Endothelial Function and Ventricular Diastolic Function in Males with Erectile Dysfunction

Erektil Disfonksiyonlu Erkeklerde Endotel Fonksiyonları ve Ventriküler Diyastolik Fonksiyonlar

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ABSTRACT Objective: Erectile dysfunction (ED) is a highly prevalent disorder in general male population and is observed most frequently in pathologies involving vascular functions. It is well known that nitrous oxide is an important mediator in endothelial functions and myocardial functions are influenced by nitrous oxide from coronary microcirculation. In this cross-sectional case-control study we evaluated endothelial functions and left ventricular diastolic functions in patients with ED. **Material and Methods:** Twenty-seven male patients with ED (mean age 52 ± 5) without overt cardiovascular involvement were compared with 31 healthy male controls (mean age 55 ± 8) in terms of endothelial functions and left ventricular diastolic functions. Endothelial functions were assessed by determining flow mediated dilatation and trinitroglycerine induced dilatation of brachial artery. Diastolic functions were assessed by tissue Doppler echocardiography. **Results:** Patient and control groups were similar in regard of the history of smoking, hypertension, body mass index, and serum lipid profiles. None of the participants was diabetic. Diastolic functions assessed by tissue Doppler echocardiographic examination were not statistically significant between groups. While trinitroglycerine-induced brachial artery dilatation was not statistically significant between groups ($p= 0.27$), flow mediated dilatation was revealed statistically significant impairment in patients with ED ($p< 0.01$). Besides, the increase in blood flow during hyperemia was significantly lower in ED patients than controls ($p< 0.01$) despite a higher baseline blood flow determined in ED patients ($p< 0.01$). **Conclusion:** Results of our study showed impaired endothelial functions which are assessed by flow-mediated dilatation of brachial artery and lower increase in blood flow during hyperemia in patients with ED than controls. However, our study group had preserved left ventricular diastolic functions.

Key Words: Erectile dysfunction; endothelium, vascular; diastole

ÖZET Amaç: Erektil disfonksiyon (ED) genel erkek popülasyonunda sıklıkla rastlanılan bir hastalıktır ve genellikle vasküler fonksiyonları etkileyen patolojilerle birliktedir. Nitrik oksit endotel fonksiyonlarında önemli bir mediyatördür ve koroner mikrosirkülasyondan salınan nitrik oksitin miyokardiyal fonksiyonları etkilediği bilinmektedir. Bu kesitsel vaka-kontrol çalışmasında ED'si olan hastalarda endotel fonksiyonları ve miyokardiyal diyastolik fonksiyonları değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Belirgin kardiyovasküler hastalığı olmayan ED'li 27 erkek hasta (ortalama yaş 52 ± 5) ve 31 sağlıklı erkek (ortalama yaş 55 ± 8) çalışmaya alınarak endotel fonksiyonları ve sol ventrikül diyastolik fonksiyonları karşılaştırıldı. Endotel fonksiyonları brakiyal arterin akım aracılı dilatasyonu ve trinitrogliserin aracılı dilatasyonu belirlenerek değerlendirildi. Diyastolik fonksiyonlar ise doku Doppler ekokardiyografiyle belirlendi. **Bulgular:** Hasta ve kontrol grupları sigara kullanımı, hipertansiyon varlığı, beden kitle indeksi ve serum lipid profilleri açısından birbirine benzerdi. Hiçbir olguda diyabet yoktu. Gruplar arasında doku Doppler incelemesiyle belirlenen diyastolik fonksiyonlar açısından istatistiksel öneme ulaşan fark yoktu. Brakiyal arterin trinitrogliserin aracılı dilatasyonu için gruplar arasında istatistiksel olarak belirgin fark saptanmazken ($p= 0.27$) akım aracılı dilatasyon ED'li olgularda istatistiksel olarak belirgin şekilde bozulmuştu ($p< 0.01$). Bunun yanı sıra başlangıçtaki kan akımı ED'li grupta kotrol grubuna göre anlamlı şekilde fazla olmasına rağmen ($p< 0.01$) hiperemi sırasında kan akımındaki artış ED'li olgularda kontrol grubuna göre anlamlı derecede azdı ($p< 0.01$). **Sonuç:** Çalışmamızın sonuçları ED'li olgularda kontrol grubuna göre brakiyal arterin akım aracılı dilatasyonu ve hiperemi sırasındaki kan akımındaki artışla belirlenen endotel fonksiyonlarının bozulduğunu ortaya koymaktadır. Ancak bizim hasta grubumuzda diyastolik fonksiyonlar korunmuştu.

Anahtar Kelimeler: Erektil disfonksiyon; endotel, vasküler; diyastol

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Erectile dysfunction (ED) is a highly prevalent disorder in the general population, as it affects almost 50% of males aged 40-70 years.[1-3] ED is multifactorial in origin; psychogenic and/or organic mechanisms were held responsible for its development, and is observed most frequently, in pathologies involving vascular functions, such as diabetes mellitus, hypertension, atherosclerosis and smoking.[4-8] Current knowledge suggest that the impairment of endothelial dysfunction is the link between ED and the aforementioned diseases.[9-11]

Noninvasive assessment and diagnosis of the endothelial dysfunction before the clinical signs and symptoms emerge is important in terms of yielding early interventions to prevent the vascular disease. Endothelial dysfunction can be detected by a noninvasive imaging technique. This technique utilizes endothelium-dependent or flow-mediated dilation (FMD) of the brachial artery, which was validated.[12,13]

It is well known that myocardial contraction itself is influenced by nitrous oxide (NO) from coronary microvascular endothelium and NO increases diastolic compliance and slightly shortens the duration of contraction, with little or no effect on systolic function.[14] Taking all this into account, we hypothesized that these may be generalized dysfunction in the NO system. If this is the case, there should also be impairment in endothelial function and left ventricular diastolic function. To ascertain the influence of systemic endothelial dysfunction we designed this cross-sectional case-control study in patients with erectile dysfunction at least for one year and free of overt cardiovascular disease.

MATERIAL AND METHODS

The patient group consisted of 27 males (with a mean age of 52 ± 5 years) complaining with ED with an International Index of Erectile Function (IIEF-5) score 16 or lower (moderate and severe ED).[15] Age-matched 31 healthy male subjects (with a mean age of 55 ± 8) were accepted as control group. None of the study group patients were diagnosed as having any obstructive vascular involvement by ultrasonography, angiography or any conventional radiologic examination within at least 5 years. This study was reviewed and approved by the local ethics committee (ethics committee number 944) and signed written informed consents were obtained from all participants.

A standard form was utilized for the documentation of the presence or absence of the known risk factors for atherosclerotic vascular disease, including diabetes mellitus, hypertension, smoking and dyslipidemia. Diabetes mellitus was defined as having a fasting blood glucose level above 126 mg/dL or being under anti-diabetic therapy. Hypertension was defined as blood pressure value above 140/90 mmHg after ten minutes rest in sitting position. Current smokers regardless of the amount and duration were accepted as smoker. Subjects with a total cholesterol level above 200 mg/dL or low density lipoprotein-cholesterol level above 130 mg/dL were accepted as dyslipidemic. Pelvic surgery or trauma, prostatic disease, neurological or psychiatric diseases, penile curvature, stroke, coronary heart disease, intermittent claudication, moderate or heavy alcohol consumption (more than 30 mL ethanol) and recreational drug users were all excluded from the study. Participants who completed a self-administered multicomponent questionnaire that explored the medical conditions such as DM, hypertension, hyperlipidemia or any other current conditions were included to this study. All this investigation was held under the routine practice of our hospital.

FMD of the brachial artery diameter was performed utilizing a high-resolution 7 MHz linear array ultrasound transducer, equipped with a standard echocardiography machine (GE VIVID III, Norway). All subjects were prepared according to the principles of International Brachial Artery Reactivity Task Force report.[16] The measurements were taken in the morning after at least 12 hours of fasting state when the patient was in supine position for 20 minutes in a quiet room. The subjects were abstained from vitamin C intake, fatty meals, cigarette smoking and caffeine-containing drinks for at least 12 h before testing. The left arm was po-

sitioned by extending the elbow and immobilized with a board. The best visualization of the brachial artery was obtained by scanning in the longitudinal section 4-5 cm above the left antecubital fossa. Gain and depth sector settings were optimized to identify the lumen-vessel wall interface. After optimal transducer positioning, the skin was marked by a permanent marker for reference of later measurements and the left arm was kept in the same position throughout the study.

The brachial artery internal diameter was measured as the distance between the intima-media border zones of the brachial artery from anterior to posterior (at the end of the diastole (peak of by the QRS complex)). The average of measurements obtained during three consecutive cardiac cycles was used in statistical analysis. In order to create forearm ischemia, the blood pressure sphygmomanometer cuff was placed approximately 3-4 cm proximal to the section of the brachial artery and inflated to above 200 mmHg until no Doppler activity was present for 5 min. Then the cuff was deflated and reactive hyperemia was measured within 60 sec after deflation.

In addition to endothelium-dependent dilation, endothelium-independent dilation was also assessed by measuring changes in brachial artery diameter following sublingual glyceryl trinitrate (400 µg Nitrolingual Spray) administration to all patients. The changes in preload, which were nitrate dependent, were assessed from the mitral annular level tissue Doppler (Em) measurements and the changes in afterload reduction were assessed as percentage change in the brachial artery diameter relative to their respective baseline measurements.

All patients underwent a complete two-dimensional transthoracic echocardiographic and Doppler study in the left lateral decubitus position from multiple windows. All studies were performed with a standard echocardiography machine (GE VIVID III, Norway) equipped with a 2.5 MHz transducer. All echocardiographic measurements were performed according to recommendations of the American Society of Echocardiography.[17] Tissue Doppler imaging (TDI) was performed with transducer frequencies of 1,8-3,6 MHz with as minimum optimal gain as possible to obtain the best signal to noise ratio. In the apical four chamber view, a 5 mm pulsed Doppler sample volume was placed at the level of the lateral mitral annulus, basal septal and lateral tricuspid annulus.[18] The incident angle between the interrogating Doppler beam and longitudinal motion of the ventricle was kept as small as possible and the measurements were performed while all individuals were holding their breath. The myocardial systolic wave (Sm) velocity, the diastolic indices of myocardial early (Em) and atrial contraction (Am) peak velocities were all measured. Tissue Doppler echocardiographic and brachial artery diameter measurements were obtained before and 3 minutes after every sublingual nitroglycerin spray application.

All variables were expressed as mean ± standard deviation. All measurements were performed by two investigators, which were blinded to all subjects and all measurements were performed three times and the final average were included into the statistical analysis.

ECHOCARDIOGRAPHIC REPRODUCIBILITY

The interobserver and intraobserver reproducibility of the echocardiographic measurements were 76% and 83% and the intraobserver reproducibility of the ultrasonographic measurements was 73% respectively. The intraobserver and interobserver variability were 10% and 15% for the echocardiographic and the intraobserver variability of the ultrasonographic brachial artery diameter assessment was 9%.

STATISTICAL ANALYSIS

A total of data were analysed by SPSS 11.5 (SPSS Inc., Chicago, Il, USA) software. Continuous variables were expressed as mean ± standard deviation, and categorical variables as percentage. In comparison of the variables student t test and Mann-Whitney U test were used according to the normality test results which were tested by Kolmogrow–Smirnow test. Statistical significance was defined as a p value < 0.05.

RESULTS

The demographic and baseline characteristics of ED patients and healthy control groups are given in Table 1. Baseline values of study group and controls were comparable in terms of age, body mass index (BMI), serum fasting glucose, serum lipids, blood pressure, history of hypertension and smoking. None of study patients were previously or finally diagnosed with DM as well as stroke or neuropathy. Both groups were examined for clinical symptoms or signs of vascular disease and none of them were previously diagnosed as vasculopathy. Erectile dysfunction group's mean IIEF-5 score was assessed as 10 ± 6.

None of ED group subjects were on any treatment (statin, angiotensin-converting enzyme inhibitor therapy). There was no difference between groups in terms of echocardiographic and tissue Doppler parameters as well as baseline brachial artery diameters (Tables 2, 3).

We have found that FMD was 15.7 ± 2.4% for the ED group, and 21.4 ± 6.4% for the control group. Flow mediated dilatation (Endothelium-dependent dilatation) demonstrated 27% impairment comparing to control group in ED group, ($p< 0.01$) (Table 3). Nitroglycerine utilized dilatation (Endothelium-independent dilatation) was not differing in ED and control groups (Table 3).

TABLE 1: Characteristics and baseline measurements of the study and control groups.

	ED Group (n= 27)	Control (n= 31)	p
Age (Years)	55 ± 8	52 ± 5	0.15
BMI (kg/m^2)	27 ± 2	26 ± 2	0.06
Smoker (%)	9 (33%)	8 (26%)	0.533
Hypertension (%)	1 (4%)	0 (0%)	0.284
Systolic blood pressure (mmHg)	123 ± 11	124 ± 9	0.78
Diastolic blood pressure (mmHg)	80 ± 5	78 ± 4	0.19
Serum fasting glucose (mg/dL)	91 ± 12	87 ± 22	0.41
Total cholesterol (mg/dL)	155 ± 70	160 ± 60	0.81
HDL cholesterol (mg/dL)	33 ± 9	31 ± 7	0.47
LDL cholesterol (mg/dL)	101 ± 29	95 ± 22	0.42
Triglycerides (mg/dL)	145 ± 55	141 ± 62	0.86

ED: Erectile dysfunction, BMI: Body mass index, HDL: High-density lipoprotein, LDL: Low-density lipoprotein.

TABLE 2: Standard and tissue Doppler echocardiographic measurements of the study and control groups.

	ED Group (n= 27)	Control (n= 31)	p
EF (%)	66 ± 4	68 ± 5	0.09
FS (%)	36 ± 4	37 ± 3	0.38
Mitral Lateral S wave (cm/sec)	9 ± 2	10 ± 2	0.06
Mitral Lateral E wave (cm/sec)	12 ± 2	11 ± 2	0.06
Mitral Lateral A wave (cm/sec)	9 ± 3	10 ± 2	0.11
Septal S wave (cm/sec)	12 ± 3	13 ± 2	0.13
Septal E wave (cm/sec)	11 ± 4	12 ± 3	0.34
Septal A wave (cm/sec)	9 ± 2	10 ± 2	0.06
RV Lateral S wave (cm/sec)	17 ± 5	18 ± 4	0.47
RV Lateral E wave (cm/sec)	15 ± 2	16 ± 3	0.19
RV Lateral A wave (cm/sec)	13 ± 4	12 ± 2	0.24

ED: Erectile dysfunction, RV: Right ventricle.

TABLE 3: Brachial artery endothelial functional measurements of the study and control groups.

Brachial artery measurements	ED Group (n= 27)	Control (n= 31)	p
Baseline vessel diameter size (mm)	4.1 ± 0.3	4.2 ± 0.2	0.19
Baseline blood flow (mL/min)	157 ± 48	121 ± 41	<0.01
Increase in vessel diameter size during hyperemia (mm)	4.6 ± 0.5	4.8 ± 0.4	0.14
Increase in blood flow during hyperemia (mL/min)	218 ± 112	366 ± 172	<0.01
FMD (%)	15.7 ± 2.4	21.4 ± 6.4	<0.01
NTG-induced vasodilation (%)	18.4 ± 6.2	20.2 ± 5.3	0.27

ED: Erectile dysfunction, FMD: Flow mediated dilation, NTG: Nitroglycerin.

Standard conventional echocardiographic measurements and mitral annular tissue Doppler parameters were also found similar for both ED and control groups (Table 2).

DISCUSSION

Our study has shown that endothelial functions were impaired with preserved both left and right ventricular diastolic functions in patients with ED group comparing to the controls. Flow-mediated vasodilatation (reactive hyperemic response) was significantly lower in ED group comparing to controls (4.2% vs. 10%), which indicates 27% impaired vascular response to reactive hyperemia in patients with ED.

NO is a key role element controlling the endothelial response to circulatory changes and circulatory demands. Its release is required for a complete vasodilator response.[18,19] Besides neural and humoral factors, local mechanisms intrinsic to the vascular wall have an important role for the regulation of tissue blood flow.[19,20] Penile erection is a vascular event whereby this nitric oxide, released by parasympathetic nonadrenergic noncholinergic nerves and vascular endothelium induces smooth muscle cell relaxation in the corpus cavernosum and cavernous arteries.[20-22] Therefore, an association between ED, endothelial dysfunction and atherosclerosis without overt vascular involvement is expected.[23-26] The high content of endothelium (compared with other organs) may make the penile vascular bed a sensitive indicator of vascular disease.[27] Moreover, the increase in blood flow during hyperemia was significantly lower in ED patients than controls despite a higher baseline blood flow determined in ED patients also reflects endothelial dysfunction.

A recent study showed impaired diastolic functions in patients with ED.[28] Left ventricular diastolic dysfunction may also be the result of systemic NO dysfunction, which decreases diastolic compliance with little or no effect on systolic function.[14] Diastolic dysfunction may also be a consequence of the adverse influence of endothelial function on diastolic function.[29] However, results of our study did not support these findings, which may be related to concomitant diseases such as hypertension and DM which are highly prevalent in patients with ED. In our study protocol DM was an exclusion criteria and only one of our participants has hypertension.

Decreasing cholesterol levels, increasing HDL-C levels or controlling hypertension slows atherosclerosis progression concomitantly with a reduced progression of coronary artery atherosclerosis and a decreased number of cardiovascular events.[24] Therefore, the presence of ED in men with known vascular risk factors may help in identifying, by ultrasonographic determination of FMD, which was clearly demonstrated in our study.[30]

Patients with an impaired FMD and increased vascular risk factors, which means the increased risk of future vascular events deserves a more aggressive treatment. Whether the correction of vascular risk factors in men with ED has an impact on erectile function is still largely undetermined.

In conclusion; the pathogenesis of vascular involvement and the tendency to atherosclerotic vascular disease have not yet been clearly identified. We recommend following all male patients with ED for the risk of endothelial dysfunction with such an easily applicable ultrasonographic method during their routine clinical follow-up, which may save time and be cost-effective. Further studies are needed to elucidate the role of endothelial dysfunction in ED, which may determine the development of vascular disease in patients with ED.

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