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VO₂ KINETICS AND CLINICAL FACTORS AMONG PATIENTS WITH PERIPHERAL ARTERY DISEASE

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Peripheral artery disease (PAD) is a burdensome condition associated with elevated rates of mortality¹ and morbidity.² Intermittent claudication, a prevalent symptom of PAD, limits walking capacity, reducing physical activity levels³ and quality of life.⁴ Measuring oxygen uptake (VO₂) kinetics quantifies the rate of increase in VO₂ during the early phase of exercise, providing information regarding muscle energetics, metabolic control, and the determinants of the efficiency of skeletal muscle contraction. Slowed oxygen uptake (VO₂) kinetics is associated with poor exercise performance, and have been observed in PAD patients during the onset of walking.^{5–7} This response has been attributed to atherosclerotic lesions that limit oxygen delivery to the active muscles and/or muscle metabolic abnormalities that limit oxygen utilization.^{5–7} Barker et al⁵ observed that tau (τ), the main indicator of VO₂ kinetics, was 2-fold slower in PAD patients compared to controls. In addition, τ was highly correlated with walking time (r = −0.72) indicating that walking impairment in PAD patients was related to VO₂ kinetics. Thus, VO₂ kinetics has been considered an important factor related to walking impairment in these patients.

Previous studies have shown that clinical characteristics predict walking capacity in PAD patients.^{8,9} Gardner et al⁸ observed that ankle brachial index (ABI), body mass index, gender, and current smoking status are independent predictors of walking capacity in patients with claudication. However, whether these factors are also associated with VO₂ kinetics remains unclear. Because walking impairment is a major problem in PAD patients, it is important to understand the factors associated with slowed VO₂ kinetics. The aim of this study was to investigate the association between VO₂ kinetics and demographic, behavioral, and clinical factors among patients with PAD. Our hypothesis was that age, smoking, and comorbid conditions are associated with slower VO₂ kinetics in patients with PAD.

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METHODS

The procedures used in this study were approved by the Institutional Review Board at the University of the authors. Written informed consent was obtained from each patient prior to investigation. Patients were recruited by referrals from vascular and primary care clinics and by newspaper advertisements for possible enrollment into a randomized controlled exercise rehabilitation study for the treatment of leg pain secondary to PAD. The data and analyses for this study were part of the baseline assessments obtained for the exercise study.

Medical Screening

Patients arrived in the morning fasted, but were permitted to take their usual morning medication regimen. Demographic information, height, weight, body mass index, waist and hip circumferences, cardiovascular risk factors, comorbid conditions, claudication history, ABI, blood samples, and a list of current medications were obtained from a medical history and physical examination at the beginning of the study.

Hypertension was identified when patient had previous diagnosis, current use of antihypertensive medication, and/or blood pressure values for systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg.¹⁰ Diabetes mellitus was identified as previous diagnosis, current use of diabetes medication, and/or fasting glucose ≥ 126 mg/dL.¹¹ Dyslipidemia was identified when the patient had previous diagnosis, current use of medication or fasting cholesterol >200 mg/dL or triglyceride >150 mg/dL or high density lipoprotein (HDL) cholesterol <40 mg/dL for men and <50 mg/dL for women or low density lipoprotein (LDL) cholesterol >130 mg/dL. Obesity was defined as body mass ≥ 30 kg/m². Metabolic syndrome was defined according to the National Cholesterol Education Program¹² as having 3 or more of the following components: (i) abdominal obesity (waist circumference >102 cm in men and >88 cm in women), (ii) elevated triglycerides (≥ 150 mg/dL), (iii) reduced HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), (iv) elevated blood pressure ($\geq 130/85$ mmHg), and (v) elevated fasting glucose (≥ 110 mg/dL) as well as those with diabetes. Chronic obstructive pulmonary disease was identified by previous diagnosis. Coronary artery disease and cerebrovascular disease were identified if the patient had at least one on these conditions: myocardial infarction, angina, coronary angioplasty, coronary stent or coronary bypass graft (for coronary artery disease); and stroke, transient ischemic attack, carotid stent, carotid endarterectomy or carotid surgery (for cerebrovascular disease).

Inclusion and Exclusion Criteria

Patients with PAD were included in this study if they met the following criteria: (a) a history of intermittent claudication, (b) ambulation during a graded treadmill test limited by intermittent claudication¹³ and (c) an ABI ≥ 0.90 at rest¹⁴ or an ABI ≥ 0.73 after exercise.¹⁵ Patients were excluded from this study for the following conditions: (a) absence of PAD (ABI >0.90 at rest and ABI >0.73 after exercise), (b) inability to obtain an ABI measure due to noncompressible vessels, (c) asymptomatic PAD determined from the medical history and verified during the graded treadmill test, (d) use of medications indicated for the treatment of intermittent claudication (cilostazol and pentoxifylline) initiated within 3 months prior to investigation, (e) exercise tolerance limited by any disease process other than PAD, (f) active cancer, (g) kidney failure defined as stage 5 chronic kidney disease, (h) abnormal liver function, (i) inability to ambulate for at least 180 seconds during the VO₂ kinetics test because steady-state in VO₂ may not have been attained, and (j) technical problems with the measurement of breath-by-breath VO₂ resulting in missing data. A total of 147 patients were evaluated for this study, and 85 patients were deemed eligible.

Primary Outcome Measures: VO₂ Kinetics

Data smoothing and processing—Breath-by-breath $\dot{V}O_2$ measures for the first 360 seconds of the treadmill test were obtained at a speed of 2 mph and at a grade of 0% with a Medical Graphics VO2000 metabolic system (Medical Graphics Inc, St. Paul, MN). To address high breath-by-breath variability in the $\dot{V}O_2$ measures, a local regression smoothing technique, using PROC LOESS in SAS (version 9.1, SAS Institute Inc., Cary, NC, USA), was used to smooth the data. A smoothing parameter, indicating the neighborhood of data containing a specified percentage of data points to be smoothed,¹⁶ was chosen to be consistent with the breath-by-breath smoothing approaches reported in the literature that utilize a 10 second neighborhood of observations.^{17–19} A smoothing parameter of 0.03 (calculated as the 10 second neighborhood divided by the maximum duration of measurement) was initially considered, but resulted in removal of some patients due to time lags between breaths of more than 10 seconds. Therefore, the smoothing parameter was increased to 0.04 (corresponding to 14 second intervals).

Nonlinear mixed-effects regression modeling—When repeated measurements are made on the same individual over time, mixed effects modeling with both fixed and random effects is used widely to account for the correlation among repeated measures.²⁰ Fixed effects are assumed to be shared by all individuals and random effects represent subject-specific effects. Nonlinear mixed models, including both fixed and random effects that entered nonlinearly into the regression model, were used to model the VO₂ kinetics.

VO₂ Kinetics Models—The smoothed $\dot{V}O_2$ measures were divided by weight and expressed as mL·kg⁻¹·min⁻¹. A single phase model, with one exponential increase, was used to predict VO₂ (mL·kg⁻¹·min⁻¹) levels while walking on a treadmill at a constant speed of 2 miles per hour with a 0% grade.⁷ Equation (1) represents the model with fixed effects including a fixed baseline (resting) oxygen uptake VO₂(b) term, a fixed τ_1 term representing the rate of increase in VO₂ uptake per kilogram of the exercise-response curve, and a fixed amplitude A₁ term representing the difference between resting and steady state VO₂ levels.

$$VO_{2(i,t)} = VO_2(b) + A_1 \left[1 - e^{-t/\tau_1} \right] + \varepsilon_{(i,t)} \quad (\text{equation 1})$$

In this single phase model, τ_1 is the value constant representing the rate of increase in $\dot{V}O_2$ of the exercise-response curve, interpreted as the time in seconds when an individual reaches 63% of their amplitude value, and $\varepsilon_{(i,t)} \sim N(0, \sigma_e^2)$ represents the random error term in the model where $i=1, n$ indexes the individual patients and t indexes time. In this study, equation (1) was extended to account for between-subject random variability in the amplitude of the curve, the correlation among repeated measures on the same subject, and the effect of patient demographic and clinical characteristics on the estimated τ_1 coefficient.

In order to account for the between-subject variability for amplitude A₁, a mixed-effect model with a random amplitude A₁ was considered in equation (2). The model fitting procedure accounted for the correlation among repeated measures made on each subject, during the course of the treadmill test, when estimating the variance parameters of the model. Baseline VO₂(b) and τ_1 were not considered as random effects in order to satisfy model convergence criteria. If $A_1 = A_2 + w_i$ where A₂ is fixed and $w_i \sim N(0, \sigma_w^2)$ is a random variable, model (1), with the substitution of a random amplitude effect, can be expressed as follows:

$$\dot{V}O_{2(i,t)} = \dot{V}O_{2(b)} + (A_2 + w_i) \left[1 - e^{-t/\tau_i} \right] + \varepsilon_{(i,t)} \quad (\text{equation 2})$$

Statistical Analyses

SAS PROC NLMIXED was used to fit the nonlinear mixed model by maximizing an approximation to the likelihood integrated over the random amplitude effect. The default optimization technique in PROC NLMIXED, dual quasi-Newton algorithm, was used (SAS/STAT 9.2 User's Guide: The NLMIXED Procedure).

Continuous clinical measures, considered as independent factors impacting the estimate of τ in the regression model, were dichotomized using the median to define categories (less than or equal to the median value vs. greater than the median value). The median cut-points were height >169.7 cm, ABI >0.68 and age >66 years. Gender, race, current smoking, diabetes, hypertension, dyslipidemia, obesity, metabolic syndrome, age, height, and ABI were considered univariately in model as independent variables in the linear predictor for τ . Based on the univariate model results, a full multivariate model was fit that included the covariate terms that were univariately significant at a two-sided 0.10 alpha level. The full multivariate model was simplified by dropping terms, one-by-one, that were not significant at a 2-sided .05 alpha level.

RESULTS

The clinical characteristics of PAD patients are shown in Table I. Patients were mostly Caucasian, dyslipidemic, hypertensive, and had metabolic syndrome.

The associations between the $\dot{V}O_2$ kinetics, expressed as the estimated difference in τ between groups, and clinical characteristics of PAD patients are shown in Table II. The univariate analyses revealed that female gender ($P=.025$), non-Caucasian race ($P=.0006$), age ≤ 66 years ($P=.0007$), hypertension ($P<.0001$) and dyslipidemia ($P=.015$) were associated with higher values of τ (ie, slowed $\dot{V}O_2$ kinetics) (Table II). Smoking, diabetes, obesity, metabolic syndrome, height, and ABI were not significantly related to the rate of $\dot{V}O_2$ kinetics. Using multiple regression procedures (Table III), female gender ($P=.0049$), non-Caucasian race ($P=.0075$), hypertension ($P=.0001$), and age ≤ 66 years ($P=.0015$) were predictors of slowed $\dot{V}O_2$ kinetics.

An additional analyses comparing the clinical characteristics of patients with ≤ 66 yrs and the patients with >66 yrs was performed. The results indicated that patients with >66 yrs had a significant lower ABI ($P=.0384$) and a higher prevalence of hyperlipidemia ($P=.0235$) compared to the patients with age ≤ 66 yrs. In addition, the patients with age ≤ 66 yrs are more likely to be current smoker ($P=.1461$) and obese ($P=.1701$), although the results did not reach the statistical significance. A representative example of $\dot{V}O_2$ kinetics response of a subject with lower τ and higher τ are presented in Figure I.

DISCUSSION

Slowed $\dot{V}O_2$ kinetics at the lungs reflects a limitation in muscle O_2 utilization or transport during the onset of exercise. Besides the limitation to oxygen delivery caused by arterial obstruction, previous studies have shown that PAD patients have muscle myopathy, which explain the slowed $\dot{V}O_2$ kinetics observed in these patients. The present study adds that the slow $\dot{V}O_2$ kinetics during ambulation was most evident in some subgroups (women, non-Caucasians, hypertensive, and younger patients). From a practical standpoint the

impairments in $\dot{V}O_2$ kinetics in these subgroups of PAD patients may negatively impact many activities of daily living.

The finding that women had slower $\dot{V}O_2$ kinetics than men supports previous observations in our laboratory. Women with PAD have shown to present a faster decline in calf muscle tissue oxygen saturation during standardized treadmill walking²¹ and lower arterial elasticity²² than men, factors which may affect oxygen delivery and uptake.^{23,24} Moreover, women with PAD are less physically active than men,²⁵ and physical exercise has been shown to improve $\dot{V}O_2$ kinetics at the onset of exercise in PAD.²⁶ Furthermore, $\dot{V}O_2$ peak in women is generally lower than in men, and thus walking at a given speed of 2 mph probably required a greater % $\dot{V}O_2$ peak for women than for men. Collectively, these findings may partially explain the gender-related differences in $\dot{V}O_2$ kinetics observed in this study.

Hypertension was associated with the greatest magnitude of slowed $\dot{V}O_2$ kinetics in the PAD patients even after adjustments for race, gender, and age. Hypertensive PAD patients had an average of 12.1 sec slower $\dot{V}O_2$ kinetics than their non-hypertensive counterparts. A previous study in elderly subjects also observed that hypertensive patients presented slower $\dot{V}O_2$ kinetics compared to normotensive subjects.²⁷ Mechanisms underlying the slower $\dot{V}O_2$ kinetics response in hypertensive patients might be related to both central and peripheral factors. Centrally, hypertensive subjects present cardiac impairments such as reduced left ventricle diastolic filling and reduced stroke volume.²⁷ Peripherally, hypertension increases arterial stiffness and peripheral vascular resistance in muscle and vascular tissue rarefaction.²⁸

This is the first study that analyzed ethnic differences in $\dot{V}O_2$ kinetics. Our findings revealed that non-Caucasian race was associated with slower $\dot{V}O_2$ kinetics in PAD patients. Previous studies, have shown that African-American PAD patients have impaired large and small arterial compliance²² and higher levels of amputation²⁹ compared to Caucasians, which may be associated with reduced oxygen delivery to active muscles and slowed $\dot{V}O_2$ kinetics. In addition, African-American PAD patients have shown lower exercise performance³⁰ and higher rates of ABI decline,³¹ which may also be related to slowed $\dot{V}O_2$ kinetics. However, whether Caucasian and non-Caucasian PAD patients present differences on muscle metabolism or oxygen extraction capacity remains unknown and requires additional research.

Several cross-sectional studies have shown that aging is associated with slower $\dot{V}O_2$ kinetics.^{27,32,33} A longitudinal study that followed elderly subjects for 9 years also reported an increase in 1.8 s/year in τ value.³⁴ Therefore, it is intriguing that in the current study, younger patients with PAD had slower $\dot{V}O_2$ kinetics than older patients. Rather than a favorable effect of aging on $\dot{V}O_2$ kinetics, a more plausible explanation for our results is that a selection bias exists, in which healthier elderly PAD patients were included in the study and less healthy elderly did not choose to participate. This is supported by the fact that younger PAD patients presented significant lower ABI and higher prevalence of hyperlipidemia and tended to have a higher prevalence of smoker and obese compared to older subjects.

Effects of Diabetes, Smoking, and Obesity on $\dot{V}O_2$ kinetics

Pathological conditions that affect cardiopulmonary function and muscle metabolic capacity would be expected to alter $\dot{V}O_2$ kinetics responses. Regensteiner et al³⁵ observed impaired maximal and submaximal cardiopulmonary responses to exercise as evident by slowed $\dot{V}O_2$ kinetics in women with type 2 diabetes. Slowed $\dot{V}O_2$ kinetics was also observed in smokers compared to nonsmokers.³⁶ In both cases, slowed $\dot{V}O_2$ kinetics have been attributed to central and peripheral factors, indicating difficulty in uptake and utilization of oxygen

during onset of exercise. However, in the present study, neither diabetes nor smoking was associated with slowed $\dot{V}O_2$ kinetics in PAD. Interestingly, the values previously reported in diabetics or smokers are lower than those observed in PAD patients, indicating that patients in the current study had the most impaired $\dot{V}O_2$ kinetics. Considering the major adverse effects of PAD on blood flow³⁷ and muscle metabolism³⁸ it is possible that maximal limitations in oxygen delivery and utilization during onset of exercise was reached, and a “ceiling effect” occurred.

In the present study, obesity and metabolic syndrome were not associated with slowed $\dot{V}O_2$ kinetics, which agrees with a previous study that observed overweight subjects did not have slowed $\dot{V}O_2$ kinetics.³⁵ Although obese subjects present greater endothelial dysfunction and vascular stiffness, they have increased capacity to oxidize fat during leg exercise and have similar mitochondrial oxidative capacity compared to nonobese subjects.³⁹ The increased capacity to oxidize fat may be a compensatory mechanism for reduced oxygen delivery.

$\dot{V}O_2$ Kinetics Analysis Using Nonlinear Mixed-effects Regression Modeling

This study utilized nonlinear mixed-effects regression modeling to investigate the association between $\dot{V}O_2$ kinetics and patient demographic, behavioral and clinical factors. The selected modeling approach accounted for the correlation among repeated breath-by-breath measures made on each patient in order to correctly estimate the variability in regression model terms. The modeling procedure also allowed for simultaneous estimation of the effect of multiple patient characteristics on the rate of $\dot{V}O_2$ and accounted for the variability in the estimated $\dot{V}O_2$ curve, and corresponding estimated curve parameter values, for each patient. Typical methods of data analysis, that assume independence of the repeated measures, are not appropriate when analyzing correlated, repeated measures. Ignoring positive correlation among repeated measures can lead to underestimation of the variability of means and therefore, lead to false positive findings (ie, test statistic values that are over-estimated leading one to reject a true null hypothesis).

The statistical modeling approach utilized in this project also accounts for the variability and uncertainty in the estimated τ parameter value. Some studies have estimated the τ parameter value for each patient separately using a nonlinear curve fitting program applied individually to each patient's data series and then analyzed these estimated τ values, comparing the distribution of τ values between groups of patients or within patients over time, as if the τ values were observed measurements.^{6,7} Instead, these τ values are estimated statistics with a corresponding variance. Ignoring the variability in the estimated τ values can again lead to false positive conclusions in hypothesis testing. Thus, ignoring the positive correlation among repeated measures and ignoring the variability in the estimated τ values may be 1 possibility for why previous studies found diabetes³⁵ and smoking³⁶ to be associated with estimated τ values in patients with PAD and intermittent claudication, whereas these variables were not associated with estimated τ values in this study that utilized nonlinear mixed-effects regression modeling.

Limitations

There are several limitations to this study. The study included a relative small number of subjects. A non-PAD control group that would strengthen the understanding of PAD on $\dot{V}O_2$ kinetics was not included. The regression coefficients calculated between $\dot{V}O_2$ kinetics and clinical, demographic and behavioral characteristics from this cross-sectional design do not allow causality to be established. The patients included in this study were volunteers that were recruited to participate in an exercise training study. Therefore, a selection bias may have occurred, especially for older patients, in which the individuals with better ambulatory function may have been included.

In conclusion for PAD patients with intermittent claudication, slowed $\dot{V}O_2$ kinetics is associated with female gender, non-Caucasian race, younger age, and hypertension. The clinical significance is that PAD patients with these characteristics present central and/or peripheral alterations that may account for their walking impairment. This information is clinically relevant to exercise professionals who rehabilitate patients with PAD, as improvements in central and/or peripheral function should be targeted to improve walking capacity. Future studies are needed to determine if exercise training improves $\dot{V}O_2$ kinetics in PAD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure I.

VO₂ responses from a subject with peripheral artery disease with lower τ (dotted line; male, with age >66 yrs, Caucasian and normotensive) and from a subject with peripheral artery disease and higher τ (continuous line; women, age $\leq$ 66 yrs, non-Caucasian and hypertensive).