Women with Polycystic Ovarian Syndrome Exhibit Reduced Baroreflex Sensitivity That May Be Associated with Increased Body Fat

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Abstract

Background: **Polycystic ovarian syndrome (PCOS) women have a high prevalence of obesity and alterations in cardiovascular autonomic control, mainly modifications in heart rate variability (HRV) autonomic modulation. However, there are few studies about other autonomic control parameters, such as blood pressure variability (BPV) and baroreflex sensitivity (BRS). In addition, there are still doubts about the obesity real contribution in altering autonomic control in these women.**

Objective: **To investigate BPV and BRS autonomic modulation alterations in PCOS women, as well as, to evaluate whether these alterations are due PCOS or increased body fat.**

Methods: **We studied 30 eutrophic volunteers [body mass index (BMI) < 25 kg/m²] without PCOS (control group) and 60 volunteers with PCOS divided into: eutrophic (BMI < 25 kg/m², N = 30) and obese women (BMI > 30 kg/m², N = 30). All volunteers were submitted to anthropometric evaluation, hemodynamic and cardiorespiratory parameters record at rest and during physical exercise, analysis of HRV, BPV and spontaneous BRS. The differences in p less than 5% (p < 0.05) were considered statistically significant.**

Results: **Related to eutrophics groups, there were no differences in autonomic parameters evaluated. The comparison between the PCOS groups showed that both PCOS groups did not differ in the BPV analysis. Although, the obese PCOS group presented lower values of spontaneous BRS and HRV, in low frequency and high frequency oscillations in absolute units.**

Conclusion: **Our results suggest that obesity did little to alter HRV in women with PCOS, but it may influence the spontaneous BRS. (Arq Bras Cardiol. 2019; 112(4):424-429)**

Keywords: **Obesity; Hypertension; Polycystic Ovary Syndrome/physiopathology; Adiposity; Body Fat Distribution; Autonomic Nervous System; Heart Rate.**

Introduction

Women with polycystic ovarian syndrome (PCOS) frequently present cardiovascular autonomic control impairments, mainly characterized by a cardiac autonomic imbalance in determining heart rate variability (HRV).[1-4] This imbalance is an important cardiovascular diseases risk predictor.[5-7] The autonomic impairment causes are still not well established. Some studies suggest that they are result of hormonal and metabolic disorders due PCOS, such as insulin resistance increased.[2,3,8] On the other hand, it is possible that they are simply due body fat percentage increase, which triggers series of systemic alterations, including metabolic and cardiovascular, that affect the cardiac autonomic control.[4,9,10]

Another important aspect is that only HRV is frequently investigated in these women, and we know little about PCOS effects on others autonomic parameters, such as baroreflex sensitivity (BRS) and blood pressure variability (BPV). More specifically, there are no studies associating PCOS to BPV, and in BRS case, studies are incipient. On this, only one study was performed and found no differences.[11] However, this study only addressed obese PCOS and non-PCOS women, which limited further findings.

Therefore, the aim of the present study was to evaluate spontaneous BRS and BPV in eutrophic PCOS women and to investigate the contribution of obesity to these autonomic parameters in these women.

Methods

Participants

With a convenience sample, ninety volunteers aged between 18 and 39 years were included, 30 non PCOS women, considered as a control group, and 60 PCOS women, according to Rotterdam consensus,[12] were subdivided according to the body mass index (BMI): eutrophic group (30 women) and obese group (30 women). All of them were sedentary, did not

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use any medication, and were screened at the outpatient clinic of the Gynecology and Obstetrics Clinic of Clinical Hospital of Ribeirao Preto Medical School (HC-FMRP/USP).

Polycystic ovary syndrome diagnostic

Transvaginal pelvic ultrasound was performed with the Voluson 730 Expert Machine (GE Medical Systems, ZIPF, Austria) to analysis the cysts presence or absence. The ovarian volume and follicles number/size were evaluated, and to calculate ovarian volume the prolate ellipsoid formula (depth x width x length x 0.5) was used.[13]

In addition, laboratory tests for serum total testosterone, androstenedione, sex hormone binding globulin and free androgen, prolactin, 17-hydroxyprogesterone and thyrotropin dosed to diagnose exclusion causes. Blood samples were collected during the follicular phase in women with regular ovulatory cycles and at any time in those with irregular cycles. All the above examinations were performed at the Gynecology Laboratory of HC-FMRP, between 07h00 and 09h00 a.m. after a previous 12-hour fast.

Ergospirometric test

The peak oxygen uptake (VO_{2peak}) was assessed by a submaximal exercise test on a treadmill (Super ATL Millenium®, Inbramed/Inbrasport, Brazil) using the Modificated Bruce protocol. The analysis of exhaled gases (VO_2 and VCO_2) was performed using a metabolic device (UltimaTM CardiO^2, Medical Graphics Corp., USA).

Anthropometric parameters

Body weight and height were obtained using an analogue scale with an altimeter (Welmy), while the body mass index (BMI) values were obtained using the formula W/H^2, where W is the weight in kilograms and H is the height of the subject in meters. Body composition was evaluated using the bioelectrical impedance method (Quantum BIA 101; Q-RJL Systems, Clinton Township, Michigan, USA). The groups were subdivided by their BMI, where the eutrophic groups had BMI < 25 kg/m^2 and the obese group had BMI > 30 kg/m^2.[14]

Analysis of the heart rate variability and blood pressure variability

The spectral analysis of HRV was recorded between 09h00 and 10h00 a.m. according to the following protocol: after remaining in a supine rest position on orthostatic bed for 20 min, the volunteers were passively placed in an inclined position (75° angle) for an additional 10 min. HRV for supine and inclined positions (that is, the tilt test) was recorded using an electrocardiogram (AD Instruments, Sydney, Australia), and a time series of RR interval (RRi) was obtained.

The HRV was obtained using the RRi from electrocardiographic record (ECG), through the modified MC5 shunt at a sampling frequency of 1000Hz. The BPV data values were obtained from the systolic arterial pressure (SAP) recorded beat-to-beat by means of digital plethysmography recording equipment, FINOMETER (Finometer Pro, Finapress Medical System, Amsterdam, Netherland). The room temperature was kept at 21ºC, the ambient light and the noise were controlled, to prevent any interference with recording of data.

The BPV and HRV analyses were performed using custom computer software (CardioSeries v2.0, http://sites.google.com/site/cardioseries). The values of the RRi and SAP intervals were redesigned in 3 Hz cubic spline interpolation, to normalize the time interval between the beats. The series of interpolated RRi and SAP follow the Welch Protocol;[15] they have been divided into half-overlapping sets of 256 data points, overlapping 50%. The stationary segment was visually inspected and those with artifacts or transients were excluded. Each RRi and SAP stationary segment were submitted to spectral analysis by Fast Fourier Transform (FFT), after Hanning window. The RRi specters were integrated in low frequency (LF; 0.04 - 0.15 Hz) and high frequency (HF; 0.15 - 0.5 Hz) bands and the results are expressed in absolute (ms^2) and normalized units (nu), while the SAP specters were integrated only in low frequency band (LF; 0,04 – 0,15Hz) and the results are expressed in absolute units (mmHg^2).

The HRV normalized values were obtained by calculating the percentage of LF and HF power related to the total power of spectrum minus the very low-frequency band (VLF; < 0.2 Hz).[16,17] In addition, normalization procedure was performed to minimize variations of total power in the absolute value of LF and HF.[18] To assess the sympathovagal balance, LF/HF ratio of RRi variability was also calculated.[19]

Spontaneous baroreflex sensitivity

The BRS was assessed in time-domain using the sequence technique, as described by Di Rienzo et al.,[20] The computer software CardioSeries v2.4 scanned beat-to-beat time series of RRi and SAP values searching for sequences of at least 3 consecutive beats in which; progressive increases in SAP were followed by progressive increases in RRi (up sequence) and progressive decreases in SAP were followed by progressive decreases in RRi (down sequence), with a correlation coefficient (r) between RRi and SAP values higher than 0.8. The mean slope of the linear regression line between the SAP and RRi values of each sequence found determined spontaneous BRS.

Statistical analysis

In a comparison between two groups the Student's t-test and in comparison of three groups the one ways variance analysis (ANOVA ONE WAY) were performed. The Shapiro-Wilk test was used to verify de the dates normality; when the distribution was not normal, non-parametric tests were used, the Mann-Whitney test to compare between two groups, and in comparison of three groups, the Kruskal-Wallis test. When the variables had a normal distribution, they were described as mean (± standard deviation), and which had non-parametric distribution they were described as median (± interquartile range). The differences in p were less than 5% ($p < 0.05$) were considered statistically significant. All statistical tests were performed with Sigma Stat 3.5 software (Systat Software Inc., San Jose, CA, USA).

Results

The volunteer's anthropometric characteristics and hemodynamic parameters are in Table 1. The obese PCOS group had higher BMI, weight and body fat percentage than the other groups. On the other hand, VO_{2peak} was lower in the obese PCOS group. In relation to blood pressure, the obese group had higher values of diastolic blood pressure and mean blood pressure compared to the control and eutrophic PCOS groups.

Table 2 presents the spectral analysis of HRV and BPV results during rest of all groups studied. The HRV analysis at rest shows the obese PCOS group had lower variance. In addition, the control groups and eutrophic PCOS presented higher LF and HF oscillations in absolute values than the obese PCOS group. There were no differences between the groups in BPV analysis.

The results of BRS analysis obtained during rest in all groups studied, control, eutrophic PCOS and obese PCOS, are seen in Table 3, that show at rest the obese PCOS group presented lower spontaneous BRS than the others groups. In addition, it is important to note that the control group demonstrated a higher baroreflex effectiveness index.

Discussion

The present study mainly findings were, at rest the obese PCOS group had lower HRV and BRS than the other two groups, BPV was similar across groups.

Regarding hemodynamic values, PCOS obese group showed the highest values of systolic, diastolic and mean blood pressure compared to other groups, despite the fact that all subjects were normotensive; some studies had also show a relation with body fat increase and increase BP values.[9,10,21,22] To VO_{2peak}, the obese PCOS group had the lowest value, similarity to literature, which some authors found a negative correlation between obesity and VO2peak.[21,22]

There are few studies in the literature about obesity and PCOS, which are contradictory, some point to this association as a negative factor in HRV,[3,4] although others report that there is no association between weight gain and PCOS.[11,23] In this sense, the lower HRV found in the obese PCOS group in the present study suggests that this change is due to obesity. The literature indicates that the obesity mechanisms may be associated with a reduced sympathetic system response in the postsynaptic region since they had found in presynaptic cleft a high sympathetic activity represented by high concentration of noradrenaline.[24,25] In addition, a recent study carried out in our laboratory showed low frequency (LF) and high frequency (HF) bands differences, in absolute and normalized units, in healthy and sedentary women with normal BMI, overweight and obesity, they verified that the obese group had lower LF and HF oscillations.[10]

Regarding BRS, the eutrophic PCOS and control groups presented similar values, agreeing with Lambert, 2015, in which the groups had similar BMI and BRS values. In relation to the obese PCOS group, it had the lowest values in all BRS parameters than the others two eutrophic groups, suggesting that obesity may be responsible for a reduction in BRS. In this sense, a study comparing BRS in women divided by BMI indicates a BRS reduction with gain weight, observed by the BRS gain value, in this way, the BRS decrease might correlate to weight increase.[26] However, it is known that BRS is also influenced by many other factors like insulin resistance, blood glucose, sodium sensibility, genetic markers and ovarian hormones.[27,28] In the present study, neither of these other factors were measuring. Thereby it is possible to suggest that obesity may influenced in BRS values, as observed in another study,[26] although further studies are needed to confirm these findings in PCOS women.

Table 1 – Hemodynamic characteristics and values among healthy women and women with polycystic ovary syndrome (PCOS), subdivided into eutrophic PCOS (BMI < 25 kg/m²) and obese PCOS (BMI > 30 kg/m²)

	Control	PCOS eutrophic	PCOS obese	p^{I}	p^{II}
Characteristics					
Age, years	31.2 ± 6.6	28.5 ± 5.2	30.2 ± 5.3	0.053	0.107
Heights, meters	1.64 ± 5.0	1.62 ± 5.8	1.62 ± 7.9	0.102	0.649
Weight, kg	64 ± 10	60.6 ± 5.7	90.3 ± 10.9*†	0.09	< 0.001
BMI, kg/m²	23.5 ± 3	22.9 ± 1.6	33.9 ± 2.4*†	0.494	< 0.001
Body fat percentage, %	25.6 ±3.6	26.4 ± 3.4	44.3 ± 3.3*†	0.325	< 0.001
VO_{2peak}, L/min/kg	35.5 ± 3.3	31.9 ± 3.9	25.3 ± 3.3*†	0.05	< 0.001
Hemodynamics Values					
HR (bpm)	76 ± 2.6	74.6 ± 2	77 ± 2	0.764	0.416
SBP (mmHg)	105 ± 8.9	101 ± 11.8	111 ± 9.5†	0.057	< 0.001
DBP (mmHg)	70 ± 10.3	66 ± 9.6	76 ± 7.4*†	0.05	< 0.001
MBP (mmHg)	84 ± 9	80 ± 9.8	90 ± 7.5*†	0.05	< 0.001

Values expressed as means ± SD: standard deviation; m: Meters; Kg: kilogram; BMI: body mass index; VO_{2peak}: volume of oxygen consumed at the peak of exercise; L/min/Kg: liters per minutes per kilo; HR: heart rate; bpm: beat per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; mmHg: millimeters of mercury; statistical difference when p < 0.05; (*) vs. Control; (†) vs. eutrophic PCOS; P^{I}: eutrophic control group vs PCOS eutrophic group; P^{II}: PCOS eutrophic group vs. PCOS obese group.

Table 2 – Parameters of the spectral analysis of the heart rate variability analysis calculated from the time series RR intervals and systolic arterial pressure variability calculated by the pulse beat-to-heart rate interval obtained between women without and with polycystic ovaries syndrome (PCOS) divided according to the body mass index eutrophic < 25 kg/m² and obese > 30 kg/m²

	Rest				
	Control	PCOS eutrophic	PCOS obese	p^{I}	p^{II}
HR variability					
RRi, ms	872 ± 31	879 ± 20.6	812 ± 18.5†	0.961	0.049
Variance, ms²	2389 ± 310	2654 ± 341	1851 ± 405*†	0.971	0.010
LF, ms²	697 ± 105	720 ± 93	413 ± 80*†	0.855	0.002
LF, un	40.3 ± 3.8	45.5 ± 3.5	46.4 ± 2.9	0.350	0.850
HF, ms²	1134 ± 188	1180 ± 229	968 ± 204*†	0.502	0.014
HF, un	59.6 ± 3.8	54.4 ± 3.5	53.4 ± 2.9	0.350	0.850
LF/HF Ratio	0.79 ± 0.1	0.92 ± 0.1	0.94 ± 0.1	0.474	0.99
BP variability					
Variance, mmHg²	22.9 ± 4.3	24.9 ± 2.2	21 ± 2	0.168	0.052
LF, mmHg²	6.7 ± 1.4	7.6 ± 0.8	5.7 ± 0.7	0.196	0.054

Values expressed as means ± SD: standard deviation; HR: heart rate; RRi: interval between R waves on the electrocardiogram; nu: normalized units; ms²: milliseconds squared; LF: low frequency band; HF: high frequency band; BP: blood pressure; significant difference p < 0.05; (*) vs rest control, (†) vs. rest eutrophic PCOS; P^{I}: eutrophic control group vs PCOS eutrophic group; P^{II}: PCOS eutrophic group vs. PCOS obese group.

Table 3 – Parameters of the baroreflex analysis by the calculated sequence series of RR intervals obtained between women with and without polycystic ovary syndrome (PCOS) divided according to the body mass index eutrophic < 25 kg/m² and obese > 30 kg/m²

	Rest				
	Control	PCOS eutrophic	PCOS obese	p^{I}	p^{II}
Baroreflex Sensitivity					
Ramp numbers	85 ± 40.7	84.3 ± 39.8	93.7 ± 42.4	0.853	0.379
BEI	0.74 ± 0.13	0.63 ± 0.12*	0.58 ± 0.15*	0.005	0.225
UP, ms/mmHg	15.1 ± 6	18 ± 11	11.7 ± 6.7 *†	0.738	0.008
DOWN, ms/mmHg	16.5 ± 5.6	18.3 ± 8.8	12.7 ± 7.5 *†	0.738	0.004
GAIN, ms/mmHg	16.1 ± 5.5	18.3 ± 9.3	12.3 ± 7.2 *†	0.687	0.003

Values expressed as means ± SD: standard deviation; BEI: baroreflex efficacy index; GAIN: total gain; DOWN: hypotensive responses associated with tachycardia responses; UP: hypertensive responses associated with bradycardic responses; significant difference p < 0.05; (*) vs rest Control, (†) vs rest eutrophic PCOS; P^{I}: eutrophic control group vs PCOS eutrophic group; P^{II}: PCOS eutrophic group vs. PCOS obese group.

Finally, in relation to BPV similarity were found between the studied groups, there are few information since there are no studies in the literature about the behaviour of BPV in PCOS women, the studies found are associated with cardiovascular diseases, unrelated to PCOS.[29-31] Although, PCOS women have a greater predisposition to develop cardiovascular diseases, the present study population were healthy and did not use medication, suggesting that PCOS does not alter the BPV. In addition, the obese PCOS group also did not present differences in relation to eutrophic groups. The studies found on BPV and obesity are contradictory, some suggest an increase[24,32] while others point out a reduction of BPV.[33] However, both suggest that the baroreflex could justify these changes. Meanwhile, in our study, although the obese PCOS group presented a decrease in BRS, the BPV, apparently, was not affected. In this way, we need more studies to elucidate these findings.

Study limitations

The present study had some limitations, as insulin, glucose and inflammatory markers dosages absence, which could contribute to results discussion; another limitation was HRV and BPV measure only in supine position. It is possible that during an autonomic provocation test, as in tilt test, we could find different responses in autonomic modulation between the studied groups. However, it is important to note that the study limitations do not invalidate the main findings in supine position and its clinical implications.

Conclusion

Although PCOS is an endocrine-metabolic disease that causes several body changes, it does not alter the autonomic cardiovascular control. However, the association with obesity resulted in a decrease in BRS values, and attenuated the HRV values. Suggesting that obesity may play a role in change hemodynamics parameters and cardiovascular autonomic control. However, further studies should be conducted to investigate the effects of metabolic and hormonal changes in these women and the association of these changes with cardiovascular autonomic control.

Author contributions

Conception and design of the research: Philbois SV, Souza HCD; acquisition of data: Philbois SV, Facioli TP, Felix ACS; analysis and interpretation of the data and critical revision of the manuscript for intellectual content: Philbois SV, Gastaldi AC, Souza HCD; statistical analysis: Philbois SV, Facioli TP; obtaining funding: Souza HCD; writing of the manuscript: Gastaldi AC, Souza HCD.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital das Clínicas de Ribeirão Preto e da Faculdade de Medicina de Ribeirão Preto under the protocol number 11487/2014. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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