**Research letters**


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**Longitudinal study of the ageing trends in QT interval and dispersion in healthy elderly subjects**

SIR—A prolongation of the QT interval and an increase of QT dispersion are associated with higher cardiovascular morbidity and mortality. This is related to electrical instability and the risk of ventricular arrhythmogenesis [1, 2]. Arrhythmias increase in frequency with ageing, probably due to age-associated degenerative changes in the conduction system, including loss of pacemaker and conducting cells and myocardial fibrosis [3]. Many previous cross-sectional population studies investigated the impact of age on QT interval and dispersion and presented conflicting results [4–8]. However, no longitudinal study, which may provide more reliable results about the changes of QT interval and dispersion with ageing, addressed this issue. Hence, this study is designed to evaluate the longitudinal changes of the QT interval and dispersion with ageing in a population of healthy elderly subjects.

**Methods**

Study subjects selected from the community were assessed by medical history, physical examination, blood examination, resting electrocardiogram (ECG) and echocardiogram. Exclusion criteria included diabetes mellitus, hypertension or other chronic diseases by history, haemoglobin <11.0 mg/dl or creatinine >1.5 mg/dl at blood examination, left ventricular hypertrophy with strain, high degree atrioventricular block, complete bundle branch block, myocardial ischaemia or rhythm other than sinus on the ECG or significant valvular heart disease, depressed left ventricular systolic function or segmental wall motion abnormality in the echocardiogram. One hundred and fifty-one elderly persons were included in this study at baseline. None of the patients was under anti-hypertensive drugs or drugs affecting ventricular repolarisation [9]. The protocol was approved by our Institutional Review Board, and all enrolled patients gave written, informed consent.

Body weight and height were measured, and body mass index (BMI) was subsequently calculated by using the following formula: BMI = body weight/(body height)^2. Blood pressures were taken after resting comfortably for 5 min. A computerised automatic mercury-sphygmomanometer (CH-5000, Citizen, Tokyo, Japan) was used on the right arm, with participants in a seated position. The reading was repeated. The mean of these two readings was used. Blood was withdrawn for the assessment of serum fasting sugar, cholesterol, blood urea nitrogen and creatinine. Then, a standard 12-lead ECG was recorded at a paper speed of 25 mm/s and a gain of 10 mm/mV. All the above examinations were repeated three times at intervals of 2 years. To avoid possible circadian variation of QT dispersion, we completed all 12-lead ECG examinations in the morning (around 8–10 a.m.). Finally, 115 persons (90 men; age 73 ± 4 years at initial study) completed all the serial examinations and formed our study group. The reason why 36 subjects did not have complete serial examinations was not for a medical problem but due to loss of contact after they moved away from this community.

The QT interval was manually measured from the beginning of the QRS complex to the end of the T wave, which was defined as the return to the TP baseline (the isoelectronic line). The U wave was excluded, and none of the study subjects had a U wave superimposed on the terminal portion of the T wave. The leads where the T wave could not be reliably determined or its amplitude was too low were excluded from analysis. The QT interval and the preceding RR interval were measured in three consecutive cycles. All ECGs, with those at the same observational stage as a pack, were analysed by a single observer blinded to the clinical data. Subjects with less than nine measurable leads in the ECG were excluded. The QT dispersion was defined as the absolute difference between the maximum and the minimum QT intervals in any of the ECG leads. Both the QT interval and the dispersion were rate-corrected with Bazett’s formula as follows: corrected QT (QTc) interval = QT/square root of the RR interval [10].

The Statistical Package for the Social Sciences (SPSS) 11.0 for Windows was used for statistical analysis. Repeated-measures analysis of variance (ANOVA) was used to determine the ageing trends in clinical characteristics and QT intervals and dispersions (uncorrected and corrected). Post hoc analysis was performed using a paired sample t-test to
Table 1. Characteristics of study subjects at baseline and different follow-up stages

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Baseline + 2 years</th>
<th>Baseline + 4 years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73 ± 4</td>
<td>75 ± 4</td>
<td>77 ± 4</td>
<td>–</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.3 ± 6.9</td>
<td>161.8 ± 6.9*</td>
<td>161.8 ± 7.0*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.4 ± 8.6</td>
<td>60.5 ± 8.7*</td>
<td>60.6 ± 9.3*</td>
<td>0.008</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.3 ± 3.0</td>
<td>23.1 ± 3.1</td>
<td>23.2 ± 3.2</td>
<td>0.082</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>125.0 ± 14.2</td>
<td>123.3 ± 14.0</td>
<td>125.7 ± 15.7</td>
<td>0.557</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>72.3 ± 9.0</td>
<td>72.5 ± 10.9</td>
<td>73.0 ± 12.5</td>
<td>0.469</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
<td>101.2 ± 9.5</td>
<td>99.4 ± 10.0*</td>
<td>105.1 ± 13.8**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting blood sugar (mg/dl)</td>
<td>193.6 ± 30.2</td>
<td>191.8 ± 28.3</td>
<td>188.8 ± 30.7*</td>
<td>0.039</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>15.6 ± 3.4</td>
<td>15.4 ± 3.5</td>
<td>15.9 ± 3.9</td>
<td>0.473</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.09 ± 0.18</td>
<td>1.14 ± 0.18*</td>
<td>1.15 ± 0.18*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P<0.05 versus baseline; **P<0.05 versus baseline and baseline + 2 years.

Table 2. QT intervals and QT dispersions (uncorrected and corrected) at baseline and at different follow-up stages

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Baseline + 2 years</th>
<th>Baseline + 4 years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT maximum (ms)</td>
<td>396 ± 25</td>
<td>397 ± 25</td>
<td>399 ± 25</td>
<td>0.071</td>
</tr>
<tr>
<td>QTc maximum (ms)</td>
<td>422 ± 20</td>
<td>425 ± 21</td>
<td>429 ± 27*</td>
<td>0.001</td>
</tr>
<tr>
<td>QT dispersion (ms)</td>
<td>32.9 ± 11.8</td>
<td>37.5 ± 12.6*</td>
<td>44.3 ± 12.5**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc dispersion (ms)</td>
<td>35.1 ± 12.5</td>
<td>40.0 ± 13.4*</td>
<td>47.8 ± 14.0**</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P<0.05 versus baseline; **P<0.05 versus baseline and baseline + 2 years.

determine which follow-up levels were significantly different in these parameters. All tests were two-sided, and the level of significance was established as P<0.05.

Results

The clinical characteristics at baseline and different follow-up stages are summarised in Table 1. During the 4-year follow-up, fasting blood sugar and serum creatinine increased (both P<0.001) and total cholesterol decreased (P = 0.039), whereas BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) kept constant.

The QT intervals and dispersions (uncorrected and corrected) at baseline and different follow-up stages are summarised in Table 2. The maximum QT interval had a trend to increase (P = 0.071), and the maximum QTc interval, QT and QTc dispersions significantly increased during the 4-year follow-up (P = 0.001, P<0.001 and P<0.001, respectively). Post hoc analysis revealed significant differences in the maximum QTc interval between baseline and baseline + 4 years and in the QT and QTc dispersions between all observational stages.

A subgroup analysis showed that the maximum QT interval did not change, and the maximum QTc interval, QT and QTc dispersions significantly increased during 4-year follow-up in both the male and female groups.

Discussion

This longitudinal study shows that the maximum QTc interval and QT and QTc dispersions display a significant ageing trend in a population of healthy elderly subjects during the 4-year follow-up. Few longitudinal studies were available to investigate the effect of ageing on QT interval and dispersion. Our findings provide reliable information about the change of QT interval and dispersion in the normal ageing process.

Previous studies investigating the relationship between age and QT interval showed conflicting results. Reardon et al. [4] and Esen et al. [8] demonstrated that QTc interval prolonged with increasing age. Mangoni et al. [11] studied the simultaneous effects of age and other physiological or lifestyle factors on QT interval in healthy subjects and showed that age independently predicted QTc interval after adjustment for gender, smoking and BP. In contrast, comparing QT interval measured by digitised ECGs in 423 normal subjects, Merri et al. [6] did not find any correlation between age and QT interval. Although the discordance in these results might be due to the different ways used to express and calculate the QT interval and the different study populations, another important reason necessarily considered was that these studies were all cross-section studies, and the individual variations were complex so that such inherent differences could not be completely excluded. In contrast, our longitudinal study can effectively avoid the influence of inter-subject variations and bring the impact of ageing on QT interval into focus.

Many previous studies explored the impact of age on QT dispersion and showed inconsistent and even opposite results. In the study by Savelieva et al. [7], QT dispersion significantly decreased with increasing age in 1,096 healthy subjects. In another large study from Macfarlane et al. [12], they divided their study subjects into four age groups (<30, 30–40, 40–50 and ≥50 years, respectively) and found no significant differences between age and QT dispersion. Mangoni et al. [11] also found that age was not a predictor of QTc dispersion. However, Esen et al. [8] compared QT dispersion between 75 elderly and 36 young subjects and found that QT dispersion increased especially over the age of 75 years. Similarly, although the divergent results in these studies may be due to different study populations and different measurement methods, the lack of longitudinal follow-up may also contribute to these discordant results. Similarly, comparing with these studies, our longitudinal study can effectively avoid the influence of inter-subject variations and bring the effect of ageing on QT dispersion into focus.
The prolongation of QTc interval and increase of QT and QTc dispersions with ageing may be secondary to age-related cardiac hypertrophy, patchy myocardial fibrosis and neurohormonal activation [13]. Elderly hearts reveal relative midmyocardial myocyte hypertrophy and a distinct increase in connective tissue matrix [14]. The myocyte hypertrophy may be associated with a significant prolongation of the transmembrane action potential and provides an explanation for the prolongation of QTc [15] interval with ageing. Increased fibrosis and calcification in the fibrous skeleton of the heart may be one of the mechanisms responsible for the increase in QT and QTc dispersions. In addition, neurohumoral systems relevant to cardiovascular regulation are affected by ageing. In the elderly, an exaggerated shift towards sympathetic activity has been reported [16], and such sympathetic overactivity has been proved to be an important factor to cause the prolongation of QT interval and the increase of QT dispersion [17–19]. Hence, the imbalance of sympathetic and parasympathetic tones in the elderly may be another explanation for the increased QT interval and dispersion.

In conclusion, our study shows that the QTc interval and QT and QTc dispersions present a significant longitudinal change in a population of healthy elderly subjects during the 4-year follow-up.

Acknowledgement

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References