This journal is the official publication of Bangladesh Society of Physiologists (BSP)
Web URL: www.banglajol.info/index.php/JBSP

Abstracted /indexed in Index Copernicus, Director of Open Access Journal, Index Medicus for South East Asia Region, Google Scholar, 12OR, infobse index, Open J gate, Cite factor, Scientific indexing services

pISSN-1983-1213; e-ISSN-2219-7508

Article

Article information:
Received on September 2019
Accepted on November 2019
DOI: https://doi.org/10.3329/jbsp.v14i2.44789

Corresponding author:
Musfika Mostafa, Department of Physiology, Bangabandhu Sheikh Mujib Medical University,Shahbag, Dhaka.
Email: mostafamusfika10@gmail.com

Cite this article:
Mostafa M, Ferdousi S, Sultana S, Akhter A. Autonomic impairment and oxidative stress: Relationship in PCOS patients
J Bangladesh Soc Physiol 2019;14(2): 82-88

Autonomic impairment and oxidative stress: Relationship in PCOS patients

Musfika Mostafa[1], Sultana Ferdousi[1], Shamima Sultana[1], Ayesha Akhter[1]

1. Department of Physiology, Bangabandhu Sheikh Mujib Medical University,Shahbag, Dhaka.

Abstract

Background: Polycystic ovary syndrome (PCOS) is one of the most common, heterogeneous endocrine disorder of reproductive aged women. Association of autonomic impairment and elevated oxidative stress may predispose these patients to increased cardiovascular risks. **Objective:** To evaluate the relationship between cardiac autonomic nerve function (CANF) and oxidative stress in patients with PCOS. **Methods:** This cross sectional study was conducted in Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from September, 2018 to August, 2019. For this study, 30 newly diagnosed PCOS patients aged 20-35 years were recruited and similar age, body mass index (BMI) 30 apparently healthy, regularly menstruating women were enrolled as control. CANF was assessed by analyzing time domain measures of Heart Rate Variability (HRV). HRV data were recorded by a digital data acquisition device, Powerlab 8/35 (AD instruments, Australia). For evaluation of oxidative stress, plasma catalase and plasma Malondialdehyde (MDA) levels were measured. Statistical analysis was done by unpaired "t" test and Pearson's correlation test as applicable. **Results:** In this study, resting pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) were significantly higher ($p<0.001$, $p<0.01$, $p<0.01$ respectively) and standard deviation of the RR intervals (SDRR) ($p<0.01$), mean R-R interval, standard deviation of the difference between successive RR intervals (SDSD), square root of mean squared differences of successive RR intervals (RMSSD), proportion of RR interval with duration >50 ms (pRR50%) were significantly lower ($p<0.001$) in PCOS than healthy controls. In addition,

plasma catalase was significantly lower ($p<0.01$) and plasma MDA was significantly higher ($p<0.001$) in PCOS patients compared to controls. On correlation analysis, mean heart rate, SDRR, SDSD, RMSSD and pRR50% showed negative correlation with plasma catalase and plasma MDA ($p<0.05$) in PCOS patients but these were not significant. **Conclusion:** The present study reveals that reduced parasympathetic activity in PCOS patients may be related to oxidative stress.

Key words: HRV, PCOS, catalase, MDA.

Introduction

PCOS is one of the most frequent reproductive hormone disorder, with a global prevalence ranging from 8 to 13%[1]. It is characterized by a oligo and/absent ovulation, higher androgen levels, large cystic ovaries[2]. This syndrome can also be associated with features of metabolic syndrome including type 2 diabetes mellitus, obesity, dyslipidemia and hypertension. These metabolic abnormalities exacerbates 4-11 fold increased risk for cardiovascular problems[3]. Ozkececi and his colleagues reported cardiovascular and metabolic disorders are closely related to autonomic impairment which has significant relationship with cardiovascular mortality[4].

For assessment of cardiac autonomic nerve function (CANF) heart rate variability (HRV) analysis has become popular, noninvasive, easy and reliable technique in cardiac and non cardiac diseases[5-7]. Among different methods used for HRV analysis, time domain method determines the heart rate at any moment in time or the intervals between successive normal QRS complex in a continuous ECG recording[5]. It includes some statistical complex measures of RR interval of normal beats such as standard deviation of the difference between successive RR intervals (SDSD), root of the mean squared differences of successive RR intervals (RMSSD), the number of interval differences of successive RR intervals greater than 50 ms (RR50) and the proportion derived by dividing RR50 by the total number of RR intervals (PRR50%)[5]. Several group of researchers observed, PCOS patients had impaired CANF, manifested by increased sympathetic[8,9] and decreased parasympathetic modulation [9]. But other group of researchers found no change in CANF[4,10].

Oxidative stress results from the imbalance between production of various oxidants including reactive oxygen species (ROS) and antioxidant defense system[11]. ROS causes damage of cellular macromolecules, leading to protein and DNA modification and lipid peroxidation[12]. Products of lipid peroxidation reactions are indices for oxidative stress. Recently, a number of clinical studies found increased oxidative stress in PCOS patients [13-15]. Several researchers also reported, increased oxidative stress contributes to increased risk of cardiovascular disease (CVD) in PCOS, which was related to their insulin resistance, hypertension, central obesity, and dyslipidemia[16,17].

Although there is abundant evidence for increased oxidative stress and decreased HRV in PCOS from separate studies but relationship between CANF and oxidative stress have not been investigated. However an early diagnosis of altered CANF and oxidative stress may lead to an effective management and reduce CVD risk. Therefore, this study has been designed to assess the relationship between CANF and oxidative stress in patients with PCOS.

Methods

This cross sectional study was carried out from September, 2018 to August, 2019 at the Department of Physiology, BSMMU, Shahbag, Dhaka to observe the relationship between time domain HRV parameters and oxidative stress in 30 newly diagnosed PCOS patients, aged 20-35 years. For comparison 30 age, BMI matched apparently healthy women with regular menstrual cycles (early follicular phase) were taken as controls. The patients were enrolled from the outpatient Department of Endocrinology, BSMMU by purposive sampling and the controls were selected through personal contact. The protocol of this study was approved by the Institutional Review Board of BSMMU. After briefing about the study, informed written consent was taken from each subject. All the subjects were free from cardiac disease, respiratory disease, renal disease, diabetes mellitus and thyroid disorders. Women who were pregnant or lactating excluded from this study. Detail family, medical and dietary history was recorded in a preformed data schedule and thorough physical examination was done. Resting pulse rate, blood pressure, height, weight were measured and BMI was calculated. Then 7 ml of venous blood was collected for estimation of fasting plasma glucose, serum SGPT, serum TSH and serum creatinine in the laboratory of Department of Biochemistry and Molecular Biology and plasma catalase and plasma MDA in the Department of Physiology. Then the subjects were advised to follow some instructions to prepare for HRV. They were advised to finish their meal by 9:00 pm on the previous night of HRV test day, avoid any type of stress and not to take any sedative hypnotic medication. They were requested to take a light breakfast without tea or coffee and to attend the autonomic nerve function test laboratory in the Department of Physiology, BSMMU between 8:00 am to 9:00 am on the test day. The subject was advised to take rest for 15-20 minutes in a controlled laboratory environment. During this period she was not allowed to talk, eat or drink, to perform physical or mental activity or sleep. ECG was recorded on lead II for 5 minutes by data acquisition device Power Lab 8/35 (AD Instrument, Australia). HRV recording was analyzed by Lab chart software.

Data were expressed as Mean ± SD. Statistical analysis was done using SPSS version 16. Independent sample 't' test and Pearson's correlation analysis were done, p value of < 0.05 was considered as statistically significant.

Results

Anthropometric details of the subjects are given in table I. Both groups were matched for age, BMI and waist hip ratio (Table I). Mean values of resting pulse rate ($p<0.001$), SBP and DBP ($p<0.01$) were significantly higher in group PCOS compared to controls (Table II). In this study, the mean values of heart rate ($p<0.001$) was significantly higher and SDRR ($p<0.01$), mean RR interval, SDSD, RMSSD, PRR50% ($p<0.001$) were significantly lower in group PCOS than that of controls (Table III).

Table I: Age, BMI and WHR in two groups (N=60)

Variables	PCOS (n= 30)	Control (n= 30)
Age (Year)	26.27±4.29 (20-35)	27.93±3.92 (22-33)
BMI (Kg/m^2)	29.65±3.50 (25.09-38.28)	29.00±2.54 (25.38-34.58)
WHR	0.88±0.07 (0.75-1.10)	0.86±0.05 (0.76-0.96)

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by Independent sample t-test; BMI- Body Mass Index; WHR- Waist Hip Ratio; PCOS- Polycystic ovary syndrome; n- Number of subjects

Table II: Resting pulse rate and blood pressure in two groups (N=60)

Variables	Control (n= 30)	PCOS (n= 30)
Pulse rate	74.97±7.85	83.47±7.06***
(beats /min)	(62-90)	(76-102)
SBP	115.07±6.80	121.27±7.80**
(mmHg)	(100-125)	(110-135)
DBP	75.63±5.47	79.73±5.09**
(mmHg)	(65-88)	(70-88)

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by Independent sample t-test; SBP- systolic blood pressure; DBP- diastolic blood pressure; PCOS - Polycystic ovary syndrome; n- Number of subjects; ***p<0.001; **p<0.01.

Table III: Time domain measures of HRV in two groups (N=60)

Variables	Control (n= 30)	PCOS (n= 30)
Mean heart rate	77.31±8.50	85.97±7.80***
(beats/min)	(64.63-95.75)	(77.09-107.80)
Mean R-R	788.11±86.62	682.83±128.66***
Interval(sec)	(627.10-931.80)	(75.60-783.30)
SDRR	45.89±13.52	35.79±9.02***
(ms)	(17.39-92.56)	(16.53-58.18)
CVRR	0.06±0.02	0.06±0.01
	(0.03-0.13)	(0.03-0.09)
SDSD	37.86±14.82	23.93±6.63***
(ms)	(16.64-86.38)	(12.20-36.54)
RMSSD	37.82±14.81	24.24±6.87***
(ms)	(16.62-86.29)	(12.19-36.50)
pRR50%	14.22±10.39	4.73±4.81***
	(0.18-35.35)	(0.16-16.85)

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by Independent sample t-test; SDRR- Standard deviation of all RR interval; CVRR- Coefficient of variance of RR interval; SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50%- Proportion of RR interval with duration > 50ms; PCOS- Polycystic ovary syndrome; n- Number of subjects; ***p<0.001; **p<0.01.

Table IV: Oxidative stress measures in two groups (N=60)

Variables	Control (n= 30)	PCOS (n= 30)
Plasma catalase	224.90±80.11	170.53±67.69**
(U/ml)	(108.00-389.00)	(79.00-282.00)
Plasma MDA	204.55±96.82	532.94±234.29***
(ng/ml)	(82.04-478.8)	(101.3-952.5)

Data were expressed as Mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by Independent sample t-test; MDA- Malondialdehyde; PCOS- Polycystic ovary syndrome; n- Number of subjects; **p<0.01; ***p<0.001. N = Total number of subjects.

Table V: Correlations of Time domain HRV measures with plasma catalase levels in PCOS (N=30)

Variables PCOS	r value	p value
Mean heart rate(beats/min)	-0.026	0.892
SDRR(ms)	-0.172	0.364
SDSD(ms)	-0.060	0.752
RMSSD(ms)	-0.112	0.557
pRR50%	-0.077	0.685

Statistical analysis was done by Pearson's correlation test; PCOS- Polycystic ovary syndrome; n- Number of subjects; SDRR- Standard deviation of all RR interval; SDSD- Standard deviation of successive RR interval differences between adjacent RR intervals; RMSSD- Square root of mean of squared differences of successive RR interval; pRR50%- Proportion of RR interval with duration > 50ms. N = Total subjects.

In group PCOS, mean values of plasma catalase (p<0.01) was significantly lower and plasma MDA (p<0.001) was significantly higher compared to control group (Table IV).

All the time domain parameters of HRV showed negative correlation with plasma catalase and plasma MDA levels in PCOS but all these were statistically non significant (p> 0.05) (Table V, VI).

Discussion

The present study investigated the relationship between CANF and oxidative stress in 30 newly diagnosed PCOS patients aged 20-35 years. Data of this study showed similar age[4, 9, 10, 18] and BMI[10] in both groups resembling to the observations in similar studies. In this study, significantly higher resting pulse rate, SBP and DBP were associated with PCOS patients which agree to others in respect of resting pulse rate but SBP and DBP were similar in PCOS and control [8] but Saranya and his colleagues found significantly higher SBP and DBP in PCOS patients[9]. These suggest more deviation of autonomic tonic activity in PCOS.

In this study, significant higher mean HR and lower mean RR interval, SDRR, SDSD, RMSSD, pRR50% in PCOS patients were consistent to the observations of others suggesting lower parasympathetic activity were associated with PCOS[8,9,19].

Oxidative stress affects rostral ventrolateral medulla (RVLM) neurons causing sympatho excitation via interactions with nitric oxide (NO). NO exerts a tonic inhibition of central sympathetic nervous system (SNS) activity by releasing

GABA in the RVLM and it also facilitates baroreceptor mediated vagal tone [20-22]. ROS interacts with NO, therefore decreased NO availability in the RVLM could result in sympathetic overactivity and decrease parasympathetic activity[23-25].

In the present study, significantly lower plasma catalase levels, a marker for antioxidant, demonstrate poor antioxidant status and higher MDA level, index of oxidant reflecting the prevalence of higher oxidative stress in PCOS agrees the observation of other studies done on PCOS patients[13,15,26-30]. These result indicates presence of higher oxidative stress in the current series of PCOS patients. Body of evidence suggested that obesity, insulin resistance and hyperglycemia contributes to an increase oxidative stress in PCOS.

Further correlation analysis between autonomic function and oxidative stress showed trends of inverse relationship between time domain parameters of HRV and oxidant and antioxidant though did not again statistical significant. But it provides a link of relationship of parasympathetic hypofunction to higher oxidative stress in PCOS.

These observations suggest that impaired autonomic function in PCOS may be attributed to oxidative stress. Therefore both oxidative stress and its associated dysautonomia may predispose the PCOS patients to the increased risk of cardiovascular morbidity if not appropriate interviewed.

Conclusion

Based on the results of this study it is concluded that autonomic dysfunction tends to be related to oxidative stress in PCOS.

Conflict of interest-None

References

1. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Okan Y. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod 2016; 31(12): 2841–55. DOI: 10.1093/humrep/dew218
2. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19(1): 41-7. DOI: 10.1093/humrep/deh098
3. 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.
4. Ozkececi G, Unlu BS, Dursun H, Akci O, Koken G, Onrat E, Avsar A. Heart rate variability and heart rate turbulence in patients with polycystic ovary syndrome. Anatol J Cardiol 2016; 16(5): 323-27. DOI:10.5152/AnatolJCardiol.2015.6307
5. Task Force of the European Society of Cardiology and the North American Society of pacing and electrophysiology. Heart Rate Variability: Standards of Measurement, Physiological Interpretation and Clinical Use. Circulation 1996; 93: 1043-65.
6. Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Med Bio Eng Comput 2006; 44: 1031-151. DOI: 10.1007/s11517-006-0119-0
7. Al-Hazimi A, Al-Ama N, Syiamic A,Qosti R, Abdel-Galil K. Time- Domain Analysis of Heart Rate Variability in Diabetic Patients with and without Autonomic Neuropathy. Ann Saudi Med 2002; 22(5-6): 400-3.
8. Hasim ZH, Hamdan FB, Al-Salihi AR. Autonomic dysfunction in women with polycystic ovary syndrome. Iran J Reprod Med 2015; 13(1): 27-34.
9. Saranya K, Pal GK, Habeebullah S, Pal P. Assessment of cardiovascular autonomic function in patients with polycystic ovary syndrome. J Obstet Gynaecol Res 2014; 40(1): 192-99. http://dx.doi.org/10.1111/jog.12154
10. Kilit C, Kilit TP. Heart rate variability in normal weight patients with polycystic ovary syndrome. Anatol J Cardiol 2017; 17(5): 404-09. DOI: 10.14744/ Anatol J Cardiol.2017.7473
11. Lee JY, Baw CK, Gupta S, Aziz N, Agarwal A. Role of oxidative stress in polycystic ovary syndrome. Curr Women's Health Rev 2010; 6(2): 96-107.
12. Pan H-Z, Zhang L, Guo M-Y, Sui H, Li H, Wu W-H, Qu N-Q, Liang M-H, Chang D. The oxidative stress status in diabetes mellitus and diabetic nephropathy. Acta Diabetol 2010; 47(Suppl 1): S71-S76. DOI 10.1007/s00592-009-0128-1

13. Santos ACSD, Azevedo GDA, Lemos TMAM. The Influence of Oxidative Stress in Inflammatory Process and Insulin Resistance in Obese Women with Polycystic Ovary Syndrome. Transl Biomed 2016; 7(4): 1-6. DOI: 10.21767/2172-0479.100100

14. Shirsath A, Aundhakar N , Kamble P. Study of oxidative stress and antioxidant levels in polycystic ovarian disease. Int J Med Biomed Res 2015; 3(4): 16-24.

15. Desai V, Prasad NR, Manohar SM, Sachan A, Narasimha SRPVL, Bitla ARR. Oxidative Stress in Non-Obese Women with Polycystic Ovarian Syndrome. J Clin Diagn Res 2014; 8(7): CC01-CC03. DOI: 10.7860/JCDR/2014/8125.4530

16. Fenkci V, Fenkci S, Yilmazer M, Serteser M. Decreased total antioxidant status and increased oxidative stress in women with polycystic ovary syndrome may contribute to the risk of cardiovascular disease. Fertil Steril 2003; 80(1): 123-27. DOI: 10.1016/S0015-0282(03)

17. Sabuncu T, Vural T, Harma M, Harma M. Oxidative stress in polycystic ovary syndrome and its contribution to the risk of cardiovascualr disease. Clin Biochem 2001; 34(5): 407-13.

18. Tekin G, Tekin A, Kilic¸ arslan EB, Haydardedeoglu B, Katircibasi T, Kocum T, Erol T, Colkesen Y, Sezgin AT, Muderrisoglu H. Altered autonomic neural control of the cardiovascular system in patients with polycystic ovary syndrome. Int J Cardiol 2008; 130(1): 49–55. DOI:10.1016/j.ijcard.2007.08.037

19. de Sa JCF, Costa EC, Da Silva E, Zuttin RS, Da Silva EP, Lemos TMAM, De Azevedo GD. Analysis of heart rate variability in polycystic ovary syndrome. Gynecol Endocrinol 2011; 27: 443-7. http://dx.doi.org/ 10.3109/09513590.2010.501881

20. Ye S, Mozayeni P, Gamburd M, Zhong H, Campese VM. Interleukin-1b and neurogenic control of blood pressure in normal rats and rats with chronic renal failure. Am J Physiol Heart Circ Physiol 2000; 279: H2786–H2796.

21. Zanzinger J. Role of nitric oxide in the neural control of cardiovascular function. Cardiovasc Res 1999; 43 (1999): 639–49.

22. Ye S, Nosrati S, Campese VM. Nitric Oxide (NO) Modulates the Neurogenic Control of Blood Pressure in Rats with Chronic Renal Failure (CRF). J. Clin. Invest 1997; 99(3): 540-48.

23. Salim S. Oxidative Stress and the Central Nervous System. J Pharmacol Exp Ther 2017; 360: 201–05. http://dx.doi.org/10.1124/jpet.116.237503

24. Campese VM, Ye S, Zhong H, Yanamadala V, Ye Z, Chiu J. Reactive oxygen species stimulates central and peripheral sympathetic nervous activity. Am J Physiol Heart Circ Physiol 2004; 286: 695–03.

25. Kishi. Regulation of the sympathetic nervous system by nitric oxide and oxidative stress in the rostral ventrolateral medulla: 2012 Academic Conference Award from the Japanese Society of Hypertension. Hypertens Res 2013; 36: 845-51. DOI:10.1038/hr.2013.73

26. Rasool M, Ahmad R, Rizwan R, Malik A, Asif M, Zaheer A, Jabbar A, Zain M, Qaisrani MM, Qaisrani TB, Mehmood A, Malik IR, Helmi N, Zeyadi M, Choudhry H, Harlev A, Agarwal A, Jamal MS. Inter-relationship of circulating biochemical markers of oxidative stress and comorbid condition in polycystic ovary syndrome. Biomed Res 2018; 29(21): 3779-83.

27. Özer A, Bakacak M, Kiran H, ErcanÖ, Köstü B, Pektaþ MK, Kýlýnç M, Aslan F. Increased oxidative stress is associated with insulin resistance and infertility in polycystic ovary syndrome. Ginekologia Polska 2016; 87(11): 733-38. DOI: 10.5603/GP.2016.0079

28. Kandasamy S, Sivagamasundari RI, Bupathy A, Sethubathy S, Gobal V. Evaluation of insulin resistance and oxidative stress in obese patients with polycystic ovary syndrome. IJABPT 2010; 1(2): 391-98.

29. Mohan SK, Priya V. Lipid peroxidation, glutathione, ascorbic acid, vitamin E, antioxidant enzyme and serum homocysteine status in patients with polycystic ovary syndrome. Biol Med 2009; 1(3): 44-9.

30. Kuscu NK, Var A. Oxidative stress but not endothelial dysfunction exists in non-obese, young group of patients with polycystic ovary syndrome. Acta Obstet Gynecol Scand 2009; 88(5): 612-17. DOI: 10.1080/00016340902859315