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Original Article

Autonomic dysfunction in patients with polycystic ovary syndrome

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ABSTRACT

Objective: To assess the autonomic system in patients with polycystic ovary syndrome (PCOS).
Materials and methods: Thirty-seven adult patients with PCOS and 33 healthy controls were enrolled in the study. The electrophysiological assessments of the autonomic nervous system function were performed using sympathetic skin response and R–R interval variation tests.
Results: The mean latency of sympathetic skin response in PCOS patients was significantly delayed compared with the controls ($p = 0.001$). The mean amplitude of sympathetic skin response was significantly lower in comparison with the controls ($p = 0.01$). Mean R–R interval variation during deep breathing was also significantly delayed ($p = 0.04$).
Conclusion: There are parasympathetic dysfunction and sympathetic dysfunction in patients with PCOS. This may be easily demonstrated with sympathetic skin response and R–R interval variation tests.

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. It occurs in about 6–10% of women [1,2]. Despite decades of research, the complex pathogenesis of PCOS remains incompletely understood. The symptoms of PCOS are amenorrhea, oligomenorrhea, hirsutism, obesity, infertility, anovulation, and acne. The disease can lead to marital and social maladjustment and can impair sexual functioning [3]. According to the Rotterdam Criteria, PCOS is diagnosed in the presence of at least two of three criteria: menstrual disorders or amenorrhoea with chronic lack of ovulation, clinical and/or biochemical features of hyperandrogenism, and the presence of polycystic ovaries in ultrasonography after the exclusion of other endocrine disorders [4].

PCOS is an important metabolic disorder, as women with PCOS may have significant insulin resistance, glucose intolerance, obesity, hypertension, and dyslipidemia. Adrenergic overactivity leads to the formation of these factors. Adrenergic overactivity is an important prognostic factor for the development of cardiovascular disorders [5–7]. Previous studies indicated that the ANS plays an important role in the regulation of ovarian physiology [8]. Few reports showed the role of increased sympathetic activity in patients with PCOS [9,10]. Autonomic dysfunction has also been reported to be associated with adverse cardiovascular events [11].There is a relationship between the ANS and cardiovascular mortality [12].

To our knowledge, there are no studies to date evaluating the relationship between the ANS and PCOS using electromyography (EMG) in current literature. The present study was conducted to assess the ANS in patients with PCOS using sympathetic skin response (SSR) and R–R interval variation (RRIV) tests in EMG.

Materials and methods

Thirty-seven adult patients with PCOS and 33 healthy controls who were referred to the Kirikkale University Gynecology Clinic, Kirikkale, Turkey were enrolled in the present study, PCOS was diagnosed according to the Rotterdam Criteria. Age-matched, healthy, regularly menstruating, and nulliparous women were included as controls. Women with menstrual irregularities, hypothyroidism, diabetes, and women on any hormonal therapy or drugs were excluded. The study was approved by the Kirikkale University local ethic committee. All research procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent/permission was obtained from all parent participants.

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Specification of phenotypes was proposed in a workshop convened by the National Institutes of Health (NIH) in 2012 [13]. There are four phenotypes. Phenotype 1 (classic PCOS) includes clinical and/or biochemical evidence of hyperandrogenism and hyperandrogenism, evidence of oligoanovulation, and ultrasonographic evidence of a polycystic ovary. Phenotype 2 (hyperandrogenic anovulation) includes clinical and/or biochemical evidence of hyperandrogenism and evidence of oligoanovulation. Phenotype 3 (ovulatory PCOS) includes clinical and/or biochemical evidence of hyperandrogenism and hyperandrogenism, and ultrasonographic evidence of a polycystic ovary. Phenotype 4 (non-hyperandrogenic PCOS) includes evidence of oligoanovulation and ultrasonographic evidence of a polycystic ovary. We classified our patients according to these classifications.

Demographic characteristics including age and body mass index (BMI) were recorded.

A detailed neurological examination was performed, and clinical autonomic symptoms including feeling faint on orthostatic change of posture, distal vasomotor dysfunction, sweating abnormalities, and gastrointestinal, genital, or urinary disorders were recorded in all participants. Individuals with neurological findings and autonomic symptoms were not included in the study.

Electrophysiological assessments

The electrophysiological assessments of ANS function were performed using SSR and RRIV, which were recorded according to the methods described Shahani et al [14,15]. All participants were studied in the supine position using the equipment Carefusion Synergy (CareFusion, USA) by the same physician (MA). All study sessions were completed in the morning at least 2 hours after a light breakfast in a quiet semidarkened room with an ambient temperature of between 23°C and 26°C ,and an extremity skin temperature over 31°C.

RRIV was used for parasympathetic function and was recorded using disk electrodes placed on the chest wall across the cardiac position with a ground electrode on the right axial line at the lowest rib. Using the triggering mode and adjusting, the sweep speed two QRS (mainly R waves) of electrocardiography were simultaneously displayed on the screen. Because the first displayed complex represented the triggering potential, the variation in timing of the second complex represents the variation in the R–R interval. Twenty traces were recorded and superimposed, and a printout was made for subsequent measurement. Five groups of 20 sweeps were recorded at rest and two during forced deep breathing at six breaths per minute. The band pass was 20–100 Hz, the sensitivity 0.2 mV, and the sweep duration was 0.2–1 seconds. The range in the 20 pairs of R– R intervals was termed as (a), and the mean R–R interval was termed as (b). The RRIV was expressed as a percentage of the average R–R interval using the formula RRIV = a/b × 100 [14,15]. The recordings and calculations were performed with computer software (SPSS 16, SPSS Inc., Chicago, IL, USA). RRIV responses at rest and deep breathing were considered abnormal when they were more than two standard deviations (SD) lower than mean responses, age-adjusted for a normal population [16].

SSR was used to measure sympathetic function. SSR recordings were performed using disc electrodes attached to the palm and dorsum of the right hand. The same device and electrical stimuli were used, and single square wave pulses of 0.1 seconds duration and 10–20-mA intensity were applied to the dominant median nerve at the wrist portion. Latency and amplitude of the response were analyzed. The latency was measured from the onset of the stimulus artifact to the onset of the first negative deflection of the signal baseline, and the amplitude was measured peak to peak [14,15].

Response latencies were considered pathological when they were more than two SD above the mean latency of the control group.

Statistical analysis

All parameters were expressed as mean ± SD, as well as percentages (for categorical variables). The patients and healthy controls were compared using a one-way analysis of variance for continuous parameters and Chi-square test for categorical parameters. Bivariate analyses were performed using Pearson correlation. A p value < 0.05 was considered to be statistically significant.

Results

The baseline clinical characteristics of patients with PCOS and controls are shown in Table 1. Phenotypic presentation of patients with PCOS are shown in Table 2. No statistically significant difference was found between the patient and the control groups in terms of age ($p = 0.58$). There was a slight statistically difference between both groups in BMI ($p = 0.05$). Patients with PCOS had significantly higher levels of testosterone and insulin than that of healthy controls (respectively; $p = 0.01$, $p = 0.02$).

Right hand SSR latency was found to be 1.37 ± 0.52 ms in the patients and 0.86 ± 0.30 ms in the controls; right hand SSR amplitude was 0.59 ± 0.53 mV in the patients and 1.13 ± 0.65 mV in the controls. The mean latency of SSR in the patients was significantly delayed, compared with the controls ($p = 0.001$). The mean amplitude of SSR in the patients was significantly lower, compared with the controls ($p = 0.01$).

Mean RRIV at rest was detected to be 91.22 ± 54.25% in patients and 87.06 ± 49.08% in controls. Mean RRIV during deep breathing was detected to be 112.28 ± 56.50% in the patients and 87.30 ± 42.51% in the controls. No statistically significant difference was found between the patients and the controls in RRIV at rest ($p = 0.73$). Mean RRIV during deep breathing was significantly delayed, compared with the controls ($p = 0.04$). There was no relationship between RRIV, age, and BMI (Table 3). There was no relationship between SSR, age, and BMI (Table 4).

Discussion

We investigated autonomic dysfunction in patients with PCOS in this present study. In this study, both sympathetic systems and parasympathetic systems were evaluated with SSR and RRIV. SSR

Table 1
Baseline characteristics of the study population.

Variables	Patients ($n = 37$)	Controls ($n = 34$)	p
	Mean ± SD	Mean ± SD	
Year (y)	21.56 ± 3.37	21.20 ± 1.85	0.58
Body mass index (kg/m^2)	22.62 ± 3.66	21.02 ± 3.22	0.05
Total cholesterol (mg/dL)	167.97 ± 28.36	163.84 ± 16.83	0.46
HDL cholesterol (mg/dL)	61.27 ± 11.52	58.24 ± 9.21	0.23
LDL cholesterol (mg/dL)	97.86 ± 21.46	94.48 ± 18.92	0.48
Triglyceride (mg/dL)	84.72 ± 39.13	74.06 ± 26.56	0.19
Blood glucose (mg/dL)	92.62 ± 9.16	89.54 ± 6.97	0.12
FSH (IU/L)	5.26 ± 1.63	5.60 ± 1.65	0.40
LH (IU/L)	10.07 ± 5.32	8.57 ± 3.69	0.18
Estradiol (pg/mL)	50.22 ± 7.60	46.94 ± 15.07	0.26
Testesterone (ng/mL)	0.49 ± 0.17	0.41 ± 0.11	0.01
DHEAS (mcg/dL)	282.59 ± 100.89	251 ± 77.90	0.15
Insulin (IU/mL)	11.15 ± 3.95	8.87 ± 3.80	0.02

DHEAS = dehydroepiandrosterone; FSH = follicle stimulating hormone; HDL = high density lipoprotein; LDL = low density lipoprotein; LH = luteinizing hormone.

Table 2
Phenotypic presentation of patients with polycystic ovary syndrome (PCOS).

Phenotype	Number of cases
Phenotype 1 (classic PCOS)	12
Phenotype 2 (hyperandrogenic anovulation)	9
Phenotype 3 (ovulatory PCOS)	6
Phenotype 4 (nonhyperandrogenic PCOS)	10

and RRIV are two simple, noninvasive electrophysiological tests, which can easily be performed using an electromyography device. RRIV is a reliable test for showing the parasympathetic nervous system. SSR is a practical method for evaluating sympathetic small unmyelinated C-fibers, which cannot be assessed with standard electrophysiological studies [16,17].

The present study showed dysfunctions in both sympathetic and parasympathetic components of the ANS in patients with PCOS. When compared with the control group, SSR latencies obtained from the right hand were delayed in the patient group and a decrease in SSR amplitude was observed. This result is compatible with sympathetic dysfunction. The RRIV values obtained during a deep breath were observed to be much lower for the patient group than the control group, indicating a parasympathetic dysfunction.

Researchers have used several different methods to assess the ANS. Cardiovascular tests, biochemical tests, and electrophysiological tests are the most commonly used tests. These tests may have some advantages and disadvantages compared with each other. Therefore, assessment using different methods will increase accuracy.

Excessive sympathetic innervation may play a role in polycystic ovaries. In a study, it was found that rats with estrogen-induced polycystic ovaries had a high uptake and level of norepinephrine, and a high degree of transmitter release after electrical stimulation of the ovary. [18]. As women with PCOS have significantly higher sympathetic nerve activity, this may be associated with hormonal and metabolic features that may be relevant to the pathophysiology of the syndrome [19]. Garcia-Rudaz et al [20] showed that there is an alteration in noradrenaline deamination and/or uptake in adolescents with PCOS. Heart rate recovery (HRR) after exercise is a marker of parasympathetic activity and attenuation of this parameter has been shown to be associated with increased long-term mortality [21–24]. A delayed recovery of systolic blood pressure after peak exercise has been found to have diagnostic value and might reflect sympathetic hyperactivity [25,26]. In addition, the analysis of variations in heart rate (HRV) has also been used to determine the balance between sympathetic and vagal nerve activities in the heart [27]. HRV in PCOS was evaluated in previous studies [9,28,29]. Yildirir et al [9] indicated a significant increase in the low frequency component of the HRV spectrum and a decrease in the high frequency component in relation to the control group. Tekin et al [29] showed a decrease in heart rate recovery and decreased 24-hour HRV measurement in patients with PCOS [28]. Tekin et al [29] founded that the systolic blood pressure of patients with PCOS remained significantly elevated when compared with controls at the first, second, and third minute of recovery.

Table 3
The correlations between R–R interval variation, age, and body mass index.

	Age	*p*	BMI	*p*
	r_p		r_p	
RRIV Rest	0.48	0.47	−0.14	0.22
RRIV Breathing	0.04	0.70	−0.19	0.11

BMI = body mass index; RRIV = R–R interval variation.

Table 4
The correlations between sympathetic skin response, age, and body mass index.

	Age	*p*	BMI	*p*
	r_p		r_p	
SSR latency	0.02	0.86	0.05	0.63
SSR amplitude	−0.01	0.97	−0.18	0.12

BMI = body mass index; SSR = sympathetic skin response.

Sverrisdottir et al [19] indicated that there is sympathetic nerve activity in women with PCOS. Tekin et al [29] showed that patients with PCOS have attenuated HRR1. Kaya et al [30] founded that HRV was significantly decreased in women with PCOS. Post exercise, slow HRR has been demonstrated as a risk factor for cardiovascular and all-cause mortality in healthy adults [31]. Mean RRIV during deep breathing was significantly delayed in the present study. These findings indicate parasympathetic dysfunction.

Previous studies have suggested that there is an autonomic dysfunction in patients with PCOS. Insulin resistance, hyperandrogenism, and obesity in patients with PCOS may be responsible for autonomic dysfunction [9,29,31,32]. The insulin resistance of women with PCOS had been reported to be the link between PCOS and cardiovascular autonomic dysfunction [33]. In this study, we reported no association between BMI, RRIV, and age; and between BMI, SSR, and age. However, we reported that patients with PCOS had significantly higher levels of testosterone and insulin than that of controls. Therefore, we considered the potential role of hyperandrogenism and insulin resistance in ANS dysfunction of women with PCOS. A previous study reported that androgen levels might regulate blood pressure levels in women with PCOS [34]. Autonomic dysfunction has been regarded as a predictor of cardiovascular events and mortality [35,36]. Therefore, early and easy diagnosis of autonomic dysfunction is very important.

This study has some limitations. Firstly, our study group was relatively small. Thus, further larger studies are required to confirm these results. Secondly, there were not any other cardiac tests used in this study.

In conclusion, SSR and RRIV tests using EMG can be easily and rapidly performed, and they may allow for separate testing of parasympathetic functions and sympathetic functions. Accordingly, both tests are very sensitive methods in assessing ANS function in patients with PCOS. The results of the present study indicate that there are both parasympathetic dysfunction and sympathetic dysfunction in patients with PCOS.

Conflicts of interest

The authors declare that they have no conflict of interest.

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