PATHOPHYSIOLOGY AND NATURAL HISTORY
ELECTROPHYSIOLOGY

The QT interval during reflex cardiovascular adaptation

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ABSTRACT We examined the relationship between changes in heart rate and the measured QT interval of the electrocardiogram in healthy subjects after exercise and during breath holding, hyperventilation, the dive reflex, the Valsalva maneuver, and the cold-pressor test. The tachycardia of exercise was accompanied by the familiar shortening of the QT interval, but substantial heart rate changes encountered in other more "sedentary" maneuvers were accompanied by very small changes in QT. Calculating the corrected QT in the latter instances, therefore, yielded spurious results. The data suggest very little, if any, direct effect of heart rate on the QT interval. The length of the interval in healthy subjects appears to be determined largely by reflexly elicited discrete autonomic influences. Those associated with exercise result in QT shortening but, during neurally mediated cardiovascular adjustments that do not involve exercise, QT is maintained within narrow limits.


PROLONGATION of the QT interval of the electrocardiogram has been correlated with susceptibility to sudden death in patients who have recovered from myocardial infarction,1 in those who have a QT interval prolonged by drugs,2,3 in liquid-protein-modified diet users,4 in association with idiopathic mitral valve prolapse,5 in drug-free depressed patients,6 and among patients afflicted with the congenital long-QT syndrome.7

An inverse relationship between the length of the QT interval and heart rate ascertained from single resting and postexercise heart rate recordings among large groups of healthy subjects led to the development of formulas for the determination of QTc, the QT interval corrected for heart rate. The formula for correction most often applied, that of Bazett,8 uses an exponential factor, although Akhras and Rickards9 found a consistent linear relationship between the uncorrected QT interval and heart rate during exercise and recovery. Changes in the heart rate during artificial cardiac pacing in human subjects10–12 are accompanied by only small changes in QT interval. Thus, calculating the QTc by the most widely used modification of Bazett's formula was shown in all three studies to overcorrect, actually yielding lengthened QT values. These and other studies have led to the suggestion that whatever direct effect heart rate may have on the QT interval must be relatively small. On the other hand there is ample evidence of autonomic nervous system influence on the QT interval, chiefly from the sympathetic innervation of the heart and from circulating catecholamines, but also to some extent from vagal activity.12–15

Whether or not the familiar shortening of the QT interval that accompanies acceleration of heart rate during exercise is attributable to associated increases in circulating catecholamines or to the local effects of the release of adrenergic neurotransmitters from activation of specific stellate ganglion neurons has not been determined. It would be anticipated, however, that the generalized influence of circulating catecholamines would differ from the effects of discrete localized activation of cardiac nerves.

The present study was designed to explore the relationship of QT and QTc to changes in heart rate during various autonomic nervous system–mediated cardiovascular reflexes unassociated with vigorous exercise. The aim was to test a widely held supposition that there is a uniform reciprocal relationship between heart rate and QT interval and thereby to determine the applicability of QTc.

Methods

The subjects were 20 healthy individuals (15 men and five women) ranging in age from 21 to 74 years. During a 60 sec control period heart rate, an electrocardiogram (lead V2), respiration (Thermistor mask), and arterial pressure at 15 sec intervals through a Korotkov sound detector (Narco electroesphygmomanometer) were recorded in resting subjects on an Ampex tape recorder and Beckman direct-writing oscillograph. Ten of
the subjects performed, while seated, the following maneuvers: breath holding for 30 sec, Valsalva maneuver for 30 sec, hyperventilation for 60 sec, cold-pressor test with water at 5°C for 60 sec, and vigorous exercise (up to 100 jumps on each foot), after which subjects were seated. Recordings were continued through the recovery period from each test. The other 10 subjects immersed their faces in water at 30°, 20°, and 10° C (for 30 sec each) during the recording of lead II of the electrocardiogram. Subjects were instructed to avoid Valsalva during breath holding in both air and water. All measurements of QT were made by a single observer from electrocardiograms recorded at a paper speed of 25 mm/sec; QT was considered to extend from the point of initial QRS complex deflection to the point of T wave termination. QT and RR measurements were made on each clearly recorded cycle present on the tracing. Each measurement was rechecked blindly and spot checking was also done by another observer and resulted in better than 90% agreement. The QTc was calculated from the formula:

\[
\text{QTc} = \frac{\text{QT (in sec)}}{\sqrt{\text{RR (in sec)}}}
\]

Results

Tachycardia after exercise was accompanied by the expected shortening of the uncorrected QT interval while QTc was maintained within fairly narrow limits. The converse was true, however, during the maneuvers unassociated with exercise. Despite a range of change in heart rate nearly as great as that observed during recovery from exercise, the uncorrected QT changed very little. Therefore, the calculation for QTc resulted in overcorrection and hence misleading values. RR, measured QT, and calculated QTc intervals for the period of most rapid heart rate (5 successive beats) were compared with those of the period of the slowest 5 beats. Figure 1 and table 1 illustrate the changes in heart rate, QT, and QTc observed during recovery from vigorous exercise and accompanying all five of the reflex maneuvers. A substantial shortening of the QT associated with accelerated heart rate was observed only after vigorous exercise. There was little change in the measured QT associated with accelerated heart rate during the “sedentary” maneuvers, so that a paradoxical result was obtained when the measured QT was corrected for heart rate. Figure 2 shows the plot of QT and QTc intervals from one of the subjects during the cold-pressor test. It also shows the relative uniformity of QT over a wide range of heart rates and how the overcorrection of QTc becomes progressively greater at high rates. With the exception of exercise, the pattern is typical of that encountered during all of the maneuvers performed by these subjects.

For each subject in each of the six maneuvers, 16 clearly recorded electrocardiographic complexes covering the full range of heart rate change were measured and analyzed statistically according to Pearson’s prod-

\[
\text{FIGURE 1. Changes in heart rate averaged for all subjects during each maneuver and associated changes in the measured QT, and calculated QTc.}
\]
TABLE 1
Mean change in heart rate QT and QTc with SD for the subjects performing each maneuver shown graphically in figure 1

<table>
<thead>
<tr>
<th>Procedure</th>
<th>ΔHeart rate SD</th>
<th>ΔQT in sec SD</th>
<th>ΔQTc in sec SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>+ 58.9 ± 19.4</td>
<td>−0.079 ± 0.034</td>
<td>−0.022 ± 0.065</td>
</tr>
<tr>
<td>Valsalva</td>
<td>+ 43.0 ± 11.2</td>
<td>−0.010 ± 0.020</td>
<td>+0.087 ± 0.021</td>
</tr>
<tr>
<td>Dive</td>
<td>−35.9 ± 17.6</td>
<td>+0.013 ± 0.017</td>
<td>−0.085 ± 0.052</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>+ 34.2 ± 9.40</td>
<td>−0.010 ± 0.014</td>
<td>+0.055 ± 0.030</td>
</tr>
<tr>
<td>Cold-pressor</td>
<td>+ 32.1 ± 17.3</td>
<td>−0.018 ± 0.006</td>
<td>+0.047 ± 0.038</td>
</tr>
<tr>
<td>Breath hold</td>
<td>+ 24.0 ± 9.50</td>
<td>−0.014 ± 0.025</td>
<td>+0.038 ± 0.023</td>
</tr>
</tbody>
</table>

sured heart rate and QT interval in a group of adults at rest, each on several occasions. In some individuals they found marked differences in QT at nearly the same heart rate, and in others they found an invariant QT despite marked differences in heart rate. These studies show that in healthy children and adults there is no fixed relationship between heart rate and QT and suggest further that they may be independently regulated. Data from artificial pacing studies are less conclusive on this point because of presumed stimulation of myocardial afferents by the pacing electrode that could in turn affect central processing and hence efferent impulses even in the presence of partial pharmacologic blockade. Mitsutaki et al.20 noted prolongation of QTc during the Valsalva maneuver in patients with the long-QT syndrome, but no significant change in healthy controls. The prolongation of QTc that resulted from the Valsalva maneuver was greatly reduced among the patients with the long-QT syndrome by premedication with 6 to 8 mg iv propranolol, suggesting that the QT prolongation among the patients was due to excessive or unrestrained activity in certain neurons in the sympathetic supply to the heart. Since the degree of heart rate acceleration in both their patients and control subjects was similar, there is further evidence that the sympathetic regulation of heart rate may activate fibers separate from those that govern the duration of QT. Sympathetic control of heart rate has been shown to be exerted mainly through the right stellate ganglion.20, 21 On the other hand, QT lengthening was found to be attributable to a predominance of impulses from the left stellate ganglion. In the healthy subjects reported here, studied during autonomically mediated reflex cardiovascular adaptations, the measured QT interval varied little despite great differences in heart rate, thereby providing further evidence of separate, discrete, and patterned discharges among sympathetic neurons. Other observed changes in autonomic effector functions included elevation of arterial pressure in the cold-pressor test, the presumed adjustments to hypocapnia during hyperventilation, and the arteriolar constriction and altered conduction that have been shown to accompany the bradycardia of the dive reflex.22

The relative stability of QT despite changes in heart rate during cardiovascular responses to stresses that, unlike exercise, do not significantly increase oxygen

TABLE 2
R values for the group of subjects correlating heart rate with measured QT during each of the six maneuvers (Pearson's product-moment correlation coefficient)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Simple R</th>
<th>R-square change</th>
<th>R square</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>−.86430</td>
<td>.19726</td>
<td>.63938</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>−.43678</td>
<td>.05806</td>
<td>.40941</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Valsalva</td>
<td>−.51137</td>
<td>.01984</td>
<td>.62524</td>
<td>.008</td>
</tr>
<tr>
<td>Cold-pressor</td>
<td>−.68371</td>
<td>.00945</td>
<td>.74030</td>
<td>.029</td>
</tr>
<tr>
<td>Breath hold</td>
<td>−.70450</td>
<td>.01244</td>
<td>.77851</td>
<td>.006</td>
</tr>
<tr>
<td>Dive reflex</td>
<td>−.28481</td>
<td>.02802</td>
<td>.38361</td>
<td>.014</td>
</tr>
</tbody>
</table>

Multiple Rs were obtained by controlling for individual differences and then examining the relationship between heart rate and measured QT. All p values were obtained with Fisher’s test. The R-square change column shows a close quantitative relationship between heart rate and QT only in the case of exercise.
consumption does not substantiate the widely held assumption of a direct effect of heart rate on the duration of the QT interval. Rather it suggests that heart rate and QT duration are subject to separate and distinct sympathetic neuronal pathways the activation of which is determined by the immediate adaptive requirements.

Abildskov has pointed out that because of "cancellation of electrocardiographic effects by opposing directions of activation or recovery boundaries" the QT interval measurement cannot provide precise information on the action potential duration of cardiac muscle cells. Nevertheless, as he points out, the measurement has been found to be a convenient and reliable clinical tool. As already noted, considerable evidence has accumulated to indicate that the duration of the QT is chiefly determined by an interplay of autonomic influences. Selective involvement of discrete portions of autonomic pathways has been demonstrated in patterned reflex responses of various types. Although both adrenergic and cholinergic effects have been implicated in determining the duration of QT, the precise nature of the autonomic regulation has not been ascertained, partly because the actions of circulating hormones have not been clearly distinguished from local effects of neurotransmitters. Concerning selective activation of sympathetic neurons, Pagani et al. have shown that in adaptive cardiac reflexes certain sympathetic fibers to the heart are activated and some remain uninvolved, while others are actually inhibited. For the time being, in view of the potential confusion that can result from overcorrection of the QT interval for heart rate, it may be helpful for the measured QT to be included in reports along with the calculated QTc.

Rather than indicating a consistent direct effect of heart rate on QT, the findings suggest that heart rate and QT interval are governed separately by different sympathetic neurons that, depending on the nature of the adaptation required, may or may not be activated together. Correction of the QT interval for heart rate appears to be applicable under circumstances such as exercise when there is a constant inverse relationship between QT and heart rate. During heart rate changes that accompany certain reflex cardiovascular adaptations but that do not involve vigorous exercise, however, correction of QT may yield misleading and even paradoxical data.

References
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