Clinical Predictors of Ventilatory Threshold Achievement in Patients with Claudication

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ABSTRACT

FARAH, B. Q., R. M. RITTI-DIAS, G. G. CUCATO, A. L. MENÊSES, and A. W. GARDNER. Clinical Predictors of Ventilatory Threshold Achievement in Patients with Claudication. *Med. Sci. Sports Exerc.*, Vol. 47, No. 3, pp. 493–497, 2015. **Purpose**: Ventilatory threshold (VT) is considered a clinically important marker of cardiovascular function in several populations, including patients with claudication, because it is related to walking capacity and hemodynamics. The purpose of this study was to identify clinical predictors for VT achievement in patients with intermittent claudication. **Methods**: One hundred and seventy-seven (n = 177) patients with intermittent claudication performed a progressive graded cardiopulmonary treadmill test until maximal claudication pain. Oxygen uptake ($\dot{V}O_2$) 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 $\dot{V}O_2$ at VT for these patients was 10.8 ± 2.4 $mL \cdot kg^{-1} \cdot min^{-1}$. Patients who did not achieve VT presented lower ankle brachial index (ABI), claudication onset time, peak walking time, and $\dot{V}O_{2peak}$, and the proportion of women was higher compared with 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 $\dot{V}O_2$ at VT. **Conclusions**: Forty-three patients (24%) 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. **Key Words:** PERIPHERAL VASCULAR DISEASE, INTERMITTENT CLAUDICATION, EXERCISE, PHYSICAL FITNESS

Peripheral artery disease (PAD) is prevalent between 12% and 20% of the United States population age ≥60 yr (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 of 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 because 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), comorbid 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. Furthermore, it remains undetermined whether the factors that are associated with walking impairment are also associated with VT. Understanding the clinical predictors of VT achievement in these patients is useful to identify those who need more attention to improve aerobic capacity. Thus, the purpose of the present study was to identify clinical predictors of VT achievement in patients with intermittent claudication.

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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 and by newspaper advertisements for possible enrolment into an exercise study. The procedures of this study were approved by the institutional review board at the University of Oklahoma HSC. A written informed consent was obtained from each patient before 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 and b) an ankle brachial index (ABI) ≤0.90 at rest (40) or an ABI ≤0.73 after exercise (20). ABI was calculated after 10 min of supine rest by measuring the ankle and brachial systolic blood pressure using the Doppler technique in the posterior tibial and dorsalis pedis arteries of both legs and the 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. 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 because of noncompressible vessels, b) exercise tolerance limited by factors other than claudication symptoms (e.g., clinically significant ECG changes during exercise indicative of myocardial ischemia, dyspnea, poorly controlled blood pressure), and c) use of medications indicated for the treatment of intermittent claudication (cilostazol or pentoxifylline) initiated within 3 months before 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. A graded treadmill test was used to obtain oxygen uptake ($\dot{V}O_2$) 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 by 2% every 2 min. All patients were familiarized with the test protocol before the experiments. During the test, the ECG, HR, and blood pressure were monitored. $\dot{V}O_2$ was continuously measured by a metabolic cart (Medical Graphics Corp., St Paul, MN), and averages of 30 s were applied for analysis. $\dot{V}O_{2peak}$ was defined as the highest $\dot{V}O_2$ achieved during the test.

VT. VT was visually detected by two experienced evaluators and was defined as a nonlinear increase in respiratory quotient ratio, carbon dioxide production and ventilation, as well as 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 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 VT.

Claudication measurements. The claudication onset time was defined as the walking time when the patient first experienced pain in the legs, and the peak walking time was defined as the walking time when the patients could not continue walking because of 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 $\dot{V}O_{2peak}$ (13).

Medical History, Anthropometry, and ABI

Medical history and anthropometry measurements obtained at the beginning of the study were used to assess 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 min after the graded treadmill test, as previously described (17).

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences software SPSS/PASW version 20 (IBM Corp., Armonk, NY). Continuous variables were summarized as mean and SD, 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*-tests 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 $\dot{V}O_2$ 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 using $P < 0.05$ for numeric variables and $P < 0.20$ for categorical variables and the criteria to remain in the final model using $P < 0.05$. 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 had Fontaine stage IIb PAD ($P < 0.05$). Table 1 shows the comparison of clinical characteristics of patients who achieved and did not achieve VT. ABI, claudication onset time, peak walking time, and $\dot{V}O_{2peak}$ were lower in patients who did not achieve VT compared with patients who achieved VT ($P < 0.05$). Furthermore, the proportion of women was higher in patients who did not achieve VT ($P < 0.05$). The mean $\dot{V}O_2$ at VT of patients who achieved VT was 10.8 ± 2.4 mL·kg^{-1}·min^{-1}.

The relations between $\dot{V}O_2$ at VT and the clinical characteristics of patients are shown in Table 2. $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 VT and these patients were mostly women and those who had lower values of ABI, $\dot{V}O_{2peak}$, and walking capacity and b) sex, body mass index, peak walking time, and ABI were predictors of $\dot{V}O_2$ at VT.

In the present study, almost 25% was unable to achieve 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 VT was achieved by all patients. However, in these studies, only patients who were able to walk for at least 2 min at 2 mph were included, which reinforces the hypothesis that the walking capacity is directly related to VT achievement in patients with intermittent claudication.

TABLE 1. Characteristics of the patients with intermittent claudication included in the study.

Variables	Did Not Achieve VT (*n* = 43)	Achieved VT (*n* = 134)	*P*
Age (yr)	63 ± 11	66 ± 10	0.071
Body mass index (kg m^{-2})	29.2 ± 1.1	29.6 ± 0.6	0.672
ABI	0.64 ± 0.04	0.74 ± 0.02	0.014
Claudication onset time (s)	87 ± 8	237 ± 15	<0.001
Peak walking time (s)	163 ± 14	481 ± 21	<0.001
$\dot{V}O_2$ at VT (mL·kg^{-1}·min^{-1})	—	10.8 ± 2.4	—
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	9.9 ± 0.5	13.0 ± 0.3	<0.001
Sex, women (%)	65	42	0.008
With diabetes mellitus (%)	49	35	0.106
With hypertension (%)	79	84	0.498
With dyslipidemia (%)	79	83	0.577
With CAD (%)	28	34	0.435
With chronic obstructive pulmonary disease (%)	33	25	0.356

TABLE 2. Relation between $\dot{V}O_2$ at VT and clinical characteristics of patients with intermittent claudication (*n* = 134).

Variables	$\dot{V}O_2$ at VT
Age (yr)	$r = 0.084$ $P = 0.339$
Body mass index (kg·m^{-2})	$r = -0.236$ $P = 0.007$
ABI	$r = 0.285$ $P = 0.001$
Claudication onset time (s)	$r = -0.015$ $P = 0.227$
Peak maximal time (s)	$r = 0.323$ $P < 0.001$
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	$r = -0.189$ $P = 0.031$
CAD: no, 0; yes, 1	$r = -0.165$ $P = 0.060$

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 m of walking) (11). In practical terms, such patients may have small cardiovascular improvements when submitted to treadmill training because the achievement of VT is considered an important factor for the improvement of cardiovascular fitness in healthy individuals (41) and patients with cardiovascular diseases (36,37).

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

$\dot{V}O_2$ at VT has been considered an important marker of aerobic metabolism because it predicts mortality in older patients and patients with cardiac diseases (18,35). A previous study on patients with chronic heart failure showed that values of VT lower than 11 mL·kg^{-1}·min^{-1} are related to a 5.1-fold–increased risk for mortality (18). In the present study, the average $\dot{V}O_2$ at VT was 10.8 mL·kg^{-1}·min^{-1} (range, 5.6–17.3 mL·kg^{-1}·min^{-1}). Although no previous study reported the association between $\dot{V}O_2$ at VT and mortality rates in patients with claudication, this low $\dot{V}O_2$ at VT highlights the importance of future studies analyzing the prognostic value of VT in these patients.

The predictors of $\dot{V}O_2$ at VT were sex, peak walking time, ABI, and body mass index. The positive relation between peak walking time and ABI with $\dot{V}O_2$ at VT confirms that patients with less severe PAD have higher cardiorespiratory fitness compared with those with greater severity (7). Atherosclerosis progression impairs blood flow to active muscles, which has been associated with lower proportion of Type

TABLE 3. Multiple regression models predicting $\dot{V}O_2$ at VT in patients with intermittent claudication (n = 134).

Dependent Variable	Independent Variables	β (EP)	b	P
$\dot{V}O_2$ at VT (mL·kg^{-1}·min^{-1})[a]	Sex: women, 0; men, 1	1.251 (0.395)	0.254	0.002
	Body mass index (kg.m^{-2})	−0.072 (0.032)	−0.181	0.024
	Peak walking time (s)	0.002 (0.001)	0.171	0.044
	ABI	2.363 (0.852)	0.228	0.006

[a] F = 10.4; r = 0.50; r^2 = 0.249; SEE, 2.1 mL·kg^{-1}·min^{-1}.
β (EP), regression coefficient (error standard); b, standardized coefficients.

I muscle fibers (1) and muscle capillary density (1), affecting oxygen consumption in skeletal muscles (2). In fact, slowed $\dot{V}O_2$ kinetics, which reflects the limitation in muscle O_2 use or transport during the onset of exercise, have been also observed in patients with PAD during the onset of walking (3–5). All these factors may explain the association between PAD severity and $\dot{V}O_2$ at VT observed in this study.

The finding that female sex is a predictor of lower $\dot{V}O_2$ at VT is in agreement with previous studies that found lower cardiorespiratory fitness in healthy individuals and in patients with chronic disease (14,32). Body mass index was negatively related with VO_2 at VT, indicating that higher obesity status is associated with lower $\dot{V}O_2$ at VT. This information is clinically relevant because obesity is becoming more prevalent among patients with PAD 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 given to weight management of patients with claudication.

This study has potential practical applications. First, VT can be identified in more patients from submaximal walking exercise testing because lower exercise intensity enables patients with severe claudication to walk for a duration long enough to reach VT. Thus, a submaximal exercise test provides an assessment of aerobic metabolism without needing to perform the maximal exercise test. Second, the identification of the patients who did not achieve VT allows physicians and health professionals to identify patients with severe walking impairment. This can help in exercise prescription because improvement in cardiopulmonary fitness and decreases in cardiovascular risk are mainly observed when exercise is prescribed above VT (36,37,41). Finally, the identification of the predictors of $\dot{V}O_2$ at VT highlights the subgroup of patients that needs 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 because 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 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 VT 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 patients with intermittent claudication with these characteristics may not improve their cardiorespiratory fitness from exercise performed on a treadmill, indicating that alternative exercise modalities should be used, 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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