Benefit of Exercise Conditioning for Patients With Peripheral Arterial Disease

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Patients with atherosclerotic peripheral arterial disease (PAD) of the lower extremities have impaired walking ability due to exercise-induced muscle ischemia and the resultant pain of intermittent claudication. To evaluate the benefit of exercise training as a treatment for patients with PAD, as well as possible mechanisms associated with improvement, we randomly assigned 19 men with disabling claudication to treated and control groups. Treatment consisted of supervised treadmill walking (1 hr/day, 3 days/wk, for 12 weeks) with progressive increases in speed and grade as tolerated. Graded treadmill testing was performed to maximal toleration of claudication pain on entry and after 12 weeks of training to define changes in peak exercise performance. After 12 weeks, treated subjects had increased their peak walking time 123%, peak oxygen consumption 30%, and pain-free walking time 165% (all p<0.05). Control subjects had no change in peak oxygen consumption, but after 12 weeks, peak walking time increased 20% (p<0.05). In treated subjects, maximal calf blood flow (measured by a plethysmograph) increased 38±45% (p<0.05), but the change in flow was not correlated to the increase in peak walking time. Elevated plasma concentrations of acylcarnitines have been associated with the functional impairment of PAD and may reflect the metabolic state of ischemic skeletal muscle. In treated subjects, a 26% decrease in resting plasma short-chain acylcarnitine concentration was correlated with improvement in peak walking time (r=−0.78, p<0.05). Thus, 12 weeks of exercise training for patients with PAD improved peak exercise performance and claudication pain severity, which in part may be due to an improvement in skeletal muscle oxidative metabolism. (Circulation 1990;81:602–609)

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therosclerotic peripheral arterial disease (PAD) of the lower extremities, when associated with intermittent claudication, results in a moderate-to-severe impairment in walking ability. Patients with PAD are unable to walk more than a short distance on level ground and have a severely limited peak exercise capacity during graded treadmill exercise1–4 in a range that allows for only very light to light activities.5 As a result, the energy requirements of many leisure- and work-related tasks exceed the peak exercise capacity of these patients.

Exercise training has been shown to improve walking ability on level ground6–8 and during constant-load treadmill exercise9–16 in patients with PAD, as defined by changes in walking distance. Increases in peak exercise capacity during graded treadmill or bicycle exercise have also been demonstrated.17–22 However, only five of these trials were controlled and randomized9,10,14,16,21 and none have shown an increase in estimated or measured peak oxygen consumption (\(\text{VO}_{2}\)).21,22 The importance of an improvement in peak exercise capacity is that patients with claudication may be able to increase their range of activities and, therefore, decrease their degree of disability.

Several mechanisms have been postulated to account for the improvement in exercise performance from training in patients with PAD. A change in the biomechanics of walking may decrease oxygen cost during constant-load exercise, which would allow the patient to walk farther before developing a mismatch between the limited oxygen supply and the metabolic demands of exercise.23 An increase in peripheral blood flow through changes in the collateral circulation,24 reduced blood viscosity,15 or regression of disease would decrease the amount of muscle ischemia during exercise, resulting in an
increase in peak exercise capacity. Finally, despite the limited blood flow, improvements in skeletal muscle metabolism would facilitate the extraction of oxygen and substrate\textsuperscript{14,20} and, thus, allow for a greater peak exercise capacity. An example of the defect in muscle oxidative metabolism is the observation that patients with PAD generate acylcarnitines during skeletal muscle ischemia and that repeated episodes of claudication lead to a chronic accumulation of acylcarnitines.\textsuperscript{2} Therefore, changes in carnitine metabolism may serve as a marker for changes in muscle metabolism with exercise training.

We hypothesized that exercise training would improve both peak and submaximal exercise performance in patients with PAD through changes in muscle metabolism, and not by improvements in peripheral blood flow. A controlled, prospective, randomized trial was conducted to evaluate changes in exercise performance and the possible mechanisms associated with improvement.

**Methods**

**Subjects**

Patients with intermittent claudication that limited daily work or leisure-time activities were evaluated for the study. In all cases, claudication was due to PAD, defined as an ankle-to-arm systolic blood pressure ratio less than 0.95 at rest or less than 0.85 after exercise.\textsuperscript{25,26} The study was approved by the University of Colorado School of Medicine Human Subjects Committee, and informed consent was obtained from all enrolled subjects.

Sixty-six male patients were screened for the study, but 41 were excluded based on one or more of the following prospectively defined criteria: leg pain at rest, ischemic ulceration, gangrene, or a resting ankle blood pressure less than 50 mm Hg. Patients who were unable to walk on the treadmill at a speed of at least 2 mph or whose exercise capacity was limited by symptoms of angina, congestive heart failure, chronic obstructive pulmonary disease, or arthritis were also excluded from the study. Diabetics were excluded because glycemic control may affect the response to a conditioning program,\textsuperscript{27} and these patients often have a severe and distal distribution of arterial occlusive disease.\textsuperscript{28} Patients taking long-term medications continued these drugs without changes in dosage. Patients taking \(\beta\)-adrenergic-blocking drugs or pentoxifylline were excluded because of the possible effects of these drugs on exercise training.\textsuperscript{29} Finally, patients who had undergone vascular surgery or angioplasty within the previous year were also excluded from the study.

Twenty-five patients were enrolled, but six were discontinued from the study. Four treated subjects were discontinued: three for noncompliance with the exercise training sessions and one for the development of medical problems unrelated to PAD. Two control subjects were discontinued: one for medical problems not due to PAD and the second for progression of arterial disease, as previously defined.\textsuperscript{1} Nineteen subjects completed the study, 10 in the treated group and nine in the control group.

On entry, an interview was performed to determine the level of physical activity using the Tecumseh Community Health Study Questionnaire,\textsuperscript{30} and the level of community-based functional impairment using the Rand Corporation Functional Impairment Questionnaire.\textsuperscript{31} This evaluation revealed that all patients were sedentary, in that none exercised on a regular basis (Table 1). None of the subjects could perform vigorous activities such as jogging, skiing, or other active sports, and all were limited in performing moderate activities such as housework, yardwork, bending, lifting, and walking. The patients spent a majority of time performing light activities such as sitting, driving, or office work. Twelve of 19 reported that they were limited as to the type of employment they could undertake because of their disease, and seven could not work at all. There were no differences in activity or impairment between treated or control groups. In addition, 11 of the 19 patients were current smokers, eight were former smokers, and 11 had hypertension. Three patients had a history of peripheral vascular surgery or angioplasty. Nine patients (six treated and three controls) had coronary artery disease determined by a history of myocardial infarction.

**Design**

On entry, treadmill testing was performed on two separate occasions to screen and familiarize the patients with the testing procedures, but these data were not used for subsequent analysis. A third treadmill test was then performed to establish baseline values. Subjects were enrolled in groups of four to six and within each group were paired by the resting ankle-to-arm blood pressure ratio in the most severely affected leg (severity of vascular disease) and by maximal treadmill walking time (functional
immediate postexercise hyperemic flow. Flow measurements were not obtained in one treated subject because of technical problems.

Finally, at entry and after 12 weeks, patients were asked to characterize their claudication-limited walking distance (in blocks) and speed (the difficulty in walking one block quickly, average speed, or slowly) in the community setting.

**Assay Methods**

Samples for carnitine analysis were obtained from subjects at rest, after an overnight fast. Three blood samples (5 ml each) were drawn, the samples centrifuged at 600g for 3 minutes in chilled centrifuge tubes, and plasma aliquots stored at −70°C. Carnitine was measured by a radioenzymatic assay as previously described. Plasma samples were prepared in perchloric acid for the determination of free carnitine and short-chain acylcarnitines (acyl groups less than 10 carbon atoms). Total acid soluble carnitine concentration refers to the sum of the free carnitine and short-chain acylcarnitine concentrations. The ratio of short-chain acylcarnitine concentration to total acid soluble carnitine concentration was also calculated from these measurements. Each assay was performed in duplicate, and the measurements from the three plasma samples were averaged to determine resting values. In three treated subjects, carnitine measurements were not made (one due to technical problems with blood drawing and two because they were not fasting at the time of the measurement).

**Exercise Training Program**

The exercise training sessions were conducted three times each week, with all 10 treated patients completing the 36 required sessions in 13±1.6 weeks. The three subjects in the treatment group that were discontinued for noncompliance completed an average of 14 sessions in 9 weeks before being discontinued. All subjects randomized to the treatment group were able to sustain the exercise prescription. Each training session was supervised and telemetry monitored. A session consisted of 5 minutes of warm-up activities, 50 minutes of intermittent exercise, and ended with 5 minutes of cool-down activities. Walking treadmill exercise was initiated at a low treadmill work load of 2 mph, 0% grade. Subjects walked until claudication pain became moderately severe, at which time the subject stepped off the treadmill and rested until claudication pain subsided. Exercise and rest periods were repeated throughout each training session, and the total exercise duration was recorded. The amount of work performed during exercise was estimated from the speed and grade of the treadmill using a standard formula and is reported in metabolic equivalents (METs). After a patient was able to walk 8–10 minutes at the initial work load, the grade was increased by 1–2%, or the speed was increased by 0.5 mph as tolerated. Treated subjects were instructed to walk for at least 30 minutes twice each week outside the hospital setting.
Peak Exercise Training

Exercise after consumption of 5.5% over entry exercise time treadmill or techniques of intermittent exercise each subjects were able to perform 26 ± 6 minutes of intermittent exercise each training session at an estimated intensity of 2.8 ± 0.5 METs. After 6 weeks of training, this had increased to 30 ± 6 minutes of exercise time and 4.7 ± 1.8 METs (both, p < 0.05), and after 12 weeks, to 32 ± 3 minutes of exercise time at 5.5 ± 1.8 METs (both p < 0.05).

Peak Exercise Performance

In treated subjects after 6 weeks of training, peak treadmill exercise time had increased by 3.5 minutes over entry values, and peak treadmill grade increased from 7.0% to 10.5% (both, p < 0.05), while peak oxygen consumption remained unchanged (Table 2). After 12 weeks of training, peak walking time had increased by 7.5 minutes compared with baseline values, peak treadmill grade had increased to 14%, and peak Vo2 increased by 3.7 ml/kg/min (30%) over resting values (all p < 0.05). In association with the increase in peak exercise performance after training, treated subjects achieved a higher peak heart rate, systolic blood pressure, ventilation, and respiratory exchange ratio during exercise (Table 2). Control subjects did not improve exercise performance at 6 weeks, and at 12 weeks increased peak treadmill walking time 1.1 minutes (p < 0.05) without an increase in peak treadmill grade, peak Vo2 oxygen consumption, or changes in hemodynamic responses.

Statistical Analysis

An analysis of variance for repeated measures was used to evaluate changes within groups (with Dunnett's test for post-hoc comparisons), and an unpaired t test was used to compare differences between groups. The Wilcoxon test was used to evaluate the responses to the questions regarding changes in claudication-limited walking distance and speed in the community. Values are reported as the mean ± SD and considered significant when p < 0.05. Linear regression techniques were used to examine the relation between changes in peak walking time to the change in blood flow or the change in carnitine metabolism.

Results

Exercise Training

In treated subjects, activity during the exercise training sessions was characterized as the total exercise time and estimated work per session. These values were averaged over three sessions each at weeks 1, 6, and 12. On entry (week 1), treated subjects were able to perform 26 ± 6 minutes of intermittent exercise each training session at an estimated intensity of 2.8 ± 0.5 METs. After 6 weeks of training, this had increased to 30 ± 6 minutes of exercise time and 4.7 ± 1.8 METs (both, p < 0.05), and after 12 weeks, to 32 ± 3 minutes of exercise time at 5.5 ± 1.8 METs (both p < 0.05).

Perceived Claudication Pain

After 6 weeks of exercise training, treated subjects reported no change in the perception of claudication pain during treadmill testing except for a delay in the onset of severe pain (p < 0.05, Figure 1). After 12 weeks of training, pain-free walking time increased 165% (p < 0.05), and the time to onset of mild, moderate, and severe pain also increased significantly (Figure 1). No change in the perception of claudication pain severity was noted in control subjects after 6 or 12 weeks, despite the modest increase in peak walking time.

Submaximal Exercise Performance

At entry, and after 6 and 12 weeks, submaximal exercise performance was evaluated at the end of the first stage of the treadmill test (3 minutes) at a work load of 2 mph, 0% grade. In treated subjects after 6 and 12 weeks of training, there was a decrease in Vo2, heart rate, and ventilation compared with entry values (p < 0.05, Table 3). On entry, all 10 treated subjects reported the onset of claudication pain within the first stage of the treadmill test (3 minutes) at a work load of 2 mph, 0% grade.
treadmill stage. After 6 weeks of training, claudication pain during the first stage of exercise was noted in five subjects and after 12 weeks in only three subjects. In control subjects after 6 and 12 weeks, there were no changes in VO₂, ventilation, heart rate, or the perception of pain during the first treadmill stage.

Community-Based Walking Ability

After 12 weeks, treated subjects reported they could walk farther (3 compared with 2 blocks) and faster (1 block quickly compared with average speed) outside the study setting than on entry (both, p<0.05). Control subjects reported no change in their ability to walk.

Hemodynamic Effects of Conditioning

The resting ankle-to-arm blood pressure ratio did not differ on entry between treated and control subjects and did not change during the course of the study in either group regardless of which leg was considered (Table 4). The 1 minute postexercise ankle-to-arm blood pressure ratios did not differ between groups on entry. However, after 12 weeks, treated subjects had significantly lower postexercise ankle-to-arm ratios than on entry, whereas control subjects had no change in this ratio during the 12-week study period. The lower ankle-to-arm ratios in treated subjects after training resulted from a higher systolic arm blood pressure with no change in ankle pressure.

Maximal exercise blood flow measured in the most diseased leg was 11.4±4.3 ml/100 ml/min in treated subjects on entry and increased 38±45% to 14.2±3.2 ml/100 ml/min on exit (p<0.05). However, the change in calf blood flow from entry to exit was not correlated to the change in peak walking time (Figure 2). In control patients, maximal exercise blood flow was 11.7±5.3 ml/100 ml/min on entry and remained unchanged at 11.7±5.3 ml/100 ml/min on exit.

Effects of Conditioning on Carnitine Metabolism

In treated subjects, the plasma concentration of short-chain acylcarnitines (a reflection of the metabolic state) was 12.5±8.4 μm on entry and decreased to 9.6±8.8 μm on exit (p<0.05). The ratio of the plasma short-chain acylcarnitine concentration to the

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**FIGURE 1.** Bar graph of claudication pain severity. Ten treated patients were tested using a graded treadmill protocol to maximal claudication pain on entry and after 6 (mid) and 12 (exit) weeks of training. During exercise testing, claudication pain was assessed every 30 seconds. Open bars, time of onset of pain; diagonal hatched bars, mild pain; cross-hatched bars, moderate pain; solid bars, severe pain. *p<0.05 compared with the value on entry.

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**TABLE 3.** Submaximal Exercise Performance in Treated and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Entry</th>
<th>6 Weeks</th>
<th>12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂ (ml/kg/min, STPD)</td>
<td>T 11.4±1.6</td>
<td>9.1±1.3*</td>
<td>9.6±1.4*</td>
</tr>
<tr>
<td></td>
<td>C 9.9±1.0</td>
<td>9.9±1.1</td>
<td>9.5±0.8</td>
</tr>
<tr>
<td>Ventilation (l/min, BTPS)</td>
<td>T 26±2</td>
<td>22±4*†</td>
<td>23±3*†</td>
</tr>
<tr>
<td></td>
<td>C 30±5</td>
<td>28±5</td>
<td>27±4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>T 100±13</td>
<td>93±12*</td>
<td>90±11*†</td>
</tr>
<tr>
<td></td>
<td>C 100±7</td>
<td>102±10</td>
<td>100±6</td>
</tr>
</tbody>
</table>

Values are mean±SD.
STPD, standard temperature and pressure, dry; BTPS, body temperature and pressure, saturated.
Exercise measurements were obtained at 3 minutes of treadmill exercise in treatment (T) and control (C) patients.
Treadmill speed was 2 mph, and grade was 0% during this 3-minute period.
*<p<0.05 from entry; †<p<0.05 treated compared with control group.

**TABLE 4.** Ankle-to-Arm Blood Pressure Ratios at Rest and 1 Minute After Exercise

<table>
<thead>
<tr>
<th></th>
<th>Entry</th>
<th>6 Weeks</th>
<th>12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>T 0.70±0.10</td>
<td>0.69±0.12</td>
<td>0.71±0.11</td>
</tr>
<tr>
<td></td>
<td>C 0.63±0.12</td>
<td>0.62±0.17</td>
<td>0.62±0.12</td>
</tr>
<tr>
<td>Postexercise</td>
<td>T 0.45±0.19</td>
<td>0.39±0.15</td>
<td>0.31±0.14*</td>
</tr>
<tr>
<td></td>
<td>C 0.37±0.20</td>
<td>0.31±0.14</td>
<td>0.29±0.18</td>
</tr>
</tbody>
</table>

Values are mean±SD.
The ankle-to-arm ratio is the ratio of systolic blood pressures in the ankle by Doppler ultrasound and in the arm by auscultation. Resting values were obtained before each treadmill test with subjects in the supine position. Immediately after exercise, patients were again placed in the supine position to arm-to-ankle pressures obtained at 1 minute postexercise.
*<p<0.05 from entry.
total acid soluble carnitine concentration (an index of the distribution of total carnitine between free and acyl carnitines) decreased in treated subjects from 0.19±0.07 on entry to 0.14±0.09 on exit (p<0.05). In control subjects, there were no changes in either the plasma concentration of short-chain acylcarnitines (8.6±5.4 μm on entry and 8.7±5.2 μm on exit) or the ratio of plasma short-chain acylcarnitine concentration to total acid soluble carnitine concentration (0.13±0.08 on entry and 0.13±0.07 on exit) during the course of the study period.

In treated subjects, the change in the ratio of plasma short-chain acylcarnitine concentration to total acid soluble carnitine concentration from entry to exit was inversely correlated to the change in peak walking time (Figure 2). Thus, treated subjects who had the greatest improvement in exercise performance also had the greatest reduction in plasma short-chain acylcarnitine concentration relative to total carnitine concentration.

Discussion

This controlled, randomized trial demonstrated that a 12-week exercise training program for patients with PAD increased peak exercise performance in all treated subjects, delayed the onset and progression of claudication pain during exercise, and improved community-based walking ability. The improvement in performance was correlated with a change in carnitine metabolism (an index of cellular metabolism) and not to a change in blood flow. In control subjects, the modest increase in peak walking time was not associated with changes in peak treadmill grade or VO2. As a result, claudication pain severity and community-based walking ability also did not change. In addition, control subjects had no changes in carnitine metabolism or calf blood flow.

After 6 weeks of training, the exercise duration and estimated work performed during the training sessions increased. Treadmill testing at this point in time revealed that treated subjects were able to walk longer and to a higher grade but without an increase in peak VO2. At a submaximal treadmill work load, fewer patients had claudication pain, and VO2, ventilation, and heart rate were reduced. These findings suggest that the initial improvement in exercise performance was related to a change in walking efficiency or improvement in the tolerance of claudication pain, leading to an ability to walk to a higher work load without increasing peak VO2. The above findings were not observed in the control group and may represent a learning effect from repeated treadmill walking during the training sessions.

After 12 weeks of training, there were further increases in exercise performance determined from the training sessions and from treadmill testing. At this point in time, treated subjects had an increase in peak VO2, possibly reflecting either an increase in muscle oxygen delivery or an improvement in muscle oxidative metabolism. These changes in peak VO2 could not be inferred from the treadmill work load alone because patients with cardiovascular disease have less of an increase in VO2 per increment in work load than normal subjects. Thus, changes in peak work capacity with training must be evaluated by direct measurements of VO2.

The peak exercise capacity of patients with PAD has been reported to be in the range of 4–5 METs.
and our subjects on entry had a peak \( \dot{V}O_2 \) of 12.8 ml/kg/min or 3.7 METs. This level of impairment is equivalent to cardiac functional Class III–IV. Patients with this peak exercise capacity are able to perform only very light or light activities such as driving a car, desk work, and self-care. Moderate activities such as climbing stairs, gardening, and dancing require a range of 5–7 METs, and heavy activities such as hiking, swimming, and jogging may require 9 or more METs. Thus, even a modest improvement in peak exercise performance and \( \dot{V}O_2 \) from exercise training may significantly improve the functional status of the patient.

In previous studies of exercise training in patients with PAD, treadmill testing was most often performed at a constant work load, and the endpoints were changes in peak walking time and the time that claudication pain first occurred. Using these evaluation techniques, several studies have shown that the improvement in treadmill walking time ranged from 50% to almost 200% without providing direct evidence of an associated increase in peak exercise performance. In our study, treated subjects had a 123% increase in treadmill walking time on a graded treadmill protocol and a 30% increase in peak \( \dot{V}O_2 \). Associated with the improvement in peak exercise performance, treated subjects experienced the onset and degree of claudication pain severity at a later time during exercise. These changes in claudication pain severity and peak exercise performance may allow patients to perform a greater range of leisure- and work-time activities. For example, treated patients also reported an improved ability to walk longer distances at faster walking speeds, suggesting that these benefits may extend to an increase in community-based functional ability.

Previous studies have demonstrated that leg blood flow did not change or increased only slightly with training. We observed that the modest increase in flow in treated subjects was not correlated to improved exercise performance. The lower postexercise ankle-to-arm blood pressure ratios after training were due to a higher arm pressure and not to a lower ankle pressure. The finding of an increase in arm systolic pressure reflected the improvement in peak exercise capacity after training. Hall and Barnard and Jonason and Ringqvist described an increase in the postexercise ankle blood pressure after training, but no change in leg blood flow. Thus, changes in the postexercise ankle-to-arm blood pressure ratio cannot be used to infer similar changes in peripheral perfusion.

Elevated plasma acylcarnitine levels at rest have been associated with the functional impairment in patients with PAD. Additionally, exercise to claudication pain has been associated with an increase in the plasma concentration of acylcarnitines, which may reflect the disordered metabolic state of ischemic muscle. Carnitine is an amino acid derivative found ubiquitously in all mammalian tissues that normally functions as an obligate cofactor for the transport of long-chain fatty acyl groups into the mitochondria for \( \beta \)-oxidation. Under abnormal metabolic conditions, carnitine interacts with the cellular acyl-CoA pool to form acylcarnitines and remove a variety of acyl groups derived from the corresponding acyl-CoA intermediates. Under these conditions, the change in carnitine metabolism is characterized by a redistribution of total carnitine between the free carnitine and acylated forms of carnitine. Thus, the formation of acylcarnitines reflects the underlying metabolic state of the cellular acyl-CoA pool. In the current study, exercise training reduced the plasma concentration of short-chain acylcarnitines and the plasma ratio of short-chain acylcarnitine concentration to total acid soluble carnitine concentration between entry and exit. Treated subjects who had the greatest response to training also had the greatest reduction in the plasma ratio of short-chain acylcarnitine to total acid soluble carnitine concentration. Thus, exercise training may improve muscle metabolism as reported by other investigators and suggested by the changes in plasma carnitine metabolism.

Patients with PAD have a chronic disease characterized by a moderate-to-severe impairment in walking ability. There are limited treatment options for these patients because surgery or angioplasty is reserved for the most severely affected and there is only one approved drug for the treatment of intermittent claudication. In the present study, exercise training resulted in clinically important improvements in peak exercise capacity, walking efficiency, and claudication pain severity. These changes in exercise performance may translate to increased activity in the home and work environments. Thus, a supervised exercise rehabilitation program should be considered an important treatment option for patients disabled from PAD. Future studies will be needed to address the role of exercise training in patients with PAD and other comorbid conditions such as diabetes or coronary artery disease.

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References


KEY WORDS • intermittent claudication • carnitine metabolism • peripheral blood flow • oxygen consumption
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