Peripheral Arterial Disease: A Case Report From the Henry Ford Hospital

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CASE PRESENTATION

A.T. is a 65-year-old black female with claudication secondary to peripheral arterial disease (PAD). She has a history of coronary artery disease, myocardial infarction, heart failure, endarterectomy, hypertension, hyperlipidemia, type 1 diabetes mellitus, and asthma.

She was referred to the Division of Vascular Surgery at Henry Ford Hospital complaining of fatigue and heaviness in her lower thighs and calves during walking. Resting ankle-brachial index (ABI) was 0.50 and 0.70 at the right and left dorsalis pedis, respectively. She was prescribed cilostazol and encouraged to "…walk through the pain as much as possible."

Due to worsening claudication, A.T. underwent an abdominal aortogram with arteriogram of the lower extremities. Results showed aortoiliac disease with multiple stenoses of varying degrees. Areas of calcification were noted from the lower aorta and iliac artery to the anterior tibial artery affecting both the left and right limbs.

Results from a stress echocardiogram showed cardiac wall motion abnormalities consistent with exercise-induced ischemia. She exercised for 5.8 minutes on the Bruce protocol, limited by general fatigue. The electrocardiogram displayed left bundle branch block, resting ejection fraction was 40%, peak blood pressure was 160/80 mmHg, and peak heart rate was 120 $b \cdot min^{-1}$. No symptoms were reported. Her medications are cilostazol, carvedilol, amlodipine, isosorbide dinitrate, clopidogrel, simvastatin, potassium, triamcinolone, ipratropium, and pirbuterol.

She began supervised exercise training in cardiac rehabilitation following a hospitalization for angina. At rest her blood pressure was 120/50 mmHg, heart rate was 79 $b \cdot min^{-1}$, blood glucose was 6.89 $mmol \cdot L^{-1}$ (266 $mg \cdot dL^{-1}$) and her HbA1c was 8.0%. Her initial exercise sessions were limited by bilateral claudication of her thighs and calves. Moderate pain occurred after 9 minutes of walking on day 1. A pain-rest walking program was initiated and followed for 12 weeks. She then joined the Henry Ford PREVENT program, which provides patients with a low-cost, long-term supervised exercise environment.

She now exercises at least 3 $d \cdot wk^{-1}$ for 60 minutes each session. She splits her exercise time between a seated stepper and a treadmill. On most days she is now able to walk 30 continuous minutes without limiting claudication pain.

DISCUSSION

The natural history of arteriosclerosis involves an intimal plaque that progressively develops until it eventually causes a significant flow limiting occlusion of the vessel and reduction of blood supply relative to demand. Arteriosclerosis is a systemic disorder affecting the major circulations, with the intimal plaque occurring segmentally in multiple locations. When the plaque occurs in the distal aorta or in the arteries of the lower extremities, it is referred to as PAD.

Epidemiology

More than 8 million individuals in the United States above the age of 40 are estimated to have PAD (1). The prevalence of PAD per ABI is 4.3% in persons older than 40 years and up (2) and 29% in those 70 years and older (3). Thus PAD afflicts more than 4 million Americans and more than 200 million people worldwide. The age-adjusted prevalence of PAD increases to approximately 12% when more sensitive vascular imaging studies are used. Unlike coronary artery disease, the incidence of PAD is similar in men and women. Coronary artery disease occurs in 60% to 90% of patients

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with PAD. The incidence of cerebral vascular disease is increased in patients with PAD as well.

Natural History

Peripheral arterial disease is part of the spectrum of atherosclerosis. It is associated with coronary and carotid artery disease. PAD increases mortality by 6-fold, due mostly to myocardial infarction and stroke. The 5-year mortality rate in patients with PAD is ≈30%, with a major lower extremity amputation rate near 1% to 2%. If the patient continues to smoke, the mortality rate doubles and the risk for amputation increases 10-fold. Aortoiliac disease has a higher mortality than femoral artery disease due to a greater prevalence of coronary artery disease in patients with the former.

Ten percent of patients with intermittent claudication will go on to have ischemic pain at rest (aka, critical limb ischemia), often leading to ulceration or amputation. The presence of diabetes mellitus also affects morbidity and mortality in patients with PAD. Sixty percent of leg amputations are the result of diabetic peripheral vascular disease. In fact, among patients with diabetes for 25 years or more, the risk of below the knee amputation is increased 12-fold.

Etiology

The risk factors for coronary artery disease are also risk factors for the development of PAD (i.e., age greater than 65 years, cigarette smoking, and diabetes mellitus). Patients with type 2 diabetes mellitus have a 4-fold increased risk for PAD, while their risk for myocardial infarction or stroke is increased only 2-fold. The severity of PAD is not related to glycemic control but rather to the number of coexisting risk factors. Therefore, hypertension, hyperlipidemia and hyperhomocysteinemia are also important risk factors for PAD. For each 0.03 $mmol \cdot L^{-1}$ (1 $mg \cdot dL^{-1}$) increase in total cholesterol, there is a 1% increased incidence of PAD. A reduced high-density lipoprotein cholesterol and increased triglyceride are also closely associated with PAD. In the presence of these risk factors and given the systemic nature of atherosclerosis and its poor prognosis, patients with PAD should be thought of as already having coronary and carotid artery disease.

Clinical Features

History

Unless there is acute occlusion by thrombosis, the symptoms of PAD occur gradually and progressively. Intermittent claudication is the major symptom of PAD. Claudication is derived from the Latin word *claudicato*, meaning *to limp*, which describes the gait of a patient with intermittent claudication. Intermittent claudication is most often described as an aching, cramping, or tightness in the muscles of the leg (usually the calf) that occurs with exercise and is relieved with rest. The pain usually disappears within several minutes after stopping exercise. The discomfort reoccurs at a constant distance. The distance is shorter if the patient is walking uphill or climbing stairs, and this pain does not occur at rest.

Despite claudication being the hallmark symptom of PAD, it is estimated that approximately 60% to 70% of individuals with disease do not have this symptom (4). The reason for this disparity is not entirely clear, but often patients with PAD may have diabetic neuropathy, which could mask symptoms, or they may simply not report discomfort because of the false assumption that it is simply pain associated with the aging process (e.g., arthritis). Another possibility could be because of avoidance of activities that may cause leg pain (e.g. exercise, yard work, walking long distances).

Some areas of the vascular tree are more likely to develop atherosclerotic plaque than others. In the abdomen, the stenosis usually occurs in the distal aorta or common iliac arteries. Distal to the inguinal ligament, the most common occlusions occur in the adductor canal, the posterior tibial artery at the ankle, and the anterior tibial artery at its origin. Stenosis of the external iliac and popliteal arteries occurs less frequently.

The location of the claudication is useful in predicting the most proximal level of occlusion. Intermittent claudication of the calf muscles does not occur with occlusions in the anterior tibial, posterior tibial, or peroneal arteries. It requires a more proximal lesion. Calf and thigh claudication suggests that the area of stenosis is proximal to the origin of the vascular supply to the thigh muscles (i.e. the profunda femoris artery). Thigh and buttock claudication with impotence in a middle-aged male is called Leriche Syndrome and signifies terminal aortic disease.

Pseudoclaudication must be differentiated from true claudication. Pseudoclaudication occurs from nonvascular causes of leg pain such as spinal stenosis, herniated nucleus pulposus, spinal cord tumors, and degenerative joint disease. It is usually described as a paresthetic discomfort (i.e., numbness, tingling, and/or weakness). The exercise-pain-rest cycle is not consistent in that standing does not relieve the pain. Sitting down may relieve it, and the time required for the pain to disappear is usually several minutes or more.

Physical Examination

Patients with isolated nonobstructive lesions frequently have normal-appearing extremities. Paresthesia, numbness, ulceration, and gangrene are also symptoms of PAD but represent an advanced stage with multiple lesions. Loss of hair, trophic nail changes, and dependent rubor (redness caused by swelling) can also be seen. Loss of the peripheral pulse distal to the occlusion occurs in chronic disease. The pulses that should be checked include the femoral, popliteal, dorsalis pedis, and posterior tibial. Pulses should be described as: 0, absent; 1, diminished; 2, normal; or 3, bounding. Auscultation for bruits should also be performed over the abdomen and femoral arteries.

Diagnosis

The resting ABI is considered the first-line test for PAD with a sensitivity ranging from 68% to 84% and a specificity of 84% to 99% compared to the gold standard of vascular imaging (1). ABI is measured by taking systolic blood

TABLE 1. Interpretation of ABI values.

	Ankle-Brachial Index Rest
Noncompressible (likely calcified)	> 1.40
Normal	> 1.00 - 1.39.95
Borderline	0.91 - 0.99
Abnormal	< 0.90

pressure in the arm (i.e., brachial artery) and dividing it by pressure in the ipsilateral ankle (greater value between the dorsalis pedis or posterior tibial arteries). A normal value is 1.0 or greater (Table 1). Values less than 0.5 are usually seen in patients with diffuse disease. A study of over 2,000 patients with PAD showed an abnormal ABI (< 0.91) to be an independent predictor of cardiovascular events and total mortality, with an annual mortality of 25% for the lowest ABI values (5). Values over 1.4 are likely due to noncompressible vessels from extensive disease and calcification.

The ABI can also be measured immediately after exercise. It should be the same or higher than the resting value. A drop in the ABI after exercise in someone who was normal or borderline at rest also suggests significant disease. As the arterioles within the exercising muscles dilate, the stenosis in the artery proximal to the muscle limits augmentation of blood flow and pressure drops. The postexercise ABI is often used to follow disease progression, as well as adequacy of medical and surgical therapy.

Ultrasonic duplex scanning, computed tomography angiography, or magnetic resonance angiography can be used to evaluate the severity of the disease and determining a treatment plan. Ultimately, angiography is necessary to localize the lesion and determine the extent of disease prior to surgery or percutaneous transluminal angioplasty.

Treatment

The goals of treatment include reducing the symptom of intermittent claudication, improving mobility and quality of life, and halting the progression of atherosclerosis. Aggressive risk factor modification should be the cornerstone of any treatment plan. Due to the poor appreciation that PAD represents systemic atherosclerosis and is associated with a poor prognosis, many patients with PAD are undertreated. Smoking cessation through educational programs, nicotine-replacement therapy, and antidepressant drugs should be strongly considered. In those patients with hyperlipidemia, low density lipoprotein cholesterol should be at least less than 2.59 mmol·L^{-1} (100 mg·dL^{-1}) and triglyceride should be less than 3.89 mmol·L^{-1} (150 mg·dL^{-1}). Statin agents, in addition to lowering cholesterol, also may improve endothelial function. The treatment of hypertension and diabetes mellitus does not alter the natural history of PAD. Similarly, hyperhomocysteinemia is easily measured and treated, but there are no clinical trials assessing efficacy, and thus the current guidelines state that homocysteine lowering is of no benefit. At present there is no role for the use of hormone replacement therapy. Antiplatelet agents (i.e., aspirin and clopidogrel) reduce the risk of fatal and nonfatal cardiovascular events and are approved by the Food & Drug Administration for secondary prevention in patients with atherosclerosis. Probably due to a long history of use and few side effects, aspirin remains the drug of choice (1). Aspirin may also be administered with clopidogrel, which may reduce the risk of myocardial infarction, stroke, and vascular death in those with symptoms (1).

Meticulous foot care is extremely important, with special attention to properly fitting shoes and immediate attention to cuts and blisters. This is especially true for patients with diabetes mellitus, because with a peripheral neuropathy they might not experience pain as a warning sign of developing foot problems.

Medical treatment has met with mixed results. Vasodilators are not effective and are not used in the treatment of PAD. Pentoxifylline is no longer recommended as treatment for claudication pain. Cilostazol inhibits platelet aggregation and smooth-muscle proliferation and causes vasodilatation. In 4 randomized placebo-controlled trials, cilostazol improved both pain-free walking and maximal treadmill walking distance, but it did not improve the incidence of cardiovascular death (6,7).

For patients with lifestyle-limiting symptoms and hemodynamically significant aortoiliac disease, percutaneous transluminal angioplasty is an excellent alternative to surgery, giving results comparable to surgery without the morbidity. The ideal lesion for percutaneous transluminal angioplasty is an iliac stenosis less than 5 cm in length or a femoropopliteal stenosis less than 10 cm in length. Long-term results are best when the lesion is above the groin area. The majority of patients with PAD will not require surgical therapy, and a class I recommendation is to offer all patients exercise training therapy initially versus revascularization (1). Patients who do develop ischemic pain at rest, ulcers, or gangrene may be helped by surgery.

EXERCISE IMPLICATIONS

Exercise Testing

Since atherosclerosis represents the most common cause of death in patients with PAD, screening for coronary artery disease is important. Exercise testing guidelines outlined by the American College of Sports Medicine are appropriate for patients with PAD (8). A common treadmill protocol used in this patient population is the Gardner protocol (9) (Box 1). In patients with PAD, a symptom-limited exercise test can help identify exercise-induced myocardial ischemia,

BOX 1. GARDNER TREADMILL PROTOCOL

- Constant speed of 2.0 mph (3.2 kph)
- Increments of elevation every 2 min
  - Start at 0%
  - Increase by 2%
- Record pain-free and maximal walking time

BOX 2. KEY ELEMENTS OF PERIPHERAL ARTERIAL DISEASE (PAD)

- Patients with PAD have 6 times the mortality as their age- and gender-matched peers.
- Intermittent claudication is the defining symptom of PAD, traditionally affecting the calves but possibly including the thighs or buttocks.
- Patients with diabetes mellitus and peripheral neuropathy may not experience claudication in spite of severe PAD.
- In addition to detecting PAD, the ankle-brachial index test is an important non-invasive predictor of cardiovascular events and total mortality.
- Smoking cessation, exercise, and modification of other risk factors are the foundation for treating PAD.

quantify aerobic capacity, evaluate postexercise ABI, identify time to initial claudication pain, and develop an exercise prescription.

Reported peak oxygen consumption values in patients with PAD is 13 to 14 $mL \cdot kg^{-1} \cdot min^{-1}$ (10,11). Tests utilizing treadmill exercise will likely be limited by claudication. Although the time to onset of pain and maximal walking time during treadmill exercise are important markers of the severity of PAD and used for outcome comparisons, tests limited by claudication may not provide sufficient myocardial stress for proper assessment of cardiovascular disease risk. Submaximal stress may be avoided by using leg or arm ergometry while still providing information useful for developing an exercise prescription.

Submaximal functional evaluations, such as the 6-minute walk test, may better reflect the impact of claudication on daily physical activities. Among patients with PAD, Montgomery et al. (12) found the 6-minute walk test to be reliable and correlated with the time to claudication pain during treadmill testing and ABI.

Exercise Training

Exercise training has been recommended to patients with intermittent claudication for many years, with several randomized controlled trials of exercise training reported. And importantly in May 2017 the Centers for Medicare and Medicaid Services (CMS) approved supervised exercise training as a reimbursable intervention for patients with symptomatic PAD who are referred by their physician. The impetus for this approval is an ever-growing amount of research demonstrating functional and quality of life improvements in those with symptomatic PAD who undergo an exercise training program. Virtually all trials that have evaluated the importance of exercise training in patients with PAD have exhibited an increase in exercise tolerance. And the evidence for exercise training benefits has resulted in the higher recommendation by the American Heart Association and American College of Cardiology for supervised exercise training (1).

BOX 3. KEYS TO EXERCISE TESTING AND TRAINING OF PATIENTS WITH PERIPHERAL ARTERIAL DISEASE (PAD)

- Patients with PAD are at increased risk of cardiovascular disease and should be appropriately evaluated for exercise-induced myocardial ischemia.
- PAD results in reduced exercise tolerance due to metabolic dysfunction, skeletal muscle abnormalities, diminished cardiorespiratory reserve, and exercise-induced inflammation. Exercise training improves pain-free and peak walking ability. Compared to stenting, improvement with walking is similar for pain-free walking and superior for peak walking time. Both are better than optimal medical therapy.
- Optimal exercise training benefits are derived from programs that include walking to moderate pain with intermittent rest, accumulating 30 to 45 minutes, 3 $d \cdot wk^{-1}$ (or more), for at least 6 months.

The Claudication: Exercise Vs. Endoluminal Revascularization (CLEVER) study was the defining study to convince the CMS to cover supervised exercise training for PAD (13). CLEVER randomized revascularization-eligible patients to either medical care alone (i.e., advice and cilostazol), medical care plus revascularization, or medical care plus exercise training. The exercise training group had equivalent pain-free walking time as compared to the revascularization group (with both better than medical care alone) at 6 and 18 months. And the exercise group improved more than both other groups in peak walking time, which improved by 4.6 minutes (95% CI, $P=0.001$) versus only 2.1 (95% CI, $P=0.04$) minutes, respectively for the supervised exercise and control groups. The authors stated that supervised exercise is a reasonable strategy, as compared to stenting, and programs should be developed that are available and affordable to patients (13).

A meta-analysis from the Cochrane database (14) involving 32 critically evaluated randomized controlled trials of exercise therapy that randomized a total of 1,835 patients reported an overall improvement in peak walking distance of 120 meters (95% CI 50.79 to 189.92, $P<0.0007$, high-quality evidence). Pain-free walking distance was also improved, as compared to a control group, by an average of 82 meters (95% CI 71.73 to 92.48, $P<0.00001$, high-quality evidence). These findings are consistent with an earlier meta-analysis that reported improvements of 179% and 122% for walking distance to the onset of pain and to maximal pain, respectively (15). It is noted that exercise training has not been shown to affect the ABI (14).

In addition to the reduction in blood flow due to PAD, several factors have been associated with the reduced exercise capacity observed among these patients (Figure 1). These include metabolic dysfunction, skeletal muscle abnormalities, reduced cardiorespiratory reserve, and exercise-induced inflammation. With exercise training there is

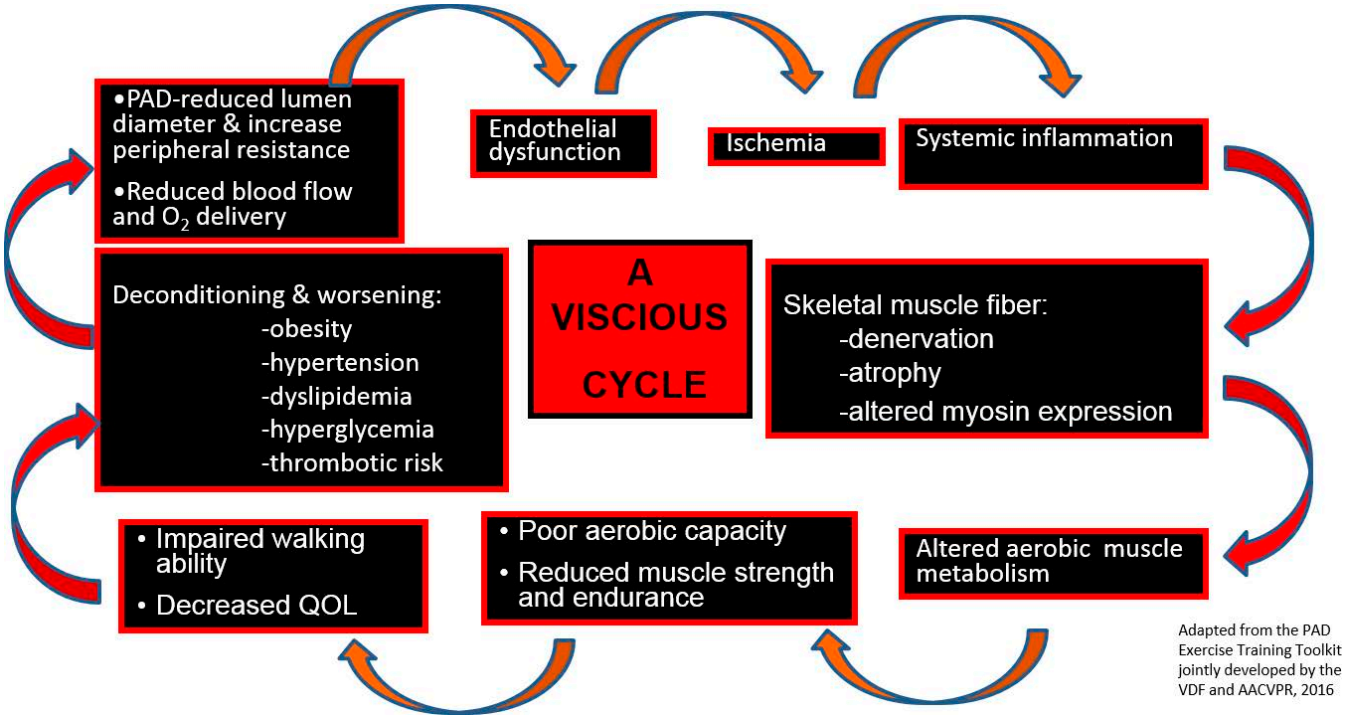

FIGURE 1. Factors associated with reduced exercise capacity in patients with PAD.

increased skeletal muscle fiber area and improved oxidative capacity, blood flow, gait biomechanics, and blood rheology (e.g., viscosity, filterability and aggregation) (16). Due to chronic ischemia and reperfusion, multiple episodes of local and systemic inflammation occur in patients with PAD and is exacerbated by acute exercise, yet its contribution to disease progression is unknown. Also unknown is the role exercise training may have on modifying this inflammatory response.

The majority of exercise training trials in patients with claudication have used walking as the exercise training mode, as well as the primary outcome measured. As a result, walking predominates in the exercise prescription even though the mechanisms by which these patients improve remain unclear. Other exercise modes have also shown benefit. Sanderson et al. (17) evaluated the training response of 42 patients with symptomatic claudication randomized to 6 weeks of leg cycling, treadmill walking, or non-exercise control. The leg cycling group improved both pain-free and peak walking time versus control. However, this improvement was not as great as the treadmill walking group. Treat-Jacobson et al. (18) assessed 12 weeks of upper-body ergometry training versus treadmill walking and reported significant improvements in both groups for pain-free and peak walking time. These data suggest a systemic effect with exercise training.

The effects of progressive resistance exercise in patients with claudication are not well investigated. Hiatt et al. (19) found lesser improvements in walking time following 12 weeks of strength training (36%), compared to treadmill exercise (74%). In addition, strength training combined with treadmill exercise did not provide additional benefits. Similarly, McDermott et al. (20) compared treadmill walking with progressive resistance training in a group of 156 patients with PAD. They noted improvements in both groups in peak walking time versus control, but the treadmill group improved more than the resistance training group (3.4 vs. 1.9 minutes).

Exercise Prescription

Exercise prescription guidelines outlined by the American College of Sports Medicine are appropriate for patients with PAD (8). The exercise prescription for maximal walking improvements in patients with claudication secondary to PAD should be walking-focused. Ideally a patient should perform intermittent walking to the point of moderately tolerable claudication pain, alternated with rest (Figure 2). Rest periods should last until pain is completely (or nearly) relieved enough to continue walking. Patients should accumulate at least 30 minutes, but preferably 45 to 60 minutes, of this type of training at least 3 $d \cdot wk^{-1}$. Exercise intensity should be slowly increased when a patient can walk more than 8 minutes without at least moderate pain. As exercise tolerance improves, some PAD patients may increase their total continuous walking time, or potentially introduce intermittent bouts throughout the day. Maximal benefits have been reported after 6 months of training, thus it is important to encourage patients to continue exercising beyond a typical 12-week supervised exercise training program. In addition to this standard recommendation, some patients may further improve cardiorespiratory function by performing additional aerobic exercise via exercise modes that are not limited by claudication (e.g., leg cycling, seated stepping, elliptical). This might be useful for select patients

Rating	Pain	Description
0	None	During rest or early exercise
1	Mild	1st feeling of any pain
2	Moderate	Level at which an exercise training bout should cease
3	Intense	Nearly maximal pain
4	Unbearable	Maximal, equivalent to most severe pain experienced

FIGURE 2. Claudication Training Pain Scale.

who either have a low functional capacity or who are not able to tolerate more than 30 minutes of the walking to moderate claudication pain protocol. Additionally, there are long-term health benefits of performing continuous exercise at an intensity that provides a cardiorespiratory stimulus (i.e., > 50% peak). And it is interesting to note that PAD patients who performed any amount of physical activity beyond light intensity showed a lower mortality rate than similar patients who were effectively sedentary (14). This reduced risk of mortality remained evident even when the findings were adjusted for age, ABI, and body mass index (21).

SUMMARY

"Stop smoking and keep walking" has long been the recommendation for people with claudication. Although significant improvements in pain-free and peak walking distance are well documented by those who perform regular exercise, the mechanisms and their relative contribution remain unclear. In addition, their impact, if any, on disease progression and mortality requires further investigation. In spite of various medical therapies (e.g,, medications, revascularization), exercise training continues to produce the most favorable outcomes and should be routinely incorporated into the treatment plan for patients with PAD.

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