QT Interval Length in Elderly Prostatic Cancer Patients on Anti-Testosterone Treatment

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ABSTRACT: **Background:** QT segment prolongation is a high risk factor for fatal arrhythmias. Several studies have indicated a possible relation between low testosterone levels and QT interval prolongation.

Objectives: To compare the QT interval length in elderly patients with prostate carcinoma who were on anti-testosterone treatment and those who were not.

Methods: We screened the electrocardiograms (ECGs) of 100 prostate cancer patients divided into two groups: 50 patients on anti-testosterone drug treatment and 50 patients not. QT interval length was measured according to the accepted methods.

Results: The mean QTc 12 leads in the entire group was 0.45 ± 0.04 sec, which is close to the upper limit. Mean QTc was actually longer in the control group and there was no QTc difference between the groups after adjustment for possible confounders. Prolonged QTc 12-lead ECG (48% in treated and 54% in non-treated) and lead L2 QT interval (50% in treated and 56% in non-treated) did not differ significantly between the groups. The analysis of QTc 12-lead ECG indicated no significant effects of anti-testosterone drug treatment. Only the use of furosemide was associated with QT prolongation.

Conclusions: The results of this preliminary study do not support our initial concern of an alarmingly prolonged QT interval in the anti-testosterone treated group. However, further prospectively designed studies are needed. In the meanwhile we call for a close follow-up of the QT interval length in patients receiving anti-testosterone treatment.

IMAJ 2015; 17: 356–359

KEY WORDS: QT interval length, anti-testosterone treatment, prostate cancer, elderly

of repolarization. Beat-to-beat QT interval variability is also a measure of repolarization liability and a predictor of sudden death [2]. Various clinical factors, including drugs, are associated with prolongation of the QT segment. In fact, the most common reason for withdrawing or restricting medications is prolongation of the QT interval [3]. Other reported risk factors for prolonged QT are female gender [4], hypokalemia [5] and congestive heart failure (CHF) [6]. With aging, there is a progressive prolongation of the QT interval, which is associated with a concomitant increase in mortality [7]. Polypharmacy, including drugs potentially causing torsade de pointes, is common in the elderly [8]. Therefore, close attention and prevention of QT prolongation in this age group is of major importance.

In our two previous studies [9,10] we screened acute geriatric patients as well as elderly residents in long-term care wards and found a surprisingly high incidence of prolonged QTc: 29% in acute and 27% in long-term care groups. An additional unexpected finding was an association of prolonged QTc interval with males in both studies. A search through recent publications revealed a relation between testosterone and cardiac repolarization, suggesting an inverse association between testosterone levels and the QT interval [11,12]. It is assumed that testosterone is an important regulator of gender-related differences in ventricular repolarization [11]. In the study by PecoryGiraldi et al. [13], the prevalence of prolonged QTc interval was considerably higher in hypogonadal patients than in a control group of men.

Prostate cancer, the most common oncologic condition in males, is prevalent among male geriatric patients and is also the sixth most common cause of cancer death among them [14]. Testosterone suppression therapy is used in cases of advanced prostate cancer, increasing survival [15].

All these data raise the concern of a possible clinical association between the QT segment length and prostate cancer in elderly men on anti-testosterone therapy, which prompted this preliminary survey. We wished to assess the prevalence and the associated conditions of QT interval prolongation in elderly patients with prostatic carcinoma on anti-testosterone treatment, as compared to a control group of prostate cancer subjects not on anti-testosterone treatment.

The QT interval reflects the total duration of ventricular myocardial repolarization. QT prolongation is associated with polymorphic ventricular tachycardia such as torsade de pointes, which can be fatal [1]. The QT interval duration exhibits a certain degree of variability between the electrocardiogram (ECG) leads, which may reflect heterogeneity in the recovery

PATIENTS AND METHODS

This retrospective cross-sectional study is based on the medical records of Shmuel Harofe Geriatric Medical Center. This university-affiliated hospital with 400 beds consists of nine wards, divided into acute, rehabilitation and long-term care geriatric wards. At admission every patient undergoes an ECG and complete blood analysis as routine evaluation. The files of all hospitalized patients were screened according to the following inclusion criteria: all patients with prostate cancer during the 6 year period 2007–2012 whose levels of calcium, potassium and magnesium were within normal range. Excluded were patients with pacemakers, bundle branch block, or atrial fibrillation. Applying these criteria, we identified two groups of 50 subjects each: those on anti-testosterone drug treatment and those not.

The standard 12-lead ECG in the patient's file was used for the QT interval evaluation. All measurements were done by two physicians. The RR and QT intervals were measured in 12 leads using a graduated lens. The QT interval was measured from the beginning of the QRS complex to the end of the down slope of the T wave. The QT interval corrected for the previous cardiac cycle length (QTc) was calculated according to Bazzet's formula: $QTc = QT/RR1/2$ [16]. Prolonged QTc was considered as $QTc \geq 0.45$ [17, 18].

The mean QT in each lead was calculated using the mean of two consecutive complexes. Two methods of measurement were performed for the evaluation of QTc prolongation: the mean of 12 leads and the QTc of lead 2 (L2) [17].

This study and the data analysis protocol were approved by the hospital's Ethics Committee.

STATISTICAL ANALYSIS

Associations of clinical and laboratory data with anti-testosterone treatment were performed using t-tests and chi-square tests. The associations between anti-testosterone treatment and QTc were performed using t-tests. Bivariate associations were followed by an adjusted analysis using Type III analysis of variance (ANOVA) to test for the effects of possible confounders. A significance level of $\alpha = 0.05$ was applied for all tests. SPSS (Statistical Package for Social Sciences, 20th version) for Windows (IBM Corporation, New York) was used to analyze the data.

RESULTS

The relevant demographic and clinical data of the patients are presented in Tables 1 and 2. The average age was 82.2 years (range 62–96, SD ± 7.0), with no significant difference between groups ($P = 0.35$).

Mean QTc of the 12-lead ECG in patients treated with anti-testosterone was 0.44 ± 0.04 sec compared to 0.46 ± 0.04 ($t = 2.4$, df = 98, $P = 0.02$) in the control group. Similarly, based on lead L2 we observed QTc of 0.45 ± 0.04 sec in the treated group

Table 1. Clinical data of 100 patients the study and control group

	Control group (n=50) (%)	Study group (n=50) (%)	P value
Relevant diseases			
Hypertension	70	56	0.15
Ischemic heart disease	38	40	0.84
Anemia	34	28	0.52
Diabetes mellitus	32	28	0.66
Chronic renal failure	30	26	0.66
Cerebrovascular accident	30	24	0.50
Congestive heart failure	28	10	0.02*
Relevant drugs			
Laxatives	26	48	0.023*
Furosemide	46	26	0.037*
Beta-blockers	50	52	0.084
ACE inhibitors	34	26	0.38
Benzodiazepines	22	30	0.36

*$P < 0.05$
ACE = angiotensin-converting enzyme

Table 2. Electrolyte levels of patients in study and control groups

Electrolyte levels (Mean ± SD)	Study group (n=50)	Control group (n=50)	P value
Calcium (mg/dl) (normal range 8.6–10.2)	8.9 ± 0.77	8.8 ± 1.15	0.47
Potassium (mEq/L) (normal range 3.5–5.3)	4.3 ± 0.5	4.2 ± 0.6	0.41
Magnesium (mg/dl) (normal range 1.8–3.5)	2.2 ± 0.4	2.0 ± 0.1	0.4 0

Table 3. QTc interval in the study group (n=50) and control (n=50) groups

Test	Study group		Control group		t, P
	Mean	SD	Mean	SD	
QTc 12 leads	0.44	0.04	0.46	0.04	2.2, 0.02*
QTc L2	0.45	0.04	0.46	0.04	2.1, 0.03*

*$P < 0.05$

compared to 0.46 ± 0.04 in the non-treated ($t = 2.19$, df = 98, $P = 0.03$) [Table 3]. The mean QTc 12-lead ECG of the entire group was 0.45 ± 0.04 sec. Prolonged QTc 12-lead ECG was found in 48% of those treated and 54% of those not. Based on lead L2, the rate of prolonged QT interval was 50% in the treated and 56% in the non-treated (no difference between groups). Age was not associated with either QTc mean or QTc prolongation.

We found that 26% of the study group and 46% of the control group used furosemide ($P = 0.037$) [Table 1], and 26% in the study group were on laxative treatment compared to 65% in the control group ($P = 0.023$). In addition, congestive heart failure (CHF) was associated with the use of anti-testosterone drugs, found in 10% of the patients in the study group compared to 28% in the control group ($P = 0.02$).

Of the clinical parameters only the use of furosemide was associated with anti-testosterone treatment and QTc. The

adjusted analysis of QTc 12-lead ECG with furosemide as a possible confounder did not indicate any significant effect of anti-testosterone treatment ($F = 1.8$, df = 1, 96, $P = 0.18$). Similarly, the analysis of lead L2 did not indicate a significant effect of anti-testosterone ($F = 2.4$, df = 1, 96, $P = 0.12$).

DISCUSSION

The main finding of this study was that contrary to our initial concern our data are not indicative of an alarming QT interval prolongation in prostate cancer patients taking anti-testosterone drugs. However, this does not ensure that this condition will not develop, and more specific research on this subject is required.

Our findings indicate a high incidence (about 50%) of QTc length at the high limit in both groups of patients with prostate cancer. This rate is even higher than in our two previously published studies (29% and 27% respectively). However, a clinical prolongation of more than 0.5 sec was detected in only 14% of all the subjects with no difference between the groups.

Patients with prostate cancer are treated for many years with periodic anti-testosterone drugs. This therapy is successful and contributes substantially to the fact that most of these elderly patients do not die because of this disease. Therefore, we should be completely knowledgeable about all its possible side effects, and if a certain risk is to be assumed it should be as closely monitored as for basic clinical signs (fever, blood pressure, pulse, pain management), prostate-specific antigen (PSA), and other laboratory parameters.

It is now well accepted that testosterone levels in men decline at a rate of about 1% per year after the age of 30. Thus, 40–70% of men older than 70 are likely to have testosterone levels that would be defined as hypogonadal in younger men [19,20]. There is a paucity of data on testosterone levels in elderly men in nursing homes, with one study characterizing levels of testosterone as very low [21] and another defining 88% of male residents in nursing homes as being hypogonadal [22].

Reports of an association between low testosterone and prolonged QT interval [11,12] prompted us to compare these two groups. That we did not find a significant difference, as presumed, could be related to several factors other than the effect of anti-testosterone treatment. One is congestive heart failure, a known clinical risk for prolonged QTc interval [6]. There were more patients with CHF in the control group than in the study group ($P = 0.02$). Another factor was the high prevalence of patients on furosemide treatment in the study group. According to Darpo [23], furosemide is one of the 20 drugs most commonly reported in association with fatal arrhythmias.

Another important aspect, particularly in prostate cancer patients on periodic anti-testosterone treatment (usually administered once in 3 months), is related to the level of blood testosterone. We assume that in the past, patients after castra-tion were acutely depleted of this hormone; however, current anti-testosterone drugs act as blockers and, being periodically administered, may have a different impact on the QT segment at different points in time. In this respect we refer to the study by Saglam et al. [24] of 63 prostate cancer patients with complete androgen blockade achieved by either surgical or medical castration. The authors state that although statistical analyses showed marked similarities between the groups in terms of QT, PR and QRS, after 3 months the hormonal levels in the surgical group were significantly different. These earlier significant changes in the surgical group may have been due to an acute drop in testosterone level. In contrast to such acute onset of low testosterone level, our patients are on repeated cycles of anti-testosterone treatment, which could explain the lack of a significant prolongation of QTc in these patients. Thus, the question arises whether during those 3 months after administration of the anti-testosterone drug there could be periods of higher vulnerability with respect to the QT segment prolongation risk. This and other questions should be explored in a larger prospective study.

The main limitation of our study is its retrospective nature and lack of data on the testosterone blood level of the participants. For a better understanding of this serious medical problem a prospective study is warranted during several therapeutic cycles and obviously with a larger number of subjects.

In the meantime we should be aware of this problem and minimize any risk factors that might endanger the life of prostate cancer patients during the years of anti-testosterone treatment. Recently, Haugaa and colleagues from the Mayo Clinic [25] reported their positive experience with a pro-active institutional QT length monitoring alert system whenever it reaches 0.5 sec. The article by Haugaa et al. [25] emphasizes the importance of QT interval monitoring and presents an efficient method to cope with it.

We conclude that more attention should be accorded to this threatening condition in elderly patients either in geriatric and oncologic settings or in general hospital wards. Their QT interval should be periodically recorded and watched closely, as is done for other vital signs.

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