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Increased prevalence of prolonged QT interval in males with primary or secondary hypogonadism: A pilot study

F. Pecori Giraldi,* P. M. Toja,* B. Filippini,* J. Michailidis,† M. Scacchi,* M. Stramba Badiale† and F. Cavagnini*

*Chair of Endocrinology, Istituto Auxologico Italiano, University of Milan, Ospedale San Luca IRCCS, Milan, Italy, and †Department of Rehabilitation Medicine, Ospedale San Luca IRCCS, Istituto Auxologico Italiano, Milan, Italy

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Correspondence:
Francesco Cavagnini, MD, Chair of Endocrinology, University of Milan, Ospedale San Luca, Istituto Auxologico Italiano IRCCS, Via Spagnoletto 3, 20149 Milan, Italy.
E-mail: cavagnini@auxologico.it

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Summary

Symptoms and signs of male hypogonadism span all organ systems, including the cardiovascular apparatus. The electrocardiographic QT interval reflects cardiac ventricular repolarization and, if prolonged, increases the risk of malignant arrhythmias. QT interval duration is similar in boys and girls during childhood, but shortens in males after puberty and experimental studies suggest that testosterone is a major contributor to shortening of QT interval in men. The aim of the present pilot study was to assess the duration of ventricular repolarization in adult males with primary or secondary hypogonadism. Standard ECG recordings were performed in 26 men (mean age 39.2 ± 2.17 years) with pituitary or testicular hypogonadism and repeated in 15 patients during testosterone replacement. Twenty-six age-matched control men were also analysed. Measured QT intervals were corrected for heart rate according to Bazzett's formula (QTc = QT/√RR interval). The prevalence of prolonged QTc was considerably higher in hypogonadal patients (four of 26 men) than in control men (none, $p < 0.05$) and in the general, healthy population (<2.5%). QTc interval normalized on hormone replacement therapy in the four patients presenting prolonged QTc in the hypogonadal state. Heart rate and left ventricular mass did not differ among the two groups and no known QT-prolonging factor was apparent in patients with abnormal QTc interval. In conclusion, a high number prolonged QT interval measurements was observed in hypogonadal men who may therefore be at increased risk for cardiac arrhythmias. This observation reveals an additional feature of male hypogonadism, which may benefit from testosterone replacement therapy.

Introduction

The prevalence of hypogonadism ranges from 0.15% for Klinefelter's syndrome (Bojesen *et al.*, 2003) to 6% in the middle-to-old age male population (Araujo *et al.*, 2004). Male hypogonadal patients present a variety of alterations, including osteoporosis, reduced lean body mass and increased fat mass, depression, asthenia and anaemia, increased autoimmune disorders, adverse lipid and glycaemic profile and greater atherosclerotic burden (Yesilova *et al.*, 2000; Vanderschueren *et al.*, 2004; Braga-Basaria *et al.*, 2006; Ferrucci *et al.*, 2006; Amiaz & Seidman, 2008). These features attest to the importance of appropriate testosterone secretion for a variety of organ systems, mainly the bone and the cardiovascular apparatus. Furthermore, androgen receptors in the heart muscle cells appear to play an important role in gender-dependent differences in heart function, in particular left ventricular size and electrical activity. It is well-known, in fact, that men present greater left ventricular mass than women (Hayward *et al.*, 2001) and shorter QT intervals, the latter an electrocardiographical measure of ventricular repolarization duration. Of note, QT interval is comparable between genders at birth (Stramba-Badiale *et al.*, 1995) and up to 10 years of age (Pham & Rosen, 2002; Surawicz & Parikh, 2002), then shortens by some 20 msec in young males at puberty (Rautaharju *et al.*, 1992; Pham & Rosen, 2002). The shorter QT interval protects men from devel-

oping malignant ventricular arrhythmias such as torsade de pointes which, indeed, occur more frequently in women (Abi-Gerges *et al.*, 2004). Testosterone is believed to play a major role in ECG changes occurring during puberty, as demonstrated both in humans and in animals (James *et al.*, 2007), but no study has so far evaluated cardiac repolarization in adult male hypogonadal patients. We therefore decided to perform a pilot, observational study to investigate whether men with primary or secondary hypogonadism present abnormal QT interval and whether testosterone replacement therapy modifies ventricular repolarization

Patients & methods

Study population

Our series comprises 26 male patients (age 39.2 ± 2.17 years, range 18–63 years) with primary or secondary hypogonadism (Table 1) and 26 age- and BMI-matched healthy eugonadal men. Diagnosis of hypogonadism was based on clinical assessment and biochemical findings (Bhasin *et al.*, 2006; Wang *et al.*, 2008) and, for patients with Klinefelter's syndrome, karyotype testing. Ten subjects were normalweight (BMI < 25 kg/m^2), seven were overweight (BMI 25–30 kg/m^2) and eight were obese (BMI 31–46 kg/m^2, see Table 1). No patient was affected by coronary or cardiac disease and two patients had diabetes (pts #5 and #24); in both cases, hypogonadism developed prior to diabetes. Patients were evaluated in the hypogonadal phase and 15 again while on adequate testosterone replacement therapy; all patients were on injectable esters except for pt #13 on transdermal patches. Table 1 shows duration of replacement therapy and testosterone levels achieved. Hormonal evaluation included measurement of plasma total testosterone, LH and FSH as well as other parameter of anterior pituitary hormone secretion. Patients were appropriately replaced for any additional hormone deficit prior to evaluation of QT interval. Clinical chemistry panel including serum electrolytes was performed in all patients. Medical history was reviewed for drugs known to prolong QT interval (The University of Arizona center for Education and Resarch on Therapeutics, 2008; De Ponti *et al.*, 2002) and the following drugs were identified: fluoxetine 20 mg/day, haloperidol 5 mg/day, glibenclamide 2.5 mg/day, each in one patient. Exclusion of patients on these drugs did not

Table 1 Features of male hypogonadal patients

Pt #	Aetiology	Other pituitary deficits	Age (yr)	BMI (kg/m^2)	At diagnosis			On RT
					TE	LH	FSH	TE (length)
1	Klinefelter's syndrome	–	63	32.9	0.59	23.4	87.6	10.3 (2 years)
2	Klinefelter's syndrome	–	20	22.6	8.00	21.2	59.7	14.5 (2 years)
3	Klinefelter's syndrome	–	33	29.9	1.61	24.8	22.3	27.0 (1 year)
4	Klinefelter's syndrome	–	46	29.0	4.06	14.8	29.6	–
5	Klinefelter's syndrome	–	37	41.8	2.78	10.2	35.0	–
6	Idiopathic hypopituitarism	None	54	46.3	1.03	0.1	0.4	–
7	Idiopathic hypopituitarism	None	18	33.3	0.82	0.1	0.3	–
8	Idiopathic hypopituitarism	None	26	24.1	1.41	0.1	0.4	23.9 (3 years)
9	Idiopathic hypopituitarism	None	48	24.9	0.91	0.1	0.2	–
10	Idiopathic hypopituitarism	GH	46	22.4	7.90	0.2	0.3	13.9 (5 years)
11	Idiopathic hypopituitarism	GH	33	24.7	0.73	0.2	0.3	25.3 (1 year)
12	Idiopathic hypopituitarism	GH, ACTH, TSH	46	21.6	0.24	0.1	0.1	19.3 (15 years)
13	Idiopathic hypopituitarism	GH, TSH, ADH	37	36.4	1.14	1.4	1.9	27.5 (3 years)
14	Idiopathic hypopituitarism	ACTH, TSH	37	25.8	0.35	0.2	0.1	–
15	Idiopathic hypopituitarism	ADH	49	25.4	1.46	1.5	5.0	14.1 (2 years)
16	Idiopathic hypopituitarism	ACTH, TSH	27	20.9	0.07	0.1	0.3	–
17	Idiopathic hypopituitarism	GH	36	40.4	4.55	1.9	0.9	–
18	Idiopathic hypopituitarism	ACTH, TSH, GH	52	29.2	7.67	5.5	3.7	24.2 (8 years)
19	Post-traumatic hypopituitarism	GH, ACTH	40	24.2	0.07	0.1	0.3	12.2 (8 years)
20	Post-surgical hypopituitarism (craniopharingioma)	GH, ACTH, TSH, ADH	28	26.0	7.45	2.7	1.2	19.8 (4 years)
21	Post-surgical hypopituitarism (craniopharingioma)	TSH	53	25.6	0.70	0.4	0.9	–
22	Post-surgical hypopituitarism (pituitary macroadenoma)	ACTH, TSH, GH	47	39.7	0.35	0.2	0.1	28.0 (7 years)
23	Post-surgical hypopituitarism (pituitary macroadenoma)	GH, ACTH	32	22.2	7.25	1.5	2.8	14.4 (4 years)
24	Post-surgical hypopituitarism (pituitary macroadenoma)	TSH	50	30.7	4.71	0.1	0.5	–
25	Post-surgical hypopituitarism (pituitary macroadenoma)	ACTH	57	28.0	6.03	1.6	1.8	–
26	Post-surgical hypopituitarism (epiphyseal neoplasia)	ACTH, ADH	29	22.4	7.29	1.3	1.4	26.8 (4 years)

TE, total testosterone (nM), LH (U/L), FSH (U/L); RT, testosterone replacement therapy; BMI, body mass index.

appear warranted as haloperidol is associated with an increased risk for torsade de pointes if administered intravenously at high doses, whereas both glibenclamide and fluoxetine fall into the group of 'drugs at conditional risk for QT prolongation', i.e. weakly associated with torsades de pointes and/or QT prolongation and unlikely to be a risk for torsades de pointes when used in usual recommended dosages and in patients without other risk factors such as concomitant QT prolonging drugs, bradycardia, electrolyte disturbances, concomitant drugs that inhibit metabolism (The University of Arizona center for Education and Resarch on Therapeutics, 2008). Medical history was negative for drugs or cardiac events in healthy controls. The study was approved by the Ethical Committee of our Institution.

Electrocardiogram

QT interval duration was measured by a single investigator who was blinded to the patient/control status. In detail, QT interval was measured from five non-consecutive beats on leads II, V5 and V6 of the conventional 12-lead electrocardiogram and corrected for heart rate (QTc) according to Bazzett's formula, i.e. the measured QT interval was divided by the square root of the preceding R-R interval. The mean of five measurements for each lead was calculated and the longest value was considered, as recommended (Schwartz *et al.*, 1993). The upper normal limit for QTc in men is 440 msec (Schwartz *et al.*, 1993). Left ventricular mass was established by gender-adjusted Cornell index and values greater than 2440 mm × msec were taken as indicative of left ventricular hypertrophy (Casale *et al.*, 1987; Mancia *et al.*, 2007).

Hormonal and biochemical evaluation

Total testosterone, LH and FSH were assayed by electrochemiluminescence (ECLIA, Roche Diagnostics, Monza, Italy). Intra- and interassay coefficients of variation were 1.4% and 2.2%, 0.8% and 2.0%, and 1.5% and 3.8% for the three hormones respectively. Clinical chemistry platform was used to determine serum electrolytes as well as routine clinical analyses (Hitachi 917; Roche Diagnostics, Monza, Italy). Normal values for total testosterone, LH and FSH in adult males are 9.9–27.8 nmol/L, 1.7-8.6 U/L and 1.5–12.4 U/L respectively.

Statistical analysis

Wilcoxon's test or Mann–Whitney's tests were used for comparison of continuous variables and chi-squared or Fisher's exact test, as appropriate, for qualitative data. Linear regression analysis was used to test for trends between variables. Statistical significance was accepted for $p < 0.05$ and power of statistics is 80% (Malik *et al.*, 2004). Data are described as mean ± SEM.

Results

Mean QTc values in hypogonadal men were comparable to those observed in healthy control subjects (398.3 ± 4.00 vs. 391.4 ± 5.55, NS), but analysis of individual values revealed an increased prevalence of prolonged QTc interval among hypogonadal patients. In fact, four hypogonadal males (pts #1, #13, #15 and #22; 16%) presented prolonged QTc interval, i.e. >440 msec (Fig. 1), whereas no abnormal value was observed among age-, BMI-matched controls ($p < 0.05$ vs. hypogonadal males), in agreement with the <2.5% prevalence of abnormal QTc in the general population (Schwartz *et al.*, 1993). Hypogonadal males were similar to controls as regards heart rate (66.3 ± 4.11 vs. 64.4 ± 3.80 beats/min, NS) and left ventricular mass (990 ± 84 vs. 843 ± 69 mm × msec, NS) and furthermore, no patient presented left ventricular hypertrophy or bradycardia. One of the four patients with prolonged QTc interval (pt #13) was on fluoxetine, a drug associated with low risk for QT prolongation and/or torsade de pointes (The University of Arizona center for Education and Resarch on Therapeutics, 2008; De Ponti *et al.*,

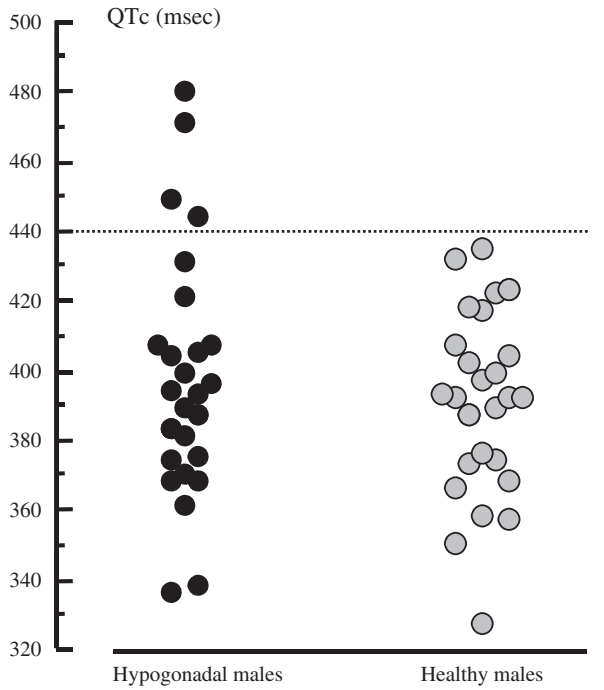

Figure 1 QTc interval in hypogonadal males and healthy age- and BMI-matched controls. Dashed line indicates upper normal limit for men.

2002), whereas no QT-prolonging drug was identified among treatments for the other three hypogonadal patients with prolonged QT. Aetiology of hypogonadism (see Table 1) varied in the four patients with prolonged QT, i.e. Klinefelter's syndrome, removal of pituitary macroadenoma and no identifiable pituitary-hypothalamic cause in two patients. As regards additional pituitary defects (see Table 1), no specific hypopituitaric profile associated with prolonged QT could be identified as GH, ACTH and TSH deficiency, as well as diabetes insipidus, were all variably represented. Eight hypogonadal patients were obese, i.e. BMI > 30 kg/m^2 and three presented prolonged QTc interval; comparison of QTc intervals in obese and non-obese hypogonadal patients nearly attained statistical significance (418 ± 15 vs. 389 ± 6 msec, respectively, $p = 0.06$). The two diabetic patients presented normal QTc measurements. No patient was hypokalemic and no correlation was detected between QTc and potassium levels ($r = 0.12$, NS). Calcium status was normal. Hypogonadal patients with prolonged QTc values showed somewhat lower total testosterone levels compared with their normal QTc counterparts (0.6 ± 0.18 vs. 3.2 ± 0.64 nM, $p = 0.09$), although regression analysis did not yield significant association between QTc and total testosterone concentrations ($r = -0.29$, NS).

Testosterone replacement therapy was associated with normalization (<440 msec) of prolonged QTc in the four patients with abnormal measurements in the hypogonadal state. QTc shortened on average by 66 ± 11 msec (range 38-92 msec) in these patients. Of note, pt #13 was still on fluoxetine 20 mg/day and furthermore, obesity persisted in the three obese patients (BMI on replacement therapy 34.4, 39.2 and 39.3 kg/m^2 in patients #1, #13 and #22, respectively) thus shortening of QTc occurred independently of these QT-prolonging factors. In the remaining hypogonadal patients, testosterone replacement was associated with small changes in QTc interval (on average shortening by 13 ± 8 msec, NS), all within the normal limits. Heart rate and left ventricular mass did not differ significantly before and during testosterone replacement therapy (62.7 ± 4.21 vs. 68.3 ± 3.91 beats/min and 924 ± 109 vs. 1024 ± 167 mm × msec, NS respectively).

Discussion

Gender is well-known to influence cardiac repolarization. In women, repolarization lasts longer and proceeds slower compared with men and, indeed, surface ECG reveals longer QT interval and lower T-wave amplitude in adult women of all ages compared with men (Bidoggia *et al.*, 2000). Moreover, the difference in QT interval between men and women is greater at long cardiac cycle lengths (Genovesi *et al.*, 2007). Gender-related differences in QTc interval and T-wave amplitude are not present at birth (Stramba-Badiale *et al.*, 1995) and during childhood, but appear during teenage years (Pham & Rosen, 2002; Surawicz & Parikh, 2002), suggesting that the secretion of sex hormones at puberty contributes to the appearance of gender-dependent differences in cardiac repolarization. In fact, longitudinal assessment of QT interval is independent of reproductive status in women whereas, in men, QT intervals shortens by some 20 msec at puberty (Rautaharju *et al.*, 1992; Surawicz & Parikh, 2002). This evidence led to the concept that testosterone could be the main determinant of gender-related differences in QT interval and, indeed, several experimental studies support this contention (James *et al.*, 2007). Testosterone administration shortens cardiac action potentials in oophorectomized rabbits (Hara *et al.*, 1998) as well as QT interval and drug-induced QT prolongation in ovariectomized bitches and orchiectomized rabbits (Liu *et al.*, 2003; Fülöp *et al.*, 2006). Along the same line, women with excess androgen secretion present shorter and faster repolarization (Bidoggia *et al.*, 2000; Vrtovec *et al.*, 2008). On the other hand, castration prolongs QT intervals in male dogs (Fülöp *et al.*, 2006). Similar findings were observed in humans, with castrated men presenting longer and slower early repolarization – measured by JT interval – compared with normal men (Bidoggia *et al.*, 2000) and hypogonadal males presenting altered T-wave morphology and duration (Kirilmaz *et al.*, 2003).

The current study was carried out to assess whether hypogonadism is associated with prolonged QT interval and, indeed, we observed prolonged QT interval in a significant proportion (16%) of adult male hypogonadal patients. Given that <3 of 100 healthy controls present prolonged QT interval (Schwartz *et al.*, 1993), the clustering of abnormal QT measurements in this series of hypogonadal patients is striking. Of note, epidemiological surveys on abnormal QTc values usually rely more on differences in the prevalence of prolonged values than in mean QTc measurements (Schwartz *et al.*, 1998; Benoit *et al.*, 2005). Furthermore, QTc normalized during testosterone replacement therapy in patients with abnormal values in the hypogonadal state, thereby strengthening the causal relationship. Indeed, normalization of QT measurement upon correction or removal of factors suspected of prolonging QT interval represents a convincing criterion for causality (Al-Khatib *et al.*, 2003; Elming *et al.*, 2003; Roden, 2004).

Analysis of factors other than hypogonadism which could contribute to the increased prevalence of prolonged QT in our series of male hypogonadal patients failed to reveal possible offenders. Obesity is associated with QT prolongation (Fraley *et al.*, 2005) and three out of four hypogonadal patients with prolonged QTc were obese.

However, shortening of prolonged QT occurred on replacement therapy while these patients were still similarly obese, thus excess weight is unlikely to be the primary determinant of abnormal QT measurements in these subjects. It is worth recalling that obesity per se is associated with hypogonadism (Seftel, 2006) and the relationship between obesity, hypgonadism and prolonged QT is likely to be extremely complex. Other known risk factors for QT prolongation, for example left ventricular hypertrophy, bradycardia, hypokalemia (Moss, 2003), were absent in our series and only one patient with prolonged QT was on a low-risk QT-prolonging drug, i.e. fluoxetine (De Ponti *et al.*, 2002; Roden, 2004). However, QTc normalized on testosterone replacement while the patient continued fluoxetine treatment and thus this drug is unlikely to have been a major contributor. Finally, our data do not suggest an involvement of other pituitary hormone deficits as additional defects appeared casually distributed among hypogonadal patients with prolonged QT interval and furthermore, patients were appropriately replaced prior to QTc measurement.

Prolonged QT interval reflects cardiac electrical instability and is a predictor for torsade de pointes, i.e. ventricular arrhythmias associated with syncope and sudden death (Ward, 1988). Men are usually less exposed than women to this risk, in keeping with their shorter QTc interval (Bidoggia *et al.*, 2000). Other factors which generally modulate QT interval are heart rate, autonomic regulation and age with bradycardia and older age associated with lengthening of ventricular repolarization (Moss, 2003). Abnormal QT prolongation can be inherited (e.g. mutations in genes that modulate cardiac repolarization) or acquired in conditions such as cardiac disease, electrolyte derangements (e.g. hypokalemia, hypocalcemia), renal (Genovesi *et al.*, 2008) or hepatic insufficiency (Genovesi *et al.*, 2009). QT prolongation may also be iatrogenic as cardiac and non-cardiac drugs are known to prolong QT interval (De Ponti *et al.*, 2002; Roden, 2004). All the abovementioned factors increase the risk for severe and even fatal ventricular arrhythmias and caution has therefore to be exercised when one or more concur in the same patient; indeed, there is a considerable body of literature underlining the need for assessment of QT prolongation even outside specialized cardiologic centres (Al-Khatib *et al.*, 2003; Elming *et al.*, 2003). As regards endocrine diseases, prolonged QT has been reported in hypothyroid as well as in hyperthyroid patients (Fazio *et al.*, 1992; Colzani *et al.*, 2001), acromegaly (Fatti *et al.*, 2006) and hypoparathyroidism (Mangat *et al.*, 2008), but none of these conditions occurred in our series. Our study indicates that QT prolongation may occur also in male hypogonadism and that these patients may therefore be at increased risk for development of torsade de pointes. Interestingly, a recent epidemiological survey in patients with Klinefelter's syndrome showed an increased cardiovascular mortality from valve and thromboembolic disease as well as from other cardiac events (Swerdlow *et al.*, 2005), the latter quite possibly, although speculative, ventricular arrhythmias. Our patient population comprised patients with structural pituitary or testicular impairment of testosterone secretion, certainly a small minority compared with the increasing proportion of apparently healthy hypogonadal middle-to-advanced age males (Araujo *et al.*, 2004). Our pilot study is clearly observational and whether reduced testosterone secretion is associated with prolonged QT interval in the latter population appears worth investigating.

Adequate testosterone replacement therapy reversed the prolonged QT interval in our four hypogonadal patients as well relieve other signs/symptoms of hypogonadism (Snyder *et al.*, 2000; Vanderschueren *et al.*, 2004; Amiaz & Seidman, 2008), and provides an additional rationale for continuous testosterone replacement therapy. Lifelong testosterone replacement requires considerable patient compliance and is often difficult to achieve (Snyder *et al.*, 2000), but seems worth enforcing in patients with prolonged QT interval.

In conclusion, male hypogonadism is associated with an increased prevalence of prolonged QT interval and hence, risk for fatal ventricular arrhythmias. QT interval measurement should be included in the evaluation of hypogonadal men and may provide an additional rationale for testosterone replacement therapy.

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