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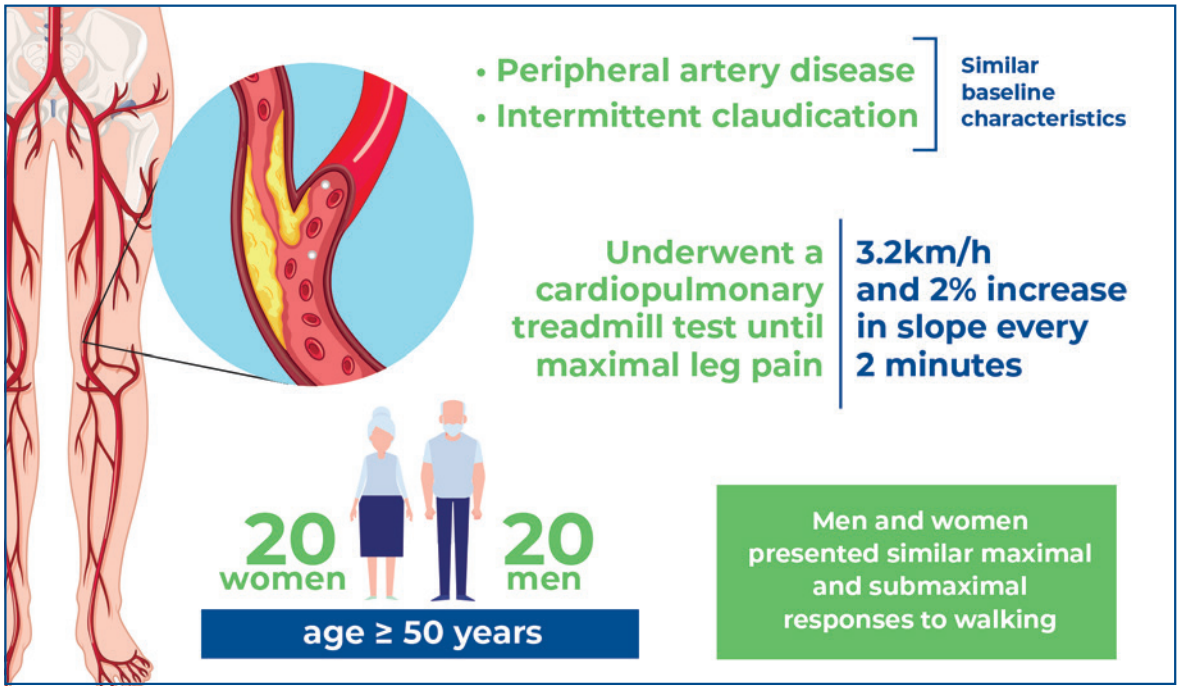

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In Brief

Miyasato et al. show that peak oxygen consumption, walking economy, anaerobic threshold, and cardiovascular responses (heart rate, blood pressure, and rate pressure product) during walking were similar between men and women with peripheral artery disease and intermittent claudication.

Highlights

- There were no differences in the physiological responses to walking between men and women with intermittent claudication.
- Sex per se is not a factor that demands changes in walking prescription for patients with intermittent claudication.

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ORIGINAL ARTICLE

Physiological responses during walking in men and women with intermittent claudication

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ABSTRACT

Objective: Peak oxygen consumption (VO_2peak), anaerobic threshold, walking economy, and cardiovascular responses during walking are used to guide and monitor walking training in patients with peripheral artery disease and intermittent claudication. Women with peripheral artery disease and intermittent claudication present greater impairments than men, and evaluating training markers according to sex for decisions regarding walking prescription in this population is important. This study aimed to compare VO_2peak, walking economy, anaerobic threshold, and cardiovascular responses during walking in men and women with peripheral artery disease and intermittent claudication. **Methods:** Forty patients (20 men and 20 women with similar baseline characteristics) underwent a cardiopulmonary treadmill test (3.2km/h and 2% increase in slope every 2 minutes until maximal leg pain). The VO_2 and rate-pressure product were assessed. Data from men and women were compared using *t*-tests. **Results:** There were no significant differences between men and women (VO_2peak: 15.0±4.8 *versus* 13.9±2.9mL·kg^{-1}·min^{-1}, p=0.38; walking economy: 9.6±2.7 *versus* 8.4±1.6mL·kg^{-1}·min^{-1}, p=0.09; anaerobic threshold: 10.5±3.2 *versus* 10.5±2.2mL·kg^{-1}·min^{-1}, p=0.98; rate pressure product at 1st stage: 13,465±2,910 *versus* 14,445±4,379bpm·mmHg, p=0.41; and rate pressure product at anaerobic threshold:13,673±3,100 *versus* 16,390±5,870bpm·mmHg, p=0.08 and rate pressure product at peak exercise: 21,253±6,141 *versus* 21,923±7,414bpm·mmHg, p=0.76, respectively). **Conclusion:** Men and women with peripheral artery disease and similar baseline characteristics presented similar responses to walking, suggesting that decisions regarding walking prescription and monitoring can be made regardless of sex in this specific population.

Keywords: Peripheral arterial disease; Exercise; Oxygen consumption; Heart rate; Blood pressure

INTRODUCTION

Peripheral artery disease (PAD) mainly results from the deposition of atherosclerotic plaques inside the peripheral arteries of the lower limbs, obstructing the arterial lumen and reducing blood flow.[1,2] Muscular ischemia elicited by PAD may trigger symptoms of pain, burning, cramping, and fatigue in the leg during walking that are released with rest, called intermittent claudication (IC).[1,2]

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Walking training is recommended as the first-line treatment for both men and women with PAD and IC.[1,2] Physiological responses during walking are markers used to guide walking training and monitor its efficacy. The VO_2 peak reflects functional capacity, whereas the anaerobic threshold (AnT), defined as the intensity of the transition from mainly aerobic to anaerobic metabolism, can be used to establish individualized aerobic training intensity[3,4] and is related to muscular capillary density in patients with PAD.[5] Walking economy (*i.e.*, oxygen consumption during walking at a fixed intensity) is a key factor for sustaining ambulatory activities in PAD[6] that improves with walking training[7-9] and is used to verify training efficacy. Heart rate (HR) and systolic blood pressure (SBP) responses during walking reflect the cardiovascular load (*i.e.*, rate-pressure product [RPP] imposed by the exercise)[4] and may express the risk of acute cardiovascular events during training.[3,4]

Patients with PAD and IC have reduced walking capacity and peak oxygen consumption (VO_2peak) than those without the disease.[5,10] Additionally, they present reduced walking economy (*i.e.,* higher VO_2 during walking at absolute velocity)[6] and achieve AnT at lower intensities than healthy individuals.[5] Moreover, progressive ischemia and pain during walking lead to higher increases in HR and SBP during progressive walking[11] and a progressive increase in these variables when walking at a fixed submaximal intensity.[12] Therefore, prescription and monitoring of walking training in this population should consider these limitations.

Much of the existing research on PAD has focused on entire populations, and sex-specific data are sparse.[13,14] Despite the similar prevalence of PAD and IC between men and women,[2,15] the effect of the disease seems to differ between sexes. Compared to men, women with PAD show a greater functional decline (*i.e.*, faster decline in walking velocity and distance achieved in the 6-min walking test), a higher rate of mobility loss due to poorer lower extremity functioning, worse surgical outcomes, and a higher risk of morbidity and mortality.[16,17] Additionally, women have a higher blood pressure and pulse wave reflection.[18] Because of these differences, the evaluation of PAD treatment according to sex is very important for daily decision-making.

Some studies have reported a lower walking capacity in women than in men with PAD and IC[19-21] while others have reported similar capacities.[22,23] In a previous study, we found no difference in walking capacity and peak increase of HR and SBP between the sexes during maximal walking in this population.[24] However, we did not evaluate physiological markers used to prescribe and monitor walking training. Knowledge regarding sex differences in these markers may help in daily decisions in rehabilitation programs, since individualized cardiopulmonary evaluations are many times not available for these patients.

OBJECTIVE

To compare the VO_2peak, walking economy, anaerobic threshold, and cardiovascular load during a maximal walking test in men and women with peripheral artery disease and intermittent claudication.

METHODS

Cardiovascular data related to maximal effort and post-exercise responses have already been published,[24] whereas the present study analyzed maximal metabolic data and cardiovascular and metabolic data at submaximal walking. Written informed consent was obtained from all patients prior to enrollment in the study.

Men and women with PAD and IC were recruited from the Intermittent Claudication Clinic of the *Hospital das Clínicas* of the *Universidade de São Paulo*. Patients were included if they met the following criteria: (i) age ≥50 years; ii) ankle brachial index (ABI) ≤0.9 in at least one of the lower limbs; iii) presence of IC; and iv) being at stage II of the Fountaine classification. Exclusion criteria included the following: i) SBP and/or diastolic blood pressure (DBP) greater than 160 and 105mmHg, respectively; (ii) inability to walk on a treadmill for at least 2 minutes at 3.2km/h; iii) presence of ischemia or complex arrhythmias during a maximal walking test; iv) interruption of a maximal walking test for reasons other than pain in the affected limb; v) reduction in ABI after a maximal walking test <10%; vi) musculoskeletal disorders that precludes exercise execution; vii) current participation in any regular exercise program; viii) taking beta-blockers, non-dihydropyridine calcium channel inhibitors, insulin or hormone therapy; and ix) being a diabetic with uncontrolled glycemia, diabetic complications, and/or clinical autonomic dysfunction. Compliance with the study criteria was verified through preliminary evaluations.

This study was part of a larger study approved by the ethics committee of the School of Physical Education and Sport at the *Universidade de São Paulo* (CAAE**:** 57194816.3.3001.0068; # 2.477.650).

Preliminary evaluations

All patients were evaluated by a physician for personal characteristics, health history, physical activity, medication, and clinical examination. The presence of IC was assessed using the San Diego Claudication Questionnaire,[25] and the disease stage was determined based on Fontaine's classification.[26] Body mass and height were measured (Welmy, 110, São Paulo, Brazil), and body mass index (BMI) was calculated. Blood pressure was measured in triplicate during two visits to the laboratory after 5 minutes of seated rest, using the auscultatory method and a mercury column sphygmomanometer (Unitec, São Paulo, Brazil).[27] For the ABI assessment, SBP was simultaneously measured in the arms and ankles with the patient in the supine position. Arm SBP was measured using a mercury sphygmomanometer (Unitec, São Paulo, Brazil), and ankle SBP was measured using Doppler (DV 6000; Martec, Ribeirão Preto, Brazil). The ABI of each side of the body was calculated by dividing the SBP of each ankle by the highest SBP between the arms.[28]

Experimental protocol

All patients underwent a cardiopulmonary walking test until maximal leg pain was experienced. They were instructed to have a light meal at least 2 hours before and to take their medications as prescribed. They were also instructed not to drink caffeine-containing beverages on the day of the test and not to exercise vigorously or drink alcoholic beverages in the previous 24 hours. Smokers were asked not to smoke in the morning before the sessions. Tests were conducted between 7 and 12 a.m. in a temperature-controlled laboratory (20-23°C).

The tests were preceded by a resting electrocardiogram in the supine position (ECG-Welch Allyn Inc., CardioPerfect, Skaneateles Falls, NY, USA) and a 3-minutes pre-exercise period of resting standing on the treadmill (Imbrasport ATL, Porto Alegre, Brazil). The exercise phase was conducted using a specific protocol for PAD (*i.e.*, fixed speed at 3.2km/h and 2% increment in grade every 2 minutes)[29] and followed by a passive 10-minutes recovery in the supine position. All tests were interrupted due to maximal leg pain. Heart rate was continuously monitored using an electrocardiogram, and auscultatory blood pressure (Unitec, São Paulo, Brazil) was measured at the end of the pre-exercise period and at every minute during the tests. Rate-pressure product was calculated as the product of HR and SBP. Inspired and expired gases were collected breath-by-breath using a metabolic card (Medical Graphics Corporation, Ultima, Welch Allyn Inc., Skaneateles Falls, NY, USA), and VO_2 was analyzed for 30 seconds.

The VO_2peak was assessed as the greatest value achieved during the effort. Walking economy was defined as VO_2 measured at the second minute of the first stage of the test (*i.e.*, 3.2km/h, 0% grade). The anaerobic threshold was identified by the nonlinear increase in the respiratory exchange ratio and ventilation, as well as the lower values of oxygen ventilatory equivalent and end-tidal oxygen partial pressure.[30] For that, two blinded experienced evaluators detected AnT, and disagreements were solved by a third evaluator. The VO_2 measured at the AnT was used for the analysis. Cardiovascular responses (HR, SBP, and RPP) during walking were evaluated at absolute (1st stage) and relative (AnT) submaximal intensities, as well as at peak effort.

Statistical analysis

The sample size was defined for the main variable of the larger study from which the present data were derived[24] and was set by convenience for this study. The normality of the data was checked using the Shapiro-Wilk test. As all variables presented a normal distribution, comparisons between the sexes for continuous variables were performed using *t*-tests, while comparisons between the sexes for categorical variables, expressed as frequency of occurrence, were performed using the χ^2 test. Statistical analyses were performed using SPSS 20.0 (IBM, New York, United States), and $p<0.05$ was considered as significant. Additionally, Cohen´s d effect sizes were calculated using a free online tool (https://www.psychometrica.de/effect_size.html) and were interpreted as small when $d<0.4$, intermediate when d was between 0.4 and 0.7, and large when $d>0.7$. Data are presented as means±standard deviations (SD).

RESULTS

Forty-eight patients signed the informed consent form, and eight were excluded (personal reasons = 4, no pain during walking = 3, and use of a pacemaker = 1). Therefore, 40 patients (20 men and 20 women) were included in this study. The patients presented with obesity (17.5 %), diabetes (27.5 %), hypertension (80%), and dyslipidaemia (92.5 %). They were receiving pharmacological treatment for these comorbidities as well as acetylsalicylic acid (82.5 %). Men and women had similar physical and functional characteristics (Table 1), as previously reported.[24]

The pre-exercise VO_2, HR, SBP, and RPP were similar between men and women (Table 2).

Considering the metabolic variables, VO_2 assessed at the first stage of the test (*i.e.*, 3.2km/h, 0% grade), at AnT, and at peak effort were similar between men and women (Table 2, Figure 1). Regarding cardiovascular variables, HR, SBP, and RPP assessed at the first stage of the test, at AnT, and at peak exercise were similar between men and women (Table 2, Figure 2).

Table 1. Characteristics of the men and women with peripheral artery disease and intermittent claudication

	Men (n=20)	Women (n=20)	p value
Age (years)	67.3±7.4	65.4±8.0	0.45
Body mass index (kg/m²)	25.6±3.0	28.2±6.8	0.12
Ankle brachial index	0.55±0.13	0.56±0.10	0.72
Functional capacity			
Claudication onset distance (m)	306±47	276±52	0.67
Maximal walking distance (m)	650±65	597±75	0.60
Medication			
Acetylsalicylic acid (%)	85	80	0.63
Statins (%)	95	90	0.55
Antihypertensives (%)	80	80	1.00
Oral hypoglycemic drugs (%)	30	25	0.72

Means±SD or frequencies of occurrence (%). Comparisons were made using *t*- or χ^2 tests.

Table 2. Oxygen consumption, heart rate, systolic blood pressure, and rate pressure product assessed before and during a cardiopulmonary walking test in men and women with perpheral artery disease and intermittent claudication

	Men (n=20)	Women (n=20)	p value	Cohen's d
Pre-exercise				
VO_2 (mL·kg^{-1}·min^{-1})	3.4±0.77	3.1±0.58	0.25	-0.44
HR (bpm)	74±15	68±11	0.23	-0.46
SBP (mmHg)	121±19	133±24	0.08	0.55
RPP (bpm·mmHg)	8,755±1,720	9,085±2,191	0.60	0.17
First Stage (3.2km/h, 0%)				
VO_2 (mL·kg^{-1}·min^{-1})	9.6±2.7	8.4±1.6	0.09	-0.54
HR (bpm)	97±12	97±17	0.92	-0.03
SBP (mmHg)	138±22	148±29	0.24	0.39
RPP (bpm·mmHg)	13,465±2,910	14,445±4,379	0.41	0.26
Anaerobic threshold				
VO_2 (mL·kg^{-1}·min^{-1})	10.5±3.2	10.5±2.2	0.98	-0.01
HR (bpm)	98±15	104±18	0.25	0.36
SBP (mmHg)	139±18	155±32	0.06	0.61
RPP (bpm·mmHg)	13,673±3,100	16,390±5,870	0.08	0.58
Peak effort				
VO_2 (mL·kg^{-1}·min^{-1})	15.0±4.8	13.9±2.9	0.38	-0.28
HR (bpm)	119±22	118±25	0.87	-0.04
SBP (mmHg)	176±28	182±32	0.54	0.20
RPP (bpm.mmHg)	21,253±6,141	21,923±7,414	0.76	0.10

Means±SD. Comparisons made by t-test, and effect size calculated by Cohen's d.
VO_2: oxygen consumption; HR: heart rate; SBP: systolic blood pressure; RPP: rate pressure product.

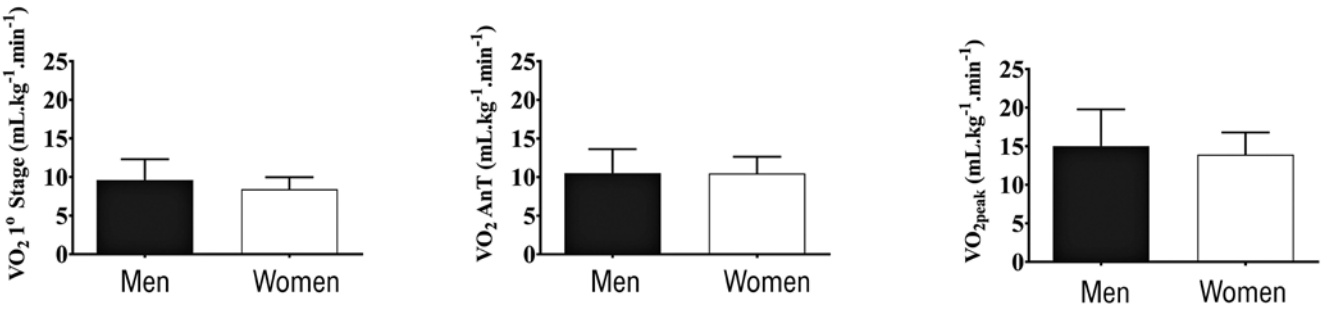
In general, comparisons between men and women for the main outcomes of the study (VO_2, HR, SBP, and RPP assessed at the first stage of the test, AnT, and peak effort) showed small effect sizes (d <0.4; Table 2).

DISCUSSION

The main findings of this study were that the VO_2peak, walking economy, AnT, HR, SBP, and RPP assessed during walking were similar between men and women with PAD and IC.

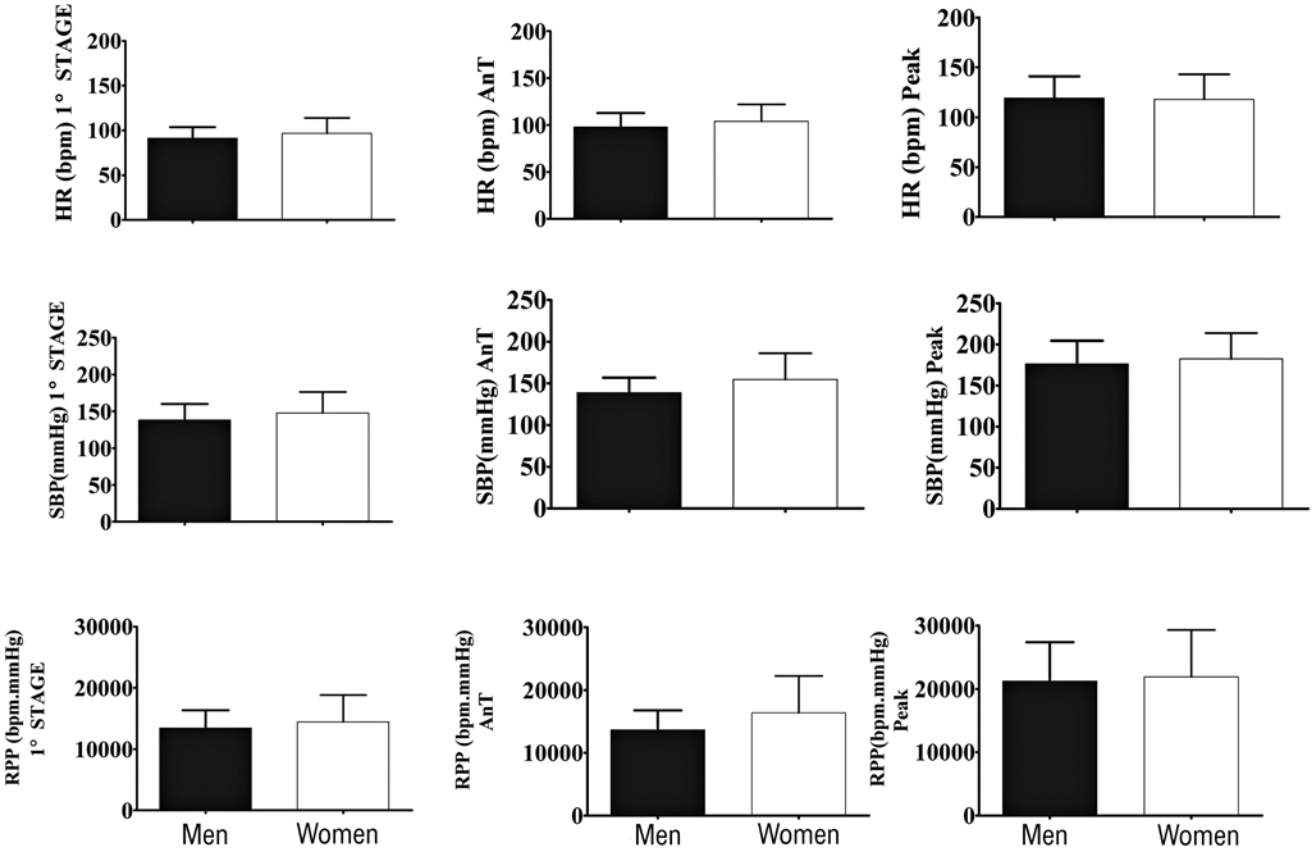
VO_2peak, a marker of aerobic power and fitness, is negatively associated with cardiovascular morbimortality in patients with PAD.[31] The present results showed no difference in the VO_2 peak between men and women, and this result is in accordance with that of studies carried out by Gommans et al.[22] and Dörenkamp et al.[23] However, studies by Gardner et al.[19] and Oka et al.[20] reported a lower VO_2peak in women than in men. The reasons for this discrepancy are not clear, but they cannot be attributed to the exercise protocol, as all these studies used the same protocol employed here. Therefore, a probable explanation may be sample characteristics. The present study employed rigorous participation criteria that guaranteed similar baseline characteristics between men and women in many possible interfering variables such as age, BMI, ABI, comorbidities, and medication use,[32] whereas previous studies mainly paired groups only by age and ABI. Additionally, the participation criteria in the present study resulted in a sample with better walking capacity than the patients involved in studies that reported a lower VO_2 peak in women. Thus, the homogeneity of the sample and/or its better walking capacity may have contributed to the absence of sex differences in the VO_2 peak in the current study.

In accordance with the absence of a difference in the VO_2 peak between the sexes, walking economy and AnT were also similar between men and women in the present study. Walking economy reflects energy consumption during submaximal activities, impacting the performance of daily activities in patients with PAD and IC.[6] AnT is a marker of aerobic capacity associated with walking tolerance[33] and is used for aerobic training prescription.[3,4] Therefore, the absence of sex differences in these three metabolic markers (peak VO_2, walking economy, and AnT) suggests that men and women with PAD and IC well-paired for baseline characteristics have similar metabolism during exercise, which indicates similar difficulty in performing daily activities, and no metabolic reason to differentiate aerobic training prescription between the sexes in this population.



Means±SD. Comparisons by *t*-tests, all p>0.05.
VO_2: oxygen consumption; HR: heart rate; SBP: systolic blood pressure; RPP: rate pressure product.

Figure 1. Oxygen consumption measured at the first stage (walking economy), the anaerobic threshold, and the maximal effort (peak) during a walking test conducted until maximal leg pain in men and women with peripheral arterial disease and intermittent claudication



Means±SD. Comparisons by *t*-tests, all p>0.05.
HR: heart rate; SBP: systolic blood pressure; RPP: rate pressure product; AnT: anaerobic threshold.

Figure 2. Heart rate, systolic blood pressure, and rate pressure product measured at absolute (first stage) and relative (anaerobic threshold) submaximal walking intensities and at peak effort during a walking test until maximal leg pain in men and women with peripheral arterial disease and intermittent claudication

Considering the cardiovascular responses during walking, there were no differences in the HR, SBP, and RPP measured at both submaximal and maximal walking intensities between men and women, which is in accordance with the absence of metabolic differences observed at these exercise intensities. Cardiovascular variables increased progressively from AnT to peak effort as expected during the maximal exercise test.[4] In addition, the peak HR was within the range expected for patients with PAD and IC, in whom tests are mainly

stopped by pain in the affected leg, and cardiorespiratory fatigue is usually not achieved, as reported in other studies.[12,34,35] Cardiovascular responses during exercise are commonly used to monitor training intensity and responses.[3,4] Thus, the absence of a difference in these responses between the sexes strengthens the idea that training management and monitoring can be similar in men and women with PAD and IC.

Therefore, the results of the present study showed that among men and women with PAD, IC, and similar baseline characteristics, the submaximal and maximal metabolic and cardiovascular responses to exercise were similar. These results may have important scientific and clinical implications, indicating the possibility of including subjects of both sexes in research designed to evaluate the exercise parameters included in the present investigation, and suggesting that parameters from training prescription and monitoring do not need to be different in men and women with PAD, IC, and similar baseline characteristics.

Limitations

This study has some limitations. All volunteers were at stage II of the disease, and the results may be different at other stages. This should be investigated in the future. This study used a specific test protocol, but there is no reason to think that the results would differ by using other maximal protocols. However, they may differ if a steady-state exercise protocol is used, which needs further investigation. The study used a well-controlled sample for the baseline characteristics, and the results would probably have been different if the baseline characteristics were different between the sexes. The sample size was not specifically calculated for this study, and the statistical power may have been small for some variables. Nevertheless, for most variables assessed during the cardiopulmonary walking test, the effect sizes were small, suggesting the absence of a clinically relevant difference between the sexes. However, future studies should include larger sample sizes.

CONCLUSION

Men and women with peripheral artery disease at stage II of the Fountaine classification and similar baseline characteristics present similar VO_2peak, walking economy, anaerobic threshold, and cardiovascular load during walking.

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AUTHORS' CONTRIBUTION

Roberto Sanches Miyasato: conceptualization, formal analysis, project administration, and writing of the original draft. Alex Jesus Felix: formal analysis and writing of the original draft. Aluísio Andrade-Lima: conceptualization, methodology, writing - review, and editing. Natan Daniel da Silva Júnior: conceptualization, formal analysis, methodology, writing, review, and editing. Raphael Mendes Ritti-Dias: methodology, supervision, and writing, review, and editing. Nelson Wolosker: conceptualization, supervision, and writing - review and editing. Véronique Cornelissen: conceptualization, investigation, writing, review, and editing. Karla Fabiana Goessler: conceptualization, data curation, methodology, writing, reviewing, and editing. Claúdia Lúcia de Moraes Forjaz: conceptualization, formal analysis, funding acquisition, project administration, supervision, and writing of the original draft.

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