Age, Gender, and Autonomic Tone Effects on Surface Electrocardiographic Indices of Ventricular Repolarization

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Background: Prolonged QT offset dispersion (QToD), an index of heterogeneity of ventricular repolarization, is thought to be an independent predictor of all-cause and cardiovascular mortality. However the influence of gender and autonomic tone in healthy adults on age-related changes in measures of ventricular repolarization are not well characterized.

Methods: QToD and T wave complexity were measured in 56 healthy subjects with no detectable heart disease (by echo and stress test)—38 young subjects with a mean age of 28 ± 4 years and 18 old subjects with a mean age of 71 ± 7 years. QToD and T wave complexity were computed from 12-lead ECGs using the GE Marquette QT Guard automated analysis program with manual over-reading at rest (baseline), following exercise, and double autonomic blockade with atropine and propranolol. Data was analyzed using factorial ANOVA.

Results: Young males had a significantly greater QToD than young and old females at baseline (28 ± 5 ms, 23 ± 5 ms, and 22 ± 5 ms, respectively, $P < 0.01$), an intrinsic effect independent of changes in autonomic tone. In contrast, females had significantly greater T wave complexity than males following exercise and double autonomic blockade with a definite trend at baseline. There was no correlation between T wave complexity and QToD.

Conclusions: Age and gender demonstrate a complex interaction on indices of myocardial repolarization with different measures behaving differently. These findings have implications for better understanding age and gender effects on myocardial electrophysiology.

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Animal studies have shown that a large dispersion of repolarization facilitates the development of conduction delay necessary to induce sustained arrhythmia by a premature stimulus.¹ In addition, prolonged repolarization, especially when heterogeneous, has been shown to contribute to clinical arrhythmias. Thus, noninvasive indices of repolarization have the potential to provide important prognostic information. One such measure, QT offset dispersion (QToD) is defined as the difference in duration between the longest and shortest QT intervals in any lead or given set of leads and has

been suggested to reflect regional variation in ventricular repolarization.² Although controversy regarding the cellular basis and physiologic significance for QToD persists,³ some, but not all, large population studies have suggested that prolonged QToD is an independent predictor of all-cause and cardiovascular mortality.^{4–7} Recent reports have suggested that principal component analysis of the T wave (T wave complexity) may be a more reproducible measure of complexity of ventricular repolarization and provide information beyond that provided by QToD.^{8,9} However, control groups to

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establish normal values of QT_{oD} and T wave complexity in healthy population subgroups in different age and gender groups have not been carefully studied. Given the conflicting results of some prior studies, these differences could account for some of the divergent results. The present study was designed to assess the influence of autonomic tone on age and gender related changes in myocardial repolarization as detected by QT dispersion and T wave complexity.

METHODS

The protocol and consent forms used in this study were reviewed and approved by the Institutional Review Board at Northwestern University. The study population consisted of 56 healthy subjects. They were divided into two subgroups based on age—38 young subjects (20 females) between the ages of 20 to 35 years with a mean age of 28 ± 4 years and 18 old subjects (11 females) between the ages of 65 to 80 years with a mean age of 71 ± 7 years. Subjects were enrolled in response to classified advertisements placed in the local newspapers.

Exclusion criteria consisted of: 1) the presence of heart disease excluded by echo and stress test, 2) the absence of normal menstrual cycle in young females or the presence of hormone replacement therapy in old females, 3) hypertension or left ventricular hypertrophy either on ECG or 2-D echo (ventricular wall thickness > 1.2 cm), 4) therapy with drugs known to affect ventricular repolarization such as anti-arrhythmic agents, phenothiazines, or terfenadine, 5) subjects with autonomic dysfunction or conditions altering the autonomic nervous system including diabetes, 6) inability to receive intravenous propranolol or atropine, i.e., subjects with diseases such as asthma, type II or greater heart block, glaucoma, or symptomatic benign prostatic hypertrophy, and 7) major ECG abnormalities—QRS duration > 110 ms, left or right ventricular hypertrophy, evidence of Q wave myocardial infarction, long QT syndrome (QT interval > 480 ms) or severe T wave abnormalities (T wave flattening or biphasic T waves).

The initial visit was a screening visit and consisted of a history and physical, a 12-lead resting ECG, a complete blood count, and renal function tests, and in the older subgroup, a cardiac 2-D echo and treadmill stress test all done during the screening visit. Subjects who did not meet any of the

exclusion criteria and who gave informed consent were enrolled in the study. Standard 12-lead ECGs were done at a paper speed of 25 mm/sec with a gain of 1 mV/10 mm. Subjects underwent baseline recordings after at least a 5 minute rest period. ECGs were repeated after each of the stages of the study, i.e., bicycle exercise, following double autonomic blockade (with intravenous propranolol using an initial dose of 0.25 mg/kg administered at a rate of 1 mg/min followed by an infusion of 0.002 mg/kg/min for the duration of the study and intravenous atropine as a single dose of 0.04 mg/kg at a rate of 1 mg/min).¹⁰ The order of administration of atropine and propranolol was random. An ECG was obtained after the first drug. A propranolol level was drawn just before the termination of the study after the last recording and these levels in all subjects were well within the range considered compatible to sympathetic blockade. The younger subjects were monitored for 4 hours after the end of the study whereas the older subjects were monitored overnight.

Data Analysis

QTD measurements were performed from median complexes on the digital ECGs by use of interactive software (QT Guard, GE Marquette Medical Systems) that detects QRS onset and T-wave offset and were validated by a single observer who was unaware of the clinical outcome. The GE Marquette QT Guard analysis software analyzes the QRS complexes in all 12 leads and develops a filtered complex which is then used for estimation of the Q wave onset. The Q wave onset is identical in each lead. The T wave peak in each lead is determined by the "regional centering method," which detects the maximum point of the T wave and for T plateau the centering of the plateau is taken as T wave peak and identifies the T wave offset from the intersection of the maximal slope of the terminal T wave with the threshold defined by the T-P segment using a least-square fitting method which has the most reproducibility.¹¹ QT_{peak} dispersion (QT_{pD}) and QT_{oD} was computed as the difference between the maximum and the minimum QT_p and QT_o intervals respectively (Fig. 1).

T wave complexity based on principal component analysis (PCA) of the T wave takes the entire morphology of the T wave into consideration. The PCA process decomposes the T wave by singular wave decomposition.¹² The 12-lead ECG signals

Figure 1. Sample data from a young female subject at baseline showing 12-lead recordings and the computation of QToD and QTpD in the 12 leads. (QToD = QT offset dispersion; QTpD = QT peak dispersion).

are stored in a columnar matrix A. Singular wave decomposition breaks down matrix A into three matrices as

$$A = USV^T$$

where matrix A is decomposed into orthogonal matrices U and V and a diagonal matrix S called a singular matrix whose elements have monotonically decreasing values. The first three diagonal components contribute more than 98% of the total energy. These singular matrices are then used to compute several ratios of which the second to the first component (S/F) ratio multiplied by 100 has most widely been reported in the literature.^{8,13,14} The S/F index provides information that can be visualized by analogy to the short and long axes of the T wave loop and provides an estimate of the "fatness" of the T wave loop with a thicker loop being more complex than a thinner loop.

Continuous variables are expressed as mean $\pm$ standard deviation (SD). Two-way analysis of variance was used to examine the effects of gender and age on measures of repolarization. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using commercial software (Statview, Abacus Concepts, Berkeley, CA, USA) on a Power Macintosh computer (Apple Computer, Cupertino, CA, USA).

RESULTS

Baseline Recordings

At rest (baseline), the mean heart rate was 64 ± 11 beats/min, mean QRS duration was 88 ± 9 msec, QT interval was 406 ± 39 ms, and the QTc interval was 415 ± 19 msec. The mean baseline global QToD was 24 ± 6 ms, precordial QToD was 17 ± 7 ms, global QTpD was 27 ± 13 ms, and the precordial QTpD was 22 ± 13 ms. The mean T wave complexity was $14 \pm 7\%$.

There were no differences in the baseline heart rate between young and old subjects. The baseline QRS duration tended to be longer in old subjects (90 ± 10 msec) than in young subjects (85 ± 6 ms, $P = 0.08$), and the QTc interval was significantly longer in old subjects (423 ± 21 ms) than in young subjects (411 ± 16 msec, $P < 0.03$). Among measures of dispersion of ventricular repolarization, older subjects tended to have longer global and precordial QTpD (29 ± 13 ms and 24 ± 13 ms, respectively, compared to younger subjects 23 ± 11 ms and 18 ± 12 ms, respectively), with P values of 0.06 and 0.07, respectively (Fig. 2). Young and old subjects had similar T wave complexities (14 ± 8 vs $14 \pm 6\%$, respectively).

At baseline, females had a faster heart rate (66 ± 10 beats/min) than males (62 ± 12 beats/min) and a significantly shorter mean QRS duration (84 ± 6 ms) than males (94 ± 10 ms, $P < 0.0001$), with a

Figure 2. Age and gender effects on dispersion of ventricular repolarization in the entire study group at baseline. Males had significantly greater global QToD than females and old subjects had a greater global and precordial QTpD than young subjects. (QToD = QT offset dispersion; QTpD = QT peak dispersion).

Table 1. Effects of Age and Gender on Dispersion of Ventricular Repolarization at Rest

	Young		Old	
	Males	Females	Males	Females
Heart rate (beats/min)	61 ± 12	67 ± 10	64 ± 13	63 ± 11
QRS (ms)	97 ± 10*	83 ± 5	85 ± 6	86 ± 6
QTc interval (ms)	409 ± 17	414 ± 16	418 ± 20	423 ± 19
Global QToD (ms)	28 ± 5*	23 ± 5	25 ± 8	22 ± 5
Precordial QToD (ms)	19 ± 7	17 ± 8	15 ± 6	15 ± 6
Global QTpD (ms)	30 ± 14	29 ± 12	22 ± 14	23 ± 9
Precordial QTpD (ms)	26 ± 15	23 ± 13	15 ± 15	19 ± 11
T wave complexity (%)	12 ± 10	13 ± 4	8 ± 2	15 ± 4†

* $P < 0.05$ young males vs young and old females, † $P < 0.05$ old females vs old males

longer QTc interval (Fig. 2). The global QToD was significantly longer in males (27 ± 6 ms) than in females (22 ± 5 ms, $P < 0.01$, Fig. 2) confirming prior observations.^{15,16} There were no significant differences in precordial QToD and global and precordial QTpD between the genders (Fig. 2). Females had significantly greater T wave complexity than males (16 ± 7 vs $12 \pm 8\%$, respectively, $P = 0.0001$).

Interaction Between Age and Gender

Table 1 shows heart rate and QRS differences based on gender and age. Females both young and old tended to have a longer QTc interval than men. The global QToD was significantly longer in young males (28 ± 5 ms) than young females (23 ± 5 ms, $P < 0.001$) and old females (22 ± 5 ms, $P < 0.01$). The differences between old males and females were not significant. Old females tended to have significantly more complex (fatter) T waves than old males with no significant differences noted between young males and females.

Effects of Exercise and Autonomic Blockade on Measures of Ventricular Repolarization

Exercise

After exercise, young subjects tended to have a longer QToD than old subjects (23 ± 8 ms and 20 ± 5 ms, respectively, $P = 0.1$), and males had a significantly longer QToD than females (25 ± 9 msec vs 20 ± 6 msec, respectively, $P < 0.05$).

The global QToD remained significantly longer in young males (27 ± 10 msec) than young females (21 ± 6 ms, $P = 0.03$), old females (18 ± 5 ms, $P =$

0.03) with a similar trend in old males (21 ± 6 ms, $P = 0.1$). There were no significant differences in the global QToD between old males and old females. Similarly there were no significant differences between the precordial QToD and QTpD in males and females, both young and old. Compared to baseline, exercise tended to decrease the QToD in old females (22 ± 5 ms vs 18 ± 5 ms, respectively, $P = 0.068$), and old males (28 ± 12 ms vs 21 ± 6 ms, respectively). Exercise did not change the global QToD in young males and females compared to baseline. T wave complexity was significantly greater in young females than young males (Table 2).

Double Autonomic Blockade

After double autonomic blockade, there were no differences between young and old subjects in global QToD although the precordial QToD was greater in young subjects (18 ± 5 ms vs 15 ± 8 ms, $P = 0.06$). There were no differences in measures of QTpD. Males had a longer global QToD than females (26 ± 7 msec vs 23 ± 8 ms, $P = 0.1$) with no differences in other measures of ventricular repolarization. Following double autonomic blockade, young males continued to have a significantly longer global QToD than young females. The precordial QTpD tended to be longer in young males than young females ($P = 0.09$). There were no statistically significant differences in the various measures of repolarization in older subjects. T wave complexity was significantly greater in young females than young males (Table 3). Because of the small numbers in the various subgroups, the effects of partial autonomic blockade were not analyzed.

Table 2. Effects of Age and Gender on Dispersion of Ventricular Repolarization with Exercise

	Young		Old	
	Males	Females	Males	Females
Global QToD (ms)	27 ± 10*†	21 ± 6	21 ± 6	18 ± 5
Precordial QToD (ms)	16 ± 8	14 ± 6	14 ± 8	16 ± 3
Global QTpD (ms)	27 ± 14	23 ± 7	23 ± 12	21 ± 5
Precordial QTpD (ms)	19 ± 11	19 ± 8	19 ± 10	19 ± 5
T wave complexity (%)	11 ± 4	16 ± 6*	14 ± 5	15 ± 5

* $P < 0.05$ young males vs young and old females, † $P = 0.1$ young vs old males

Pooled results from young and old subjects showed that females had significantly higher T wave complexity than males following exercise (16 ± 6 vs $12 \pm 5\%$, respectively), after autonomic blockade (15 ± 6 vs $10 \pm 5\%$, respectively) with a very definite trend at baseline (Fig. 3). Compared to baseline, double autonomic blockade did not significantly change measures of QTD. Young females had significantly higher T wave complexity than young males with a very similar trend in the older cohort. Males and females did not show significant differences between T wave offset and T peak estimation in the different leads.

Correlation of PCA with QToD

There was no correlation between the PCA and QT or QTc interval ($R^2 = 0$ and 0.07 , respectively) or QToD ($R^2 = 0$).

DISCUSSION

Major Findings

Young healthy males have a significantly longer global QToD than young and old females that is intrinsic and not modified by alterations in autonomic tone. The differences are due to differences

in limb lead repolarization as they were not present in precordial QToD. These findings extend prior observations on the interaction between age related changes in repolarization and gender and are consistent with an in vivo effect of androgens on repolarization.

T wave complexity was significantly greater in females than males, was not clearly age related, in contrast to QToD, and did not correlate with QToD. Aging modestly decreased QToD but not T wave complexity. Thus, the higher incidence of ventricular ectopy that occurs with aging is not due to alterations in repolarization that can be detected electrocardiographically.

Prior Studies

QT Dispersion

While the cellular basis of QTD is incompletely understood, it has generally attributed to heterogeneities in ventricular repolarization perhaps secondary to regional differences in the duration of the M cell action potential.³ Animal studies have shown that M cells with the longest action potential are generally deep subendocardial to midmyo-

Table 3. Effects of Age and Gender on Dispersion of Ventricular Repolarization with Double Autonomic Blockade

	Young		Old	
	Males	Females	Males	Females
Global QToD (ms)	27 ± 6*	22 ± 7	24 ± 9	24 ± 9
Precordial QToD (ms)	18 ± 4	19 ± 6	18 ± 10	13 ± 6
Global QTpD (ms)	27 ± 10†	21 ± 10	20 ± 8	25 ± 8
Precordial QTpD (ms)	20 ± 10	19 ± 11	15 ± 10	20 ± 10
T wave complexity (%)	10 ± 4	15 ± 6**	11 ± 5	14 ± 5

* $P < 0.05$ vs young females, † $P = 0.09$ vs young females, ** $P < 0.01$ vs young males

Figure 3. Pooled results from young and old subjects showing females had a significantly increased T wave complexity compared to males postexercise and double autonomic blockade. (* $P < 0.05$ females vs males, † $P \leq 0.07$ old vs young).

cardial in the anterior and lateral walls and the outflow tract.^{17–20}

The findings of our study that QToD is gender related differ from an earlier report by Macfarlane et al. who concluded that QToD in healthy subjects is age and sex independent.²¹ The differing results could be due to the differences in the algorithm used for determination of T wave end and the inclusion of flat T waves in the earlier study. Also in the study by MacFarlane et al. the subjects were not carefully screened for the absence of coronary or structural heart disease. Gender differences in QToD in young adults have previously been demonstrated both by us¹⁶ and others.¹⁵ In our earlier study, although autonomic blockade reduced QToD, the differences between genders persisted.¹⁶ Aging was associated with a small decrease in QToD in both genders although the difference did not reach statistical significance. While the possibility of a beta error cannot be excluded, aging which prolonged the QTc interval clearly did not prolong QToD.

While QToD has been hypothesized to reflect regional variations in repolarization, it has been criticized as being unreliable and poorly reproducible based on the presence of a multitude of measurement algorithms,^{22,23} the inherent complexities of T wave morphology, and has been called the greatest "fallacy of electrocardiography."²³ Kors et al. have suggested that QToD is really an attribute of T wave morphology.²⁴ They analyzed a database of 1220 ECGs and showed that QToD were smallest for large, narrow T loops and largest for small, wide loops leading them to suggest that QToD is an attribute of T-loop amplitude and width. Thus in

the present study, in addition to examining QToD, we analyzed a quantitative measure describing T wave loops.

Principal Component Analysis

T wave analysis based on PCA is called T wave complexity analysis and is an extension of earlier studies using PCA for analysis of body surface mapping recordings.²⁵ PCA of the T wave defines the components of repolarization, which may help resolve some of the controversy surrounding QToD. The first component typically accounts for most of the repolarization, whereas inhomogeneous repolarization is indicated by a relevant contribution of the second and other components. The most widely used PCA ratio is S/F ratio and has been suggested that QT interval analysis based on S/F component analysis has very good reproducibility.¹¹ Reports of clinical application of T wave complexity, while scant,^{8,13} suggest that T wave complexity is significantly increased after myocardial infarction ($23 \pm 12\%$) as opposed to controls ($9 \pm 3\%$)¹³ and is also significantly greater in patients with the long QT syndrome ($34 \pm 12\%$) as compared to controls ($13 \pm 3\%$) with a negative predictive value of 88%.⁸ In both these studies, as also in the present study, there was no correlation between the PCA and either the QT or QTc interval suggesting that this algorithmically derived parameter may provide information that is independent of QTc measurement. In the present study, although the PCA was longer in women, the QToD was smaller. The dichotomy between measures of QToD and T wave complexity suggests that at least in part they measure different characteristics of repolarization. Although the smaller QToD in women may be "protective" the higher T wave complexity may predispose to the higher incidence of congenital and acquired long QT syndrome in women.²⁶ One of the potential strengths of the PCA may be that it is independent of the T wave vector and also the technical difficulties in QToD measurement.

Limitations

A significant limitation of the study was the small number of patients in the older population cohort. In addition, the results may be subject to the inherent limitations in automated measurement software although the least square fitting method of measuring QToD used in the present

study has been shown to have the highest reproducibility.¹¹ Finally, beat-to-beat variability in repolarization was not evaluated in the present study.

CONCLUSIONS

Surface ECG indices of myocardial repolarization demonstrate a complex interaction between age and gender and importantly different indices may behave differently. While the mechanisms of these interactions need to be better understood, large population studies that address the long-term predictive value of measures of cardiac repolarization need to account for these complex interactions.

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