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

TIMOTHY A. BAUER, JUDITH G. REGENSTEINER, ERIC P. BRASS, AND WILLIAM R. HIATT

Section of Vascular Medicine, Division of General Internal Medicine, Geriatrics, and Cardiology, University of Colorado Health Sciences Center, Denver, Colorado 80262; and Department of Medicine, Harbor-UCLA Medical Center, Torrance, California 90509

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.

heart rate; oxygen consumption; muscle metabolism

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

http://www.jap.org 8750-7587/99 $5.00 Copyright © 1999 the American Physiological Society 809
PAD was confirmed by the measurement of the ankle-brachial index (ABI; described below). Patients with PAD were enrolled who had an ABI ≤ 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-yr history (packs/day × no. of yr of smoking) of >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 (30).

Nonsmoking control subjects had no chronic medical diseases (by history and a normal physical exam), were taking no medications, and had no prior 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 ≥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 V˙O2 kinetics (25, 33).

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 (14). Subjects without PAD (nonsmoking controls and smoking controls) performed a standard Bruce treadmill protocol to maximal effort (10). All tests were performed on a Quinton 4000 treadmill (Quinton Instruments, Seattle, WA). Heart rate (HR) was measured minute-by-minute by using 12-lead ECG recordings. Blood pressure was monitored by auscultation during every stage of graded exercise.

All subjects performed multiple exercise tests at a constant work rate from rest to 2.0 miles/h, 0% grade on 1 day and at 2.0 miles/h, 4% grade on another day that was separated from the first test by 1 wk. These workloads were chosen because they were well tolerated by all subjects and could be sustained for at least 6 min. These workloads elicited a 450–700 ml/min change in absolute V˙O2 from baseline. The exercise at 4% grade corresponded to V˙O2 values well below the ventilatory anaerobic threshold (VAT) for the healthy subjects. In patients with PAD, the steady-state V˙O2 at 4% grade was below the peak V˙O2 (V˙O2peak was attained during claudication-limited exercise). The VAT could not be measured in PAD patients, because the incremental tests were terminated due to claudication before attaining gas-exchange criteria for establishing VAT. To minimize intertest variance, subjects were familiarized with the testing protocol on the first day, with six to ten 30-s transitions from rest to exercise. As part of the familiarization, each subject initiated walking on a moving treadmill (2.0 miles/h) with the same foot for each transition; one hand was on the handrail, the other was held at the side. The tests for assessment of V˙O2 kinetics consisted of obtaining 3 min of resting data, followed by 6 min of constant-rate walking. Each of the 0 and 4% grade tests were repeated four times to allow an average response to be calculated. Subjects rested for 20 min in a seated position between exercise tests.

Measurement of gas exchange. With the use of a Medical Graphics CPX/D metabolic system (Medical Graphics Corporation, St. Paul, MN), rates of V˙O2 and CO2 output (V˙CO2) were measured breath by breath and averaged to 20-s intervals for the determination of V˙O2peak. V˙O2peak was defined as the highest V˙O2 achieved during the graded test. Respiratory exchange ratio (RER) was calculated as the ratio of V˙CO2 to V˙O2. Breath-by-breath data for kinetic analysis were acquired for V˙O2 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˙O2 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 the average response curves by using nonlinear regression techniques. A single-exponential model without a time delay was used to assess the overall V˙O2 kinetic response at 2.0 miles/h, 0% grade because the V˙O2 response curve was monophasic and no phase 1 was observed. The curve is described by the formula

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

(1)

In the single-exponential model, \( \dot{V}O_2(t) \) is the V˙O2 at time \( t \), \( \dot{V}O_2(b) \) is the resting baseline V˙O2 (in ml/min) before exercise, \( A_1 \) (in ml/min) is the difference between the baseline value and the new steady state, and \( b \) (in s) is defined as the time constant representing the rate of increase in V˙O2 of the exercise-response curve [equal to time (in s) to 63% of the change in V˙O2 from baseline to steady-state exercise].

In contrast to the V˙O2 responses at 0% grade, the test at 4% grade resulted in a much larger increase in V˙O2; thus a two-phase model was used to describe three distinct phases of V˙O2 kinetics.

\[ \dot{V}O_2(t) = \dot{V}O_2(b) + A_1(1 - e^{-(t-b)}) + A_2(1 - e^{-(t-TD1)}) + A_3(1 - e^{-(t-TD2)}) \]  

(2)

where \( \dot{V}O_2(b) \) is the resting V˙O2 at 4% grade before exercise, \( A_1 \) is the steady-state V˙O2 attained during claudication-limited exercise, \( A_2 \) and \( A_3 \) are the increments above the new steady state, and \( T_D1 \) and \( T_D2 \) are the time constants corresponding to phases 2 and 3. The two phases of the exercise-response curve were determined by using a statistical program [BMDP (1988), Los Angeles, CA] to fit a two-exponential model to the data.
The first exponential fit the initial rapid increase in VO₂ at the onset of exercise, which represents an increase in pulmonary blood flow (cardiodynamic phase of VO₂ kinetics: phase 1) (Fig. 1) (36). For comparisons of phase 1, τ₀ (in s) described the rate of rise in VO₂ during phase 1, and A₀ described the change in amplitude of VO₂ (in ml/min). After a time delay (TD₁; in s), the second exponential fit phase 2 of the response curve, reflecting peripheral O₂ delivery and VO₂ (6, 7, 36). Phase 2 comparisons between groups were made by using τ₁ (the rate of rise in VO₂ during phase 2) and A₁ [the change in amplitude of VO₂ (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 VO₂ kinetics), which would follow a second time delay (TD₂; in s). A phase 3 increase in VO₂ 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 VO₂ data were also derived at 4% grade, independent of curve-fit modeling techniques, by the sum of breath-by-breath VO₂ (∑VO₂) over several intervals of exercise (from exercise onset to 60, 90, 120, 180, and 300 s). By using the raw breath-by-breath VO₂ data (Bᵣ; in ml/min) and the duration of each breath (Dᵣ; in s), ∑VO₂ was calculated as the milliliters of VO₂ consumed over a selected interval minus the product of resting baseline average (VO₂ₓ; in ml/min) and the duration of the selected interval in minutes (tᵢᵣₘᵢₚ). 

$$\sum \dot{V}O_2 = \sum_{0}^{n-1} (Bᵣ/60)(Dᵣ) - (\dot{V}O_2)(x)(tᵢᵣₘᵢₚ) \tag{3}$$

$$\Sigma \dot{V}O_2$$ was normalized to body weight to minimize the influences of weight on absolute VO₂ 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 641, Parks Medical Electronics, Beaverton, OR). The pressures in the dorsalis pedis and posterior tibial 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 $\Sigma \dot{V}O₂$ 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>
<thead>
<tr>
<th>Table 1. Subject characteristics</th>
<th>Control Subjects</th>
<th>PAD Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmoking</td>
<td>Unilateral</td>
</tr>
<tr>
<td>n</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Age, yr</td>
<td>65 ± 3</td>
<td>58 ± 7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82.5 ± 11.0</td>
<td>73.5 ± 7.8</td>
</tr>
<tr>
<td>Pack-yr</td>
<td>0</td>
<td>46.6 ± 24.7</td>
</tr>
<tr>
<td>Less-affected leg ABI pre</td>
<td>1.24 ± 0.09</td>
<td>1.17 ± 0.08</td>
</tr>
<tr>
<td>Worse-affected leg ABI pre</td>
<td>1.14 ± 0.05</td>
<td>1.12 ± 0.17</td>
</tr>
<tr>
<td>Less-affected leg ABI post</td>
<td>1.16 ± 0.11</td>
<td>1.11 ± 0.10</td>
</tr>
<tr>
<td>Worse-affected leg ABI post</td>
<td>1.12 ± 0.05</td>
<td>0.30 ± 0.04†</td>
</tr>
</tbody>
</table>

*Values are means ± SD; n, no. of subjects. PAD, peripheral arterial disease; pack-yr, packs/day yr of cigarettes smoked; ABI pre and ABI post, pre- and postexercise ankle-brachial index, respectively. †Values in bilateral PAD patients significantly lower than that of individual control groups and less-affected leg of unilateral PAD patients, P < 0.05. †Values in worse-affected leg in PAD patients significantly lower than that of individual control groups, P < 0.05.
Table 2. Peak performance characteristics

<table>
<thead>
<tr>
<th>Control Subjects</th>
<th>PAD Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmoking</td>
</tr>
<tr>
<td>n</td>
<td>9</td>
</tr>
<tr>
<td>VO2peak, ml·kg⁻¹·min⁻¹</td>
<td>30.0±4.0</td>
</tr>
<tr>
<td>HRpeak, beats/min</td>
<td>151±10</td>
</tr>
<tr>
<td>RERpeak</td>
<td>1.12±0.11</td>
</tr>
<tr>
<td>Time delay, s</td>
<td>0.11±0.07</td>
</tr>
</tbody>
</table>

Values are means ± SD; n: n: no. of subjects. VO2peak: 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. VO2 kinetics, 0% grade exercise

<table>
<thead>
<tr>
<th>Control Subjects</th>
<th>PAD Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmoking</td>
</tr>
<tr>
<td>n</td>
<td>9</td>
</tr>
<tr>
<td>Baseline VO2, ml/min</td>
<td>316±52</td>
</tr>
<tr>
<td>τ0, s</td>
<td>19.5±10.5</td>
</tr>
<tr>
<td>τ1, s</td>
<td>545±164</td>
</tr>
</tbody>
</table>

Values are means ± SD; n: no. of subjects. Multiexponential curves were fit to the VO2 data for exercise at 0% grade, τ0: phase 1 time constant; τ1: phase 2 time constant; A0: change in VO2 from exercise onset to end of phase 1; A1: change in VO2 from end of phase 1 to end of phase 2; A2: total change in VO2 from exercise onset to steady state; time delay: time from onset of exercise to start of phase 2. *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.

VO2 kinetics, 4% grade. There were no differences in resting VO2 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 VO2 response and the absence of a phase 3 exponential component of the curve fit for any subject in any group.

![Fig. 2. Individual phase 2 time constant data from 2.0 miles/h, 4% grade treadmill exercise for all groups. Tau, phase 2 time constant from multiple exponential (in s); NS, nonsmoking control; Smoking, smoking control; Uni, unilateral PAD patients; Bi, bilateral PAD patients.](http://jap.physiology.org/)
Subjects. *Values for individual group different from other 3 groups.

HR response control subjects. Baseline and steady-state HR were elevated in response for exercise at 0% grade was greater in PAD patients than in control group than in other 3 groups during exercise at 0% grade. HR end of exercise; resting HR before exercise onset; steady state, steady-state HR at the end of exercise;
P,

The mean steady-state HR achieved at the end of the 0% grade exercise was lower described the HR response. The mean steady-state HR at the onset of exercise was lower in the nonsmoking control group than in the smoking control and in the unilateral and bilateral PAD groups.

HR responses. Before exercise at 0% grade, resting HRs were comparable between the smoking controls and the unilateral and bilateral PAD patients (Table 6), but resting HRs of nonsmoking controls were lower compared with the other three groups (P < 0.05). HR kinetic analyses for 0 and 4% grades were attempted by using monoeXponential curve-fitting techniques. However, the exercise-response curves for HR were neither exponential nor linear and could not be fit reliably by using these methods. Therefore, time constants or mean response times may not have appropriately described the HR response. The mean steady-state HR achieved at the end of the 0% grade exercise was lower in the nonsmoking control group than in the smoking control and in the unilateral and bilateral PAD groups.

Table 5. \( \Sigma V'O_2 \) 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>Sb</td>
<td>V'O_2, ml/kg</td>
<td></td>
</tr>
<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>12.82 ± 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. \( \Sigma V'O_2 \) 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.

\( \Sigma V'O_2 \) measures. \( \Sigma V'O_2 \) measures at 4% grade were lower in all patients with PAD compared with the combined control groups from rest to 60, 90, and 120 s (P < 0.05 for PAD group vs. combined control group; Table 5). Measures from exercise onset to 180 and 300 s did not differ between the PAD patient population and the combined control subjects.

DISCUSSION

The present study demonstrates that during constant-load treadmill exercise, the kinetics of \( V'O_2 \) at the onset of exercise were markedly slowed in patients with PAD compared with control subjects. The impaired \( V'O_2 \) 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 V\( O_2 \) time constant was not associated with the degree of reduction in ABI or whether one or both legs were affected. Furthermore, the \( V'O_2 \) 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 VO₂ kinetics. Although less optimal than cycle exercise, treadmill exercise was used in the present study to assess the VO₂ 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 VO₂ kinetic responses. In the present study, neither the total change in VO₂ from resting to steady state at 0% grade (A₀) nor the absolute steady-state VO₂ 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 VO₂ between PAD and control groups nor by the presence of a slow component of VO₂ (phase 3). Furthermore, phase 2 VO₂ kinetics have been shown to be workload independent during cycling exercise at workloads below the lactate threshold (6). An exponential phase 3 VO₂ 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 claudication-limited exercise in PAD patients (18, 20).

Limited peripheral blood flow may only partially account for the slowing of the time constant during phase 2. A second contributor to phase 2 VO₂ kinetics is the responses 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 O₂. However, the stores of these high-energy phosphates can only supply 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 VO₂. 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 O₂ 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 VO₂ kinetics (5). Therefore, anything that alters the ADP vs. mitochondrial respiration relationship will alter the kinetics of VO₂. This concept has been observed by the
improvement of $V_\text{O}_2$ 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 sequellae 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 needed by control subjects to sustain a given level of mitochondrial function. The present demonstration of slowed respiratory $V_\text{O}_2$ kinetics in patients with PAD is in complete concordance with the $^{31}$P-nuclear magnetic resonance spectroscopy of Kemp et al. (22). These data suggest that altered muscle mitochondrial function may contribute to the delayed $V_\text{O}_2$ kinetic response, although a detraining effect may present an alternate contributor to the slowed kinetic response in PAD patients. 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).

$\Sigma V_\text{O}_2$, $\Sigma V_\text{O}_2$ was used to evaluate 4% grade $V_\text{O}_2$ kinetics in a manner independent of curve-fit modeling techniques. This measure of $V_\text{O}_2$ 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 $V_\text{O}_2$ 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, $\Sigma V_\text{O}_2$ can differentiate between diseased and nondiseased patients over the early portions of an exercise transition and can confirm curve-fit analyses of the slowed $V_\text{O}_2$ 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 $V_\text{O}_2$ kinetics. Smoking status and pack-yr history may have influenced the time constant of $V_\text{O}_2$ kinetics, either through an acute impairment in $V_\text{O}_2$-carrying capacity by formation of carboxyhemoglobin or through systemic changes in $V_\text{O}_2$ 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 $V_\text{O}_2$ time constants compared with nonsmoking controls. Therefore, the impairment in $V_\text{O}_2$ kinetics observed in PAD patients was not a direct function of smoking status or pack-yr history.

Summary. The present data demonstrate that the $V_\text{O}_2$ kinetic responses 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.

We thank the patients who gave of their time. We also acknowledge Andria Vogelsong, Susan Smith, and Amy Thomas for their assistance with the study and an Ingebritsen for development of the kinetic analysis software.

Address for reprint requests and other correspondence: W. R. Hiatt, Section of Vascular Medicine, Univ. of Colorado Health Sciences Center, Box B-179, 4200 E. Ninth Ave., Denver, CO 80262 (E-mail: Will.Hiatt@UCHSC.edu).

Received 3 September 1998; accepted in final form 31 March 1999.

REFERENCES