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CLINICAL PREDICTORS OF VENTILATORY THRESHOLD ACHIEVEMENT IN CLAUDICANTS

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Abstract

Purpose—Ventilatory threshold (VT) is considered a clinically important marker of cardiovascular function in several populations, including patients with claudication, as it is related to walking capacity and hemodynamics. The purpose of this study was to identify clinical predictors for the VT achievement in intermittent claudication patients.

Methods—One hundred seventy-seven (n=177) patients with intermittent claudication performed a progressive graded cardiopulmonary treadmill test until maximal claudication pain. Oxygen uptake (VO₂) was continuously measured during the test and afterwards VT was visually detected. Clinical characteristics, demographic data, comorbid conditions, and cardiovascular risk factors were obtained. Patients who achieved and did not achieve VT were compared, as well as the workload that VT occurred in the former group.

Results—VT was achieved in 134 patients (76%) and the mean VO₂ at VT for these patients was $10.8 \pm 2.4 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Patients who did not achieve VT presented lower ankle brachial index (ABI), claudication onset time, peak walking time, and peak VO₂, and the proportion of women was higher compared to patients who achieved VT (p<0.05). Multiple linear regression analysis identified that sex (b=0.25, p=0.002), body mass index (b=-0.18, p=0.025), peak walking time (b=0.17, p=0.044), and ABI (b=0.23, p=0.006) were predictors of the VO₂ at VT.

Conclusion—Forty-three patients (24%) with intermittent claudication did not achieve the VT and these patients were mostly women and those with greater severity of disease. Moreover, in those who reached VT, the predictors of poor VT were female sex, high body mass index, low peak walking time, and low ABI.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

Keywords

peripheral vascular disease; intermittent claudication; exercise; physical fitness

INTRODUCTION

Peripheral artery disease (PAD) is prevalent between 12 to 20% of the United States population aged 60 years (31). Intermittent claudication, which is the most prevalent symptom of PAD (29), leads to walking impairment reducing physical activity levels (30) and, consequently, worsening the physical fitness in these patients (28).

Cardiopulmonary fitness has been related to better prognosis and lower mortality in patients with PAD (21), suggesting that cardiopulmonary exercise testing is useful for these patients. Ventilatory threshold (VT), defined as the exercise intensity above which metabolic predominance changes from aerobic to anaerobic (38), is an important variable obtained during exercise testing, since it provides information about aerobic capacity during exercise. In fact, VT is related to walking impairment in patients with intermittent claudication (7), indicating that the capacity to sustain exercise under aerobic metabolism is a key factor in these patients.

Previous studies have shown that walking impairment in patients with claudication is related to factors, such as sex (14), progression of disease (26), co-morbid conditions (9,10) and presence of risk factors (6). Although walking impairment limits the achievement of VT in some patients (12,43), it is not clear what patient characteristics are associated with not reaching VT. Further, it remains undetermined whether the factors that are associated with walking impairment are also associated with VT. Understanding the clinical predictors of the VT achievement in these patients is useful to identify those who need more attention to improve aerobic capacity. Thus, the purpose in the present study was to identify clinical predictors of the VT achievement in intermittent claudication patients.

METHODS

Recruitment

Patients with Fontaine Stage II PAD (11) were evaluated in the General Clinical Research Center at the University of Oklahoma Health Sciences Center (HSC). Patients were recruited by referrals from the HSC vascular clinic, as well as by newspaper advertisements for possible enrollment into an exercise study. The procedures of this study were approved by the Institutional Review Board at the University of Oklahoma HSC. Written informed consent was obtained from each patient prior to participation.

Screening

Patients performed an initial progressive, graded treadmill exercise test to determine study eligibility. Patients were included in the study if they met the following criteria: (a) graded treadmill test limited by intermittent claudication, (b) an ankle brachial index (ABI) ≥ 0.90 at rest (40), or an ABI ≥ 0.73 after exercise (20). ABI was calculated after 10 minutes of

supine rest by measuring the ankle and brachial systolic blood pressure using Doppler technique in the posterior tibial and dorsalis pedis arteries of both legs and brachial artery of both arms (15). The higher of the two systolic pressures from the more severely diseased leg was recorded as the resting ankle systolic pressure. Similarly, the higher systolic pressure of the arms was recorded as the resting brachial systolic blood pressure. The ABI was then calculated as ankle systolic pressure/brachial systolic pressure.

Patients were excluded from this study under the following conditions: (a) inability to obtain an ABI measure due to non-compressible vessels, (b) exercise tolerance limited by factors other than claudication symptoms (e.g. clinically significant electrocardiographic changes during exercise indicative of myocardial ischemia, dyspnea, poorly controlled blood pressure), (c) use of medications indicated for the treatment of intermittent claudication (cilostazol or pentoxifylline) initiated within three months prior to investigation. A total of 177 patients were deemed eligible for and participated in the study, and 88 patients were ineligible.

Graded treadmill test

Oxygen uptake at VT—Graded treadmill test was used to obtain the oxygen uptake (VO_2) at VT and to assess walking capacity. Patients performed a progressive graded cardiopulmonary treadmill test until maximal claudication pain, as previously described for these patients (16). The test started at 2 mph with 0% grade and the workload was increased 2% every 2 minutes. All patients were familiarized with the test protocol before the experiments. During the test, the electrocardiogram, heart rate and blood pressure were monitored. VO_2 was continuously measured by a metabolic cart (Medical Graphics Corp, St Paul, Minnesota, USA) and averages of 30 s were applied for analysis. VO_2 peak was defined as the highest VO_2 achieved during the test.

Ventilatory Threshold—VT was visually detected by two experienced evaluators and 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, and a lowest value before increasing in ventilatory equivalent for oxygen, as previously described (39). A third researcher compared the results in order to check possible discrepancies. In this case, the analysis was performed once again by both evaluators and the third evaluator made the final determination. If patients did not present any of these aforementioned respiratory parameters during the progressive graded cardiopulmonary treadmill test, they were considered as not having achieved the VT.

Claudication Measurements—The claudication onset time was defined as the walking time which the patient first experienced pain in the legs, and the peak walking time was defined as the walking time which the patients could not continue walking due the pain in the legs. Using these procedures, the test-retest intraclass reliability coefficients are $r=0.89$ for claudication onset time, $r=0.93$ for peak walking time and $r=0.88$ for peak VO_2 (13).

Medical history, anthropometry and ABI

A medical history and anthropometry measurements obtained at the beginning of the study was used to assess the secondary outcome variables that might be related to VT achievement. Demographic, body mass index, cardiovascular risk factors (physical inactivity and smoking), comorbid conditions (hypertension, diabetes dyslipidemia, chronic obstructive pulmonary disease, heart disease, cancer and cerebrovascular disease) and ABI were assessed. ABI measures were obtained from the more severely diseased lower extremity before and at 1, 3, 5, and 7 minutes after the graded treadmill test, as previously described (17).

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences software – SPSS/PASW version 20 (IBM Corp, New York, USA). Continuous variables were summarized as mean and standard deviation, whereas categorical variables were summarized as relative frequency. Patients were grouped according to whether or not they achieved VT, and the clinical characteristics between the two groups were compared using independent t-test for continuous variables and chi-square test for categorical variables.

Univariate and multiple linear regression analyses were conducted to identify whether demographic data, cardiovascular risk factors, comorbid conditions, ABI and walking capacity are predictors of VO_2 at VT. In the univariate linear regression analysis, each variable was included in a separate regression analysis. In multiple linear regression modeling, stepwise forward techniques were used to enter the covariates into the linear models, with the criteria for entry utilizing a $p < 0.05$ for numeric variables and $p < 0.20$ for categorical variables, and the criteria to remain in the final model utilizing a $p < 0.05$. A residual analysis was performed, homoscedasticity was analyzed by graphical analysis (scatterplot) and adherence to the normal distribution was tested using the Kolmogorov-Smirnov test. Multicollinearity analysis was performed assuming variance inflation factors less than five and tolerance below 0.20.

RESULTS

VT was not achieved in 43 patients (24%), all these patients were Fontaine Stage IIb PAD ($p < 0.05$). Table 1 shows the comparison of clinical characteristics of patients who achieved and who did not achieve the VT. ABI, claudication onset time, peak walking time and peak VO_2 were lower in patients who did not achieve the VT compared with patients who achieved the VT ($p < 0.05$). Furthermore, the proportion of women was higher in patients who did not achieve the VT ($p < 0.05$). The mean VO_2 at VT of patients who achieved the VT was $10.8 \pm 2.4 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

The relationships between VO_2 at VT and clinical characteristics of patients are shown in Table 2. VO_2 at VT was positively correlated with ABI ($r = 0.29$; $p = 0.001$), peak walking time ($r = 0.32$; $p < 0.001$) and sex ($b = 0.34$; $p < 0.001$); and negatively correlated with body mass index ($r = -0.24$; $p = 0.007$) and diabetes ($b = -0.19$; $p = 0.031$). Using multiple regression

procedures (Table 3), the predictors of the VO_2 at VT were sex, body mass index, peak walking time, and ABI.

DISCUSSION

The main findings of the study were as follows: a) out of 177 patients who performed a graded treadmill test, 43 (24%) did not achieve the VT, and these patients were mostly women and those who had lower values of ABI, peak VO_2 and walking capacity; and b) sex, body mass index, peak walking time, and ABI were predictors of the VO_2 at VT.

In the present study almost 25% were unable to achieve the VT because of early interruption of the treadmill test due to the symptoms of claudication. This is in contrast to previous studies (7,33) in which the VT was achieved by all patients. However, in these studies, only patients who were able to walk for at least 2 minutes at 2 mph were included, which reinforces the hypothesis that the walking capacity is directly related to VT achievement in intermittent claudication patients. In fact, in the current study 100% of patients who did not achieve VT showed moderate to severe claudication, being considered patients with Fontaine Stage IIb PAD (i.e. intermittent claudication after less than 200 meters of walking) (11). In practical terms, it is possible that such patients will have small cardiovascular improvements when submitted to treadmill training, since the achievement of VT is considered an important factor for improvement of cardiovascular fitness in healthy individuals (41) and patients with cardiovascular diseases (36,37).

The patients who did not achieve the VT presented 14% lower ABI and poor walking capacity compared to patients who achieved the VT (63% lower claudication onset time and 66% peak walking time). Furthermore, most of the patients who did not achieve the VT were women, who have lower walking capacity compared to men (14,24). Taken together, these results indicate that the achievement of VT is directly related with the severity of PAD and claudication symptoms.

The VO_2 at VT has been considered an important marker of aerobic metabolism, since it predicts mortality in older and cardiac patients (18,35). A previous study with chronic heart failure patients showed that values of VT lower than $11 \text{ mL.kg}^{-1}.\text{min}^{-1}$ are related to a 5.1-fold-increased risk for mortality (18). In the present study the average VO_2 at VT was $10.8 \text{ mL.kg}^{-1}.\text{min}^{-1}$ (range 5.6 to $17.3 \text{ mL.kg}^{-1}.\text{min}^{-1}$). Although no previous study reported the association between VO_2 at VT and mortality rates in patients with claudication, this low VO_2 at VT highlights the importance of futures studies analyzing the prognostic value of VT in these patients.

The predictors of VO_2 at VT were sex, peak walking time, ABI, and body mass index. The positive relationship between peak walking time and ABI with VO_2 at VT confirms that patients with less severe PAD have higher cardiorespiratory fitness compared to those with greater severity (7). The atherosclerosis progression impairs blood flow to active muscles, that have been associated with lower proportion of type I muscle fibers (1) and muscle capillary density (1), affecting the oxygen consumption in skeletal muscles (2). In fact, slowed VO_2 kinetics, which reflects the limitation in muscle O_2 utilization or transport

during the onset of exercise, have been also observed in PAD patients during the onset of walking (3–5). All these factors may explain the association between PAD severity and VO_2 at VT observed in this study.

The finding that female sex is a predictor of lower VO_2 at VT is in agreement with previous studies that found a lower cardiorespiratory fitness in healthy individuals and in patients with chronic disease (14,32). The body mass index was negatively related with VO_2 at VT, indicating that higher obesity status is associated with lower VO_2 at VT. This information is clinically relevant because obesity is becoming more prevalent among PAD patients, and has been associated with walking impairment (9,23), arterial stiffness and endothelial dysfunction (8,19). Given that body mass index, which is the main indicator of obesity, was associated with cardiorespiratory fitness, special attention should be done in weight management in patients with claudication.

This study has potential practical applications. First, VT can be identified in more patients from submaximal walking exercise testing because the lower exercise intensity enables patients with severe claudication to walk for long enough duration to reach VT. Thus, a submaximal exercise test provides an assessment of aerobic metabolism without need to perform the maximal exercise test. Second, the identification of the patients who did not achieve the VT allows physicians and health professionals to identify patients with severe walking impairment. This can help in exercise prescription, as improvement in cardiopulmonary fitness and decreases in cardiovascular risk are mainly observed when exercise is prescribed above anaerobic threshold (36,37,41). Finally, the identification of the predictors of VO_2 at VT highlights the subgroup of patients that need to receive additional attention for improvements of cardiorespiratory fitness.

The present study has some limitations. The cross-sectional design of this study is an evident limitation of this study, as no causality can be inferred. This study included only patients with PAD with Fontaine Stage II, and the results cannot be extrapolated to patients with other stages. The present findings are also limited by the relatively small sample size, particularly in patients that did not achieve the VT. Finally, the measure of calf muscle strength was not obtained in this study. Calf muscle strength is directly associated with walking capacity in claudicants (25,27), and thus could be a predictor of ventilatory threshold achievement in patients with intermittent claudication.

In conclusion, one-quarter of the patients with intermittent claudication did not achieve VT, and these patients were mostly women and those with greater severity of disease. Moreover, in those who reached VT, the predictors of poor VT were female sex, high body mass index, low peak walking time, and low ABI. The clinical significance is that intermittent claudication patients with these characteristics may not improve their cardiorespiratory fitness from exercise performed on a treadmill, indicating that alternative exercise modalities should be utilized, such as resistance exercise (22,34) or arm-crank ergometry (42). This information is clinically relevant to exercise professionals who rehabilitate patients with intermittent claudication, because it identifies patients who need more attention.

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Table 1

Characteristics of the intermittent claudication patients included in the study.

Variables	Did not achieve VT (n = 43)	Achieve VT (n = 134)	p
Age, years	63 ± 11	66 ± 10	0.071
Body mass index, kg ⁻¹ m ²	29.2 ± 1.1	29.6 ± 0.6	0.672
Ankle brachial index	0.64 ± 0.04	0.74 ± 0.02	0.014
Claudication onset time, seconds	87 ± 8	237 ± 15	<0.001
Peak walking time, seconds	163 ± 14	481 ± 21	<0.001
Oxygen uptake at VT, mL.kg ⁻¹ .min ⁻¹	-	10.8 ± 2.4	-
Peak oxygen uptake, mL.kg ⁻¹ .min ⁻¹	9.9 ± 0.5	13.0 ± 0.3	<0.001
Sex, % women	65	42	0.008
Diabetes mellitus, % yes	49	35	0.106
Hypertension, % yes	79	84	0.498
Dyslipidemia, % yes	79	83	0.577
Coronary artery disease, % yes	28	34	0.435
Chronic obstructive pulmonary disease, % yes	33	25	0.356

VT - Ventilatory threshold

Table 2

Relationship between VO_2 at ventilatory threshold and clinical characteristics of intermittent claudication patients (n=134).

Variables	VO_2 at ventilatory threshold
Age, years	$r=0.084$ $p=0.339$
Body mass index, $\text{kg}^{-1}.\text{m}^2$	$r=-0.236$ $p=0.007$
Ankle-brachial index	$r=0.285$ $p=0.001$
Claudication onset time, seconds	$r=-0.015$ $p=0.227$
Peak maximal time, seconds	$r=0.323$ $p<0.001$
Sex, women=0; men=1	$r=0.336$ $p<0.001$
Chronic obstructive pulmonary disease, no=0; yes=1	$r=-0.152$ $p=0.083$
Hypertension, no=0; yes=1	$r=-0.139$ $p=0.114$
Diabetes mellitus, no=0; yes=1	$r=-0.189$ $p=0.031$
Coronary artery disease, no=0; yes=1	$r=-0.165$ $p=0.060$

Table 3

Multiple regression models predicting VO_2 at ventilatory threshold in intermittent claudication patients (n=134).

Dependent variable	Independent variables	β (EP)	b	p
$^a\text{VO}_2$ at ventilatory threshold, $\text{ml.kg}^{-1}.\text{min}^{-1}$	Sex, women=0; men=1	1.251 (0.395)	0.254	0.002
	Body mass index, $\text{kg}^{-1}.\text{m}^2$	-0.072 (0.032)	-0.181	0.024
	Peak walking time, seconds	0.002 (0.001)	0.171	0.044
	Ankle brachial index	2.363 (0.852)	0.228	0.006

β (EP) – Regression coefficient (error-standard); b – Standardized coefficients.

$^a\text{F}=10.4$; $r=0.50$; $r^2=0.249$; $\text{SEE}=2.1 \text{ ml.kg}^{-1}.\text{min}^{-1}$.