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Characteristics of heart rate variability in women with polycystic ovary syndrome

A retrospective cross-sectional study

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Abstract

We aimed to compare the modulation of the autonomic nervous system (ANS) in women with polycystic ovary syndrome (PCOS) with that in healthy ovulatory women on the basis of heart rate variability (HRV), and to analyze the characteristics of the ANS in PCOS.

In a retrospective chart review, HRV, body mass index, and physical examination data in women with PCOS and those with regular menstrual cycles were collected. Approval from the institutional review board (IRB) was obtained (IRB No. 2017-05-007-001) for this study. 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 the mean heart rate turbulence (mean HRT)] and frequency [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).

There was no significant difference in the values of the time domain (SDNN, rMSSD, and mean HRT) between the groups. In the frequency domain, women with PCOS showed significantly higher LF (598.63 ± 94.38 vs 459.13 ± 163.64, $P = .028$), LF norm (48.64 ± 3.39 vs 36.49 ± 2.82, $P = .009$), and LF/HF ratio (1.49 ± 0.31 vs 0.73 ± 0.13, $P = .009$) than the control group. HF norm was significantly lower in the women with PCOS than in the controls (51.38 ± 3.39 vs 63.51 ± 2.82, $P = .009$). The TP, VLF, and HF showed no significant difference between the groups.

The results of the present study indicated that PCOS is related to increased sympathetic modulation in HRV.

Abbreviations: ANS = autonomic nervous system, BMI = body mass index, BP = blood pressure, HF norm = normalized high-frequency power, HF = high-frequency power, HRV = heart rate variability, IRB = institutional review board, LF norm = normalized low-frequency power, LF = low-frequency power, mean HRT = mean heart rate turbulence, mRNA = messenger RNA, MSNA = muscle sympathetic nerve activity, PCO = polycystic ovaries, PCOS = polycystic ovary syndrome, rMSSD = the square root of the sum of the square of the difference between the adjacent normal R-R intervals, SBP = systolic blood pressure, SDNN = mean of the standard deviation of all normal R-R intervals, SNS = sympathetic nervous system, TP = total power, VLF = very low-frequency power.

Keywords: autonomic nervous system, heart rate variability, polycystic ovary syndrome, sympathetic nervous system

1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by menstrual dysfunction and infertility in reproductive-aged women. The clinical signs of the affected women include irregular menstrual cycle, increased androgens, hirsutism, and severe acne. In addition, metabolic disorders such as high insulin levels and risk of type II diabetes; cardiovascular diseases; and reproductive disorders such as increase in ovarian volume, lack of ovulation, and infertility have been reported.[1,2] PCOS is also associated with hypertension, dyslipidemia, and central obesity,[3,4] which are known to be related to sympathetic hyperactivity.[5,6] In recent years, the correlation between increased sympathetic activity and PCOS has been reported, as assessed by microneurography, the estimation of noradrenaline spillover, and heart rate variability (HRV).

The measurement of HRV has been widely used to evaluate the modulation of the autonomic nervous system (ANS), using cardiovascular function.[7,8] The sympathetic and parasympathetic modulation could be assessed by power spectral analysis of HRV. Diminished HRV, which indicates increased low-frequency power

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(LF) and decreased high-frequency power (HF), is known to be related to increased sympathetic modulation and decreased parasympathetic activity.

Few studies have reported the characteristics of HRV in women with PCOS.[9–11] Yildirir et al[11] and Lee et al[10] reported that the PCOS group had significantly higher LF and lower HF than the control group. On the contrary, De Sá et al[9] reported that women with PCOS showed significantly lower LF and HF compared to controls. The results of these studies were controversial, and some of these studies did not analyze age-matched women with PCOS and controls. Therefore, we analyzed the characteristics of the ANS in women with PCOS compared with those in age-matched healthy women, using HRV.

2. Materials and methods

Our study was a retrospective chart review, which compared the HRV values between women with PCOS and those with regular menstrual cycles. We obtained approval from the Institutional review board (IRB) to publish these data (IRB No. 2017-05-007-001).

2.1. Participants

A total of 35 women diagnosed with PCOS according to the Rotterdam PCOS diagnostic criteria[12] who visited the Korean Medicine Obstetrics and Gynecology Clinic of Kyung Hee University Hospital at Gangdong between April 2014 and March 2017 were included in the PCOS group. The control group consisted of 32 women with regular menstrual cycles and without clinical and/or biochemical signs of PCOS. Pregnant women, those with diabetes mellitus, those who had reached menopause, those with hyperlipidemia or hypertension, and those receiving medications that could affect the ANS at the time of the study were excluded. All study participants were examined for HRV and body mass index (BMI), and their blood pressure (BP) was measured.

2.2. Measurement of HRV

HRV was recorded using SA-2000E (Medicore Co, Ltd, Seoul, Korea), a practical and reliable device for measuring heart rate to analyze the HRV. The participants were examined using electrodes attached to both radial arteries in the wrist and peroneal arteries in the ankle; they were placed in the supine position for 5 minutes in a bright and silent room at 18°C to 23°C.

The time and frequency domains in the HRV were measured. For the time domain, the mean of the 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 the mean heart rate turbulence (mean HRT) were assessed. The values of the frequency domain were obtained at total power (TP: approximately $\leq$0.4 Hz), very low-frequency power (VLF: 0.003–0.04 Hz), LF (0.04–0.15 Hz), normalized low-frequency power (LF norm), HF (0.15–0.4 Hz), normalized high-frequency power (HF norm), and LF/HF ratio.

2.3. Measurement of BMI

The recordings for height, weight, and BMI were obtained using InBody 720 (Biospace Co, Ltd, Seoul, Korea), a practical and reliable device for measuring height, weight, and BMI. To obtain data on BMI, the participants stayed still on the sole electrodes, grabbing the hand electrodes simultaneously, for less than a minute.

2.4. Statistical analyses

The measured outcomes of the PCOS group and the controls were statistically analyzed using SPSS version 22.0 for Windows (SPSS Inc, Chicago, IL) and compared using Mann-Whitney *U* test. The results were represented as the mean ± standard deviation, and statistical significance was set at $P < .05$.

3. Results

3.1. Baseline characteristics of participants

The baseline clinical characteristics of the women with PCOS and the control group are presented in Table 1. The 2 groups were matched for age ($P > .05$). However, significant differences in BMI and BP were observed between the groups. Women with PCOS showed higher BMI, systolic blood pressure (SBP), and diastolic blood pressure than the control group.

3.2. Time domain in HRV

The results of the time domains in the HRV analysis for the women with PCOS and the control group are shown in Table 2. There was no significant difference in the values of SDNN, rMSSD, and mean HRT between the groups.

3.3. Frequency domain in HRV

The values of the frequency domains in the HRV analysis for the PCOS group and the control group are presented in Figure 1. The TP, VLF, and HF showed no significant differences between the groups. However, women with PCOS showed significantly higher LF (598.63 ± 94.38 vs 459.13 ± 163.64, $P = .028$), LF norm (48.64 ± 3.39 vs 36.49 ± 2.82, $P = .009$), and LF/HF ratio (1.49 ± 0.31 vs 0.73 ± 0.13, $P = .009$) than women in the control group. The HF norm was significantly lower in women with PCOS than in the controls (51.38 ± 3.39 vs 63.51 ± 2.82, $P = .009$).

4. Discussion

PCOS is a common endocrine disorder that induces menstrual dysfunction and infertility. The exact etiology of PCOS is unknown, and it affects approximately 5% to 10% of

Table 1

Baseline clinical features of the participants with polycystic ovary syndrome and the controls.

	PCOS (n = 35)	Control (n = 32)	*P*
Age, y	29.91 ± 0.73	31.06 ± 0.68	.115
Height, cm	162.02 ± 0.76	163.13 ± 1.04	.429
Weight, kg	58.50 ± 1.80	53.64 ± 1.01	.071
BMI, kg/m^2	22.21 ± 0.59	20.17 ± 0.34	.011*
SBP, mm Hg	121.40 ± 2.18	111.69 ± 2.10	.005**
DBP, mm Hg	74.06 ± 1.34	67.63 ± 1.60	.005**

BMI = body mass index, DBP = diastolic blood pressure, PCOS = polycystic ovary syndrome, SBP = systolic blood pressure.

Statistically significant by Mann-Whitney *U* test.

*$P < .05$.

**$P < .01$.

Table 2

Comparison of SDNN, rMSSD, and mean HRT between the women with PCOS and the controls.

	PCOS (n = 35)	Control (n = 32)	*P*
SDNN, ms^2	50.12 ± 3.12	48.68 ± 5.57	.297
rMSSD, ms^2	43.19 ± 3.20	45.63 ± 3.29	.581
Mean HRT, ms^2	68.09 ± 1.50	68.59 ± 1.70	.860

HRT = heart rate turbulence, PCOS = polycystic ovary syndrome, rMSSD = square root of the sum of the square of the difference between the adjacent normal R-R intervals, SDNN = standard deviation of all normal R-R intervals.
Statistically significant by Mann-Whitney *U* test.

reproductive-aged women worldwide. PCOS is diagnosed when 2 of the following 3 criteria are present: hyperandrogenism (clinical or biochemical), oligo/amenorrhea, and appearance of polycystic ovaries (PCOs) on ultrasound, according to the Rotterdam PCOS diagnostic criteria.[12] PCOS is characterized by reproductive sequelae, such as oligo/anovulation, hyperandrogenism (either clinical or biochemical), and altered ovarian morphology, as well as endocrine features, including central obesity, hyperinsulinemia, insulin resistance, dyslipidemia,[13] and hypertension.[14] The common features of PCOS, namely increased insulin resistance and adiposity, have been known to correlate with sympathetic hyperactivity,[5,6] which suggests that sympathoexcitation could be associated with the pathogenesis of PCOS.

Several methods have been developed to measure the ANS. These include microneurography, estimation of noradrenaline spillover, and HRV. There is no single criterion standard method for assessing the ANS. Among these methods, HRV has been frequently used in clinical situations owing to its viability and noninvasiveness. HRV, a statistical measure of the heart rate, is known to be associated with ANS and is used to predict the risk of a variety of metabolic disorders.[8]

Some studies reported that increased sympathetic nerve activity correlates with PCOS in terms of ovarian sympathetic outflow. Stener-Victorin et al[15] reported that a rodent model of PCO showed increased alpha-1 adrenoceptor messenger RNA (mRNA) and decreased alpha-2 adrenoceptor mRNA (a sympathoinhibitory receptor), which is interpreted as an increased sympathetic activity. According to Luza et al,[16] rats with PCO showed increased noradrenergic activity in the anterior hypothalamic nerve terminals. Furthermore, Lara et al[17] showed that intraovarian synthesis of the nerve growth factor, associated with the modulation of the sympathetic nervous system (SNS), increased in rats with PCO.

In addition, women with PCOS tend to show a generalized increase in the activity of the SNS, which could increase the ovarian sympathetic activity. The increase of sympathetic activity in PCOS was investigated by measuring catecholamine and its metabolites in previous studies. It was observed that women with PCOS reportedly had decreased urinary 3-methoxy-4-hydroxyphenylglycol,[18,19] which is consistent with noradrenergic excess. Recently, the muscle sympathetic nerve activity (MSNA) and postexercise SBP have been used to measure the modulation of the SNS. According to Sverrisdottir et al,[20] women with PCOS have higher MSNA, which is a direct measure of the SNS, than their age- and BMI-matched controls. Tekin et al[21] showed that women with PCOS showed higher SBP response to exercise, which is accompanied by a continued sympathetic stimulation.

Limited studies have assessed the function of the ANS in women with PCOS on the basis of HRV. Yildirir et al[11] and Lee et al[10] reported that the PCOS group had significantly higher LF norm and lower HF norm than the controls. Contrary to the abovementioned studies, De Sá et al[9] reported that women with PCOS showed significantly lower LF and HF than the controls. The results of our study indicated that women with PCOS had significantly higher LF, LF norm, and LF/HF ratio than the controls. Meanwhile, HF norm was significantly lower in women with PCOS than in the controls. These results are in line with those of the studies conducted by Yildirir et al[11] and Lee et al,[10] which suggested that women with PCOS had increased sympathetic activity and decreased parasympathetic modulation in HRV, with reference to higher LF and LF/HF ratio and a lower HF.

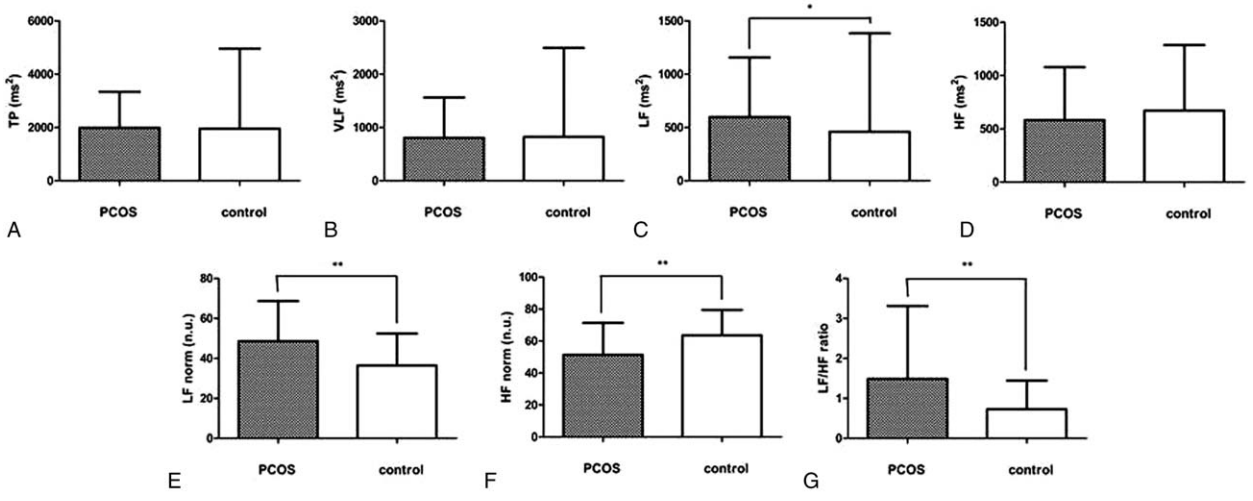

Figure 1. Heart rate variability values of the frequency domain in the PCOS group (n = 35) and the control group (n = 32), A = TP, B = VLF, C = LF, D = HF, E = LF norm, F = HF norm, G = LF/HF ratio. HF = high frequency power, HF norm = normalized high frequency power, LF = low frequency power, LF norm = normalized low frequency power, LF/HF ratio = low frequency power-to-high frequency power ratio, PCOS = polycystic ovary syndrome, TP = total power, VLF = very low-frequency power. Statistically significant by Mann-Whitney *U* test ($^{*}P < .05$, $^{**}P < .01$).

A limitation of our study is the imbalance of BMI and BP between the groups. In addition, HRV assessment was not conducted on a specific day of the menstrual cycle of the participants. Although the results of this study support that sympathetic modulation may be increased in women with PCOS, further investigation is required to determine whether an imbalance of BMI and BP between the groups affects the HRV. Individuals with high BP tend to have decreased HRV[22,23];however, the influence of BMI on HRV has been controversial.[24,25] Hence, the effects of BMI and BP on the results of HRV in our study are difficult to evaluate. Therefore, further studies including a BMI- and BP-matched control group are warranted. Despite the controversy regarding menstrual cycle and HRV outcomes,[26–28] menstrual cycle-controlled analyses are also required.

5. Conclusion

In the present study, LF, LF norm, and LF/HF ratio were found to be significantly higher in the PCOS group than in the control group, whereas HF norm was significantly lower in the PCOS group. Thus, we can propose that sympathetic modulation may be increased in women with PCOS. Further studies with a BMI- and BP-matched control group are warranted to analyze the characteristics of ANS in PCOS.

Author contributions

HRJ and KSP contributed to the study concept and design. HRJ performed the statistical analyses and wrote the first draft of the manuscript. YJP, JML, CHL, and KSP contributed to the acquisition of data. All authors were responsible for interpretation of the results and critical revision of the manuscript, and approved the final manuscript.

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