TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2015) 45: 751-757

doi:10.3906/sag-1407-69

Cardiac factors affecting the success of vardenafil in erectile dysfunction

Kürşad ZENGİN[1,*], Hüseyin EDE[2], Serhat TANIK[1], Sebahattin ALBAYRAK[1], Savaş SARIKAYA[2], Alirıza ERBAY[2], Muhammet Abdurrahim İMAMOĞLU[1], Mesut GÜRDAL[1]

[1]Department of Urology, Faculty of Medicine, Bozok University, Yozgat, Turkey
[2]Department of Cardiology, Faculty of Medicine, Bozok University, Yozgat, Turkey

Received: 15.07.2014 • **Accepted/Published Online:** 26.08.2014 • **Printed:** 30.07.2015

Background/aim: To evaluate the predictability of vardenafil success in patients with erectile dysfunction (ED) by using cardiological tests.

Materials and methods: Patients diagnosed with ED who did not benefit from lifestyle changes (n = 68) were evaluated with an abridged 5-item version of the International Index of Erectile Function (IIEF-5). The pretreatment and posttreatment IIEF-5 scores were compared with pretreatment data obtained from cardiological examinations.

Results: When pretreatment scores were compared with test parameters, mitral flow E/A ratio and tissue Doppler imaging (TDI) E′/A′, exercise test duration, exercise capacity in MET, and percentage of maximum heart rate were found to be statistically significant. Furthermore, there was a significant negative correlation between mitral flow E/A ratio, TDI E′/A′, exercise test duration, exercise capacity in MET, and the difference in post- and pretreatment IIEF-5 scores.

Conclusion: As a diastolic function indicator, TDI E′/A′ positively correlates with pretreatment IIEF-5 scores and negatively correlates with the beneficial effect of vardenafil treatment. As a result, the cardiological status of the patient correlates with individual IIEF-5 scores, and it seems to be useful in predicting vardenafil success.

Key words: Erectile dysfunction, phosphodiesterase type 5 inhibitor, diastolic dysfunction

1. Introduction

Erectile dysfunction (ED) is a sexual dysfunction characterized by the inability to develop or maintain an adequate erection during sexual performance. It is estimated that 150 million men worldwide have ED (1). Its prevalence only increases with age. This increment is probably due to the fact that prevalence of underlying comorbidities, such as cardiovascular disease and diabetes mellitus, increase with age (2). The first phosphodiesterase type 5 inhibitor (PDE5I) for ED treatment available on the market was sildenafil. Sildenafil revolutionized ED treatment. Sildenafil, and later tadalafil and vardenafil, proved highly efficacious in studies.

However, these drugs did not demonstrate the same efficacy in all patients. It was seen that some patients effectively used the drug, and some patients discontinued usage because of inefficiency (3). Currently, urologists cannot predict in which patient PDE5Is can be used effectively.

Vascular pathologies are the most common etiological factors in ED. Vascular pathologies can be diagnosed by penile Doppler ultrasound and are subgrouped into arteriogenic insufficiency and veno-occlusive dysfunction (4). There is strong evidence of an association between cardiovascular disease (CVD) and ED. The risk factors are similar and lead to endothelial dysfunction (5). As a result, CVD and ED frequently coexist (6).

In this study we evaluated all ED patients with serum laboratory tests, an echocardiogram, and a treadmill exercise test before prescribing vardenafil. The significance of these tests in predicting the efficacy of drug was evaluated.

2. Materials and methods

2.1. Study design and patient population

The study was approved by the local ethics committee of Bozok University (604/02-2013).

Patients with ED complaints who did not benefit from lifestyle changes were evaluated with a full physical examination, basic neurologic and psychiatric assessments (suspected cases were presented to specialists), complete blood count, fasting blood glucose, serum lipid profile,

* Correspondence: kursadzengin@gmail.com

hormonal profile with total testosterone, prolactin, thyroid-stimulating hormone, an abridged 5-item version of the International Index of Erectile Function (IIEF-5), cardiology consultation, electrocardiogram (ECG), echocardiogram, and a treadmill exercise test on the first visit. Patients with surgical conditions of ED (hypospadias, congenital penile curvature, Peyronie's disease), hormonal or neurologic pathologies, serious cardiovascular disease, a history of previous PDE5I usage, and who were on medications that may cause ED (e.g., diuretics, antidepressants, antiandrogens, antipsychotics) were excluded from the study. The patients treated with vardenafil were then reevaluated after 2 months (with usage of at least 8 pills of vardenafil). Their IIEF-5 scores were assessed again.

This study was conducted between June and December 2013. There were 132 patients diagnosed with ED during this period. Thirty-six of the patients had used PDE5Is before, 12 patients were using nitrates or were diagnosed with cardiac instability by cardiologist, 4 patients had histories of cerebrovascular accident, and 4 patients had hyperprolactinemia or thyroid hormone abnormalities; they were excluded from the study. There were 76 patients with primary ED. Eight patients did not come to the follow-up visit after 2 months, so the study group was created from 68 patients.

2.2. Cardiological tests

Resting ECGs of all patients and controls were obtained after a rest of 5 min in the room. A Modified Bruce treadmill protocol was used to assess exercise capacity and heart rate recovery (Quinton Q-Stress 4.0, 2008; Cardiac Science Corporation, Germany). The test was stopped due to either patient's demand or reaching maximal targeted heart rate (220 – age in years). None of the patients revealed ischemic changes in the exercise treadmill test. Heart rate recovery (HRR) was defined as the difference between heart rate at peak exercise and at both the first (HRR1) and second (HRR2) minutes after exercise. Maximal heart rate in percent of targeted heart rate, rate-pressure product (heart rate × blood pressure at the moment of maximal exercise), maximal exercise capacity in the standard metabolic equivalent (MET) (defined as the amount of oxygen consumed at rest, sitting quietly in a chair, approximately 3.5 mL O_2 kg^{-1} min^{-1} (1.2 kcal/min for a 70-kg person)), and exercise duration derived from exercise treadmill test were used for analysis.

In the echocardiographic examination (Presound Alpha 7, IPF 1701 Model, 2009; Hitachi Aloka Medical, Ltd., Japan), left ventricle dimensions, and posterior wall and interventricular septum diastolic thicknesses were measured at M-mode images. Left atrial size (LA) was measured at the aortic sinus Valsalva level by using M-mode images. From the images of apical two- and four-chamber echo windows, LV ejection fractions (LVEFs) were obtained using a modified Simpson method and the average of two values was determined as the LVEF. In an apical four-chamber window, by using pulse wave (PW) Doppler, samples of transmitral diastolic inflow were obtained and then mitral E and A waves were measured. E/A ratios of all patients were calculated. All measurements were carried out at the end of expiration. By using PW tissue Doppler imaging (TDI), all diastolic and systolic myocardial velocities were obtained. In this study, to make the evaluation simple, a sample volume at the LV lateral wall basal segment was used to obtain E′ and A′ wave velocities in an apical four-chamber window. E/E′ ratios were calculated accordingly. Pulmonary artery systolic pressure of every patient was measured indirectly by using tricuspid valve continuous wave velocity at the apical four-chamber view. In the apical five-chamber view, left ventricle outflow tract diameter (LVOT) and time-velocity integral (TVI) of pulse wave sample volume at left ventricle outflow were used to measure stroke volume (SV) by using the formula of SV (mL) = $3.14 \times (LVOT/2)^2 \times TVI$. SV divided by body surface area yielded cardiac index. All Doppler measurements were carried out for five subsequent cycles and the average of all five measurements was used for statistical analysis.

2.3. Statistical analysis

The data obtained were analyzed with SPSS 18. Whether quantitative variables had normal distribution was tested with the Kolmogorov–Smirnov test. Except for diastolic blood pressure, E′/A′ ratio, and exercise capacity in MET, all variables had normal distribution. Continuous variables were expressed as mean ± standard deviation, while categorical variables were shown as frequency and percentage. In comparison of groups with normally distributed variables, independent t-test or ANOVA were used accordingly, while the Mann–Whitney U-test was used for variables without normal distribution. For correlation analysis of IIEF-5 values with ECG, exercise test, and blood chemistry parameters, Pearson's correlation was carried out for normally distributed data, while Spearman's correlation was used for others. For all analysis, $P < 0.05$ was accepted as statistically significant.

3. Results

The mean age of patients was 54.5 ± 8.1 years. The demographical data are summarized in Table 1. The mean pretreatment IIEF-5 score was 9.1 ± 2.5, and the posttreatment score was 17.9 ± 2.7. There was a statistically significant difference between posttreatment and pretreatment IIEF-5 scores ($P < 0.01$). The severity level of pretreatment and posttreatment ED was classified according to the description of Rosen et al. (7). Table 2 summarizes pre- and posttreatment levels of ED.

Table 1. Demographical data and erectile dysfunction scores of the patients.

N = 68	Mean ± SD
Age (years)	54.5 ± 8.1
Weight (kg)	80.8 ± 11.9
Height (m)	1.72 ± 0.07
BMI (kg/m^2)	27.3 ± 3.5
SBP (mmHg)	111 ± 13
DBP (mmHg)	75 ± 8
Pretreatment IIEF-5 score	9.1 ± 2.5
Posttreatment IIEF-5 score	17.9 ± 2.7
Difference between post- and pretreatment IIEF-5 scores	8.8 ± 2.7

SBP: Systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, IIEF-5: International Index of Erectile Function.

Table 2. Pre- and posttreatment levels of ED.

Level of ED	Pretreatment n (%)	Posttreatment n (%)
Severe	12 (22%)	0
Moderate	29 (54%)	3 (6%)
Mild–moderate	13 (24%)	10 (18%)
Mild	0	39 (72%)
No ED	0	2 (4%)

ED: Erectile dysfunction.

The serum laboratory, echocardiographic examination, and treadmill exercise test results are summarized in Table 3. In the echocardiographic examination, mean LVEF was 62.5 ± 2.7%. The mean treadmill exercise test duration was 10.4 ± 2.3 min.

Pretreatment IIEF-5 score and differences between post- and pretreatment IIEF-5 scores were compared with age, body mass index, systolic blood pressure, and diastolic blood pressure as demographical data. The statistical analysis revealed significance only with age, and there was a negative correlation between age and pretreatment IIEF-5 scores ($P < 0.005$, $r = -0.539$). There was also a statistically significant positive correlation between difference in IIEF-5 scores and age ($P < 0.05$, $r = 0.365$).

When pretreatment IIEF-5 scores were compared with echocardiographic parameters, mitral flow E/A ratio and TDI E′/A′ were statistically significant ($P < 0.001$, $r = 0.636$; $P < 0.001$, $r = 0.862$). Furthermore, there was a significant negative correlation between mitral flow E/A ratio, TDI E′/A′, and the difference in post- and pretreatment IIEF-5 scores ($P < 0.005$, $r = -0.487$; $P < 0.001$, $r = -0.569$).

Similarly, pretreatment and difference in post- and pretreatment IIEF-5 scores were compared with the parameters obtained from treadmill exercise test. Exercise test duration, exercise capacity in MET, and percentage of maximum heart rate were statistically significant when compared with pretreatment IIEF-5 scores ($P < 0.005$, $r = 0.486$; $P < 0.01$, $r = 0.461$; $P < 0.05$, $r = 0.418$). There was a positive correlation observed in all of these statistically significant variables. When we compared the difference in post- and pretreatment IIEF-5 scores with these variables, it was seen that there was a statistically significant negative correlation observed in exercise test duration and exercise capacity in MET ($P < 0.05$, $r = -0.401$; $P < 0.05$, $r = -0.363$). To clarify these findings and to describe a cut-off value for exercise test duration, we further analyzed the results. We grouped the patients according to their exercise test

Table 3. Laboratory, echocardiographic examination, and treadmill exercise test results of patients.

Parameter	Mean ± SD	Pretreatment IIEF-5 score	Difference between post- and pretreatment IIEF-5 scores
Total testosterone (mg/dL)	612 ± 133	P < 0.05 r = 0.424	P < 0.05 r = –0.350
Triglyceride (mg/dL)	176 ± 104	P = 0.846 r = 0.036	P = 0.728 r = –0.064
Total Cholesterol (mg/dL)	201 ± 32	P = 0.676 r = 0.077	P = 0.160 r = –0.255
LDL(mg/dL)	129 ± 24	P = 0.815 r = 0.043	P = 0.371 r = –0.164
HDL (mg/dL)	40 ± 8	P = 0.749 r = 0.059	P = 0.902 r = 0.023
Prolactin (ng/mL)	8.6 ± 4.0	P = 0.134 r = –0.271	P < 0.05 r = 0.364
TSH (uIU/mL)	1.39 ± 0.55	P = 0.633 r = 0.088	P = 0.291 r = 0.192
FBG (mg/dL)	108 ± 29	P = 0.916 r = –0.019	P = 0.082 r = –0.312
Hgb (g/dL)	14.5 ± 0.9	P = 0.220 r = 0.223	P = 0.142 r = –0.265
LVEF (%)	62.5 ± 2.7	P = 0.596 r = 0.094	P = 0.394 r = –0.151
LA diameter (cm)	3.98 ± 0.31	P = 0.341 r = –0.168	P = 0.713 r = –0.066
PASB (mmHg)	24.6 ± 3.6	P = 0.295 r = –0.185	P = 0.123 r = 0.269
Mitral flow E/A ratio	1.13 ± 0.52	P < 0.001 r = 0.636	P < 0.005 r = –0.487
TDI E′/A′ ratio	1.03 ± 0.49	P < 0.001 r = 0.862	P < 0.001 r = –0.569
E/E′ ratio	6.0 ± 1.6	P = 0.080 r = –0.305	P = 0.768 r = 0.052
Stroke volume (mL)	71.9 ± 15.2	P = 0.755 r = –0.055	P = 0.960 r = 0.009
Cardiac index (mL/m^2)	36.5 ± 9.2	P = 0.608 r = –0.105	P = 0.891 r = 0.028
Exercise test duration (min)	10.4 ± 2.3	P < 0.005 r = 0.486	P < 0.05 r = –0.401
Exercise capacity in MET	11.0 ± 2.1	P < 0.01 r = 0.461	P < 0.05 r = –0.363
Cardiovascular product (mmHg × bpm)	25565 ± 4672	P = 0.408 r = 0.163	P = 0.428 r = –0.156
Percentage of max heart rate (%)	95 ± 6	P < 0.05 r = 0.418	P = 0.333 r = –0.194
HRR1 (beats/min)	28 ± 10	P = 0.477 r = 0.140	P = 0.694 r = 0.078
HRR2 (beats/min)	48 ± 11	P = 0.270 r = 0.216	P = 0.450 r = 0.149

LDL: Low-density lipoprotein, HDL: high-density lipoprotein, TSH: thyroid-stimulating hormone, FBG: fasting blood glucose, Hgb: hemoglobin, LVEF: left ventricle ejection fraction, LA diameter: left atrium diameter, PASB: pulmonary artery systolic pressure, TDI E′/A′ ratio: left ventricle lateral wall basal segment tissue Doppler imaging E′/A′ ratio, E/E' ratio: mitral flow E/TDI E′ ratio, Percentage of max heart rate: percentage of achieved heart rate at maximum exercise level compared to targeted heart rate, MET: metabolic equivalent of task, HRV: heart rate recovery, Cardiovascular product: product of heart rate × systolic blood pressure at maximum exercise level (mmHg

duration. We observed that pretreatment IIEF-5 scores were higher in patients with exercise test durations of longer than 10 min (n = 32, mean ± SD = 10.1 ± 2.8) than in patients with exercise test durations shorter than 10 min (n = 36, mean ± SD = 8.2 ± 1.9) ($P < 0.05$). The difference in post- and pretreatment IIEF-5 scores was lower in patients with exercise test durations of longer than 10 min than in patients with exercise durations pf shorter than 10 min (mean ± SD = 7.6 ± 2.9 vs. 9.8 ± 1.7, $P < 0.05$).

The relation between the severity of pretreatment ED and the difference between post- and pretreatment IIEF-5 scores were compared with the TDI E′/A′ ratio by using one-way ANOVA and Student's t-test. Both the pretreatment severity and the difference in IIEF-5 scores were found as statistically significant, as demonstrated in the Figure ($P < 0.001$; $P < 0.005$).

4. Discussion

The coexistence of CVD and ED has been subjected to different studies. It was shown that these entities have similar risk factors and a strong correlation (5,6). The severity of CVD and ED was studied by Canat et al. They reported a statistically significant correlation between number of occluded coronary arteries and presence of hypertension with ED (8).

Solak et al. reported a higher incidence of CVD in ED patients. They also reported that ED is more frequent in patients with chest pains of cardiac origin (9). The quality of erection was assessed with the IIEF-5 in ischemic heart disease (IHD) patients, and they were subjected to a 6-month cardiac rehabilitation exercise schedule to investigate the efficacy for changes in quality of erection. The study group (IHD patients with similar characteristics who are subjected to cardiac rehabilitation exercise) was compared with a control group. The study drew two conclusions: in the patients with IHD, erection quality was significantly correlated with exercise tolerance; and the cardiac rehabilitation exercise schedule had a positive effect both on exercise tolerance and erection quality.

The Figure illustrates the relation between the severity of ED and TDI E′/A′ ratio, and the relation between the difference of post- and pretreatment IIEF-5 scores and TDI E′/A′ ratio. The TDI E′/A′ ratio is an indicator of diastolic dysfunction. As the TDI E′/A′ ratio decreases below 1, the severity of diastolic dysfunction increases. Statistical analysis revealed a significant difference and a positive correlation between the pretreatment scores of IIEF-5 and TDI E′/A′ ratio. In the Figure, it is also seen that there is a statistically significant difference between the improvement in posttreatment IIEF-5 scores and TDI E′/A′ ratio ($P = 0.005$). The results revealed that as the degree of diastolic dysfunction increases, the severity of ED increases in the same manner. Likewise, when we grouped the patients as TDI E′/A′ ratio below 1 (mean pretreatment IIEF-5 score = 7.3 ± 1.5; difference between post- and pretreatment IIEF-5 scores = 10.1 ± 2.0), and over 1 (mean pretreatment IIEF-5 score = 11.4 ± 1.5; difference between post- and pretreatment IIEF-5 scores = 7.2 ± 2.8), the patients who had diastolic dysfunction (with TDI E′/A′ ratio below 1) responded better to vardenafil

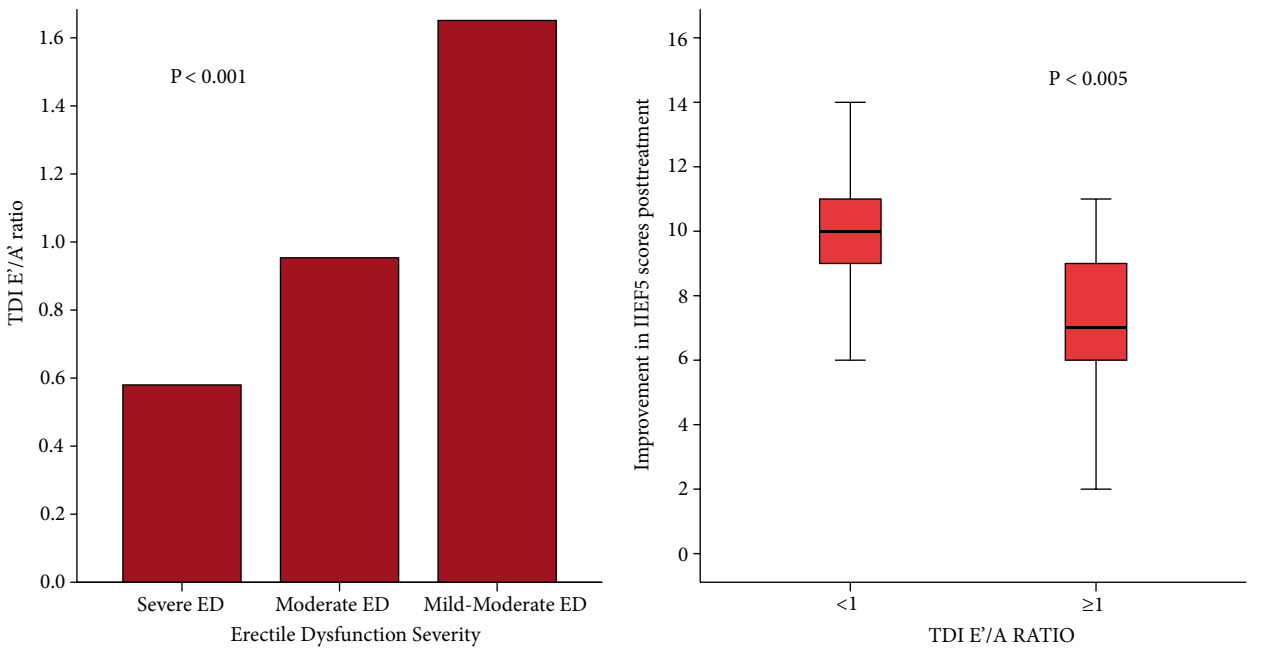

Figure. The relationship between the severity of pretreatment ED, the difference between post and pretreatment IIEF-5 scores, and TDI E′/A′ ratio.

treatment ($P < 0.005$).

HRR1 and HRR2 are parameters related to autonomic dysfunction. The normal range of HRR1 is over 12 beats/min. A result of 12 beats/min or below is an indicator of autonomic dysfunction in patients (10). In our patient population, the mean value of HRR1 was 28 ± 10 beats/min. None of our patients were in the limits of autonomic dysfunction. Doğru et al. reported the presence of autonomic dysfunction in ED patients (11). When we compared HRR1 values and pretreatment IIEF-5 scores, we did not find any significant difference, but there was a weak positive correlation ($P = 0.477$, $r = 0.140$). When we subgrouped patients according to the severity of ED, the mean values of HRR1 in severe and moderate ED patients were 22.7 ± 3.6, and 30.1 ± 11.8, respectively. The comparison of severe and moderate ED patients by means of HRR1 yielded a statistically significant difference ($P < 0.05$). These results demonstrated that if the severity of ED increases, HRR1 as an indicator of autonomic dysfunction decreases. In the study by Doğru et al., patients were only classified as having ED or not; there was no subgrouping such as severe, moderate, and mild. This was the probable cause of statistically significant values gathered in their study.

The endothelium is the major contributor of vascular homeostasis; it provides vasodilatation, inhibition of inflammation, and suppression of smooth muscle growth. These effects are mostly mediated by nitric oxide. Nitric oxide inhibits atherosclerosis by providing vasodilatation, decreases low-density lipoprotein oxidation, reduces platelet aggregation to the endothelium, inhibits smooth muscle proliferation, and prevents leukocyte adhesion and infiltration into the vessel (12).

Flow-mediated dilatation (FMD) is the most widely used noninvasive test for assessing endothelial function. In a prior study, ED severity, clinical response to PDE5I, and structural/vascular changes in hypertensive patients were evaluated. Responders to vardenafil were younger and had a lower cardiovascular risk profile, higher FMD in brachial artery, and higher baseline IIEF-5 score. The study also noted that intima-media thickness of the carotid artery was an independent factor associated with ED severity, and FMD was the best predictor of clinical response to vardenafil. The study revealed that even though there was no clinical sign of vasculogenic dysfunction, ED was associated with vascular changes, probably because of endothelial dysfunction (13). In our study, none of the patients had systolic dysfunction or known vasculogenic disease, but results showed a statistical correlation between diastolic dysfunction parameters and baseline IIEF-5 scores. Patients with worse diastolic functions had lower baseline IIEF-5 scores and responded better to vardenafil treatment.

Systolic dysfunction causes decrement in exercise capacity, as measured by the treadmill exercise test. In our patient population, ejection fraction and stroke volume values were within the normal range, and cardiac instability was one of our exclusion criteria. Based on these variables, we can conclude that none of our patients had clinical systolic dysfunction. Exercise test duration and exercise capacity in MET are parameters directly related with exercise capacity. Diastolic dysfunction also causes decrement in exercise capacity.

It can be said that the difference between post- and pretreatment IIEF-5 values shows us the beneficial effects of treatment. With the help of correlation analysis, we can propose that treadmill exercise test duration has a positive significant correlation with pretreatment IIEF-5 scores and a negative significant correlation with the difference of post- and pretreatment IIEF-5 scores. This indicates that in the patients with better cardiac performance, pretreatment IIEF-5 scores were higher, and if the treadmill exercise test duration of the patient is lower, the beneficial effect of vardenafil becomes more evident. The same correlation was seen also in exercise capacity in MET.

In the present study, the patients had neither systolic dysfunction nor significant diastolic dysfunction. As a diastolic function indicator, TDI E′/A′ positively correlates with pretreatment IIEF-5 scores and negatively correlates with the beneficial effect of vardenafil treatment. Similarly, it seems that cardiac performance is positively correlated with pretreatment IIEF-5 scores and negatively correlated with the beneficial effect of vardenafil treatment. As a result, the cardiological status of the patient correlates with individual IIEF-5 scores, and it seems to be useful in

References

1. Nagao K, Kimoto Y, Marumo K, Tsujimura A, Vail GM, Watts S, Ishii N, Kamidono S. Efficacy and safety of tadalafil 5, 10, and 20 mg in Japanese men with erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled study. Urology 2006; 68: 845–851.
2. Brisson TE, Broderick GA, Thiel DD, Heckman MG, Pinkstaff DM. Vardenafil rescue rates of sildenafil nonresponders: objective assessment of 327 patients with erectile dysfunction. Urology 2006; 68: 397–401.
3. Souverein PC, Egberts AC, Meuleman EJ, Urquhart J, Leufkens HG. Incidence and determinants of sildenafil (dis) continuation: the Dutch cohort of sildenafil users. Int J Impot Res 2002; 14: 259–265.
4. Murad Basar M, Atan A, Tekdogan ÜY, Batislam E. A classification based on peak systolic velocity and end diastolic velocity predicts sildenafil citrate success. Scand J Urol Nephrol 2003; 37: 502–506.

5. El-Sakka AI, Morsy AM, Fagih BI. Severity of erectile dysfunction could predict left ventricular diastolic dysfunction in patients without overt cardiac complaint. J Sex Med 2011; 8: 2590–2597.

6. Jackson G, Nehra A, Miner M, Billups KL, Burnett AL, Buvat J, Carson CC, Cunningham G, Goldstein I, Guay AT et al. The assessment of vascular risk in men with erectile dysfunction: the role of the cardiologist and general physician. Int J Clin Pract 2013; 67: 1163–1172.

7. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999; 11: 319–326.

8. Canat L, Cicek G, Atis G, Gurbuz C, Caskurlu T. Is there a relationship between severity of coronary artery disease and severity of erectile dysfunction? Int Braz J Urol 2013; 39: 465–473.

9. Solak Y, Akilli H, Kayrak M, Aribas A, Gaipov A, Turk S, Perez-Pozo SE, Covic A, McFann K, Johnson RJ et al. Uric acid level and erectile dysfunction in patients with coronary artery disease. J Sex Med 2014; 11: 165–172.

10. Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. Circulation 2006; 114: 2070–2082.

11. Dogru MT, Basar MM, Haciislamoglu A. The difference of heart rate recovery between males with and without erectile dysfunction. Ann Noninvasive Electrocardiol 2010; 15: 223–229.

12. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation 2004; 109: III27–III32.

13. Javaroni V, Queiroz-Miguez M, Abreu-Casanova M, Oigman W, Neves MF. Brachial flow-mediated dilation correlates with vardenafil response in hypertensive men with vasculogenic erectile dysfunction. Urology 2011; 78: 368–374.