Research Article

Power spectral analysis of cardiovascular autonomic functional modulation in response to acute mental stress in polycystic ovarian syndrome—an observational study

Nagalakshmi Vijaykumar[1], Shama Jorammanavvar[2], Sharankumar TM[3], Shobha C Nallulwar[1]

[1]Department of Physiology, Sri Dharmasthala Manjunatheshwara Medical College, Dharwad, Karnataka, India.
[2]Department of Physiology, Kempegowda Institute of Medical Sciences, Bangalore, Karnataka, India.
[3]Phase II Student, Sri Dharmasthala Manjunatheshwara Medical College, Dharwad, Karnataka, India.

Correspondence to: Nagalakshmi Vijay Kumar, E-mail: drlakshmi26@yahoo.com

Received January 17, 2016. Accepted February 3, 2016

Abstract

Background: Patients with polycystic ovary syndrome (PCOS) can experience cardiac autonomic dysfunction. Heart rate variability (HRV) is used in assessing cardiac autonomic functions. **Aims and Objective:** To evaluate cardiovascular autonomic functional modulation by using HRV during rest and acute mental stress in female subjects with PCOS. **Materials and Methods:** Thirty patients with PCOS (mean age 27.13 ± 4.53 years) and 30 healthy female volunteers who were matched for body mass index and age (mean age 25.87 ± 6.54 years) were enrolled in the study. The study was conducted during the follicular phase for control subjects and in amenorrheic phase for subjects with PCOS. Frequency-domain power spectral analysis of HRV was carried out using nonparametric method of fast Fourier transform using Kubios HRV analysis software. Mental stress was induced by arithmetic mental challenge under time pressure. **Result:** On comparison with the control subjects, female subjects with PCOS demonstrated a significant reduction in total power of HRV and high frequency (Hf) during rest (p = 0.016) (p = 0.00) and significant increase in low frequency (Lf) (p = 0.0134) and Lf/Hf ratio (p = 0.000). There is significant reduction in total power of HRV, Hf (nu), and Lf/Hf ratio during stress in subjects with PCOS when compared with control subjects. **Conclusion:** We conclude that female subjects with PCOS exhibit altered cardiac autonomic modulation during rest in terms of decreased parasympathetic tone and increased sympathetic tone. They also show failure to cope up to mental stresses as shown by insufficient sympathetic response to stress.

KEY WORDS: Stress; ParasympatheticTone; Hyperandrogenism

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder of women in their reproductive years, with a prevalence of up to 10%.[1] In addition to the typical association of hyperandrogenism and ovulatory dysfunction, an increase in cardiovascular risk factors has also been identified in several studies in patients with PCOS when compared with healthy women of the same age, including obesity, lipid abnormalities,[2,3] insulin resistance (IR),[4] hypertension,[5] and elevations in C-reactive protein.[6] That, in turn, has led to concern about the effect of PCOS on long-term health, particularly with regard to diabetes, hypertension, and coronary heart disease.

It has been recognized that there is a significant relationship between the autonomic nervous system (ANS) and cardiovascular mortality.[7] Metabolic and cardiovascular disorders are related to autonomic dysfunction, in which there is a

Access this article online	
Website: http://www.njppp.com	Quick Response Code:
DOI: 10.5455/njppp.2016.6.17012016119	

compromise of blood pressure, heart rate, and reduced heart rate variability (HRV).[8]

It has long been known that earliest indicator of cardiovascular autonomic imbalance is reduced HRV. Frequency-domain measurements got by power spectral analysis (PSA) of HRV can quantify both sympathetic and parasympathetic components of ANS and recognize sympathovagal imbalance. 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.[9]

Various studies have shown sympathovagal imbalance in PCOS.[10,11] But, there is limited data to prove the sympathovagal imbalance is owing to underlying obesity or insulin resistance or occur independently.

Stress is a huge problem in the present scenario, which may lead to work-related illness directly or indirectly. Mental stress affects autonomic activity in the form of increase in sympathetic activity and decrease in parasympathetic activity.[12] Enough response to stress is must to cope up the situation. Studies show that greater response to stress and poor recovery to stress were associated with increased risk of cardiovascular mortality.[13] As per our knowledge, studies have not been done till now to see the autonomic responses to stress in PCOS. So, the aim of our study is to evaluate cardiovascular autonomic functional modulation during rest and acute mental stress in patients with PCOS. We hypothesize that there is decreased HRV in PCOS associated with poor response to stress.

Materials and Methods

The proposed study was conducted in the Department of Physiology and Gynecology, after obtaining approval from the Institutional Ethical Committee and consent from the female subjects with PCOS and the control subjects for participation in the study.

Thirty newly diagnosed PCOS patients (n = 30) in the age group of 15–35 years who are attending to Department of Obstetrics and Gynecology considering the exclusion criterion were taken as cases. PCOS was diagnosed according to the Rotterdam criteria: clinical hyperandrogenism and oligo/amenorrheic cycles; <9 cycles/year; with polycystic ovary (PCO) appearance at ultrasound. Hirsutism was defined based on modified Ferriman–Gallwey score > 8.[14] Age-matched female subjects with normal, regular menstrual cycles (cycle duration of 28–35 days) were considered as control subjects (n = 30).

PCOS female subjects who are already on the treatment were excluded from the study. Selected control subjects were not under the effects of drugs known to interfere with hormonal levels (such as oral contraceptive pills, antiandrogens, metformin, fibrates, statins) for at least 3 months before the study. Women diagnosed with other hyperandrogenic disorders (nonclassical congenital adrenal hyperplasia, Cushing syndrome, and androgen-secreting neoplasms), thyroid disorders, or hyperprolactinemia were excluded.

The study was conducted during the follicular phase for control subjects and in amenorrheic phase for subjects with PCOS. Participants were instructed to abstain from caffeine, other products containing stimulants, alcoholic beverages, and heavy exercise for 24 h before the test. Subjects rested quietly in the supine position in a silent and semidark room for 20 min. At the end of 5 min of rest in supine position, resting heart rate (HR) was recorded. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were recorded using mercury sphygmomanometer. HRV analysis was done using electrocardiogram (ECG) recorded at rest in supine position for 5 min. ECG was recorded using disposable Ag/AgCl electrodes. ECG data in standard lead II configuration was acquired using portable ECG data acquisition equipment (Niviqure Meditech Systems, Bangalore, India). Frequency-domain analysis was done using nonparametric method of fast Fourier transform using Kubios HRV analysis software. In the frequency domain, the following values were recorded: (1) very low frequency (VLF) power, defined as the power $\leqslant$ 0.04 Hz, (2) low-frequency power, the power between 0.04 and 0.15 Hz, (3) high-frequency power, the power between 0.15 and 0.40 Hz, and (4) total spectral power, the power between 0.0 and 0.40 Hz were measured. Measurement of Lf and Hf power components were presented in absolute values of power (ms^2) and (nu). Mental stress was induced by arithmetic mental challenge under time pressure. The subjects were asked to rapidly subtract seven from a three- or four- digit number, depending on the participant's skill level. During acute mental stress, HRV was recorded.

Statistical Analysis

Statistical analysis has done using IBM SPSS 20 software. Comparison of the HR, SBP, DBP, HRV during rest and acute mental stress between subjects with PCOS and control subjects were done by unpaired Student's t-test. Within the PCOS subjects and control subjects, comparison of the data at rest and during acute mental stress was done by paired t-test. With the confidence interval of 95%, $p < 0.05$ was considered as significant and $p < 0.001$ as highly significant.

Result

This is a cross-sectional study done on 30 subjects with PCOS (n = 30) and 30 healthy control subjects (n = 30). The mean age groups of subjects with PCOS and control subjects were 27.13 ± 4.53 and 25.87 ± 6.54 years, respectively.

Values were expressed as mean ± SEM.

Table 1 shows PSA of frequency-domain HRV parameters during rest and stress in control subjects. (n = 30) There is a significant reduction in total power of HRV during stress (p = 0.04). Even though there is no significant reduction in Lf (ms^2) and Hf (ms^2), there is significant increase in Lf (nu) (p = 0.048) and significant decrease in Hf (nu) (p = 0.001). There is a significant increase in Lf/Hf ratio (p = 0.003).

Table 1: Power spectral analysis of frequency-domain HRV parameters during rest and stress in control subjects (n = 30)

Parameters	Rest	Stress	T	p
Total power (ms^2)	2983.03 ± 320.14	1842.166 ± 225.03	2.915	0.04*
Lf (ms^2)	992.43 ± 150.97	683.73 ± 95.19	1.730	0.089
Lf (nu)	44.32 ± 2.97	49.6 ± 2.87	-1.274	0.048*
Hf (ms^2)	1335.05 ± 316.02	1020.366 ± 275.05	0.751	0.456
Hf (nu)	53.46 ± 2.50	21.93 ± 2.24	3.423	0.001**
Lf/Hf ratio	0.9452 ± 0.12	3.86 ± 0.19	-2.188	0.033*

Lf, low frequency; Hf, high frequency.
Values expressed as mean ± SEM.
*$p < 0.05$ considered as significant, **$p < 0.01$ considered highly significant.

Table 2 shows PSA of frequency-domain HRV parameters during rest and stress in subjects with PCOS (n = 30). There is significant reduction in total power of HRV during stress (p = 0.02). Even though there is no significant change in other HRV parameters, there is significant reduction in Hf (nu) during stress (p = 0.000).

Table 3 shows the comparison of study parameters during rest in control subjects and subjects with PCOS. There is a significant reduction in total power of HRV in subjects with PCOS during rest compared with control subjects (p = 0.016). There is significant reduction in Lf (ms^2) and Hf (nu). There is significant increase in Lf (nu) (p = 0.0134) and Lf/Hf ratio (p = 0.000).

Table 4 shows comparison of study parameters during stress in control subjects and subjects with PCOS. There is significant reduction in total power of HRV during stress in subjects with PCOS when compared with control subjects (p = 0.056). There is significant reduction in Lf (ms^2), Hf (nu), and Lf/Hf ratio in subjects with PCOS.

Discussion

Our study evaluated HRV in PCOS female subjects during rest and stress and compared with control subjects. Mental stress in the form of mental arithmetic increased Lf power, Lf (nu), and

Table 2: Power spectral analysis of frequency-domain HRV parameters during rest and stress in PCOS (n = 30)

Parameter	Rest	Stress	T	p
Total power (ms^2)	1786.60 ± 338.33	1228.04 ± 206.53	3.032	0.02*
Lf (ms^2)	536.86 ± 87.32	424.43 ± 66.59	1.024	0.312
Lf (nu)	53.76 ± 4.35	54.77 ± 4.27	-0.165	0.870
Hf (ms^2)	740.73 ± 118.88	688.23 ± 88.79	0.432	0.67
Hf (nu)	31.40 ± 1.42	20.74 ± 1.80	4.268	0.000*
Lf/Hf ratio	1.988 ± 0.16	2.10 ± 0.12	-0.692	0.493

Lf, low frequency; Hf, high frequency.
Values expressed as mean ± SEM.
*$p < 0.05$ considered as significant, **$p < 0.01$ considered highly significant.

Table 3: Comparison of frequency-domain HRV parameters during rest in controls and PCOS (n = 30 each)

Parameter	Rest (controls)	Rest (PCOS)	T	p
Total power (ms^2)	2983.03 ± 320.14	1786.60 ± 338.33	2.499	0.016*
Lf (ms^2)	992.43 ± 150.97	536.86 ± 87.32	2.363	0.022*
Lf (nu)	44.32 ± 2.97	52.24 ± 4.23	-3.575	0.0134*
Hf (ms^2)	1335.05 ± 316.02	740.73 ± 118.88	1.516	0.136
Hf (nu)	53.46 ± 2.50	31.40 ± 1.42	6.921	0.000**
Lf/Hf	0.9452 ± 0.12	1.988 ± 0.16	-5.043	0.000**

Lf, low frequency; Hf, high frequency.
Values expressed as mean ± SEM.
*$p < 0.05$ considered as significant, **$p < 0.01$ considered highly significant.

Table 4: Comparison of frequency-domain HRV parameters during mental stress in controls and PCOS (n = 30 each)

Parameter	Stress (controls)	Stress (PCOS)	T	p
Total power (ms^2)	1842.166 ± 225.03	1228.04 ± 206.53	1.953	0.056*
Lf (ms^2)	683.73 ± 95.19	424.43 ± 66.59	2.099	0.041*
Lf (nu)	49.6 ± 2.87	54.77 ± 4.27	-1.041	0.303
Hf (ms^2)	1020.366 ± 275.05	688.23 ± 88.79	0.988	0.120
Hf (nu)	41.93 ± 2.24	20.74 ± 1.80	7.019	0.000**
Lf/Hf	3.86 ± 0.19	2.10 ± 0.12	1.079	0.05*

Lf, low frequency; Hf, high frequency.
Values expressed as mean ± SEM.
*$p < 0.05$ considered as significant, **$p < 0.01$ considered highly significant.

Lf/Hf ratio and decreased Hf (nu) in both PCOS and control subjects; however, rise in Lf power and Lf (nu) during stress were less in PCOS subjects. This study shows the PCOS phenotype associated with a reduction in cardiovascular autonomic functional modulation in response to stress and during rest. Results are similar to an earlier study, which has recorded HRV in different phenotypes of PCOS (classic and ovulatory) in response to mental stress.[15] There is significant reduction in total power of HRV during stress in PCOS subjects when compared with control subjects as evidenced by significant reduction in Lf (ms^2), Hf (nu), and Lf/Hf ratio in PCOS subjects. During a situation requiring quick and effective autonomic modulation, the PCOS phenotype was associated with an impaired response. This autonomic imbalance implies a failure in the adaptation to stressors that may predispose to the development of a sustained perturbation of sympathovagal balance over time, possibly with higher risk of developing hypertension. Impaired HRV in response to mental stress has also been reported in patients with diabetes mellitus[16] or recovering from myocardial infarction,[17] in whom the ANS is compromised. This disturbed autonomic modulation has been regarded as a predictor of cardiovascular events and mortality in the general population.

Androgens could be responsible for blunted autonomic responses seen in PCOS. Even though this is the limitation of the study that we have not measured the total androgen levels, studies show negative correlation between androgen levels and frequency domain of HRV in PCOS women.[18] Even the insulin resistance (IR) found in PCOS could also be responsible for the blunted response to stress in PCOS. Again this is the limitation of the study that parameters to assess IR have not measured; studies show evidence of an association between IR and cardiovascular risk reflected by changes in HRV in hyperinsulinemic and diabetic patients,[16] regardless of age.

Our study also evaluated HRV during rest in PCOS, and it showed impaired autonomic modulation even during rest, predominantly in vagal HRV indices, as evidenced by reduction in Hf (nu) with significant increase in Lf (nu) and Lf/Hf ratio compared with controls. A few earlier studies have evaluated HRV in PCOS, which show impaired cardiac autonomic modulation at rest[10,11] and during 24 h[9] in women with PCOS in comparison with control subjects.

Augmentation of the sympathetic innervations may play a role in the PCOs. Rats with estrogen-induced PCOs have been shown to have high uptake and levels of norepinephrine and a high degree of transmitter release after electrical stimulation of the ovary.[19] Moreover, there are data suggesting altered peripheral noradrenalin deamination and/or uptake in adolescent patients with PCOS. IR, observed both in obese and lean subjects with PCOS, and sympathetic activity are linked in a positive-feedback fashion that leads to their reciprocal reinforcement. Small sample size is the main limitation of this study that limits the generalization of our findings. Use of instrument that measures sympathetic activity accurately such as MSNA should be followed to assess the exact increase in sympathetic activity.

Conclusion

From this study, we conclude that female subjects with PCOS show altered cardiac autonomic modulation during rest in terms of decreased parasympathetic and increased sympathetic tones. They also show failure to cope up to mental stresses as shown by insufficient sympathetic response to stress. We also conclude that frequency-domain analysis of HRV during induced acute mental stress is a powerful noninvasive tool for early diagnosis of cardiovascular autonomic neuropathy in asymptomatic PCOS patients. More studies with large sample size are needed to support our findings.

References

1. Carmina E, Lobo RA. Polycystic ovary syndrome (PCOS): arguably the most common endocrinopathy is associated with significant morbidity in women. J Clin Endocrinol Metab. 1999;84(6):1897–9.
2. Berneis K, Rizzo M, Hersberger M, Rini GB, Di Fede G, Pepe I, et al. Atherogenic forms of dyslipidaemia in women with polycystic ovary syndrome. Int J Clin Pract. 2009;63(1):56–62.
3. Wild RA, Painter PC, Coulson PB, Carruth KB, Ranney GB. Lipoprotein lipid concentrations and cardiovascular risk in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 1985; 61(5):946–51.

4. Dunaif A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes. 1989;38(9):1165–74.
5. Giallauria F, Orio F, Palomba S, Lombardi G, Colao A, Vigorito C. Cardiovascular risk in women with polycystic ovary syndrome. J Cardiovasc Med (Hagerstown). 2008;9(10):987–92.
6. Boulman N, Levy Y, Leiba R, Shachar S, Linn R, Zinder O, et al. Increased C-reactive protein levels in the polycystic ovary syndrome: a marker of cardiovascular disease. J Clin Endocrinol Metab. 2004;89(5):2160–5.
7. Lown B, Verrier RL. Neural activity and ventricular fibrillation. N Engl J Med. 1976;294(21):1165–70.
8. Tsuji H, Larson MG, Venditti FJ, Manders ES, Evans JC, Feldman CL, et al. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation. 1996;94(11): 2850–5.
9. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 1996;17(3):354–81.
10. Yildirir A, Aybar F, Kabakci G, Yarali H, Oto A. Heart rate variability in young women with polycystic ovary syndrome. Ann Noninvasive Electrocardiol. 2006;11(4):306–12.
11. Tekin G, Tekin A, Kilicarslan EB, Haydardedeoglu B, Katircibasi T, Kocum T, et al. Altered autonomic neural control of the cardiovascular system in patients with polycystic ovary syndrome. Int J Cardiol. 2008;130(1):49–55.
12. Jadhav SB, Jatti GM, Jadhav AS, Rajderkar SS, Naik JD, Nandimath VA. Stressing 'mental stress' in hypertension: a rural background study. J Clin Diagn Res. 2014;8(6):JC04–7.
13. Chida Y, Steptoe A. Greater cardiovascular responses to laboratory mental stress are associated with poor subsequent cardiovascular risk status: a meta-analysis of prospective evidence. Hypertension. 2010;55(4):1026–32.
14. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19–25.
15. Di Domenico K, Wiltgen D, Nickel FJ, Magalhães JA, Moraes RS, Spritzer PM. Cardiac autonomic modulation in polycystic ovary syndrome: does the phenotype matter? Fertil Steril. 2013;99(1): 286–92.
16. Adler GK, Bonyhay I, Failing H, Waring E, Dotson S, Freeman R. Antecedent hypoglycemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. Diabetes. 2009; 58(2):360–6.
17. Kleiger RE, Miller JP, Bigger JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol. 1987;59(4):256–62.
18. Lobo RA, Granger LR, Paul WL, Goebelsmann U, Mishell DR. Psychological stress and increases in urinary norepinephrine metabolites, platelet serotonin, and adrenal androgens in women with polycystic ovary syndrome. Am J Obstet Gynecol. 1983;145(4):4 96–503.
19. Lara HE, Ferruz JL, Luza S, Bustamante DA, Borges Y, Ojeda SR. Activation of ovarian sympathetic nerves in polycystic ovary syndrome. Endocrinology. 1993;133(6):2690–5.

How to cite this article: Vijaykumar N, Jorammanavvar Sharankumar, TM S, Nallulwar SC Power spectral analysis of cardiovascular autonomic functional modulation in response to acute mental stress in polycystic ovarian syndrome—an observational study. Natl J Physiol Pharm Pharmacol 2016;6:236-240

Source of Support: Nil, **Conflict of Interest:** None declared.