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Impact of age on QT interval and QT dispersion in healthy subjects: a regression analysis†

ARDUINO A. MANGONI, MARK T. KINIRONS, CAMERON G. SWIFT, STEPHEN H. D. JACKSON

Department of Health Care of the Elderly, Guy's, King's, and St Thomas' School of Medicine, King's College London, UK

Address correspondence to: Arduino A. Mangoni, Department of Health Care of the Elderly, King's College Hospital (Dulwich), East Dulwich Grove, London SE22 8PT, UK. Fax: (+44) 207 346 6370. Email: arduino.mangoni@kcl.ac.uk

Abstract

Objective: although the isolated effects of age on QT interval and QT dispersion (QTd) have been previously investigated, no data are available on the simultaneous effects of age and other physiological or lifestyle factors on QT interval and QTd in healthy subjects. We studied the effects of age, gender, body mass index, smoking status, and blood pressure on these electrocardiographic parameters.
Design: observational study.
Setting: academic medical centre.
Participants and measurements: age, gender, body mass index, smoking status, and blood pressure were obtained from 191 consecutive healthy subjects (101 males and 90 females, age range 19–89 years). The subjects were divided into three groups according to their age: <30 ($n=56$), 30–65 ($n=49$), and >65 years ($n=86$).
Results: heart-rate corrected QT interval (QTc, Bazett's formula) progressively increased with advancing age (389 ± 3 vs. 411 ± 4 vs. 418 ± 3 ms, means $\pm$ SEM; $P<0.01$). By contrast, no differences in QTd were observed across the three groups (36 ± 2 vs. 35 ± 3 vs. 40 ± 2 ms, P=NS). A multivariate regression analysis showed that age ($P<0.01$) and body mass index ($P=0.04$) independently predicted QT interval while gender was a weak ($P=0.09$) predictor of QTd.
Conclusions: after adjusting for gender, smoking status, and blood pressure, age and body mass index independently predicted QT interval in healthy subjects. By contrast, age is not a predictor of QTd. The increase of QT interval associated with ageing and body mass index might be secondary to cardiac hypertrophy and myocardial action potential prolongation.

Keywords: *QT interval, QT dispersion, ageing, electrocardiogram*

Introduction

The QT interval is an indirect measure of the duration of ventricular depolarisation and repolarisation [1]. The duration of QT interval varies between different leads and this range of intervals is referred to as QT dispersion (QTd) [2]. A prolongation of the QT interval and an increased QTd are associated with an increased rate of cardiovascular morbidity and mortality. This is related to electrical instability and the risk of ventricular arrhythmogenesis [3, 4].

Several authors have previously investigated the relationship between age, QT interval and QTd and obtained conflicting results [5–9]. The interpretation of the data deriving from these studies is difficult because the effect of multiple physiological factors, potentially affecting the relationship between age and these electrocardiographic parameters, was rarely addressed. Moreover, high-risk patients with QT interval prolongation and/or abnormal QTd were often studied [10–15]. Therefore, little information is available on the effect of ageing on these electrocardiographic intervals after considering other physiological or lifestyle factors in absence of cardiovascular disease. We addressed this issue by studying the impact of age, gender, body mass index, smoking status, and blood pressure on QT interval and QTd in a population of healthy subjects.

Methods

Subjects and data analysis

One hundred and ninety-one consecutive subjects, aged between 19 and 89 years, underwent a screening visit at

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our Clinical Age Research Unit between 1990 and 2001. All subjects had normal cardiac physical examination, no history of heart disease including hypertension or other morbid conditions known to affect QT interval and QTd [1]. None of the patients was under treatment with drugs able to affect ventricular repolarisation [1].

The subjects were divided into three groups according to their age: young (<30 years), middle-aged (30–65 years) and elderly (>65 years). Body weight (kg) and height (cm) were measured and body mass index (BMI, kg/m^2) was subsequently calculated by using the following formula: BMI = body weight/(body height)^2. Blood pressure (BP, mmHg) and heart rate (HR, beats/min) were measured three times after each subject rested comfortably in the supine position for 5 min (Dinamap® 8100 Monitor, Critikon, Tampa, FL, USA). The mean of the last two readings was calculated. Blood was withdrawn for the assessment of serum electrolytes. Then, a standard 12-lead electrocardiogram (ECG) was recorded at a paper speed of 25 mm/s and a gain of 10 mm/mV (Cardiofax V, Nihon Kohden Corp, Tokyo, Japan).

The QT interval was manually measured from the lead with the longest interval, by using hand-held calipers to the nearest 10 ms from the beginning of the QRS complex to the end of the T-wave [16]. The end of the T-wave was defined as the intersection between a tangent to the terminal slope of the T-wave and the PR baseline. Only monophasic well defined T-waves were accepted for measurement. If the end of the T-wave could not be identified because of the low amplitude of the T-wave, then the lead was excluded from analysis. If a U-wave was present, then a tangential line was drawn on the terminal slope of the T-wave and the end of the T-wave was determined as the point of intersection of this line with the isoelectric base. The QT interval and the preceding RR interval were measured in three consecutive cycles. All electrocardiograms were analysed by a single observer blinded to the clinical data. Subjects with complete bundle branch block, atrial fibrillation, second or third degree atrio-ventricular block, or less than six measurable leads in the ECG were excluded. The heart rate-corrected QT interval (QTc, ms) was calculated by using Bazett's formula [$QT_c = QT/(RR)^{1/2}$] [17]. The QTd (ms) was defined as the absolute difference between the maximum and minimum QT interval in any of the ECG leads. The coefficients of variation for QT and QTd values, obtained from 20 electrocardiograms (within-observer variability), averaged 1% and 6%, respectively. The study was performed according to the Declaration of Helsinki after being approved by the local research ethics committee. Each subject gave written informed consent before starting the study.

Statistical analysis

Data are presented as means ± SEM. The differences in continuous variables across the groups were assessed by one-way ANOVA and unpaired Student's *t*-test. Pearson's correlation analysis was used to assess the relationship between numerical variables. A backward deletion stepwise multiple regression analysis was performed to identify independent predictors of QT interval and QT dispersion (SPSS for Windows, Copyright SPSS Inc, Chicago, IL, USA). A *P*-value less than 0.05 indicated statistical significance.

Results

Baseline clinical characteristics, QTc, and QTd values are illustrated in Table 1. QTc intervals increased with advancing age. By contrast, no significant differences in QTd were observed across the three groups (Table 1). Blood pressure also increased with advancing age (Table 1). Gender-related differences in QTc and QTd values across the three groups are illustrated in Figure 1. Females had a slightly longer QTc than males in the young and middle-aged group. This difference, however, was no

Table 1. Clinical characteristics, QT interval and QT dispersion values

	Young ($n=56$)	Middle-aged ($n=49$)	Elderly ($n=86$)
Age (years)	23.3 ± 0.3	50.4 ± 2.0	73.8 ± 0.6
M:F	46:10	20:29	35:51
Smokers/non smokers	17:39	22:25	9:77
BMI (kg/m^2)	23.0 ± 0.3	26.6 ± 1.1**	24.5 ± 0.4
Serum K^+ (mmol/l)	4.2 ± 0.1	4.2 ± 0.1	4.3 ± 0.1
SBP (mmHg)	120 ± 2	129 ± 2	144 ± 2**
DBP (mmHg)	69 ± 1	75 ± 1	81 ± 1**
MAP (mmHg)	86 ± 1	94 ± 2	102 ± 1**
HR (beats/min)	63 ± 1	68 ± 1*	66 ± 1
QTc (ms)	389 ± 3	412 ± 4	418 ± 3**
QTd (ms)	36 ± 2	35 ± 3	40 ± 2

M, male; F, female; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; QTc, corrected QT interval; QTd, QT dispersion.

Means ± SEM. *$P<0.05$, **$P<0.01$.

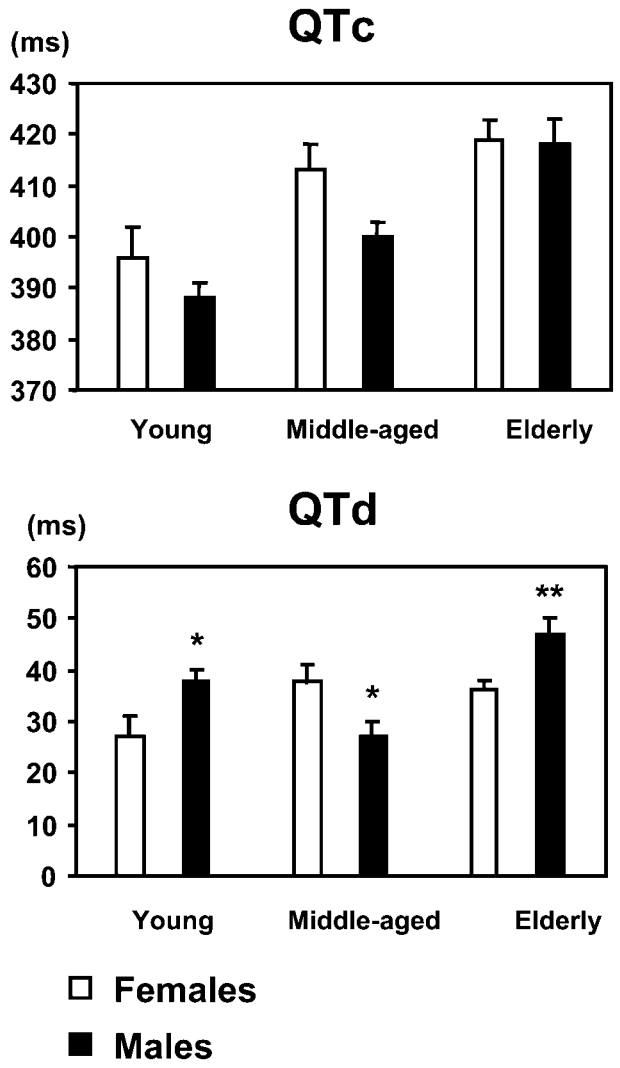

Figure 1. Gender differences in QT interval and QT dispersion in young, middle-aged, and elderly subjects. QTc, heart-rate corrected QT interval; QTd, QT dispersion. Means ± SEM. $^{*}P<0.05$, $^{**}P<0.01$.

longer evident in the elderly group (Figure 1). QTd in middle-aged and elderly females was greater than the younger group. However, while females had smaller QTd than males in the young and elderly group, this parameter was smaller in males in the middle-age group.

A univariate regression analysis showed that QTc was significantly correlated with age ($r=0.44$, $P<0.01$), BMI ($r=0.17$, $P=0.04$), SBP ($r=0.33$, $P<0.01$), DBP ($r=0.26$, $P=0.01$), and MAP ($r=0.32$, $P<0.01$). QTd was positively correlated with age ($r=0.15$, $P=0.04$) and negatively correlated with HR ($r=-0.15$, $P=0.04$). After adjusting for smoking status, BMI, and blood pressure, a backward stepwise multivariate regression analysis showed that age and BMI were independent predictors of QTc ($P<0.01$ and $P=0.04$, respectively) whilst gender weakly ($P=0.092$) predicted QTd (Tables 2 and 3).

Discussion

QT interval

Our study shows that age and body mass index independently predicted QTc interval in a population of healthy subjects, after correcting for other variables such as gender, smoking status, and blood pressure. To our knowledge, this is the first study to investigate the multiple effects of different physiologic parameters on ventricular repolarisation over a wide age range. Although the effect of disease states and therapeutic drugs on the QT interval has been extensively studied in an attempt to understand the relationship between QT and the risk of arrhythmias, few data are available on the physiologic determinants of QT interval in healthy subjects.

Conflicting results have been obtained in previous studies investigating the relationship between age and QT interval. Reardon *et al.* [5] studied the relationship between ageing and QTc interval in 96 healthy subjects aged between 40 and 102 years. A significant correlation

Table 2. Multiple regression analysis of QT interval (dependent variable: heart rate corrected QT interval)

Model	B	SE	Beta	*t*	Sig	*R*	R^2	Adj. R^2
Age	0.366	0.131	0.278	2.782	0.006	0.435	0.189	0.159
Gender	−4.843	5.178	−0.082	−0.935	0.351			
Smoking	5.013	5.465	0.076	0.917	0.361			
BMI	1.528	0.811	0.149	1.885	0.062			
MAP	0.327	0.226	0.131	1.446	0.151			
Age	0.338	0.128	0.257	2.644	0.009	0.429	0.184	0.160
Gender	−5.753	5.079	−0.097	−1.133	0.259			
BMI	1.554	0.810	0.152	1.919	0.057			
MAP	0.306	0.225	0.122	1.361	0.176			
Age	.392	0.119	0.298	3.305	0.001	0.420	0.176	0.158
BMI	1.673	0.804	0.164	2.082	0.039			
MAP	0.280	0.224	0.112	1.250	0.213			
Age	0.465	0.104	0.354	4.493	<0.001	0.409	0.167	0.155
BMI	1.656	0.805	0.162	2.056	0.042			

BMI, body mass index; MAP, mean arterial pressure.

Table 3. Multiple regression analysis of QT dispersion (dependent variable: QT dispersion)

Model	B	SE	Beta	*t*	Sig	*R*	R^2	Adj. R^2
Age	0.09	0.083	0.131	1.196	0.234	0.180	032	−0.004
Gender	6.305	3.276	0.183	1.925	0.056			
Smoking	−0.567	3.457	−0.015	−0.164	0.870			
BMI	−0.008	0.513	−0.014	−0.158	0.874			
MAP	−0.008	0.143	−0.059	−0.595	0.553			
Age	0.009	0.083	0.129	1.192	0.235	0.179	0.032	0.003
Gender	6.368	3.240	0.185	1.966	0.051			
Smoking	−0.587	3.443	−0.015	−0.170	0.865			
MAP	−0.008	0.143	−0.059	−0.597	0.552			
Age	0.102	0.080	0.133	1.268	0.207	0.178	0.032	0.010
Gender	6.477	3.165	0.188	2.047	0.043			
MAP	−0.008	0.141	−0.057	−0.585	0.560			
Age	0.007	0.070	0.103	1.129	0.261	0.171	0.029	0.015
Gender	6.285	3.140	0.183	2.001	0.047			
Gender	4.907	2.896	0.143	1.694	0.092	0.143	0.020	0.013

BMI, body mass index; MAP, mean arterial pressure.

between advancing age and QTc was observed in both men and women. Taneja *et al.* [6] studied the effects of gender and age differences in cardiac electrophysiological properties in three groups of subjects (0–40, 41–60, and >60 years) without structural heart disease undergoing cardiac electrophysiologic testing. Ageing was associated with a significant prolongation of QT interval in this study. By contrast, Merri *et al.* [7] looked at descriptive ECG features of ventricular repolarisation. They did not find any relationship between age and QT interval. These studies, however, did not take into account the potential impact of other important factors such as blood pressure, smoking status, and body mass index, potentially affecting the relationship between age and QT interval. The discordance in the results obtained might be related to the different ways used to express and calculate the QT interval. The latter was not always corrected for heart rate [7]. Also, the QT interval may be obtained from the average of QT intervals from all ECG leads or the QT interval from the lead with the longest QT interval. As QT interval can vary considerably between leads within the same ECG, the latter is the method currently adopted by investigators and clinicians.

The relationship between advancing age and QT interval in our study might be explained by the changes in heart and vasculature observed in healthy elderly subjects. These include cardiac hypertrophy, increased vascular stiffness and aortic impedance. The increase in vascular impedance, in conjunction with its effects leading to an increase in systolic arterial pressure (within the clinical normal range), means that the pulsatile component of external cardiac work must increase [18]. The stroke work, expressed as the product of stroke volume and systolic blood pressure, has been shown to increase with age in clinically normotensive subjects. This occurs even in elderly subjects in whom stroke volume at rest is decreased compared to younger subjects [19]. The increase in stroke work appears to be an aetiological factor in the moderate (about 30% between ages 20 and 80 years) but definite increase in left ventricular wall thickness that occurs with ageing in normotensive subjects [20]. This cardiac hypertrophy is due in large measure to an increase in size of cardiac myocytes. The latter is associated with a significant prolongation of the transmembrane action potential and might provide an explanation for the prolongation of QT interval associated with advancing age [21].

The relationship between physiologic body mass index and QT interval confirms and extends previous reports showing a positive relationship between these variables in human obesity [22, 23]. Frank *et al.* [22] and El-Gamal *et al.* [23] evaluated the electrocardiogram of obese outpatients and found a significant linear association between degree of overweight and QTc. Our study shows a relationship between body mass index and QT interval in non-obese subjects. The mechanisms underlying such a relationship are not known although it is possible that an increase in cardiac output in subjects with higher body mass index might be responsible for the development of subclinical cardiac hypertrophy [24].

The relationship between gender and QT interval has also been investigated. Previous studies showed that women have longer (~10–20 ms) QTc values than men. Molnar *et al.* [25] evaluated the range and variability of QTc intervals over 24 h in 21 healthy subjects aged between 36 and 76 years and observed that the percentage of readings >450 ms was significantly greater in women. Data from the Framingham Study confirm this finding. Sagie *et al.* [26] measured QTc interval in 5,018 subjects without cardiovascular disease and observed that women had a consistently longer QTc over a wide range of RR intervals. This gender-related difference seems to be caused by a prolongation of repolarisation duration in women [7]. This phenomenon might be related to different sex hormones blood levels since it is not present at birth and appears only after puberty [27, 28].

Our study shows that gender differences in QT interval, although not statistically significant, might be of some relevance in young and middle-age subjects. However, no difference in QT interval between males and females was observed in elderly subjects, thus supporting the hypothesis of a hormone-mediated phenomenon, which is lost after the menopause.

QT dispersion

Age did not have any impact on QTd in our study. QTd values were similar to the range of 30 and 60 ms that have been obtained previously in normal subjects [29]. Age-related differences <10 ms have been reported and appeared to be statistically significant in some larger studies. In the study from Savelieva *et al.* [8] on 1,096 healthy subjects, QT dispersion was 29 ± 18 ms in the age group 17–29 years, 26 ± 16 ms in the age group 30–49 years, and 22 ± 13 ms in the age group 50–80 years ($P < 0.0001$). However, in another large study, Macfarlane *et al.* [9] found no significant age differences (QT dispersion of 24 ± 8 ms, 25 ± 8 ms, 25 ± 8 ms, and 24 ± 10 ms in the age groups <30, 30–40, 40–50, and >50 years, respectively). These two studies, however, did not take into account other confounding variables such as blood pressure, body mass index, and smoking status.

Gender was only a weak predictor of QTd in our study, with women showing less dispersion. Previous studies showed either no statistically significant difference in QTd between genders or marginally greater values in men. Macfarlane *et al.* [9] showed that males and females had similar QTd values obtained from 1501 adult normal subjects divided into four different age groups (<30, 30–40, 40–50, and >50 years). Tran *et al.* [30] measured QTd in 150 healthy subjects and observed that males had higher QTd than females. A similar finding was obtained when a subgroup of elderly subjects was analysed. Kassotis *et al.* [31] assessed the impact of gender on QTd in 250 subjects aged between 20 and 86 years. A significant difference was noted in QTd between men and women with the former showing a greater QTd. Savelieva *et al.* [8] measured QTd in 1,096 normal subjects and showed that this parameter was significantly greater in male subjects. However, when all the subjects were divided into three age groups (17–29, 30–49, and 50–80 years), the difference in QTd was only observed in the elderly group. Our study shows the overall effect of gender on QTd is weak when other factors were taken into account. Also, in a univariate analysis middle-aged females actually had a longer QTd than males. This phenomenon might be secondary to hormonal factors regulating QT dispersion or differences in other physiologic factors. Saba *et al.* [32] measured QTd in healthy adult women and showed that QTd was significantly prolonged (54 ms) in the post-menopausal group compared with pre-menopausal women (30 ms) and post-menopausal women receiving hormonal replacement therapy (40 ms). The progestin component of hormonal replacement therapy seems to play a major contribution to the reduction of the dispersion of ventricular repolarisation [33]. In our study, the majority of females in the middle-age group were in the post-menopausal phase and this might explain our findings.

The limitations of the present study are related to its partially retrospective nature and to the fact that QT measurements were obtained from a relatively small sample of subjects and need to be confirmed in other racial groups. Also, the regression models account for $<50\%$ of the variance of the QT interval and QT dispersion. This indicates that several other factors such as changes in autonomic neural tone and metabolic factors might play an important role in determining these electrocardiographic parameters [34, 35]. Nevertheless, the multiple impact of several important parameters has been first reported, which provides additional information on the factors determining QT interval and QT dispersion in healthy subjects.

Key points

- After adjusting for gender, smoking status, and blood pressure, age and body mass index independently predict QT interval in healthy subjects.
- Age is not a predictor of QT dispersion.
- The increase of QT interval associated with ageing and body mass index might be secondary to cardiac hypertrophy and myocardial action potential prolongation

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