Gender Differences in the ST Segment
– Effect of Androgen-Deprivation Therapy and Possible Role of Testosterone –

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**Background:** ST-segment elevation in a structurally normal heart is observed in Brugada- and early repolarization syndrome. The incidence of both syndromes is much higher in males than females. Clinical and basic studies suggest that testosterone plays an important role in ventricular repolarization.

**Methods and Results:** Standard surface 12-lead electrocardiograms recorded in 640 healthy subjects were studied (310 males, 330 females ranging in age from 5 to 89 years) (Study 1). The 3 ST levels (ST-J, -M, and -E) were measured in leads V2 and V5, which are representative of the right and left ventricles, respectively. The effect of androgen-deprivation therapy on the ST segment was also evaluated in 21 prostate cancer patients (Study 2). In both leads, the 3 ST levels were significantly higher in adult males than females (P<0.0001) due to a marked increase after puberty in males. As their age increased, males manifested a gradual reduction in the ST level in both leads; in females, there was a reduction in lead V5 only. In both sexes, all 3 ST levels were significantly higher in lead V2 than V5 (P<0.0001). Androgen-deprivation therapy significantly decreased all 3 ST segments in both leads.

**Conclusions:** Significant age- and gender differences in the ST segment in healthy adults were found, suggesting that testosterone modulates the early phase of ventricular repolarization. *(Circ J 2010; 74: 2448–2454)*

**Key Words:** Gender difference; ST level; ST segment; Testosterone

Gender differences in the incidence of various types of ventricular arrhythmias have been reported. Torsades de pointes associated with long QT syndrome is more common in females than males.1,2 The higher incidence of Brugada syndrome in males than females3,4 is associated with gender differences in the early phase of ventricular repolarization, that is, the greater transient outward potassium current (Ito)-mediated phase 1 notch in the right ventricular epicardium in males than females.5 Early repolarization syndrome is characterized by a prominent J wave and by ST-segment elevation in the left precordial leads; it is most commonly seen in young males.7 Although the mechanisms underlying early repolarization syndrome remain unknown, it has been suggested to share notable cellular and ionic similarities with Brugada syndrome.7–10

Studies on gender-related repolarization differences have focused on the duration of repolarization, such as the longer QT11,12 and JT intervals13 in females than in males. While these sex differences in ventricular repolarization are not observed before, they become obvious after puberty, suggesting an important effect of sex hormone. In contrast, gender differences have been reported in the configuration of the ST segment in healthy subjects.14 Previous studies showed that after puberty, the J point amplitude is higher and the ST segment angle is steeper in males.15,16 However, little is currently known about age- and gender-related differences in the ST levels in the different leads that represent the right and left ventricles.

Androgen-deprivation therapy,16,17 a neoadjuvant treatment for prostate cancer, might strongly inhibit the hormonal modulation of not only prostate cells but also of cardiac ventricular myocytes. Although this therapy is associated with increased risks of cardiovascular death in patients with prostate cancer,18,19 its effects on ventricular repolarization including the ST segment remain to be elucidated.

We studied healthy subjects to identify age- and gender differences in the ST segments in leads V2 and V5, which are

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Methods

Study Population and ECG Recordings

Our study involved 2 different subject groups and protocols. Study 1 evaluated gender- and age differences in the ST segment of healthy subjects. Study 2 was designed to assess the effect of androgen-deprivation therapy on the ST segment in prostate cancer patients.

Study 1

From among 5,274 consecutive resting ECGs recorded at our hospital at screening studies performed between July 2005 and February 2006, 2 experienced cardiologists first selected subjects with normal resting ECGs determined with an automatic digital ECG analysis program (ECAPS12C; Nihon Kohden Inc, Tokyo, Japan). Individuals with a history of cardiovascular or pulmonary disease, hypertension, diabetes mellitus, or receiving medications known to affect ECG readings were excluded and only subjects with normal serum electrolytes were included. Consequently, ECGs obtained from 640 subjects (310 males, 330 females ranging in age from 5 to 89 years) were analyzed. With the subject resting in the supine position, standard 12-lead surface digital ECGs were recorded using Cardiofax (Nihon Kohden Inc, Tokyo, Japan) connected to a personal computer. Various ECG parameters were automatically measured in each ECG using a commercially available program (ECAPS12C; Nihon Kohden). We selected leads V2 and V5 to analyze the repolarization parameters because they reflect the electrical potential from the right ventricular outflow tract and the left ventricular free wall, respectively.

Study 2

To investigate the effect of androgen-deprivation therapy on ECG parameters of ventricular repolarization, we studied 21 prostate cancer patients diagnosed in the urology department of our hospital between February 2004 and June 2007. Their age ranged from 50 to 80 years (mean 68.0±7.6 years). At the start of the study, 13 received medical treatment for hypertension, 4 for type 2 diabetes, 13 for hyperlipidemia, and 1 was treated for ischemic heart disease. Their condition was stable and their medications did not change during the period covered by this study. We excluded patients with atrial fibrillation, frequent atrial or ventricular arrhythmias, clinical evidence of heart- or renal failure, and those with a history of myocardial infarction or cerebrovascular disease. No patients included in the study received drugs known to affect the ECG parameters such as anti-arrhythmic drugs.

All patients were treated with androgen-deprivation therapy for 1–14 months before a radical prostatectomy. Therapy consisted of neoadjuvant treatment comprised of a gonadotropin-releasing hormone agonist (leuprolinel acetate, 30μg/kg per 4 weeks or goserelin acetate, 3.6mg/4 weeks by hypodermic injection) and/or an anti-androgen drug (bicalutamide, 80mg/day). Of the 21 prostate cancer patients, 19 received both gonadotropin-releasing hormone and an anti-androgen drug. The other 2 were treated with either gonadotropin-releasing hormone or an anti-androgen drug.

Standard 12-lead surface ECGs were recorded pre-prostatectomy both before and after androgen-deprivation therapy and the recordings were compared in each patient. We used averaged parameter values from Study 1 patients (90 males and 97 females) in their 6th and 7th decade of life as the age-matched control values. The median interval between the 2 ECG recordings was 207 days (range 42–1,000 days). The patients’ baseline characteristics including body weight, body mass index (weight/height^2 (kg/m^2)), and plasma concentration of electrolytes (K, Na, Cl) at the time of the 1st and 2nd ECG study were compared to avoid the possibility that these parameters had an effect on ECG changes.

Definition of ECG Variables

ECG variables in the ST segment were pre-selected to record the characteristics shown in Figure 1. These were: (1) the J point level (ST-J) recorded at the end of the QRS complex as measured in μV with respect to the baseline; (2) the middle of the ST level (ST-M), that is, the level at 1/16th of the preceding RR interval of the following ST segment with respect to the baseline; and (3) the end of the ST level (ST-E), that is, the level at 2/16th of the preceding RR interval of the following ST segment with respect to the baseline. The amplitude of the T-wave was defined as the absolute distance from the apex of the T-wave to the baseline. The rate-corrected QT interval (QTc) was calculated using the method of Fridericia (QTc=QT/RR^{1/2}).
Statistical Analysis

Data are presented as the mean±SE. We used 2-way analysis of variance (ANOVA) followed by the Bonferroni post-hoc and unpaired t-test to evaluate gender- and age differences for each parameter. A Student’s t-test for paired observations was used to analyze changes produced by androgen-deprivation therapy. A P value of <0.05 was considered to be statistically significant.

Results

Age and Gender Differences in the ST Level

Both the subjects’ age and gender had a significant effect on the 3 ST levels (ST-J, -M, and E) in lead V5 (P<0.0001). In contrast, while gender also had a significant effect on the 3 ST-levels in lead V2 (P<0.0001), age had a significant effect only in males (P<0.0001).

As shown in Figure 2, in pre-pubescent subjects of both sexes (aged from 5 to 12 years), the ST-J, -M, and -E levels in leads V2 and V5 were not significantly different. However, males and females manifested different patterns of age-related changes in the ST levels; in 15–19 and 20–29-year-old males, they increased significantly and progressively and then decreased gradually with increasing age in both leads.

In females, the pattern of age-related changes in the ST levels differed between leads V2 and V5. In lead V2, the ST levels remained almost constant in all age groups. In contrast, in lead V5, they gradually decreased with age after the 15th year of life; however, we did not observe the abrupt increase seen in males after age 15. Consequently, in both leads, the ST levels were significantly higher in males older than 15 years than in females of a corresponding age.

Comparisons showed that in subjects of both sexes, all 3 ST levels were significantly higher in lead V2 than in lead V5 (P<0.0001). The gender difference in all ST levels was significantly more pronounced in lead V2 than in lead V5 (P<0.0001).

Age and Gender Differences in Other ECG Parameters

Table 1 shows age- and gender differences in the heart rate (HR), and the PR, QRS, QT, and QTc intervals. The QRS interval was significantly shorter in females than males of all age groups. While there were no significant gender differences in the PR- and QT interval, the QTc interval was significantly longer in females than males after puberty.

The T-wave amplitude was significantly higher in males than females in both leads (Figure 3). Especially in lead V2, the gender difference in the T-wave amplitude was significantly more pronounced after puberty.

Effect of Androgen-Deprivation Therapy

Figure 4 summarizes the ST levels before and after androgen-deprivation therapy and shows these levels in age-matched male and female Study 1 controls. Before deprivation therapy, there were no significant differences in the 3 ST levels between control males and patients scheduled for prostatectomy. Androgen-deprivation therapy produced a significant decrease in all 3 ST levels in both leads. With the exception of ST-J and -M in lead V2, after deprivation therapy, the ST levels were significantly lower in prostate cancer patients than in male controls. In addition, the post-deprivation therapy ST levels were not significantly different from those recorded in the female controls, except for ST-J in lead V2.

Figure 5 shows representative ECG recordings obtained before and after androgen-deprivation therapy in a 50-year-old male with prostate cancer. On the baseline ECG, the ST
Testosterone and ECG ST Segment

levels in the precordial leads were markedly elevated and a diagnosis of early repolarization syndrome was made. After therapy, the ST levels decreased. In our prostate cancer patients, there were no significant changes in the baseline characteristics, except for the red blood cell count and hemoglobin level after androgen-deprivation therapy (Table 2).

Discussion

Age and Gender Differences in the ST Levels

We found that 3 different ST levels, ST-J, ST-M, and ST-E, exhibited a similar pattern of age- and gender-related changes in each lead (Figure 2). In pre-pubescent subjects (5–12 years of age), there were no significant gender differences in all 3 ST levels in both leads V2 and V5. These levels increased significantly after puberty in males; they peaked in both leads in males between 20 and 29 years of age and then decreased after the 3rd decade of life.

In females, the age-related changes in the ST levels were different in leads V2 and V5. In lead V5, all 3 ST levels decreased with increasing age and the abrupt changes noted around puberty in males were not observed. Consequently, in lead V5, the ST levels after puberty were significantly higher in males than in females. In contrast, irrespective of age, in
Figure 4. Effect of androgen-deprivation therapy on the ST levels. ST-J (A), -M (B), and -E (C) of lead V2 and ST-J (D), -M (E), and -E (F) of lead V5 are presented for age-matched male and female controls, and before and after androgen-deprivation therapy. Data are the mean±SE. *P<0.05, **P<0.001.

Figure 5. Representative 12-lead ECG recordings obtained before and after androgen-deprivation therapy in a 50 year-old patient with prostate cancer. On the baseline ECG, the ST levels in the precordial leads were markedly elevated resulting in a diagnosis of early repolarization syndrome. The ST levels decreased after therapy.
lead V2, the ST levels remained low and almost constant in females. Therefore, after puberty, the ST levels in V2 were also significantly higher in males than in females, suggesting that the effect of sex hormones might be smaller in females than in males, especially in lead V2.

Our findings suggest the important role that the male hormone testosterone plays in the observed sex differences in the ST segment. The plasma testosterone concentration increases around puberty, peaks at 20–30 years of age, and decreases gradually due to the physiologic effects of aging in both males and females. In contrast, our findings suggest that the female sex hormone, which also increases around puberty, has little effect on the ST levels because they did not change in pubescent females.

**Effect of Androgen Deprivation Therapy and Role of Testosterone on the ST Segment**

We examined the effect of androgen-deprivation therapy on the ST segment to clarify the role of testosterone. Deprivation therapy was comprised of neoadjuvant treatment for prostate cancer with a gonadotropin-releasing hormone agonist or an anti-androgen drug. Androgens are derived from the adrenal cortex, testes, and ovary. The administration of a gonadotropin-releasing hormone agonist renders the plasma testosterone level almost undetectable. Androgen receptors have been identified in the atria and ventricles, whereas estrogen receptors appear to be largely confined to atrial myocytes. As anti-androgen drugs block androgen receptors in cardiac ventricular myocytes, androgen-deprivation therapy by either a gonadotropin-releasing hormone agonist or an anti-androgen drug strongly inhibits the hormonal modulation of ventricular repolarization. We found that androgen-deprivation therapy significantly lowered all 3 ST levels in both leads and that they closely resembled the ST levels in age-matched control females. These results together with our findings on gender- and age differences suggest that the ST segment is modulated by testosterone.

Earlier studies focused on ST segment changes resulting from low plasma testosterone levels induced by castration or hypogonadism. Compared to healthy males, the J point amplitude was significantly lower in males with secondary hypogonadotropic hypogonadism and in castrated males. In prostate cancer patients with asymptomatic Brugada syndrome, the typical coved-type ST-segment elevation disappeared after orchietomy. Our current findings confirm these earlier results. Interestingly, males with Brugada syndrome manifested significantly higher testosterone levels than control males, and males with Brugada-like ECG results were at an increased risk for prostate cancer. Our findings of a prominent ST elevation in males after puberty and of the lower ST level after androgen-deprivation therapy in lead V2 might support a significant association between Brugada syndrome and hypogonadism.

**Mechanisms Underlying ST Segment Elevation and Gender Differences**

It has been suggested that the more prominent Jv-mediated spike-and-dome action potential morphology in the ventricular epicardium than the endocardium creates a transmural voltage gradient during early repolarization, such as in phase 1 and 2. This gradient has been proposed as the cellular basis for the J point and ST-segment characteristics. Even in normal subjects, there is a small degree of heterogeneity in transmural repolarization that accounts for a minimal ST-segment elevation. In addition, Is density in the epicardium is higher in males than females, resulting in the greater phase 1 notch and a higher transmural voltage gradient during phase 2. This gradient produces the subsequent higher J point and ST levels in males than in females.

In dogs, the phase 1 notch is much larger in the right than in the left ventricular epicardium, therefore, the transmural voltage gradient is greater in the right than in the left ventricle in these animals. Furthermore, the Is-mediated phase 1 notch in the right but not the left ventricular epicardium was larger in male- than in female dogs. We found that in humans of both sexes, the ST levels were significantly higher in the right- (V2) than in the left precordial lead (V5), and that gender differences in the ST levels were significantly greater in lead V2 than V5. These findings are consistent with previous animal experiments. Although the mechanisms underlying these findings are remain unclear, the gender-related differences in the density and distribution of various ion channels including Is in both ventricles might contribute to this phenomenon.

Individuals with a structurally normal heart manifested Brugada syndrome, idiopathic ventricular fibrillation, and early repolarization syndrome; these manifestations were characterized by J-wave- and ST-segment elevation in the right precordial (V1–3), inferior (II, III, aVf), and left precordial leads (V4–6), respectively. Clinically, Brugada- and early repolarization syndrome share many similarities, including a young age at onset and a male preponderance. These 2 syndromes differ with respect to the localization of ST elevation and their prognosis. Brugada syndrome is associated with a high incidence of ventricular fibrillation while early repolarization syndrome has been thought to be benign, although some exceptions have been reported. One of the possible mechanisms underlying these differences might be a prominent interventricular difference in Is density, that is, it might be larger in the right than the left ventricular epicardium. The differences between the ST levels in leads V2 and V5 we observed in our normal subjects might in part explain the clinical differences between the 2 syndromes.

**Study Limitations**

In Study 2, we did not measure the serum testosterone concentration because our investigation was retrospective.

**Table 2. Changes in Baseline Clinical Characteristics in Study 2**

<table>
<thead>
<tr>
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<th>Before therapy</th>
<th>After therapy</th>
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<tbody>
<tr>
<td>Body weight (kg)</td>
<td>62.8±7.7</td>
<td>65.2±6.7</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>23.3±2.1</td>
<td>24.1±2.2</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>68.0±3.3</td>
<td>69.6±2.6</td>
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<tr>
<td>Systolic BP (mmHg)</td>
<td>126.3±3.9</td>
<td>124.6±4.1</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77.2±2.2</td>
<td>75.7±2.3</td>
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<tr>
<td>Red blood cells (×10¹²/l)</td>
<td>456.8±8.7</td>
<td>421.0±9.7</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.46±0.30</td>
<td>13.42±0.34*</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>15.87±0.85</td>
<td>16.78±0.96</td>
</tr>
<tr>
<td>Creatinin (mg/dl)</td>
<td>0.786±0.043</td>
<td>0.781±0.030</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>4.23±0.28</td>
<td>4.25±0.31</td>
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<tr>
<td>Na (mEq/L)</td>
<td>141.9±2.3</td>
<td>140.7±3.0</td>
</tr>
<tr>
<td>CI (mEq/L)</td>
<td>104.5±2.4</td>
<td>103.9±3.3</td>
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</table>

The subjects were 21 patients with prostate cancer. Data are expressed as mean ± SE. BMI, body mass index; HR, heart rate; BP, blood pressure; BUN, blood urea nitrogen. *P<0.001 vs before therapy.
However, it has been established that plasma testosterone becomes almost undetectable after the administration of a gonadotropin-releasing hormone agonist. Androgen-deprivation therapy increases visceral fat and is associated with an increased risk of diabetes and cardiovascular disease. However, in our study population, the body-mass index, calculated as a parameter of visceral fat, and other physiological and biochemical data did not change significantly after this therapy. Androgen-deprivation therapy usually induces mild anemia, as observed in this study, which has little effect on the ST levels.

Clinical Implications and Contribution

Our findings suggest that the difference in the ST levels between adult males and females is associated with testosterone, which might modulate early ventricular repolarization. The ST elevation observed in young males might contribute to the male predominance among individuals with Brugada and early repolarization syndrome. In addition, the difference in the ST levels in leads V2 and V5 might partly explain the clinical differences between the 2 syndromes. Further studies are needed to evaluate different mechanisms underlying ST elevation in healthy subjects and patients with other pathological conditions.

References