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·*Original Article*·

Assessment of the autonomic nervous system is an appropriate biological marker for the well-being in erectile dysfunction*

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Abstract

Aim: To investigate whether the autonomic nervous system (ANS) components are suitable biological markers for representing well-being in patients with erectile dysfunction (ED). **Methods:** The present study included 74 male patients who had applied for check-ups in the cardiology outpatient clinic at Kirikkale University (Kirikkale, Turkey) and who had been diagnosed as having hyperlipidemia. Of these patients, 26 had an additional diagnosis of ED and made up the patient group. The remaining 48 patients formed the control group. Well-being was assessed with short-form 36 (SF-36). The International Index of Erectile Function (IIEF) was used as a measure of libido and erectile function. Quantitative assessment of the ANS was made based on the analysis of heart rate variability by means of 24-h holter monitorization. **Results:** Comparisons between the ED and control groups showed significant differences only in energy scale of SF-36. The ED group also had significantly higher values of sympathetic activity. Except for the general health score of SF-36, which was found to be correlated with parasympathetic activity only in ED group, there were similar correlation patterns within the groups. Although well-being and sympathetic activity were correlated negatively, parasympathetic activity and well-being were correlated positively. **Conclusion:** Quantitative assessment of the ANS by heart rate variability analysis might be a suitable marker for well-being of patients with ED. *(Asian J Androl 2008 Jul; 10: 643–650)*

Keywords: erectile dysfunction; well-being; autonomic nervous system; heart rate variability

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1 Introduction

Well-being is defined as a person's state of satisfaction and happiness in the mental, social, psychological and physical sense [1]. Hypothetically, there should be some biological links to well-being. It is expected that medical patients will display differences in qualitative rather than quantitative properties of well-being than healthy people. Contrary to expectations, previous stud-

ies have revealed that positive and negative emotions are not strongly correlated with each other [2]. Moreover, the absence of ill-being does not mean that well-being is present [3, 4]. Ryff *et al*. [5] assessed association between well-being and different neuroendocrine and cardiovascular functions and concluded that distinct biological markers were correlated either with well-being or with ill-being. However, they noticed that there was no marker correlated with both well-being and ill-being. In their study, ill-being was defined according to the participants' psychological state, such as the patients' depression and anxiety levels [5]. Although biological markers of well-being and ill-being have been studied in depression and anxiety, how biological markers in somatic illnesses represent well-being has not yet been clarified.

The autonomic nervous system (ANS) is the most probable link between physical health status and its mental representation. The ANS has an integrative role between the central nervous system (CNS) and other systems of the body. This fundamental role advocates the ANS as a somatic marker for well-being. Ryff *et al*. [5] studied the epinephrine, norepinephrine and waste-hip ratio as sympathetic system markers and reveal that these markers are associated with either well-being or ill-being. Their study, however, does not focus on direct evaluation of autonomic system components. In addition, the ANS functions as a whole, where the sympathetic and parasympathetic systems work together in a dialectic manner, as in Ying-Yang [6].

Heart rate variability (HRV) can be used as a method for quantitative assessment of the ANS analysis because primary neural control of the heart is maintained by the ANS [7]. HRV power spectral analysis is one of the many means of analyzing the electrocardiogram. HRV power spectral analysis can provide relative measures of the power or tone of various underlying physiologic influences on the control of the heart rate; including hormonal, enzymatic, circadian, respiratory, and neural influences.

An imbalance in the functionality of the ANS can cause some physical problems, such as heart disease and erectile dysfunction (ED) [8]. ED is defined as the inability to achieve or maintain an erection sufficient for sexual performance [9]. Overall, approximately half of men aged between 40 and 70 years have some degree of ED. Several studies suggest that a psychological component, in addition to the underlying cause, contribute to the pathogenesis of ED [10]. Sympathetic system dysregulation in ED is also well-known [11]. In terms of physical health, the negative impact of ED on well-being has been reported previously [12].

The present study focuses on the biological representations of well-being in ED. This is a preliminary study that aims to determine whether the ANS components (sympathetic, parasympathetic and global components) could represent biological markers of well-being in ED. In this study, it is hypothesized that well-being is positively correlated with parasympathetic activity and negatively correlated with sympathetic activity in ED patients. ANS variables were expected to represent well-being in ED and non-ED subjects differently.

2 Materials and methods

2.1 Subjects

Both the ED and control groups were recruited as patients who presented at the cardiology outpatient clinic at Kirikkale University hospital for check-ups. All subjects gave written informed consent to the study, which was approved by a local ethics committee. None of the participants had any persistent or clinically meaningful cardiovascular complaints and all were diagnosed with hyperlipidemia. Hyperlipidemia is a well-known risk factor for cardiovascular, autonomic and erectile functions. Recent studies reveal that hyperlipidemia itself is a risk factor for ED, and that approximately half of ED patients have only hyperlipidemia without any other common disease [13–16]. Owing to the fact that there is a well-documented relationship between hyperlipidemia and ED [17], and that there is no known disturbing effect of hyperlipidemia on well-being, hyperlipidemia was not considered as an exclusion criterion. However to eliminate the possible disturbing effects of different lipid levels on the results, subjects with normal cholesterol levels were excluded. The participants were then examined during and after a cardiovascular exercise stress test (Treadmill), and a colored Doppler echocardiography was performed in the cardiology clinic.

Erectile function of the subjects was assessed using the International Index of Erectile Function (IIEF) [17] scale and the penile Doppler test [14] was used to determine the vascular etiology of the ED. The major vessels of the penis were evaluated using the penile color Doppler. Patients with abnormal penile Doppler results were excluded from the study, because we aimed to investigate the relationship between well-being and erectile

dysfunction which is not associated with vascular pathology.

Seventy-four male outpatients were included in the study. Both the ED and the control group had hyperlipidemia. Of the 74 patients, the 26 who also suffered from ED constituted the study group, while the remaining 48 patients without ED were assigned as the control group. The well-being of the patients was measured using Short Form-36 (SF-36) [18] and autonomic functions were assessed by HRV [7]. The mean ± SD of the ages of the ED and the control groups were 44.27 ± 7.37 and 45.35 ± 6.72 years, respectively. Except for the low-density lipoprotein (LDL) levels, the differences in the lipid profiles of the ED and the control patients were not statistically significant (Table 1).

2.2 Instruments

2.2.1 IIEF

The IIEF is a 15-item, self-administered questionnaire, specifically used for the assessment of male erectile function and treatment-related changes occuring in the previous 4 weeks. Of the 15 questions, six (1–5, 15) are related to erectile function; three (6–8) to satisfaction with intercourse, two (9 and 10) to orgasm, two (11, 12) to sexual desire and two (13, 14) to overall satisfaction [13]. IIEF was administered to both groups.

2.2.2 SF-36

The SF-36 is a multi-purpose, short-form health survey containing 36 questions. It yields an 8-scale profile of functional health and well-being, as well as psychometrically based physical and mental health summary measures and a preference-based health utility index. The scales are: physical functioning (PH), role-physical (RP), bodily pain (BP), general health (GH), vitality (V), social functioning (SF), role-emotional (RE) and mental health (MH). The questionnaire items selected also represent multiple operational indicators of health, including behavioral function and dysfunction, distress and well-being, objective reports and subjective ratings, and both favorable and unfavorable self-evaluations of general health status [18]. It is a convenient instrument for investigating the quality of life and well-being in disorders of physical health. Tests of the validity and the reliability of the Turkish version have been carried out by Kocyigit *et al.* [19]. The Turkish version of the SF-36 was administered to both groups.

2.2.3 Twenty-four-hour holter monitorization and HRV measurements

The patients were monitored for 24 h using the Delmar–Impresario, General Electric holter system (Irvine, CA, USA). HRV was assessed from the records collated over the 24-h records, after extracting artifacts using the Fast Fourier transformation system (Irvine, CA, USA).

HRV analysis is widely used for indirect quantitative and noninvasive measurement of autonomic changes. Two main analyses are performed for HRV: time domain and frequency domain analysis. Frequency domain analysis was preferred in the present study. Although many methods are being used to calculate and determine the power spectral analysis of heart rate variability, fast fourier transformation analysis is the most commonly used method. Three main spectral components are distinguished in a spectrum, calculated from short-term re-

Table 1. Comparisons of the lipid and hormone values between erectile dysfuncion (ED) and control groups. HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; DHESO4, dehydroepiandrosterone sulphate. $^{*}P < 0.05$.

Lipids and hormones	ED (mean ± SD)	Control (mean ± SD)	*P*-value
Total cholesterol (mg/dL)	245.55 ± 34.91	241.86 ± 35.48	0.693
LDL (mg/dL)	160.02 ± 33.03	139.80 ± 38.14	0.044*
HDL (mg/dL)	43.99 ± 12.21	43.45 ± 9.83	0.762
Triglyceride (mg/dL)	224.84 ± 95.04	189.79 ± 93.35	0.175
Total testosterone (ng/mL)	4.43 ± 1.96	4.81 ± 1.25	0.402
Free testosterone (pg/mL)	11.13 ± 7.22	11.17 ± 5.99	0.986
Estrogene (pg/mL)	27.71 ± 15.09	27.64 ± 12.96	0.988
Estrogene/total testosterone (pg/mL)	8.36 ± 5.65	5.59 ± 3.15	0.075
Estrogene/free testosterone (pg/mL)	5.20 ± 4.72	5.29 ± 4.40	0.774
DHESO4 (μg/dL)	230.09 ± 98.42	223.45 ± 84.47	0.790

cordings of 2–5 min: very low frequency (VLF), low frequency (LF) and high frequency (HF) components. The distribution of the power and the central LF and HF bands are not fixed but may vary in relation to changes in autonomic modulations of heart periods. The physiological explanation of the VLF band is much less defined, and the existence of a specific physiological process attributable to these heart period changes might even be questioned. The measurements of VLF, LF and HF power components were usually made in absolute values of power (milliseconds squared, msn^2). LF and HF may also be measured in normalized units, which represent the relative value of each power component in proportion to the total power minus the VLF component. The representation of LF and HF in normalized units emphasizes the controlled and balanced behavior of the two branches of the autonomic nervous system. Moreover, the normalization tends to minimize the effect of the changes in total power on the values of LF and HF components. Nevertheless, normalized units should always be quoted with absolute values of the LF and HF power to describe completely the distribution of power in spectral components [7, 20, 21].

In the present study, maximal heart rate, minimal heart rate, mean heart rate, LF, HF, LF/HF ratio, total power, normalized LF (LFn), normalized HF (HFn), the global sympathetic index and the logarithmic forms of the frequency domain of the HRV indexes (LF, HF and LF/HF ratio) were measured as heart rate variables.

• LF (0.04–0.15 Hz) (msn^2): LF band reflects both sympathetic and parasympathetic activity and is associated with baroreflex activity [7].

• HF (0.15–0.4 Hz) (msn^2): HF band is associated with respiratory frequency and respiration-related heart rate changes (respiratory sinus arrhythmia) and reflects cardiac vagal tonus [7].

• LF/HF ratio: LF/HF ratio is thought by some authors to reflect sympathetic/parasympathetic activity ratio [7].

• Normalized LF (LFn): This parameter is thought to reflect sympathetic activity. It was calculated as: LF power in normalized units LF/(total power – VLF) × 100.

• Normalized HF (HFn): This parameter is thought to reflect parasympathetic activity and is calculated as: HF power in normalized units HF/(total power – VLF) × 100.

• Total power (msn^2): It is the total band width consisting of VLF, LF, HF and VHF and it reflects the global state of ANS [7].

• Global sympathetic index (GSI): It is a marker of sympatho-vagal balance and shows a positive correlation with sympathetic tonus like LF/HF. GSI was calculated as [(VLF + LF)/HF] [22].

2.3 Statistical analysis

Data was expressed as mean ± SD. Differences between the means of groups were determined using the unpaired *t*-test or the Mann-Whitney *U*-test according to the distribution of the data. The correlations were tested by Pearson and partial correlation analysis. A *P*-value less than or equal to 0.05 was considered statistically significant. SPSS version 10.0 (SPSS, Chicago, IL, USA) was used for the analyses.

3 Results

The unpaired *t*-test revealed that there was no significant difference between the groups according to age (mean ± SD of the ED and the control groups were 45.35 ± 6.72 and 44.27 ± 7.37 years, respectively, and $P = 0.539$). Both ED and libido sub-scores of IIEF of ED patients were significantly lower than that of controls. The mean ± SD of the ED scale score in IIEF on the ED and the control groups were 18.81 ± 7.01 and 28.58 ± 1.29, respectively. The mean ± SD of the libido scale scores in IIEF on the ED and the control groups were 16.04 ± 3.59 and 21.27 ± 2.94, respectively ($P < 0.001$ for both of IIEF scales, according to the unpaired *t*-test).

The comparisons between the groups for SF-36 scales showed that only vitality was significantly lower in the ED group than in the control group ($P = 0.01$). The comparisons of the lipid and hormone profiles are presented in Table 1. The ED group had significantly higher LDL levels than the control group. To eliminate the effects of LDL levels on the results, we performed partial correlation analysis using the LDL scores as a covariate variable. Even after controlling the effects of lipid levels, there was a statistically significant negative correlation between ED and vitality ($r = –0.285$, $P = 0.027$).

Correlations between the scores of SF-36 and HRV for both the ED and the control groups are shown in Table 2. Although both parasympathetic and sympathetic activities were correlated with SF-36 energy and emotion scales in the control group, there was no correlation between the sympathetic activity and the SF-36 scales in the ED group.

The mean ± SD of HRV scores and comparisons between the groups is shown in Table 3. The ED group

Table 2. The correlations between heart rate variability (HRV) and short form 36 (SF-36) scale scores between erectile dysfunction (ED) and control groups. LF, low frequency; HF, high frequency; LFn, normalized LF; HFn, normalized HF; GSI, global sympathetic index; GH, general health; EM, emotion; V, vitality; N, non-significant.

	HRV		GH	EM	V
ED group	LF	Pearson	0.480	*N*	*N*
		P	0.015		
	Log LF	Pearson	*N*	*N*	*N*
		P			
	HF	Pearson	*N*	*N*	0.495
		P			0.012
	Log HF	Pearson	*N*	*N*	0.394
		P			0.050
	Total power	Pearson	0.436	*N*	*N*
		P	0.029		
	LF/HF	Pearson	*N*	*N*	*N*
		P			
	Log LF/HF	Pearson	*N*	–0.413	–0.415
		P		0.04	0.039
Control group	LF	Pearson	*N*	*N*	*N*
		P			
	Log LF	Pearson	N	*N*	*N*
		P			
	HF	Pearson	*N*	*N*	0.363
		P			0.012
	Log HF	Pearson	*N*	*N*	0.452
		P			0.001
	Total power	Pearson	*N*	*N*	0.379
		P			0.008
	LF/HF	Pearson	*N*	*N*	–0.372
		P			0.010
	Log LF/HF	Pearson	*N*	–0.286	–0.379
		P		0.050	0.009

Table 3. The comparisons of heart rate variability (HRV) between erectile dysfunction (ED) and control groups. LF, low frequency; HF, high frequency; LFn, normalized LF; HFn, normalized HF; GSI, global sympathetic index. $^{*}P < 0.05$.

HRV parameters	ED	Control	*P*-value
LF (msn^2)	409.99 ± 240.76	382.68 ± 250.18	0.651
HF (msn^2)	149.10 ± 147.02	177.93 ± 164.29	0.292
Total (msn^2)	1242.15 ± 688.18	1177.41 ± 736.70	0.713
LF/HF	4.08 ± 2.07	3.05 ± 1.64	0.022*
LFn	0.76 ± 0.12	0.71 ± 0.12	0.105
HFn	0.24 ± 0.12	0.28 ± 0.12	0.105
GSI	11.79 ± 8.19	8.28 ± 4.84	0.023*

had significantly higher values of sympathetic activity indicators (LF/HF ratio and GSI) than the control group, but there was no difference between groups in terms of parasympathetic activity indicators (HF, HFn).

4 Discussion

This study aimed to determine whether the ANS variables could be correlated with well-being in ED. It is well known that ED, as a psychosomatic disease, is associated with lower well-being, which is supported by the relevant literature [10]. In the present study it was also shown that the patients with ED had significantly lower SF-36 vitality scores than the control group; but scores of the other scales were not found to be significantly different between the groups. This result is congruent with Kushiro *et al.* [23], who show lower vitality of SF-36 in hypertension patients with ED. Our result can be explained by the ages and the medical status of the subjects included in our study. In the present study, ED patients were mostly middle aged (the mean age in this group was 45 years). It can be assumed that serious physical complaints are rare in this period of life. The ED patients had no restricting medical problems that might negatively influence their life. All of them applied to the cardiology outpatient clinic for a check-up. It is not surprising, therefore, that the ED patients do not report decreased well-being levels in physical health scales of SF-36.

The ED group had significantly higher LF/HF and GSI values than the control group. Both LF/HF and GSI were associated with sympathetic activity [22]. This result supports the idea that ED patients have excessive sympathetic activity. There are many studies that highlight the increased sympathetic activity in ED [24–27]. The effects of sympathetic activity on vascular functioning and the sympatho-vagal balance can account for why the ED patients have higher sympathetic activity [24, 25]. However, it can be concluded that ED itself causes stress and, hence, an elevation in sympathetic activity.

Separate analysis of the groups showed both different and similar correlation patterns between the ANS variables and the SF-36 scales. In the ED group, general health was positively correlated with LF and total power. In the same group, Log LF/HF was negatively correlated with emotion and vitality. HF and Log HF were also correlated positively with vitality. In the control group, GH was not correlated with any ANS variable. Nevertheless, Log LF/HF was negatively correlated with emotion and vitality, as in the ED group. In the ED group; HF, Log HF and total power were positively correlated with vitality, and LF/HF and Log LF/HF were negatively correlated with vitality.

The significant negative correlations between Log LF/HF and vitality and Log LF/HF and emotion in both groups support a negative effect of the sympathetic activity on well-being. Sympathetic activity is the key autonomic response to anxiety to produce fight, flight or freeze reactions [28].

The parasympathetic activity, however, was positively correlated with vitality in both groups. There are studies reporting a positive relationship between well-being and parasympathetic activity [29, 30]. Decreased levels of parasympathetic activity were also reported in depression and posttraumatic stress disorder [31, 32]. Friedman [33] considers the relationship between the parasympathetic activity and anxiety in the context of adaptive functioning and autonomic flexibility.

The correlations in the present study show that well-being in the ED patients and the controls were related to different ANS variable patterns. The ED group's physical health was associated with LF and total power. However, the control group did not display the same association. The observed correlations between general health and total power (the sum of sympathetic and parasympathetic activity) and correlations between general health and LH (LH having properties of both sympathetic and parasympathetic activity) suggest that ED patients' perception of general health is more sensitive to global ANS alterations. Hence, the well-being of patients with physical problems could be associated with the alteration of the level of global autonomic activity rather than its level.

Correlations between vitality and HRV displayed different patterns between groups. Both groups showed positive correlations between vitality and the parasympathetic activity variables (HF and Log HF). The marker of sympathetic activity (Log LF/HF) was found to be negatively correlated with vitality in both groups. LF/HF and vitality correlation, however, was found only in the control group. Total power was also found to be correlated with vitality in only the control group. The significantly higher LF/HF values in the ED group and these correlations (observed vitality and Log LF/HF correlation without observation of vitality and LF/HF correlation) together suggest that the linear correlation of the sympathetic activity with vitality disappears over a definite level of sympathetic activity. In this situation, even increased parasympathetic activity might not increase the vitality when one considers that parasympathetic activity is posi-

tively correlated with energy. This can account for the significantly lower level of vitality in the ED group than in the controls. The parasympathetic system is the energetic component of the autonomic system and it can be supposed that because of the decreased parasympathetic activity, the ED group's vitality has decreased.

The present study was designed as a preliminary study to determine how patients experience well-being at the biological level and if HRV measurements are suitable markers of well-being. The state of well-being is shaped by interactions between multiple systems. The ANS is one of these systems and maintains cooperation between the body and the CNS. It seems that, according to our results, the disturbance in the systems, which create a disturbed well-being state, influences the ANS. However, whether the situation of this state is linked to the ANS or to the other factors that influence the ANS is still unknown. For example, an infectious disease can cause both lower well-being (or ill-being) and ANS imbalance via cytokines. At the same time, cytokine trafficking can alter the state of well-being via the ANS.

HRV analysis might be a good way to determine the state of well-being via the assessment of the ANS. Future studies addressing the relationship between well-being status and the ANS are undoubtedly warranted. In addition, the question of how changes in the biological markers of well-being are labeled as ill-being by the ANS components is still problematic.

The measurement of well-being was measured only by means of SF-36. This should be taken into consideration when interpreting the results, given that SF-36 is a general instrument of quality of life that does not directly focus on well-being. The lack of age-controlled ED patients who directly applied to the urology clinic with an ED complaint was another main limitation of the current study. Studies addressing these issues are needed for better understanding of biological representations of well-being.

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