Introduction
Polycystic ovary syndrome (PCOS) is the common endocrine disorder that affects reproductive age group women. Polycystic ovarian disease shows features like hirsutism and enlarged ovaries with multiple cysts. As per an estimate of the World Health Organization, more than 116 million women are affected by PCOS worldwide. It is now accepted as a common, heterogeneous, heritable disorder affecting women throughout their lifetime. Hirsutism, hyperandrogenism, severe acne, and irregular menstrual cycle are some of the consequences associated with this disorder. Anovulatory cycles are present in PCOS patients. It has been accepted as a considerable cardiovascular and metabolic risk factor. Autonomic dysfunction has a significant relationship with cardiovascular mortality.

Cardiovascular risk factors like hypertension, lipid abnormalities, endothelial dysfunction, increased C-reactive protein and homocysteine levels are associated with PCOS.

Abstract
Background: Polycystic ovary syndrome (PCOS) patients show common features like increased insulin resistance and adiposity, which have been known to correlate with sympathetic hyperactivity. Objective: The aim of this study is to analyze the characteristics of heart rate variability (HRV) between women with PCOS and apparently healthy women. To study the impact of cardometabolic parameters such as BMI and blood pressure on frequency-domain HRV parameters. Methods: A total of 30 women with PCOS aged 20 to 40 years (as per Rotterdam criteria) were enrolled as cases and 30 age-matched women having normal ovulatory cycles were enrolled as controls. HRV was recorded using an electrocardiography machine (ECG) machine. The following frequency-domain parameters were assessed: Total power, Very low frequency (VLF), VLF%, Low Frequency (LF), LF%, LF nu, High frequency (HF), HF%, HF nu, LF/HF ratio, short-term variability (SD1), and long-term variability (SD2), respectively. Results: Mean age of cases was 28.03 ± 5.33 years. Mean BMI of PCOS women was 25.39 ± 2.69 kg/m². A total of 18 (60%) had BMI >25 kg/m². Majority of cases (66.7%) had systolic blood pressure/diastolic blood pressure (SBP/DBP) >130/85 mmHg as compared with only 6 (20%) of controls (P < 0.001). For different frequency domain parameters, no statistically significant difference between two groups was observed for VLF and LF. Mean VLF%, LF%, LF (nu), and LF/HF were significantly higher in cases as compared with controls. For all, the other mean value was significantly lower in cases as compared with that of controls (P < 0.05). Conclusions: Autonomic nervous system is affected by PCOS status of women, and sympathetic hyperactivity is seen.

Keywords: Frequency domain, heart rate variability, HF, LF, PCOS, VLF

Comparison of frequency domain parameters of heart rate variability between women with polycystic ovarian disease and apparently healthy women

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Polycystic ovaries establish due to hyperandrogenism, especially increase testosterone, hyperinsulinemia, and decrease levels of sex-hormone binding globulin which results in increased free androgens. Ultrasound of PCOD women shows multiple immature antral follicles, caused by disturbed ovarian function. The follicles align along the periphery of ovaries become visible as a “string of pearls” on ultrasound.

High LH/FSH ratio due to increase in frequency of GnRH and hyperinsulinemia increases GnRH frequency. Patients with PCOS have insulin resistance and/or obesity. Hypothalamic-pituitary-ovarian axis abnormalities seen because of raised insulin levels effectuate to PCOS. LH/FSH ratio increases, hyperandrogenaemia, reduction in follicular maturation. Entirely these factors come up to the occurrence of PCOS.

**ROTTERDAM CRITERIA: Require presence of any two of the following:**

1) USG criteria of ROTTERDAM
   - >12 follicles each <10 mm.
   - Ovarian volume >10 cc
2) Oligomenorrhea
3) Hyperandrogenism.

Heart Rate Variability (HRV). In this method, the autonomic nervous function is estimated indirectly. It combines both the sympathetic and parasympathetic nervous functions. The differentiation between two is done through the help of frequency assessment. The high-frequency components reflective of vagal and low-frequency component is reflective of sympathetic activity. The ratio of two (LF/HF) denotes sympathovagal balance. The HRV studies have been found to be quite useful clinically and low HRV has been linked with an heightened mortality risk among patients with heart failure and after myocardial infarction.

**Materials and Methods**

This study conducted in Department of Physiology, in collaboration with Department of Obstetrics and Gynaecology, after receiving approval from the Institutional Ethics Committee, King George's Medical University (KGMU), Lucknow. The study duration of 1 year (August 2019 to July 2020). The study type was case and control.

Total of 60 subjects were enrolled in the study after acquiring written informed consent. HRV analysis of the subjects/patients was done on AD instrument HRV machine in premises of autonomic laboratory Physiology department. All Women of reproductive age (20–40 year) group discover with Polycystic ovarian disease as stated by ROTTERDAM criteria visiting the Obstetrics and Gynaecology Department of KGMU, Lucknow, were covered in PCOS group. The control group is made up of apparently healthy women without any menstrual irregularities: Pregnant women, subjects suffering from Diabetes mellitus, hypertension, dyslipidaemia, and History of substance abuse.

**Methodology**

Approval to carry out the study was obtained from the institutional ethical committee (Ref code: 96 ECM II B- Thesis/P33). Participants were selected from the OPD of the Department of Obstetrics and Gynaecology King Georges Medical University, Lucknow, and informed consent was obtained from them and were grouped as follows:

- **GROUP 1 (Cases; n = 30):** Women aged 20 to 40 years with PCOS, from obstetrics and gynaecology department. PCOS patients will be diagnosed according to ROTTERDAM criteria.
- **GROUP 2 (Controls; n = 30):** Women aged 20 to 40 years having normal ovulatory cycles without PCOS were selected from amongst attendants accompanying the patients.

After obtaining informed consent, demographic and medical history of participants was obtained. A general examination was performed. Following which weight, height, waist, and hip circumference of the participants was taken and body mass index was calculated. Following which blood pressure measurements were taken using a sphygmomanometer.

All the patients were thereafter subjected to HRV studies using the AD Machine in Autonomic nervous system Laboratory of the Department of Physiology.

**Procedure for heart rate variability studies**

HRV was recorded using an ECG Machine (AD Instruments, India), a practical and definitive device for measuring heart rate to interpret the HRV. HRV were recorded in the supine position for 5 min. Before recording it, 10 min rest is mandatory. Domain of frequency is measured in HRV.

“R-R interval records time between beats, it is used to calculate the heart rate. Its normal value ranges from 600 to 1000 ms. In an ECG, the RR interval is the time between QRS complexes.”

**For frequency domain, the following parameters were recorded**

- Total Power: “The total power of RR interval variability is the total variance and corresponds to the sum of the four spectral bands, LF, HF, ULF, and VLF.”
- VLF: “Very Low Frequency is a band ranges between 0.003 and 0.04 Hz. It indicates slow mechanisms of sympathetic activity.”
- VLF %: “Percentage of VLF frequency band in total power spectrum.”
- LF: “Low Frequency (LF) is a band of power spectrum range between 0.04 and 0.15 Hz. It indicates sympathetic activity.”
LF%: “Percentage of LF frequency band in total power spectrum”.

LF nu: “relative power of the low-frequency band in normal units. It is calculated using the following formula”

\[
LF\text{nu} = \frac{LF}{(Total\ Power - VLF)} \times 100
\]

HF: “High Frequency is a respiratory band range between 0.15 and 0.4 Hz. This reflects parasympathetic (vagal) activity.”

HF%: “Percentage of HF frequency band in total power spectrum.”

HF nu: “relative power of the high-frequency band in normal units. It is calculated using the following formula”

\[
HF\text{nu} = \frac{HF}{(Total\ Power - VLF)} \times 100
\]

LF/HF: “It is the ratio between the Low Frequency and High Frequency bands. It reflects the overall balance between sympathetic and parasympathetic systems. Higher values show the domination of the sympathetic activity, while lower ones - domination of the parasympathetic system. This ratio shows the sympathovagal balance.”

SD1: “Short term variability of heart rate, and is mainly influenced by parasympathetic modulation.”

SD2: “Long term variability of heart rate and is reflective of sympathetic activation.”

**Statistical analysis**

“Data analysis was done using SPSS (Statistical package for social sciences) Version 21.0 statistical analysis software. Independent samples “F”-test, Chi-square test, and analysis of variance (ANOVA) were used to compare the data. A “P” value less than 0.05 was considered as statistically notable.”

**Results**

This study was carried out to study the consequences of PCOS on ANS in terms of HRV. For this purpose, a total of 30 PCOS women falling in sampling frame were enrolled as cases and a total of 30 women with normal ovulatory cycles without PCOS were enrolled as controls in the study.

The age of PCOS cases and normal healthy controls was found to be comparable. PCOS cases had significantly higher body weight, BMI, SBP, and DBP [Table 1].

PCOS females had significantly higher BMI > 25.0 kg/m² (60.0% vs 0.0%) as compared with non PCOS group but none of them more than 30 kg/m² and also the cases had high SBP/DBP (66.7% vs 20.0%) (not more than 140/90).

The frequency domain HRV parameters except VLF%, LF%, LF (nu), and LF/HF ratio of PCOS females were lower than that of controls. Differences between PCOS and non PCOS females were found to be significant for all the above parameters except VLF and LF (ms²) [Table 2].

Among 60 females enrolled in the study, 42 had BMI < 25 kg/m² and rest 18 had BMI ≥25 kg/m². On studying the HRV parameters, all the above parameters were elevated in lower BMI, that is, <25 kg/m² (except Average rate, VLF%, LF%, LF (nu), and Low Frequency/High Frequency Ratio). Significant contrast between low BMI and high BMI (≥25 kg/m²) were found for all the above parameters except VLF (ms²), LF (ms²), and SD2 [Table 3].

Relationship of BP with none of the above HRV parameters [except LF (nu)] was found to be statistically significant for non PCOS women alone [Table 4].

Significantly higher LF (nu) was found among those with high range of blood pressure as compared with those with low range of blood pressure [Table 5].

Inference: PCOS had a definitive influence on HRV; however, cardiometabolic factors have their own incidental effect on HRV, although, in this study, they were dominated by presence of PCOS and did not show an independent effect. One of the limitations of the study was absence of data regarding insulin resistance and other cardiometabolic factors that could influence HRV. Further studies with inclusion of more variable on a larger sample size are recommended.

**Table 1: Comparison of general, anthropometric, and blood pressure profile of cases and controls**

| Characteristic                  | Cases (n=30) | Controls (n=30) | Statistical significance |
|--------------------------------|-------------|-----------------|-------------------------|
| Mean Age±SD (Range) in years   | 28.03±5.33 (20-40) | 27.27±5.69 (20-40) | t=0.539; P=0.592 |
| Mean body weight±SD (kg)       | 61.51±6.23  | 54.30±5.15      | t=4.884; P<0.001* |
| Mean height±SD (cm)           | 156.00±4.43 | 151.22±6.67     | t=3.572; P=0.001* |
| Mean BMI±SD (kg/m²)           | 25.39±2.69  | 20.88±1.66      | t=7.813; P<0.001* |
| No. of women with BMI >25 kg/m²| 18 (60.0%)  | 0               | χ²=25.714; P<0.001* |
| Mean WHR±SD                   | 0.82±0.07   | 0.73±0.08       | t=4.833; P<0.001* |
| No. of women with WHR >0.79   | 19 (63.3%)  | 6 (20.0%)       | χ²=11.589; P<0.001* |
| Mean SBP±SD (mmHg)            | 127.10±6.69 | 116.00±7.75     | t=5.937; P<0.001* |
| Mean DBP±SD (mmHg)            | 85.80±5.97  | 78.73±7.75      | t=3.963; P<0.001* |
| No. of women with SBP/DBP >130/85 mmHg | 20 (66.7%)  | 6 (20.0%)       | χ²=13.303; P<0.001* |
Discussion

In this study, though, all the PCOS women were in non-obese category, their weight of the body, BMI, and waist hip-ratio was significantly higher as compared with that of controls. As such, PCOS has a strong link with obesity and despite our effort to include non-obese PCOS women in the study, a number of PCOS women were in overweight category and it was difficult to get BMI-matched women with normal ovulatory cycle as controls. Although, we made an attempt to find the BMI matched controls, we could not do so owing to their occurrence in exclusion criteria. Apart from body mass index, PCOS women in this study also had significantly higher SBP and DBP values (within normotensive range) as compared with non PCOS group. These findings suggest that within same age range, PCOS women tend to have a higher body weight/obesity as well as increased cardiometabolic risk though not manifested in form of a disorder. Balamurugan et al.[4] found the mean HF and HF (nu) values to be significantly lower in cases as compared with that in controls. They also found LF (nu) and LF/HF to be undoubtedly higher in cases as compared with that in controls, thus showing a dominance of lower frequency domains in cases as is equate to that in non PCOS group as also observed in this study. Bulsara et al[3] explained the pathophysiology of PCOS which mainly focus on hormonal dysfunction, insulin resistance, and hyperandrogenism leading to impaired folliculogenesis.

Table 2: Comparison of frequency-domain HRV parameters between cases and controls

| Characteristic | Cases (n=30) | Controls (n=30) | Statistical significance |
|---------------|-------------|----------------|--------------------------|
|               | Mean        | SD            | Mean                     | SD          | T   | P       |
| Total Power   | 2097.11     | 1403.29       | 3534.22                  | 2178.68     | -3.057 | 0.004* |
| VLF (ms²)     | 659.88      | 418.85        | 731.66                   | 479.73      | -0.619 | 0.539   |
| VLF%          | 36.08       | 15.00         | 25.04                    | 13.68       | 2.977  | 0.004* |
| LF (ms²)      | 916.60      | 693.07        | 975.77                   | 664.34      | -0.338 | 0.737   |
| LF%           | 41.28       | 8.17          | 26.76                    | 6.09        | 7.806  | <0.001* |
| HF%           | 66.15       | 9.71          | 35.99                    | 9.87        | 11.925 | <0.001* |
| HF (ms²)      | 511.11      | 378.85        | 1674.47                  | 1192.27     | -5.093 | <0.001* |
| HF(nu)        | 33.50       | 8.83          | 59.70                    | 6.64        | -12.988| <0.001* |
| LF/HF         | 2.34        | 1.64          | 0.62                     | 0.17        | 5.687  | <0.001* |
| SD1           | 21.28       | 9.48          | 44.72                    | 26.67       | -4.537 | <0.001* |
| SD2           | 56.12       | 19.26         | 68.70                    | 28.16       | -2.020 | 0.048* |

Table 3: Evaluation of effect of Higher BMI on Frequency Domain parameters(a) Overall Study Population (n=60)

| Characteristic | BMI <25 kg/m² (n=42) | BMI ≥25 kg/m² (n=18) | Statistical significance |
|---------------|------------------------|-----------------------|--------------------------|
|               | Mean                   | SD                    | Mean                     | SD          | T   | P       |
| Frequency Domain |                        |                       |                          |             |
| Total Power   | 3224.16                | 2003.61               | 1862.52                  | 1490.86     | 2.588 | 0.012* |
| VLF (ms²)     | 731.72                 | 449.72                | 611.89                   | 441.75      | 0.951 | 0.346   |
| VLF%          | 26.89                  | 13.10                 | 39.12                    | 16.91       | -3.032 | 0.004* |
| LF (ms²)      | 1006.32                | 649.11                | 805.87                   | 727.62      | 1.057 | 0.295   |
| LF%           | 31.40                  | 9.89                  | 40.12                    | 8.42        | -3.263 | <0.001* |
| HF (ms²)      | 1374.17                | 1124.79               | 436.23                   | 400.84      | -5.957 | <0.001* |
| HF(nu)        | 53.02                  | 12.66                 | 31.60                    | 9.34        | 5.714  | <0.001* |
| LF/HF         | 1.97                   | 0.68                  | 2.65                     | 2.02        | 6.451  | <0.001* |
| SD1           | 38.75                  | 24.71                 | 19.60                    | 10.36       | 3.158  | 0.003* |
| SD2           | 66.23                  | 24.98                 | 53.48                    | 22.35       | 1.868  | 0.067   |

Table 4: Comparison of frequency domain HRV parameters of those with low and high range of blood pressure (SBP/DBP >130/85): PCOS Women (30)

| Characteristic | SBP/DBP ≤130/85 mmHg (n=10) | SBP/DBP >130/85 mmHg (n=20) | Statistical significance |
|---------------|-----------------------------|-----------------------------|--------------------------|
|               | Mean                        | SD                          | Mean                     | SD          | T   | P       |
| Frequency Domain |                          |                             |                          |             |
| Total Power   | 2129.96                    | 1248.23                     | 2080.69                  | 1505.57     | 0.089 | 0.930   |
| VLF (ms²)     | 623.02                     | 282.37                      | 678.32                   | 475.79      | -0.337 | 0.738   |
| VLF%          | 34.07                      | 14.74                       | 37.08                    | 15.41       | -0.512 | 0.613   |
| LF (ms²)      | 976.76                     | 718.17                      | 886.52                   | 697.13      | 0.331  | 0.743   |
| LF%           | 42.53                      | 8.95                        | 40.66                    | 7.93        | 0.582  | 0.565   |
| LF (nu)       | 66.05                      | 10.15                       | 66.20                    | 9.76        | -0.037 | 0.970   |
| HF (ms²)      | 527.85                     | 339.80                      | 502.74                   | 405.15      | 0.168  | 0.868   |
| HF (nu)       | 34.18                      | 9.21                        | 33.16                    | 8.86        | 0.293  | 0.772   |
| LF/HF         | 2.14                       | 0.95                        | 2.43                     | 1.92        | -0.450 | 0.656   |
| SD1           | 19.93                      | 8.37                        | 21.96                    | 10.12       | -0.546 | 0.590   |
| SD2           | 51.53                      | 15.72                       | 58.41                    | 20.80       | -0.920 | 0.365   |
Cases had significantly higher body weight, height, and BMI as compared with controls. Mean BMI of cases was 25.93 ± 2.69 kg/m² as compared with 20.88 ± 1.66 kg/m² for controls. A total of 18 (60%) PCOS women had body mass index >25 kg/m² as compared with none in non PCOS group.

PCOS group had undoubtedly elevated waist-hip ratio and SBP as compared with controls. A total of 19 (63.3%) cases and 6 (20%) controls had waist hip ratio (WHR) >0.79. Proportion of those with SBP/DBP >130/85 was 20 (66.7%) in cases as compared with 6 (20%) in controls.

Significantly no difference between two groups was observed with reference to VLD (ms²) and LF (ms²). However, mean total power, HF (%), HF (ms²), HF (nu), SD1, and SD2 values were calculated to be significantly lower in cases as compared with that in controls, while mean VLF%, LF%, LF (nu), and LF/HF values were found to be significantly higher in cases as compared with that in non PCOS group.

On evaluation of effect of BMI on HRV parameters, in overall evaluation (both cases as well as controls), except for SDARR (s), SD Rate, VLF (ms²), LF (ms²), and SD2, all the other parameters were found to be significantly affected by BMI change. It was seen that total power, HF%, HF (ms²), HF (nu), and SD1 were found to be significantly lower in lower Body Mass Index (<25 kg/m²) as compared with that in higher Body Mass Index (≥25 kg/m²), whereas mean average rate, VLF%, Low Frequency %, Low Frequency (nu), and LF/HF were estimated to be significantly higher in elevated Body Mass Index (≥25 kg/m²) as compared with that in lesser BMI (<25 kg/m²) groups.

The findings of the study show that PCOS patients are at a high risk of HRV and thus at a higher level of cardiometabolic risk. From the primary care point of view, this finding holds a significance indicating the need of cardiometabolic risk assessment among PCOS patients at frequent time intervals.

### Conclusion

This study showed that PCOS has a significant impact on the HRV parameters as compared with controls. It was further shown that cardiovascular risk factors like obesity and blood pressure modulate these effects. Owing to a strict exclusion criteria, the role of cardiometabolic risk factors in modulation of these heart-rate variability changes could not be elucidated in detail; however, the trends indicate that insulin resistance in PCOS women alters the cardiometabolic equilibrium which eventually leads to HRV. Further studies on larger population with inclusion of cases and controls with a versatile cardiometabolic profile are recommended. Role of PCOS in heart-rate variability should be interpreted in multifactorial model rather than a direct cause–effect relationship.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

### References

1. Zacur HA. Epidemiology, clinical manifestations and pathophysiology of polycystic ovary syndrome. Adv Stud Med 2003;3:5733-9.
2. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol 1935;29:181–91.
3. Bulsara J, Patel P, Soni A, Acharya S. A review: Brief insight
into polycystic ovarian syndrome. Endocrine and Metabolic Science 2021;3:100085.
4. Ormazabal V, Nair S, Elfeky O, Aguayo A, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol 2018;17:122.
5. Qu X, Donnelly R. Sex Hormone-Binding Globulin (SHBG) as an early biomarker and therapeutic target in polycystic ovary syndrome. Int J Mol Sci 2020;21:8191.
6. Lee TT, Rausch ME. Polycystic ovarian syndrome: Role of imaging in diagnosis. Radiographics 2012;32:1643-57.
7. Nafiye Y, Sevtap K, Muammer D, Emre O, Senol K, Leyla M. The effect of serum and intrafollicular insulin resistance parameters and homocysteine levels of nonobese, nonhyperandrogenemic polycystic ovary syndrome patients on in vitro fertilization outcome. Fertil Steril 2010;93:1864-9.
8. Pateguana NB, James A. The contribution of hyperinsulinemia to hyperandrogenism of polycystic ovary syndrome. J Insulin Resistance 2019;4:a450.
9. La Rovere MT, Bigger JT Jr, Marcus FL, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes after Myocardial Infarction) Investigators. Lancet 1998;351:478-84.
10. Heart Rate Variability Analysis System. MediCore. Clinical Information version 3.0. Available from: http://medi-core.com/download/HRV_clinical_manual_ver 3.0.pdf.
11. Burr RL. Interpretation of normalized spectral heart rate variability indices in sleep research: A critical review. Sleep 2007;30:913-9.
12. Brennan M, Palaniswami M, Kamen P. Do existing measures of Poincaré plot geometry reflect nonlinear features of heart rate variability? IEEE Trans Biomed Eng 2001;48:1342-7.
13. Woo MA, Stevenson WG, Moser DK, Trelease RB, Harper RM. Patterns of beat-to-beat heart rate variability in advanced heart failure. Am Heart J 1992;123:704-10.
14. Balamurugan M, Balamurugan M, Ramanathan G. Heart rate variability and lipid profile in non obese young Indian women with polycystic ovary syndrome. J of Evolution of Med and Dent Sci 2015;4:4092-4109.