Oxygen uptake kinetics during exercise are slowed in patients with peripheral arterial disease

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Bauer, Timothy A., Judith G. Regensteiner, Eric P. Brass, and William R. Hiatt. Oxygen uptake kinetics during exercise are slowed in patients with peripheral arterial disease. J. Appl. Physiol. 87(2): 809–816, 1999.—Patients with peripheral arterial disease (PAD) have arterial occlusions that limit peripheral blood flow. This study evaluated the dynamic response in O2 consumption (VO2) at the onset of constant-load exercise (VO2 kinetics) in patients with PAD. Eight patients with bilateral PAD, seven patients with unilateral PAD, nine age-matched nonsmoking controls, and seven smoking controls performed graded treadmill exercise to assess peak VO2. Subjects also performed constant-load exercise tests at 2.0 miles/h at 0 and 4% grade to determine VO2 kinetics. Peak VO2 was reduced 50% in patients with PAD compared with both control groups (P < 0.05). At 4% grade, phase 2 VO2 kinetics were significantly slowed for the PAD groups compared with controls (60.1 ± 15.7 and 58.7 ± 8.3 s, unilateral and bilateral PAD groups, respectively; compared with 28.4 ± 19.3 and 27.9 ± 8.1 s, nonsmoking and smoking controls, respectively; P < 0.05). No relationship was found between VO2 kinetics and disease severity. These data demonstrate that VO2 kinetics are markedly slowed in patients with PAD. The impairment in VO2 kinetics is not related to smoking status or arterial disease severity and therefore may reflect altered control of skeletal muscle metabolism.

WITH THE TRANSITION from rest to constant-load exercise, the rate of change in O2 uptake (VO2 kinetics) reflects the ability of the cardiopulmonary system to deliver O2, as well as the rate at which O2 is taken up and utilized by exercising skeletal muscle. Changes in VO2 kinetics with disease may provide insight into the alterations in physiological regulation that are associated with an impairment in exercise performance and functional capacity.

Cardiovascular diseases are associated with a profound impairment in both submaximal and peak exercise performances. Slowed VO2 kinetics have been well documented in patients with cardiovascular diseases that affect the central “cardiac” component of VO2 kinetics (coronary artery disease and cyanotic congenital heart disease) as well as in disease that exhibits both central and skeletal muscle defects (congestive heart failure) (2, 8, 13, 24, 26, 34, 35, 38). These observations are consistent with the concept that an impaired cardiac output response to exercise limits O2 delivery to skeletal muscle, resulting in a slower response of VO2 to any externally imposed work demand. This is in contrast to healthy subjects whose VO2 kinetics are limited by either a maldistribution of blood flow to the working tissues or inertia of oxidative enzyme activities (6, 15).

In patients with peripheral arterial disease (PAD), arterial occlusions in the lower extremity limit peripheral blood flow; this results in impaired functional walking ability (17, 28). Patients with claudication typically have adequate resting blood flow to maintain tissue viability. However, with walking exercise, the inadequate delivery of O2 and substrate to match metabolic demand results in muscle ischemia, claudication pain, and alterations in skeletal muscle metabolism (17, 20). Furthermore, these patients have on average a 50% reduction in peak exercise performance as well as a decreased VO2-work rate slope during incremental exercise (16). These observations suggest that the rate of VO2 adaptation to an increase in work rate is attenuated in PAD and reflects an attenuation of the dynamic response of VO2 as well as a defect in oxidative metabolism in meeting energy demands. Potentially, the obstruction of blood flow through the major conduit vessels, alterations in skeletal muscle metabolism associated with PAD, or both, could slow the kinetic response of VO2 during the transition from rest to exercise. To directly test the hypothesis that PAD is associated with slowed VO2 kinetics, we measured VO2 kinetics in patients with unilateral and bilateral PAD, and in healthy, nonsmoking subjects and otherwise healthy controls who smoked. The specific aims of the present study were 1) to determine if VO2 kinetics were slowed in patients with PAD compared with healthy, age-matched, nonsmoking controls and otherwise healthy smoking controls, 2) to characterize VO2 kinetics in patients with unilateral PAD vs. bilateral PAD, and 3) to determine whether the hemodynamic severity of PAD could account, in part, for altered VO2 kinetics.

METHODS

Subjects. Thirty-one subjects were enrolled in this study: eight patients with bilateral PAD; seven patients with unilateral PAD; nine healthy, age-matched, nonsmoking controls; and seven smoking, but otherwise healthy, controls. The study was approved by the University of Colorado Multiple Institutional Review Board, and informed consent was obtained from all subjects.
PAD was confirmed by the measurement of the ankle-brachial index (ABI; described below). Patients with PAD were enrolled who had an ABI \( \leq 0.85 \) in the worse affected leg (the most symptomatic had the lowest ABI). All PAD patients had claudication, defined as aching in the calf muscles that occurred only with exercise and was completely relieved after 10 min of rest. Patients with bilateral disease exhibited claudication symptoms and decreased ABIs in both legs. Patients with unilateral disease were defined as exhibiting claudication symptoms meeting ABI criteria for PAD in the worse affected leg, and with no claudication symptoms and a normal ABI (\( >0.95 \) at rest) in their less affected leg. All PAD patients were current smokers, with a pack-year history (packs/day \( \times \) no. of yr of smoking) of \( \geq 30 \) yr. Of the 14 PAD patients accepted for study, 7 were taking calcium channel blockers, 3 were treated with diuretics, 2 with lipid-lowering drugs, 2 with angiotensin-converting enzyme inhibitors, and 2 with nitrates. Patients were excluded if they exhibited ischemic rest pain or were exercise limited by symptoms other than PAD (heart failure, pulmonary disease, angina). Patients with diabetes and patients taking medications which may alter exercise responses (i.e., beta blockers) were also excluded.

Nonsmoking control subjects had no chronic medical diseases (by history and a normal physical exam), were taking no medications, and had no cigarette smoking history. Non-smoking control subjects had no history of claudication, had normal ABIs at rest, and had normal electrocardiograms (ECGs) at rest as well as during and after exercise. Smoking controls were all current smokers with a self-reported history of \( \geq 20 \) pack-yr, but they were otherwise healthy as defined above. Smoking subjects were included in the study design to aid in discrimination between potential effects of smoking vs. PAD on the time constant of Vo2 kinetics.

Exercise protocol. Subjects were not allowed to smoke within 60 min before the start of any of the exercise testing. After familiarization with the treadmill, all subjects were initially tested with a graded treadmill protocol. Patients with PAD (unilateral and bilateral) performed a graded treadmill test at a constant speed of 2.0 miles/h starting at 0% grade and increasing 2.0% every 2 min until maximal claudication pain occurred. Subjects without PAD (nonsmoking controls and smoking controls) performed a standard Bruce treadmill protocol to maximal effort. All tests at each workload were then time aligned and averaged by the superimposition of data files. A five-point filter was used to eliminate aberrant breaths from the average response curve. For each value in a response curve, two values preceding and two values after the value in question were considered in the calculation of an expected datum value. Rejection criteria were defined as a range of acceptable values determined as a percentage of the calculated mean for each time-interpolated interval. Rejection criteria and weighting of each of the five points in the calculation were predetermined before filtering. By using a statistical program [BMDP (1988), Los Angeles, CA], two mathematical models were employed to fit to the average-response curves by using nonlinear regression techniques. A single-exponential model without a time delay was used to fit the average-response curves by using nonlinear regression techniques. A single-exponential model without a time delay was used to fit the average-response curve. 

Measurement of gas exchange. With the use of a Medical Graphics CPX/D metabolic system (Medical Graphics Corporation, St. Paul, MN), rates of V\( \dot{O}_2 \) and CO\( _2 \) output (V\( \dot{CO}_2 \)) were measured breath by breath and averaged to 20-s intervals for the determination of V\( \dot{O}_2 \)-peak. V\( \dot{O}_2 \)-peak was defined as the highest V\( \dot{O}_2 \) achieved during the graded test. Respiratory exchange ratio (RER) was calculated as the ratio of V\( \dot{CO}_2 \) to V\( \dot{O}_2 \). Breath-by-breath data for kinetic analysis were acquired for V\( \dot{O}_2 \) and minute ventilation by using the same metabolic system. HR data were recorded and calculated simultaneously with each ventilatory data point by the CPX/D system via Transistor Type Logic signaling from the ECG recorder. All breath-by-breath data collected were saved as ASCII files and were stored to disk for later analysis.

Kinetic analysis. Specific analytic software for the kinetic analysis was developed at the University of Colorado Health Sciences Center Vascular Research Metabolic Laboratory. Breath-by-breath V\( \dot{O}_2 \) and HR data from the constant work-load tests were time interpolated to 1-s intervals. The four tests at each workload were then time aligned and averaged by the superimposition of data files. A five-point filter was used to eliminate aberrant breaths from the average response curve. For each value in a response curve, two values preceding and two values after the value in question were considered in the calculation of an expected datum value. Rejection criteria were defined as a range of acceptable values determined as a percentage of the calculated mean for each time-interpolated interval. Rejection criteria and weighting of each of the five points in the calculation were predetermined before filtering. By using a statistical program [BMDP (1988), Los Angeles, CA], two mathematical models were employed to fit to the average-response curves by using nonlinear regression techniques. A single-exponential model without a time delay was used to fit the average-response curve.

The curve is described by the formula:

\[
\dot{V}O_2(t) = \dot{V}O_2(0) + A_1[1 - e^{(-t/\tau)}]
\]  

(1)

In the single-exponential model, \( \dot{V}O_2(t) \) is the \( \dot{V}O_2 \) at time \( t \), \( \dot{V}O_2(0) \) is the resting baseline \( \dot{V}O_2 \) (in ml/min) before exercise, \( A_1 \) (in ml/min) is the difference between the baseline value and the new steady state, and \( \tau \) (in s) is defined as the time constant representing the rate of increase in \( \dot{V}O_2 \) of the exercise-response curve [equal to time (in s) to 63% of the change in \( \dot{V}O_2 \) from baseline to steady-state exercise].

In contrast to the \( \dot{V}O_2 \) responses at 0% grade, the test at 4% grade resulted in a much larger increase in \( \dot{V}O_2 \); thus a phase 1 and 2 component of the curves were observed. Multieponential mathematical modeling was used to fit the average \( \dot{V}O_2 \) response curves at 2.0 miles/h, 4% grade exercise and was utilized to describe three distinct phases of \( \dot{V}O_2 \) kinetics.

\[
\dot{V}O_2(t) = \dot{V}O_2(0) + A_1[1 - e^{(-t/\tau_1)}] + A_2[1 - e^{(-t/\tau_2)}] + A_3[1 - e^{(-t/\tau_3)}]
\]  

(2)

In the single-exponential model, \( \dot{V}O_2(t) \) is the \( \dot{V}O_2 \) at time \( t \), \( \dot{V}O_2(0) \) is the resting baseline \( \dot{V}O_2 \) (in ml/min) before exercise, \( A_1 \) (in ml/min) is the difference between the baseline value and the new steady state, and \( \tau_1 \) (in s) is defined as the time constant representing the rate of increase in \( \dot{V}O_2 \) of the exercise-response curve [equal to time (in s) to 63% of the change in \( \dot{V}O_2 \) from baseline to steady-state exercise].

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The first exponential fit the initial rapid increase in $\dot{V}O_2$ at the onset of exercise, which represents an increase in pulmonary blood flow (cardiodynamic phase of $\dot{V}O_2$ kinetics: phase 1) (Fig. 1) (36). For comparisons of phase 1, $\tau_0$ (in s) described the rate of rise in $\dot{V}O_2$ during phase 1, and $A_0$ described the change in amplitude of $\dot{V}O_2$ (in ml/min). After a time delay ($TD_1$; in s), the second exponential fit phase 2 of the response curve, reflecting peripheral $O_2$ delivery and $\dot{V}O_2$ (6, 7, 36). Phase 2 comparisons between groups were made by using $\tau_1$ (the rate of rise in $\dot{V}O_2$ during phase 2) and $A_1$ [the change in amplitude of $\dot{V}O_2$ (in ml/min) from the end of phase 1 to the new steady state]. There was also the possibility of a third exponential fit, phase 3 (the slow component of $\dot{V}O_2$ kinetics), which would follow a second time delay ($TD_2$; in s). A phase 3 increase in $\dot{V}O_2$ would be expected under exercise conditions of high intensity and accumulation of systemic blood lactate (6, 7, 36). These conditions were not observed in PAD patients at these low work rates (19).

Kinetic $\dot{V}O_2$ data were also derived at 4% grade, independent of curve-fit modeling techniques, by the sum of breath-by-breath $\dot{V}O_2$ ($\Sigma\dot{V}O_2$) over several intervals of exercise (from exercise onset to 60, 90, 120, 180, and 300 s). By using the raw breath-by-breath $\dot{V}O_2$ data ($B_{m}$; in ml/min) and the duration of each breath ($D_{m}$; in s), $\Sigma\dot{V}O_2$ was calculated as the milliliters of $\dot{V}O_2$ consumed over a selected interval minus the product of resting baseline average ($\dot{V}O_2X_{m}$; in ml/min) and the duration of the selected interval in minutes ($t_{(int)}$).

$$\Sigma\dot{V}O_2 = \sum_{0}^{n-1} (B_{m}/60)(D_{m}) - (\dot{V}O_2 X)(t_{(int)}) \quad (3)$$

$\Sigma\dot{V}O_2$ was normalized to body weight to minimize the influences of weight on absolute $\dot{V}O_2$ requirements during treadmill exercise.

ABI. The ABI was calculated in all subjects before exercise testing. ABIs in patients with PAD and in smoking controls were also obtained 1 min after graded exercise. The postexercise ABIs of nonsmoking control subjects were not measured. While subjects were in the supine position, systolic blood pressure was measured in both arms with a Doppler ultrasonic instrument (model 841, Parks Medical Electronics, Beaverton, OR). The pressures in the dorsalis pedis and posterior tibialis vessels of each ankle were also measured in duplicate. The ratio of ankle-to-brachial systolic pressure was determined by taking the highest arm pressure divided into the higher of the two vessels in each ankle.

Data analysis. The data for all PAD patients (unilateral + bilateral) were combined and compared against the combined control groups (nonsmoking + smoking) for $\Sigma\dot{V}O_2$ analyses. This was done to increase sample size and to provide better discrimination between differences in the PAD and control groups. All other analyses were made by using the means from each of the four separate groups. Between-subject analysis of variance was used to test for differences between groups at baseline. Paired differences were described by using Tukey-Kramer post hoc tests. Paired t-tests were used to compare changes within group means. The alpha level was set to 0.05 for statistical significance. Data are presented as means ± SD for each group.

RESULTS

Subject characteristics. Patients with PAD and control groups were similar in age and weight (Table 1). Pack-yr of cigarette use did not significantly differ between the smoking control, unilateral PAD, or bilateral PAD groups but differed from the values observed for the nonsmoking control group ($P < 0.05$). ABIs differentiated PAD patients with unilateral disease from those with bilateral disease. The resting ABI in the less affected leg of unilateral PAD patients was similar to the resting ABI of nonsmoking controls and smoking controls. However, the resting ABI in the worse affected leg of unilateral patients was compa-
Table 2. Peak performance characteristics

<table>
<thead>
<tr>
<th>Control Subjects</th>
<th>PAD Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmoking</td>
<td>Smoking</td>
</tr>
<tr>
<td>n</td>
<td>9</td>
</tr>
<tr>
<td>V˙O2peak, ml·kg⁻¹·min⁻¹</td>
<td>30.0 ± 4.0</td>
</tr>
<tr>
<td>V˙O2peak range, ml·kg⁻¹·min⁻¹</td>
<td>24.4–35.7</td>
</tr>
<tr>
<td>HRpeak, beats/min</td>
<td>151 ± 10</td>
</tr>
<tr>
<td>HRpeak range, beats/min</td>
<td>140–166</td>
</tr>
<tr>
<td>RERpeak</td>
<td>1.12 ± 0.11</td>
</tr>
<tr>
<td>RERpeak range</td>
<td>1.00–1.30</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. V˙O2peak, peak O2 uptake; HRpeak, peak heart rate; RERpeak, peak respiratory exchange ratio. *Values in PAD groups less than that in individual control groups, P < 0.05.

Table 3. V˙O2 kinetics, 0% grade exercise

<table>
<thead>
<tr>
<th>Control Subjects</th>
<th>PAD Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsmoking</td>
<td>Smoking</td>
</tr>
<tr>
<td>n</td>
<td>9</td>
</tr>
<tr>
<td>Baseline V˙O2, ml/min</td>
<td>316 ± 52</td>
</tr>
<tr>
<td>τ0, s</td>
<td>19.5 ± 10.5</td>
</tr>
<tr>
<td>A1, ml/min</td>
<td>545 ± 164</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. Monoexponential curves were fit to the V˙O2 data for exercise at 0% grade. Baseline V˙O2, resting V˙O2 before exercise onset; τ, monoexponential time constant; A1, change in V˙O2 from exercise onset to steady state. *Values in PAD groups different from that of individual control groups, P < 0.05.

There were no differences between the kinetic responses of the nonsmoking and the smoking control groups, all of which were monoexponential.

V˙O2 kinetics, 4% grade. There were no differences in resting V˙O2 between groups before exercise at 4% grade. Phase 1 kinetic parameters (τ0, A0) were not different between groups (Table 4). The time delay (TD1) until the beginning of phase 2 was comparable between all groups. The phase 2 time constant (τ1) was similar between the unilateral and bilateral PAD groups (see individual data points in Fig. 2), but a significant slowing of the phase 2 time constant was observed in the unilateral and bilateral PAD patients compared with nonsmoking and smoking control subjects (P < 0.05 for PAD groups vs. combined control groups). The amplitude of phase 2 (A1) was not different between the PAD and control groups. Kinetic parameters did not differ between nonsmoking and smoking control groups. Under the exercise protocols that were used, steady-state exercise conditions were confirmed by a plateau of the V˙O2 response and the absence of a phase 3 exponential component of the curve fit for any group in any exercise.
Table 5. $\Sigma V_\text{O}_2$ at 4% grade exercise

<table>
<thead>
<tr>
<th>Time Duration, s</th>
<th>Control Subjects (18)</th>
<th>PAD Subjects (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–60</td>
<td>4.99 ± 0.63</td>
<td>4.25 ± 1.01*</td>
</tr>
<tr>
<td>0–90</td>
<td>8.73 ± 0.95</td>
<td>7.57 ± 1.68*</td>
</tr>
<tr>
<td>0–120</td>
<td>12.62 ± 1.35</td>
<td>11.15 ± 2.66*</td>
</tr>
<tr>
<td>0–180</td>
<td>21.10 ± 2.31</td>
<td>19.51 ± 3.56</td>
</tr>
<tr>
<td>0–300</td>
<td>37.59 ± 4.18</td>
<td>35.92 ± 6.73</td>
</tr>
</tbody>
</table>

Values are means ± SD; no. of subjects in parentheses. $\Sigma V_\text{O}_2$ was calculated from onset of exercise (time 0) to specified duration (in s). *Values in PAD groups different from that of individual control groups, P < 0.05.

Table 6. Heart rate responses

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>PAD Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmoking</td>
<td>Smoking</td>
</tr>
<tr>
<td>n</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Exercise at 0% grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>76 ± 13*</td>
<td>82 ± 11</td>
</tr>
<tr>
<td>Steady state</td>
<td>82 ± 11*</td>
<td>95 ± 12</td>
</tr>
<tr>
<td>$\Delta HR$</td>
<td>6 ± 4</td>
<td>3 ± 7</td>
</tr>
<tr>
<td>Exercise at 4% grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>77 ± 13</td>
<td>77 ± 7</td>
</tr>
<tr>
<td>Steady state</td>
<td>92 ± 16</td>
<td>90 ± 3</td>
</tr>
<tr>
<td>$\Delta HR$</td>
<td>14 ± 5</td>
<td>14 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SD in beats/min; n, no. of subjects. Baseline, resting HR before exercise onset; steady state, steady-state HR at end of exercise; $\Delta HR$, change in HR from exercise onset to steady state. Baseline and steady-state HR were lower in nonsmoking control group than in other 3 groups during exercise at 0% grade. HR response for exercise at 0% grade was greater in PAD patients than in control subjects. Baseline and steady-state HR were elevated in unilateral PAD patients compared with other 3 groups. HR response to exercise at 4% grade was greater in PAD patients than in control subjects. *Values for individual group different from other 3 groups P < 0.05.†Value for PAD different from individual control groups, P < 0.05.

DISCUSSION

The present study demonstrates that during constant-load treadmill exercise, the kinetics of $V_\text{O}_2$ at the onset of exercise were markedly slowed in patients with PAD compared with control subjects. The impaired $V_\text{O}_2$ kinetic responses in PAD patients appeared to be related to the presence of vascular disease but not to the hemodynamic severity, because the prolongation in the $V_\text{O}_2$ time constant was not associated with the degree of reduction in ABI or whether one or both legs were affected. Furthermore, the $V_\text{O}_2$ kinetic impair-
ment in PAD could not be explained by phase 1 kinetic differences, reduced HR responses, or current smoking status. This suggests that neither central cardiac factors nor smoking status could account for the marked slowing of the phase 2 time constant observed in patients with PAD.

Typically, to eliminate weight-bearing influences and allow accurate measures of work rate, cycle exercise has been used to determine \( \dot{V}O_2 \) kinetics. Although less optimal than cycle exercise, treadmill exercise was used in the present study to assess the \( \dot{V}O_2 \) kinetics, because walking is the activity that produces the claudication pain observed in patients with PAD. Differences in body weight between groups were not significant and, therefore, were not expected to confound \( \dot{V}O_2 \) kinetic responses. In the present study, neither the total change in \( \dot{V}O_2 \) from resting to steady state at 0% grade \((A_0)\) and 4% grade \((A_0 + A_1)\) nor the absolute steady-state \( \dot{V}O_2 \) achieved was different between groups. Therefore, the actual work rate and walking efficiency appeared to be similar between groups. The exponential curve fitting was influenced neither by differences in steady-state \( \dot{V}O_2 \) between PAD and control groups nor by the presence of a slow component of \( \dot{V}O_2 \) (phase 3). Furthermore, phase 2 \( \dot{V}O_2 \) kinetics have been shown to be workload independent during cycling exercise at workloads below the lactate threshold \((6)\). An exponential phase 3 \( \dot{V}O_2 \) kinetic response (slow component) was not observed in any subject during either 0 or 4% grade exercise testing. The absence of a slow component was due to the low level of walking exercise (sub-VAT) and was corroborated by RER values well below 1.00. Although no direct measures of blood lactate concentration were made, previous studies have reported only small increases in systemic lactate levels, even at peak claudication-limited exercise in PAD patients \((18, 20)\). These observations support the finding in the present study that lactate accumulation and the presence of a phase 3 component of \( \dot{V}O_2 \) are not likely a significant contributor to the slowed kinetics.

Kinetic responses. Phase 1 \( \dot{V}O_2 \) kinetics at 4% grade (representing the cardiac component of \( \dot{V}O_2 \) kinetics) were not different, as assessed by either the time constant \( (\tau_0) \) or change in \( \dot{V}O_2 \) \((A_0)\) between the PAD and control groups. However, a significantly greater dynamic HR response from rest to steady state \((\Delta HR)\) was apparent in the PAD groups compared with the control groups. This could reflect greater cardiac sympathetic stimulation in PAD patients compared with controls. Importantly, a defect in the central cardiac component of the \( \dot{V}O_2 \) kinetic response is possible, although the present data suggest that this may be unlikely.

The time delays of \( \dot{V}O_2 \) \((TD_0)\) observed in the present study are longer compared with values observed during measurements made during cycling exercise \((6, 7, 31, 36)\). Multiexponential modeling with time delays of human \( \dot{V}O_2 \) kinetics has not been previously described during low-level walking exercise. Potentially, the mode of exercise (treadmill walking vs. cycling), exercise intensity, or physiological changes associated with aging (such as alterations in vascular conductance) may elicit an exercise \( \dot{V}O_2 \) response profile that is different from that observed for cycle exercise.

Phase 2 \( \dot{V}O_2 \) kinetic time constants were notably slowed in patients with PAD during treadmill walking at 4% grade. These observations are consistent with the findings of a reduced \( \dot{V}O_2 \)-work rate relationship during incremental cycle exercise in patients with PAD compared with normal controls \((16)\). The \( \dot{V}O_2 \) kinetic data, from curve-fitting procedures, also confirm observations by Auchincloss et al. \((2, 3)\) of a reduced 1-min \( \dot{V}O_2 \) in PAD patients compared with controls. Auchincloss et al. concluded that the reduction appeared to be the result of a primary impairment in peripheral flow, because improvement of flow through surgical bypass interventions improved 1-min \( \dot{V}O_2 \) to nearly normal values. However, if limited total peripheral blood flow is solely responsible for the slowed \( \dot{V}O_2 \) response in PAD, a relationship would be expected between the \( \dot{V}O_2 \) kinetic response and worsening degrees of disease severity (as conventionally measured by ABI) as well as a difference between patients with unilateral vs. bilateral disease. The data in the present study revealed no differences in time constants \((\tau)\) between the unilateral and bilateral PAD groups, despite substantially different quantitative amounts of total lower extremity flow limitation. Furthermore, there was no correlation between worst affected leg ABI and \( \tau \) in unilateral and bilateral PAD patients. This implies that hemodynamic disease severity (ABI) could not predict the degree of \( \dot{V}O_2 \) kinetic impairment.

Limited peripheral blood flow may only partially account for the slowing of the time constant during phase 2. A second contributor to phase 2 \( \dot{V}O_2 \) kinetics is the response intrinsic to the exercising muscle. The transition from rest to a fixed workload requires an enhanced production of ATP to meet an elevated ATP requirement. Immediately after the onset of exercise, this energy demand is met by preformed ATP, and the rapid conversion of creatine phosphate \((CrP)\) to ATP. Neither of these energy sources requires the catabolism of substrates or the consumption of \(O_2\). However, the stores of these high-energy phosphates can only support exercise for brief periods. As ATP and CrP are consumed, the free ADP concentration in muscle increases. Although the regulation of mitochondrial respiration in muscle is complex, the ADP concentration is a potential major control point for stimulating \( \dot{V}O_2 \). Thus mitochondrial respiration can be described as a function of ADP concentration in vivo \((23, 37)\). As ADP accumulates with the onset of exercise, mitochondrial \(O_2\) consumption (and hence ATP production) increases until the ADP level sustains an ATP production that matches the ATP demands of the imposed workload. The time constant for the accumulation of ADP in muscle can be equated with the respiratory \( \dot{V}O_2 \) kinetics \((5)\). Therefore, anything that alters the ADP vs. mitochondrial respiration relationship will alter the kinetics of \( \dot{V}O_2 \). This concept has been observed by the
improvement of VO$_2$ kinetics in older and younger subjects after training and has been validated in patients with mitochondrial myopathies by using $^{31}$P-nuclear magnetic resonance spectroscopy (4, 23, 31).

Although peripheral blood flow at rest is normal in PAD patients, there is considerable evidence that skeletal muscle metabolic regulation is altered, secondary to the sequelae of muscle ischemia with exercise (9). For example, skeletal muscle in patients with PAD has a 19–36% increase in expression of mitochondrial enzymes, accumulation of oxidative intermediates, and evidence of acquired mitochondrial DNA injury (8a, 11, 12, 18, 21, 23, 32). These metabolic changes appear to be relevant, because they correlate with patients' functional performance, in contrast to lack of correlation of hemodynamic measurements (1, 20, 29). Importantly, the ADP vs. mitochondrial respiration relationship is altered in PAD, and more ADP is required than is hemodynamic measurements (1, 20, 29). Importantly, taken together, these data support the hypothesis that PAD is associated with an alteration in the ADP vs. mitochondrial respiration relationship that potentially results from an acquired mitochondrial myopathy and that strategies to improve metabolic function may be an important therapeutic target (9).

$\Sigma$VO$_2$, $\Sigma$VO$_2$ was used to evaluate 4% grade VO$_2$ kinetics in a manner independent of curve-fit modeling techniques. This measure of VO$_2$ kinetics revealed differences between the PAD groups and the combined control groups from exercise onset to 60, 90, and 120 s but not from onset to 180 and 300 s. The loss of discrimination of $\Sigma$VO$_2$ at 180- and 300-s time intervals suggests that the kinetic response is not well described by time intervals beyond 120 s of exercise. Importantly, $\Sigma$VO$_2$ can differentiate between diseased and nondiseased patients over the early portions of an exercise transition and can confirm curve-fit analyses of the slowed VO$_2$ kinetic response in PAD.

Effects of smoking. Because most PAD patients are present or former cigarette smokers, a control group of healthy smoking subjects was included to address the impact of smoking status and pack·yr on the time constant of VO$_2$ kinetics. Smoking status and pack·yr history may have influenced the time constant of VO$_2$ kinetics, either through an acute impairment in O$_2$-carrying capacity by formation of carboxyhemoglobin or through systemic changes in O$_2$ utilization caused by chronic cigarette use (25, 33). However, in smoking control subjects, pack·yr and smoking status were not associated with slowing of the VO$_2$ time constants compared with nonsmoking controls. Therefore, the impairment in VO$_2$ kinetics observed in PAD patients was not a direct function of smoking status or pack·yr history.

Summary. The present data demonstrate that the VO$_2$ kinetic response to low-level, constant-load treadmill exercise are slowed in patients with PAD. Further research will be necessary to definitively assess whether peripheral flow limitations or changes in the regulation of skeletal muscle oxidative function, or both, are responsible for the observed response in patients with PAD.

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