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CARDIOVASCULAR DISEASE

The association of serum testosterone levels and ventricular repolarization

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Abstract It is assumed that testosterone is an important regulator of gender-related differences in ventricular repolarization. Therefore, our aim was to study whether serum levels of testosterone are associated with QTc, QT and RR interval variation. Setting: two independent population-based cohort studies. Participants: 445 male participants (≥55 years) from the Rotterdam study cohort and 1,428 male participants from the study of health in Pomerania (SHIP) with an electrocardiogram who were randomly sampled for assessment of serum testosterone at baseline, after exclusion of participants with testosterone altering drugs, QTc prolonging drugs or dig(it)oxin, left ventricular hypertrophy and left and right bundle branch block. Endpoints: length of the QTc, QT and RR intervals. Analysis: linear regression model, adjusted for the two individual studies and a pooled analysis of both studies. The pooled analysis of the Rotterdam study and SHIP showed that the QTc interval gradually decreased among the tertiles (*P* value for trend 0.024). The third tertile of serum testosterone was associated with a lower QTc interval compared to the first tertile [−3.4 ms (−6.5; −0.3)]. However, the third tertile of serum testosterone was not associated with a lower QT interval compared to the first tertile [−0.7 ms (−3.1; 1.8)]. The RR interval gradually increased among the tertiles (*P* value for trend 0.002) and the third tertile of serum testosterone showed an increased RR interval compared to the first tertile [33.5 ms (12.2; 54.8)]. In the pooled analysis of two population-based studies, serum testosterone levels were not associated with the QT interval, which could be due to a lack of power. Lower QTc intervals in men with higher serum testosterone levels could be due to the association of serum testosterone with prolongation of the RR interval.

Keywords Serum testosterone · Ventricular repolarization · QTc interval · RR interval

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Introduction

There are well known gender-related differences in human cardiac repolarization [1, 2]. This is demonstrated by a longer heart-rate corrected QT (QTc) interval in women, which is the traditional clinical measurement for assessing the duration of ventricular repolarization [3]. Prolongation of ventricular repolarization may result in early after depolarizations, which

in turn may induce re-entry and thereby provoke Torsade de Pointes and fatal ventricular arrhythmias [4–7].

The gender differences in the QTc interval are not present in young children, whereas at the time of onset of puberty the duration of the QTc interval in boys shortens, which results in a longer QTc interval in adult women compared to men [8–10]. These gender differences remain detectable until around the age of 50 years [10]. Since the period between puberty and 50 years of age coincides with the highest circulating levels of androgens in males, male sex hormones may play a role in the shorter QTc interval in men. Furthermore, virilized women exhibit QTc intervals similar to those of healthy men, whereas castrated men had QTc intervals similar to those of normal women [11]. Testosterone therapy also reduces QT dispersion in men with congestive heart failure [12].

These data suggest that testosterone might be an important regulator of ventricular repolarization, which might explain the gender-related differences in ventricular repolarization. Therefore, our aim was to study whether testosterone is associated with QTc, QT and RR interval duration. Since bio-available testosterone decreases with age, we studied this association in two cohorts. First, in a cohort of elderly (the Rotterdam study) and second, in a cohort with a younger mean age (the Study of Health In Pomerania (SHIP)) [13].

Methods

Setting and study design

Rotterdam study

The Rotterdam study is a prospective population-based cohort study, which started with a baseline visit between 1990 and 1993. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, the Netherlands, approved the study. All inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and over, were invited to participate ($n = 10{,}275$). Of them, 7,983 (78%) gave their written informed consent and took part in the baseline examination. Objectives and methods of the Rotterdam study have been described in detail elsewhere [14, 15]. At baseline, all participants were visited at home for a standardized questionnaire, and 7,151 were subsequently examined at the research center. The cohort is continuously monitored for major morbidity and mortality through linkage with general practitioner and municipality records. Drug prescriptions dispensed to participants by automated pharmacies are routinely stored in the database since January 1, 1991.

All male cohort members of the Rotterdam study ($n = 3{,}105$), who had an ECG as well as serum testosterone and dehydroepiandrosterone sulfate (DHEAS) measurements at baseline were enrolled in the study population. Digitally stored ECGs were available for 2,200 male participants at the time of the first visit. Missing ECGs were mainly due to temporary technical problems with ECG recording. Androgen status was assessed in different random subsets of these males. Male participants with an ECG and with both a serum testosterone measurement and a DHEAS measurement ($n = 540$) were included. Participants who received anabolic steroids (anatomic therapeutical chemical (ATC) code A14A; $n = 1$) were excluded. None of the participants received sexual hormones (ATC code G03), testosterone 5α-reductase inhibitors (ATC code G04CB), sexual hormone antagonists (ATC code L02B) or had a pacemaker. Participants who used digoxin ($n = 25$), which is a QTc shortening agent, or QTc prolonging drugs ($n = 6$) as well as persons with evidence of left ventricular hypertrophy ($n = 36$) or left ($n = 13$) and right bundle branch block ($n = 36$) were excluded, since these conditions are associated with an altered QTc interval [16, 17]. Overall, 445 participants were included in the Rotterdam study population.

The Study of Health In Pomerania

The Study of Health In Pomerania is a cross-sectional population-based study in West Pomerania, a region in the northeast of Germany. The total population of West Pomerania selected for SHIP comprised 212,157 inhabitants. A two-stage cluster sampling method adopted from the WHO MONICA Project Augsburg, Germany yielded 12, 5 years age strata (20–79 years) for both genders, each including 292 individuals [18]. The sampling was performed from population registries where all German citizens are registered. Data collection started in October 1997 and was finished in March 2001. The net sample comprised 6,267 eligible subjects. Finally, 4,310 subjects (69%) participated. The study was monitored by a board of independent scientists. All participants gave written informed consent. The study conformed to the principles of the Declaration of Helsinki as reflected by an a priori approval of the Ethics Committee of the University of Greifswald. Use of medication at baseline was recorded by a computer-aided method using the ATC code.

All male cohort members of SHIP ($n = 2{,}118$) with ECG, testosterone and DHEAS measurements at baseline were enrolled in the study population. Digitally stored ECGs were available for 1,826 male participants at the time of the first visit. Male participants with an ECG and with both a testosterone and a DHEAS measurement ($n = 1{,}677$) were included. Participants who received sexual hormones (ATC code G03) ($n = 3$), testosterone 5α reductase inhibitors (ATC code G04CB; $n = 4$) or sexual

hormone antagonists (ATC code L02B; $n = 3$) were excluded. None of the participants reported to receive anabolic steroids (ATC code A14A). Furthermore, participants who used digoxin ($n = 5$) or digitoxin ($n = 153$), QTc prolonging drugs ($n = 13$), persons with a pacemaker ($n = 15$), as well as persons with evidence of left ventricular hypertrophy ($n = 4$) or left ($n = 1$) and right bundle branch block ($n = 48$) were excluded. Overall, 1,428 participants were included in the SHIP study population.

QTc, QT and RR interval

The endpoints of the study were the lengths of the QTc, QT and RR intervals in ms. A 12-lead resting ECG was recorded with an ACTA electrocardiograph (ESAOTE, Florence, Italy) at a sampling frequency of 500 Hz and stored digitally. All ECGs (both from the Rotterdam study as well as SHIP) were centrally processed in Rotterdam using the modular ECG analysis system (MEANS) to obtain ECG measurements, in agreement with the FDA guidance for clinical evaluation of QT/QTc interval prolongation [19]. The MEANS program has been evaluated and validated extensively [20–23]. In one of these validation studies, ECGs with selected abnormalities were analyzed by five cardiologists and 11 different computer programs of which MEANS performed as one of the best [23]. In a study in which QT intervals by manual measurement were compared with QT measurement by ECG machines, manual and automated measurements generated similar numerical results in three studies in healthy volunteers, which all included a positive control [24]. MEANS determines common onsets and offsets for all 12 leads together on one representative averaged beat, with the use of template matching techniques [21]. The QT interval is determined from the start of the QRS complex until the end of the *T* wave. To adjust for heart rate, Bazett's formula ($QTc = QT/\sqrt{RR}$) was used [25]. The RR interval was taken as the median of the RR intervals in the recording. Additionally, the MEANS program determines left ventricular hypertrophy and left and right bundle branch block.

Steroids

Rotterdam study

At baseline, non-fasting blood samples were obtained. Time of sampling was recorded. Testosterone and DHEAS were estimated using coated tube or double antibody RIAs, respectively, purchased from diagnostic systems laboratories [26].

SHIP

At baseline, non-fasting blood samples were obtained. Time of sampling was recorded. Testosterone and DHEAS were measured using competitive chemiluminescent enzyme immunoassays on an Immulite 2500 analyzer (DPC Biermann GmbH, Bad Nauheim, Germany).

Covariates

Rotterdam study

Hypertension was identified through the use of antihypertensive medication and/or the assessment of blood pressure measurements, according to the guidelines of the World Health Organisation [27]. Prevalence and incidence of myocardial infarction were assessed as previously described [28, 29]. Diabetes mellitus was defined as the use of blood glucose–lowering medication and/or a non-fasting serum glucose level of 11.1 mmol/l or higher and/or fasting serum glucose levels $\geq$7 mmol/l [30]. Prevalence and incidence of heart failure were assessed by the presence of suggestive signs and symptoms as previously described [31, 32]. Potassium and calcium were measured by means of a Microlyte device. During the home interview, smoking status and use of alcohol were assessed. Creatinine clearance was computed with the Cockroft Gault method. Renal failure was defined by the internationally accepted criterion of a GFR below 60 ml/min [33]. Gamma-glutamyl transferase (GGT), aspartate-amino transferase (ASAT), alanine-amino transferase (ALAT) levels above the upper limit of normal were used to determine hepatic dysfunction.

SHIP

Hypertension was identified through the use of antihypertensive medication and/or the assessment of blood pressure measurements, according to the guidelines of the World Health Organisation [27]. Diabetes mellitus and myocardial infarction were defined as self-reported physician's diagnosis. Determination of calcium was performed by a colorimetric assay and potassium by ion-selective electrodes (Roche/Hitachi 717; Roche Diagnostics GmbH, Mannheim, Germany). During the home interview, smoking status and use of alcohol were assessed. Creatinine clearance was computed with the Cockroft Gault method. Renal failure was defined by the internationally accepted criterion of a GFR below 60 ml/min [33]. GGT, ALAT and ASAT were used to determine hepatic dysfunction.

Statistical analysis

The association between the QTc, QT, RR intervals and testosterone was assessed through linear regression with log-transformed testosterone and testosterone measurements divided in tertiles. Since DHEAS was associated with both the QTc and the RR interval, we adjusted all analyses for DHEAS. Furthermore, all analyses were adjusted for age, time of blood withdrawal (recorded in hours and minutes), hypertension, myocardial infarction, diabetes mellitus, potassium, calcium and in the Rotterdam study also for heart failure.

First, a linear regression analysis was conducted with QTc, QT (adjusted for the length of the RR interval) and RR interval as dependent and testosterone as independent variables for the Rotterdam study and SHIP separately. Second, we conducted a pooled analysis of the Rotterdam study and SHIP. Furthermore, we performed several sensitivity analyses: first, by stratification for age. Second, in additional analyses we adjusted for smoking, alcohol abuse, renal failure, hepatic failure and use of beta-blockers. All analyses were performed using SPSS for Windows version 15.0 (Chicago, Illinois, USA).

Results

Subject characteristics

The baseline characteristics of the participants are presented in Table 1. The mean age of the study population of the Rotterdam study was 68.0 years [standard deviation (SD) 7.8 years]. The mean testosterone level was 11.3 nmol/l (SD = 3.7). The mean age of the study population of SHIP was 49.1 years (SD 16.0 years). Mean testosterone levels were 17.0 nmol/l (SD = 5.9).

Androgens and QTc interval

The mean duration of the QTc interval was approximately similar in both studies, the mean duration of the QT and RR interval was slightly longer in the Rotterdam study than in SHIP (Table 1). Comparison of the highest testosterone tertile with the lowest tertile showed no significant association between testosterone and QTc [−5.9 ms (95% CI- 13.8; 2.1) and −2.9 ms (95% CI- 5.9; 0.1) respectively] nor with the QT interval [–2.4 ms (95% CI- 8.8; 4.0) and −0.6 ms (95%CI- 3.0; 1.8) respectively] in the Rotterdam study and SHIP separately (Table 2). The logarithmic transformation of testosterone was associated with the QTc interval in SHIP [−7.9 ms (95% CI- 15.3; −0.6)].

In SHIP, the RR interval increased gradually with increasing testosterone levels (*P* value for trend 0.004) and the second and third tertiles of testosterone had longer RR intervals compared to the first tertile [24.0 ms (95% CI 3.8; 44.1) and 31.3 ms (95% CI 10.3; 52.3) respectively]. The logarithmic transformation of testosterone was associated with the RR interval in both the Rotterdam study and SHIP [149.8 ms (95% CI 30.6; 269.1) and 55.9 ms (95% CI 5.2; 106.6) respectively].

Table 1 Baseline characteristics of study population

	Rotterdam study	SHIP
Number of participants	445	1,428
Age (years, mean, SD)	68.0 (7.8)	49.1 (16.0)
Mean QTc interval (ms; SD)	423.2 (25.0)	423.5 (24.4)
Mean QT interval (ms; SD)	398.2 (28.6)	394.1 (29.9)
Mean RR interval (ms; SD)	896.2 (156.7)	876.0 (156.2)
Body mass index (kg/m^2; SD)	26.6 (3.4)	27.7 (4.2)
Diabetes mellitus (n, %)	50 (11.2)	95 (6.7)
Myocardial infarction (n, %)	84 (18.9)	59 (4.1)
Hypertension (n, %)	111 (24.9)	594 (41.6)
Heart failure (n, %)	7 (1.6)	–
Mean potassium (mmol/l; SD)	4.1 (0.3)	4.1 (0.3)
Mean calcium (mmol/l; SD)	2.4 (0.1)	2.4 (0.1)
Mean DHEAS (μmol/l; SD)	4.3 (2.7)	5.3 (3.3)
Mean testosterone (nmol/l; SD)	11.3 (3.7)	17.0 (5.9)

SD standard deviation

DHEAS dehydroepiandrosterone sulfate

Pooled analysis

There was a gradual decrease of the QTc interval among the tertiles (*P* value for trend 0.024), while the third tertile of testosterone was significantly associated with the QTc interval compared to the first tertile [−3.4 ms (95% CI- 6.5; −0.3); Table 3]. Compared to the first tertile of testosterone, the third tertile was not associated with the QT interval [–0.7 ms (95% CI- 3.1; 1.8)].

There was a gradual increase of the RR interval among the tertiles (*P* value for trend 0.002), while the third tertile of testosterone was significantly associated with the RR interval compared to the first tertile [33.5 ms (95% CI 12.2; 54.8)]. Sensitivity analyses revealed no effect modification by age. Additional adjustment for smoking, alcohol, renal failure, hepatic failure or use of beta-blockers did not change the estimates.

Discussion

In this pooled analysis of two population-based studies, we found that serum testosterone levels were associated with shortening of the QTc interval and prolongation of the RR

Table 2 Association of testosterone with QTc, QT and RR interval

	Testosterone	QTc-interval in ms (95% CI)[a]	QT-interval in ms (95% CI)[b]	RR-interval in ms (95% CI)[a]
Rotterdam study ($n = 445$)	Log-transformation	−6.5 (−23.7; 10.8)	5.9 (−8.2; 20.1)	**149.8 (30.6; 269.1)**
	Tertiles			
	1	Reference	Reference	Reference
	2	3.8 (−4.1; 11.7)	5.5 (−0.8; 11.9)	29.2 (−27.3; 85.8)
	3	−5.9 (−13.8; 2.1)	−2.4 (−8.8; 4.0)	42.4 (−14.3; 99.2)
	P value for linear trend	0.132	0.419	0.143
SHIP ($n = 1,428$)	Log-transformation	**−7.9 (−15.3; −0.6)**	−3.4 (−9.2; 2.4)	**55.9 (5.2; 106.6)**
	Tertiles			
	1	Reference	Reference	Reference
	2	−0.7 (−3.6; 2.2)	1.5 (−0.8; 3.9)	**24.0 (3.8; 44.1)**
	3	−2.9 (−5.9; 0.1)	−0.6 (−3.0; 1.8)	**31.3 (10.3; 52.3)**
	P value for linear trend	0.061	0.623	**0.004**

CI confidence interval

[a] Adjusted for age, time of blood withdrawal, diabetes, hypertension, myocardial infarction, potassium, calcium, BMI, dehydroepiandrosterone sulfate (DHEAS) and in the Rotterdam Study also for heart failure

[b] Adjusted for age, time of blood withdrawal, diabetes, hypertension, myocardial infarction, potassium, calcium, BMI, DHEAS, RR interval and in the Rotterdam study also for heart failure

Testosterone in nmol/l. For the Rotterdam study the tertiles were defined as (1) ≤9.9; (2) 10.0–12.6; (3) ≥12.7. For SHIP the tertiles were defined as (1) ≤13.9; (2) 14.0–18.6; (3) ≥18.7

The bold values indicate significance at $P < 0.05$

Table 3 Association of testosterone with QTc, QT and interval: pooled analysis of the Rotterdam study and SHIP ($n = 1,873$)

Testosterone	QTc-interval in ms (95% CI)[a]	QT-interval in ms (95% CI)[b]	RR-interval in ms (95% CI)[a]
Log-transformation	**−8.1 (−14.8; −1.4)**	−3.1 (−8.4; 2.3)	**62.5 (15.7; 109.2)**
Tertiles			
1	Reference	Reference	Reference
2	−0.7 (−3.6; 2.1)	0.5 (−1.8; 2.8)	10.8 (−9.1; 30.8)
3	**−3.4 (−6.5; −0.3)**	−0.7 (−3.1; 1.8)	**33.5 (12.2; 54.8)**
P value for linear trend	**0.024**	0.529	**0.002**

CI confidence interval

[a] Adjusted for age, time of blood withdrawal, diabetes, hypertension, myocardial infarction, potassium, calcium, BMI, dehydroepiandrosterone sulfate (DHEAS) and cohort

[b] Adjusted for age, time of blood withdrawal, diabetes, hypertension, myocardial infarction, potassium, calcium, BMI, RR interval, DHEAS and cohort

Testosterone in nmol/l. The tertiles were defined as (1) ≤12.5; (2) 12.6–17.3; (3) ≥17.4

The bold values indicate significance at $P < 0.05$

interval in men, whereas we did not find an association between serum testosterone levels and the uncorrected QT interval, which could be due to a lack of power. Earlier, it has been suggested that the shorter QTc interval in men than in women may be explained by the fact that testosterone influences repolarization by its effect on Ca^{2+} and K^+ channels, as well as on hERG K^+ channels [34]. Since the QT interval was not significantly associated with serum testosterone, our findings could suggest that the difference in the QTc interval in men is mainly due to the underlying association with the RR interval. Since QTc is calculated by Bazett's formula, an increase in RR interval will lead to a shorter QTc interval. However, the QTc interval calculated by Bazett's formula is clinically relevant and is often used in epidemiological and clinical investigations. The QTc interval has been associated with an increased risk of all-cause mortality and sudden cardiac death [1, 2]. In addition, low testosterone levels are associated with an increased risk of all-cause mortality in men, [3] which is consistent with our findings of an increased QTc interval

and decreased RR interval in males with low testosterone levels. The use of testosterone supplementation is increasing, [4] in spite of limited knowledge on benefits and long-term safety and therefore it is important to know the effects of endogenous testosterone levels.

The gender differences in the QTc interval remain detectable until around the age of 50 years [10], this could be due to the fact that bio-available testosterone decreases with age [13]. In SHIP and the pooled analyses the direction of change was as expected for the QTc and RR-adjusted QT interval. In the Rotterdam study, however, the direction of change differed, which could be due to limited power. In addition, we did not find a significant association with the RR interval in the Rotterdam study, which could also be due to limited power. It is well known that women have a longer QTc interval than men, [2] whereas the uncorrected QT intervals are rather similar in men and women [10]. Since women have a faster heart rate, and therefore shorter RR intervals compared to men, women have a prolonged QTc interval when the same heart rate correction formula is applied. Recently it has been demonstrated in eleven hypogonadic men, that the difference in the heart-rate-independent QT interval duration is dependent on testosterone levels [35]. The gender differences in the RR interval remain after autonomic blockade, which suggests a possible gender-related difference in sino-atrial node function [36]. However, this difference appears to be related to a difference in maximum exercise capacity between men and women rather than to intrinsic sinus node gender-related differences [36]. Since androgen levels increase in response to exercise [37], the increased RR interval in men with high testosterone levels could be due to increased exercise capacity, which affects the sino-atrial node function.

Our investigation has several strengths that include the population-based design of participating studies and the central ECG data management, which facilitates best comparability between both studies. Although we did not use the complete population in the Rotterdam study, selection bias is unlikely because the characteristics of the study population were comparable to the baseline characteristics of the whole population of the Rotterdam study. Furthermore, information bias is unlikely because data were gathered prospectively and because the use of digital ECG recordings all measured using the automatic MEANS system likely reduced intra- and interobserver variability in the assessment of the QTc, QT and RR intervals. Confounding was minimized by adjusting for most known risk factors. However, our study has also some limitations. Because of the cross-sectional design we cannot exclude that QTc shortening or RR interval prolongation was already present in some participants before the decrease of testosterone. Several measurements within a person would be needed to assess intra-individual differences. Therefore, the results from this study should be confirmed with longitudinal data from other large cohorts. Another limitation of our study is that repeated blood sampling in men with initially low serum testosterone levels is recommended to confirm androgen deficiency [38], but this and other epidemiologic studies [39–42] were based on a single measurement of serum testosterone. In addition, two different methods were used to measure testosterone levels. However, as can be expected because of the higher average age, testosterone levels were somewhat lower in the Rotterdam study (Table 1), which is in agreement with the fact that testosterone levels decrease with age [5]. The results of the pooled analyses did not substantially change after adjustment for age. In addition, the direction of change of the QTc and RR interval were comparable and as expected (Table 2).

However, misclassification of men with low serum testosterone levels would be expected to underestimate, not overestimate associations.

Conclusion

We demonstrated in two population-based studies that serum testosterone is associated with shortening of the QTc interval and prolongation of the RR interval in men, whereas we did find a minor non-significant association between serum testosterone levels and the QT interval, possibly due to a lack of power. The fact that the strongest decrease was in the clinically relevant QTc interval in men is partly explained by the effect of RR-prolongation in the denominator of Bazett's formula for the QTc-interval.

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