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Research Article

ASSESSMENT OF CARDIOVASCULAR AUTONOMIC REACTIVITY IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME

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ABSTRACT

Polycystic ovary syndrome (PCOS) in association with obesity poses a significant cardiovascular risk. Autonomic dysfunction is an early marker of cardiovascular risk. The conventional autonomic function tests (CAFT) are standard noninvasive methods of evaluating cardiovascular autonomic re activities. The study was conducted to assess the autonomic reactivity in patients with PCOS using CAFT. Forty newly diagnosed patients with PCOS and 36 age-matched controls were recruited. Body mass index (BMI), waist-hip ratio (WHR), cardiovascular parameters such as basal heart rate (BHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and rate-pressure product (RPP), were measured in them. CAFT assessed were HR and BP response to standing (30:15 ratio), deep breathing (E:I ratio) and isometric handgrip (ΔDBP_{ihg}). Association of CAFT reactivity parameters with RPP was assessed by Pearson correlation. Individual association of CAFT reactivity parameters to RPP was assessed by multiple regression analysis. The cases had significantly increased BMI, WHR, BHR, SBP, DBP, MAP and RPP. E:I ratio was decreased and 30:15 ratio and ΔDBP_{ihg} were increased in cases. 30:15 ratio and ΔDBP_{ihg} had a significant positive correlation with RPP and E:I ratio showed negative correlation. Multiple regression analysis demonstrated independent association of RPP with E:I ratio and ΔDBP_{ihg}. We conclude that PCOS patients have altered autonomic modulation in the form of increased sympathetic and decreased parasympathetic reactivity. The autonomic dysregulation is linked to myocardial performance in PCOS, which could expose PCOS patients to cardiovascular morbidities.

Keywords: Polycystic ovary syndrome, Autonomic reactivity, Rate pressure product, Cardiovascular risks, Obesity, Sympathovagal imbalance

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most frequent endocrine disorder seen in women of reproductive age group, affecting 5 to 10 % of the population[1]. It is characterized by menstrual irregularities, biochemical or clinical hyperandrogenism and polycystic ovary[1,2]. Obesity is a very common clinical feature in women with PCOS with a prevalence of around 50 %[1,3]. Obesity is known to be associated with alterations in cardiovascular autonomic status in the form of increased sympathetic neural outflow[4]. With this potent comorbid factor, PCOS poses a significant cardiovascular (CV) risk which warrants an early assessment of CV health of patients suffering from this condition[5]. A significant relation between the adverse CV events and autonomic dysfunction has been evidenced from previous studies[6]. Few studies have reported CV autonomic involvement in the form of decreased heart rate variability (HRV) and increased sympathetic tone in patients with PCOS[7,8]. But no studies have been conducted till date on the detailed assessment of the reactivity of the sympathetic and parasympathetic division of the autonomic nervous system in PCOS. Both sympathetic and parasympathetic outflows are activated in a co-ordinate fashion according to the physiological requirements. Therefore, the interplay between the sympathetic and parasympathetic systems is essential to the maintenance of normal CV homeostasis and provides the basis for various CV reflexes in beat to beat regulation of heart rate (HR) and blood pressure (BP)[9]. The conventional

autonomic function tests (CAFT) to assess specifically sympathetic and parasympathetic outflows, have proved to be objective, reproducible and noninvasive methods of evaluating the cardiovascular risks[10-12]. The prime concern of CAFT is to assess the integrity of the autonomic reflex arc in the regulation of HR and BP during various physiological perturbations[13]. Therefore, in this study, an attempt has been made to assess specifically the reactivity of the sympathetic and parasympathetic outflows of the autonomic nervous system in patients with PCOS and elucidate whether autonomic dysfunction exists in them.

MATERIALS AND METHODS

Study design

This was an analytical cross sectional study, conducted in the autonomic function testing (AFT) laboratory, Department of Physiology, JIPMER, Puducherry, India. The approval of the Institute Research Council and Institute Ethics Committee for human studies was obtained prior to the commencement of the study.

Subjects

Seventy-six subjects were included in the study. Forty cases from the outpatient department of Obstetrics and Gynecology of JIPMER, Puducherry, India as per ESHRE / ASRM criteria[1] and thirty-six controls were recruited for the study. The cases included patients with newly diagnosed PCOS in the age group of 15-35 years. Patients already on treatment for PCOS were excluded from the study. Age-matched healthy regularly menstruating and nulliparous women were included as controls. Women with menstrual irregularities, hypothyroidism, diabetes, and women on any hormonal therapy or drugs were excluded. Written informed consent was obtained from all the subjects prior to the commencement of the study.

Procedure

The study was conducted during the follicular phase of the menstrual cycle in control subjects to allow uniform influence of ovarian hormones on AFT[14]. In the study group, the test was conducted during amenorrheic period[7]. The subjects were asked to report to AFT laboratory at 07.00 hours after overnight fasting.

Anthropometric measurements and metabolic parameters

Waist circumference was measured as the circumference of the abdomen at its narrowest point between the lower costal (10^{th} rib) border and the top of the iliac crest. Hip circumference was measured at the level of greatest posterior protuberance of the buttocks. Subject's height was measured to the nearest millimeter by a wall mounted stadiometer and weight was measured with a spring balance to the nearest half a kilogram avoiding zero and parallax errors. Body mass index (BMI) and waist-hip ratio (WHR) were calculated. BMI was calculated by Quetelet's index. Asian criterion for BMI was followed for grouping the subjects based on the level of BMI[15].

Baseline cardiovascular parameters

After 5 minutes of sitting rest, basal heart rate (BHR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) was recorded using automated BP monitor (Omron Healthcare Co. Ltd, Kyoto, Japan) and mean arterial pressure (MAP) was calculated. Rate-pressure product (RPP), a major determinant of myocardial oxygen consumption and work load was calculated using the formula,

$$RPP=(BHR\times SBP)\times 10^{-2}\ ^{16}$$

Cardiovascular autonomic function tests

The subjects were explained about the tests. The room temperature at 23°C and the humidity between 25 % and 35 % were maintained[17]. The following conventional autonomic function tests (CAFTs) were recorded in all the subjects, as per the standard protocol[10,17].

HR and BP response to standing

After five minutes of supine rest, the subjects were asked to stand after 30 seconds with simultaneous recording of lead II ECG. The postural change was obtained within 3 seconds. BP and HR were serially measured for next 5 minutes of stand i.e. immediate, first, second, third, fourth and fifth minute. Following this, the subjects were asked to sit down and allowed to rest for 5 minutes to achieve baseline HR and BP values.

HR response to deep breathing

Deep breathing was performed at the rate of 6 breaths per minute with inspiratory and expiratory cycles for 5 seconds each. The subjects performed deep breathing synchronized to a voice metronome and if necessary guided by hand movement for the next one minute with continuous lead II ECG recording. Subjects were encouraged to perform deep and maximal respiration. A period of 5 minutes rest was given after the maneuver for the HR and BP to return to basal state.

BP response to sustained isometric hand grip

Initially the maximal voluntary contraction (MVC) during sustained isometric handgrip by the subjects was measured using handgrip dynamometer (Inco, Ambala, India). Then the subjects were instructed regarding sustaining the handgrip at one third of their MVC. The ECG recording was started and at the fifteenth second subjects was instructed to perform one third of their MVC for 3 minutes. The maximum DBP attained during the maneuver was noted. After the procedure BP and HR were measured after 2 minutes to confirm if they have returned to basal levels.

Quantification of HR and BP response

During standing, 30:15 ratio (ratio of longest RR interval at 30^{th} beat to shortest RR interval at 15^{th} beat) was computed. From the deep breathing maneuver E: I ratio, the ratio of longest RR interval during expiration to the shortest RR interval during inspiration averaged over 6 cycles of respiration was calculated. During the IHG test, the magnitude of DBP rise during the maneuver given as ΔDBP_{ihg} (difference between this highest DBP recorded during sustained handgrip and baseline supine DBP) was calculated. 30:15 ratio and E:I ratio depict parasympathetic modulation[17]. The ΔDBP_{ihg} represents the sympathetic modulation[17].

Statistical analysis

Sample size was calculated using PS programme version 3.0.43. Sample size was estimated for three parameters LFnu, HFnu and LF-HF ratio. The calculation with LFnu yielded the highest sample size of 30, with an expected mean

difference of 13 from the previous study done for a power of 0.8 and type I error of 0.01[7]. Statistical analysis was done using SPSS Statistics software, Version 19 (SPSS Software Inc., Chicago, IL, USA). For data analysis, all values were expressed as mean ± SD. The data were subjected to Kolmogorov-Smirnov normality test. The inter-group differences between the controls and cases were compared using Student's unpaired *t* test for normally distributed data. Association of CAFT reactivity parameters with RPP was assessed by Pearson correlation. Multiple regression analysis was done to assess the contribution of individual factors to RPP. P value of less than 0.05 was considered statistically significant.

RESULTS

Age, anthropometric and basal cardiovascular parameters

Both the cases and control subjects belonged to the same mean age group (P = 0.169) (Table 1). The cases had significantly high (P < 0.001) BMI and WHR compared to that of controls. The CV parameters i.e. BHR, SBP, DBP, MAP and RPP were significantly high (P < 0.001) in cases compared to that of controls.

HR and BP response during CAFT

The 30:15 ratio was significantly more (P = 0.0106), E:I ratio was significantly less (P = 0.0035) and ΔDBP_{ihg} was significantly high (P < 0.001) in cases compared to that of controls (Table 2).

Correlation analysis of RPP with CAFT reactivity parameters

There was a significant positive correlation of RPP with 30:15 ratio (P = 0.035), and ΔDBP_{ihg} (P = 0.027). A negative correlation was observed between RPP and E:I ratio (P = 0.041) (Table 3).

Multiple regression analysis of RPP with CAFT reactivity parameters

There was no significant contribution of 30:15 ratio to RPP. However, E:I ratio (P = 0.019) and ΔDBP_{ihg} (P = 0.003) had independent association with RPP (Table 4).

DISCUSSION

In the present study, it was observed that the baseline CV parameters (BHR, SBP, DBP and MAP) were significantly high in patients with PCOS compared to the controls (P < 0.001). Since BHR is mainly under vagal modulation, an increased BHR in these patients could be attributed to the decreased vagal activity[18]. The raised SBP, DBP and MAP observed in patients with PCOS could be due to increased sympathetic drive as regulation of BP is mainly under sympathetic control[19]. The RPP, an indirect measure of myocardial load and oxygen demand was found to be significantly elevated among the cases indicating that PCOS patients are constantly under the stress of increased myocardial performance[20]. Significantly elevated 30:15 ratio (P = 0.0106) during the orthostatic stress test (BP response to standing); in cases reveals decreased vagal reactivity in these patients[21]. This was confirmed by the deep breathing test, in which E:I ratio was significantly reduced (P = 0.0035) in cases further establishing the decreased vagal tone in PCOS patients, as E:I ratio is a standard measure of parasympathetic reactivity[17]. The isometric handgrip test that assesses the sympathetic reactivity demonstrated a significantly accentuated ΔDBP_{ihg} among the cases (P < 0.001) depicting an exaggerated adrenergic modulation in PCOS patients[22,23]. Thus, in the present study, in PCOS patients there is a significant alteration in autonomic modulation in the form of increased sympathetic and decreased parasympathetic reactivity. There was a significant positive correlation of the CAFT reactivity parameters (30:15 ratio, ΔDBP_{ihg}) with RPP. Also, a significant negative correlation was observed with E:I ratio. The E:I ratio and ΔDBP_{ihg} showed independent contribution to RPP as demonstrated by multiple regression analysis. This suggests that in PCOS patients, the increased sympathetic reactivity and decreased vagal reactivity leads to an elevated RPP, thereby straining the myocardial activity. Overweight and obesity have often been associated with PCOS. Studies have reported that more than 50 % of these patients are either overweight or obese[1]. In the present study, most of the cases were obese as assessed by Asian criteria of assessment of BMI[15]. In addition to increased BMI, these patients also had significantly increased WHR compared to the controls (P < 0.001). Thus, apart from generalized increase in weight, these PCOS patients had an android type of obesity. Obesity has long been known to cause derangement in autonomic functions in the form of increased adrenergic and decreased vagal modulation[4]. Further, android type of obesity has been reported to accentuate the autonomic derangement[24]. In addition, there are reports of decreased HRV in patients with PCOS with increased weight gain[25]. Therefore, obesity could be a significant contributing factor to the development of dysfunction observed in the autonomic reactivity. Autonomic tone i.e. the vagal and sympathetic tone depicts the sympathovagal balance at rest. The basal heart rate and blood pressure are functions of vagal and sympathetic tone at rest respectively[18]. Apart from maintenance of hemodynamic parameters at rest, the CV responses to various physiological changes and challenges are also integrated via neural arc involving the autonomic system[9,13]. In the present day scenario of increased stress, stable sympathetic and parasympathetic control mechanisms play vital role in maintaining the effective autonomic homeostasis and cardiovascular health in day to day life. Therefore, the assessment of the sympathetic and parasympathetic response to various reactivity tests would be more appropriate in assessing CV risks in various disease states. Previous studies have assessed the resting sympathovagal balance by short-term HRV analysis and have reported decreased parasympathetic and increased sympathetic tone in patients with PCOS[7]. Recently, we have reported increased sympathetic and decreased parasympathetic tone in patients with PCOS assessed by short-term HRV analysis[26]. Hence, the novelty of the present study is that we have assessed the reactivity of the sympathetic and parasympathetic limb independently in response to physiological perturbations in PCOS patients and also assessed their association with RPP. PCOS has emerged as a syndrome in which various CV risk factors have been interlinked. The increased sympathetic and decreased parasympathetic modulations are markers of poor CV health as evidenced from studies on patients with myocardial infarction[20]. Therefore, these patients having deranged autonomic reactivity would be unable to cope up with physiological requirements viz. during stand or any other form of stress leading to CV dyshomeostasis in control of HR and BP[12].

Table 1: Comparison of age, anthropometric and basal cardiovascular parameters between controls and cases

Parameters	Controls (n = 36)	Cases (n = 40)	P value
Age (years)	25.237 ± 2.863	24.108 ± 3.950	0.169
BMI (kg/m^2)	22.617 ± 3.095	28.281 ± 5.801	<0.001
WHR	0.761 ± 0.038	0.869 ± 0.064	<0.001
BHR (beats/min)	64.18 ± 7.593	86.137 ± 9.836	<0.001
SBP (mmHg)	104.493 ± 7.073	118.258 ± 8.470	<0.001
DBP (mmHg)	73.438 ± 6.825	86.358 ± 7.921	<0.001
MAP (mmHg)	83.794 ± 5.638	91.993 ± 9.017	<0.001
RPP	67.175 ±14.531	101.934 ± 18.268	<0.001

Values expressed as Mean + SD; analysis was done by Student's unpaired t test
Controls: women with regular menstrual cycle; Cases: women with PCOS. BMI: body mass index; WHR: waist hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; RPP: rate pressure product

Table 2: Comparison of heart rate and blood pressure changes during CAFT between controls and cases

Parameters	Controls (n = 36)	Cases (n = 40)	P value
Response to stand 30:15 ratio	1.487 ± 0.134	1.583 ± 0.179	0.0106
Response to deep breathing E:I ratio	1.495 ± 0.318	1.315 ± 0.194	0.0035
Response to IHG ΔDBP_{ihg}	22.73 ± 5.835	29.179 ± 6.957	<0.001

Values expressed as Mean + SD; analysis was done by Student's unpaired t test
Controls: women with regular menstrual cycle; Cases: women with PCOS. 30:15 ratio: ratio of longest RR interval at 30th beat to shortest RR interval at 15th beat; E:I ratio : ratio of longest RR interval during expiration to shortest RR interval during inspiration averaged over 6 cycles of respiration;ΔDBP_{ihg}: diastolic BP rise during isometric hand grip

Table 3: Correlation analysis of RPP CAFT reactivity parameters among the controls and cases

Parameters	Controls (n = 36)		Cases (n = 40)	
	r	P	r	P
30:15 ratio	0.542	0.368	0.217	0.035
E:I ratio	-0.308	0.274	-0.183	0.041
ΔDBP_{ihg}	0.493	0.174	0.319	0.027

Controls: women with regular menstrual cycle; Cases: women with PCOS. RPP: rate pressure product 30:15 ratio: ratio of longest RR interval at 30th beat to shortest RR interval at 15th beat; E:I ratio: ratio of longest RR interval during expiration to shortest RR interval during inspiration averaged over 6 cycles of respiration; ΔDBP_{ihg}: diastolic BP rise during isometric hand grip

Table 4: Multiple regression analysis of RPP with CAFT reactivity parameters in cases

Parameters	Standardized Beta	P
30:15 ratio	0.409	0.173
E:I ratio	0.542	0.019
ΔDBP_{ihg}	0.597	0.003

Cases: women with PCOS. RPP: rate pressure product 30:15 ratio: ratio of longest RR interval at 30th beat to shortest RR interval at 15th beat; E:I ratio: ratio of longest RR interval during expiration to shortest RR interval during inspiration averaged over 6 cycles of respiration; ΔDBP_{ihg}: diastolic BP rise during isometric hand grip

This sympathovagal reactivity imbalance can further lead to the genesis of hypertension and CV dysfunctions[27]. Apart from this, the elevated resting HR and BP have also been recently proposed as independent CV risk factors[27,28]. The state of CV derangement among the PCOS patients due to the autonomic dysregulation in the present study is supported by the elevated RPP in them, which depicts their increased myocardial oxygen demand and the underlying CV stress[19]. From the present study, we conclude that in PCOS there is derangement in autonomic function in the form of increased sympathetic and decreased parasympathetic reactivities, disturbing the CV homeostasis. As detection of autonomic imbalance heralds the onset of CV risk, future studies should elucidate if an early detection of autonomic imbalance could help design intervention to yield a better CV health to these patients. In this study, the patients with PCOS were obese. Insulin resistance, which is known to be the consequence of increased adiposity, has been proposed to be one of the pathophysiologic mechanisms of PCOS[29,30]. But, PCOS patients even with normal BMI have been observed to have insulin resistance, which can predispose them to autonomic imbalance[31,32]. Therefore, future studies should address the magnitude of autonomic dysfunction in PCOS patients with normal BMI (lean cases) and high BMI (obese cases) to assess the independent contribution of PCOS to autonomic dyshomeostasis. The limitation of the present study is that we have not assessed insulin resistance.

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