorten the QT interval, which agrees well with the positive experience of therapeutic overdrive pacing to suppress ventricular tachyarhythmias that accompany a prolonged QT<sub>e</sub> interval, as seen in quinidine intoxication. Whether atropine offers an additional therapeutic effect in these conditions must be investigated.

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