Comparison of Electrocardiographic Repolarization Patterns between Hypogonad Males and Normal Subjects

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Background: There is a significant difference in repolarization on the surface ECG between men and women. The effect of testosterone on repolarization of myocardium may provide a basis for the physiological and pathophysiological importance of these distinctions between sexes. The purpose of this study is to compare the repolarization characteristics of surface ECG in patients with secondary hypogonadotropic hypogonadism to those of healthy men and women.

Methods: The study consisted of 45 consecutive patients with the diagnosis of secondary hypogonadotropic hypogonadism (study group) and age-, weight- and height-matched normal healthy men (n = 35) and women (n = 39) (control group). 12-lead ECG recordings were obtained and electronic calipers were used for measurements of ECG repolarization variables. ECG variables were compared with those of control groups.

Results: J point amplitude (0.12 ± 0.07 vs 0.05 ± 0.05 mV, respectively), T max (0.74 ± 0.28 vs 0.60 ± 0.27 mV, respectively), T wave area (81 ± 36 vs 60 ± 29 mVms, respectively) and T wave descending time (93 ± 16 vs 85 ± 15 ms, respectively) were significantly higher in healthy subjects than hypogonadal men. In comparison with those of healthy women, hypogonad males have higher J point (0.05 ± 0.05 vs 0.02 ± 0.02 mV), taller T wave (0.60 ± 0.27 vs 0.34 ± 0.13 mV), consequently less T wave area (60 ± 29 vs 34 ± 16 mVms), ascending (62 ± 18 vs 53 ± 11) and descending angle (67 ± 17 vs 55 ± 12). Corrected QT was not different among groups.

Conclusions: Testosterone deprivation in hypogonadotropic hypogonadism attenuates J point, T wave peak, T wave area, and T wave descending time, but does not reach to the level of those in healthy women. Testosterone has no effect on QT interval in this group of age. Hormone replacement therapy of these patients will provide informative contribution.

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There is a significant difference particularly in repolarization on the surface ECG between men and women. Understanding the effects of sex hormones on repolarization of myocardium may provide a basis for the physiological and pathophysiological importance of these distinctions between sexes. Because testosterone replacement therapy in men with hypotestosteronemia has been offered to prevent or ameliorate age-related osteoporosis, sarcopenia, and the abdominal obesity/glucose intolerance/hyperlipidemia syndrome (syndrome X), a complete understanding of the early and late effects of testosterone on electrocardiographic coun-

terparts of myocardial repolarization is needed.^{1–6} The purpose of this study is to compare the repolarization characteristics of surface ECG in patients with secondary hypogonadotropic hypogonadism to those of healthy men and women.

METHODS

Study Population

ECG analysis of cardiac repolarization was performed in a study population of 45 consecutive patients with a diagnosis of secondary

hypogonadotropic hypogonadism (study group) and age-, weight- and height-matched normal healthy men and women (control group, men/women, $n = 35/39$). The diagnosis of hypogonadotropic hypogonadism was based on physical examination, serum concentrations of sex hormones (total testosterone, free testosterone, sex-hormone binding globulin, follicle stimulating hormone, and luteinizing hormone) and stimulation tests when necessary.

After a supine rest period of 10 minutes, baseline 12-lead ECG recordings were obtained at standard amplification ($1 \text{ mV} = 10 \text{ mm}$) and at a recording rate of 25 mm/s using a HP Pagewriter XLi ECG recorder (Hewlett-Packard, Andover, MA) on the same day when a blood sample was drawn for sex hormone analysis. Analog outputs were then scanned in high resolution and electronic calipers were used for measurements with a sensitivity of 0.1 mm (corresponding to 4 ms or 0.01 mV) and

an angle of 0.1 degrees. Two different investigators, who were blinded to the cases, analyzed all the ECG recordings. The precordial lead with the greatest amplitude of T wave was selected and all of the measurements were calculated from this particular lead. For each ECG recording, if a difference greater than 10% in any of the variables measured by both investigators was found, the patient was not included. If the difference was less than 10% , both measurements were averaged. In the presence of discrepancy between investigators in selecting the lead, a third investigator's decision was accepted as final.

Definition of ECG Variables

The following ECG variables were selected for analysis as illustrated and explained in Figure 1. J point, T wave amplitude, T wave ascending limb

Figure 1. The definitions of electrocardiographic measurements in one of the normal men. V4 was selected for this particular case. J point: Amplitude of J point in respect to baseline (in mV). T wave amplitude (T max): T wave amplitude measured at peak of the T wave (in mV). T asc ° (The angle of the ascending limb of the T wave): The angle between the baseline and the line from the onset to the peak of the T wave to the baseline. T desc ° (Angle of the descending limb of the T wave): The angle formed by the baseline and the line from the peak to the offset of T wave to the baseline. T asc time/T desc time: The duration of the ascending and the descending limb of T wave measured from the onset/offset of the T wave to the T max, respectively. T wave ascending and descending area was derived from the duration of the corresponding time and peak T wave amplitude by the formulas of $(T_{asc} \text{ time} \times T_{max})/2$ and $(T_{desc} \text{ time} \times T_{max})/2$, respectively. The offset and the onset of the T wave were defined by the intersection of the line between the peak of the T wave and the baseline.

angle, T wave descending limb angle, the duration of the ascending and descending limb of T wave, and T wave area. The variables in duration were expressed either as their absolute values or corrected for heart rate (expressed in $\text{ms}^{1/2}$) according to Bazett's formula.

Hormone Analysis

Ten milliliters of blood was collected in plain tubes. The serum obtained was then stored at -80°C for a maximum of 2 weeks. Total testosterone, Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) were assessed by immunochemiluminometric assay (ICMA) method using ADVIA Centaur (Bayer Corporation, Tarrytown, NY). Sex hormone binding globulin was assessed by IMMULITE 1000 (DPC-Diagnostic Products Corporation, Los Angeles, CA) by ICMA method. A commercially available diagnostic kit (Diagnostic System Laboratories, TX) was used to access free testosterone by radioimmunoassay.

Statistical Analysis

Values of selected variables were summarized by standard descriptive statistics and expressed as mean $\pm$ SD. Independent-samples *t*-test (Mann-Whitney U test when the Levene test is significant) was used to compare continuous variables among groups. Statistical significance was defined by a *P* value < 0.05 .

RESULTS

Table 1 summarizes hormonal and physical characteristics of the hypogonad males. Total and free testosterone levels were under the normal limits, as well as FSH and LH. Physical characteristics of the patients were also typical for hypogonadism.

The precordial leads V3 and V4 were the most selected leads (35 cases) followed by V2, V5, and V6 (6, 3, 1 cases, respectively) in hypogonad males and were not different among groups. Cardiac repolarization patterns in hypogonad men markedly differed from those in healthy subjects. Figure 2 depicts the characteristic ECGs of the groups. Table 2 summarizes the comparison of the electrocardiographic parameters among groups.

Comparison between Hypogonad Males and Healthy men

The most striking difference was the higher J point in normal men than hypogonad males. Addi-

Table 1. Hormonal and Physical Characteristics of Hypogonad Patients

Hormonal and Physical Characteristics	Hypogonad Males (n = 45)
TT (ng/dL)	71 $\pm$ 92
FT (pg/mL)	2.6 $\pm$ 3.1
SHBG (nmol/L)	37 $\pm$ 21
FSH (mIU/mL)	0.6 $\pm$ 0.9
LH (mIU/mL)	0.5 $\pm$ 0.6
Bell/Hip (cm)	78 $\pm$ 9/92 $\pm$ 7
Vertex-Pubis/Pubis-Heel (cm)	82 $\pm$ 6/92 $\pm$ 7
Arm expand/height (cm)	177 $\pm$ 11/173 $\pm$ 9

FSH: Follicle Stimulating Hormone, FT: Free testosterone, LH: Luteinizing hormone, SHBG: Sex hormone binding globulin, TT: Total testosterone.

Normal ranges for hormones: TT (241–827 ng/dL), FT (9–55 pg/mL), SHBG (13–71 nmol/L), FSH (1.4–18 mIU/mL), LH (1.5–9.3 mIU/mL).

tionally, T wave was lower in amplitude in hypogonadal patients. The area under the T wave and the T wave ascending and descending times were also higher in normal subjects. This significance was still valid when the values in ms was corrected for heart rate according to Bazett's formula. However, T wave ascending and descending arm angles were not different between groups. Interestingly, there was no difference between groups in mean QT and corrected QT (QTc) intervals.

Comparison between Hypogonad Males and Healthy Women

The most striking difference was the higher T wave amplitude in hypogonad males than healthy

Figure 2. The representative example of the precordial leads in a hypogonad male (A), a healthy man (B) and a woman (C).

Table 2. Comparison of the Electrocardiographic Parameters Among Groups

Parameters	Hypogonad Males (n = 45)	Healthy Men (n = 35)	Healthy Women (n = 39)
Age (year)	21 ± 1	21 ± 2	21 ± 1
Height (cm)	174 ± 7	173 ± 7	170 ± 6
Weight (kg)	66 ± 9	68 ± 10	65 ± 8
Heart rate (bpm)	73 ± 13	77 ± 21	73 ± 12
QRS duration (ms)	92 ± 8	90 ± 8	88 ± 15
QT (ms)	368 ± 33	363 ± 29	379 ± 27
QTc (ms)	403 ± 36	408 ± 25	416 ± 40
J point (mV)	0.05 ± 0.05	0.12 ± 0.07 ^a	0.02 ± 0.02 ^{ab}
T asc °	60 ± 22	65 ± 10	53 ± 11 ^a
T asc time (ms)	111 ± 21	124 ± 20 ^a	113 ± 26 ^b
T desc °	65 ± 23	70 ± 9	55 ± 12 ^{ab}
T desc time (ms)	85 ± 15	93 ± 16 ^a	82 ± 18
T max (mV)	0.60 ± 0.27	0.74 ± 0.28 ^a	0.34 ± 0.13 ^{ab}
T wave area (mVms)	60 ± 29	81 ± 36 ^a	34 ± 16 ^{ab}

bpm: beats per minute, ms: millisecond, mV: milivolt, NS: Not significant, QT: QT interval, QTc: Corrected QT interval according to Bazett's formula.

^a P value < 0.05 vs hypogonad males. ^b P value < 0.05 vs healthy males.

women. Since the peak of T wave is lower, decreased ascending and descending limb angle and the T wave area were remarkable in healthy women. QTc interval was not different between groups.

DISCUSSION

J point and T wave amplitude has been shown in previous studies as a striking difference in ECG parameters not only between healthy men and women but also between castrated and virilized counterparts.^{7,8} Deprivation of testosterone in the setting of secondary hypogonadotropic hypogonadism clearly attenuates the J point and the T wave peak in our study. However, this attenuation does not reach to those levels measured in healthy women. This finding supports the finding that testosterone is not solely responsible for the higher J point and T wave amplitude in healthy men when compared to those of healthy women.

Yan and Anzelevitch⁹ have proposed that a more prominent transient outward current- (I_{to}) mediated spike-and-dome action-potential morphology in the ventricular epicardium than in the endocardium creates a transmural voltage gradient, which corresponds to electrocardiographic J wave. This gradient has been proposed as the cellular basis for the J point and ST-segment characteristics. Considering this possibility and in conjunction with

recent experimental data regarding sex differences in both I_{to} and IK_1 in isolated rabbit myocytes,¹⁰ androgens may have an affect on I_{to} channels creating more prominent J wave and increase the ventricular dispersion of repolarization between epicardial and endocardial myocardium.

We selected the precordial lead having the greater amplitude of the T wave. This methodology was supported by other investigators giving the fact that sex repolarization differences are usually seen in orthogonal Z lead which corresponds to leads V1 through V4.

Since there is no difference in QT and QTc interval between groups in this study, we might speculate that total or free testosterone has no affect on repolarization time at least in that particular age group. Additionally, considering the taller T wave amplitude, J point and more T wave area in healthy subjects, we may suggest that testosterone has increased dispersion of repolarization transmurally. A recent study by Pham et al.¹¹ demonstrates that testosterone shortens baseline Action Potential Duration₉₀ (APD₉₀) at CL = 1000 ms in rabbit heart. However, it may be misleading when this finding is translated into human heart. Female rabbit ventricles have 20% less IK_r density than males, thus contributing to a shorter baseline APD when treated with testosterone. At faster heart rates, APDs were found to be equivalent in normal and testosterone-treated rabbits.

Our study demonstrates that deprivation of testosterone has no significant effect on QT interval and may not be responsible for prolonged QT interval in women. Although, this result should emphasize the possible role of female hormones responsible for longer QT interval in women, QTc interval was not different between hypogonad males and women. In a recent study by Surawicz and Parikh,¹² the difference between QTc interval in men and women did not reach a significant level before the age of 17–24 years. Similarly, QTc interval before puberty is indistinguishable between boys and girls.¹³ Conversely, Merri et al.,¹⁴ found significantly prolonged QTc in women when compared to men in their original study designed to improve the description of ventricular repolarization on the digitized electrocardiograms. However, our group of healthy women represents height- and weight-selected cases in a narrow range of age (21 ± 1). This bias as well as difference in race may be responsible for similar QTc interval among groups.

Significantly longer T wave ascending time may be secondary to higher J point in healthy subjects in this study. A higher J point causes the ascending limb of the T wave less steep and increase the prematurity of the onset of the T wave ascending limb, thus causing longer T wave ascending time and T wave ascending area. The longer T wave descending time and T wave area in healthy men might reflect selective effect of testosterone in prolonging repolarization at different level of myocardium (endocardial-epicardial). Although, this is inconsistent with the fact that men have shorter QT intervals than women, it was determined that testosterone produced a 35% reduction in Health Economics Research Group (HERG) current and may indeed prolong APD.¹⁵

Androgen receptors are reported to be present in some cell types within the myocardium and can modulate to produce hypertrophy by direct, receptor-specific mechanisms.^{16–18} Since an echocardiographic comparison is lacking, we do not know whether the cardiac mass itself has an effect on these electrocardiographic differences between groups in this study. Nevertheless, we tried to minimize the effect of body weight and height by selecting a matched control group.

In conclusion, testosterone increases the J point and T wave amplitude at physiologic levels, although near total absence is not enough to provide female type of repolarization. The effect of

hormone replacement therapy on ECG in these patients will provide complimentary insights.

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