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Original Article UROLOGY

Relationship between heart rate recovery index and erectile dysfunction

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ABSTRACT

OBJECTIVE: Heart rate recovery (HRR) is a cardiac parameter that can be used to evaluate autonomic nervous system (ANS) function problems. We examined the possible relationship between erectile dysfunction (ED) and HRR which is a clinical condition associated with ANS dysfunction.

METHODS: Seventy-six male patients that were examined with an exercise stress test and completed the International Index of Erectile Function Questionnaire Form (IIEF-5) were included in the study. The patients were divided into two groups as those with a normal HRR index (≥12, n=42) and those with an abnormal HRR index (<12, n=34). Then, statistical analyses were conducted to evaluate the correlations between ED and HRR.

RESULTS: There were no differences between the groups in terms of risk factors, such as laboratory findings, age, BMI, hypertension, and smoking. However, in the group with an abnormal HRR index, the IIEF-5 score was significantly lower than the other group (11.2±4.2 vs. 20.3±4.6, p<0.001). A statistically significant positive correlation was observed between the IIEF-5 score and HRR index (r=0.702, p<0.001). In addition, the presence of diabetes mellitus and HRR index was independent risk factors for lowering the IIEF-5 score.

CONCLUSION: The HRR index can be considered as an independent predictor of ED since a reduced value, which is associated with cardiovascular mortality and also causes ANS dysfunction.

Keywords: Autonomic dysfunction; erectile dysfunction; heart rate recovery.

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Erectile dysfunction (ED) is defined as the inability to maintain or maintain penile stiffness for the proper duration of sexual intercourse [1]. The coexistence of ED and cardiovascular diseases is common since they share many etiological causes, such as hypertension, diabetes, hyperlipidemia, obesity, decreased physical activity, smoking, malnutrition, excessive alcohol consumption, and psychological stress [2, 3]. Physiologically, autonomic activity affects many other processes, including penile erection in men. Erection is a physiological condition formed by the control of the autonomic nervous system (ANS). During the formation of an erection, cyclic guanosine-5'-monophosphate is synthesized with the activation of the parasympathetic system, leading to an increase in the blood flow to the penis with the relaxation of the muscles in corpora cavernosa [4]. In a recent study, it was suggested that ANS dysfunction that develops with the impairment of the balance between sympathetic and parasympathetic activity can cause ED [5].

The heart rate recovery (HRR) index is expressed as the arithmetic difference between the highest heart rate and the heart rate observed during a certain time of a

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rest period [6]. Normally, during rest after intense exercise, the fastest decrease in the heart rate is observed within the first 30 s, followed by a slower decrease [7]. It was reported that the decrease in the heart rate in the early period occurred due to the activation of the parasympathetic system, and the decrease in the heart rate in the late period developed due to the loss of the effect of the sympathetic system [8]. It is considered that the major cause of this disorder in HRR is probably associated with both vagus nerve dysfunction and increased sympathetic activity [9]. ANS plays a key role in the regulation of cardiac and vascular systems, and ANS dysfunction has also been associated with cardiovascular morbidity and mortality [10]. The HRR index is one of the non-invasive clinical tests used to detect cardiac autonomic dysfunction [6]. Furthermore, a reduction in the HRR index has also been shown to be an independent risk factor for cardiovascular mortality [11].

An important feature of HRR is that it can also be a modifiable risk factor for cardiovascular diseases. There are studies showing that regular physical activity, which is an essential component of cardiac rehabilitation programs, leads to an improvement in HRR due to its sympatholytic and parasympathetic activity and results in a proven improvement in erection quality related to ANS activity in men [12, 13]. In this study, starting from this idea, we planned to explain the common pathogenesis between HRR and ED and to investigate whether the HRR index could be used as an ED predictor.

Highlight key points

- Erection is a physiological process that is regulated by the autonomic nervous system and occurs as a result of parasympathetic activity.
- Heart rate recovery (HRR) is a non-invasive cardiac parameter and is a useful diagnostic tool in demonstrating autonomic dysfunction.
- In our study, we found that decreased HRR was associated with erectile dysfunction.
- Although we usually detect erectile dysfunction due to vasculogenic causes in clinical practice, we emphasize that ED can also be seen as a result of autonomic dysfunction and HRR should be kept in mind as a diagnostic tool when autonomic dysfunction is suspected in erectile dysfunction.

MATERIALS AND METHODS

This cross-sectional study was conducted in the department of urology and cardiology. Male patients that underwent the stress test with the suspicion of coronary artery disease were included in the study. Blood samples were analyzed in terms of a detailed biochemical profile, serum lipid profile, and complete blood count, and hormonal analysis, including luteinizing hormone (LH), prolactin, total testosterone (TT), free testosterone, and dehydroepiandrosterone sulfate (DHEA-S). All serum samples were taken after 12 h of fasting. The stress test was applied according to the Bruce protocol consisting of the parameters of resting pulse rate, resting systolic blood pressure, resting diastolic blood pressure, peak heart rate, percentage of heart rate achieved, exercise duration, maximum heart rate, maximum systolic blood pressure during testing, and maximum diastolic blood pressure during testing. HRR was determined by subtracting the 1st min resting heart rate from the highest heart rate reached during the stress test.

As explained previously, the patient's inability to reduce the heart rate by 12 beats while standing up within the 1st min after the stress test was considered abnormal HRR [14]. Estimated maximum heart rate was calculated by subtracting the age of the participant in 220. The International Index of Erectile Function Questionnaire (IIEF-5) was administered by the department of urology to all patients to assess sexual satisfaction. Patients with IIEF-5 scores <22 were considered as having ED.

Patients with severe hypertension (≥230/120 mmHg) and malignant arrhythmia, who were unable to reach 85% of the maximal heart rate during the stress test, an indicator of chronotropic incompetence, and those that were shown to be isochemically positive during the test were excluded from the study. Further excluded were patients with chronic heart failure, coronary artery disease, heart valve disease, chronic liver disease, end-stage chronic renal failure (glomerular filtration rate <30 mL/min), those undergoing hemodialysis treatment, those with thyroid dysfunction, cancer history, autoimmune and connective tissue disease, bradycardia or tachycardia, obstructive or restrictive lung disease or neurological/psychiatric disorder, obese patients with a body mass index (BMI) of >30, and patients using drugs, such as antiarrhythmics, phosphodiesterase inhibitors and beta-blockers, or receiving hormonal treatment. In addition, considering the levels of TT, free testosterone, DHEA-S, and LH in the hormone panel, patients with hypogonadism were excluded from the study due to affect erectile function. After applying the exclusion criteria, the remaining 76 patients were further evaluated. These patients were divided into two groups as those

with a normal HRR index (≥12, n=42) and those with an abnormal HRR index (<12, n=34), and comparative statistical analyses were undertaken between the groups.

The Ataturk University Faculty of Medicine Clinical Research Ethics Committee of our hospital approved the study procedures (IRB Number: B.30.2.ATA.0.01.00/355).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 20.0 (SPSS, Inc., Chicago, IL). Variables with normal distribution were presented as mean±standard deviation, and those without normal distribution were presented as median with minimum and maximum range. To compare parametric continuous variables, Student's t-test was used; to compare non-parametric continuous variables, the Mann–Whitney U-test was used. Categorical variables were expressed as percentages and compared between the groups using the Chi-square. The variables showing significant differences between the abnormal HRR index and normal HRR index group were included in a correlation analysis. For the correlation analysis, Pearson's and Spearman's rank tests were used. Variables showing significant correlations were further included in multivariate regression analysis to test whether or not they might be independent risk factors for lowering IIEF-5 score. For this purpose, significant factors obtained from the univariate analysis ($p<0.02$) were included in the multivariate analysis. Differences were considered significant at $p<0.05$.

RESULTS

The main characteristics of the patients are shown in Table 1. There were no statistical differences between the normal HRR and abnormal HRR groups in terms of height, weight, BMI, smoking status, and hormone levels; however, diabetes mellitus, dyslipidemia, low-density lipoprotein (LDL) cholesterol, exercise duration, and resting 1st min heart rate were significantly different ($p<0.05$ for all). In addition, in the patient group with an abnormal HRR index, the IIEF-5 score was significantly lower than the other group (11.2±4.2 vs. 20.3±4.6, $p<0.001$). In correlation analysis, IIEF-5 score was significantly positively correlated with HRR index, exercise duration, and resting 1st min heart rate ($r=0.702$, $p<0.001$, $r=0.302$, $p=0.024$, and $r=0.406$, $p<0.002$, respectively), and significantly negatively correlated with LDL cholesterol ($r=-0.458$, $p<0.001$). Multivariate regression analysis of our study revealed that the presence of diabetes mellitus and HRR index was the independent risk factors for significantly lowering the IIE F-5 score (Table 2).

DISCUSSION

ANS is one of the building blocks required for the normal functioning of the cardiovascular system. In clinical practice, ANS can be evaluated indirectly using heart rate variability (HRV) [15]. Although HRV provides some important information about the body's autonomous activities, this parameter is not able to present clear information about ANS response to the stress exercise test [7]. In other words, dynamic changes in autonomous activity cannot be sufficiently detected with HRV alone. Therefore, in our study, we used the exercise stress test since it offers the opportunity to evaluate both the cardiovascular system and autonomic pathology at the same time. During exercise, the heart rate increases, and after the end of exercise, it slows down, which is a process controlled by ANS. It has been shown that during exercise, sympathetic activity increases and parasympathetic activity is suppressed, leading to an increase in the heart rate [16]. At rest, the balance increases in favor of the parasympathetic system, and thus, the heart rate slows down [16]. HRR has been shown to occur with the reactivation of the parasympathetic system, which is suppressed between the 30 s and the 2nd min of the rest phase [7]. These findings show that parasympathetic system activity is suppressed during exercise and during the 1st min of recovery, and then increases continuously up to 4 min after exercise and remains stable for up to 10 min after recovery [17]. The HRR index is a non-invasive parameter used to evaluate the autonomic response of the heart, and it is a direct indicator of parasympathetic system activity [18]. In patients with abnormal HRR index, heart rate cannot be decreased more than 12 heartbeats per minute at rest, since the parasympathetic system, which should be active during the resting phase, is not active enough. In patients with abnormal HRR index, it is assumed that a suppressed parasympathetic system generally affects the whole body [19]. The parasympathetic system must be activated for an erection to occur. Furthermore, some researchers reported that an imbalance between the sympathetic and parasympathetic system, especially increased sympathetic system activity and decreased parasympathetic

Table 1. Baseline demographic, clinical, laboratory, and exercise stress test data of the participants

	Abnormal HRR index (n=34)	Normal HRR index (n=42)	p
Age, years	54.2±7.9	48.2±8.3	0.433***
Diabetes mellitus, %	53	29	0.014**
Hypertension, %	41	32	0.645**
Smoker, %	27	26	0.713**
Dyslipidemia, %	44	50	0.038**
BMI (kg/m^2)	26.2±3.3	26.4±4.1	0.862***
Blood glucose	132 (79–173)	121 (68–184)	0.076*
Creatinine (mg/dL)	0.77±0.15	0.73±0.14	0.613***
eGFR (mL/min/1.73 m^2)	89.1±11.2	87.4±13.2	0.372***
Total cholesterol (mg/dL)	174 (147–203)	191 (152–232)	0.072*
HDL (mg/dL)	56.2±8.5	55.1±9.7	0.159***
LDL (mg/dL)	124 (89–152)	87 (64–133)	0.024*
Total testosterone (ng/ml)	4.6±1.2	5.0±1.8	0.543***
Free testosterone (pg/ml)	10 (4–16)	11 (5–17)	0.689*
DHEA-S (µ/ml)	225 (274–302)	192 (132–247)	0.385*
LH (mIU/ml)	4.3±1.2	4.5±0.9	0.536***
Triglyceride (mg/dL)	188 (137–231)	191 (162–225)	0.182*
Hemoglobin (g/dL)	14.3±1.3	13.8±1.6	0.107***
White blood cell (10^3/µl)	5.3 (2.1–7.3)	6.6 (3.4–8.4)	0.431*
Lymphocytes 10^3/µL	2.1±1.6	2.2±1.1	0.284*
Platelet 10^3/mm^3	263 (199–356)	281 (201–332)	0.185*
Rest systolic BP (mmHg)	123.4±6.1	118.3±5.2	0.204***
Rest diastolic BP (mmHg)	76.2±5.2	73.4±4.5	0.328***
Exercise duration (min)	9.3±1.3	10.7±1.5	<0.001***
Resting 1st min heart rate (bpm)	126 (93–143)	143 (121–158)	0.002*
Peak heart rate (bpm)	143.4±16.8	166.3±18.4	0.058***
Starting heart rate	85 (67–103)	87 (69–108)	0.351*
HRR index	7.4±4.1	23.3±8.1	<0.001***
IIEF-5 score	11.2±4.2	20.3±4.6	<0.001***

*: Mann–Whitney U-test (data are given as median [IQR]); **: Chi-square test; ***: t-test (data are given as mean±SD); BMI: Body mass index; eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; DHEA-S: Dehydroepiandrostenedione sulfate; LH: Luteinizing hormone; HRR: Heart rate recovery; IIEF-5: International Index of Erectile Function Questionnaire.

system activity, could cause ED [15, 20]. Therefore, as we found in our study, we consider that increase in the incidence of ED in people with abnormal HRR index is probably related to due to the suppression of the parasympathetic system that takes an active role in erection. This is consistent with the study by Chen et al. [21] who evaluated patients with inorganic ED and determined that cardiac sympathetic hyperactivity increased in proportion to the severity of ED.

It is known that a well-functioning cardiovascular system is required for erection to occur. Observations in male groups with ED show that physical activity can have a beneficial effect on endothelial activity and simultaneously improve erection quality [22]. In addition, in patients with an abnormal HRR index, the sympathetic system cannot be activated sufficiently due to ANS dysfunction and a chronotropic incompetence occurs [18]. Similarly, in our study, although the heart rate of the patients at the beginning of exercise was similar, the peak heart rate was not sufficiently increased in patients with abnormal HRR index (143.4±16.8 vs. 166.3±18.4). Another result obtained from the current study is that

TABLE 2. Multivariate regression analysis results for determination of predictors of IIEF-5 score

Variables	β±SE	95% CI		p
		Lower	Upper	
Exercise duration (min)	0.804±0.303	0.187	1.211	0.062
Diabetes mellitus	−2.370±0.566	−4.104	−1.337	0.019
LDL (mg/dL)	−0.386±0.161	−0.706	−0.066	0.087
HRR index	2.942±0.732	1.136	4.273	<0.001

IIEF-5: International Index of Erectile Function Questionnaire; β: Regression coefficients; SE: Standard error; CI: Confidence interval; LDL: Low-density lipoprotein; HRR: Heart rate recovery.

the exercise duration was longer in patients with a normal HRR index. This supports the findings of Katka et al. [23] who reported that a reduced incidence of ED among patients with good exercise capacity. As a result, we think that chronotropic incompetence, low exercise capacity, and ANS dysfunction in this patient group all predispose to ED.

There are many complex methods to evaluate the ANS function; however, most are difficult to use in daily practice due to the need for special training and equipment. Therefore, the HRR index remains a useful and non-invasive tool used to measure autonomic activation [24]. The relationship between the changes in the HRR index and various diseases has been investigated, and it has been reported that a deterioration in HRR is an independent indicator of mortality due to cardiovascular causes [16, 19]. In our study, we investigated whether there is a difference in ED between patients with normal HRR and abnormal HRR index under exercise stress test. We examined that the HRR index could be a predictor for ED. In our multivariate regression analysis, we determined the HRR index as an independent risk factor of ED, as well as diabetes mellitus, which is also known to be a potential risk factor of this dysfunction. Therefore, we consider that in ED patients, the HRR index is a useful method that can be used to predict the risk of autonomic dysfunction and cardiovascular morbidity and mortality, based on reduced values. We believe that this issue will become clearer with further prospective studies.

The limitations of our study include broad exclusion criteria, relatively small sample size, and the lack of Doppler ultrasonographic confirmation for the ED diagnosis.

Conclusion

Reduced HRR after the stress test can be considered as an indicator of impaired autonomic function in ED patients. For this reason, we consider that in patients presenting with ED complaints and detected to have a decreased HRR index in the stress test, the collaboration of urologists and cardiologists can guide early diagnosis and planning of other diseases caused by autonomic dysfunction.

Ethics Committee Approval: The Ataturk University Clinical Research Ethics Committee granted approval for this study (date: 26.06.2020, number: B.30.2.ATA.0.01.00/355).

Informed Consent: Written informed consent form was signed by all participants.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. Am J Med 2007;120:151–7. [CrossRef]
2. Gupta BP, Murad MH, Clifton MM, Prokop L, Nehra A, Kopecky SL. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med 2011;171:1797–803. [CrossRef]
3. Jackson G. The importance of risk factor reduction in erectile dysfunction. Curr Urol Rep 2007;8:463–6. [CrossRef]
4. Ralph DJ. Normal erectile function. Clin Cornerstone 2005;7:13–8.
5. Jung J, Jo HW, Kwon H, Jeong NY. Clinical neuroanatomy and neurotransmitter-mediated regulation of penile erection. Int Neurourol J 2014;18:58–62. [CrossRef]
6. Lauer MS. Autonomic function and prognosis. Cleve Clin J Med 2009;76 Suppl 2:S18–22. [CrossRef]
7. Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yokoyama H, et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J Am Coll Cardiol 1994;24:1529–35. [CrossRef]
8. Sears CE, Choate JK, Paterson DJ. Inhibition of nitric oxide synthase slows heart rate recovery from cholinergic activation. J Appl Physiol (1985) 1998;84:1596–603. [CrossRef]
9. Ushijima A, Fukuma N, Kato Y, Aisu N, Mizuno K. Sympathetic excitation during exercise as a cause of attenuated heart rate recovery in patients with myocardial infarction. J Nippon Med Sch 2009;76:76–83.
10. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-rate recovery immediately after exercise as a predictor of mortality. N Engl J Med 1999;341:1351–7. [CrossRef]
11. Perret-Guillaume C, Joly L, Benetos A. Heart rate as a risk factor for cardiovascular disease. Prog Cardiovasc Dis 2009;52:6–10. [CrossRef]

12. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Heart rate recovery predicts sudden cardiac death in heart failure. Int J Cardiol 2010;144:121–3. [CrossRef]
13. Mensink GB, Ziese T, Kok FJ. Benefits of leisure-time physical activity on the cardiovascular risk profile at older age. Int J Epidemiol 1999;28:659–66. [CrossRef]
14. Youn HJ, Park CS, Moon KW, Oh YS, Chung WS, Kim JH, et al. Relation between Duke treadmill score and coronary flow reserve using transesophageal Doppler echocardiography in patients with microvascular angina. Int J Cardiol 2005;98:403–8. [CrossRef]
15. Giuliano F, Rampin O. Neural control of erection. Physiol Behav 2004;83:189–201. [CrossRef]
16. Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. J Am Coll Cardiol 2003;42:831–8. [CrossRef]
17. Kannankeril PJ, Le FK, Kadish AH, Goldberger JJ. Parasympathetic effects on heart rate recovery after exercise. J Investig Med 2004;52:394–401. [CrossRef]
18. Okutucu S, Karakulak UN, Aytemir K, Oto A. Heart rate recovery: a practical clinical indicator of abnormal cardiac autonomic function. Expert Rev Cardiovasc Ther 2011;9:1417–30. [CrossRef]
19. Jae SY, Carnethon MR, Heffernan KS, Fernhall B, Lee MK, Park WH. Heart rate recovery after exercise and incidence of type 2 diabetes in men. Clin Auton Res 2009;19:189–92. [CrossRef]
20. Cheitlin MD. Sexual activity and cardiac risk. Am J Cardiol 2005;96:24M–8M. [CrossRef]
21. Chen CJ, Kuo TB, Tseng YJ, Yang CC. Combined cardiac sympathetic excitation and vagal impairment in patients with non-organic erectile dysfunction. Clin Neurophysiol 2009;120:348–52. [CrossRef]
22. Lee JY, Joo KJ, Kim JT, Cho ST, Cho DS, Won YY, et al. Heart rate variability in men with erectile dysfunction. Int Neurourol J 2011;15:87–91. [CrossRef]
23. Kałka D, Domagała Z, Dworak J, Womperski K, Rusiecki L, Marciniak W, et al. Association between physical exercise and quality of erection in men with ischaemic heart disease and erectile dysfunction subjected to physical training. Kardiol Pol 2013;71:573–80. [CrossRef]
24. Kałka D, Domagała Z, Rusiecki L, Karpiński Ł, Gebala J, Kolęda P, et al. Heart rate recovery, cardiac rehabilitation and erectile dysfunction in males with ischaemic heart disease. Anatol J Cardiol 2016;16:256–63.