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Aerobic exercise improves cardiac autonomic modulation in women with polycystic ovary syndrome☆

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ABSTRACT

Background: This study aimed to evaluate the effects of aerobic exercise on cardiac autonomic modulation in women with polycystic ovary syndrome (PCOS).
Methods: Thirty women with PCOS (25.8 ± 4.8 years old; body mass index, BMI ≥ 25 kg/m^2) were divided into two groups; exercise group (n = 15) and control group (n = 15). R–R interval was recorded during 15-min at rest in the supine position. Heart rate variability (HRV) was analyzed by linear (rMSSD, SDNN, LF, HF, LFnu, HFnu, and LF/HF) and nonlinear methods (Shannon entropy, SE; symbolic analyses, 0 V%, 1 V%, 2LV%, and 2UV%) at baseline and after 16 weeks. The multivariate analysis of covariance was used to analyze the effects of exercise on HRV indexes, adjusted for changes in BMI, fasting insulin, and testosterone level.
Results: The exercise group increased parasympathetic modulation (rMSSD, HF, HFnu, 2UV%; ($p < 0.05$)) and decreased sympathetic modulation (LF, LFnu, 0 V%; ($p < 0.05$)) independently of changes in BMI, fasting insulin, and testosterone level. Moreover, the exercise group decreased resting HR and systolic blood pressure ($p < 0.05$). All parameters remained unchanged in the control group.
Conclusions: Aerobic exercise increased vagal modulation and decreased sympathetic modulation in women with PCOS. This finding reinforces the recommendations for exercise during the clinical management of these patients.

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age [1,2]. The main features of PCOS include chronic anovulation, hyperandrogenism and altered ovarian morphology [3]. Additionally, women with PCOS have an increased prevalence of cardiometabolic risk factors, such as insulin resistance [3], type 2 diabetes [4], visceral obesity [5], metabolic syndrome [6], hypertension [7], and dyslipidemia [8]. These cardiometabolic risk factors and diseases are associated with alterations in the autonomic nervous system [9–12]. A recent review suggested that chronic sympathetic overactivity may be implicated in PCOS pathogenesis [13]. In fact, some studies reported that women with PCOS have an impaired cardiac autonomic modulation when compared to healthy ovulatory women [13–15].

Heart rate variability (HRV) (i.e., the spontaneous beat-to-beat variations of the HR) is a noninvasive, reproducible, and easy to obtain measurement of cardiac autonomic nervous system function [16]. Reduced HRV indicates cardiac autonomic nervous system dysfunction and, in turn, a higher risk for cardiovascular disease [17]. Recently, our group showed that women with PCOS have lower HRV, suggesting an impaired cardiac autonomic modulation (i.e., higher sympathetic and lower parasympathetic autonomic modulations) [18].

Currently, physical exercise and healthy diet are recommended as the first-line therapy for women with PCOS, especially for those that are overweight or obese [1,19]. Previous clinical trials have reported that aerobic exercise has several benefits on cardiometabolic risk factors

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in women with PCOS, including improvements in cardiorespiratory fitness, blood pressure, dyslipidemia, insulin resistance, inflammatory pattern, and visceral obesity [2,20,21].

Additionally, two previous studies reported that aerobic exercise may improve cardiac autonomic system function in women with PCOS. Giallauria et al. [22] showed better HR recovery after maximal cardiopulmonary exercise test and Stener-Victorin [23] observed reduced muscle sympathetic nerve modulation (MSNA) after aerobic exercise interventions. Despite the attenuation of sympathetic autonomic activity in the aforementioned studies, Giallauria et al. [22] and Stener-Victorin [23] found that the patients decreased body mass index (BMI), which may also play a role on sympathetic autonomic modulation [24,25]. Therefore, it is not clear whether aerobic exercise improves cardiac autonomic modulation in women with PCOS, since several potential confounders (BMI, fasting insulin, and testosterone level) may influence this parameter. Moreover, to the best of our knowledge, no previous study has investigated the effects of aerobic exercise on HRV in women with PCOS.

Thus, this study aims to investigate the effects of a structured aerobic exercise intervention on cardiac autonomic modulation through HRV analysis in women with PCOS. It is hypothesized that aerobic exercise increases vagal autonomic modulation and decreases sympathetic autonomic modulation in women with PCOS, independently of changes in BMI, fasting insulin, and testosterone level.

2. Methods

2.1. Subjects

Overweight and obese sedentary women with PCOS, aged from 18 to 34 years, were eligible for this open randomized clinical trial. Subjects were allocated to the exercise group (n = 15) and control group (n = 15) and clinical, anthropometric, cardiopulmonary measures, and blood samples were taken from all patients. The diagnosis of PCOS was made according to the Rotterdam ESHRE-ASRM-sponsored PCOS criteria [26] by two independent observers. Patients with type 2 diabetes, non-classical congenital adrenal hyperplasia, thyroid dysfunction, and hyperprolactinemia were excluded. Other exclusion criteria were renal or hepatic dysfunction or use of medications known to affect reproductive, autonomic, cardiovascular and/or metabolic function within 90 days of study entry. This study was approved by the Institutional Ethics Committee (protocol 400/09), and all subjects gave their written informed consent.

2.2. Blood samples

Blood samples were collected after a 12-h overnight fast. Levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone, and insulin were determined by using commercially available diagnostic kits in the IMMULITE 2000® automated chemiluminescence immunoassay system following the manufacturer's recommendations (Diagnostic Products Corporation, Los Angeles, CA). Exclusion of nonclassic congenital adrenal hyperplasia was based on a basal morning 17-hydroxyprogesterone level less than 200 ng/dL.

2.3. Heart rate variability

2.3.1. Procedures

HRV data acquisition was carried out in the morning to prevent circadian changes. The room temperature was kept at 22 °C to 24 °C and relative air humidity was maintained between 40 and 60%. Subjects were acquainted with the experimental protocol and instructed to abstain from stimulants and alcoholic beverages during 24 h preceding the evaluation, as well as to ingest a light meal at least 2 h prior to measurement. Subjects were interviewed and examined prior to the beginning of the test to confirm their continued good health and to verify whether they had a normal night's sleep. After 15 min at rest in the supine position, blood pressure (BP) and HR were measured to determine whether the basal conditions of the subjects were adequate for the HRV assessment. All subjects presented adequate values of BP and HR before HRV data acquisition.

2.3.2. Data acquisition

To obtain the HR data, the subjects were monitored in the supine position during 15 min using a Polar S810i HR monitor (Polar Electro®, Finland), a reliable and practical device for monitoring beat-to-beat HR for HRV analysis. This device captures R–R intervals (RRi) by means of electrodes attached to an elastic band placed around the thorax. Electronic signals are continuously transmitted and stored in a receiver via an electromagnetic field for later analysis and calculation of HRV values [27]. The data obtained by the advice were transferred to the computer by means of an interface with an infrared device for signal emission.

2.3.3. Analysis

Stationary frames of 300 RRi values were selected, according to Magagnin et al. [28]. The same frames were analyzed using both linear (time and frequency domain methods) and nonlinear techniques (Shannon entropy, conditional entropy and symbolic analysis).

HRV was assessed in both time and frequency domains using a specific MatLab® software program (The Math Works®, USA), which calculates HRV values based on the RRi values. In the time domain we computed the RRi mean, the RRi standard deviation of all RR intervals (SDNN) and the square root of the mean of the sum of the squares of difference between adjacent normal RR-i in the record divided by the number of the RR-i within a given time minus one (rMSSD). SDNN reflected the overall magnitude of the HRV, whereas rMSSD was considered to be an index of parasympathetic modulations of HR [16].

For the frequency domain, the powers in the low (LF: 0.04 to 0.15 Hz) and high (HF: 0.15 to 0.4 Hz) frequencies were computed. The power spectrum was calculated via fast Fourier transformation over the RRi frame after subtraction of a linear trend. Spectral indexes were expressed in absolute units (ms^2) and normalized units (HFnu and LFnu). The power in the LF band is modulated by both the sympathetic and the parasympathetic branches of the autonomic nervous system and the power in the HF band is correlated with vagal modulation [16].

For symbolic analysis, the RRi values were distributed into six levels, where each RRi was coded with a symbol (from 0 to 5). Next, patterns were constructed from the sequence of three symbols and grouped into four families classified as: a) patterns without variation (0 V); b) patterns with one variation (1 V); c) patterns with two similar variations (2LV); and d) patterns with different variations (2UV) [29]. Previous studies indicated that the distribution of the above-mentioned patterns varies with the state of the autonomic nervous system [30–33]. The percentage occurrences of 0 V and 2UV families were computed and indicated as 0 V% and 2UV%. Studies with pharmacological blockade [31] and autonomic tests [34] indicated that 0 V% and 2UV% are indexes for assessing sympathetic and parasympathetic modulation, respectively. The Shannon entropy (SE) was also analyzed. Unlike traditional linear HRV parameters, the SE of a pattern lasting three symbols is a measure of the patterns' distribution complexity in the RRi series. SE is high if the distribution is flat (all patterns are identically distributed and the series carries the maximum amount of information). On the other hand, SE is low if there is a subset of more likely patterns, while others are missing or infrequent [29,33].

2.3.4. Cardiopulmonary exercise test

Subjects performed an incremental cardiopulmonary exercise test (CPET) before exercise intervention to measure cardiopulmonary fitness and for exercise prescription. The oxygen uptake (VO2), carbon dioxide output (VCO2), and minute ventilation (VE) were assessed using the VO2000 VO2 testing system (MedGraphics®, St. Paul, EUA) every 20 s while patients exercised on a treadmill (Inbrasport®, Porto Alegre, BRA). After a 1-minute warm-up period, a ramp protocol was started at 2 km/h without grade. The exercise protocol was gradually increased until exhaustion with increments fixed every minute at 0.5 km/h and 1% of grade. This ramp protocol was based on previous studies that assessed the cardiopulmonary fitness of overweight and obese women with PCOS using a treadmill [2,35]. During every minute of CPET and during three minutes after its end, HR was recorded. The 12-lead electrocardiogram was used for continuous monitoring of individuals during the test. Maximal oxygen consumption (VO2max) was determined by the presence of at least one of the following criteria: i) presence of respiratory exchange ratio (VCO2/VO2) > 1.1; ii) occurrence of plateau in oxygen uptake; iii) physical exhaustion [36,37].

2.3.5. Aerobic exercise intervention

While the control group continued their usual physical activity pattern, the intervention group carried out structured exercise bouts (walking and/or jogging) three times per week during 16 weeks. The exercise group performed 40 min of walking and/or jogging during each workout, which was preceded by five minutes of warm-up and followed by

Table 1
Characteristics of the sample.

	Control group (n = 15)	Exercise group (n = 15)	p[a]
BMI (kg/m^2)	32.3 ± 5.8	32.1 ± 4.0	0.91
SBP (mmHg)	113.4 ± 9.1	119.1 ± 7.9	0.08
DBP (mmHg)	73.4 ± 8.5	78.6 ± 7.4	0.08
Resting HR (bpm)	77.2 ± 11.3	80.5 ± 8.6	0.37
Peak HR (bpm)	184.9 ± 14.1	186.2 ± 8.1	0.61
VO_2max ($mL \cdot kg^{-1} \cdot min^{-1}$)	27.1 ± 1.5	27.6 ± 0.8	0.81
Insulin (lU/mL)	12.9 ± 2.9	15.4 ± 6.6	0.73
Total testosterone (ng/dL)	103.5 ± 8.7	120.1 ± 15.3	0.35
DHEAS (μg/dL)	186.1 ± 119.6	207.6 ± 134.7	0.44
FSH (mUI/mL)	3.6 ± 1.7	3.2 ± 1.9	0.47
LH (mUI/mL)	5.6 ± 5.0	4.3 ± 3.4	0.83

Note: BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; VO_2max = maximal oxygen uptake; FSH = follicle-stimulating hormone; LH = luteinizing hormone; DHEA = dehydroepiandrosterone sulfate.

[a] Independent-samples t-test.