Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 62, No. 17, 2013
ISSN 0735-1097/$36.00

CORRESPONDENCE

Research Correspondence

Relationship Between Testosterone Level and Early Repolarization on 12-Lead Electrocardiograms in Men

To the Editor: An inferolateral early repolarization (ER) electrocardiographic (ECG) pattern has been associated with an increased risk of sudden cardiac death (1–4). A strong male predominance in the prevalence of an ER ECG pattern has been observed, with a higher prevalence in young men (5). The aim of this study was to test the hypothesis that testosterone level is associated with an ER ECG pattern.

We analyzed electrocardiograms from 6,306 subjects in the Health 2000 study. The mean age of the study subjects was 53 ± 15 years. We excluded all subjects with bundle branch blocks from the analysis (n = 144). We also excluded all females (n = 3,407) due to the expected low testosterone levels. We included 2,755 men in our study.

The ECG analysis of digital electrocardiograms was performed manually using custom software for a prior joint analysis in the Framingham study population (5). An electrocardiogram was defined as having an ER ECG pattern if there was J-point elevation of ≥0.1 mV in ≥2 leads in the inferior (II, II, aVF) or lateral (I, aVL, V_{4-6}) territory or both. Morphology of the ST-segment related to the ER ECG pattern J-point elevation was assessed 100 ms after the J-point; it was determined to be rapidly ascending when the ST-segment amplitude was >0.1 mV and horizontal/descending when the amplitude was ≤0.1 mV (4).

After ECG analysis for all 2,755 male subjects in the study (mean age, 51 ± 14 years), serum testosterone levels were determined with an Architect ci8200 analyzer using chemiluminescent microparticle immunoassay (Abbott Laboratories, Abbott Park, Illinois).

Statistical analysis was performed using IBM SPSS 19 software (IBM, Armonk, New York). All prevalence data are presented as percentages and continuous variables as mean ± SD. The association between testosterone level and categorical variables (i.e., ER subgroups) was tested with the Student *t* test. The threshold for significance was set at $p < 0.05$.

The prevalence of an ER ECG pattern was 3.0%, with 0.7% in the inferior leads, 1.9% in the lateral leads, and 0.4% in both. A rapidly ascending ST-segment after the ER ECG pattern J-point elevation was seen in 52%, and 48% had horizontal/descending ST-segment morphology.

Testosterone levels were significantly higher in men with an ER ECG pattern in the inferior and/or lateral leads (17.81 ± 6.24 nmol/l) compared with those without ER (15.73 ± 6.10 nmol/l; $p < 0.001$). There was a "dose effect" between testosterone level and the prevalence of an ER ECG pattern because the prevalence increased almost 2-fold between the first and second tertiles of testosterone and also between the second and third tertiles (Fig. 1). Men with an ER ECG pattern in both the inferior and lateral leads had the highest testosterone levels (20.01 ± 6.90 nmol/l; p = 0.001) compared with those without an ER ECG pattern. On the other hand, testosterone levels were not significantly higher on separate analysis of inferior ER (17.6 ± 5.7 nmol/l; p = 0.076) but were significantly higher in the lateral ER group (17.4 ± 6.2 nmol/l; p= 0.015).

Testosterone levels were significantly higher among men with an ER ECG pattern with a rapidly ascending ST-segment when compared with men without (18.14 ± 6.80 nmol/l vs. 15.73 ± 6.10 nmol/l, respectively; p = 0.001). Subsequently, in men with an inferior or lateral ER ECG pattern with a horizontal/descending ST-segment (17.39 ± 5.44 nmol/l), the association with testosterone level was somewhat weaker yet significant (p = 0.035).

Our main finding was that testosterone levels were significantly higher among men with an ER ECG pattern than in those without ER. Higher prevalence of an ER ECG pattern in young adults and decreasing prevalence in middle-aged and elderly men have been described (3), which can be explained by gradually descending testosterone levels with age. Testosterone levels also explain the male predominance in the prevalence of an ER ECG pattern.

Testosterone levels were most closely associated with the lateral and the rapidly ascending ST-segment after J-point elevation. Both the lateral ER ECG pattern and an ER ECG with an ascending ST-segment have been suggested to be benign variants of the ER ECG pattern that occurs frequently in male athletes. The weaker, albeit significant, relationship between testosterone level and ER ECG pattern with a horizontal/downsloping ST-segment suggests that the more "malignant" type of ER ECG

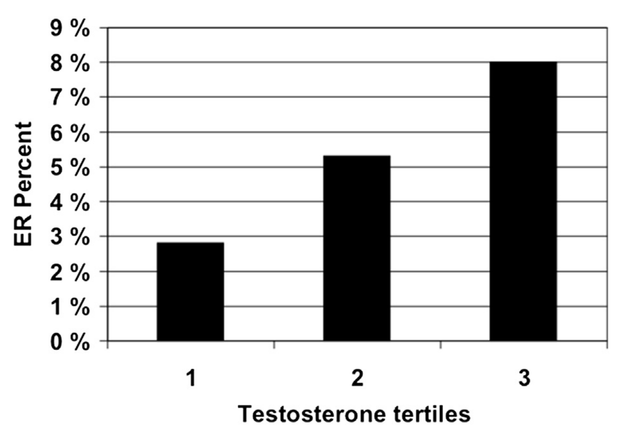

Figure 1 **Prevalence of Early Repolarization ECG Pattern by Testosterone Tertile**

1 is the lowest, 2 the middle, and 3 the highest testosterone tertile, and the bars show the prevalence of an inferolateral ER ECG pattern in the respective tertile. A clear "dose effect" of testosterone can be seen in the prevalence of an inferolateral ER ECG pattern. ECG = electrocardiographic; ER = early repolarization.

JACC Vol. 62, No. 17, 2013
October 22, 2013:1633–7

pattern may not be as strongly influenced by a hormonal effect on channel function.

A genome-wide association study recently suggested an intriguing associated locus near the *KCND3* (Kv4.3) gene, which encodes a subunit of the Ito channel (5). The association was not significant genome-wide, and it did not replicate in other study populations.

Nevertheless, the biological plausibility of Ito channel involvement in ER ECG formation seems to be more than a coincidence. Future studies in this field should perhaps focus on finding genetic variants of the ER ECG pattern followed by a horizontal/downsloping ST-segment, which could highlight better the genetic background of the ER syndrome.

The presence of an inferolateral ER ECG is affected by testosterone level, which probably explains the male predominance and the decline with aging of this ECG pattern. Furthermore, the ER ECG pattern with a rapidly ascending ST-segment seems to be the pattern most closely associated with testosterone level.

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http://dx.doi.org/10.1016/j.jacc.2013.07.015

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Please note: This study was supported by grants from the Finnish Foundation for Cardiovascular Research, Aarne Koskelo Foundation, Finnish Medical Foundation, Orion-Farmos Research Foundation, and the Sigrid Juselius Foundation. The authors have reported that they have no relationships relevant to the content of this paper to disclose.

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Letters to the Editor

Higher N-Terminal Pro–B-Type Natriuretic Peptide May Be Related to Very Different Conditions

We read the paper by Hijazi et al. (1) with interest. The authors investigated the incremental value of measuring N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels in addition to established risk factors (including the CHA_2DS_2VASc [heart failure, hypertension, age 75 years and older, diabetes, and previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (female sex, respectively)] score) for the prediction of cardiovascular and bleeding events. They concluded that NT-proBNP levels are often elevated in atrial fibrillation (AF) and independently associated with an increased risk for stroke and mortality. NT-proBNP improves risk stratification beyond the CHA_2DS_2VASc score and might be a novel tool for improved stroke prediction in AF. The efficacy of apixaban compared with warfarin was independent of the NT-proBNP level.

Although most widely used as a marker of systolic heart failure, elevated NT-proBNP has been reported in patients with diastolic dysfunction (2). Therefore, it is important to determine diastolic and systolic function by echocardiography. Performing echocardiography also is important for measurement of pulmonary artery pressure. Pulmonary arterial hypertension is common with rheumatic diseases, and NT-proBNP levels may be a result of the increase in pulmonary pressure (3). On the other hand, high levels of NT-proBNP can be seen in many conditions that increase cardiac output and cardiac stress, such as sepsis, cirrhosis, and hyperthyroidism (4). That is why determination of liver test results and thyroid hormone profile may reveal stronger results in such a study.

NT-proBNP is an important prognostic factor for cardiovascular diseases; however, besides cardiac diseases, elevated NT-proBNP levels may be seen in several diseases. A prominent disease with elevated NT-proBNP is a respiratory system disease, such as chronic obstructive pulmonary disease, pulmonary embolism, and interstitial lung disease, in which B-type natriuretic peptide levels are elevated in response to the pressure of the right side of the heart (5). In addition, cor pulmonale, secondary pulmonary hypertension, or hypoxemia may represent important stimuli for the release of NT-proBNP from the right side of the heart. Given that hypoxemia alone is a risk factor for the development of AF, respiratory system disorders should not be ignored in such a study.

Furthermore, Hijazi et al. (1) used the Cockcroft-Gault (CG) equation to determine the glomerular filtration rate (GFR). However, the CG equation may measure a lower GFR in younger age groups, and GFR can be higher in older individuals. Although the Chronic Kidney Disease Epidemiology Collaboration recently published an equation for GFR using the same variables (serum creatinine level, age, sex, and race) as the CG equation, the Chronic Kidney Disease Epidemiology Collaboration equation more accurately categorized individuals with respect to long-term clinical risk compared with the CG equation (6).