Original Article

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Assessment of Exercise Stress Test Parameters in Patients with Erectile Dysfunction

Erektil Disfonksiyonlu Hastalarda Treadmill Stres Testi Parametrelerinin Değerlendirilmesi

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ABSTRACT

Objective: Erectile dysfunction (ED) has a significant impact on quality of life, given its high prevalence and association with cardiovascular diseases. In the present study, we aimed to evaluate exercise treadmill parameters in patients with ED.

Methods: A total of 178 patients who were admitted to the cardiology clinic was enrolled in the study. Patients were divided into two groups according to their International Index of Erectile Function-5 (IIEF-5) score. Exercise time, maximum heart rate (HR), resting HR, chronotropic index (CI), HR recovery at one minute (HRR1) and two minutes (HRR2) were evaluated for each patient.

Results: Subjects with ED were older, had similar rates of diabetes mellitus and hypertension compared to control group. Exercise time was longer and peak HR was higher in patients with ED compared to the healthy counterparts [556.00 (61) sec. vs 575.5 (84) sec. p=0.025, and 156.00 (13) bpm vs 160.50 (11) bpm p=0.001, respectively]. We did not find statistically significant differences with respect to resting HR, HRR1, HRR2, CI, maximum systolic and diastolic blood pressure, or rate pressure product between two groups. IIEF-5 score was negatively correlated with age (r=-0.54, p=<0.001), TC (r=-0.32, p=<0.001), LDL-C (r=-0.34, p=<0.001), TG (r=-0.17, p=0.02) and positively correlated with exercise time (r=0.19, p=0.01) and maximal HR (r=0.24, p=0.001). Prevalence of abnormal HRR1 values was significantly higher in study group (n=29, 23.6%) compared to control group (n=6, 10.9 %) (p=004). According to Quade's ANCOVA results, exercise time and maximal

ÖZ

Amaç: Bu çalışmada erektil disfonksiyonlu (ED) hastalarda treadmill egzersiz testi parametrelerini incelemeyi amaçladık.

Yöntemler: Kardiyoloji polikliniğine başvuran 178 hastaya Uluslararası Erektil İşlev Formu-5 (UAEİF-5) doldurtuldu. Sonuçlara göre hastalar iki gruba ayrıldı. Hastaların egzersiz zamanı, maksimum kalp hızı (KH), istirahat KH, kronotropik indeksi (Kİ), birinci ve ikinci dakikadaki KH toparlanma indeksleri (KHTİ 1 ve KHTİ 2) hesaplandı.

Bulgular: ED'si olan hastalar daha yaşlı idi, diyabet ve hipertansiyon açısından her iki grup arasında fark gözlenmedi. Egzersiz zamanı ED'li hastalarda kontrol grubuna göre daha uzundu ve maksimum KH daha yüksekti [556,00 (61) dk ile 575,5 (84) dk p=0,025 ve 156,00 (13) vuru/dk ile 160,50 (11) vuru/dk p=0,001]. İstirahat KH, KHTİ 1, KHTİ 2 ve Kİ açısından gruplar arasında fark saptanmadı. UAEİF-5 skoru yaş (r=-0,54, p=<0,001), total kolesterol (r=-0,32, p=<0,001), LDL-K (r=-0,34, p=<0,001) ve TG (r=-0,17, p=0,02) ile pozitif, egzersiz süresi (r=0,19, p=0,01) ve maksimum KH (r=0,24, p=0,001) ile negatif korrelasyon gösterdi. Anormal KHTİ 1 değerleri çalışma grubunda kontrol grubuna göre anlamlı olarak yüksek bulundu (sırası ile, n=29, %23,6 ile n=6, %10,9, p=0,04). Quade ANCOVA sonuçlarına göre yaş kovaryant olarak alındığında egzersiz zamanı ve maksimum KH iki grup arasında farklı bulunmadı (sırası ile, F=1,032 p=0,311 and F=1,264, p=0,262).

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HR were not different between two groups when age was used as a covariate (F=1.032 p=0.311 and F=1.264, p=0.262, respectively).

Conclusion: Abnormalities of autonomic system activity is more prevalent in patients with ED. Exercise treadmill testing can be used to assess autonomic activity in that group of patients.

Keywords: Erectile dysfunction, heart rate recovery, stress

Sonuç: ED'li hastalarda anormal değerdeki KHTİ 1 daha fazla gözlenmektedir. Egzersiz treadmill testi bu hasta grubunda otonom aktiviteyi değerlendirmek için kullanılabilir.

Anahtar Sözcükler: Erektil disfonksiyon, kalp hızı toparlanma indeksi, stres

Introduction

Erectile dysfunction (ED), failure to maintain an adequate erection for satisfactory intercourse, has a high prevalence ranging from 9% to 54% depending on age and cardiovascular risk factors of the subjects (1). It is considered as a reflective of vascular disorders and predictive of cardiovascular mortality (2). Various conditions may cause ED including advanced age, hypogonadism, hypertension, diabetes mellitus, hyperlipidemia and depression (3). Normal erectile function requires proper interaction of the vascular, autonomic, and somatic nervous systems. Erection is mediated through parasympathetic mediated vascular dilatation, whereas ejaculation is mainly under the control of sympathetic nervous system (4). Hence, functional abnormalities of the autonomic nervous system may be exhibited as erectile dysfunction.

An intact heart rate (HR) response during and after exercise is essential for good cardiovascular performance. Exercise induced increase in sympathetic activity, together with the withdrawal of the parasympathetic influence, results in increased HR, cardiac output and restriction of blood flow to the skeletal muscles (5). An inability to raise HR during exercise, (i.e., chronotropic incompetence) is a major contributor of exercise intolerance and has prognostic value in cardiovascular diseases. Chronotropic response is usually assessed by chronotropic index (CI) which is defined as percentage of the HR reserve achieved by the patient (6). HR begins to decelerate soon after the termination of exercise, which is directly related to parasympathetic efferent nerve activity. The decrease of HR shows bimodal pattern: a slow decline after a steep reduction in the first 30 seconds, which is blunted by atropine (7,8). As with chronotropic incompetence, delayed HR recovery (HRR) is a predictor of cardiovascular disease and death (9). Therefore, abnormalities of sympathetic and/or parasympathetic systems can emerge through HR responses during treadmill testing.

Since both exercise testing and sexual performance could give information about autonomic nervous system activity, we aimed to investigate treadmill exercise indices in patients with ED and compare them with controls.

Methods

This was a cross-sectional, single center study that included 178 patients who were admitted to treadmill laboratory between November 2019 and December 2020. Patients with ischemic heart disease, valvular disease, rhythm-conduction disorder, left bundle branch block, hypo-hyperthyroidism, renal and/or hepatic failure were excluded from the study. The study was approved by local ethical committee and informed consents were obtained from all participants. This study was conducted in accordance with the Declaration of Helsinki.

For evaluation of ED within past 6 months, international index of erectile function-5 (IIEF-5) questionnaire was used. It is composed of 5 Likert-type questions scored from 1 (severe dysfunction) to 5 (no dysfunction), with lower scores indicating greater disability. Severity of ED is classified into four groups: severe (5-7 points), moderate (8-11 points), mild-moderate (11-16 points), mild (17-21 points) and normal erectile function (22-25 points). Turkish validation study of IIEF-5 questionnaire was conducted by Turunç et al (10). Participants were divided in to two groups according to their IIEF-5 score; patients with a score of 1-21 (n=123) and 22-25 (n=55) constituted study and control group, respectively.

Venous blood samples of the subjects were obtained from antecubital vein after an overnight fast. Biochemical analysis was done to measure total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol and triglyceride (TG) levels. Bruce protocol was used for exercise testing (Schiller CS-200, Switzerland). B-blockers and Ca-channel blockers were stopped 48 hour before the test. Blood pressure of the participants was measured in every stage and recovery period. Exercise testing was stopped if the patient developed chest pain, dyspnea, ischemic electrocardiogram changes, hypo/hypertensive response or when 85% of the maximum predicted HR was achieved. Exercise time was calculated in seconds. Maximal predicted HR was calculated using the formula "220-age". HRR at one minute (HRR1) and two minutes (HRR2) were estimated by subtracting first and second minute post-exercise HR from maximal HR, respectively. In our treadmill laboratory, cessation of the exercise testing was performed with either in standing or sitting position without cool-down period. Since studies performed previously showed that HRR1 values of ≤12 bpm and ≤18 bpm were abnormal in protocols with and without cool-down period, respectively, we accepted HRR1 value of ≤18 bpm as abnormal (11,12). CI was calculated by dividing the difference of maximum HR and resting HR to the difference of maximum predicted HR and resting HR. Values greater than 0.80 were accepted as normal. Multiplication of HR with BP gave us the result of rate-pressure product.

Statistical Analysis

Parametric data were expressed as mean standard deviation, non-parametric data were expressed as median and interquartile range [IQR (IQR1-IQR3)]. For comparison of two groups; independent sample t-test (normally distributed data) or Mann-Whitney U test (not normally distributed data) was used. Correlation between parameters was assessed by Spearman's correlation analysis. Quade's ANCOVA was used to test the differences of exercise time and maximal HR between groups where age served as covariate.

Result

Subjects with ED were older, had similar rates of DM and HT compared to control group. Frequency of smoking and alcohol consumption were higher in the control group than in the study group. Exercise time was longer and peak HR was higher in patients with ED compared to the healthy counterparts [556.00 (61) sec. vs 575.5 (84) sec. p=0.025, and 156.00 (13) bpm vs 160.50 (11) bpm p=0.001, respectively]. We did not find statistically significant differences with respect to resting HR, HRR1, HRR2, CI, maximum systolic and diastolic blood pressure, or rate pressure product between two groups. Baseline demographic, biochemical and exercise stress values of the groups is presented in Table 1.

According to their IIEF-5 scores, 3 (1.7%) subjects had severe-moderate disease, 35 subjects (19.6%) had mild-moderate disease, 85 (47.8%) had mild disease and the rest (n=55, 30.9%) had normal erectile function. Frequency distribution of IIEF-5 score is shown in Figure 1.

The IIEF-5 score was negatively correlated with age (r=-0.54, p=<0.001), TC (r=-0.32, p=<0.001), LDL-C (r=-0.34, p=<0.001), TG (r=-0.17, p=0.02) and positively correlated with exercise time (r=0.19, p=0.01) and maximal HR (r=0.24, p=0.001) (Table 2).

We further investigated the prevalence of abnormal HRR1 values between two groups. Twenty-nine subjects (23.6%) had abnormal HHR1 values in the study group, whereas 6 subjects (10.9 %) had abnormal HRR1 values in the control group (p=004).

According to Quade's ANCOVA results, exercise time and maximal HR were not different between two groups when age was used as a covariate (F=1.032 p=0.311 and F=1.264, p=0.262, respectively).

Discussion

In the present study we found that patients with ED had lower exercise capacity and HR response to exercise. IIEF-5 score was negatively correlated with age, exercise duration, maximal HR, TC, LDL-C and TG levels. These correlations imply common pathophysiological mechanisms between ED and cardiovascular diseases. Although we did not find any statistically significant differences in the HRR1 and HRR2 values of the two groups, the prevalence of abnormal HRR1 values was statistically significantly higher in patients with ED.

Table 1. Demographic, biochemical and treadmill parameters of the patients

	Study group (n=123)	Control group (n=55)	p
Age (years)	46.83±6.752	40.38±6.072	<0.001
Exercise time (second)	556.00 (61)	575.5 (84)	0.025
Resting HR (bpm)	84.91±12.827	86.10±13.696	0.332
Max HR (bpm)	156.00 (13)	160.50 (11)	0.001
HRR1 (bpm)	26.00 (8.00)	28.00 (13.00)	0.111
HRV2 (bpm)	42.00 (11)	45.00 (18)	0.297
CI	0.77 (0.14)	0.815 (0.15)	0.059
HRR1 (≤18 bpm) (n, %)	29 (23.6)	6 (10.9)	0.040
Max SBP (mmHg)	150.00 (25.00)	150.00(30.00)	0.254
Max DBP (mmHg)	80.00 (10.00)	85.00 (10.00)	0.617
RPP (mmHg*bpm)	23400.00 (5660)	23885.00 (5108)	0.190
TC (mg/dL)	199.77±43.832	195.75±39.125	0.761
TG (mg/dL)	121.00 (100.00)	125.00 (113.00)	0.517
HDL -C(mg/dL)	43.00 (12.0)	42.00 (10.5)	0.143
LDL-C(mg/dL)	125.00 (53.0)	123.55 (56.5)	0.336
Smoking (n, %)	49 (39.8)	32 (58.2)	0.023
Alcohol (n, %)	24 (19.5)	21 (38.2)	0.010
DM (n, %)	7 (5.7)	2 (3.6)	0.552
HT (n, %)	11 (9.1)	4 (7.3)	0.685

CI: Chronotropic index, DBP: Diastolic blood pressure, DM: Diabetes mellitus, HDL-C: High density lipoprotein cholesterol, HR: Heart rate, HRR1: Heart rate recovery 1 minute, HRR2: Heart rate recovery 2 minutes, HT: Hypertensiton, LDL-C: Low density lipoprotein cholesterol, RPP: Rate pressure product, SBP: Systolic blood pressure, TC: Total cholesterol, TG: Triglyceride

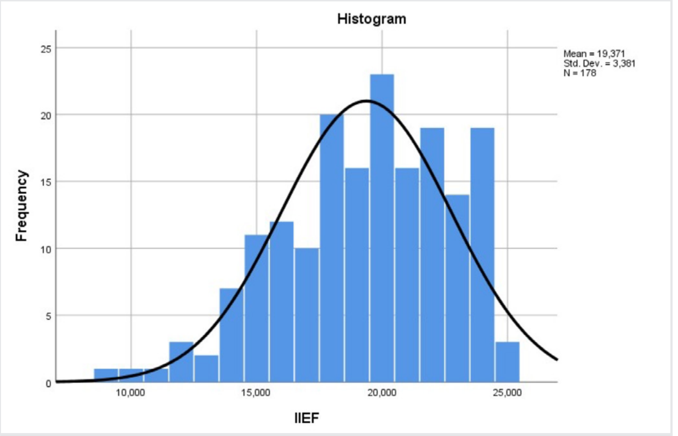

Figure 1. Frequency distribution of IIEF-5 score among subjects.

Table 2. Correlation analysis of IIEF-5 score

	R value	P value
Age	-0.54	**<0.001**
TC	-0.32	**<0.001**
LDL -C	-0.34	**<0.001**
HDL-C	0.14	0.06
TG	-0.17	**0.02**
Exercise time	0.19	**0.01**
Resting HR	0.05	0.49
Max HR	0.24	**0.001**
HRR1	0.12	0.09
HRR2	0.08	0.29
Cl	-0.11	0.14
Max SBP	-0.11	0.11
Max DBP	-0.02	0.79
RPP	-0.02	0.71

CI: Chronotropic index, DBP: Diastolic blood pressure, DM: Diabetes mellitus, HDL-C: High density lipoprotein cholesterol, HR: Heart rate, HRR1: Heart rate recovery 1 minute, HRR2: Heart rate recovery 2 minutes, HT: Hypertensiton, LDL-C: Low density lipoprotein cholesterol, RPP: Rate pressure product, SBP: Systolic blood pressure, TC: Total cholesterol, TG: Triglyceride

ED is the most common sexual abnormality in males. Although vascular pathologies are the leading cause of ED, abnormalities of autonomic function are among the well-recognized etiologic factors in its development (13). Thus, there has been increasing interest in evaluating autonomic functions in patients with ED. Because exercise stress testing could provide sufficient information regarding dynamic changes in autonomic function, investigation of exercise stress test parameters in males with ED has attracted attention of many researchers.

Hemodynamic changes during exercise mainly reflects the complex interaction between the sympathetic and parasympathetic nervous systems. Increase in HR during exercise is mainly related to the stimulation of adrenoceptors by catecholamines (14). Immediately after exercise with the activation of baroreflex arch and other mechanisms, parasympathetic activation and sympathetic withdrawal occur and the HR gradually slows (8). Many studies have shown the prognostic value of exercise test indices in various diseases, including coronary artery disease, hypertension, and myocardial infarction (15, 16).

Dogru et al.(17) showed that males with ED had an attenuated HR response to exercise and had an abnormal decline in HR during postexercise period. In their study, the HRR1 values of subjects with and without ED were 14.3±8.2 bpm and 20.8±8.4, respectively. Cardiac rehabilitation in patients with ischemic heart disease has been reported to result in significant improvement in erectile quality and HRR, indicating enhanced autonomic balance in this group (18). Ulucan et al. (19) investigated HRR indices of 90 patients with ED and 50 healthy subjects and found that patients with ED had lower values of HRR1, HRR2, and HRR3 and decreased effort capacity than their healthy counterparts. The HRR1 values of the two groups were 34.8±11.2 bpm and 41.7±15.5 bpm, respectively (p<0.001). HRR1 and HRR3 were independent predictors of ED. Abnormal values of HRR may differ according to the protocol used during treadmill test which can be stopped abruptly (no cool down period) or gradually with a predetermined speed and slope. In the former case ≤18 bpm is considered abnormal, and in the latter case ≤12 bpm is considered as abnormal (11,12). When we carefully looked at the results of the study by Ulucan et al. (19), 95% of the values fell into normal range. Kucukdurmaz et al. (20) compared exercise duration, CI, and first, second, and third minute HRR values in patients with or without ED. In their study, total exercise duration was statistically significantly shorter and HRR indices were lower in patients with ED. Specifically, HRR1 values of the study and control groups were 30.6±11.9 and 36.9±9.9, respectively (p=0.01). They also evaluated the number of patients who had abnormal HRR1 values. The percentage of patients with HRR1 below 18 bpm were 12% and 3% in the study and control groups, respectively (p=0.03). Ioakeimidis et al. (21) studied endothelial function and exercise test parameters in patients with ED. Exercise capacity and CI were found to be decreased in patients with ED whereas they could not find any differences with respect to HRR1 and HRR2 indices after exercise. When they divided patients with ED into three groups according to their IIEF-5 score, severity of ED was correlated with exercise time, HRR2 and CI. On post-hoc analysis, patients with severe ED had statistically significantly lower CI and HRR2 values compared to patients with mild and moderate disease.

In our study, although exercise time was longer and maximal HR was higher in control group, with age included as a covariate, the differences became statistically insignificant. This also explained the similar values of CI in two groups. Hence, differences in exercise time and peak HR between groups were attributed to younger age and better physical performance of the subjects in control group. Although we did not find any differences in HRR indices, further analysis showed that prevalence of abnormal HRR1 values was higher in study group than that of control group. It has been reported that exercise-induced increase in HR is primarily mediated by sympathetic activity whereas post-exercise 1 minute decrease in HR depends on parasympathetic activation (22,23). Our results were in accordance with previous data, suggesting that parasympathetic system had an important role in the pathogenesis of ED or impotence.

Study Limitations

Limitations of our study were as follows: (1) the sample size was small; (2) it was a single center study; (3) number of patients who had severe-moderate ED was relatively low (1.7 %); and (4) testosterone levels of the subjects were not measured.

Conclusion

Abnormalities of autonomic system activity is more prevalent in patients with ED. Since, exercise treadmill testing is a useful tool for the assessment of autonomic nervous system activity, it can be used to assess autonomic activity in that group of patients.

Ethics

Ethics Committee Approval: The study was approved by local ethical committee and informed consents were obtained from all participants.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: E.O., A.S.E., F.N.T.Ç., İ.F.A., Design: E.O., A.S.E., F.N.T.Ç., İ.F.A., Data Collection or Processing: E.O., C.Y., D.K., Analysis or Interpretation: C.Y., D.K., A.S.E., F.N.T.Ç., Literature Search: E.O., C.Y., İ.F.A., Writing: C.Y.

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