Impaired muscle oxygen use at onset of exercise in peripheral arterial disease

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Objectives: **In patients with peripheral arterial disease (PAD), abnormal muscle metabolism and impaired oxygen delivery distal to the arterial occlusions may contribute to the exercise limitation observed in this population. Muscle tissue hemoglobin saturation (StO_2), measured with near-infrared spectroscopy, reflects the relative contributions of oxygen delivery and oxygen use. Thus differences in the kinetics of StO_2 in response to exercise may yield important insight into the potential mechanisms associated with the PAD exercise impairment. The purposes of this study were to characterize the muscle oxygenation responses in patients with PAD and in healthy control subjects at the onset of exercise, and to compare the kinetics of StO_2 desaturation. We hypothesized that at the onset of exercise the kinetics of StO_2 desaturation would be slowed in PAD compared with control responses.**

Material and methods: **Six patients with PAD and 6 healthy control subjects from a university center were examined in a prospective cross-sectional analysis that evaluated the desaturation kinetics of StO_2 at the onset of walking exercise. On separate visits subjects performed graded treadmill exercise and 3 constant work rate treadmill tests equivalent to ~60% (low), ~80% (medium), and 100% (peak) of their peak exercise work rate. Gastrocnemious muscle StO_2 response profiles (InSpectra tissue spectrometer) were measured at rest and across the rest to exercise transition. Muscle StO_2 responses were characterized by an exponential mathematical model. The end point value was taken as the time constant of StO_2 desaturation after onset of exercise (ie, equivalent to time to reach approximately 63% of StO_2 decrease).**

Results: **The patients with PAD and the control subjects were of similar age and activity level. The qualitative patterns of StO_2 responses at onset of exercise were also similar between patients and control subjects at all work rates. However, the kinetic time constants of StO_2 desaturation were prolonged in patients with PAD versus control subjects (averaged time constant across all work rates, 21.9 ± 9.4 seconds vs 4.9 ± 2.2 seconds; $P < .01$).**

Conclusions: **The slowed muscle StO_2 kinetics in PAD are consistent with an impairment in muscle oxygen use at the onset of walking exercise. Impaired muscle metabolism may contribute to the altered physiologic responses to exercise and to exercise impairment in patients with PAD. (J Vasc Surg 2004;40:488-93.)**

Patients with peripheral arterial disease (PAD) and claudication have a 50% reduction in peak exercise performance that limits daily walking activities and functional capacity.[1] In PAD, atherosclerotic arterial occlusions limit blood flow and oxygen delivery to the working muscles of the leg during exercise. However, patients with PAD also have increased oxidative stress and a spectrum of muscle metabolic abnormalities that may have functional implications.[2-4]

Near-infrared spectroscopy (NIRS) has use in monitoring local muscle hemoglobin oxygen saturation (StO_2) at rest and during exercise and recovery from exercise.[5] Because muscle StO_2 reflects the relative contributions of oxygen delivery and oxygen use, differences in the dynamic StO_2 response across transitions from rest to exercise may provide insight into the pathophysiologic features of the exercise limitation in PAD. For example, in many patients with PAD resting blood flow and the initial increment in blood flow with low levels of exercise are not limited.[6] Thus, in the absence of a defect in tissue oxygen use, the dynamic StO_2 responses immediately after onset of exercise should be similar in patients with PAD and control subjects. However, at higher work rates patients with PAD cannot deliver sufficient blood flow and oxygen to meet muscle metabolic demand. Under these conditions muscle metabolism would require a rapid desaturation response as oxygen extraction increases in the absence of an adequate increase in oxygen delivery. In contrast, if PAD were associated with impaired ability of muscle to use oxygen, the rate of hemoglobin desaturation at onset of exercise would be slowed. Thus quantitative differences in StO_2 kinetics at onset of exercise would identify whether a defect in metabolic oxygen use contributes to the exercise pathophysiologic features of PAD.

METHODS

Subjects. Six men with PAD and 6 healthy men of similar age and body mass index were included in the study, which was approved by the Colorado Multiple Institutional Review Board, and all subjects gave informed consent. Patients with PAD were defined by resting ankle-brachial index (ABI) less than 0.90, determined as the ratio of

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highest ankle systolic blood pressure (in each leg) to the highest brachial systolic pressure. The index leg was defined by the lowest ABI value in patients with PAD, and the dominant leg in control subjects. All patients with PAD had symptoms of claudication (pain or cramping in muscles of the affected legs), which was the only limiting symptom during graded treadmill exercise. Patients with diabetes or who were taking β-adrenergic antagonists were excluded, because exercise responses are altered by these factors.[7,8] Patients with PAD who were taking other medications were not excluded, and the 6 patients in the PAD group included 5 patients who were taking a statin drug, and all 6 were taking aspirin and antihypertensive drugs.

Exercise protocols. Subjects performed a graded treadmill exercise test (Astrand protocol or Gardner protocol) to maximally tolerated workloads for identification of peak exercise capacity (Q-stress; Quinton Instruments).[9,10] On subsequent days subjects performed 6-minute constant work rate (CWR) treadmill tests at workloads equal to approximately 60% (low), 80% (medium), and 100% (peak) of their peak exercise work rate. Thus the CWR exercise tests were individualized to induce similar exercise intensity (relative to peak exercise capacity) and thus a measurable StO_2 desaturation response. Systemic pulmonary gas exchange measurements of oxygen consumption (VO_2), carbon dioxide production, and minute ventilation (CPX/D; Medical Graphics) were measured to quantify the relative exercise work rate of each CWR bout, as described.[11] Arterial hemoglobin saturation was monitored and recorded with pulse oximetry during all exercise tests (Ohmed Corp).

Skeletal muscle hemoglobin saturation. Noninvasive muscle StO_2 was measured with a continuous-wave, near-infrared spectrometer (InSpectra model 325; Hutchinson Technology). The NIRS signal is derived from the hemoglobin in the microvasculature (precapillary, capillary, postcapillary) of the tissue sampled, although contribution from intracellular myoglobin cannot be definitively excluded. Thus NIRS can be considered to reflect local tissue oxygenation. The InSpectra tissue spectrometer was modified for rapid sample measurement and data acquisition (6 Hz). Before each study the InSpectra device was calibrated with a single light-scattering standard, and validated against standard references equivalent to 38% and 90% hemoglobin saturation. StO_2 was determined with the second derivative of the absorbance as a function of wavelength at near-infrared wavelengths associated with changes in oxyhemoglobin and deoxyhemoglobin or myoglobin concentrations. The ratio of this second derivative at 720 and 760 nm has been empirically scaled to hemoglobin saturation, and is used by the instrument to calculate the reported StO_2 values (*User and Service Manual.* Hutchinson Technology; 2004). Optical data were acquired with a 25-mm NIRS probe attached to the skin over the lateral gastrocnemious muscle of the index limb with an adhesive patch.

Analysis of StO_2 kinetics. The 6-Hz StO_2 data for each individual CWR test were time-bin averaged to yield 1-Hz data files. With a statistical graphing program (Sigmaplot 2002), a 2-component mathematical curve-fitting model was used to describe the StO_2 kinetic response with nonlinear regression techniques.

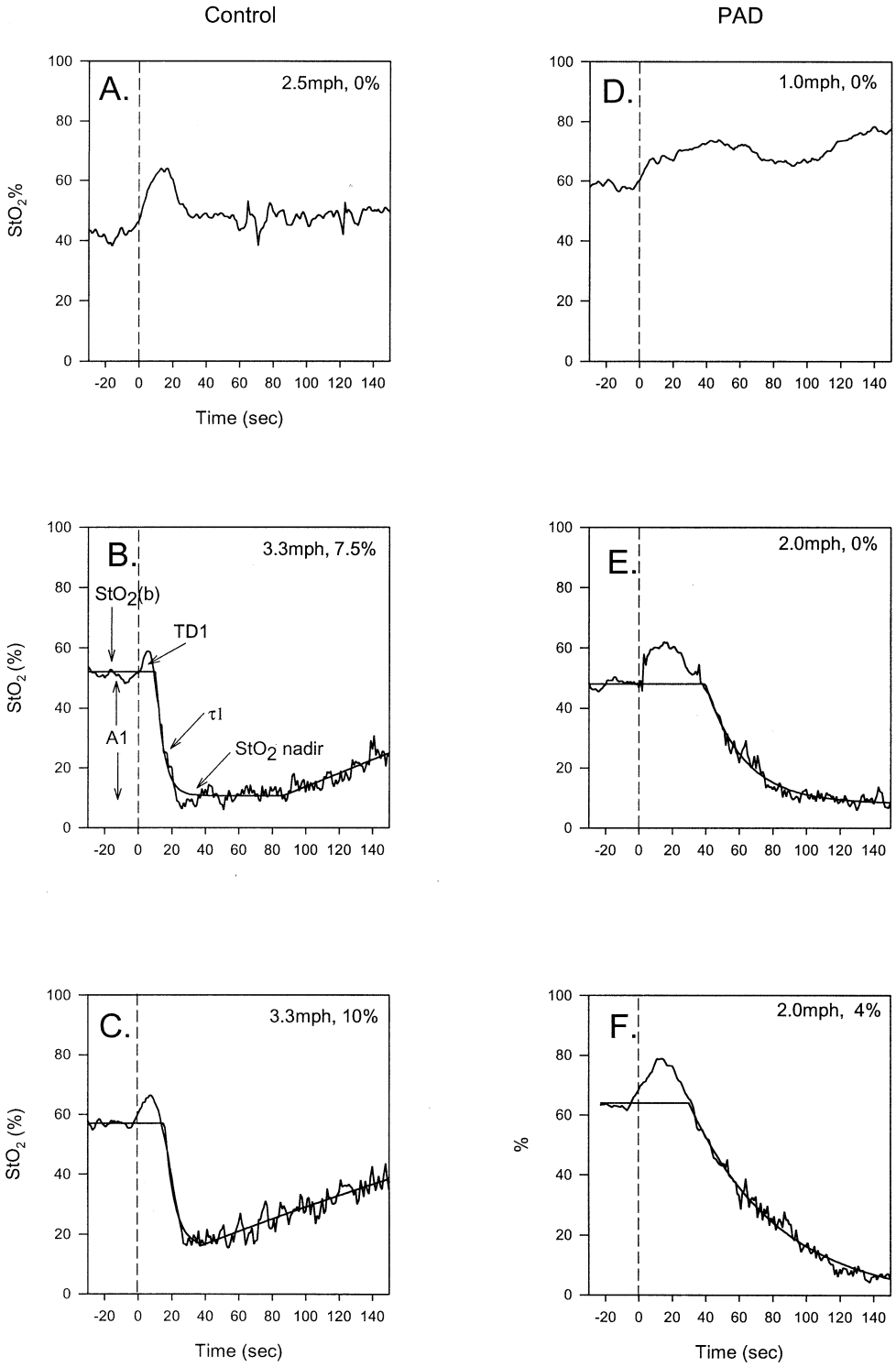
$$StO_2(t) = StO_2(b) + A_1(1 - e^{-(t-TD1)/\tau 1}) + A_2(1 - e^{-(-t-TD2)/\tau 2})$$

In each curve fit (Fig, *B*), $StO_2(b)$ was the resting baseline value. After onset of exercise there was an initial time delay (TD1), followed by a primary desaturation in StO_2 (below baseline), described with an exponential time constant ($\tau 1$) representing the time to reach ~63% of the desaturation response. The difference between the resting StO_2 and the nadir of the primary StO_2 desaturation was calculated as A_1. Where a subsequent StO_2 increase was observed, a second exponential function (Eq 2) was used so that the overall model would allow a best fit of the primary StO_2 desaturation response. Data for A_2, TD2, and $\tau 2$, are not presented, but contributed to the model that yielded the reported values for A_1, TD1, and $\tau 1$.

RESULTS

Patients with PAD were of similar age (66 ± 7 years) as control subjects (65 ± 7 years), but had a lower ABI in the index leg (0.62 ± 0.13 vs 1.24 ± 0.08 in control subjects; $P < .01$) and reduced peak exercise oxygen uptake (16.4 ± 4.2 mL/kg/min) compared with control subjects (26.0 ± 4.2 mL/kg/min; $P < .01$). No subject demonstrated arterial hemoglobin desaturation during any of the exercise tests.

The qualitative patterns of the initial StO_2 response were similar between groups during low, medium, and peak CWR exercise (Fig). At low CWR, 3 healthy subjects and 1 patient with PAD demonstrated an StO_2 profile with no desaturation below baseline levels (Fig, *A and D*). One control subject demonstrated no desaturation response below baseline levels during medium CWR exercise. The remaining control subjects and patients with PAD exhibited a desaturation response at all work rates. After onset of exercise (eg, Fig, *B*), there was an initial increase in StO_2 (characterized by TD1), which was followed by a rapid decrease in StO_2 to a plateau below baseline (StO_2 nadir). In control subjects the nadir of StO_2 desaturation typically occurred within 40 seconds, followed by a slow phase of increase in StO_2. In contrast, the initial StO_2 desaturation was slower in patients with PAD, reaching a nadir at approximately 100 seconds into exercise (Fig, *E and F*). The StO_2 nadir was similar at the same relative work rates between PAD and control groups, with the total decrease in StO_2 proportionate to increases in exercise intensity. However, as previously reported, the magnitude of StO_2 desaturation at similar absolute work rates was greater in patients with PAD than in control subjects.[12] Specifically, the StO_2 desaturation with peak CWR exercise in patients with PAD was greater than observed during low CWR exercise in control subjects (A_1 –18% controls vs –44% PAD), despite similar absolute work rates performed (1330



Muscle oxygen saturation responses *(StO_2)* from a representative patient with peripheral artery disease and a control subject during low **(A, D),** medium **(B, E),** and peak **(C, F)** constant work rate exercise. Exercise was initiated at time 0 *(vertical dashed line)*. During low constant work rate exercise there was no decrease in StO_2. With the higher work rates there was an initial increase, followed by a rapid decrease in StO_2. *StO2(b),* Baseline; *TD1,* time delay (seconds) during period of increase in StO_2; A_1, difference between baseline and nadir of initial StO_2 desaturation; $\tau 1$, time constant of StO_2 desaturation.

Constant work rate StO_2 characteristics

	Control		*PAD*	
	Mean ± SD	*Range*	*Mean ± SD*	*Range*
Low	N = 3		N = 5	
Work intensity (% peak Vo_2)	58 ± 15	43-73	68 ± 17	48-90
Sto_2(b)	50 ± 10	38-57	53 ± 10	42-60
τ1 (s)	4.0 ± 0.9	2.9-4.6	24.0 ± 2.9†	19.9-28.1
TD1 (s)	13.9 ± 3.1	11.0-17.2	27.6 ± 9.4*	14.9-37.0
A1 (%)	−18 ± 5	13-23	−22 ± 3	14-26
Medium	N = 5		N = 6	
Work intensity (% peak Vo_2)	86 ± 5	78-93	77 ± 13	56-93
Sto_2(b)	63 ± 9	52-70	54 ± 6	46-59
τ1 (s)	5.2 ± 2.8	1.8-9.5	20.0 ± 12*	9.3-42.4
TD1 (s)	8.7 ± 3.4	3.7-11.8	21.6 ± 10.7*	10.5-39.7
A1 (%)	−38 ± 10	20-48	−32 ± 14	17-56
Peak (100% peak Vo_2)	N = 6		N = 6	
Sto_2(b)	66 ± 14	50-89	55 ± 10	37-64
τ1 (s)	5.7 ± 3.1	2.4-11.0	19.2 ± 18.6‡	6.7-53.5
TD1 (s)	8.3 ± 4.0	5.3-15.5	13.2 ± 11.2	0.0-29.9
A1 (%)	−41 ± 9	29-57	−44 ± 17	20-65

Three control subjects and 1 patient with PAD had no desaturation response during low constant work rate exercise, and thus no kinetic parameters were calculated.

PAD, Peripheral arterial disease; *Sto_2(b)*, resting muscle oxygenation (%); *Vo_2*, volume of oxygen use; *τ1*, Sto_2 time constant; *TD1*, time delay; *A1*, amplitude of Sto_2 response.

*$P < .05$, PAD vs control.

†$P < .01$, PAD vs control.

‡$P = .14$, PAD vs control.

± 105 mL/min for patients with PAD vs 1354 ± 219 mL/min for control subjects).

Control subjects had a short time delay and rapid StO_2 time constant (τ1), which was consistent between subjects and independent of work intensity (Table). In contrast, patients with PAD had a longer time delay and slowed StO_2 desaturation kinetics that displayed considerable heterogeneity between patients with PAD. Nonetheless, within the PAD cohort as a whole, or when analyzed on an individual subject basis, there was no relationship between τ1 and workload. The StO_2 time constant (τ1) was statistically different between patients with PAD and control subjects at low and medium CWR ($P < .05$), and tended to separate at peak CWR ($P = .14$). Inasmuch as the time constant did not vary as a function of increasing workload in individual subjects, the time constants for all CWR tests performed by an individual were averaged to yield the best estimate for this parameter for each subject. Analyzed in this manner, the time constant average was 4.9 ± 2.2 seconds for control subjects and 21.9 ± 9.4 seconds for patients with PAD (n = 6 per group; $P < .01$).

DISCUSSION

This study demonstrated that while muscle StO_2 responses at the onset of treadmill exercise are qualitatively similar between patients with PAD and control subjects, the kinetics of StO_2 desaturation were markedly slowed in the PAD group. In both groups a low relative work rate could be identified in selected subjects that was not associated with StO_2 desaturation below resting values. Thus workloads could be identified in which patients with PAD appeared to have increases in blood flow that matched oxygen demand, resulting in no StO_2 desaturation. At higher relative work rates all subjects had StO_2 responses characterized by an initial increase in StO_2 saturation followed by a primary decrease in StO_2, the magnitude of which increased with increasing relative exercise intensity. In contrast, the StO_2 kinetic responses (time constants) in both groups appeared independent of the relative work rate, and remained slowed even at similar absolute work rates, which suggests that the observed differences in StO_2 kinetic responses cannot be explained solely on the basis of a difference in absolute work performed. Thus, whether the groups were compared at the same absolute or relative work rates, the time constants were clearly different, which supports the conclusion that the differences in StO_2 kinetics observed reflects the PAD population and not the absolute workloads evaluated.

Previous investigations have described a greater decrease in muscle oxygenation during incremental exercise and slowed StO_2 dynamics in recovery from exercise in PAD, attributing these differences from healthy subjects to the impaired hemodynamics of the PAD condition.[12,13] The current study confirms the greater decrement in StO_2 observed in patients with PAD at similar absolute work rates. However, the analysis of metabolic processes during recovery from exercise is complicated by the clear differences in blood flow between PAD and control groups provoked by higher workloads, and the accumulation of lactate and other metabolic intermediates that can modulate cellular metabolism associated with the exercise bout. In contrast, our approach provided a unique perspective on

the interaction between the metabolic and hemodynamic factors at the onset of exercise that may contribute to the exercise limitation in PAD.

Patients with intermittent claudication have relatively normal resting lower limb blood flow, and blood flow can increase with exercise.[6] However, as exercise continues, arterial occlusions restrict exercise hyperemia, and oxygen delivery reaches a plateau.[6] When increases in metabolic demand exceed increases in oxygen delivery, muscle oxygen extraction increases, as reflected by a decrease in StO_2. Thus in PAD a limitation in oxygen delivery at the onset of exercise would be expected to accelerate the rate of StO_2 desaturation within the muscle, provided that oxygen diffusion and mitochondrial function were normal. This response was not observed in this cohort of patients with PAD (Fig; Table), despite reports of increased muscle capillary density and thus potentially enhanced microvascular oxygen diffusion in this patient population.[14] In contrast, the slowed rate of StO_2 desaturation after onset of treadmill exercise in patients with PAD may be explained by the abnormalities of muscle oxidative metabolism previously described in this patient group. For example, patients with PAD have alterations in the regulation of oxidative adenosine triphosphate generation, abnormalities of electron transport chain enzyme activities, and an accumulation of short-chain acylcarnitines in affected skeletal muscle, which are inversely correlated with exercise performance.[3,4,15] The inherent delay to increase muscle oxidative metabolism in the face of increasing adenosine triphosphate requirements has been termed "metabolic inertia," and has been hypothesized to be an important physiologic characteristic of the exercise response.[16,17] These observations support the concept that patients with PAD develop a mitochondrial myopathy. Moreover, these findings support previous reports of slowed pulmonary oxygen uptake kinetics in PAD[11,18,19] and extend these observations to suggest that metabolic abnormalities specific to the affected skeletal muscle in PAD may contribute in part to the observed exercise limitation in this patient population.

Limitations. Factors other than the balance between oxygen delivery and oxygen use may influence the integrated StO_2 measurement at onset of exercise. Although the StO_2 signal is empirically scaled to hemoglobin saturation, the contribution of myoglobin cannot be definitively excluded, and its proportion to the overall NIRS signal remains a topic of controversy. Without entering into this debate, NIRS measurements can be considered to reflect local tissue oxygenation inclusive of hemoglobin and myoglobin. Thus we consider our measurements to reflect a general view of muscle StO_2, and cannot address interactions between microvascular and intracellular oxygen stores. The StO_2 measurement may also be influenced by the redistribution of oxyhemoglobin and deoxyhemoglobin within the sample window representing a mixture of capillary and venular blood with different saturations.[20] For example, at onset of exercise, activation of the muscle pump was associated with a rapid decrease in the total absorbance of hemoglobin (data not shown), and thus may in part explain the transient increase in muscle StO_2 observed immediately after exercise onset.

CONCLUSIONS

In patients with PAD, StO_2 desaturation kinetics were slowed at the onset of treadmill exercise, consistent with impaired muscle oxygen use. These findings provide further evidence of the interplay between the metabolic and hemodynamic factors that may contribute to the exercise impairment in patients with PAD. Muscle metabolic function may be an important therapeutic target in PAD.[17,21]

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