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Original Research Article

A Cross Sectional Study of Heart Rate Variability and Androgen parameters in Polycystic Ovary Syndrome

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Abstract:

Background: Polycystic Ovary Syndrome **(**PCOS) is a multisystemic disorder characterized by endocrine, metabolic, and reproductive system abnormalities. The diagnostic criteria include chronic anovulation and hyperandrogenism. The autonomic nervous system plays a role in pathogenesis. Women with PCOS often experience conditions like oscillatory sleep apnea, hypertension, depression, obesity, and type 2 diabetes linked to an autonomic nervous system imbalance.

Objectives: The aim and objective of this study to compare the heart rate variability (HRV) and estimated androgen levels in patients with polycystic ovary syndrome (PCOS) and in healthy controls.

Material and Methods: Thirty newly diagnosed PCOS cases and thirty controls with similar anthropometric measurements had their HRV assessed. DHEAS and serum testosterone levels were also assessed. The mean outcomes were the values of HRV in the time [standard deviation of all normal R-R intervals (SDNN), the square root of the sum of the squares of the differences between the adjacent normal R-R intervals (rMSSD), and total power (TP), very-low-frequency power (VLF), low-frequency power (LF), normalized low-frequency power (LF norm), high-frequency power (HF), normalized high-frequency power (HF norm), and LF/HF ratio] domains. Differences between the 2 groups were analyzed by Mann-Whitney U test, using SPSS for Windows (version 22.0).

Results: HRV frequency domain parameters, including LF (p = 0.00*), HF (p = 0.00*), and LF/HF ratio (p = 0.00*), as well as time domain parameters, including RMSSD (p = 0.00*), SDNN (p<0.03*), NN50 (p = 0.00*), and total power (p = 0.00*), were significantly reduced in PCOS patients. Serum testosterone (p<0.000*) and DHEA-S (p<0.03*) were two androgen parameters that were significantly higher in PCOS cases than in healthy controls.

Conclusions: The results of the present study indicated that PCOS is related to increased sympathetic over activity, Impaired HRV and increased androgen levels. Therapeutic modalities may adversely affect the cardiovascular system, highlighting the need for ways to reduce these risks. We therefore suggest that HRV is an accurate and sensitive marker to detect early signs of cardiovascular impairment and enables timely measures to avoid further morbidity.

Keywords: autonomic nervous system, heart rate variability, polycystic ovary syndrome, parasympathetic tone, androgen parameters.

Introduction

The common endocrine disorder known as PCOS is characterized by irregular menstruation and infertility in women who are of reproductive age. [1,2] The affected women have high testosterone levels, irregular menstrual cycles, hirsutism, and severe acne. In addition, reports of cardiovascular diseases, metabolic disorders such as elevated insulin levels and an increased risk of type II diabetes, and reproductive disorders such as increased ovarian volume, infertility, and lack of ovulation have been made. [1,2] Furthermore, central obesity, dys lipidemia, and hypertension have been connected to sympathetic hyperactivity and PCOS. [3, 4] Recently, there has been a connection between PCOS

and increased sympathetic activity as measured by heart rate variability (HRV), micron urography, and noradrenaline spillover assessment. [5,6] The evaluation of cardiovascular function's influence on the autonomic nervous system (ANS) has been made easier by the use of heart rate variability (HRV) measurements.[7,8] The sympathetic and parasympathetic modulation could be assessed using HRV power spectral analysis. Diminished HRV, which is defined by decreased high-frequency power (HF) and increased low-frequency power (LF), has been associated with reduced parasympathetic activity and elevated sympathetic modulation.

The characteristics of HRV in women with PCOS are not well studied. [9–11] In contrast to the control group, the PCOS group showed noticeably higher LF and lower HF, according to Yildirir et al. and Lee et al. [10,11] On the other hand, De Sá et al. found that women with PCOS had significantly lower LF and HF compared to controls. [9] A number of these studies yielded controversial results because they did not examine age-matched PCOS women and controls. In order to compare the autonomic nervous system (ANS) characteristics of women with PCOS to those of age-matched healthy women, our goal is to assess HRV and androgen parameters.

Material and Methods

This cross-sectional study was carried out at the physiology department between January and July of 2024. The ethical clearance and permission to conduct research were provided by the institutional ethics committee. The participants were instructed to avoid caffeine, alcohol, and strenuous exercise 24 hours prior to the test and to report to the autonomic function laboratory two hours after a light breakfast. They were advised to read the patient information sheet, put on loose, comfortable clothing, and drink plenty of water before the HRV started. After being asked to sign an informed consent form, the subjects underwent a quick physical examination to rule out any serious medical conditions. Every subject underwent testing for the following parameters: [12]

HRV measurement: This study assessed HRV characteristics in the spectral and temporal domains. We primarily examined the following parameters in the time domain: RR intervals, standard deviations of the RR intervals (SDNN), percentage of adjacent NN intervals differing by more than 50 milliseconds (pNN50), and root mean square of consecutive differences between normal heartbeats (RMSSD). While pNN50 and RMSSD are linked to high-frequency (HF) power and, consequently, to parasympathetic activity, SDNN is associated with low-frequency (LF) power. In the spectrum domain, the following characteristics were examined: LF/HF ratio, high frequency (HF: 0.15 to 0.4 Hz), low frequency (LF: 0.04 to 0.15 Hz), and very low frequency (VLF: 0.003 to 0.04 Hz). Variations in the activity of the renin-angiotensin system, the thermoregulation mechanism, and the peripheral chemo-receptor function are reflected in VLF. Moreover, the Sinoatrial (SA) node's parasympathetic activity is shown by HF, the sympathetic nervous system is indicated by LF, and the sympathovagal balance is represented by the LF/HF ratio.

Biochemical parameters: Five milliliters of venous blood were collected and placed in vials with the proper labels. The serum layer was separated by centrifugation. Biochemical Assays (i) Testosterone Levels: The ELISA technique was used to measure serum testosterone levels. (ii) DHEA-S levels: An ELISA kit from Calbiotech Inc. was used to detect it.

Statistical Analysis: Using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL), the measured outcomes of the PCOS group and the controls were statistically analyzed and compared using the Mann-Whitney U test. Unpaired t-test was used. The data were displayed as the mean± standard deviation, with a significance level of P less than 0.05

Results

The mean age of PCOS patients was 28.32 ± 9.58 years, whereas the mean age of the healthy controls was 29.43 ± 8.14 years. Table 1 shows that there is a difference in BMI between the anthropometric measurements of patients with PCOS and healthy controls (25.87 ± 1.13 vs. 25.45 ± 1.30, P < 0.548). There is a significant difference in the systolic blood pressure between PCOS patients and healthy controls (121.17 ± 3.91 vs. 115.5 3 ± 4.27, P < 0.00*).

Table 2 shows the significant differences in the time domain parameters of HRV, SDNN (p = 0.03*), RMSSD (p = 0.00*), NN50 (p = 0.00*), and total power (p = 0.00*) between the PCOS patients and the control group.

In the context of short-term HRV, our study revealed that people with PCOS showed significantly lower overall HRV in comparison to controls. Table 3 shows that patients with PCOS had significantly lower HF (p = 0.00), LF (p = 0.00*), and LF/HF ratio of the frequency domain parameter (p = 0.00) when compared to healthy controls. as displayed in Table 3.

Table 4 indicates that there was a significant difference in serum testosterone and dehydroepiandrosterone sulfate (DHEA-S) between PCOS cases and controls.

Table 1: Basal characteristics and Cardiovascular Parameters in PCOS patients and Healthy Controls

Parameters	PCOS patients (Mean ± SD)	Healthy Controls (Mean ± SD)	p-value
Age	28.32 ± 9.58	29.43 ± 8.14	NS
BMI	25.87 ± 1.13	25.45 ± 1.30	0.548
Heart Rate (bpm)	84.55 ± 12.48	83.23 ± 13.58	0.763
Systolic BP	121.17 ± 3.91	115.5 3 ± 4.27	0.00*
Diastolic BP	76.79± 7.92	75.33 ± 6.51	0.624

***p<0.05 statistically significant. BMI: Body mass index, BP: Blood pressure, SD: Standard deviation**

Table 2: Time Domain Parameters in PCOS patients and Healthy Controls

Parameters	PCOS patients (Mean ± SD)	Healthy Controls(Mean ± SD)	p-value
RMSSD (ms)	29. 71±11.97	36. 43±10.53	0.00*
SDNN (ms)	34. 16 ± 17.31	42. 11± 19.07	0.03*
pNN50	10. 97±4.63	36. 42 ± 2.63	0.00*
Total power	971.92 ±86.44	1882.34±76.93	0.00*

***p<0.05 statistically significant. Values are expressed as mean±SD, SD: Standard deviation**

Table 3: Frequency Domain Parameters in PCOS patients and Healthy Controls

Parameters	PCOS patients(Mean ± SD)	Healthy Controls(Mean ± SD)	p-value
LF (ms^2)	218.32 ± 29.31	514.9 2 ± 23.23	0.00*
HF (ms^2)	239.63 ± 54.53	562.93 ± 41.43	0.00*
LF/HF ratio	1.43 ± 0.153	1.18 ± 0.689	0.00*

***p<0.05 statistically significant. LF-low frequency; HF-high frequency; LF/HF ratio (low frequency to high frequency ratio), SD: Standard deviation**

Table 4: Comparison of Androgen parameters in PCOS patients and Healthy Controls

	PCOS patients(Mean ± SD)	Healthy Controls(Mean ± SD)	P-value
S. Testosterone (ng/ml)	0.98 (0.40-1.18)	0.48 (0.43-0.60)	0.000*
S. DHEA-S (ng/ml)	3.75 (1.80-3.88)	2.02 (2.00-2.48)	0.03*

***p-value < 0.05 Significant, SD- standard deviation, DHEA-S-dehydroepiandrosterone sulphate**

Discussion

The main findings of this study show that patients with PCOS exhibited higher levels of sympathetic nervous system activity as measured by HRV parameters than did healthy individuals. We found that in PCOS patients, there was a greater tendency toward sympathetic tone and less activation of parasympathetic tone, as indicated by lower time domain or frequency domain indices. This could point to either increased sympathetic flow or decreased vagal tone in people who are in pain. Serum testosterone and DHEA levels were found to be significantly elevated, suggesting that PCOS patients have higher levels of androgen.

PCOS is a prevalent endocrine disorder that results in irregular menstruation and infertility. Five to ten percent of women worldwide who are of reproductive age suffer from PCOS; its exact etiology is unknown. According to the Rotterdam PCOS diagnostic criteria, oligo/amenorrhea, polycystic ovaries (PCOs) on ultrasound, and hyperandrogenism (clinical or biochemical) are the three criteria that must be met for PCOS to be diagnosed. [13] PCOS can lead to oligo/anovulation, clinical or biochemical hyperandrogenism, altered ovarian morphology, and hypertension, among other reproductive consequences. Central obesity, hyperinsulinemia, insulin resistance, dyslipidemia, and hypertension are endocrine characteristics linked to PCOS. [14] It has been discovered that sympathetic hyperactivity is correlated with obesity and increased insulin resistance, two traits common to PCOS. [5, 6] This implies that the pathophysiology of PCOS may involve sympathoexcitation. Several methods have been developed for ANS calculation. These include micron urography, HRV, and noradrenaline spillover estimation. There isn't a single, widely recognized set of standards for assessing the ANS. Since HRV is a practical and noninvasive technique, it has been regularly employed in clinical settings. Heart rate variability, or HRV, is a statistical measure of heart rate that is linked to ANS and is used to predict the risk of a number of metabolic disorders.[8] Some studies have found a connection between increased sympathetic nerve activity in terms of ovarian sympathetic outflow and PCOS. A rodent model of PCO showed elevated alpha-1 adrenoceptor messenger RNA (mRNA), which is interpreted as increased sympathetic activity, and decreased alpha-2 adrenoceptor mRNA, a sympathoinhibitory receptor, according to Stener-Victorin et al. [15] Luza et al. reported that rats with PCO showed increased noradrenergic activity in the anterior hypothalamic nerve terminals. [16] Furthermore, the study conducted by Lara and colleagues

demonstrated that rats suffering from PCO exhibited increased intraovarian synthesis of nerve growth factor, a substance associated with sympathetic nervous system (SNS) modulation. [17]

Moreover, women with PCOS frequently exhibit a widespread increase in SNS activity, which may raise ovarian sympathetic activity. In earlier research, catecholamine and its metabolites were measured to examine the elevated sympathetic activity in PCOS. According to reports, women with PCOS had lower urinary 3-methoxy-4-hydroxy phenyl glycol levels, [18, 19] which is consistent with an excess of noradrenaline. Measurements of SNS modulation have recently included muscle sympathetic nerve activity (MSNA) and postexercise SBP. Sverrisdottir et al. report that compared to age- and BMI-matched controls, women with PCOS had higher MSNA, a direct measure of the SNS. [20] According to Tekin et al. women with PCOS had increased SBP in response to exercise, which is followed by ongoing sympathetic stimulation. [21]

Only a small number of studies have used HRV to evaluate the ANS's performance in PCOS-affected women. According to Yildirir et al. and Lee et al., the PCOS group exhibited a notably higher LF norm and a lower HF norm in comparison to the control group. [10-11] De Sá et al. found that women with PCOS had significantly lower LF and HF than the controls, in contrast to the previously mentioned studies. [9]

Our study's findings showed that compared to the controls, women with PCOS had considerably higher LF/HF ratios. In contrast to the controls, women with PCOS had a substantially lower HF norm. These findings are consistent with research by Yildirir et al. and Lee et al. which revealed that women with PCOS had lower parasympathetic modulation and increased sympathetic activity in HRV, as evidenced by higher LF and LF/HF ratios as well as a lower HF. [10-11]

The PCOS group showed a significant decline in all-time domain HRV measures, indicating lower total sympathovagal modulation compared to the healthy control group. The LF/HF ratio was higher in the PCOS group, suggesting a more active sympathetic nervous system. Elevated DHEA and serum testosterone levels were observed, indicating higher androgen levels in PCOS PCOS patients.

Strength of Study

Measuring heart rate variability (HRV) at rest may be a crucial clinical tool for PCOS patients. In addition, compared to the healthy control group, our data showed a significant increase in sympathetic reactivity and a decrease in parasympathetic reactivity. This implies that sympathetic tone predominates and parasympathetic tone decreases in PCOS patients. The results of these tests may provide important information about the long-term likelihood of predicting the morbidity and mortality of cardiovascular problems in PCOS patients.

Limitations of the study

We advise carrying out additional longitudinal research with larger samples in order to get more reliable results evaluating HRV and androgen parameters, considering the limitations of this study. There weren't many patients in the trial, consisting of only 30 patients. More comprehensive results require a larger sample size.

Conclusions

In this study, the PCOS group had significantly higher LF, LF norm, and LF/HF ratio than the control group, while the PCOS group had significantly lower HF norm. Therefore, we can suggest that women with PCOS may have higher sympathetic modulation. Serum testosterone and DHEA-S were significantly higher in PCOS cases than in controls. Thus, we propose that HRV is a sensitive and accurate marker to identify cardiovascular impairment early on and allows prompt intervention to prevent further morbidity.

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