Is there a correlation between heart rate recovery and androgen parameters in polycystic ovary syndrome? Heart rate recovery in polycystic ovary syndrome

Karee Angu
Post graduate student, Department of Physiology, VMMC & Safdarjung Hospital, New Delhi, India.
Email: kareeangu@gmail.com

Renuka Sharma
Professor, Department of Physiology, VMMC & Safdarjung Hospital, New Delhi, India.

Waqas Alauddin
Assistant Professor, Department of Physiology, HBTMC & Dr. RN Cooper Hospital, Juhu, Mumbai, India.
Email: dr.waqas7@gmail.com

Musharaf Bashir
Lecturer, Department of Physiology, GMC & SMHS hospital, Srinagar, J&K, India.
Email: dr.musharaf.mb@gmail.com

Shams Aaghaz
Post graduate student, Department of Physiology, VMMC & Safdarjung Hospital, New Delhi, India.
Email: drshamsaaghaz@icloud.com

Abstract---Objectives: In our preliminary study, we assessed heart rate recovery (HRR) in patients with polycystic ovary syndrome (PCOS) and controls by subjecting them to moderate exercise and estimating androgen levels, and examined the correlation between HRR and androgen levels. Methods: 30 newly diagnosed cases of PCOS and 30 controls with comparable anthropometric measurements performed isotonic moderate exercise. Serum testosterone and DHEAS levels were measured. The HRR was calculated as the difference between the maximum heart rate and the 1st, 5th and 10th minute after the end of the exercise. Results: Heart rate recovery at 1 minute (p=0.001) and 5 minutes, (p=0.002) was significantly impaired in PCOS patients.

Testosterone (p=0.100) and DHEAS (p=0.061) were elevated in PCOS patients compared to normal controls, although this was not statistically significant. A positive correlation was observed between HRR and androgen levels (testosterone: r=0.318; p=0.08, DHEAS: r=0.064; p=0.07). Conclusion: Decreased cardiovascular fitness and increased androgen levels have been observed in PCOS patients. Impaired HRR, reflecting sympathetic overactivity, has also been observed in newly diagnosed cases of PCOS. We therefore suggest that HRR is an accurate and sensitive marker to detect early signs of cardiovascular impairment and enables timely measures to avoid further morbidity.

Keywords---Polycystic Ovary Syndrome, Heart rate recovery, Androgens, Heart rate variability.

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrinopathy characterized by chronic oligo-anovulation, polycystic ovaries, and hyperandrogenism.[1] Globally, PCOS is the most common endocrine disorder in women, affecting 5–26% of them during their reproductive years.[2,3] Metabolic dysfunction in women with PCOS subsequently leads to exaggerated risk for diabetes, dyslipidemia and cardiovascular diseases with ageing.[4]

Exercise in PCOS has been successfully used as a treatment modality.[5,6] A regular exercise routine in PCOS has been shown to alleviate body mass index (BMI), waist circumference, and biochemical variables such as total cholesterol, insulin resistance and lipid profile, consequently lowering metabolic syndrome and further vulnerable factors associated with PCOS.[7] However, exercise challenge as a tool to assess cardiac fitness has not been studied in detail. A key role in the cardiac response to exercise is involved by the autonomic nervous system, and it can be assessed by calculating heart rate recovery (HRR).[8] Heart rate recovery (HRR) can be derived by calculating the decrease in heart rate following peak exercise. Fall in heart rate <18 beats/min after 1 minute of cessation of exercise is considered abnormal.[9] HRR is a marker of autonomic function and is directly correlated to parasympathetic activity and cardiovascular fitness.[10] A reduced HRR signifies impaired cardiorespiratory parameters.

Hyperandrogenism is present in approximately 80% of PCOS diagnosed cases.[11] It is associated with a worse cardiometabolic profile.[12] Plasma levels of total and free testosterone and dehydroepiandrosterone sulfate (DHEA-S) are significantly elevated in PCOS.[13] The precise mechanism by which hyperandrogenemia causes obesity, insulin resistance, increases in blood pressure, and endothelial dysfunction in PCOS and the interplay between these cardiovascular risk factors and PCOS patient is yet to be elucidated.

Evaluation of Cardiac fitness and the role of androgens in determining the same in Polycystic Ovary Syndrome is a relatively unexplored field. Hence, this study

was designed to examine cardiac fitness during incremental exercise and androgen levels in women with Polycystic Ovary Syndrome.

Material and Methods

This was a cross-sectional, case-control study carried out a total of 60 female subjects after ethical clearance of Institutional Ethics Committee, approval number IEC/VMMC/SJH/Thesis/2019-10/258, informed written consent was obtained from each participating woman for enrolment. Subjects were categorized into two groups:

Group A: 30 cases, i.e. subjects, aged 20- 35 yrs, attending the Gynaecology outpatient department were freshly diagnosed cases of PCOS and previously diagnosed cases of PCOS but have not taken any medication for past 3 months.

Group B: 30 controls were selected from ordinarily menstruating women.

Study started on 1st Dec 2019 and ended on 30th June 2021. Inclusion criteria were Group A subjects with documented evidence of PCOS fulfilling at least 2 out of 3 of Rotterdam criteria in the age group between 20-35 years and Group B healthy subjects in the reproductive of 18-35 age group with regular menstrual cycles.[4] Exclusion criteria were Pregnancy, Menstrual Cycle abnormalities, Endocrinal disorders like Diabetes, Hypothyroidism, Hyperprolactinemia, Cushing's syndrome, subjects on oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents, neoplastic, hepatic, cardiovascular disorder, respiratory and renal disease were also excluded.

Study design

The subjects were asked to report to the Exercise Physiology Laboratory, 2 hours after a light breakfast and abstain from caffeine, alcohol and heavy exercise 24 hours before the test. After reading the patient information sheet, they were instructed to wear loose, comfortable clothing and be adequately hydrated before the commencement of the exercise test. The subjects were asked to sign the informed consent form, following which they had a brief physical examination, to rule out any acute health condition. All the subjects were examined for the following parameters:

1. **Biochemical parameters:** Sample collection of 5 ml of venous blood sample was collected in appropriately labelled vials. Centrifugation was done to separate the serum layer.
   Biochemical Assays
   (i) Testosterone levels- Serum testosterone was detected by the ELISA method.
   (ii) DHEA-S levels- It was detected using Calbiotech Inc. DHEA-S ELISA kit.
2. **Heart Rate Recovery:** This was recorded continuously during the entire warm-up, exercise, and recovery phases of the exercise test. Heart rate was derived from ECG analysis which was acquired using the Bio amplifier module of the Power Lab system® (AD Instruments, Australia).

Heart Rate Recovery (HRR): Heart Rate Recovery was calculated as the decrease in heart rate following peak exercise. (11) HRR at 1 minute <18 beats/minute was considered abnormal. (11)

Exercise protocol: The subjects were seated in a comfortable position on the bicycle ergometer (Proline Fitness Systems). The test commenced by pedaling at a light workload for two minutes as the warmup phase. The workload was increased incrementally (i.e., progressively increasing work rate every 3 min) using the inbuilt module in the bicycle ergometer. The exercise test was terminated when the subject reached 70% of her heart rate reserve, i.e. equivalent to 85% of age-predicted Heart rate maximum. The maximum heart rate was calculated as per the formula 220-age (years). The test would be terminated earlier if the subject reported any kind of discomfort.

Recovery phase: Following the termination of exercise, subjects were rested for 20 minutes while the ECG continued to be recorded. Heart Rate, and blood Pressure, was noted after 1 min, 5 min and 20 min of cessation of exercise.

Statistical method: Statistical analyses were performed using SPSS version 21 (SPSS, Inc., Chicago, IL). Data were analyzed for normal distribution using the Kolmogorov-Smirnov test. Quantitative variables were compared using an Unpaired t-test for normally distributed parameters and Mann-Whitney Test for non-normally distributed parameters. Pearson correlation coefficient was used to assess the correlation between cardiac fitness and androgen levels in Polycystic Ovary Syndrome and controls. P-value <0.05 was considered significant.

Results

The mean age of PCOS cases (23 ± 4.50 years) was observed to be lower than the controls (24.57 ± 4.61 years), but it was not statistically significant. [Table 1]. The mean value for the height of the cases (152.40 ± 7.26 cm) was significantly lower than the cases (157.58 ± 5.31 cm) (p = 0.003) [Table 1]. There was no significant difference between the cases (63.10 ± 11.8) and the controls (63.50 ± 11.70) with regards to their weight [Table 1]. BMI was calculated by dividing weight by the square of height (in kg/m^2), and there was no significant statistical difference observed between the BMI of PCOS cases (27.40 ± 4.96 kg/m^2) and controls (25.54 ± 4.20 kg/m^2) [Table 1]. The body surface area of the cases (1.60 ± 0.16 m^2) was lesser than the controls (1.64 ± 0.18 m^2) [Table 1].

Table 1
Anthropometric Parameters

Parameters	Controls	PCOS Cases	p value
Age (years)	24.57 ± 4.61	23.37 ± 4.50	0.292
Height (cm)	157.58 ± 5.31	152.40 ± 7.26	0.003*
Weight(kgs)	63.50 ± 11.70	63.10 ± 11.85	0.896
BMI (kg/m^2)	25.54 ± 4.20	27.40 ± 4.96	0.227
WHR	0.78 ± 0.08	0.75 ± 0.07	0.163

BSA (m^2)	1.64 ± 0.18	1.60 ± 0.16	0.795

Values are expressed as mean +_SD. p value <0.05 was considered as significant.
*BMI: Body mass index, BSA: Body surface area, WHR: waist hip ratio.*
Height was significantly lesser in PCOS cases compared to the controls(p= 0.003).

The median value of serum testosterone in the PCOS cases was 0.85 (0.40-1.18) ng/ml which was higher than 0.50 (0.43-0.60) ng/dl found in controls [Table 2, Figure 1]. On the same lines, serum DHEAS was also recorded to be greater in the cases 3.15 (1.80-3.88) ng/ml than controls 2.20(2.00-2.48) ng/ml [Table 2, Figure 2]. Testosterone (p= 0.100) and DHEAS (p= 0.061) were elevated in PCOS patients compared to normal controls though it was not statistically significant.

Table 2
Biochemical Parameters

Parameters	Controls	PCOS Cases	p value
S. Testosterone (ng/ml)	0.50(0.43-0.60)	0.85(0.40-1.18)	0.100
S. DHEA-S (ng/ml)	2.20(2.00-2.48)	3.15(1.80-3.88)	0.061

Values are expressed as median and interquartile range for both parameters. p-value <0.05 was considered significant. DHEA-S- dehydroepiandrosterone sulphate
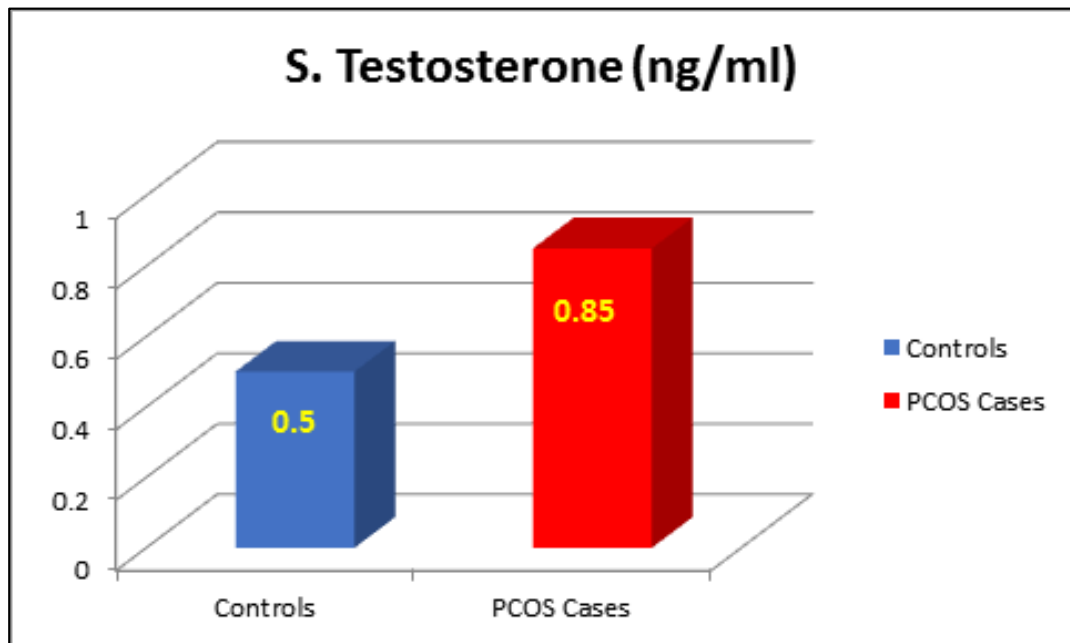
PCOS cases had higher serum testosterone levels than controls. However, the difference was not statistically significant. (p= 1.00)
Figure 1. Comparison of serum testosterone between PCOS cases and controls.
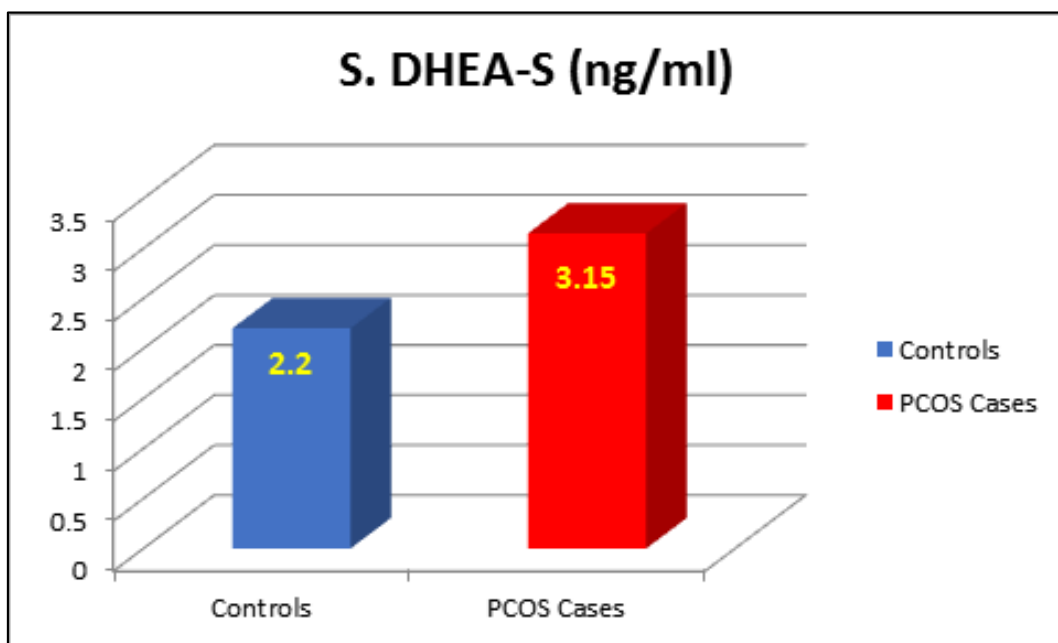
Higher serum DHEA-S (dehydroepiandrosterone sulfate) levels were recorded in PCOS cases though the difference was not statistically significant. (p=0.061)
Figure 2. Comparison of serum DHEA-S between PCOS cases and controls

The resting heart rate of the cases (78.43 ± 10.70 beats/min) in our study was observed to be significantly higher (p= 0.032) than the resting heart rate of the controls (72.83 ± 8.92 beats/min) [Table 3, Figure 3]. During peak exercise, the heart rate peaked at 171.47± 3.99 beats/min in PCOS cases and 170. 03 ± 4.20 beats/min in controls with no significant difference in the two groups. (p= 0.157). After 1 min the heart rate was significantly higher (p= 0.000*) 157.93 ± 3.60 in PCOS cases as compared to control cases 149.50 ± 6.91 and After 5 min the heart rate was significantly higher (p= 0.000*) in PCOS cases 97.30 ± 7.26 as compared to control cases 84.70 ± 14.40 [Table 3, Figure 3].

Table 3
Changes in Heart Rate, Pre and Post Exercise

Parameters (beats/minute)	Controls	PCOS Cases	p value
At rest	72.83 ± 8.92	78.43 ± 10.70	0.032*
Peak exercise	170.03 ± 4.20	171.47 ± 3.99	0.157
Immediately after	155.43 ± 3.16	164.63 ± 10.64	0.127
After 1 min	149.50 ± 6.91	157.93 ± 3.60	0.000*
After 5 mins	84.70 ± 14.40	97.30 ± 7.26	0.000*
After 15 mins	75.83 ± 9.96	76.50 ± 9.02	0.787

Values are expressed as mean +_SD. p value <0.05 was considered as significant
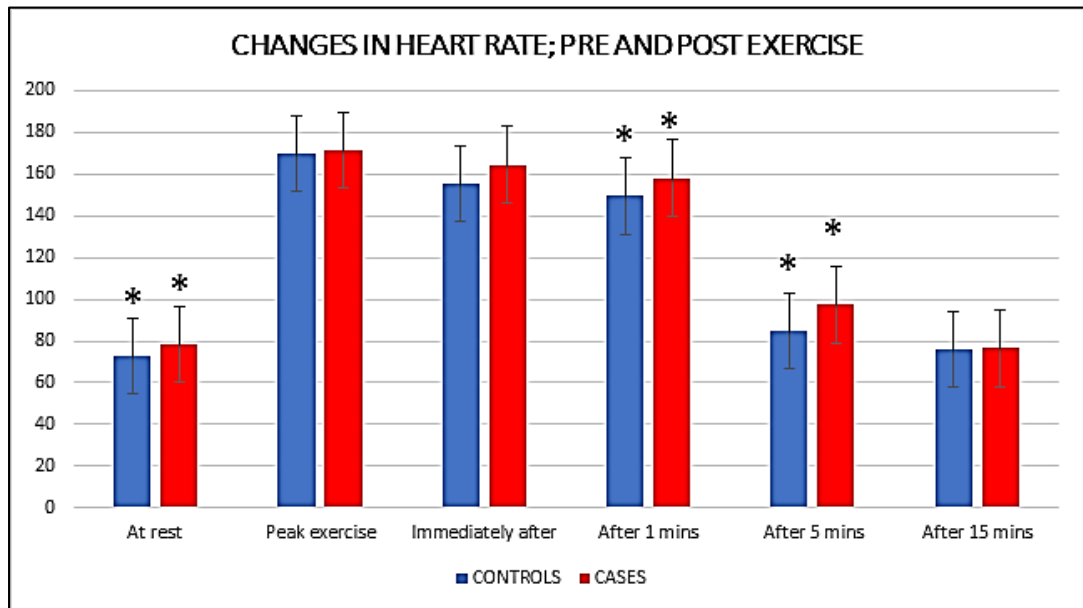
Resting heart rate (p= 0.032), after 1 min (p= 0.000) and after 5 min (p= 0.000*) of the cases was significantly higher as compared to the controls. p-value <0.05 was considered significant.*

Figure 3. Comparison of changes in heart rate, pre and post exercise, between PCOS cases and controls

HRR was significantly impaired at the 1st minute (p = 0.001) and 5th minute (p = 0.002) in the PCOS cases compared to the controls [Table 4, Figure 4] Women with PCOS had an HRR of 13.50 ± 3.81 beats/min at the first minute compared to controls who had better recovery of 20.53 ± 7.61 beats/min [Table 4, Figure 4]. Similarly, after 5 minutes of termination of exercise, it was noted that PCOS women had a recovery of 74.16 ± 7.4 beats/min, which was significantly lower than the controls who had a recovery of 85.33 ± 13.51 beats/min, demonstrating that HRR was comparatively impaired even after 5 mins [Table 4, Figure 4]. However, no significant difference was observed at the 15th minute (p >0.05) between the PCOS patients (94.97 ± 8.93 beats/min) and healthy controls (94.20 ± 9.09 beats/min) [Table 4, Figure 4].

Table 4
Heart Rate Recovery at 1, 5 And 15 Minutes in PCOS Cases and Controls

Parameters (Beats)	Controls	PCOS Cases	p value
HRR 1 min	20.53 ± 7.61	13.50 ± 3.81	0.001*
HRR 5 mins	85.33 ± 13.5	74.16 ± 7.46	0.002*
HRR 15 mins	94.20 ± 9.09	94.97 ± 8.93	0.728

Data expressed as Mean ± SD, p-value <0.05 was considered significant. HRR-Heart rate recovery.
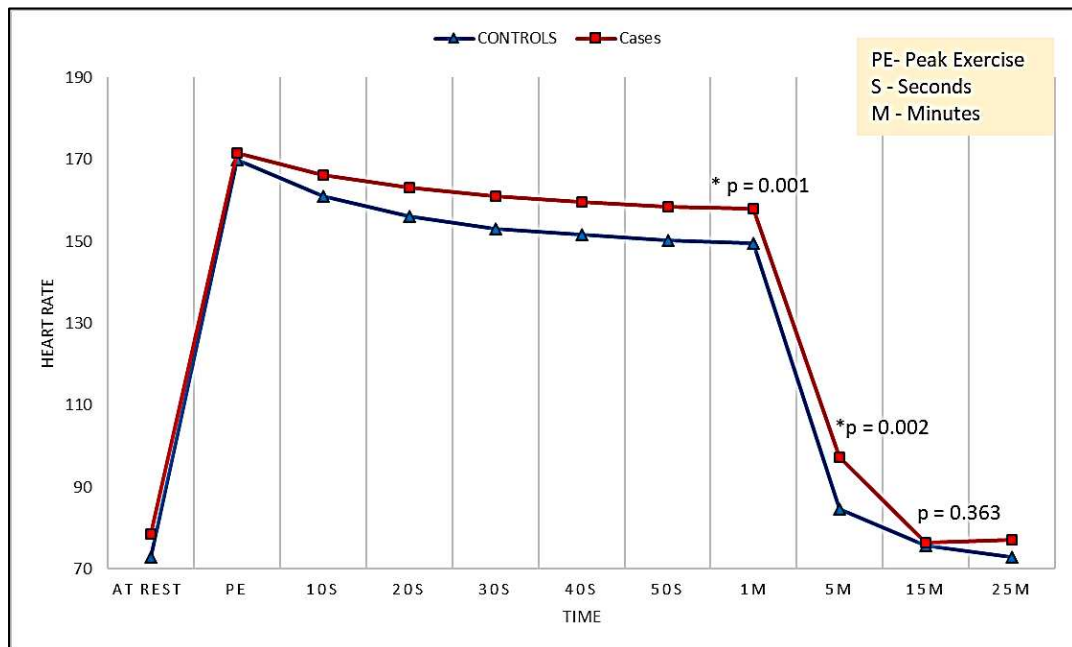
Heart rate profile observed after isotonic exercise in pcos cases and controls.
p value <0.05 was considered significant. HRR- Heart rate recovery.
HRR at 1 minute (p= 0.001) and 5 minutes (p= 0.002) was significantly impaired in PCOS patients. There was no significant difference observed between both the groups at 15th minute (p= 0.728)

Figure 4. Comparison of heart rate profile, before, during and after exercise, between cases and controls

A positive correlation was noted between the two parameters in PCOS women (Testosterone: r= 0.318; p=0.08, DHEAS: r=0.064; p= 0.07) [Table 5].

Table 5

Pearson Correlation of HRR (Heart Rate Recovery) At 1 Minute, 5 Minutes And 15 Minutes Post Exercise, With Serum Testosterone and Serum DHEA-S (Dehydroepiandrosterone Sulfate)

Parameters		Controls		PCOS Cases	
		r	p	r	p
HRR1 min	Serum testosterone	-0.253	0.178	0.318	0.087
	Serum DHEA-S	-0.468	0.009	0.064	0.735
HRR 5 min	Serum testosterone	-0.136	0.4912	0.285	0.059
	Serum DHEA-S	-0.157	0.1997	0.193	0.534
HRR 15 min	Serum testosterone	-0.051	0.79	0.344	0.062
	Serum DHEA-S	-0.033	0.862	-0.188	0.319

A positive correlation was observed between HRR at 1 minute and 5 minutes with both serum testosterone and serum DHEA-S in the PCOS cases. Similarly, serum testosterone was positively correlated with HRR at 15 minutes, but a negative

association was reported with serum DHEA-S. All these correlations, failed to attain statistical significance.
p-value <0.05 was considered significant

Discussion

In our study, we measured serum testosterone and serum DHEAS, and it was observed that both values were higher in the cases compared to the controls, however, it was not statistically significant. Free testosterone is more sensitive than measuring total testosterone to detect hyperandrogenism.[14] This is very likely as our subjects are newly diagnosed cases of PCOS who were possible in the early stages of the syndrome and therefore had normal androgen levels. In addition, PCOS is not always characterized by hyperandrogenism and shows multiple phenotypes depending on the severity and time of detection.[15]

The usual range of DHEAS is 0.9-3.6 ng/dL, and DHEAS levels are elevated in about 30-35% of PCOS patients.[16] In our study, a median value of 3.15 (1.80-3.88) ng/dL was found in PCOS women, which is within the normal range, although higher than controls, which had a value of 2.20 (2.00-2.48) ng/dl reported, does not contribute significantly to the diagnosis. It has been estimated that only 5% of patients with PCOS have an exclusive elevation in DHEAS.[17] Another reason for the unreliability of the diagnosis is variance due to multiple factors such as age, stress, and anticipation of a blood draw. It also shows diurnal variation and wide intra-individual variation.[14,16] Therefore, the measurement of DHEA for the diagnosis of PCOS has limited diagnostic utility.

At rest, the heart rate of the cases in our study was significantly higher than the heart rate of the controls. Sympathetic hyperactivity has been well documented in PCOS and is the most likely reason for increased in resting heart rate in PCOS cases.[18] In addition to the autonomic nervous system, the resting heart rate is also influenced by the myocardial oxygen demand and the coronary blood flow it is of central importance for adapting the cardiac output to the metabolic demand.[19] At rest, the heart rate has been identified as an indicator for outcomes in hypertension, atherosclerosis, cardiac arrest, and congestive cardiac failure.[20] The mechanisms of this association are not fully understood, but may include endothelial dysfunction, decreased arterial compliance and, or compliance, increased arterial wall loading, and increased pulse wave velocity, leading to increased afterload and systemic hypertension.[21] Several studies have reported the negative impact of an elevated resting heart rate on the cardiovascular system. Aune et al.[22] estimated that a 10 bpm increase in resting heart rate rises all-cause mortality by 17%. Reimers et al.[23] reported that regular exercise and yoga lowered resting heart rate. As is well known, PCOS patients have a significantly increased risk of heart disease.[24] Therefore, resting heart rate becomes a significant predictor of adverse cardiac events.

In our study. Following stoppage of exercise, heart rate decreased significantly more slowly in PCOS women, indicating an altered sympathovagal response, as detailed below. [Figure 4] Heart rate recovery (HRR) is measured as the distinction between the heart rate at maximum exercise and the heart rate at fall of the exercise.[8] It was estimated at the 1st, 5th and 15th minutes. An HRR of < 18 bpm

in less than the first minute following stoppage of exercise is deemed abnormal.[9] HRR reflects the resurgence of the parasympathetic nervous system and the abolition of the sympathetic nervous system and potentially circulating catecholamines after exercise.[25] Imai et al.[26] showed that parasympathetic reactivation was the primary determinant of heart rate decrease in the initial 30 seconds of regaining. This mechanism was autonomous of age and exercise intensity. Another study by Savin et al.[10] also hypothesized that the HRR depends not only on the ANS but also on the intrinsic properties of an intact circulatory system. During exercise, cardiovascular parameters change to deliver oxygen to working muscles and maintain blood flow to vital organs. During the start of exercise, the elevation in heart rate (and cardiac output) is arbitrated mainly by central command signals via vagal retraction. On increment in work intensity, the heart rate approaches 100 beats/min, sympathetic activity begins to increase, further increasing heart rate and plasma norepinephrine concentration and constricting vessels in the visceral organs.[26] Upon cessation of exercise, loss of central command, baroreflex activation, and other mechanisms contribute to an increase in parasympathetic activity, resulting in a decrease in heart rate despite sustained sympathetic activation.[27] Later, sympathetic post-exercise withdrawal also occurs.[28] Therefore, HRR is widely accepted as an indicator of parasympathetic activity.[29]

Among adults with normal health, it has been proven that there was an inverse association of HRR with insulin resistance and other risk determinants such as body mass index (BMI), abdominal obesity and low high-density lipoprotein (HDL) cholesterol, and elevated fasting glucose and triglyceride clusters in insulin resistance syndrome.[30-33] Cole et al.[34] calculated HRR in candidates undergoing coronary angiography and reported that a slow decline of heart rate following exercise was positively associated with overall mortality. Subsequently, they concluded that since HRR is a simple marker that is easily calculated based on data contained in a standard exercise test, used to assess autonomic dysfunction. HRR has also been established as a forecaster of cardiovascular, non-cardiovascular and all-cause mortality.[35-37] McCrory et al.[38] calculated HRR after an orthostatic challenge and hypothesized that HRR at 20 seconds was a firm determinant of mortality. However, Yegte et al.[25] considered that at 10 seconds, HRR following peak exercise as a higher determinant of mortality than HRR measured at any other time. They hypothesized that HRR is more predictive of mortality when measured early after exercise cessation, as this might better reflect PNS reactivation.

In our study, HRR was significantly impaired at 1st minute and 5th minute in the PCOS cases compared to the controls. Women with PCOS had a HRR of 13.50 ± 3.81 beats/min at the first minute compared to controls who had better recovery of 20.53 ± 7.61 beats/min. [Table 4, Figure 4]. Hence, PCOS patients in our study demonstrated an impaired HRR. Similarly, after 5 minutes of termination of exercise, it was noted that PCOS women had a recovery of 74.16 ± 7.4 beats/min, which was significantly lower than the controls which had a recovery of 85.33 ± 13.51 beats/min demonstrating that HRR was comparatively impaired even after 5 mins. [Table 4, Figure 4].

HRR reflects the balance between parasympathetic and sympathetic system.[8] Sympathetic overactivity has been widely reported in PCOS, primarily through HRV (heart rate variability) and other autonomic function tests.[31,39] However, there are few studies, that have measured HRR to depict autonomic dysfunctions. The abnormal HRR seen in PCOS patients in our study reflects sympathetic overactivity and indicates that it is an accurate and sensitive marker to detect early signs of cardiovascular impairment and enables timely measures to avoid further morbidity.

A positive correlation was noted between androgen levels and cardiovascular fitness, using HRR as a marker in PCOS women (Testosterone: r= 0.318; p=0.08, DHEAS: r=0.064; p= 0.07) [Table 5]. This further confirms the role of HRR as a marker for PCOS induced attenuation of cardiovascular performance. However, this correlation failed to achieve statistical significance.

A study by Sverrisdóttir et al.[18] studied 20 PCOS patients with age and BMI matched to 18 controls. They observed that sympathetic nerve activity was distinctly elevated in women with PCOS in contrast with controls and Muscle sympathetic nerve activity (MSNA) correlated positively with total and free testosterone in the PCOS group. The authors hypothesized that, because the severity of PCOS can be reflected by hyperandrogenism, the association between Muscle sympathetic nerve activity and testosterone may specify the degree of sympathetic excitement depending on the severity of the syndrome.[18]

In a similar study done by Bacchi et al.[40] also, Androgen levels have been associated with impaired cardiovascular wellness. They observed that serum-free testosterone levels were inversely and independently associated with maximal oxygen consumption, a marker for cardiovascular fitness. Interestingly, the authors have also observed that, PCOS women without androgen excess displayed impaired cardiorespiratory fitness too. Hence, we cannot rule out the hypothesis that the association between serum testosterone and cardiorespiratory fitness may result from an indirect confounding factor or other phenomena related to the endocrine or metabolic abnormalities of PCOS. Further studies with a large sample size are required to comment further.

Conclusion

In our preliminary study, we came concluded that Heart rate recovery (HRR) is a marker of autonomic function and is directly correlated to parasympathetic activity and cardiovascular fitness. Impaired HRR reflecting sympathetic overactivity was observed in newly diagnosed cases of PCOS, which implies that it is an accurate and sensitive marker to detect early signs of cardiovascular impairment and enables timely measures to avoid further morbidity.

Our study detected increased androgen in PCOS cases compared to healthy controls, but it was not statistically significant. This observation can be explained as PCOS displays multiple phenotypes according to its severity and time of detection as our cases were all newly diagnosed. Regular screening for resting pulse, blood pressure and Heart Rate Variability needs to be monitored in PCOS

patients during OPD visits as they are more at risk of hypertension due to impaired cardiac fitness.

References

1. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nature Reviews Endocrinology. 2011; 33:14.
2. Yanes Cardozo LL, Romero DG, Reckelhoff JF. Cardiometabolic Features of Polycystic Ovary Syndrome: Role of Androgens. Physiology. 2017; 32:357–66.
3. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod. 2016; 31:2841–55.
4. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. FertilSteril. 2004; 81:19–25.
5. Thomson RL, Buckley JD, Brinkworth GD. Exercise for the treatment and management of overweight women with polycystic ovary syndrome: a review of the literature. Obes Rev. 2011; 12:202-210.
6. Bisgaard H, Dela F. [Physical exercise is a help for lean women with polycystic ovary syndrome]. UgeskrLaeg. 2017;179
7. Shetty D, Chandrasekaran B, Singh AW, Oliverraj J. Exercise in polycystic ovarian syndrome: An evidence-based review. Saudi Journal of Sports Medicine. 2017;17:123.
8. Shetler K, Marcus R, Froelicher VF, Vora S, Kalisetti D, Prakash M, et al. Heart rate recovery: validation and methodologic issues. J Am Coll Cardiol. 2001; 38:1980–7.
9. Giallauria F, Palomba S, Manguso F, Vitelli A, Maresca L, Tafuri D, et al. Abnormal heart rate recovery after maximal cardiopulmonary exercise stress testing in young overweight women with polycystic ovary syndrome. Clin Endocrinol. 2008; 68:88–93.
10. Savin WM, Davidson DM, Haskell WL. Autonomic contribution to heart rate recovery from exercise in humans. Journal of Applied Physiology. 1982;53:1572–5.
11. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Criteria for Defining Polycystic Ovary Syndrome as a Predominantly Hyperandrogenic Syndrome: An Androgen Excess Society Guideline. The Journal of Clinical Endocrinology & Metabolism. 2006;91:4237–45.
12. Zeng X, Xie Y-J, Liu Y-T, Long S-L, Mo Z-C. Polycystic ovarian syndrome: Correlation between hyperandrogenism, insulin resistance and obesity. Clin Chim Acta. 2020; 502:214–21.
13. DeVane GW, Czekala NM, Judd HL, Yen SSC. Circulating gonadotropins, estrogens, and androgens in polycystic ovarian disease. American Journal of Obstetrics and Gynecology. 1975; 121:496–500.
14. Lizneva D, Gavrilova-Jordan L, Walker W, Azziz R. Androgen excess: Investigations and management. Best Practice & Research Clinical Obstetrics &Gynaecology. 2016;37:98–118.

15. Dewailly D, Catteau-Jonard S, Reyss A-C, Leroy M, Pigny P. Oligoanovulation with Polycystic Ovaries but Not Overt Hyperandrogenism. The Journal of Clinical Endocrinology & Metabolism. 2006;91:3922–7.

16. Burger HG. Androgen production and mechanisms. The Journal of Clinical Endocrinology & Metabolism. 1998; 22:40-3.

17. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocrine Reviews. 2016; 37:467–520.

18. Sverrisdóttir YB, Mogren T, Kataoka J, Janson PO, Stener-Victorin E. Is polycystic ovary syndrome associated with high sympathetic nerve activity and size at birth? Am J Physiol Endocrinol Metab. 2008; 294:576-581.

19. Böhm M, Reil J-C, Deedwania P, Kim JB, Borer JS. Resting Heart Rate: Risk Indicator and Emerging Risk Factor in Cardiovascular Disease. The American Journal of Medicine. 2015; 128:219–28.

20. Böhm M, Reil J-C. Heart rate: surrogate or target in the management of heart failure? Heart. 2013; 99:72–5.

21. Tadic M, Cuspidi C, Grassi G. Heart rate as a predictor of cardiovascular risk. Eur J Clin Invest. 2018;48.

22. Aune D, Sen A, ó'Hartaigh B, Janszky I, Romundstad PR, Tonstad S, et al. Resting heart rate and the risk of cardiovascular disease, total cancer, and all-cause mortality - A systematic review and dose-response meta-analysis of prospective studies. NutrMetab Cardiovasc Dis. 2017; 27:504–17.

23. Reimers AK, Knapp G, Reimers C-D. Effects of Exercise on the Resting Heart Rate: A Systematic Review and Meta-Analysis of Interventional Studies. J Clin Med. 2018; 7:503.

24. Zore T, Joshi N, Lizneva D, Azziz R. Polycystic Ovarian Syndrome: Long-Term Health Consequences. Semin Reprod Med. 2017; 35:271–81.

25. Van de Vegte YJ, van der Harst P, Verweij N. Heart Rate Recovery 10 Seconds After Cessation of Exercise Predicts Death. JAHA. 2018;7.

26. Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yokoyama H, et al. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J Am Coll Cardiol. 1994; 24:1529–35.

27. O'Leary DS. Autonomic mechanisms of muscle metaboreflex control of heart rate. J Appl Physiol. 1993; 74:1748–54.

28. Forjaz CL, Matsudaira Y, Rodrigues FB, Nunes N, Negrão CE. Post-exercise changes in blood pressure, heart rate and rate pressure product at different exercise intensities in normotensive humans. Braz J Med Biol Res. 1998; 31:1247–55.

29. Tekin G, Tekin A, Kılıçarslan EB, Haydardedeoğlu B, Katırcıbaşı T, Koçum T, et al. Altered autonomic neural control of the cardiovascular system in patients with polycystic ovary syndrome. International Journal of Cardiology. 2008; 130:49–55.

30. Panzer C, Lauer MS, Brieke A, Blackstone E, Hoogwerf B. Association of fasting plasma glucose with heart rate recovery in healthy adults: a population-based study. Diabetes. 2002; 51:803–7.

31. Lind L, Andrén B. Heart rate recovery after exercise is related to the insulin resistance syndrome and heart rate variability in elderly men. Am Heart J. 2002; 144:666–72.

32. Shishehbor MH, Hoogwerf BJ, Lauer MS. Association of triglyceride-to-HDL cholesterol ratio with heart rate recovery. Diabetes Care. 2004; 27:936–41.
33. Kizilbash MA, Carnethon MR, Chan C, Jacobs DR, Sidney S, Liu K. The temporal relationship between heart rate recovery immediately after exercise and the metabolic syndrome: the CARDIA study. Eur Heart J. 2006; 27:1592–6.
34. Cole CR, Blackstone EH, Pashkow FJ, Snader CE, Lauer MS. Heart-Rate Recovery Immediately after Exercise as a Predictor of Mortality. N Engl J Med. 1999;341:1351–7.
35. Lipinski MJ, Vetrovec GW, Froelicher VF. Importance of the first two minutes of heart rate recovery after exercise treadmill testing in predicting mortality and the presence of coronary artery disease in men. Am J Cardiol. 2004; 93:445–9.
36. Morshedi-Meibodi A, Larson MG, Levy D, O'Donnell CJ, Vasan RS. Heart rate recovery after treadmill exercise testing and risk of cardiovascular disease events (The Framingham Heart Study). Am J Cardiol. 2002; 90:848–52.
37. Jouven X, Empana J-P, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. N Engl J Med. 2005 May 12; 352:1951–8.
38. McCrory C, Berkman LF, Nolan H, O'Leary N, Foley M, Kenny RA. Speed of Heart Rate Recovery in Response to Orthostatic Challenge. Circ Res. 2016; 119:666–75.
39. Savin WM, Davidson DM, Haskell WL. Autonomic contribution to heart rate recovery from exercise in humans. Journal of Applied Physiology. 1982;53:1572–5.
40. Bacchi E, Negri C, Di Sarra D, Tosi F, Tarperi C, Moretta R, et al. Serum Testosterone Predicts Cardiorespiratory Fitness Impairment in Normal-Weight Women with Polycystic Ovary Syndrome. Clin Endocrinol. 2015;83:895–901.
41. Hashim ZH, Hamdan FB, Al-Salihi AR. Autonomic dysfunction in women with polycystic ovary syndrome. Iran J Reprod Med. 2015; 13:27–34.