Pulmonary $\dot{V}O_2$ dynamics during treadmill and arm exercise in peripheral arterial disease

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Bauer, Timothy A., Eric P. Brass, Mark Nehler, Thomas J. Barstow, and William R. Hiatt. Pulmonary $\dot{V}O_2$ dynamics during treadmill and arm exercise in peripheral arterial disease. J Appl Physiol 97: 627–634, 2004. First published April 16, 2004; 10.1152/japplphysiol.00612.2003.—Slowed pulmonary $O_2$ uptake ($\dot{V}O_2$) kinetics in peripheral arterial disease (PAD) have been attributed to impaired limb blood flow and/or peripheral muscle metabolic abnormalities. Although PAD results from atherosclerotic occlusive disease in the arteries to the lower extremities, systemic abnormalities affecting whole body $O_2$ delivery or vascular function in PAD could also partially explain the exercise impairment. To date, the effects of these systemic abnormalities have not been evaluated. To test the hypothesis that the slowed pulmonary $\dot{V}O_2$ kinetics in PAD reflects local and not systemic abnormalities, $\dot{V}O_2$ kinetics were evaluated after the onset of constant-load exercise of the upper and lower limbs in PAD patients and healthy controls (Con). Ten PAD patients and 10 Con without significant cardiopulmonary dysfunction performed multiple transitions from rest to moderate-intensity arm ergometry and treadmill exercise to assess their $\dot{V}O_2$ kinetic responses. Reactive hyperemic (RH) blood flow was assessed in the arms and legs as a measure of endothelial function. Compared with Con, PAD $\dot{V}O_2$ kinetic phase 2 time constants were prolonged during treadmill exercise (PAD 34.3 ± 9.2 s vs. Con 19.6 ± 3.5 s; P < 0.01) but not arm exercise (PAD 38.5 ± 7.5 s vs. Con 32.5 ± 9.0 s; P > 0.05). RH blood flow was significantly reduced in the legs (PAD 20.7 ± 8.3 s vs. Con 46.1 ± 17.1 ml·100 ml⁻¹·min⁻¹; P < 0.01) and arms of PAD subjects (PAD 34.0 ± 8.6 vs. Con 50.8 ± 12.2 ml·100 ml⁻¹·min⁻¹; P < 0.01) compared with Con, but RH limb flow was not correlated with arm or treadmill $\dot{V}O_2$ kinetic responses in either group. In summary, slowed pulmonary $\dot{V}O_2$ kinetics in PAD patients occur only with exercise of the lower limbs affected by the arterial occlusive disease process and are not slowed with exercise of the unaffected upper extremities compared with controls. Furthermore, the slowed pulmonary $\dot{V}O_2$ kinetics of the lower extremity could not be explained by any abnormalities in resting cardiac or pulmonary function and were not related to the magnitude of reduction in limb vascular reactivity.

PATIENTS WITH PERIPHERAL ARTERIAL DISEASE (PAD) have atherosclerotic arterial occlusions that predominantly affect the lower limbs (22, 32). The principal symptom of PAD is claudication pain in the muscles of the lower extremity that results in a profound reduction in exercise tolerance and community-based walking ability (16, 17).

After the onset of walking exercise in PAD patients, pulmonary $O_2$ uptake ($\dot{V}O_2$) kinetics are slowed, indicating an impaired rate of $O_2$ to meet the increased muscle metabolic demand of exercise (1, 2, 5, 13). Previous observations of slowed $\dot{V}O_2$ kinetics in PAD have attributed the impaired kinetic response to the arterial occlusions of the lower extremity limiting $O_2$ delivery (1) and/or to abnormalities of peripheral skeletal muscle metabolism (2, 5). However, it remains unresolved whether the observed pulmonary $\dot{V}O_2$ kinetic responses in PAD result from systemic rather than local abnormalities secondary to atherosclerosis that could influence $O_2$ delivery. For example, abnormalities in cardiac or pulmonary function could slow pulmonary $\dot{V}O_2$ kinetics by altering systemic $O_2$ delivery via a central cardiopulmonary impairment, as observed in patients with atherosclerotic coronary artery disease (21) or obstructive pulmonary disease (30). Furthermore, $O_2$ delivery in PAD could be influenced not only by the large artery occlusions but also by reductions in systemic vascular reactivity that are observed in atherosclerotic diseases (14). Thus, given the complex pathophysiology of PAD, distinguishing between these potential systemic and regional influences on pulmonary $\dot{V}O_2$ kinetics would further clarify and localize potential causes of the exercise impairment in PAD.

The present investigation tested the hypothesis that the abnormal pulmonary $\dot{V}O_2$ kinetics in PAD reflect local and not systemic abnormalities. To differentiate the impact of systemic sequelae from atherosclerotic disease as a factor in the abnormal $\dot{V}O_2$ kinetics, pulmonary $\dot{V}O_2$ kinetics were measured during leg (affected by the arterial occlusive disease process) and arm (no gross evidence of arterial disease) exercise in PAD patients compared with healthy control subjects. Reactive hyperemic responses in the arms and legs were assessed to quantify the anticipated systemic dysfunction, and the relationships between the hyperemic response and $\dot{V}O_2$ kinetics were defined. Formal evaluations were conducted to ensure that no participants in the studies had significant cardiac or pulmonary dysfunction, thus partially excluding the influence of any central $O_2$ delivery impairment on the PAD $\dot{V}O_2$ kinetic responses.

MATERIALS AND METHODS

Subjects. Ten patients with PAD and 10 healthy control subjects of similar ages were recruited for this investigation. The University of Colorado Multiple Institutional Review Board approved the study.

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and informed consent was obtained from all subjects before study participation.

All subjects underwent screening pulmonary function tests, resting echocardiography, and peak exercise testing with electrocardiograph (ECG) monitoring to exclude cardiopulmonary disease that could affect systemic O₂ delivery. Subjects were excluded from study if they exhibited 1) a history of coronary artery disease, previous myocardial infarction, or coronary revascularization; angina, stroke, congestive heart failure, or diabetes mellitus; 2) hematology or chemistry laboratory values outside of normal limits; 3) evidence of impaired pulmonary function [forced expiratory volume in 1 s (FEV₁) forced vital capacity (FVC) of <0.70 or >1.20]; 4) echocardiographic findings of impaired cardiac performance (resting ejection fraction of <50%, diastolic dysfunction, or any left ventricular wall motion abnormalities); or 5) evidence of ischemic ECG changes during graded maximal exercise testing.

Healthy, nonsmoking control subjects, who had no chronic medical diseases by medical history and a normal physical examination, were studied. Healthy subjects had an ankle-brachial index (ABI) of >1.00 in both legs at rest, no history of PAD or other cardiovascular disease, and no ischemic ECG changes at rest or with graded, maximal exercise testing. All subjects were sedentary, as defined by not participating in a regular exercise program (<1 episode of exercise/ wk) and having similar scores on the low-level physical activity recall questionnaire with PAD patients (Table 1) (27). Two healthy control subjects were treated with statin drugs, but the remaining healthy subjects were taking no medications.

PAD was confirmed in patients by a resting ABI of <0.90, which fell at least 0.10 after peak exercise. All PAD patients exhibited symptoms of claudication during walking, defined as localized discomfort or cramping in the muscles of the affected legs, which occurred only with exercise and was completely relieved after 10 min of rest. The absence of upper extremity occlusive arterial disease was confirmed by equal arm blood pressures and pulse examinations and the absence of ischemic arm symptoms during arm ergometry testing. Patients with ischemic rest pain or ischemic ulceration in either leg were excluded from study. Patients with PAD included eight subjects with bilateral occlusive disease and two subjects with unilateral disease (defined as a reduced ABI and claudication symptoms in 1 leg but no symptoms and an ABI of >0.90 at rest that did not decrease with exercise in the other leg). All patients with PAD were taking aspirin, seven were treated with statin drugs, four were treated with calcium channel-blocking agents, two with diuretics, and one with an angiotensin-converting enzyme inhibitor. Because β-adrenergic blocking drugs may alter the V̇O₂ kinetic response to exercise (25), subjects taking these medications were excluded from study.

Protocol design. Each study participant visited the Vascular Research Laboratory at the University of Colorado-Health Sciences Center on seven occasions for evaluation. Subjects were instructed to avoid the consumption of alcohol, caffeine, and smoking (only 2 PAD patients and no control subjects were current smokers) within the 12 h before each visit and to avoid food consumption within 4 h before each visit. All exercise testing visits took place at the same time of day for each subject. The first visit was used to obtain initial screening measurements and for subject familiarization with the exercise testing equipment. At the second visit, all subjects underwent a resting echocardiogram. The subsequent five visits consisted of peak treadmill and arm ergometry testing, arm and leg limb blood flow measurements, and constant work rate (CWR) exercise tests for the analysis of V̇O₂ kinetics.

Graded exercise testing. Subjects performed a single graded treadmill test and an incremental arm ergometry test on separate days for the determination of peak arm and peak treadmill exercise performance (peak V̇O₂). Patients with PAD performed their graded treadmill test using the Gardner protocol (speed constant at 2 miles/h, 2% increase in grade every 2 min) to maximal claudication pain, which preceded any further walking (20). Healthy subjects performed a standard Bruce protocol to maximal effort (9). All treadmill tests were performed on a Quinton 4000 treadmill (Quinton Instruments, Seattle, WA). For determination of upper extremity peak V̇O₂, subjects performed an incremental arm ergometry test (ramping function of 7–10 W/min) on an electrically braked cycle ergometer modified for this purpose (Lode Excalibur). For all graded exercise tests, heart rate (HR) was measured continuously by 12-lead ECG recordings.

CWR exercise testing. On 2 separate days, subjects performed exercise transitions from rest to a CWR of treadmill walking (2.0 miles/h, 4% grade) as previously described (5). This particular work rate was selected because all subjects (including PAD) could sustain 6 min of CWR exercise without stopping and because the work rate was sufficient to elicit a measurable increase in V̇O₂ suitable for determination of the V̇O₂ kinetic responses. Each exercise transition consisted of a resting baseline period to obtain gas-exchange data followed by 6 min of CWR walking exercise. On a different day, subjects performed three 6-min CWR arm exercise transitions at a moderate workload equal to ~90% of the individual subject’s arm-specific lactate threshold (LT) by gas-exchange criteria (i.e., 10% below the individual LT). Each arm transition was separated by 10 min of rest. Respiratory gas-exchange measurements and HR data were recorded throughout the resting baseline, exercise, and recovery of each CWR bout.

Reactive hyperemia blood flow measurements. Limb blood flow was measured in the supine position by venous occlusion strain-gauge plethysmography (DE Hokanson, Issaquah, WA) at rest and during reactive hyperemia (RH) immediately after release of cuff occlusion, as previously described (15). The limb to be assessed was supported just above the level of the heart, and a mercury-in-Silastic strain gauge that was inhaled to 50 mmHg above systolic pressure to eliminate hand or foot circulation from the measurement. A pneumatic cuff was placed on the arm or thigh and inflated to 30 mmHg to achieve venous occlusion. The cuff occlusion was maintained for several cardiac cycles (4–6 cycles) to obtain resting blood flow measurements. Blood flow was expressed as milliliters of flow per 100 milliliters of tissue per minute. Resting blood flow was calculated as the average of six separate measurements in each limb. Peak RH blood flow was determined after limb ischemia induced by a proximal cuff which was inflated 50 mmHg above systolic blood pressure for 5 min. Postocclusion RH blood flow measurements were made every few seconds, and the highest value achieved was taken as the peak value. Resting blood flow, peak RH

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Control</th>
<th>Range</th>
<th>PAD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>63.1 ± 5.5</td>
<td>53–70</td>
<td>57.5 ± 12.4</td>
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<tr>
<td>Weight, kg</td>
<td>82.1 ± 12.5</td>
<td>70–100</td>
<td>80.3 ± 16.0</td>
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<tr>
<td>BMI, kg/m²</td>
<td>26.5 ± 4.06</td>
<td>22–31.7</td>
<td>26.5 ± 3.75</td>
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<tr>
<td>Pack-years</td>
<td>4.6 ± 9.6</td>
<td>0–15</td>
<td>41.1 ± 20.2*</td>
</tr>
<tr>
<td>Current smokers, n</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>79±4</td>
<td>73–84</td>
<td>78±7</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>67±6</td>
<td>57–75</td>
<td>63±7</td>
</tr>
<tr>
<td>LOPAR, MET h/wk</td>
<td>264±42</td>
<td>213–279</td>
<td>254±26</td>
</tr>
<tr>
<td>ABI Best leg resting</td>
<td>1.20±0.09</td>
<td>1.09–1.23</td>
<td>0.89±0.18*</td>
</tr>
<tr>
<td>Postexercise</td>
<td>1.17±0.10</td>
<td>1.09–1.25</td>
<td>0.66±0.12*</td>
</tr>
<tr>
<td>Worse leg resting</td>
<td>0.32±0.16*</td>
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</table>

Values are means ± SD; n, no. of subjects. PAD, peripheral arterial disease; LOPAR, low-level physical activity recall; ABI, ankle-brachial index; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MET, metabolic equivalent. ABI data include 2 unilateral subjects in PAD group. *P < 0.01 for PAD vs. control. †P < 0.01 for difference in ABI from resting to postexercise.
blood flow, and the change in blood flow from rest to peak RH (Δblood flow = peak RH – resting blood flow) are presented as the sum of the individual values from both arms or both legs.

ABI. The ABI was calculated in all subjects at rest and in PAD patients within 1 min after graded treadmill exercise, as previously described (5). 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.

Spirometry. Lung volumes and flow rates were measured by the flowmeter and pulmonary function software of a metabolic system (Medical Graphics, BreezeEx, St. Paul, MN). Tidal volumes, FVC, and FEV₁ were assessed.

Echocardiography. A cardiologist blinded to study group assessed resting cardiac function using echocardiography (Sonos 5500, Philips Medical Systems, Andover, MA). Measurements of left ventricular size and wall thickness were determined in standard fashion, as recommended by the American Society of Echocardiography (29). Specifically, systolic function was assessed by visual inspection, fractional shortening, and measurement of left ventricular ejection fraction by the method of disks (29). Diastolic function was assessed with left ventricular inflow Doppler and tissue Doppler measurements as previously described (26). Any regional wall motion abnormalities were noted and considered as a disqualifying index of cardiac dysfunction.

Measurement of pulmonary gas exchange. For all exercise tests, VO₂, CO₂ production, minute ventilation, and other respiratory variables were measured and recorded breath by breath with a metabolic measurement system (MedGraphics CPX/D, Medical Graphics). We calibrated the system O₂ and CO₂ analyzers before each test using gases of known concentrations. Inspired and expired volumes were also calibrated by a syringe of known volume (3.0 liters). All breath-by-breath data collected were stored to computer disk for analysis. During graded exercise, the highest VO₂ averaged over 20 s was defined as peak VO₂. The respiratory exchange ratio (RER) was calculated as the ratio of CO₂ production to VO₂. Estimated LT was determined from graded exercise gas exchange data for each individual’s arm and leg exercise using the V-slope method (point of nonlinear increase of CO₂ production in relation to VO₂) (6). Individual LTs could be determined for all subjects (PAD and control) during graded arm exercise. However, no PAD patients demonstrated a measurable V-slope point of inflection during graded treadmill exercise, and thus a LT by gas exchange could not be determined.

Data analysis. We processed breath-by-breath gas-exchange data for each exercise transition using a software program developed by our laboratory as previously described (5). Breath-by-breath data for each exercise transition were time interpolated to 1-s intervals. The first CWR treadmill exercise transitions from each day of testing were time aligned and averaged to provide a single VO₂ kinetic response for each subject (e.g., average of 2 CWR transitions). In a similar fashion, the breath-by-breath data from three transitions of CWR arm exercise were processed to achieve a single kinetic response for arm ergometry exercise.

The pulmonary VO₂ kinetic responses at the onset of CWR exercise were evaluated with two- and three-component exponential mathematical models (e.g., 1 and 2).

\[ \text{VO}_2(t) = \text{VO}_2(t) + A_1[1 - e^{-u-TD_{1}}] \text{ phase 1} \]

\[ A_1[1 - e^{-u-TD_{2}}] \text{ phase 2} \]

\[ A_1[1 - e^{-u-TD_{3}}] \text{ phase 3} \]

The models provided estimates of the baseline (b) VO₂, amplitude of the individual exponential components (A₁, A₂, A₃), independent time delays for the onset of each exponential phase (TD₁, TD₂, TD₃), and time constants of the individual exponential components (τ₁, τ₂, τ₃) using nonlinear regression (SigmaPlot 2001, SPSS, Chicago, IL) as previously described (5). For each subject, the best-fit model (decision to include 2 vs. 3 components) was determined across all exercise data points by an F test and confirmed by examination of the residuals between 20 and 180 s (i.e., phase 2 of the response). The latter criterion was included to ensure that data points within the likely period of phase 2 of the response were appropriately represented. All CWR arm exercise transitions were performed at an exercise intensity of 90% of arm LT (moderate exercise), and the pulmonary VO₂ kinetics were best fit with a two-component exponential model. The physiologically relevant amplitude of VO₂ for each phase of the transition was computed from the individual kinetic parameter estimates (Eqs. 1–6 in APPENDIX).

HR kinetics. The HR half-time (HRₜₕₑₜ) was calculated as the time for HR to achieve 50% of the change in HR from rest to end-CWR exercise.

Statistical analysis. Unpaired Student’s t-tests were used for comparisons between groups for all variables. Planned comparisons within groups for arm and leg variables were made with paired t-tests. The planned comparisons were PAD vs. control for arm and leg responses and within PAD or control groups for arm vs. leg responses with the primary end point of VO₂ kinetics. The Pearson’s R product was used to evaluate significant correlations. Statistical significance for all comparisons was declared at P < 0.05.

RESULTS

Subject characterization. Subject characteristics are presented in Table 1. PAD and control subjects were of similar age, weight, and body mass index (BMI). Two PAD subjects were current smokers, and the PAD group had a significantly greater smoking history than control subjects as assessed by pack-years (P < 0.05). No differences were observed between PAD and control subjects for measures of pulmonary function (FEV₁/FVC) (resting cardiac function (ejection fraction of <56% in all subjects), or in habitual physical activity (low-level physical activity recall). Furthermore, no subject demonstrated evidence of cardiac diastolic dysfunction or regional wall motion abnormalities. As expected, resting ABI values were lower in the PAD group than in control subjects (2 unilateral and 8 bilateral subjects are combined in PAD group mean). Furthermore, after graded treadmill exercise, the ABI significantly decreased in both legs of bilateral subjects in the PAD group and in the affected leg of the two unilateral PAD subjects (P < 0.05).

Peak performance. The peak lower and upper extremity exercise responses are presented in Table 2. As previously described in the PAD patient population, claudication-limited peak VO₂ during graded treadmill exercise was reduced ~50% in PAD subjects compared with age-matched healthy controls (P < 0.01) (16). This was associated with a reduced peak RER and peak HR in PAD patients compared with control subjects during graded treadmill exercise (P < 0.01). In the control subjects, the VO₂ at the LT was 19.3 ± 2.7 ml·kg⁻¹·min⁻¹. However, no PAD patient demonstrated a measurable V-slope point of inflection during graded treadmill exercise, and, therefore, a LT by gas exchange could not be determined. During peak arm exercise, peak VO₂ was similar between groups, and no PAD subject was limited by ischemic arm symptoms (i.e., arm muscle cramping or localized arm symptoms) during upper extremity exercise. There were also no differences with graded arm exercise in peak RER or peak HR between PAD and control groups. With arm exercise, PAD patients did not demonstrate a LT by gas-exchange criteria that occurred at a
PAD, the RER was significantly greater in PAD subjects compared with control subjects at end-treadmill CWR exercise (0.93 ± 0.05 in PAD vs. 0.87 ± 0.03 in control, P < 0.05). In contrast, there were no differences in exercise characteristics during CWR arm exercise at an individual relative intensity of 90% of mode-specific LT in both PAD and control groups. Specifically, HR kinetics were similar between PAD and control groups during arm exercise.

**V̇O₂ kinetics.** Kinetic data from all control subjects and 3 of 10 PAD subjects’ treadmill CWR tests were best fit using a two-component model, whereas 7 PAD patients required threecomponent modeling due to the presence of a slow, phase 3 component. Consistent with previous reports (5, 13), the pulmonary V̇O₂ time constant for phase 2 during treadmill CWR exercise was 75% longer in PAD patients than in control subjects (Table 4, P < 0.01). In contrast, during CWR arm ergometry, the phase 2 V̇O₂ time constant was similar in PAD and control subjects (Fig. 1). Individual subject data are presented in Fig. 2.

The amplitude parameter of V̇O₂ during phase 1 was significantly lower in PAD subjects than in control subjects during both treadmill (P < 0.05) and arm CWR exercise (P < 0.05). The V̇O₂ amplitude of phase 2 was also reduced in PAD during treadmill CWR exercise (P < 0.01) but not arm exercise. However, the total amplitude of V̇O₂ during treadmill and arm CWR exercise was similar between groups. In the seven PAD subjects whose V̇O₂ kinetics were best fit with a three-component model, the magnitude of the slow component (phase 3) accounted for ~20% of the total increase in end-exercise V̇O₂.

**Limb hemodynamics.** Resting blood flow measurements of the upper and lower limbs were not different between groups (Table 5). Peak RH change in blood flow was reduced 33% compared with control subjects (P < 0.01). In PAD, the upper extremity change in blood flow was reduced 33% compared with control subjects (P < 0.01), despite equal brachial systolic pressures across the upper extremities in PAD patients. Whereas there were no

### Table 2. Peak exercise characteristics

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<th>Control</th>
<th>Range</th>
<th>PAD</th>
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<tbody>
<tr>
<td><strong>Treadmill</strong></td>
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<tr>
<td>V\̇O₂, ml·kg⁻¹·min⁻¹</td>
<td>30.1 ± 4.8; 22.7–35.6</td>
<td>15.6 ± 2.6; 12.4–20.2</td>
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<tr>
<td>RER</td>
<td>1.14 ± 0.09; 1.00 ± 0.07</td>
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<tr>
<td>HR, beats/min</td>
<td>164 ± 12</td>
<td>113 ± 18</td>
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<tr>
<td>V\̇O₂ at LT, ml·kg⁻¹·min⁻¹</td>
<td>19.3 ± 2.7</td>
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<tr>
<td>ICT, s</td>
<td>113 ± 63</td>
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<tr>
<td>ACT, s</td>
<td>471 ± 201</td>
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<tr>
<td><strong>Arm ergometry</strong></td>
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<tr>
<td>V\̇O₂, ml·kg⁻¹·min⁻¹</td>
<td>18.2 ± 3.4; 13.3–23.9</td>
<td>15.1 ± 4.1; 10.0–21.4</td>
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<tr>
<td>RER</td>
<td>1.21 ± 0.09; 1.23 ± 0.09</td>
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<tr>
<td>HR, beats/min</td>
<td>144 ± 17</td>
<td>129 ± 16</td>
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<tr>
<td>V\̇O₂ at LT, ml·kg⁻¹·min⁻¹</td>
<td>10.7 ± 2.1</td>
<td></td>
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<tr>
<td>Peak workload, W</td>
<td>97 ± 22</td>
<td>73 ± 23</td>
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Values are means ± SD. LT, lactate threshold; ICT, time to onset of claudication symptoms; ACT, claudication limited total walking time; V\̇O₂, O₂ uptake; RER, respiratory exchange ratio; HR, heart rate. *P < 0.05, †P < 0.01 for PAD vs. control. ‡P < 0.05 for arm vs. leg.

**CWR exercise.** All PAD subjects experienced claudication pain during the CWR treadmill exercise with a mean onset at 142 s (Table 3). No PAD patient stopped exercise before completing 6 min of CWR exercise. HR kinetics during lower extremity exercise, assessed by HRₙ₀, was prolonged in PAD (P < 0.01), but the PAD group had a greater change in HR from onset to the end of 6 min of CWR treadmill exercise compared with control subjects. End-exercise V\̇O₂ was similar between PAD and control groups during treadmill CWR walking exercise. However, the relative intensity of CWR treadmill exercise as a percentage of peak exercise V\̇O₂ was greater in the PAD group (83 ± 17%) compared with controls (43 ± 9%) (P < 0.01). Consistent with a high relative exercise intensity in

### Table 3. CWR exercise characteristics

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<thead>
<tr>
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<th>Control</th>
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<tr>
<td><strong>Treadmill</strong></td>
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<tr>
<td>ICT, s</td>
<td>142 ± 72</td>
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<tr>
<td>HRₙ₀, time, s</td>
<td>19 ± 12</td>
<td>72 ± 41†</td>
</tr>
<tr>
<td>ΔHR, beats/min</td>
<td>12 ± 9</td>
<td>20 ± 6§</td>
</tr>
<tr>
<td>End-exercise V\̇O₂, ml/min</td>
<td>1.042 ± 0.228</td>
<td>1.108 ± 0.197</td>
</tr>
<tr>
<td>End-exercise V\̇O₂ % of peak</td>
<td>43 ± 7</td>
<td>83 ± 14†</td>
</tr>
<tr>
<td>End-exercise RER</td>
<td>0.87 ± 0.03</td>
<td>0.93 ± 0.05†</td>
</tr>
<tr>
<td><strong>Arm ergometry</strong></td>
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<tr>
<td>Workload, w</td>
<td>32 ± 8</td>
<td>26 ± 10</td>
</tr>
<tr>
<td>HRₙ₀, time, s</td>
<td>31 ± 17</td>
<td>49 ± 26</td>
</tr>
<tr>
<td>ΔHR, beats/min</td>
<td>19 ± 7</td>
<td>21 ± 7</td>
</tr>
<tr>
<td>End-exercise V\̇O₂, ml/min</td>
<td>830 ± 106</td>
<td>777 ± 147</td>
</tr>
<tr>
<td>End-exercise RER</td>
<td>0.98 ± 0.03</td>
<td>0.98 ± 0.06</td>
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Values are means ± SD. All subjects exercised for 6 min. Constant work rate (CWR) treadmill exercise was performed at 2.0 miles/h, 4% grade. CWR arm ergometry was performed at 90% of LT. All PAD subjects experienced claudication symptoms during CWR treadmill testing. HRₙ₀, time, to achieve 50% of the HR response (ΔHR), ΔHR, 6-min HR minus resting baseline. *P < 0.05, †P < 0.01 for PAD vs. control.
differences in RH blood flow responses between the arms and legs of control subjects, patients with PAD had reduced RH blood flow responses in the legs compared with the arms ($P < 0.05$).

**Relationships between exercise and hemodynamic parameters.** There were no significant relationships between RH blood flow responses and the phase 2 time constants for arm or treadmill CWR exercise within either group. Whereas there were slowed HR kinetics (HR$50$) during CWR treadmill exercise in PAD patients, this was not correlated with the prolonged phase 2 time constants. Consistent with previous reports, no relationships between the ABI and exercise performance parameters were observed. However, a significant relationship was observed between the lower extremity change in RH blood flow and treadmill peak $\dot{V}O_2$ in patients with PAD ($y = 0.22x + 10.98; R = 0.70, P < 0.03$). This relationship was not observed in the control group.

**Fig. 1.** Comparison of pulmonary $O_2$ uptake ($\dot{V}O_2$) kinetic responses from a representative peripheral arterial disease (PAD) patient (B and D) and control subject (A and C) during the transition from rest to treadmill (A and B) and arm ergometry (C and D) constant work rate exercise. Treadmill exercise was performed at 2.0 miles/h, 4% grade, and arm ergometry was performed at 90% of individual lactate threshold. Exercise was initiated at time 0. Note presence of $\dot{V}O_2$ slow component and modeling of third component during PAD constant work rate treadmill exercise.

**Table 5. Limb blood flow**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg blood flow, ml·100 ml tissue$^{-1}$·min$^{-1}$</td>
<td>7.01±1.57</td>
<td>5.86±0.98</td>
</tr>
<tr>
<td>Peak</td>
<td>58.17±11.73</td>
<td>26.60±8.37$^*$</td>
</tr>
<tr>
<td>$\Delta$Blood flow</td>
<td>46.12±17.08</td>
<td>20.73±8.31$^+$</td>
</tr>
<tr>
<td>Arm blood flow, ml·100 ml tissue$^{-1}$·min$^{-1}$</td>
<td>9.24±3.04</td>
<td>9.17±1.73</td>
</tr>
<tr>
<td>Peak</td>
<td>60.01±12.57</td>
<td>43.17±9.33$^*$</td>
</tr>
<tr>
<td>$\Delta$Blood flow</td>
<td>50.79±12.23</td>
<td>34.01±8.57$^+$</td>
</tr>
</tbody>
</table>

Values are means ± SD. Measurements were made at rest and during reactive hyperemia. Rest, peak, and change ($\Delta$) in blood flow are presented as sum of right and left limbs. $\Delta$Blood flow = peak – resting flow. Data include 2 unilateral subjects in the PAD group mean. $^*$P < 0.01 for PAD vs. control. $^+$P < 0.05 for arm vs. leg.
DISCUSSION

Consistent with our hypothesis, compared with healthy subjects, PAD patients with no cardiac or pulmonary dysfunction demonstrated a specific defect (slowed time constant) in pulmonary \( \dot{V}O_2 \) kinetics during leg but not arm exercise. A systemic abnormality in vascular reactivity (reduced RH blood flow responses) was demonstrated in both the arms and legs of PAD patients compared with control subjects. However, the RH blood flow abnormality in PAD was not correlated with the \( \dot{V}O_2 \) kinetic responses of either the upper or lower extremity. These data suggest that the slowed PAD pulmonary \( \dot{V}O_2 \) kinetic responses appear localized to the lower extremities directly affected by the arterial occlusive disease process and cannot be explained by a systemic defect in endothelial function (RH blood flow) or by any systemic impairment in cardiac or pulmonary function. Thus the altered \( \dot{V}O_2 \) kinetic responses to leg exercise are likely related to the peripheral impairment in O2 delivery or O2 utilization in the PAD-affected lower limbs.

Previous studies have described prolonged pulmonary \( \dot{V}O_2 \) kinetics in PAD patients during CWR treadmill walking (1, 2, 5, 13). Aucinclos and colleagues (1) attributed a lower 1-min \( \dot{V}O_2 \) in PAD to the limitation of lower limb blood flow, whereas more recently our laboratory and others have suggested that peripheral muscle metabolic abnormalities may play a significant role in \( \dot{V}O_2 \) kinetic impairment (2, 5). However, these studies did not evaluate the potential confounders of impairments in systemic O2 delivery from cardiac or pulmonary disease or the potential contributions of altered vascular function (reduced vascular reactivity) that occur in patients with atherosclerotic disease. The present study demonstrates that the abnormal pulmonary \( \dot{V}O_2 \) kinetics in PAD are specific to exercise of the lower limbs affected by the arterial occlusive disease process. \( \dot{V}O_2 \) kinetics of the exercising muscles reflect the interrelated influences of local muscle O2 delivery, O2 diffusion, and mitochondrial \( \dot{V}O_2 \). As described by Barstow et al. (3), impairment of O2 delivery may influence the expression of pulmonary \( \dot{V}O_2 \) kinetics. However, in these modeling experiments (where muscle \( \dot{V}O_2 \) was assumed to be normal), a reduction in O2 delivery was associated with a paradoxical speeding of the primary exponential phase of pulmonary \( \dot{V}O_2 \) kinetics (phase 2) as O2 extraction across the exercising muscle (3). Thus our findings of slowed phase 2 time constants in PAD compared with control subjects during treadmill exercise may not be consistent with a simple reduction in the rate of O2 delivery but could also indicate a localized defect in O2 diffusion or mitochondrial \( \dot{V}O_2 \) that was not observed during arm exercise. Indeed, using magnetic resonance spectroscopy, Kemp and colleagues (19, 20) have previously suggested a significant impairment in muscle oxidative metabolism during calf-muscle exercise that could alter the kinetics of mitochondrial respiration in PAD. Taking into account these considerations, our findings confirm that the defect of slowed pulmonary \( \dot{V}O_2 \) kinetics during treadmill walking reflects the disease-associated abnormalities specific to the lower extremities in PAD.

HR dynamics (HR\(_{50}\)) were slowed during treadmill walking exercise in patients with PAD. Moreover, although resting HRs were similar between groups, PAD patients had a greater absolute increase in HR during fixed-rate treadmill walking than did control subjects. In contrast, the HR responses (HR\(_{50}\) and change in HR) during arm exercise were not different between groups. In consideration that the HR\(_{50}\) was not correlated with pulmonary \( \dot{V}O_2 \) kinetics during arm or leg exercise, it is unlikely that any alterations in the HR component of cardiac output affected the slowed \( \dot{V}O_2 \) kinetics during leg exercise. Rather, the slowed HR\(_{50}\) during PAD leg exercise may have been related to their greater change in HR or other factors.

Limb blood flow during RH increased above baseline in the arms and legs of PAD patients after suprasystolic cuff occlusion. Thus all PAD patients demonstrated a functional limb blood flow reserve. However, the RH blood flow responses were reduced 33% in the arms and by 50% in the legs of PAD patients compared with control subjects. Impaired vascular reactivity, measured as flow-mediated vasodilation or reactive hyperemic blood flow, has been demonstrated in the lower (occluded) and upper (nonoccluded) arterial circulations in PAD patients, indicating a systemic defect in endothelial vasodilator function (7, 8, 33). Presumably, the reduction in arm RH response in PAD patients was not the result of arterial occlusive disease because systolic pressures were equal between the arms in the PAD patients. Moreover, no patient experienced muscle cramping or other evidence of muscle ischemia during arm exercise. Thus we conclude that the reduction in the arm reactive hyperemic responses in the present PAD patients most likely reflected a systemic nonocclusive limitation in limb vascular reactivity related to their endothelial dysfunction.

The reductions in reactive hyperemic blood flow were not correlated with arm or leg pulmonary \( \dot{V}O_2 \) kinetics in either group. In the upper extremity of PAD patients, the lack of a direct correlation between RH blood flow and pulmonary \( \dot{V}O_2 \) kinetics suggests that these changes in vascular function alone were insufficient to compromise (i.e., slow) the arm \( \dot{V}O_2 \) kinetic response. Thus, in the present study, we conclude that the PAD-associated systemic reduction in vascular reactivity alone does not significantly impair the pulmonary \( \dot{V}O_2 \) kinetic responses in these highly selected PAD patients.

Despite the inferences above, we cannot exclude the possibility that the arterial occlusions in PAD combined with the impaired vascular reactivity contributed to the slowed lower extremity \( \dot{V}O_2 \) kinetics. Bartoli and Dorigo (4) previously described that RH responses in PAD are quantitatively less than the blood flow response immediately after exercise. Thus our measure of RH likely does not elicit the same level of hyperemia achieved during exercise and could partially explain the lack of correlation with \( \dot{V}O_2 \) kinetic and peak arm responses. However, the PAD lower extremity RH responses did correlate with claudication-limited peak exercise performance. This result emphasizes the significance of limb atherosclerosis and impaired arterial flow in contributing to the limitation of peak exercise function in PAD (12). Moreover, the reactive hyperemic blood flow response not only may reflect the severity of the arterial obstruction but also may be a surrogate for the magnitude of oxidative perturbation and altered regulatory processes that occur distal to the arterial obstruction in PAD. This could include metabolic dysfunction of the affected skeletal muscle mitochondria, which may relate to a portion of the mechanism of exercise limitation and claudication symptoms in PAD (31). Thus the correlation between reactive hyperemic measures and peak exercise performance in PAD may also
suggest that the PAD exercise impairment is more than simply
a flow-limited phenomenon. This could explain why RH, but
not resting blood flow or resting ABI measurements, is corre-
lated with peak exercise function. Clearly, the mechanism of
exercise limitation in PAD is multifactorial, with contributions
from both the blood flow limitation and the distal responses to
the ischemic condition.

Study limitations. Treadmill walking was employed in the
present study to assess lower extremity pulmonary VO₂ kinetics
because walking is the mode of exercise that predominantly
produces the symptoms of claudication pain and exercise
intolerance in PAD. Whereas the arm CWR transitions were of
low exercise intensity (below the individual’s LT) for all
subjects, the treadmill CWR exercise represented a higher
relative percentage of peak exercise performance in PAD (83% of
claudication-limited peak VO₂) than in control subjects (43% of
peak VO₂) at the same absolute treadmill work rate. This
resulted in a heterogeneous exercise response during treadmill
CWR exercise in PAD patients such that seven patients dem-
onstrated an apparent VO₂ slow component, consistent in
healthy subjects with exercise in the heavy domain (i.e., >LT).
Although there is evidence that heavy exercise may alter the
phase 2 time constants from that observed during moderate
eexercise due to a potential O₂ delivery limitation in healthy
subjects (11, 23), others have described invariant or faster
phase 2 time constants using similar modeling methods during
heavy or severe exercise (18, 24, 28). From the present data,
we cannot directly evaluate the influence of exercise intensity
on the pulmonary VO₂ kinetic responses in PAD. However,
consistent with previous observations (5, 13), the phase 2 time
constants during treadmill CWR exercise were slowed in PAD
compared with control subjects, irrespective of modeling pro-
cedure. Moreover, the phase 2 time constants were similar in
PAD patients who demonstrated a VO₂ slow component (n = 7)
to those without a phase 3 VO₂ increase (n = 3) (subject
means of 35.9 vs. 36.9 s).

A second limitation of the study is that we did not conduct
imaging studies of the upper extremity circulation to exclude
potential upper extremity occlusive disease. However, previous
studies have suggested that significant arterial occlusive in-
volveoment occurs ~20 times less frequently in the arms than in
the legs in the PAD patient population (22, 32). Thus our
findings of preserved peak arm exercise capacity along with the
absence of any symptoms of muscle ischemia during arm
exercise suggest that the arm exercise comparison with control
subjects may provide a valid basis for evaluating potential
systemic influences on pulmonary VO₂ kinetics in PAD.

In conclusion, the present results show that, in PAD patients
without apparent cardiopulmonary disease, pulmonary VO₂
kinetics are slowed during exercise of the affected lower
extremities but not during exercise of the unaffected upper
extremities compared with control subjects. The fact that the
leg pulmonary VO₂ kinetic responses were slowed in these
highly selected PAD patients supports the presence of a sig-
nificant peripheral VO₂ impairment that is localized to the PAD
lower extremity and not related to their abnormal vascular
reactivity. Local abnormalities distal to the lower extremity
arterial occlusions in patients with PAD offer putative expla-
nations for their slowed pulmonary VO₂ kinetics.

APPENDIX
Following are the equations to define the amplitude parameters
during phases 1–3 (A₁–A₄, respectively) and total amplitude of VO₂
(Aₜ₀ₙ)

\[
A'_1 = A_1 \left[ 1 - e^{-(TD/TD)} \right]
\]

(3)

\[
A'_2 = A' + A_2
\]

(4)

\[
A'_3 = A_0 \left[ 1 - e^{-(ED/ED)} \right]
\]

(5)

\[
A_{tot} = A'_2 + A'_3
\]

(6)

where ED is total exercise duration (in seconds).

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