The Difference of Heart Rate Recovery between Males with and without Erectile Dysfunction

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Aim: In this study, we aimed to investigate the relationship between heart rate recovery (HRR) time and Chronotropic Index (CHIND) parameters, which also reflect autonomic function, after exercise stress test (EST) in males with or without erectile dysfunction (ED), and we investigated the relationship between HRR and CHIND and serum steroid hormone levels.

Material and Methods: A total of 135 participants (mean age: 45.0 ± 11.8 years) were enrolled into the study. Detailed biochemical and hormonal analyses, 12-lead electrocardiography and EST (Treadmill) were performed in all participants. Erectile function was assessed using the International Index of Erectile Function (IIEF) questionnaire form. Patients were categorized into two groups according to their IIEF scores as ED (+) (IIEF < 26) and ED (−) (IIEF $\geq$ 26). Afterward, statistical analyses were performed to evaluate the correlations between ED and HRR and CHIND.

Results: A total of 65 patients were ED (+) (mean age 44.9 ± 6.4 years), while 70 patients (mean age 43.7 ± 7.7 years) had normal erectile status. There were statistically significant differences in CHIND ($P = 0.015$) and HRR time ($P = 0.037$) between ED (+) and ED (−) patients. In correlation analysis, IIEF score was found positively correlated with HRR and metabolic equivalent (MET) values ($r_{\text{HRR}} = 0.293$, $P = 0.037$; $r_{\text{METs}} = 0.388$, $P = 0.011$, respectively). Linear regression analysis revealed that METs value and total exercise time had a more linear relationship with IIEF score compared to the other EST parameters ($p_{\text{METs}} = 0.002$ and $p_{\text{TET}} = 0.015$, respectively).

Conclusion: Chronotropic incompetence and dynamic postexercise autonomic dysfunction are present in ED patients. This condition may reflect decreased functional capacity and exercise intolerance in these patients.

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The effect of the autonomic nervous system (ANS) on erectile function is well known. Parasympathetic activity is inevitably necessary to maintain penile erection in physiologic conditions.¹ However, many pathologic conditions that can cause autonomic dysfunction affect erectile function and result in erectile dysfunction (ED).^{2–7} In clinical practice, autonomic functions are investigated indirectly with heart rate variability (HRV) measurements.^{8–10} Additionally, exercise stress test (EST), which is used for detecting exercise and functional capacity, can provide useful indirect data about autonomic functions.¹¹ Chronotropic Index (CHIND) and heart rate recovery (HRR) time after an exercise period, which are calculated from the EST data, can reflect chronotropic competence and autonomic functions. HRR is considered an

indirect reflector of parasympathetic reactivation after an exercise period.¹¹ Furthermore, a sustainable penile erection requires a healthy cardiovascular system, which affects exercise capacity and penile vascular functions.¹ Therefore, the EST is gaining in interest for diagnosis, and some authors have pointed out the importance of EST with regard to ED. However, there are few data in the literature about the relationships between HRR, CHIND, and EST performance and erectile function.

We aimed in this study to investigate HRR and CHIND parameters after EST in males suffering from ED and compared our results to those obtained in healthy controls. We also investigated the relationship between HRR and CHIND and serum steroid hormone levels.

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MATERIAL AND METHODS

The study was approved by the Local Ethical Committee. Detailed information was given to enrolled patients, and Informed Consent Forms were signed by all participants.

Patients

All patients admitted to the Andrology Outpatient Clinic with erectile problems and the Cardiology Department for general health examination were evaluated with detailed history and physical examination. A total of 354 consecutive participants were screened in the time period between October 2005 and October 2008.

At last, 135 participants (mean age: 45.0 ± 11.8 years) were enrolled into the study.

Patient Selection

After these investigations, patients with the following physical or laboratory features were excluded from the study: acute or chronic renal dysfunction (serum creatinin level > 1.2 mg/dl), diabetes mellitus (fasting blood glucose level ≥ 126 mg/dl), metabolic syndrome (according to definition criteria of American Heart Association (AHA)/American College of Cardiology (ACC) guideline¹²), impaired glucose tolerance (fasting blood glucose level ≥ 110 mg/dl), hypogonadism, hypertension ($\geq 140/90$ mmHg), white-coat hypertension, heart failure (EF $< 50\%$), congenital heart disease, valvular heart disease (except minimally valvular insufficiency), history of coronary artery disease or proven coronary artery disease according to coronary angiography or noninvasive tests (the history of positive EST results, ischemic areas in SPECT analysis, etc.), peripheral arterial disease, familial hyperlipidemia, obesity (body mass index [BMI] > 30 kg/m²), asthma or chronic obstructive lung disease, concurrent therapy with medications that might affect blood pressure and cardiac rhythm (antihypertensive and antiarrhythmic drugs), aortic disease (Marfan's syndrome, coarctation of aorta, aortic aneurysm or aortic surgery, etc.), connective tissue disorders, neurological problems, psychiatric diseases (psychotic and major depressive patients and the patients with anxiety disorders) endocrine disease, alcohol usage (> 3 oz of beer or the beverage equal content of alcohol per week), drug abuse, and use of medications for hormonal treatment, espe-

cially ED, within the last 6 months. Moreover, patients with pathologic echocardiography (the patients with echocardiographic findings related above-mentioned pathological conditions and incidentally echocardiographic findings that are not accompanied with any symptoms), exercise test stress results (submaximal or maximal positive EST) were also not included in this study.

Andrologic Evaluation

International Index of Erectile Function (IIEF) was performed in all subjects to assess sexual satisfaction by the Department of Urology. IIEF score < 26 was accepted as ED. In these patients, serum luteinizing hormone (LH) and total testosterone (TT) levels were taken into consideration, and the patients having hypogonadism were excluded from the study.

Cardiologic Evaluation

Patients were kept in a silent and quiet test room at 20°C, and were rested for 15 minutes in the supine position at the beginning of the test in the Cardiology Department. Subsequently, measurement of arterial blood pressure and 12-channel electrocardiography (ECG) recordings were performed. After obtaining detailed medical history and physical examination, all subjects were subjected to EST (Treadmill). Biochemical analysis, 12-lead ECG, and EST (Quinton 4500 treadmill; Seattle, WA, USA) were performed in all subjects. Additionally, posteroanterior chest radiography was also performed for differential diagnosis, when necessary.

Color Doppler Echocardiography

Color Doppler echocardiography (GE-Vivid 7 Pro, General Electric; Clearwater, FL, USA) was performed for all participants.

ECG

After the skin was rubbed, electrodes were applied. 12-channel ECG (Cardioline Delta1 plus, Remco; Milan, Italy) was applied first, followed by EST.

EST (Treadmill)

All of the participants were tested using Bruce protocol between 14:00 and 16:00 (Quinton 4500

treadmill; Seattle, WA, USA). A mild lunch and a 30-minute rest was applied. In the case of excessive tea, alcohol, or coffee intake or excessive physical activity, the test was delayed. Exceeding the target heart rate ($220 - \text{age}$), symptoms of angina or equivalents, ischemic electrocardiographic changes during the test, severe arrhythmia (supraventricular tachycardia, ventricular tachycardia, couplet or triplet ventricular extrasystole, etc.), hypotension, dizziness, and severe hypertension during EST ($\geq 230/120$ mmHg) were accepted as the ending criteria of EST. Additionally, any pathologic changes in ECG, positive test criteria or symptoms of angina or equivalents, and claudication were accepted as exclusion criteria. After terminating the test, ECG was recorded in the first and third minutes of the cool-down period. Whole of the recovery phases of the patients were evaluated in the sitting position. All patients performed uniform exercise and recovery protocol systematically.

EST Parameters

EST was performed using Bruce protocol, and the following parameters were taken into consideration: rest heart rate, rest systolic blood pressure, rest diastolic blood pressure, target heart rate, achieved heart rate percentage, total exercise time, maximal heart rate (MHR-EST), maximal systolic blood pressure during test, maximal diastolic blood pressure during test, METs, CHIND, and HRR.

METs: (3.5 ml/kg of body weight per minute for an average adult). METs values were determined by using a nomogram, which is introduced by AHA.¹³

CHIND: Chronotropic incompetence was considered present if less than 80% of a patient's heart rate reserve (calculated as $[220 - \text{age}] - \text{resting heart rate}$) was achieved at peak exercise.¹⁴

$$\frac{(\text{Heart rate at peak exercise} - \text{resting heart rate})}{([220 - \text{age}] - \text{resting heart rate})}.$$

HRR: HRR was defined as the decrease in heart rate between peak exercise and 1 minute in recovery. A cutoff value of 22 bpm or less for HRR was considered abnormal.¹⁴

$$(\text{Heart rate at peak exercise} - \text{Heart rate at the end of first minute of recovery period}).$$

Psychiatric Consultation

A psychiatric consultation was performed for all participants to determine and exclude psychotic and major depressive patients and the patients with anxiety disorders.

Biochemical and Hormonal Analysis

A nonfasting blood sample was drawn between 09.00 and 10.00 hours. Laboratory workup involved detailed biochemical analysis (SMA-24), serum lipid profile, complete blood count and hormonal analysis, including LH, prolactin, TT, estradiol (E_2), and dehydroepiandrosterone-sulfate (DHEA-S). Serum hormone levels were determined by electrochemiluminescence immune assay with the Roche Elecsys 2010 immunoassay analyzer using Roche kit (Roche Diagnostic Corporation, Mannheim, Germany).

Statistical Analysis

All statistical analyses were performed using SPSS version 11.5 (SPSS; Chicago, IL, USA). The data are presented as mean $\pm$ standard deviation (SD). Student's *t*-test was used for comparing age, IIEF, and EST parameters. Pearson's and partial correlation analyses were performed to assess the strength of the association between IIEF score and HRR, CHIND and METs. Besides, multivariate analysis of covariance (MANCOVA) was performed to evaluate the differences about EST parameters between ED (−) and ED (+) patient groups. Subsequently, the relation between these parameters was evaluated using linear regression analysis. A *P*-value of <0.05 was accepted as statistically significant.

RESULTS

During the study period, 354 participants were enrolled in the study as patient and control groups. After the patient selection according to above mentioned criteria, at last, 135 participants (mean age: 45.0 ± 11.8 years) were included into the study.

In this group, 65 patients had ED (mean age 44.9 ± 6.4 years), while 70 patients (mean age 43.7 ± 7.7 years) had normal erectile status.

There was no difference in anthropometric values and sex hormone levels between the patients with and without ED (Table 1).

Table 1. Anthropometric Values, IIEF Scores, and Serum Hormone Levels in Patients with/without ED

	ED (–) Mean ± SD n = 70	ED (+) Mean ± SD n = 65	P
Age (years)	43.7 ± 7.7	44.9 ± 6.4	0.502
Weight (kg)	80.8 ± 11.9	84.3 ± 13.2	0.143
Body mass index (kg/m ²)	27.5 ± 4.7	28.9 ± 5.6	0.170
Waist (cm)	96.0 ± 9.3	99.2 ± 11.6	0.109
Height (cm)	171.7 ± 7.0	171.5 ± 7.6	0.860
Hip (cm)	92.0 ± 6.67	92.3 ± 8.0	0.800
Waist/hip ratio	1.05 ± 0.085	1.07 ± 0.085	0.071
LH (mIU/ml)	4.6 ± 2.0	4.0 ± 1.8	0.379
FSH (mIU/ml)	6.2 ± 3.9	4.3 ± 1.8	0.100
Prolactin (ng/ml)	11.5 ± 4.9	10.8 ± 3.9	0.781
Total testosterone (ng/ml)	4.7 ± 1.3	4.6 ± 1.8	0.664
Free testosterone (pg/ml)	11.7 ± 6.4	11.5 ± 7.0	0.987
Estradiol (pg/ml)	25.4 ± 12.1	27.6 ± 13.3	0.802
DHEA-S (μ/ml)	234.0 ± 107.1	248.8 ± 79.9	0.585

IIEF = international index of erectile function; ED = erectile dysfunction; LH = Luteinizing hormone; FSH = follicle stimulating hormone; DHEA-S = Dehydroepiandrosterone-sulfate.

Student's *t*-test, **P* < 0.05 statistically significant.

EST parameters are given in Table 2. There was a statistically significant difference between ED (–) and ED (+) patients about maximal heart rate during EST (MHR-EST), CHIND, and HRR.

According to our study results, patients with ED had significantly lower HRR and CHIND than those with normal erectile capacity (*P* = 0.005 and *P* = 0.019, respectively). On the other hand, maximal heart rate values achieved by patients during the EST (MHR-EST) were lower than those in ED (–) patients (*P* = 0.018).

Additionally, METs values, which are related with exercise performance and functional capacity,

were lower than in patients with normal erectile capacity (*P* = 0.028).

In correlation analysis, IIEF score showed positive correlation with total exercise time (TET), METs values, and HRR (Spearman r_{TET} = 0.220, *P* = 0.010; r_{METs} = 0.257, *P* = 0.003, and Pearson r_{HRR} = 0.302, *P* = 0.024, respectively).

We performed partial correlation analysis to control the effects of age, weight, body mass index, and blood pressure values on the statistical analysis results.

After controlling the effects of age, weight, body mass index, and blood pressure (Systolic and

Table 2. Exercise Test Parameters in Patients with/without ED

Exercise Test Parameters	ED (–) Mean ± SD n = 70	ED (+) Mean ± SD n = 65	P
Rest heart rate (1/min)	88 ± 13	85 ± 13	0.418
Rest systolic blood pressure (mmHg)	122.5 ± 19.7	126.4 ± 14.7	0.585
Rest diastolic blood pressure (mmHg)	80.0 ± 14.7	80.8 ± 10.3	0.881
Total exercise time (min) ^a	9.2 (9.0–10.9)	9 (7.2–11.3)	0.081
Maximal heart rate during EST (MHR-EST) (1/min)	167 ± 12	160 ± 9	0.018*
Maximal systolic blood pressure during EST (mmHg)	144 ± 29	158 ± 15	0.453
Maximal diastolic blood pressure during EST (mmHg)	76 ± 7	79 ± 7	0.743
Metabolic equivalent value (METs) ^a	10.5 (10.0–11.3)	8.3 (10.0–12.0)	0.028*
Chronotropic Index (CHIND)(%)	91 ± 12	82 ± 15	0.019*
Heart rate recovery (HRR) (1/min)	20.8 ± 8.4	14.3 ± 8.2	0.005*

ED = erectile dysfunction. Student's *t*-test, **P* < 0.05 statistically significant.

^aMann-Whitney U test. Median (25–75%).

diastolic) values, METs values and HRR ($r_{\text{METs}} = 0.215$, $P = 0.027$ and $r_{\text{HRR}} = 0.314$, $P = 0.031$, respectively) were still positively correlated with IIEF scores.

On the other hand, MANCOVA was also performed to evaluate the differences about EST parameters between ED (–) and ED (+) patient groups. In the multivariate statistical analysis, which included the factors of age, weight, body mass index, waist/hip ratio, blood pressure (Systolic and diastolic), estradiol, free testosterone, estradiol/free testosterone ratio simultaneously, we detected that HRR, CHIND, and METs values were statistically significantly different between ED (–) and ED (+) patient groups ($F[\text{Wilks-Lambda}] = 6.387$, $P = 0.027$).

Linear regression analysis (Backward) was performed to evaluate the most related anthropometric values and EST parameters with IIEF scores. Age, weight, body mass index, waist circumference, waist/hip ratio, blood pressure (Systolic and diastolic), MHR-EST, HRR and CHIND were included in the analysis. HRR was found as the most related factor with IIEF scores ($\text{Beta} = 0.295$, $t = 2.205$, $P = 0.032$; 95% CI 0.019–0.409).

DISCUSSION

Vascular pathologies are one of the most common causes of ED in male. Men with hypertension have a 15% probability of developing complete ED (increasing to 20% if they smoke).⁵ Other studies have demonstrated that men with a history of ischemic heart disease and/or peripheral vascular disease have incidences of ED ranging from 39% to 64%.⁶ Although autonomic dysfunction is one of the well-known etiologic factors of ED, it is difficult to determine the primary responsible factor for ED. In most cases, vasculogenic factors go to the fore. Nevertheless, the detection of autonomic dysfunction in ED has emerged recently as a topic of increasing interest. It is well known that increased sympathetic activity and/or diminished parasympathetic activity can cause ED.^{15–18} Most of ED etiologies can also cause this type of autonomic dysfunction.^{19–22} Although HRV data can give some data about autonomic activities, it is generally not possible to maintain any data about the response of the ANS to exercise stress. In other words, dynamic changes in autonomic activities due to exercise stress could not be sufficiently detected by HRV. At this point, EST is of

critical importance to investigate both cardiovascular (e.g., exercise-induced myocardial ischemia, arrhythmias, and functional capacity) and autonomic pathologies (e.g., chronotropic incompetence, HRR after exercise period).^{11,23–25} Thus, investigation of the EST parameters, which reflect dynamic autonomic response to exercise and the post-exercise period, is important in males with ED. Heruti et al. showed that functional capacity and METs values were closely related with the Sexual Health Inventory for Men test scores.²⁶ Moreover, some studies have shown that EST could play a critical role in the determination of ED treatment.^{12,26–30} However, most of the studies about the relationship between EST parameters and ED have been performed in males with diabetes mellitus and ischemic heart disease.^{21,25–32}

In this study, we investigated the correlation of EST parameters and IIEF scores in healthy men with ED. According to our data, the patients with ED had significant chronotropic incompetence to exercise. MHR-EST was lower in these patients, but recovery to normal heart rate values after exercise period (HRR) was longer than in ED (–) males. Additionally, METs values were detected as lower in patients with ED than in those with normal erectile capacity. IIEF score was found to be positively correlated with HRR and METs values, and tended to show a positive correlation with MHR-EST. However, after controlling for age, waist, and waist/hip ratio effects on the autonomic activities⁸ and functional capacity, the IIEF score was not found correlated with HRR. On the other hand, the IIEF ED score was still found positively correlated with MHR-EST. Therefore, we considered that important chronotropic incompetence as well as a disorder in dynamic autonomic changes was present after an exercise period in ED patients. These results are concordant with some previous studies that showed increased sympathetic or diminished parasympathetic activity in ED patients.^{15–18} Some of these autonomic changes could also be attributed to waist circumference and waist/hip ratio, which were already shown as risk factors for ED. However, the decreased MHR-EST reflected a discordant response to exercise stress in ED. Furthermore, we detected that the correlation between IIEF score and MHR-EST continued even after controlling for the anthropometric values. Our study results additionally suggested that pathologic autonomic changes could also affect patients during and after the exercise period. This condition

could also reflect the decreased exercise capacity of the patients with ED.^{26,32–34} Moreover, results of the studies that have shown the close relationship between ED and severity of coronary artery disease and of those demonstrating the close relationship between decreased HRR, CHIND, and mortality of ischemic heart disease further support our results.³⁵ Our study results also revealed an independent relationship between the exercise test results and autonomic activities and erectile function.

Many of the studies have shown no correlations between exercise performance and steroid hormone levels.^{36,37} We also could not determine any correlation between EST parameters and steroid hormone levels in the patients with and without ED.

CONCLUSION

Chronotropic incompetence and dynamic postexercise autonomic dysfunction are present in ED patients independent of steroid hormone levels. This condition may reflect decreased functional capacity and exercise intolerance in these patients. As a result, the EST may become more important in the evaluation of ED patients because of its capacity in evaluating autonomic activities.

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