Pain Threshold Is Achieved at Intensity Above Anaerobic Threshold in Patients With Intermittent Claudication

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■ PURPOSE: Walking training is considered as the first treatment option for patients with peripheral arterial disease and intermittent claudication (IC). Walking exercise has been prescribed for these patients by relative intensity of peak oxygen uptake (VO2peak), ranging from 40% to 70% VO2peak, or pain threshold (PT). However, the relationship between these methods and anaerobic threshold (AT), which is considered one of the best metabolic markers for establishing training intensity, has not been analyzed. Thus, the aim of this study was to compare, in IC patients, the physiological responses at exercise intensities usually prescribed for training (% VO2peak or % PT) with the ones observed at AT.

■ METHODS: Thirty-three IC patients performed maximal graded cardiopulmonary treadmill test to assess exercise tolerance. During the test, heart rate (HR), VO2, and systolic blood pressure were measured and responses were analyzed at the following: 40% of VO2peak; 70% of VO2peak; AT; and PT.

■ RESULTS: Heart rate and VO2 at 40% and 70% of VO2peak were lower than those at AT (HR: −13 ± 9% and −3 ± 8%, P < .01, respectively; VO2: −52 ± 12% and −13 ± 15%, P < .01, respectively). Conversely, HR and VO2 at PT were slightly higher than those at AT (HR: +3 ± 8%, P < .01; VO2: +6 ± 15%, P = .04). None of the patients achieved the respiratory compensation point.

■ CONCLUSION: Prescribing exercise for IC patients between 40% and 70% of VO2peak will induce a lower stimulus than that at AT, whereas prescribing exercise at PT will result in a stimulus above AT. Thus, prescribing exercise training for IC patients on the basis of PT will probably produce a greater metabolic stimulus, promoting better cardiovascular benefits.

Intermittent claudication (IC) is the most common symptom of peripheral arterial disease (PAD). Peripheral arterial disease reduces walking capacity, levels of physical activity, and quality of life.1–4 Moreover, it increases the risk of mortality due to cardiovascular events.5 In many IC patients, a progressive walking program increases exercise tolerance, improves quality of life, and reduces morbidity and mortality.6 Therefore, it has been recommended as the first treatment option for these patients.7

KEY WORDS
exercise intensity
exercise prescription
peripheral arterial disease

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Walking training can be prescribed using different methodologies; however, anaerobic threshold (AT) has been considered the gold standard for exercise intensity prescription. Anaerobic threshold is defined as “the exercise intensity above which metabolic predominance changes from aerobic to anaerobic.” Nevertheless, for AT determination, a test with gas exchange analysis is needed, implying in an expensive evaluation. Thus, AT is not generally used for exercise prescription for PAD patients in clinical practice.

For PAD patients, exercise is commonly prescribed using relative intensities of VO2peak or pain threshold (PT). However, there is no consensus about the ideal intensity of exercise training to promote greater health benefits for PAD patients. The Transatlantic Inter-Society of Vascular Surgery recommends an intensity that elicits claudication symptoms within 3 to 5 minutes. The American College of Sports Medicine, which includes the prescription based upon claudication symptoms, also recommends an intensity between 40% and 70% of VO2peak. Although both prescriptions increase walking capacity in PAD patients, their effects on cardiovascular function in PAD patients have not been studied. This is an important issue because patients with IC show high risk of cardiac events and mortality due to cardiovascular problems.

Studies have shown that cardiovascular adaptations are mainly achieved when aerobic training is prescribed at an intensity above AT and below respiratory compensation point. However, it is not known whether exercise prescriptions commonly used in PAD patients (40% and 70% of VO2peak, and PT) can elicit an intensity above AT. Thus, the objective of this study was to compare, in PAD patients with symptoms of IC, the physiological responses obtained at exercise intensities usually prescribed for these patients with the ones observed at AT.

**METHODS**

The study comprised 33 PAD patients with stable symptoms of IC. Patients were included if they met the following criteria: Fontaine stage II PAD; symptoms of IC for more than 6 months; ankle-brachial index at rest of 0.90 or less in 1 or 2 legs; and whether they were able to walk for at least 2 minutes at 2 mph on a treadmill. In all patients, arterial obstruction was present either at femoral-popliteal or iliac-femoral sites.

Before the study, patients were screened for other diseases (interview and exercise stress test), use of drugs, and medical history. Patients were excluded under the following conditions: presence of obesity (body mass index ≥ 30 kg/m²), presence of chronic lung disease, current use of β-blockers, inability to obtain ankle-brachial index measurement because of noncompressible vessels, exercise tolerance limited by factors other than claudication (eg, dyspnea, poorly controlled blood pressure), presence of electrocardiogram response suggestive of myocardial ischemia during the exercise test, and history of revascularization in the previous year.

Patients were asked about their physical activity level, smoking habits, and associated diseases. Patients were classified into physical inactive (<150 min/wk of leisure or transport physical activity) or active (≥150 min/wk of leisure or transport physical activity). Patients were also classified into smokers (including both daily and occasional smokers) or ex-smokers (those who had not smoked a cigarette in the past 6 months). Hypertension was identified when patients had previous diagnosis, current use of antihypertensive medication, and/or blood pressure values for systolic blood pressure (SBP) of 140 mm Hg or more and/or diastolic blood pressure of 90 mm Hg or more. Diabetes mellitus was identified as previous diagnosis, current use of diabetes medication, and/or fasting blood glucose level of 126 mg/dL or more. The presence of heart disease was determined by previous history of coronary arterial disease, angina pectoris, and/or history of coronary angioplasty or revascularization.

This study was approved by the University of São Paulo Joint Committee on Ethics of Human Research of the institution of the first author (process 1370/05). Each patient was informed of the risks and benefits involved with the study and signed a written informed consent before participation.

**Maximal Exercise Test**

Patients performed a progressive graded cardiopulmonary treadmill test until maximal claudication pain, as previously described for these patients. The test started at 2 mph/0% grade and the workload was increased 2% every 2 minutes. All patients were already familiarized with the test protocol before the experiments. During the test, electrocardiogram was continuously monitored and heart rate (HR) was averaged at the end of each stage. Oxygen uptake (VO2) was continuously measured by a metabolic cart (Medical Graphics Corp, St Paul, Minnesota), and it was averaged every minute for analysis. Systolic blood pressure was measured at the end of each stage (every 2 minutes) during all exercise tests. The rate pressure product (RPP) was obtained at each stage by multiplying SBP by HR.

Anaerobic threshold and respiratory compensation point were visually detected by 2 experienced
reviewers. It was defined as a nonlinear increase in the respiratory quotient ratio, carbon dioxide production and ventilation, as well as the increase in end-tidal oxygen pressure, whereas respiratory compensation point was established by the second nonlinear increase in ventilation and the decrease in the end-tidal carbon dioxide pressure, as previously described.\textsuperscript{20} Pain threshold was defined as the intensity at which patients reported the onset of claudication pain, whereas peak exercise was defined as the intensity at which patients could no longer tolerate the exercise because of the pain in the leg.

Statistical Analysis

Normality and homoscedasticity were checked by Shapiro-Wilks and Levene tests, respectively. One-way analysis of variance was used to compare HR, \( V_{O2} \), blood pressure, and RPP measured at different exercise intensities (40\% of \( V_{O2\text{peak}} \), 70\% of \( V_{O2\text{peak}} \), PT, AT, and \( V_{O2} \)). Newman-Keuls post hoc test was performed when a significant effect was observed. The significance level adopted was \( P < .05 \). Data are presented as the mean \( \pm \) standard deviation.

RESULTS

The clinical characteristics of the sample are presented in Table 1. Most subjects were physically active, hypertensive men.

On average, AT was achieved at 80 \( \pm \) 11\% of \( V_{O2\text{peak}} \) and PT at 84 \( \pm \) 11\% of \( V_{O2\text{peak}} \). The comparisons of \( V_{O2} \) and HR among different exercise intensities are presented in Figures 1 and 2, respectively. Heart rate and \( V_{O2} \) at 40\% and 70\% of \( V_{O2\text{peak}} \) were lower than those at AT (HR: \(-13 \pm 9\% \text{ and } -5 \pm 8\% \); \( P < .01 \); respectively; \( V_{O2} \): \(-52 \pm 12\% \text{ and } \pm 15\% \); \( P < .01 \); respectively). In all patients, \( V_{O2} \) at 40\% of \( V_{O2\text{peak}} \) was lower than that at AT, whereas in 30 patients, \( V_{O2} \) at 70\% of \( V_{O2\text{peak}} \) was equal to or lower than that at AT. Conversely, HR and \( V_{O2} \) at PT were higher than those at AT (HR: \(+3 \pm 8\% \text{ and } +6 \pm 15\% \); \( P = .04 \)). Twenty-three patients showed \( V_{O2} \) at PT equal to or greater than AT. None of the patients achieved the respiratory compensation point.

Cardiovascular responses are presented in Table 2. Systolic blood pressure and RPP at 40\% and 70\% \( V_{O2\text{peak}} \) were significantly lower than those at AT (SBP: \(-11 \pm 10\% \text{ and } -4 \pm 8\% \); and RPP: \(-22 \pm 14\% \text{ and } -14 \pm 24\% \), respectively). Nevertheless, SBP and RPP at PT were not different from those at AT.

| Table 1 • CLINICAL CHARACTERISTICS OF EXPERIMENTAL GROUP (N = 33) |
|-----------------|----------------|
| Age, y          | 66.4 \( \pm \) 8.8 |
| Weight, kg      | 65.8 \( \pm \) 11.3 |
| Height, m       | 1.62 \( \pm \) 0.08 |
| Body mass index, kg/m² | 25.0 \( \pm \) 3.0 |
| Ankle-brachial index | 0.56 \( \pm \) 0.08 |
| Gender, % men   | 74.3 |
| Risk factors    |                 |
| Physical inactivity, % | 62.9 |
| Current smoker, % | 28.6 |
| Hypertension, % | 77.1 |
| Diabetes mellitus, % | 34.3 |
| Heart disease, % | 28.6 |
| Medications     |                 |
| Antihypertensive agent, % | 80.0 |
| Lipid lowering, % | 66.7 |
| Antiplatelets, antiplatelet agents, % | 82.9 |
| Cilostazol, %   | 11.9 |

Walking exercise prescription in PAD patients is generally performed by 2 methods: relative intensity of \( V_{O2\text{peak}} \), or PT. When relative intensity is used, 40\% to 70\% of \( V_{O2\text{peak}} \) is recommended.\textsuperscript{10} When claudication symptoms are employed, it is recommended as an exercise that elicits pain within 3 to 5 minutes.\textsuperscript{9,10} The present study revealed that metabolic demands for these 2 recommendations are different in IC patients.

For all patients, 40\% of \( V_{O2\text{peak}} \) was lower than that at AT; 91\% of the patients presented \( V_{O2} \) at 70\% of \( V_{O2\text{peak}} \) at lower than or equal to AT. Thus, in most of the patients, the prescription at 70\% of \( V_{O2\text{peak}} \) was insufficient to achieve AT. The range of AT in healthy subjects is approximately 55\% to 65\% of \( V_{O2\text{peak}} \).\textsuperscript{21} The present study revealed that in IC patients, AT was achieved at 80 \( \pm \) 11\% of \( V_{O2\text{peak}} \). The difference that is achieved between healthy subjects and PAD patients in the percentage of \( V_{O2\text{peak}} \) at AT is due to claudication symptoms,\textsuperscript{22,23} limiting the PAD patients before they achieve a true \( V_{O2\text{peak}} \). This hypothesis was confirmed by the fact that all patients in the present study stopped exercising before achieving the respiratory compensation point.

Conversely, the results of the present study showed that PT occurs at an intensity above AT. On average, PT was achieved at 84 \( \pm \) 11\% of \( V_{O2\text{peak}} \), which represents a slightly higher intensity than that at AT (80 \( \pm \) 11\% of \( V_{O2\text{peak}} \)). In fact, more than half of the patients (70\%) presented PT at intensity higher or equal at AT. Because none of the patients achieved the respiratory compensation point, it is possible that

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PT was achieved at an intensity between AT and respiratory compensation point, which is considered the best exercise intensity to promote cardiovascular adaptations in cardiac patients.\textsuperscript{14,15}

It is important to note, however, that PAD patients show low physical fitness and poor walking capacity. Thus, any exercise program, using intensities below\textsuperscript{11} or above\textsuperscript{12,13} PT, can improve walking capacity in patients with intermittent claudication.

**Figure 1.** Oxygen uptake ($V_{O_2}$) measured at 40% and 70% of peak oxygen exercise ($V_{O_2peak}$), at anaerobic threshold (AT), at pain threshold (PT), and at $V_{O_2peak}$ in patients with intermittent claudication. *More than 40% $V_{O_2peak}$, **More than 70% $V_{O_2peak}$, ***More than AT, ****More than PT ($P < 0.05$).

**Figure 2.** Heart rate (HR) measured at 40% and 70% of peak oxygen uptake ($V_{O_2peak}$), at anaerobic threshold (AT), at pain threshold (PT), and at $V_{O_2peak}$ in patients with intermittent claudication. *More than 40% $V_{O_2peak}$, **More than 70% $V_{O_2peak}$, ***More than AT, ****More than PT ($P < 0.05$).
these patients. Nevertheless, the effects of exercise intensity on cardiovascular adaptations to training have not been studied in PAD patients. The present investigation addressed the probable effect of exercise intensity, assuming that an intensity above AT promotes an adequate metabolic stress necessary for improvement in cardiovascular function.

On the basis of these considerations, the present results suggest that prescribing exercise at PT would promote a better metabolic stimulus for cardiovascular adaptations than that at 40% or 70% of VO₂peak. However, exercising at the PT induces lower leg ischemia, stimulating a systemic inflammatory response that is associated with a worse prognosis of the disease. Nevertheless, it has been shown that acute inflammatory effects of exercise are reversed with long-term training in IC patients. Moreover, the present study showed higher SBP and RPP at PT than those at 40% and 70% of VO₂peak, which implies that training at PT might represent a higher cardiovascular risk for these patients. Although the influence of exercise intensity on cardiovascular safety has not been adequately investigated in PAD patients, studies with other populations have confirmed a higher risk for adverse cardiovascular events during vigorous exercise than during light to moderate exercise. Therefore, to minimize cardiovascular risk during exercise, PAD patients should be screened for myocardial ischemia and arrhythmias during exercise before beginning a training program and specific exercise prescription should be followed in case of positive results. Moreover, large trials of exercise training in PAD patients are needed to directly assess this risk.

In summary, the results of the present study give scientific support for the practical recommendation to prescribe exercise at PT for PAD patients. According to these results, when exercise is prescribed at PT, an intensity above AT is achieved without the need of performing a cardiopulmonary exercise test to determine AT, which is not feasible in clinical practice. Conversely, the prescription using 40% and 70% of VO₂peak does not seem intense enough to promote cardiovascular benefits in PAD patients. However, it is important to consider that the prescription based on the percentage of VO₂peak is more useful for PAD patients who do not report claudication symptoms.

This study is limited by its cross-sectional design that does not allow establishing which prescription (40% and 70% of VO₂peak, or PT) promotes greater improvements on walking distance and cardiovascular health, causing lower cardiovascular risk in IC patients. However, the results suggest that a prescription based on PT might elicit greater benefits. Future studies are needed to address this issue. Moreover, it is important to point out that other exercise prescription variables such as session duration, number of sessions, and interval between exercise bouts might also influence walking capacity improvement after training, and these aspects were not addressed in the present study.

In conclusion, prescribing exercise training for IC patients between 40% and 70% of VO₂peak elicits an intensity below AT, whereas using PT elicits an intensity above AT. These results suggest that prescribing exercise at an intensity equal or higher than PT may elicit greater cardiovascular adaptations in IC patients than prescribing it between 40% and 70% of VO₂peak.

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References


Table 2 • SYSTOLIC BLOOD PRESSURE AND RATE PRESSURE PRODUCT MEASURED AT 40% AND 70% OF PEAK OXYGEN UPTAKE (VO₂peak), AT ANAEROBIC THRESHOLD, AT PAIN THRESHOLD, AND AT VO₂peak IN PATIENTS WITH INTERMITTENT CLAUDICATION (N = 33)

<table>
<thead>
<tr>
<th>40% VO₂peak</th>
<th>70% VO₂peak</th>
<th>AT</th>
<th>PT</th>
<th>VO₂peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>159 ± 29</td>
<td>171 ± 28</td>
<td>181 ± 32</td>
<td>180 ± 27</td>
</tr>
<tr>
<td>Rate pressure product</td>
<td>14,362 ± 4,151</td>
<td>16,621 ± 2,881</td>
<td>18,670 ± 4,115</td>
<td>19,523 ± 5,425</td>
</tr>
</tbody>
</table>

Abbreviations: AT, anaerobic threshold; PT, pain threshold.

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