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Original article

Patients with metabolic syndrome present decreased cardiorespiratory fitness facing maximum progressive exercise

Pacientes com síndrome metabólica apresentam diminuição da aptidão cardiorrespiratória frente ao exercício progressivo máximo

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ABSTRACT

Background: Metabolic Syndrome represents a set of predisposing factors for the development of cardiovascular diseases and other pathophysiological repercussions such as decreased aerobic capacity, an important marker of mortality. Due to limitations in the measurement of VO_{2max}, studies on the behavior of ventilatory parameters in submaximal phases of exercise are necessary so that it can be reproduced the patient's general performance during maximum physical effort. **Objective:** Compare cardiorespiratory fitness between women with MetS and sedentary eutrophic women. **Methods:** 277 female individuals (42.1 ± 5.5 years) were evaluated, divided into two groups, Group 1 – Metabolic Syndrome (MetS =210) and Group 2 – Heath Control (HC = 67), all patients underwent the ergospirometric test, which consists of performing a graduated exercise with direct analysis of respiratory gases. The data were expressed as mean and standard deviation and the inferential analysis performed with the Test T student. For multivariate correlations, the linear regression model stepwise. For all tests, the level of significance adopted was 5%. **Results:** MetS Group showed loss when compared to the HC Group in weight, BMI and risk factors for MetS, $P<0.05$. In the Cardiopulmonary exercise test, had lower values of VO_{2peak} (21.2±4.6; and 27.5±9.3 ml/kg/min, respectively, Interaction; $P<0.05$) and a lower value for VO_2 at the anaerobic threshold (14.3±7.1; and 12.1±4.0; $p<0.05$), corretating directly with the BMI (R=-0.48; P=0.001) and CA (R=-0.46; P=0.001). **Conclusion:** Patientes with MetS have decreased cardiorespiratory efficiency compared to maximum progressive exercise.

Keywords: metabolic syndrome; cardiorespiratory efficiency; sedentary women.

RESUMO

Fundamento: A síndrome metabólica representa um conjunto de fatores predisponentes para desenvolvimento de doenças cardiovasculares e outras repercussões fisiopatológicas como diminuição da capacidade aeróbia, importante marcador de mortalidade. Devido a limitações na mensuração do VO_{2max}, estudos sobre o comportamento dos parâmetros ventilatórios em fases submáximas do exercício se fazem necessários para que possa reproduzir o desempenho geral do paciente durante esforço físico máximo. **Objetivo:** Comparar a capacidade cardiorrespiratória entre mulheres com SMet e mulheres eutróficas sedentárias. **Métodos:** Foram avaliados 277 indivíduos (42,1 ± 5.5 anos) do sexo feminino, divididos em dois grupos, Grupo 1 – Síndrome Metabólica (SMet= 210) e Grupo 2 – Controle Saudável (CS= 67), todos os pacientes realizaram o teste ergo-espirométrico, que consiste na execução de exercício graduado com análise direta dos gases respiratórios. Os dados foram expressos em média e desvio-padrão e a análise inferencial realizada com o Teste T student. Para as correlações multivariadas, foi utilizado o modelo de regressão linear de stepwise. Para os testes, o nível de significância adotado foi de 5%. **Resultados:** O Grupo com SMet apresentou prejuízo comparado ao Grupo CS no peso, IMC e nos fatores de risco da SMet, P<0,05. No TECP, apresentou menores valores de VO_{2pico}, (21,2±4,6; e 27,5±9,3 ml/kg/min, respectivamente, p<0,05) e menor valor para VO_2LA (14,3±7,1; e 12,1±4,0; Interação; P<0,05), correlacionando-se diretamente com as IMC (R=-0,48; P=0,001) e CA (r=-0,46; P=0,001). **Conclusão:** Pacientes com SMet apresentam diminuição da eficiência cardiorrespiratória frente ao exercício progressivo máximo.

Palavras-chave: síndrome metabólica; eficiência cardiorrespiratória; mulheres sedentárias.

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Introduction

The Metabolic Syndrome (MetS) is considered as a complex metabolic disorder for the development of cardiovascular diseases [1,2]. Regardless of the entity or group that defines MetS, the components/risk factors are always the same, associated with the development of cormobidities with pathophysiological repercussions [1].

Studies show that in addition to metabolic changes, MetS also had a negative impact on cardiorespiratory adjustments, such as, for example, decreased aerobic capacity, an important marker of mortality [3].

The maximum oxygen consumption (VO_{2max}) is directly related to cardiac output, arterial oxygen content and alveolar-capillary gas exchange, a gold standard technique for assessing the relationship of cardiorespiratory and musculoskeletal systems [4,5].

Patients with MetS, according to the data in the literature, present a decrease in aerobic competence, being one of the justifications for such alteration, the decrease in the mandatory adequate muscle strength [6-8].

According to the study by Yokota *et al.* [9], it was characterized that there is a relationship between decreased aerobic capacity and abnormalities in skeletal muscle metabolism. The decrease in VO_2 in relation to exercise is very present in .com MetS, however, the literature must also include this decrease, which can be proven by the influence of patient and professional motivation [10-12].

Due to these limitations in the measurement of VO_2, ventilatory parameters are being used by researchers in submaximal phases of the exercise so that they can reproduce the patient's general performance [13-15].

To date, there are few investigations and studies on the behavior of cardiorespiratory parameters in relation to submaximal effort in patients with MetS, not scientifically evidencing whether this set of risk factors that classify MetS, impairs the cardiorespiratory efficiency of individuals during the performance physical exercise.

The aim of the present study was to compare cardiorespiratory fitness between women with MetS and sedentary eutrophic women during progressive physical exercise and their relationship with the risk factors involved.

Methods

277 female individuals were evaluated, considering the high frequency of this gender in the search for our rehabilitation service (42.1 ± 5.5 years), separated into MetS Group (MetS) (n = 210) and Healthy Control Group (HC) (n = 67), followed by the PROCárdio LTDA Rehabilitation Clinic and the UNIFESP Physical and Experimental Training Laboratory. Initially, they were screened and received information about the project so that they could be invited to participate in the study. Then, they unde-

rwent clinical and laboratory evaluation to determine their health condition. Those who did not present the factors that characterize the MetS were invited to participate in the study as a healthy control group with the objective of comparing parameters.

This study was sent to the Research Ethics Committee of the Federal University of São Paulo (UNIFESP), Santos, SP and approved under number 3,036,417.

All volunteers signed the Free and Informed Consent Form, authorizing their participation in the study.

We included sedentary women with Metabolic Syndrome according to the diagnostic criteria of the National Cholesterol Education Program, Adult Treatment Panel III (NCEP III) and sedentary women, between 18 and 50 years old, without metabolic syndrome, for the control group. We excluded women enrolled in physical activity or training programs, or dietary treatment, smokers, with a history of alcohol consumption, cardiovascular disease or any other pathology or physical limitation that made it impossible to perform the cardiopulmonary stress test (TECP) and women who did not participate in any of the stages of this project.

Procedures

Individuals who agreed to participate in the study underwent medical evaluation and underwent all initial examinations. Three blood pressure measurements were taken before the cardiopulmonary test.

The body composition was evaluated, and height (m) and body weight (kg) were measured on a Filizola scale. The body mass index (BMI) was determined by calculating the weight divided by the height squared [BMI = weight (kg)/height^2 (m)].

The evaluation of abdominal circumference was measured at the midpoint between the last rib and the iliac crest because many obese patients had their navel directed downwards due to the excessive curvature of the abdominal wall. Three consecutive measurements were taken, always by the same appraiser, and the value that most repeated was recorded.

Laboratory tests were performed in the morning, with the individual fasting for 12 hours. An antecubital vein was catheterized to collect venous blood for laboratory evaluations: complete blood count (it was performed by automated electronic counting and a morphological study in smears stained with panoptic dyes), blood glucose (it was carried out by the enzymatic, automated method - Roche), total cholesterol and fractions , triglycerides and HDL-cholesterol (made by the colorimetric enzymatic method) and the calculation of LDL-cholesterol (Low Density Lipoproteins or low density Lipoproteins) according to the Lipid Research Clinics Program. Following the guidance of the IV Brazilian Guidelines on Dyslipidemias of the Brazilian Society of Cardiology (2007), direct measurement of LDL-cholesterol was made (and not calculated by the equation) whenever the results of triglycerides are greater than or equal to 400 mg/dL.

The cardiopulmonary stress test was performed on the Cortex equipment of Meta Analysis 3s. The values were collected with each breath and converted into an average of 30 seconds. The parameters analyzed were: oxygen consumption (VO_2 L min^{-1} or mL kg^{-1} min^{-1} STPD); carbon dioxide production (VCO_2 mL/min^{-1}STPD); pulmonary ventilation (VE L/min BTPS); tidal volume (VCL/min BTPS); respiratory rate (RR rpm); estimated functional dead space (VD/VT); respiratory exchange ratio (RER); ventilatory equivalents of oxygen (VE/VO_2) and carbon dioxide (VE/VCO_2) and final expiratory pressures of oxygen and carbon dioxide ($PetO_2$ and $PetCO_2$ mmHg). Before each assessment, the metabolic analyzer was calibrated using gases with carbon dioxide and oxygen balanced with nitrogen, and the flow meter was calibrated with a 3-liter syringe. The test was performed on a treadmill (Micromed), using the ramp protocol with constant increase in speed and/or inclination every minute until exhaustion, with load increments calculated by the maximum load predicted until exhaustion.

For the analysis of the heart rate behavior during the exam, an electrocardiogram with twelve standard leads was used (D1, D2, D3, aVR, aVL, aVF, V1, V2, V3, V4, V5, V6 - *ECG Marquette Medical Systems, InC.CardioSoft, Wisconsin*, USA) and to evaluate blood pressure the auscultatory method was used. The test was considered maximum when the patient reached respiratory exchange ratio values ≥ 1.10 associated with the exhaustion reported by the patient himself. Physical capacity was determined by peak oxygen consumption (VO_{2peak}) at the end of the exam. At rest, during and after the cardiorespiratory functional assessment, electrocardiographic recording was performed, in addition to periodic blood pressure measurements by an auxiliary. Periodically, the patient was asked about his symptoms on exertion, such as tiredness, heaviness in the legs and dizziness.

The ventilatory anaerobic threshold (LAV) was measured by the V-slope method (Beaver *et al.* 1986), which consists of the loss of linearity between the production of VCO_2 and the consumption of VO_2.

At the end, the group with MetS was compared with the healthy control group to analyze the results.

Diagnosis of MetS

The MetS was diagnosed according to the National Cholesterol Education Program - Adult Treatment Panel III (NCEP ATPIII) where the individual is characterized as having the syndrome in the presence of three of the five cardiovascular risk factors, as it follows:

- Abdominal circumference ≥ 102 cm for men and ≥ 88 cm for women;
- Triglycerides ≥ 150 mg/dL;
- HDL-cholesterol < 40 mg/dL for men and < 50 mg/dL for women;
- Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg;
- Fasting blood glucose ≥ 110 mg/dL.

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Statistical analysis

The sample size was calculated using the *OpenEpi99* statistical program. A power of 80% was proposed, with a 95% confidence interval (two-tailed) to admit the probability of type 1 error in only 5%. Thus, it was found that at least 23 patients per group should be recruited.

The variables analyzed in this study were subjected to the Kolmogorov-Smirnov test to verify whether they had a normal distribution. The variables that did not show this distribution were analyzed after logarithmic transformation.

The data on the anthropometric, metabolic and baseline cardiorespiratory characteristics of both groups were submitted to Student's t-test statistical analysis for non-repeated measures.

For multivariate correlations, the stepwise linear regression model was used. For all tests, the level of significance adopted was 5%.

Results

Baseline evaluation and characteristics according to MetS

In Tables I, II and III we observed baseline data regarding anthropometric, metabolic, and cardiorespiratory characteristics of the studied groups (MetS Group and HC Group).

Significant differences were observed between the groups studied in anthropometric, metabolic, and cardiorespiratory parameters.

Anthropometric parameters

The evaluation of the anthropometric parameters, according to the comparison of the groups, gave the patients significant differences regarding the BMI, the body composition (abdominal waist, lean mass, fat mass) as expected for the group with Met (Table I).

We did not observe differences in relation to age and height in the groups studied (Table I).

Table I - Clinical characteristics of the 277 individuals studied according to the separation of the metabolic syndrome (MetS) and healthy control groups (HC)

Parameters	MetS (n = 210)	HC (n = 67)	p
Age (years)	41.0 ± 5.3	42.0 ± 6.0	0.50
Height (m)	1.60 ± 0.2	1.63 ± 0.7	0.59
Weight (kg)	86.3 ± 10.5	58.5 ± 4.8	$p < 0.05$
BMI (kg/m²)	33.5 ± 1.8	22.9 ± 2.1	$p < 0.05$
AC (cm)	105.8 ± 6.7	76.9 ± 4.5	$p < 0.05$

Values are expressed as mean ± SD; No statistical significance $p > 0.05$. Statistical significance $p < 0.05$; AC = Abdominal circumference; HC = Healthy Control; BMI = Body Mass Index; Met = Metabolic Syndrome

Metabolic parameters

Following the same pattern of organization and comparison of the groups, the influence of MetS on metabolic parameters was evaluated. In Table II, the MetS group conferred significant differences on the metabolic variables to the patients.

Table II - Laboratory characteristics of the 277 individuals studied according to the separation of the metabolic syndrome (MetS) and healthy control groups (HC)

Parâmetros	SMet (n = 210)	CS (n = 67)	P
Fasting glycemia (mg/dL)	134.6 ± 14.4	81.0 ± 12.5	$p < 0.05$
Cholesterol (mg/dL)	181.2 ± 44.4	152.7 ± 21.0	$p < 0.05$
TG (mg/dL)	196.6 ± 21.6	117.1 ± 66.4	$p < 0.05$
LDL-C (mg/dL)	120.5 ± 42.0	108.4 ± 27.7	0.02
HDL-C (mg/dL)	40.9 ± 12.2	50.3 ± 8.9	$p < 0.05$

Values are expressed as mean ± SD, Statistical Significance $p < 0.05$. HC =Healthy Control; HDL-c = High Density Lipoprotein Cholesterol; LDL-c = Low Density Lipoprotein Cholesterol; TG = triglycerides; Met = Metabolic Syndrome

Hemodynamic and cardiorespiratory parameters

About baseline cardiorespiratory data, significant differences were observed in systolic blood pressure (SBP) and in maximum functional capacity (VO_{2peak}) between the MetS groups and the healthy control group (Table III).

Table III - Cardiorespiratory characteristics of the 277 individuals studied according to the separation of the metabolic syndrome (MetS) and healthy control (HC) groups)

Parameters	MetS (n = 210)	HC (n = 67)	p
SBP (mmHg)	144 ± 13.2	128 ± 13.0	$p < 0.05$
DBP (mmHg)	80 ± 13.7	79 ± 7.6	0.77
HR (bpm)	72 ± 15.2	72 ± 8.4	0.64
VO_{2peak} (mL/kg/min)	21.2 ± 4.6	27.5 ± 9.3	$p < 0.05$

Values are expressed as mean ± SD; without statistical significance $p > 0.05$; Statistical significance $p < 0.05$; HR = Heart Rate; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure

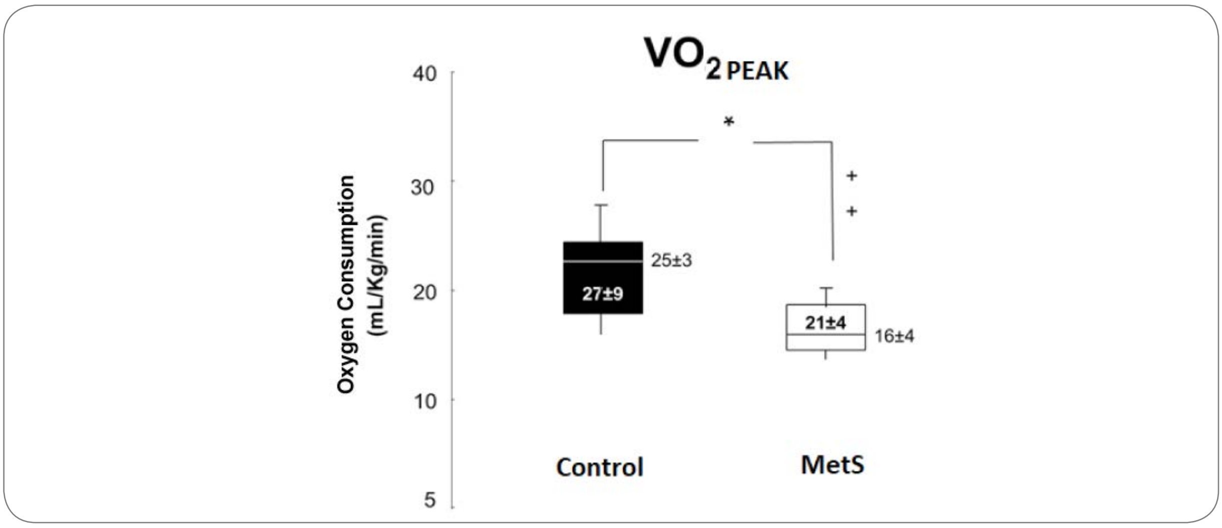

Figure 1 – Comparison of VO_{2peak} values between the metabolic syndrome (MetS) and control groups. Values are expressed as mean ± standard deviation; *$p < 0.05$. mL/kg/min vs control group

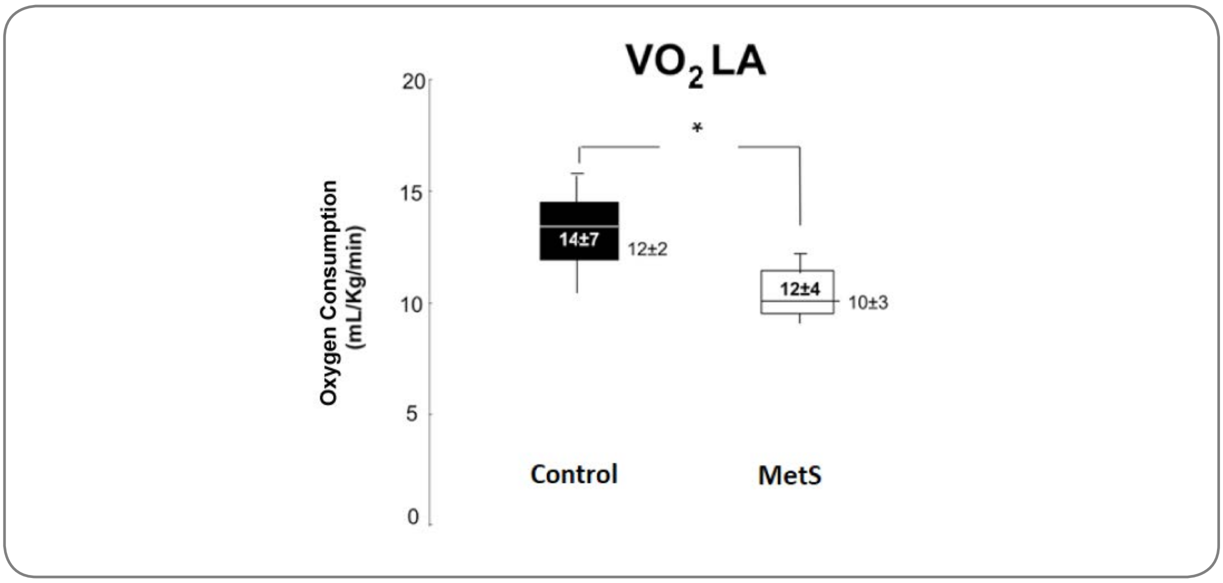

Figure 2 – Comparison of VO_2LA values between the metabolic syndrome (MetS) and control groups. Values are expressed as mean ± standard deviation, *$p < 0.05$. mL/kg/min vs control group

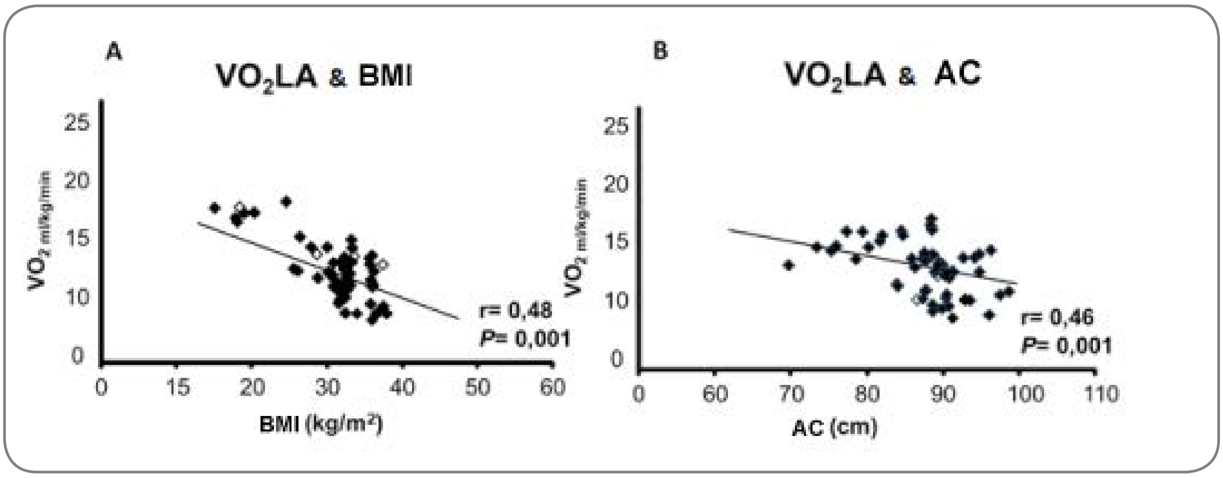

Figure 3 – In the analysis of VO_2LA multivariate correlation between risk factors for MetS, as expected there was an inverse and significant correlation of Body Mass Index (BMI) (Figure 3A) and the Abdominal Circumference (AC) (Figure 3B)

Discussion

The present study expanded the current knowledge about the factors that influence the harmful effects of MetS on the behavior of the cardiorespiratory system in the face of a situation of physical stress in women with MetS during progressive physical exercise. The hypothesis suggested was that the cluster of abnormalities and pathologies that make up patients with MetS, could negatively modulate cardiorespiratory adjustments during a situation of physical stress. It was found in this investigation that the relative oxygen consumption at peak effort (VO_{2peak}) and aerobic efficiency (VO_2LA) were reduced in patients with MetS when compared with eutrophic individuals and the direct influence of the accumulation of adipose tissue on the physical capacity of this population.

Corroborating, Miyatake N *et al.* [8] studying the influence of MS in the Japanese population noticed that this population showed a decrease in VO_{2peak} and VO_2LA, when compared to eutrophic individuals [8]. The authors evidenced the influence of the increase in fat mass and decrease in the percentage of lean mass, reflecting in the lower physical capacity of individuals with MetS [8].

Yokota *et al.* [9] observed that the metabolic changes present in patients with MetS, mainly to insulin resistance, are strongly associated with changes in skeletal muscle metabolism, the study demonstrated a decrease in mitochondrial metabolism for oxidative phosphorylation and ATP production impairing the aerobic capacity of individuals with MetS.

In this sense, researchers have described that mortality increases in the period of 14 years as there is a decrease in VO_{2peak}, both in healthy individuals and in cardiac patients [3]. However, the literature has shown that the measurement of VO_{2peak} may have a bias as it is highly influenced by the motivation of the patient and the investigator [17,18]. Due to these limitations in the measurement of VO_{2peak}, several researchers have used submaximal exercise parameters to reproduce the individual's overall performance [19-21].

In addition to the use of VO_{2peak} as an important predictor of mortality, assessments of oxygen consumption in submaximal loads have already been described as a marker of poor prognosis, such as VO_2 at the anaerobic threshold (VO_2LA) [19] and the oxygen consumption ratio and workload ($\Delta VO_2/\Delta W$) [8], which indicate the individual's metabolic efficiency. Studies have observed that patients who reach VO_2LA $\leq$ 11 ml/kg/min are at higher cardiovascular risk [22].

Likewise, we demonstrated that the aerobic capacity (VO_{2peak}), and the submaximal index (VO_2LA) were reduced in patients with MetS. Thus, we show that, in fact, the changes in the MetS are the main factors for the decrease in the TECP indexes.

Finally, this investigation showed a strong correlation to the direct influence of BMI and AC on the oxygen consumption evaluated in submaximal loads (VO_2LA) with VO_{2peak}. The data from this investigation demonstrate an inverse relationship between weight gain and cardiopulmonary capacity efficiency during the ergospirometric test. Therefore, the increase in body weight interfered negatively in the response of oxygen consumption to submaximal exercise in individuals with MetS.

Excessive concentration of body fat has a profound influence on aerobic fitness, showing that adiposity reduces maximum aerobic power in relation to weight (VO_2max/kg) [23-24] and that functional fitness during exercise is negatively related to the degree of obesity [24-25].

There is a negative relationship between the increase in abdominal waist and VO_2LA during submaximal physical exercise. These data are consistent with previous findings that demonstrated that changes in ventilatory function were attributed to extrinsic mechanical compression of adiposity, which can cause a reduction in chest wall compliance and, consequently, increase in respiratory work, thus, determining factors for the decrease in aerobic capacity [26-28]. There was no direct relationship between the other risk factors for MetS and the ventilatory responses during the examination of ergospirometry. Results of previous studies [8] support the notion that

VO_2 at peak effort, as well as hemodynamic responses to exercise, is directly influenced by obesity during cardiopulmonary assessment [8]. Thus, it can be observed that obesity has a direct interference with the cardiorespiratory efficiency of the patient with MetS, leading to a greater risk of cardiovascular complications in the future.

It is worth mentioning that a new health perspective arises due to the current situation, a pandemic caused by Sars-Cov2 where the population most vulnerable to gravity and mortality is precisely the one studied in this investigation. The knowledge provided by this research can help to better understand the relationship between the risk factors for cardiovascular diseases and the main system affected by Sars-Cov2, the respiratory system.

In the same context, individuals with MetS, due to changes in cardiorespiratory efficiency mainly due to pulmonary limitations, such as abnormalities in the ventilation-perfusion ratio, become more predisposed to depend on mechanical ventilation and other intensive care if they contract Covid-19 [29].

Conclusion

Based on the results, we can conclude that patients with MetS presented a decrease in Maximum Oxygen Consumption compared to the maximum progressive exercise and that among the various risk factors for MetS, BMI and AC have a direct relationship in physical capacity in this population group.

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Conflict of interest
No potential conflict of interest.

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Academic affiliation
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Authors' contribution
Conception and design of the research: Teixeira HC, Rocco DDFM, Silva AG. **Data gathering:** Teixeira HC, Corrêa MA, Carvalho JC, Rocco DDFM, Silva AG. **Analysis and interpretation of data:** Medeiros A, Rocco DDFM, Silva AG. **Statistical analysis:** Silva, AG. **Fund Raising:** not applicable. **Writing of the manuscript:** Teixeira HC, Medeiros A, Rocco DDFM, Silva AG. **Critical review of the manuscript for important intellectual content:** Gardenghi G.

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