Exercise Training for Peripheral Arterial Disease

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BACKGROUND

Ms. PC is a 69-year-old, very pleasant, retired African American female who experienced lifestyle-limiting bilateral intermittent claudication pain (IC) in her buttocks, thighs, and calves. The most severe pain occurred on her left side. The onset of her leg pain typically occurred shortly after starting to walk at a normal pace on level ground, progressively worsened, and caused her to stop and rest after approximately one city block. The pain always diminished after a few minutes of seated rest and eventually resolved. These symptoms were most disruptive to her when walking to the bus station, grocery store, church, or doctor appointments and when playing with her young niece.

She reported the following medical history: chronic rhinitis, tinea cruris, hypertension, hypercholesterolemia, type 1 diabetes mellitus, obesity (current body mass index [BMI] = 30.6 $kg \cdot m^{-2}$), smoking (10 pack-yr), right hemispheric stroke in 1999 without residual deficits, and peripheral arterial disease (PAD) initially diagnosed in January 2006. She also had a positive family history for atherosclerosis. Her medications included glyburide 2.5 mg daily (insulin secretagogue), metformin 1000 mg twice daily (insulin sensitizer), metoprolol 50 mg twice daily (beta-blocker), simvastatin 40 mg daily (antihypercholesterolemic), pentoxifylline 400 mg three times daily (platelet inhibitor), hydrochlorothiazide 50 mg daily (diuretic), lisinopril 40 mg daily (antihypertensive), and azelastine 137 mcg by intranasal administration twice daily (antirhinitic).

A pulse assessment revealed a trace pulse of the left femoral and popliteal arteries; an absent pulse of the dorsalis pedis (DP) and posterior tibialis (PT) arteries; and right side diminished pulses of the femoral, popliteal, and DP; and an absent PT pulse. There was no evidence of tissue breakdown or critical limb ischemia (CLI). Ms. PC denied any pain during rest.

Ms. PC was then clinically evaluated to determine the extent of her disease. Her resting segmental leg pressure assessments, echo Doppler waveforms (Figure 1), and aorto-iliac echo duplex imaging results (Table 1) confirmed the diagnosis of bilateral multilevel PAD in the iliac and common femoral arteries. To summarize these exam results, 1) her high thigh-brachial and ankle-brachial indexes were reduced and indicated reduced absolute common femoral arterial (CFA) pressure relative to her brachial pressure; 2) her CFA Doppler waveforms were abnormal and indicated reduced pulsatility; and 3) her peak systolic flow velocities (PSV) in both iliac arteries were more than doubled as compared with the distal abdominal aorta, indicating an accelerated blood flow through narrow stenoses. This combination of observations indicated that significant diffuse stenoses were present. Ms. PC was then referred to the Henry Ford Hospital Preventive Cardiology unit in September 2008 by a vascular surgeon for supervised exercise to treat her IC.

As part of her pre-exercise training assessment, a treadmill exercise test was performed by using the Gardner protocol (2 mph [3.2 kph] at 0% grade, increasing by 2.0% every 2 min) (3). Claudication onset occurred at 136 s (2.0 mph and 2.0% grade) that progressively worsened until exercise was terminated due to severe pain (+4/4 point scale; Table 2) at 238 s (2.0 mph and 2.0% grade). Pre- and post-exercise ankle pressure measurements confirmed that IC induced by

TABLE 1. Aorto-iliac peak systolic flow velocity ($cm \cdot s^{-1}$) based on duplex ultrasound.

Vessel	Velocity	
Distal aorta	60	
Common iliac artery	**Right**	**Left**
Proximal	58	60
Mid	205	537
Distal	165	239
External iliac artery	91	191
Common femoral artery	Plaque visualized	Plaque visualized

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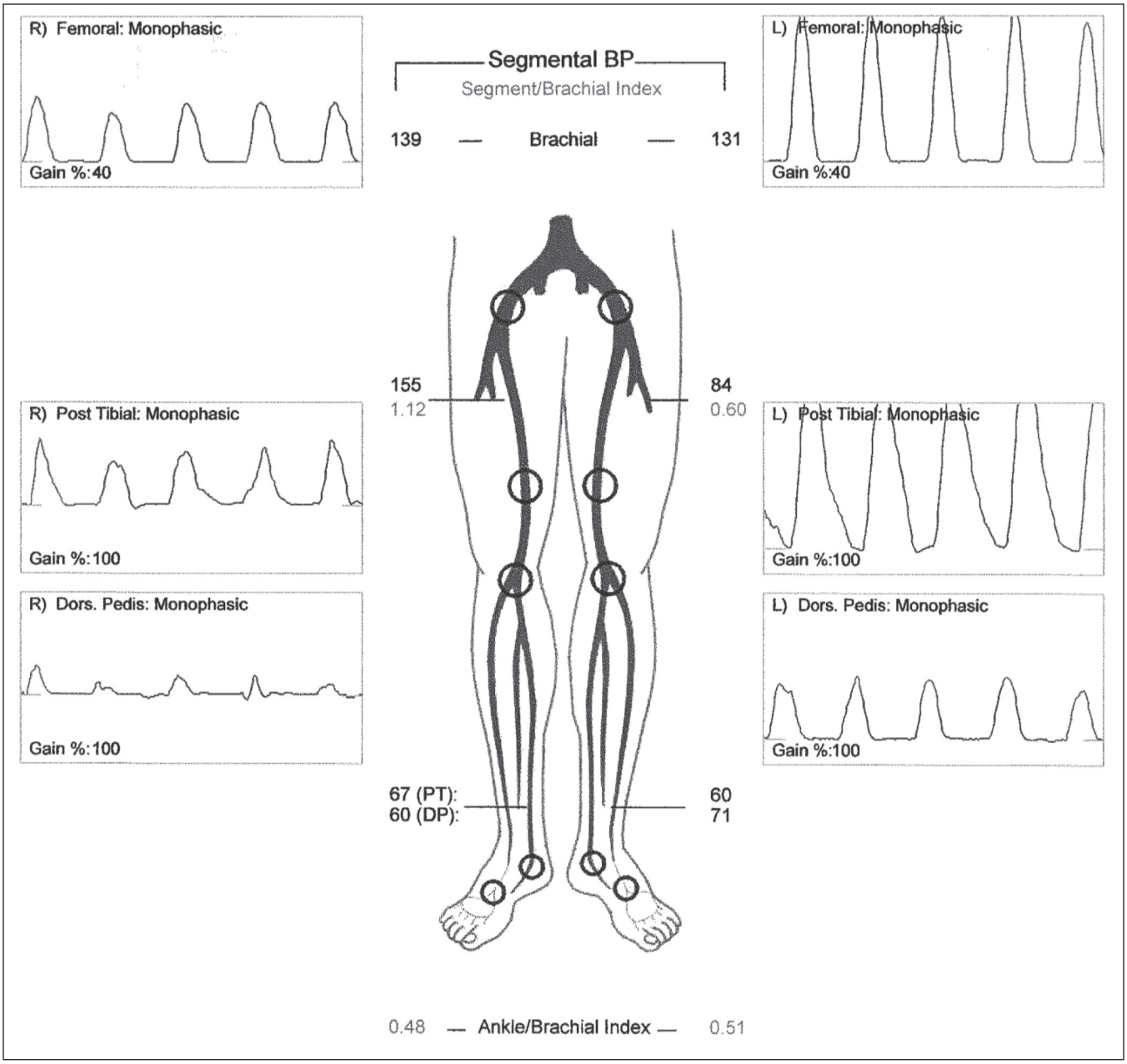
FIGURE 1. Segmental leg pressure indexes and doppler ultrasound waveforms.



PAD was her limiting factor during walking, as evidenced by an immediate post-exercise left ankle pressure decrease from 81 millimeter of mercury (mmHg) at rest to 0 mmHg.

Supervised exercise training sessions were initiated under the guidance of a clinical exercise physiologist. The following protocol was initially implemented for each training session: a 5 min, slow-paced warm-up walk on a treadmill followed by walking at 2.0 mph and 2.0% until an intense pain level (3 on a 4-point claudication scale; Table 2) was experienced. This workload was selected to match the onset of leg pain during the treadmill exercise test. When intense pain occurred, the treadmill was stopped and Ms. PC sat in a chair next to the treadmill and rested until her leg pain was completely resolved. This walk-rest cycle was then repeated until a cumulative (rest + exercise) total of approximately 50 min elapsed. A goal of walking at least 8 min without intense leg pain was set to determine when the treadmill speed and/or grade was to be increased for the next exercise training session. Static leg muscle stretching was

TABLE 2. Claudication pain scale.

Pain Level	Description
0	No pain
1	Initial or mild to moderate discomfort or pain
2	Moderate but tolerable discomfort or pain
3	Intense pain
4	Excruciating and unbearable pain

Adapted from American College of Sports Medicine. Guidelines for exercise testing and prescription. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2010. 259 p.

also performed following a 5 min active cooldown. These exercise training sessions were scheduled 3 d·wk^{-1} for 6 mo.

From September 2008 through March 2009, a total of 76 supervised exercise sessions were completed. Ms. PC was never able to walk longer than 8 min without intense pain and thus treadmill workload was not increased. However, her initial walking bout duration (before the first rest period) progressively increased over the 6 mo of training. For example, during the first 3 sessions, her initial walking bout duration averaged 164 s. During the final week of training, her initial walking bout duration increased to an average of 245 s, an increase of 81 s. Despite this change, her cumulative walk and rest times at each session were variable and did not show a trend toward improvement (Figure 2). Ms. PC reported by diary that she was able to perform home exercise on most days that supervised exercise was not performed. Her home walking typically consisted of 30 min of hallway walking in her apartment complex and 30 min of stationary cycling or seated stepping while watching television. This was followed by a brief stretching routine.

In March 2009, approximately 6 mo after beginning supervised exercise training sessions, Ms. PC performed another graded treadmill test to assess walking tolerance, pain profiles, and pre- and post-exercise ankle pressures. Her peak walking time (PWT) increased by 159 s (67%) compared with pre-training (Table 3). Also, the workload at peak exercise was greater than baseline (2.0 mph and 6% grade or 4.2 MET vs. 2.0 mph and 2% grade or 3.1 MET). Interestingly, time to claudication onset decreased by 26 s.

Over the next 12 mo, no supervised exercise occurred. However, Ms. PC reported performing approximately 120 min of daily home-based exercise, and she continued taking her prescribed medications. Reported exercises included stationary cycling, seated stepping, walking, use of a Leg Magic machine consisting of thigh abduction and adduction, use of an Ab Rocker to strengthen the abdominal muscles, and general leg stretching.

In March 2010, approximately 18 mo after beginning supervised exercise and 12 mo after completion, another graded treadmill test was performed. Peak walking time increased by 262 s (110%) compared with pre-training and by 103s as compared with the post-supervised training test (Table 3). Additionally, the workload at peak walking time increased to 2.0 mph (3.2 kph) and 8% grade (4.7 MET) from a pre-training workload of 2.0 mph and 2% grade (3.1 MET). Claudication onset increased by 78 s (57%) as compared with baseline.

FIGURE 2. Cumulative walk and rest durations by exercise sessions.

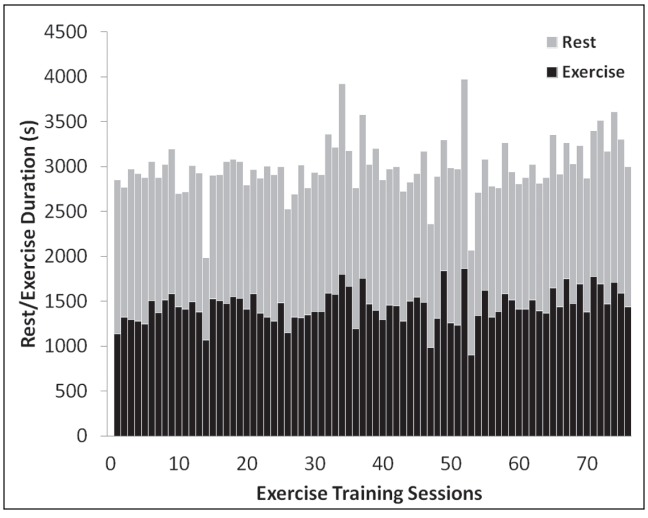


TABLE 3. Change in peak walking duration and claudication onset time after 6 and 18 mo of exercise training.

	Pre-training	6 mo	% Change at 6 mo	18 mo	% Change at 18 mo
Peak walking duration (s)	238	397	67	500	110
Claudication onset time (s)	136	110	-19	214	57

DISCUSSION

Epidemiology

Approximately 8 million adults have diagnosed PAD in the United States, and this number is anticipated to grow with the aging baby boom population (5). The most common symptom of PAD of the lower extremities is IC. Classic IC symptoms—such as pain, ache, cramp, or discomfort of the calves, thighs, or buttocks that worsens with exertion and diminishes with rest—develop due to oxygen supply-demand mismatch (1). However, PAD may be present without classic IC symptoms (i.e., silent ischemia). It is estimated that only 10 to 15% of patients with PAD have IC symptoms (5). Eighty five to 90% of patients with PAD are either asymptomatic or have atypical leg pain symptoms (5). The prevalence of PAD increases with age for men and women; however, differences between genders are not well established (7). Men present with IC symptoms approximately three times more frequently than women (2), while women present more frequently with asymptomatic PAD (7). Regardless of the presence or absence of symptoms, PAD is associated with an increased 5 yr risk of morbidity, including stroke, myocardial infarction, embolism, and death (5).

Etiology

Risk factors for the development of PAD are similar to those for coronary artery disease and ischemic stroke (11). These include smoking, diabetes mellitus, hypercholesterolemia, hypertension, hyperhomocysteinemia, elevated C-reactive protein, sedentary lifestyle, age, gender, genetic predisposition or family history of early onset arterial disease (5,6,11). The greatest risk factors for development of PAD are smoking and diabetes. Each increase risk two to fourfold compared with nonsmokers and nondiabetics (6). A history of arterial trauma (e.g., blunt force, gunshot wound, laceration, crush, or tear) is also a risk factor for PAD (6).

Diagnosis and Clinical Manifestations

The simplest, least expensive, and most common method of diagnosing PAD of the legs is the resting ankle-brachial

index (ABI) (1). The ABI is performed by measuring supine systolic arterial blood pressure with a Doppler ultrasound at the ankle and brachial arteries. The index is then calculated by dividing the highest ankle pressure in each limb (the greater of the dorsalis pedis [DP] and posterior tibialis [PT] arteries) by the highest brachial artery pressure. Normal and abnormal resting ABI values are presented in Table 4. For example, a left DP pressure of 100 mmHg divided by a right brachial pressure of 120 mmHg would yield an index of 0.83 in the left leg and is associated with mild PAD. Imaging techniques are also often performed to diagnose PAD, including duplex ultrasound, computed tomography arteriogram (Figure 3), magnetic resonance imaging, and peripheral arteriography.

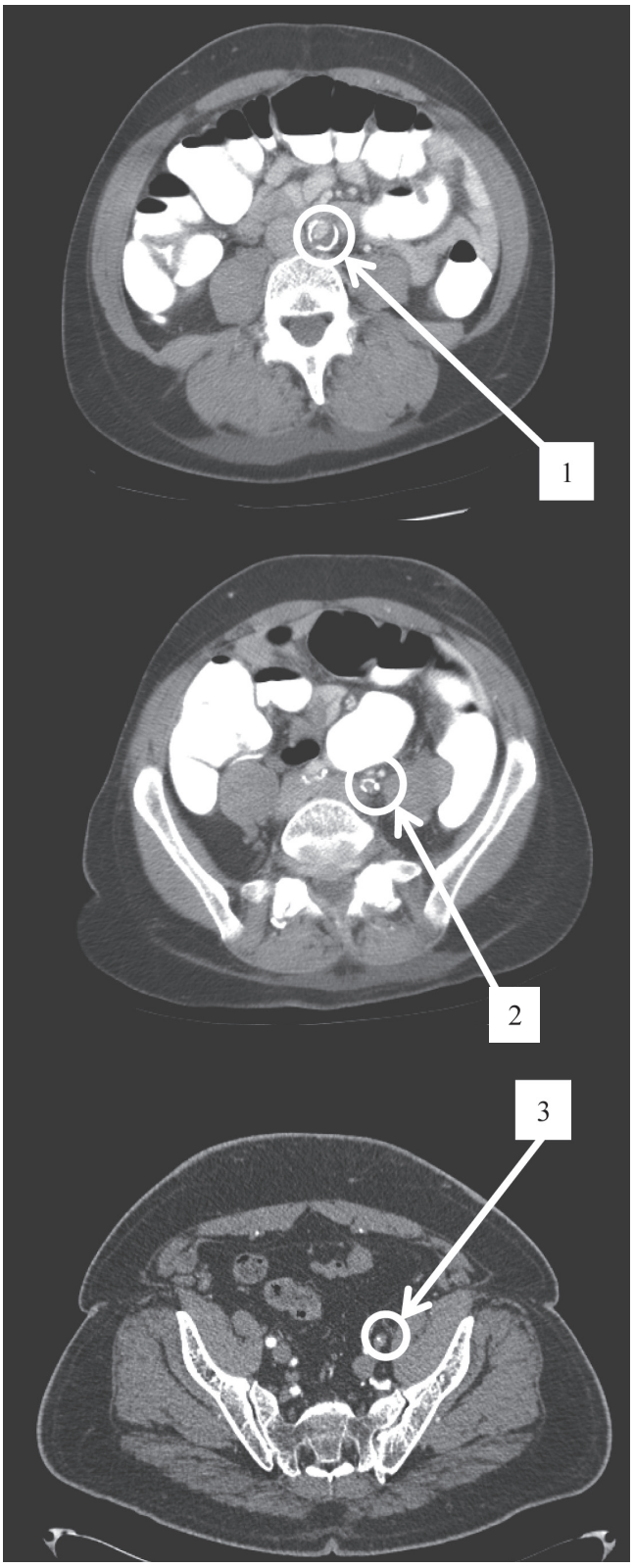
Peripheral arterial disease may progress to high-grade stenoses (total occlusions). Clinically, this may manifest in IC, chronic ischemic rest pain, and, ultimately, tissue necrosis. The level of pain involved depends on several factors. The degree to which collateral circulation develops to tissues distal to the occluded artery also plays a significant role in pain development. If adequate collateral circulation to meet the oxygen demands of the tissue is present, then ischemia and resultant pain tends to be reduced and tissues preserved. If circulation is inadequate, IC pain is more likely to occur. If atherosclerotic lesions are significant, symptoms of CLI may occur, including rest pain, skin eschars that progress to slow to nonhealing open wounds, tissue breakdown,

TABLE 4. Peripheral arterial disease (PAD) interpretation based on ankle-brachial index (ABI) values.

Interpretation	Resting ABI	Post-Exercise ABI
Noncompressible (likely calcified)	>1.40	Not applicable
Normal	1.00 to 1.39	No change or increase
Borderline (equivocal)	0.91 to 0.99	No change or increase
Mild PAD	0.80 to 0.90	>0.50
Moderate PAD	0.41 to 0.80	>0.20 to 0.50
Severe PAD	0.00 to 0.40	<0.20

Adapted from American College of Sports Medicine. Guidelines for exercise testing and prescription. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2010. 120, 258-259 p, and Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM Jr., White CJ, White J, White RA, Antman EM, Smith SC Jr., Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B; American Association for Vascular Surgery/Society for Vascular Surgery; Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology; ACC/AHA Task Force on Practice Guidelines. ACC/AHA Guidelines for the Management of Patients with Peripheral Arterial Disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Associations for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (writing committee to develop guidelines for the management of patients with peripheral arterial disease)—summary of recommendations. J Vasc Interv Radiol. 2006 Sep;17(9):1383-97.

FIGURE 3. Sample computed tomography images.



Arrow #1 identifies the abdominal aorta calcified with 40 to 60% occlusion.
Arrow #2 identifies the left common iliac, calcified with 100% occlusion.
Arrow #3 identifies the left external iliac, noncalcified, 90 to 95% occlusion.

and, ultimately, gangrene requiring tissue removal or amputation. The presence of open wounds increases the risk of infection and should be adequately protected when someone is exercising. Exercise mode may need to be altered to avoid aggravating an open wound.

Treatment

Treatment of PAD can be split into three distinct categories for those who are 1) at risk for PAD and either asymptomatic or have atypical leg pain or 2) have PAD with classic IC symptoms or 3) have chronic rest pain or CLI (6).

Treatment for those at risk for PAD typically involves risk factor modification and elimination when possible. Medications are commonly used to favorably alter certain risk factors, such as hyperlipidemia, hypertension, and diabetes, among others (6). Lifestyle changes are also recommended, including regular exercise, smoking cessation, adoption of a nonatherogenic diet, and stress management techniques (6).

Treatment for patients with PAD with classic IC symptoms includes risk factor modifications as previously described for those who are at risk for PAD. Additionally, supervised exercise and pharmacotherapies (e.g., cilostazol, pentoxifylline) are first-line therapies to improve IC symptoms and increase walking ability (6). For patients with inflow disease, typically aorto-iliac atherosclerosis, or who do not respond well to supervised exercise and pharmacotherapy, endovascular or surgical treatments may be considered (6).

Treatment for chronic rest pain and CLI may include endovascular interventions such as angioplasty, stenting, or endarterectomy and surgical interventions with native, synthetic, or porcine arterial bypass. The major goals of treatment are to reduce or relieve pain and to preserve tissue and avoid amputation. Risk factor modification is also very important for patients treated with invasive therapies to reduce secondary risk of disease progression (6).

Supervised exercise is listed in the American Heart Association guidelines for the management of PAD and assigned a Class IA recommendation. This guideline states: "A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication" (6). An additional Class IA guideline states: "Supervised exercise training should be performed for a minimum of 30 to 45 min, in sessions performed at least 3 times per week for a minimum of 12 weeks" (6). This type of exercise training can increase pain-free walking time by as much as 180% and maximal walking time by 120%. These improvements exceed those that can be attained with drug therapy. Supervised exercise is generally more effective than home exercise, possibly because of better exercise adherence and a better understanding of the need to exercise into mild/moderate pain.

A question one might have is "Why is it effective and safe to push the skeletal muscles of the legs into ischemia while it is unsafe for exercise to result in ischemia of the myocardium?" The answer lies in the metabolic capabilities of each tissue. The myocardium is a predominantly aerobic organ requiring adequate oxygenation for adenosine triphosphate (ATP) development used for contraction and other cell functions. Skeletal muscle has a greater ability to produce ATP by anaerobic metabolism (i.e., glycolysis). Thus, it can sustain adequate function and avoid injury during transient periods of ischemia.

Another question might be "Why does the peripheral skeletal muscle respond to this type of exercise training performed for improvements in intermittent claudication?" There are likely multiple interconnected physiologic processes occurring simultaneously that result in benefits. Specific peripheral adaptations commonly occurring from this type of exercise training include improved systemic and regional blood flow, positive changes in aerobic metabolism, and enhanced pain tolerance. It is also likely that overall improvements in cardiorespiratory fitness occur independent of peripheral adaptations, both of which improve exercise ability (5).

CLINICAL EXERCISE IMPLICATIONS

Exercise Testing

Graded treadmill testing for patients with PAD is particularly useful in helping to determine limiting symptoms. For example, atypical leg pain (e.g., arthritis, neuropathy), deconditioning, or IC may all be present, and the treadmill test will help to determine which is most limiting. Use of the perceived exertion (i.e., Borg scale) and claudication pain scales during testing can help determine if leg pain is limiting. Walking limitations due to PAD tend to be highly reproducible from test to test when using a constant speed and progressive grade protocol, such as the Gardner (3). Thus, repeat testing—ideally less than a week apart—can be used to help confirm walking limitations due to PAD. Post-intervention (e.g., 6 mo of supervised exercise, pharmacotherapy, or revascularization) treadmill testing can determine degree of walking improvement.

The diagnostic sensitivity of the resting ABI is increased by taking immediate post-exercise ABI measurements (Table 4) (1,6,13). Thus, post-exercise ABI measurements can diagnose the presence of PAD in those who are at risk for PAD, have atypical leg pain symptoms, or have classic IC but who have a normal resting ABI. If either the absolute or indexed post-exercise ankle pressure decreases, it is considered diagnostic for PAD (6). The physiologic reason that immediate post-exercise decreases in ankle pressure are considered diagnostic of PAD is the result of ischemic vasodilation induced by exercise in the diseased limb that results in pressure decreases distal to hemodynamically significant lesions, and the ankles are distal to most atherosclerotic lesions of the leg arteries (6).

Exercise Prescription and Training

Current ACSM guidelines recommend weight-bearing exercise, such as walking 3 to 5 $d \cdot wk^{-1}$, and resistance

exercise twice weekly for the treatment of IC. Moderate intensity exercise to an IC pain score of 3 (on a 4-point scale)—followed by rest until IC pain resolves and then repeated until a total exercise time of 30 to 60 min is reached—is recommended.

Recent data from the Exercise Therapy in Peripheral Arterial Disease (EXITPAD) study suggests that a minimum training volume of at least two training sessions a week, each lasting more than 30 min for at least 3 mo, is needed to optimize improvement of maximum walking distance in those with IC (10).

Recent 6 mo outcomes of the Claudication: Endoluminal Revascularization Versus Exercise Training (CLEVER) trial demonstrated superiority of supervised exercise over optimal medical care (risk factor modification and home-based walking) and stenting treatments (9). Peak walking time was increased on average by 5.8, 3.7, and 1.2 min in the supervised exercise, stent, and optimal medical care groups, respectively (9). The pending 18 mo outcomes of the CLEVER trial will provide further insights into the longevity of supervised and home exercise, stenting, and optimal medical care treatment effects.

Home-based, unsupervised exercise for PAD currently carries only a class IIb AHA/ACC treatment recommendation. However, Gardner and colleagues (4) recently reported good adherence to a home-based exercise program (>80% of session completed over 12 wk) that resulted in significantly increased peak walking and claudication onset times. These improvements were similar to those obtained by subjects who performed supervised exercise. A major methodological improvement compared with most prior studies of home-based exercise was accurate measurement of the exercise sessions with the use of a step activity monitor (4). It is possible that much of the difference in attained improvements between supervised and the exercise training in prior studies was primarily due to lower adherence to the home-based training protocol.

Very little data exists that examines the effect of exercise training on patients with PAD without IC. This is a relatively large gap in knowledge because the majority of patients with PAD do not have classic IC symptoms. However, McDermott recently reported that supervised treadmill exercise improved walking ability similarly for patients with PAD—with and without IC. Additionally, lower-extremity resistance training improved measures of functional performance (8).

Finally, although walking is well established to improve walking ability in patients with PAD, arm ergometry may also improve walking ability to a similar extent (12). Arm ergometry and walking are recommended exercise modes per ACSM guidelines (1). Leg cycling is suggested as a mode for warm-up and cooldown (1).

SUMMARY

Ms. PC's experience is typical of others with PAD and IC who have engaged in supervised exercise. Although not all patients respond favorably, most tend to increase their ability to walk before leg pain begins and walk longer before needing to stop and rest. These functional improvements often result in meaningful increases in quality of life and may help to reduce the risk of morbidity.

Keywords: intermittent claudication, walking, ankle-brachial index

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