Review Article

Medical Progress

Exercise Training for Claudication

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Peripheral arterial disease, a manifestation of systemic atherosclerosis, affects approximately 8 million to 10 million people in the United States, with an age-adjusted prevalence of 12 percent that increases to 20 percent if only persons older than 70 years are considered.[1,2] Claudication, defined as walking-induced pain in one or both legs (primarily affecting the calves) that does not go away with continued walking and is relieved only by rest, is present in 15 to 40 percent of patients with peripheral arterial disease[3] and is associated with a diminished ability to perform daily activities.[3-5]

The treatment of this condition focuses on decreasing the functional impairment caused by symptoms of claudication. It is also critical to treat the underlying systemic atherosclerosis in patients with claudication, because of the high risk of cardiovascular ischemic events.[6,7] The ankle-to-arm ratio of systolic blood pressure (ankle–brachial index), which is readily obtainable with standard blood-pressure cuffs and a Doppler device, is a useful tool for the diagnosis of peripheral arterial disease.[6] The medical[6-8] and surgical[8] therapies for claudication have recently been reviewed (Table 1). The growing recognition of the adverse effect of claudication on functional capacity and the quality of life and the observation that exercise training can serve as an effective primary nonpharmacologic treatment for claudication symptoms[6,7] have led to the establishment of a Current Procedural Terminology code (93668) for exercise rehabilitation for claudication.

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Functional Benefits of Exercise Training

Because of their impaired walking ability, patients with claudication have considerable difficulty in carrying out routine daily activities.[5,24] Many affected patients are so deconditioned from lack of exercise that they become housebound or dependent on others.[4,25] The cycle of disability resulting from claudication, the mechanisms involved, and the role of exercise training are shown in Figure 1.

Prospective studies have demonstrated a benefit of exercise training in patients with claudication.[10,11,26,27] Because most patients studied have had mild-to-moderate claudication, little is known about the clinical benefits of exercise in patients with asymptomatic peripheral arterial disease or in patients with critical leg ischemia. Although exercise-induced improvement in walking ability is well established, the magnitude of the responses to training across studies has varied. Such variability may be explained by study-specific differences in the intensity, duration, and frequency of the exercise prescription and the methods of measuring exercise capacity. One meta-analysis[10] that examined both nonrandomized and randomized trials showed that exercise training improved pain-free walking time in patients with claudication by an average of 180 percent and improved maximal walking time by an average of 120 percent. The greatest improvements in walking ability occurred when each exercise session lasted more than 30 minutes, when sessions took place at least three times per week, when the patient walked until near-maximal pain was reached, and when the program lasted six months or longer. A meta-analysis from the Cochrane Collaboration[11] that considered only randomized, controlled trials concluded that exercise improved maximal walking time by an average of 150 percent (range, 74 to 230 percent). It would appear that the exercise-induced increases in maximal walking ability exceeded those attained with medication, which has been estimated to result in improved maximal walking distance (20 to 25 percent with pentoxifylline and 40 to 60 percent with cilostazol).[28]

Exercise-induced improvement in walking ability results in improvement in routine daily activities.[29,30] In one uncontrolled study,[31] six months of exercise training improved treadmill walking distance to onset of pain by 115 percent and maximal walking distance by 65 percent; there was also a 31 percent increase in the ability to carry out routine daily activities, as measured by accelerometry. Self-reported physical activity increased by 62 percent, confirming that func-

TABLE 1. TREATMENTS FOR CLAUDICATION.

TREATMENT	DOSE OR INTERVENTION	EFFICACY	SAFETY
Exercise[9-11]	35–50 min per day 3–5 times per week, treadmill or track walking	100–150% improvement in maximal walking distance; improved quality of life	Well tolerated; cardiovascular complications are rare
Angioplasty[12-14]	Based on anatomy	Improvement in maximal walking distance equivalent to that from exercise; improvement in quality of life equivalent to that from surgery	<0.5% morbidity and mortality
Surgery[15]	Based on anatomy	75–100% improvement in maximal walking distance; improved quality of life	2–3% mortality; 5–10% morbidity
Pharmacotherapy*			

*Pharmacotherapy for claudication has recently been reported and reviewed in the *Journal*[6] and elsewhere.[16-23]

tional improvement was evident to the subjects. Controlled studies involving patients with claudication have also demonstrated improved capacity to perform routine daily activities after exercise training.[5] Such increases in activity, if associated with improvements in cardiovascular risk factors, might also reduce the risk of adverse cardiovascular events, thereby potentially improving the poor prognosis with respect to survival in this population.[5]

The time course of the response to a program of exercise has not been fully established. Clinical benefits have been observed as early as four weeks after the initiation of exercise and may continue to accrue after six months of participation.[32] Improvements in walking ability after 6 months of supervised exercise rehabilitation three times per week were sustained when patients continued to participate in an exercise maintenance program for an additional 12 months.[33]

POTENTIAL MECHANISMS OF IMPROVEMENT

Exercise training for claudication follows a pattern of short periods of walking that induce discomfort of moderate intensity, interspersed with short rest periods. The physiological, metabolic, and mechanical alterations that occur during the period of exercise presumably stimulate an adaptive response that ultimately reduces claudication symptoms. Evidence from studies of animals and humans suggests several mechanisms for such clinical benefits (Table 2).

Formation of Collateral Vessels and Increased Blood Flow

If adaptation to exercise training induces angiogenesis, increased blood flow to skeletal muscle distal to an arterial occlusion or stenosis might ensue. Although the mechanisms that underlie endogenous angiogenesis are complex, reduced oxygen tension or related metabolic alterations in the muscle and increased blood flow and muscle contraction are possible proangiogenic stimuli.[68] In healthy subjects, a single session of exercise up-regulated the expression of vascular endothelial growth factor (VEGF) messenger RNA (mRNA) in calf muscle, with the size of the increase related in a dose-dependent fashion to the degree of metabolic stress.[69] This increase in VEGF mRNA expression during short-term exercise implies an association between VEGF and the promotion of angiogenesis. One might speculate that exercise training causes transient hypoxia in the legs that up-regulates VEGF mRNA and protein expression and enhances endogenous angiogenesis. Indeed, after eight weeks of exercise training sufficient to increase exercise capacity by 36 percent, patients with chronic heart failure had a doubling of VEGF mRNA and protein in skeletal muscle.[70] The muscle content of basic fibroblast growth factor, another important angiogenic growth factor, does not seem to be altered in response to exercise of the hypoxic skeletal muscle.[71,72]

In animal models of occlusive arterial disease, exercise training has been shown to enhance collateral-dependent blood flow to the hind-limb muscles.[73,74] However, studies demonstrating collateral development in response to exercise training or effects on calf blood flow in humans are limited. In 1990, Hiatt et al.[34] reported that maximal calf blood flow increased moderately in response to exercise training, but the increase was not correlated with improved exercise performance. Gardner et al.[37] showed that six months of exercise increased reactive hyperemic blood flow by 27 percent and maximal calf blood flow by 30 percent; these changes were associated with improved walking ability ($r=0.38$, $P<0.05$). Despite the clinical improvement, neither resting calf blood flow nor the ankle–brachial index changed. An uncon-

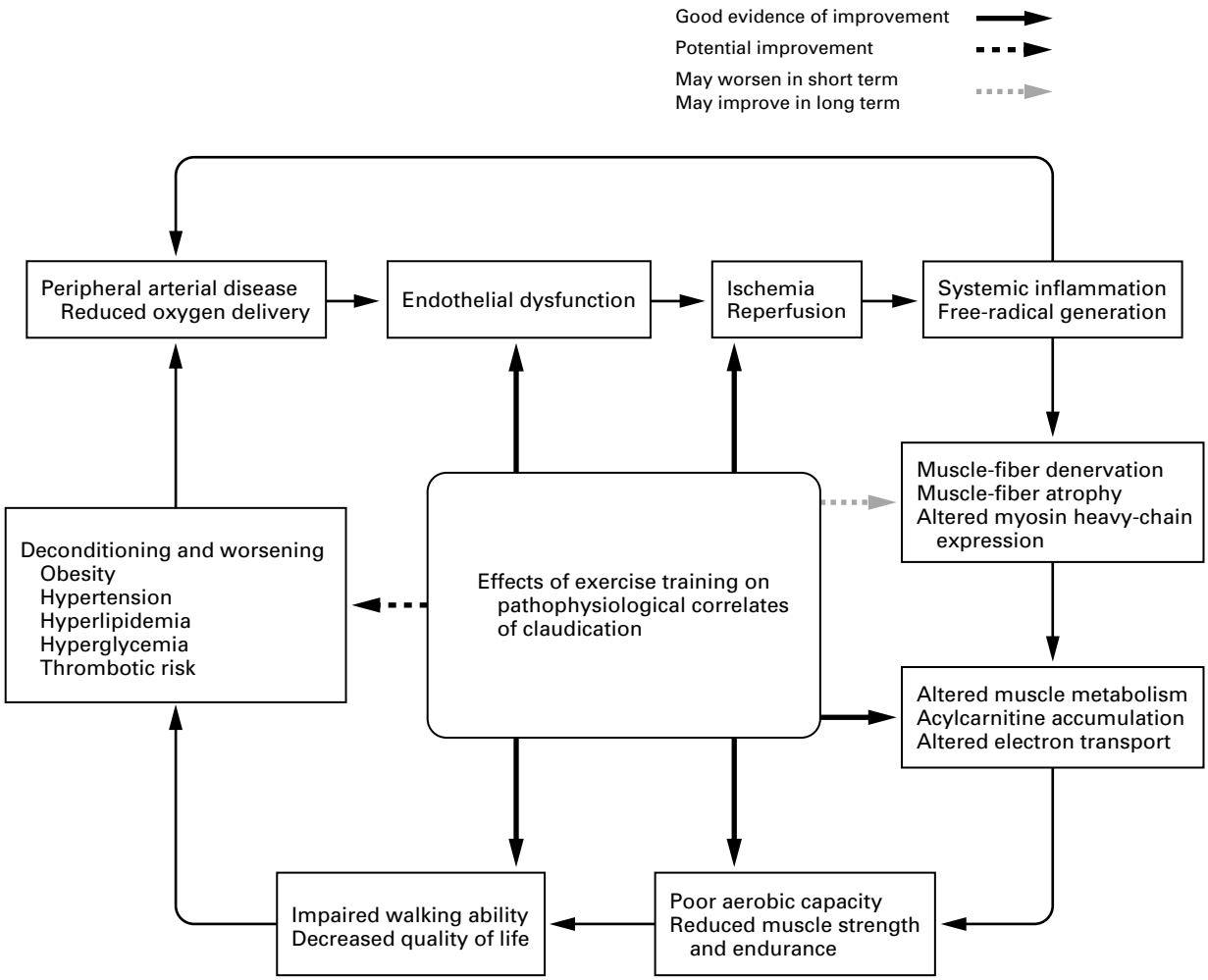

Figure 1. The Cycle of Disability Associated with Peripheral Arterial Disease and Claudication and the Potential Role of Exercise Training in Improving Systemic and Limb Pathophysiologic Effects, Functional Capacity, and Quality of Life.

The boxes along the top and right-hand side of the figure represent potential pathophysiological cellular and end-organ mechanisms that underlie the disability of peripheral arterial disease and claudication. The boxes along the bottom and left-hand side represent the adverse consequences of peripheral arterial disease for functional capacity, symptoms, quality of life, and atherosclerosis risk factors. The thicker solid arrows show the pathophysiological mechanisms and patient outcomes for which there is good evidence of improvement with exercise training. The dashed black arrow represents the potential improvements with exercise training; the effects of exercise training on these mechanisms have not been studied prospectively in patients with claudication. The dashed gray arrow indicates that exercise training may worsen selected end-organ mechanisms in the short term. These potential deleterious short-term responses may be attenuated as a result of long-term adaptation to exercise training.

trolled study from the same group of investigators[38] reported increases in maximal calf blood flow and reactive hyperemic blood flow after six months of exercise in patients with claudication.

A number of other studies have not documented increased leg blood flow in patients with improved walking ability.[15,35,36] Blood flow measured at the femoral artery and systolic blood pressure measured at the ankle were not increased after a three-month exercise program in patients with claudication, although walking ability improved.[35] In a three-way comparison study,[15,36] patients with claudication were randomly assigned to arterial reconstruction surgery, surgery followed by exercise training, or exercise alone. Surgery increased the ankle–brachial index and maximal calf blood flow, accounting for 80 to 90 percent of the changes in walking performance. Exercise training did not improve calf blood flow, although walking performance increased to a degree similar to that after surgery.

Exercise training may also cause redistribution of blood flow from inactive to active muscles, a response

TABLE 2. SUMMARY OF POTENTIAL MECHANISMS BY WHICH EXERCISE TRAINING MIGHT IMPROVE CLAUDICATION.

MECHANISM OR PATHOPHYSIOLOGICAL ABNORMALITY	EFFECT OF EXERCISE TRAINING
Collateral circulation: limited limb blood flow and low ankle–brachial index	Minimal, with moderate to no increase in ankle–brachial index or calf blood flow in humans[15,34-38]; no correlation of blood flow with walking capacity[34]; redistribution of blood to working muscle in animal models[39]
Microcirculation and endothelial function: endothelial vasodilator dysfunction; decreased nitric oxide activity[40,41]	Increased nitric oxide activity and capillary density[42]; improved endothelium-dependent vasodilatation and improved hyperemic blood flow[39]; improvements in lipid profile, obesity, blood pressure, neurohormonal modulation, and glucose metabolism may also enhance endothelial function[43]
Muscle metabolism and oxygen extraction: imbalance of oxygen supply and demand; inadequate adenosine triphosphate production; accumulation of muscle lactate and acylcarnitines[44-46]	Improved oxidative metabolism and oxygen extraction; decreased acylcarnitines; change in muscle metabolism correlates with increased walking ability[34,47]
Hemorheology: increased blood viscosity and red-cell aggregation; decreased blood filterability	Improved blood viscosity and filterability enhance oxygen availability to the muscles[48,49]
Inflammation: ischemia increases free-radical formation, neutrophil activation, and systemic vascular endothelial damage[50-52]	Lessened ischemia at any achieved workload; evidence of decreased markers of systemic inflammation[53]
Walking economy: decline in walking speed; increased energy cost at a given workload; high cardiac burden[54-58]	Improved walking biomechanics; reduction in oxygen cost of exercise; lessened cardiac burden[34,59,60]
Systemic atherosclerosis risk factors: synergistic worsening of multiple risk factors, including hypertension, diabetes, hyperlipidemia, and obesity; increased prothrombotic status[61]	Improved weight loss[62-64]; improved glycemic control[62,63]; improved blood pressure[65-67]; increased high-density lipoprotein cholesterol and lessened triglycerides[64]; release of tissue plasminogen activator and plasminogen activator inhibitor-1[34,59,60]

that has been shown in animal models[39] but has not been evaluated in humans. Overall, the evidence for exercise-induced increases in collateral blood flow in patients with claudication is limited and inconsistent. Furthermore, whether or not blood flow increases with training, the correlation with walking ability is typically absent[34] or only moderate.[37] Hence, mechanisms other than increased blood flow must account for the large exercise-induced improvements in function and symptoms that occur in patients with claudication.

Changes in Microcirculation and Endothelial Function

Nitric oxide of endothelial origin is thought to augment exercise-induced hyperemia in the peripheral and coronary circulations.[75] It is possible that the impairment of nitric oxide synthesis in patients with claudication limits exercise capacity.[76] Impaired endothelial vasodilator function has been demonstrated in patients with peripheral arterial disease[40] and in patients with risk factors for atherosclerosis, such as type 2 diabetes,[77-82] hypertension,[83] hyperlipidemia,[84,85] and the so-called metabolic syndrome, a clustering of medical conditions that may include these risk factors plus abdominal obesity, hypertriglyceridemia, and insulin resistance.[86] Such risk factors are common in patients with claudication.

Studies in animal models[87] suggest that short-term exercise stimulates endothelium-dependent vasodilatation. Exercise training exposes the vessels to repeated episodes of hyperemia. The elevated shear stress from the increased blood flow of exercise augments vasodilatation over the long term by increasing the vascular expression of nitric oxide synthase and by enhancing the release of nitric oxide and prostacyclin.[43] In an animal model of peripheral ischemia, exercise training increased both nitric oxide activity and muscle-capillary density.[42] Studies of exercise training and endothelial vasodilator function in patients with claudication are limited. One uncontrolled study[38] found that six months of exercise training increased endothelial-dependent vasodilatation by 61 percent.

Data from studies in patients with other chronic diseases, such as heart failure,[88] type 2 diabetes,[89] the metabolic syndrome,[90] and mild-to-moderate hypertension,[91,92] suggest that exercise training improves endothelial-dependent vasodilatation. Exercise-induced weight loss and decreases in blood pressure, together

with improvements in neurohormonal modulation, lipid profile, and glucose metabolism, may also contribute to amelioration of endothelial function.[43] Medications, such as statins, angiotensin-converting–enzyme inhibitors, and calcium-channel blockers, and dietary supplements, such as arginine, may also improve endothelial function.[93] The extent to which the combination of exercise training and such therapies may result in additive benefits to the endothelium in patients with claudication has not been studied.

In addition to regulating vasomotor tone, the endothelium is essential to many aspects of cardiovascular health, mediating the balance between fibrinolytic and prothrombotic processes, the control of the inflammatory response, and the growth of vascular smooth muscle.[94] Further research seems warranted on the effects of exercise training on these mechanisms in patients with claudication.

The Hemorheologic Hypothesis

Hemorheology refers to the behavior of flowing blood and its interaction with tissue in providing cells with oxygen, nutrients, hormones, and vitamins. Exercise training may improve abnormal hemorheology in patients with claudication, thereby facilitating oxygen delivery.[34] Ernst and Matrai[48] reported that two months of treadmill exercise improved blood and plasma viscosity, the ability of autologous red cells to be filtered, and red-cell aggregation.[48] They concluded that hemorheology improved to a degree similar to that seen with medications such as pentoxifylline. However, the efficacy of available medications is limited.[6] In a study designed to model ischemic preconditioning,[49] patients with claudication performed treadmill walking for short periods of moderate intensity before a maximal exercise test. The patients also took two daily walks. After one week, treadmill walking ability improved, and blood viscosity and filterability decreased.[49] Plasma adenosine levels in response to short-term exercise decreased, also suggesting a decrease in ischemia.[49] Such data, although limited, suggest that exercise training may improve or reverse the hemorheologic abnormalities observed in patients with peripheral arterial disease. The extent to which this mechanism contributes to the clinical improvements seen after exercise training remains unclear.

Changes in Muscle Metabolism and Oxygen Extraction

Patients with claudication have an exercise-induced imbalance between oxygen supply and demand to active leg muscles. Chronic ischemia leads to an accumulation of lactate and intermediates of oxidative metabolism (e.g., short-chain acylcarnitines) in muscle. Hiatt et al. have shown an inverse correlation between markers of carnitine accumulation and exercise performance ($r=-0.75$, $P<0.05$).[46] Although improvement in calf-muscle blood flow with exercise training has been inconsistent, an increase in the oxidative capacity of calf skeletal muscle, yielding greater oxygen extraction per unit of blood delivered, has been a more consistent finding. We documented a 123 percent increase in peak walking time, a 30 percent increase in peak oxygen uptake, and a 165 percent increase in pain-free walking time after 12 weeks of treadmill walking in patients with claudication.[34] Plasma short-chain acylcarnitine concentrations at rest, which reflect muscle metabolic state, correlated with increases in peak walking time ($r=-0.78$, $P<0.05$). Control subjects who did not undergo exercise training had no changes in carnitine metabolism, calf blood flow, peak treadmill grade, or maximal oxygen uptake, although they had a moderate increase in maximal walking time during testing.

In a subsequent study,[47] we confirmed the decrease in plasma acylcarnitine concentrations and demonstrated improved muscle carnitine metabolism in patients who completed 12 weeks of treadmill walking to a level that intentionally produced claudication pain. Such metabolic changes were not observed in patients randomly assigned to a nonexercising control group or to a group that performed strength training three times per week. In patients undergoing revascularization surgery, exercise training led to no improvement in limb blood flow but did cause favorable changes in muscle enzyme activity. Such changes accounted for 31 percent of the variability in improvement in their walking ability. In contrast, such enzyme changes did not occur in patients who had their blood flow restored surgically or who both underwent surgery and received exercise training. These data suggest that both exercise and a reduced calf blood flow are necessary conditions for enzymatic adaptation. Although up-regulation of oxidative enzymes in muscle with exercise training has not been a universal finding,[47] improvements in muscle oxidative metabolism appear to be an important component of the training response.

Inflammation and Muscle Injury

Exercise to the point of calf pain produces muscle ischemia. Such ischemia induces a local inflammatory and oxidant stress response, with free-radical formation, neutrophil activation, and systemic vascular endothelial damage.[95] Since an inflammatory response could worsen atherosclerosis or muscle function, the question has been raised that exercise training might be harmful. Brass et al. from our group found diffuse mitochondrial DNA injury and reduced activity of components of the electron transport chain in muscle from affected limbs of patients with claudication, changes that might reflect systemic oxidant injury.[51,96] However, other evidence suggests that exercise train-

ing causes a long-term attenuation of the inflammatory response. Tisi et al. found that exercise training improved claudication symptoms and concomitantly reduced the levels of inflammatory markers such as serum amyloid, C-reactive protein, and the urinary ratio of albumin to creatinine.[53]

Our group found that 12 weeks of exercise improved walking capacity but also increased the number of denervated fibers in calf muscle.[47] England et al. from our group followed patients for 3 to 23 months and reported that claudication was associated with the development of a multifocal neuropathy that predominantly involved motor neurons. However, exercise training did not exacerbate the development of neuropathy in patients with claudication, suggesting a possible long-term adaptive response.[97] It would appear that the small risk of muscle-fiber damage is outweighed by the improvement in walking.

Walking Economy

Patients with claudication respond to their leg pain by adopting a walking pattern that favors greater gait stability at the expense of velocity.[55-57,98] This disadvantageous alteration in biomechanics increases the oxygen cost of walking. Consequently, a given amount of walking is performed at a higher percentage of maximal oxygen consumption capacity, which is already reduced by half in this group of patients because of claudication. When exercise is performed by normal subjects at an intensity at which blood lactate levels begin to rise, oxygen consumption progressively rises, increasing the energy cost of performing at the same rate of work. In patients with claudication, this rise in oxygen consumption occurs at a relatively low walking rate (below a systemic lactate threshold) and further exacerbates impaired walking economy.[60]

After four months of exercise training, patients with claudication used less oxygen at a given workload.[60] This improvement in walking economy probably resulted from a reduction in claudication pain, leading to improved biomechanical efficiency. Hiatt et al.[59] reported that in exercise-trained patients, the values for oxygen uptake, heart rate, respiratory exchange ratio, and blood lactate concentration at a fixed exercise level were lower than in patients randomly assigned to a nonexercising control or strength-training group. We also reported that the heart rate at the same workload was lower after exercise training.[34] These results support the concept that exercise training improves the biomechanical aspects of walking and metabolic efficiency.

Atherosclerosis and Prothrombotic Risk Factors

The treatment of patients with claudication should include modification of risk factors for atherosclerosis and antiplatelet drug therapy (Table 3).[6,99,100] The 2001 National Cholesterol Education Program Adult Treatment Panel III identified peripheral arterial disease as equivalent to established coronary heart disease, the highest risk category for future coronary events, and emphasized the importance of lowering low-density lipoprotein cholesterol to target levels.[99] The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure suggested that patients with peripheral arterial disease deserve the most aggressive blood-pressure–lowering therapy.[100] Pharmacologic therapies for secondary prevention in patients with claudication have been reviewed and should be used as the initial treatment for these patients.[6,7] Data from other populations suggest that exercise training has an independent beneficial effect on atherosclerotic risk factors. Exercise training has been shown to decrease triglyceride levels and increase high-density lipoprotein cholesterol levels,[64] reduce blood pressure,[66,67,101-103] maintain glycemic control in patients with type 2 diabetes,[62,63] and reduce central adiposity.[104-106] Additional studies in patients with claudication are needed.

Peripheral arterial disease is also associated with worsening endogenous fibrinolysis.[61] Womack et al.[107] found that patients who walked for short periods to a level of moderate claudication pain, with periods of rest interspersed, for a total of 30 minutes of walking, had an improvement in their fibrinolytic profiles that persisted for at least 1 hour after exercise. Patients with peripheral atherosclerosis showed signs of abnormal up-regulation of coagulation and fibrinolysis at rest.[108] These subjects had increased thrombin generation after short-term exercise, but they also had an increase in the levels and activity of tissue plasminogen activator and levels of fibrin D-dimer, suggesting a concomitant protective mechanism against clot formation. Exercise training may also improve prothrombotic mechanisms, such as the expression of adhesion molecules.[109] Asymptomatic patients with peripheral arterial disease appear to have a risk of cardiovascular morbidity and mortality similar to that of those with claudication[110-112] and are presumably candidates for the same treatments,[6] although there are no direct data to show additive effects of exercise and drug therapy.

EXERCISE PRESCRIPTION

The clinical investigations to date provide the scientific basis for exercise rehabilitation that is appropriate for most patients with claudication. The key elements of such a therapeutic exercise program are summarized in Table 4. Since patients with claudication often have concomitant clinical or occult coronary artery disease, hypertension, or diabetes, adverse cardiovascular and physiological responses during exercise training are possible. Although serious adverse

TABLE 3. RISK-FACTOR MODIFICATION FOR PATIENTS WITH PERIPHERAL ARTERIAL DISEASE.*

Smoking cessation
Low-density lipoprotein cholesterol <100 mg/dl (2.6 mmol/liter)
Glycosylated hemoglobin <7.0 percent
Blood pressure <130/85 mm Hg
Angiotensin converting–enzyme inhibition
Antiplatelet therapy
Aspirin or clopidogrel

*All patients with peripheral arterial disease, regardless of the severity of symptoms, should undergo risk-factor modification and should receive antiplatelet therapy with aspirin or clopidogrel. Angiotensin-converting–enzyme inhibition should be considered because of the potential for prevention of ischemic events that is independent of blood-pressure lowering. Elsewhere we provide extensive discussion on lowering the risk of ischemic events in patients with claudication.[6,7]

TABLE 4. KEY ELEMENTS OF A THERAPEUTIC EXERCISE-TRAINING PROGRAM FOR REHABILITATION FROM PERIPHERAL ARTERIAL DISEASE IN PATIENTS WITH CLAUDICATION.

Role of primary clinician
Establish the diagnosis of peripheral arterial disease with the ankle–brachial index measurement or other objective vascular laboratory test[6]
Determine that claudication is the major symptom limiting exercise
Discuss the risks and benefits of therapeutic alternatives, including pharmacologic, percutaneous, and surgical interventions
Initiate modification of risk factors for systemic atherosclerosis[6,7]
Perform treadmill stress testing
Provide formal referral to a claudication exercise-rehabilitation program
Exercise guidelines for claudication*
Warm-up and cool-down periods of 5–10 min each
Types of exercise
Treadmill and track walking are the most effective exercises for claudication
Resistance training has benefit for patients with other forms of cardiovascular disease,[116] and its use, as tolerated, for general fitness is complementary to walking but not a substitute for it
Intensity
The initial workload of the treadmill is set to a speed and grade that elicits claudication symptoms within 3 to 5 min
Patients walk at this workload until claudication of moderate severity occurs, then rest standing or sitting for a brief period to permit symptoms to subside
Duration
The exercise–rest–exercise pattern should be repeated throughout the exercise session
The initial session will usually include 35 min of intermittent walking; walking is increased by 5 min each session until 50 min of intermittent walking can be accomplished
Frequency
Treadmill or track walking 3 to 5 times per week
Role of direct supervision
As the patient's walking ability improves, the exercise workload should be increased by modifying the treadmill grade or speed (or both) to ensure that the stimulus of claudication pain always occurs during the workout
As walking ability improves, and a higher heart rate is reached, there is the possibility that cardiac signs and symptoms may appear. These symptoms should be appropriately diagnosed and treated.

*These general guidelines should be individualized on the basis of the results of treadmill stress testing and the clinical status of the patient. Full discussion of the exercise precautions for patients with concomitant diabetes,[113] hypertension,[114] and coronary artery disease[115] can be found elsewhere.

events have been rare in clinical practice and research investigations, it is prudent to perform treadmill exercise testing with 12-lead electrocardiographic monitoring before an exercise program is initiated, so that ischemic symptoms, ST–T wave changes, and arrhythmias may be identified.[115]

Although this group of patients will, by definition, have claudication-limited exercise (and therefore will not achieve a true maximal exercise performance), the findings from the exercise test can be used to determine that there are no untoward cardiovascular responses at the exercise level reached. The exercise test also provides information about claudication thresholds and heart-rate and blood-pressure responses for use in establishing an exercise prescription. Enrollment of the patient in a medically supervised exercise program with electrocardiographic, heart-rate, blood-pressure, and blood glucose monitoring is encouraged. We suggest routine monitoring during the initial exercise sessions; individual clinical responses can then determine the need for monitoring in subsequent sessions. Many cardiac-rehabilitation exercise programs can accommodate patients with claudication, providing an environment conducive to the lifestyle change that underlies long-term compliance with exercise and risk-factor modification.

The methods of exercise prescription include establishing a training intensity that produces moderate claudication pain within the first five minutes of treadmill walking (Table 4). Each training session consists of short periods of treadmill walking interspersed with rest throughout a 50-minute exercise session, three times weekly. Many patients with claudication also have reduced muscle mass,[117] as well as a lack of muscle strength and endurance, which exacerbates their physical impairment. Resistance training, when appropriately prescribed, is generally recommended by the American Heart Association for most patients with other manifestations of cardiovascular disease, because of its beneficial effects on strength and endurance, cardiovascular function, metabolism, coronary risk factors, and psychosocial well-being.[113] Nevertheless, in patients with claudication, resistance training does not directly improve walking ability, whereas walking itself is most effective in increasing claudication-limited walking capacity.[5,59]

Although between 5 percent and 10 percent of patients with peripheral arterial disease undergo amputation,[112] little is known about the efficacy of exercise training for amputees. Arm ergometric stress testing to assess cardiovascular status is an alternative for patients who cannot perform leg exercise, and exercise

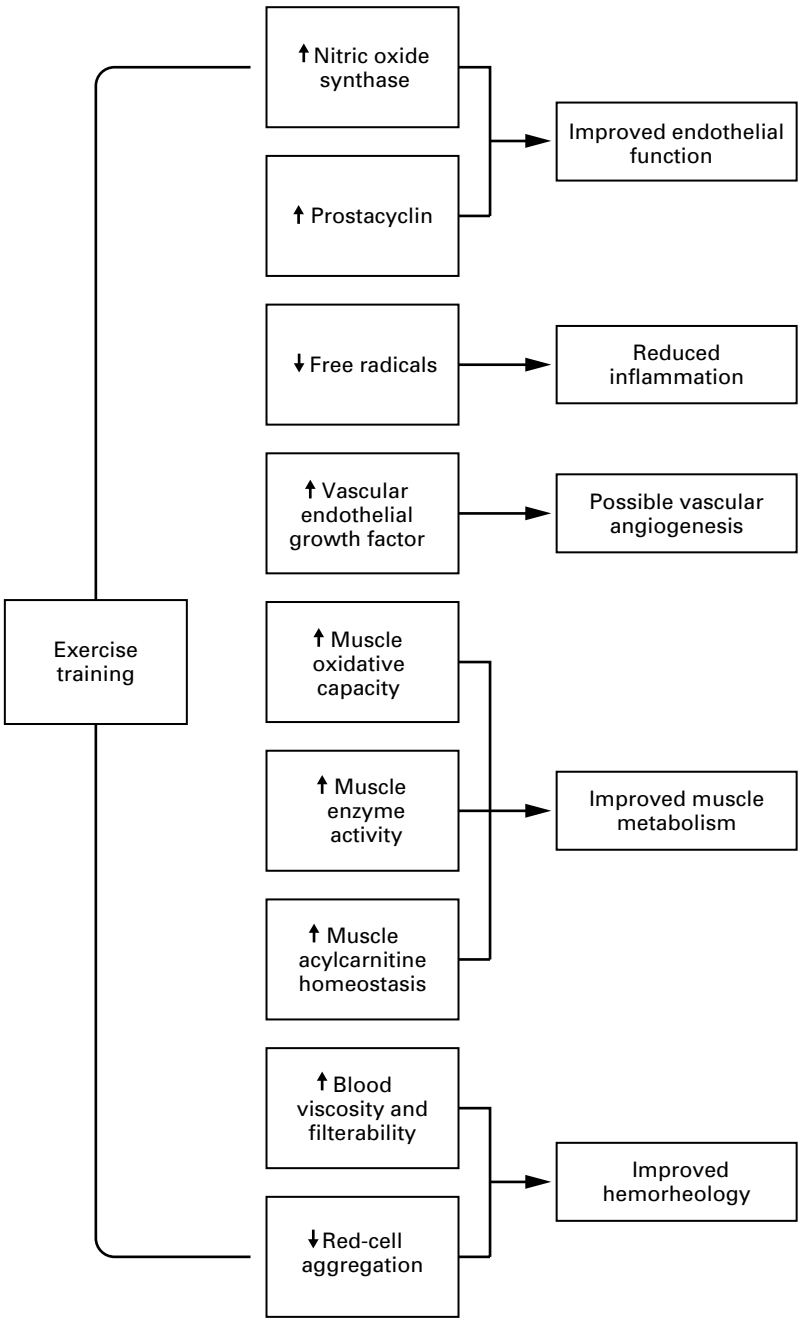

Figure 2. Schematic Overview of the Potential Favorable Effects of Exercise Training on Selected Cellular and Tissue Physiologic Pathways Involved in Claudication.

Although improvements in all of these mechanisms contribute to the well-established increases in walking ability, the data at present are insufficient for their relative importance to be estimated accurately. The up arrows indicate increases, and the down arrows indicate decreases.

training with the arms may improve cardiovascular endurance and upper-body strength in poorly conditioned patients.[118]

Clinicians should recognize that there are no data to support the efficacy of the informal "go home and walk" advice that is still the most typical exercise prescription for patients with claudication.[119] In contrast, a supervised hospital- or clinic-based program, which ensures that patients are receiving a standardized exercise stimulus in a safe environment, is effective.[120-122]

EXERCISE COMBINED WITH OTHER TREATMENTS

Although exercise training is effective as a single intervention, it may augment the effects of other treatments for claudication. Revascularization by either bypass surgery or angioplasty can be effective for the relief of claudication symptoms and the improvement of walking ability in patients with progressively worsening claudication in whom initial conservative management has failed (Table 1).[9,15,123,124] In one randomized study, the combination of revascularization procedures and exercise was more effective than either intervention alone.[15]

Patients with claudication may also benefit from the use of pharmacologic therapies, as reviewed recently in the *Journal*.[6] At present, the two approved medications for treating symptoms of claudication in the United States are pentoxifylline and cilostazol. It is beyond the scope of this article to consider drug therapy in detail.

CONCLUSIONS

Exercise training appears to be an effective treatment for claudication, the primary symptom of peripheral arterial disease. Exercise-induced increases in functional capacity and lessening of claudication symptoms may be explained by several mechanisms, including measurable improvements in endothelial vasodilator function, skeletal-muscle metabolism, blood viscosity, and inflammatory responses (Fig. 2). The evidence of exercise-training–induced increases in leg blood flow and oxygen delivery is less robust, and these mechanisms are unlikely to account for the large improvements in pain-free walking that can be achieved. Improvements in the biomechanics of walking also contribute to increased walking ability. Although exercise training has multiple beneficial effects, current knowledge does not permit accurate estimation of the relative contribution of each mechanism.

Exercise training has additional benefits that go beyond improvements in functional capacity and claudication symptoms. Exercise-induced enhancement of endothelial function may also improve systemic cardiovascular health. Additional potential benefits of exercise include reduced blood pressure, an improved lipid profile, better glycemic control in patients with diabetes, and reduced central obesity, although the magnitude and durability of these effects have yet to be studied prospectively in patients with claudication.

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