CLINICAL REVIEW

Management of Peripheral Arterial Disease and Intermittent Claudication

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Background: **Peripheral arterial disease (PAD) is the chronic obstruction of the arteries supplying the lower extremities. The most common symptom is intermittent claudication resulting in aching pain, numbness, weakness, or fatigue in the muscle groups of the lower extremities.**

Methods: **Using the key words "peripheral arterial disease," "intermittent claudication," "atherosclerosis," and "cardiovascular disease," MEDLINE databases were searched from 1970 to the present. The most recent articles pertinent to current treatment recommendations for PAD and intermittent claudication were selected to document this review.**

Results and Conclusions: **Symptoms of intermittent claudication are induced by walking or exercise and usually resolve with rest. Disease severity varies from patients who are asymptomatic to those who have unremitting symptoms. A high overlap exists between PAD and coronary artery and cerebrovascular disease. Risks for long-term morbidity and mortality are identical for PAD, intermittent claudication, and coronary artery disease. Treatment of PAD is aimed at maintaining or improving functional status, reducing or eliminating ischemic symptoms, and preventing disease progression. Exercise and aggressive risk factor modification represent the cornerstones of treatment. Risk factors include smoking, diabetes, lipid abnormalities, hypertension, C-reactive protein, lipoprotein(a), and hyperhomocystinemia. Antiplatelet and lipid-altering therapies decrease risk of atherosclerotic vascular complications and are being studied to improve intermittent claudication. Cilostazol, a new antiplatelet, antithrombotic agent, reduces claudication symptoms. Angiogenic growth factors have shown preliminary success in patients with rest pain and ischemic ulcers and are being investigated for use in patients with intermittent claudication. Invasive revascularization procedures can be considered for patients with critical limb ischemia or when medical therapy fails. (J Am Board Fam Pract 2001;14:443–50.)**

Peripheral arterial disease (PAD) is a common manifestation of systemic atherosclerosis. The most frequent symptom is intermittent claudication, which results from poor oxygenation of the muscles of the lower extremities and is experienced typically as an aching pain, cramping, or numbness in the calf, buttock, hip, thigh, or arch of the foot. Symptoms are induced by walking or exercise and are relieved by rest.

Patients can be stratified into groups according to symptom severity. One half of all PAD patients older than 55 years are asymptomatic.[1] Of the symptomatic patients, approximately 40% experience intermittent claudication, and 10% have critical limb ischemia.[1] Intermittent claudication is usually accurately diagnosed based on the vascular history and physical examination, which should include palpation of the abdomen and peripheral pulses. Because palpation of the peripheral pulses alone is too insensitive a measure of PAD, noninvasive vascular tests, such as determining the ankle-brachial index, should be performed to quantify the degree of limb ischemia. The ankle-brachial index, which is the ratio of the ankle systolic pressure to the brachial artery systolic pressure (Table 1), is useful in assessing disease severity. An ankle-brachial index greater than 0.90 is considered normal; greater than 0.70 to 0.89 is considered mild disease; 0.5 to 0.69, moderate disease; and less than 0.5, severe disease.[2]

Methods

The key words "peripheral arterial disease," "intermittent claudication," "atherosclerosis," and "car-

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Table 1. Understanding The Ankle-Brachial Index (Ankle Systolic Pressure/Brachial Artery Systolic Pressure).

Tools
Use standard blood pressure cuff and 5- to 7-MHz Doppler ultrasound device
Take 2 standard blood pressure readings in both arms
Take 2 blood pressure readings in legs over dorsalis pedis and posterior tibial arteries
Ankle-brachial calculation
Divide highest systolic ankle pressure by highest systolic brachial pressure, and calculate an ankle-brachial index for each respective limb

diovascular disease," were used to search MEDLINE databases from 1970 to the present. The most recent articles pertinent to current treatment recommendations for PAD and intermittent claudication, as well as research on emerging options, were selected to document this review.

Prevalence of Peripheral Arterial Disease and Intermittent Claudication

Determination of intermittent claudication is often based on the highly specific WHO/Rose questionnaire, or the self-administered Edinburgh Claudication Questionnaire.[3,4] The latter was designed as an improvement over the WHO/Rose and has a higher degree of specificity for the diagnosis of intermittent claudication. Both measurement tools, however, are considered too rigorous (with a low degree of sensitivity) and therefore might tend to underestimate the true prevalence of intermittent claudication.[5] In addition, many elderly patients with intermittent claudication might consider their symptoms to be a normal part of aging and do not consult their physicians. Physicians would do well to ask their elderly patients whether they experience pain or cramping in either or both of their legs when walking. On the other hand, the absence of one or more pulses tends to overestimate the prevalence of intermittent claudication.[6] Hence estimates of the incidence and prevalence of PAD and intermittent claudication, based on patient or physician reporting or a cursory clinical examination, could be prone to error.

The true prevalence of PAD, as indicated by standardized noninvasive testing procedures, such as measurement of the ankle-brachial index or treadmill exercise testing, is age related and at least five times higher than would be expected based on patient-physician reports.[6] Table 1 illustrates the proper procedure for measuring the ankle-brachial index. PAD prevalence rates by noninvasive testing are reported to be 2.5% at ages 40 to 59 years, 8.3% at ages 60 to 69 years, and 18.8% at ages 70 to 79 years.[7] Prevalence has been shown to be higher in men than in women.[6,8]

Co-morbid Conditions

There is a high degree of overlap between PAD and cardiovascular disease; the latter has been found in 29% of patients with PAD compared with only 11% of patients without PAD.[6] In fact, depending on the sensitivity of the diagnostic technique used, cardiovascular disease can be detected in as many as 90% of patients with intermittent claudication.[5] Furthermore, numerous studies have consistently shown a high mortality rate in patients with PAD and intermittent claudication. In a Swedish study of 439 men, an ankle-brachial index of less than 0.9 was associated with a 2.4-fold higher mortality rate and a twofold higher cardiac event rate.[9] Other studies have corroborated these findings, showing up to a twofold to fourfold increased risk of mortality in patients with intermittent claudication, predominantly from cardiovascular disease.[10]

The prevalence of cerebrovascular disease in PAD patients is higher than 50% and can be as high as 75% if sensitive assessments such as Doppler ultrasound are used.[6] There is a 5% overlap between PAD, coronary artery disease, and cerebrovascular disease in men and women aged 62 years and older.[11] The 5-, 10-, and 15-year mortality rates for intermittent claudication from all causes are approximately 30%, 50%, and 70%, respectively,[5] with a cardiovascular cause estimated to be responsible for 70% to 80% of deaths.[5]

Complications and Outcomes

Progression of PAD can result in critical limb ischemia, manifested by ischemic pain at rest or in breakdown of the skin (ulcers or gangrene). Severe PAD can result in tissue ischemia in the lower extremities, causing gangrene and requiring amputation in 3% to 8% of patients.[12,13] Aggressive investigation for revascularization options, either surgical or percutaneous, are warranted in such instances. Only a small proportion of patients with severe disease ultimately requires a major amputation.

Table 2. Risk Factors for Peripheral Arterial Disease and Intermittent Claudication.

Smoking
Hypertension
Diabetes
Lipid abnormalities
Increased LDL-cholesterol
Elevated triglycerides
Decreased HDL-cholesterol
Elevated homocysteine
Age
Increased fibrinogen and blood viscosity
Male sex
Lipoprotein(a)

LDL—low-density lipoprotein; HDL—high-density lipoprotein.

Recognizing Patients at Risk

The probability of developing PAD can be assessed by determining the presence of several risk factors (Table 2). Smoking is the most significant risk factor and is associated with disease progression and a threefold increased risk of amputation and death in patients with intermittent claudication.[5] The 5-year mortality rate for patients with intermittent claudication who continue to smoke is 40% to 50%.[14]

Diabetes and impaired glucose tolerance are also considered important risk factors for the development and progression of PAD.[8] Hypertension also has been found to increase PAD risk and is particularly associated with the development of severe disease. Hypertension has been shown to increase the risk of claudication by twofold to threefold.[15] In the 1997 guidelines issued by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI), the aggressive treatment of hypertension and its risk factors is emphasized to prevent target-organ disease.[15]

Because PAD-intermittent claudication is an atherosclerotic disease, lipid abnormalities are also important contributing risk factors. Patients with increased low-density lipoprotein (LDL) cholesterol, as well as those with elevated triglyceride levels and decreased levels of high-density lipoprotein (HDL) cholesterol, have been shown to be at increased risk for PAD.[6] Increasing age,[8] elevated homocysteine levels (>14 μmol/L),[16] lipoprotein(a),[17] and increased fibrinogen and blood viscosity[5] have also been described as risk factors for PAD.

Screening Guidelines

The US Preventive Services Task Force has recommended guidelines for screening for PAD and intermittent claudication.[2,18] Routine screening for asymptomatic PAD patients in the general population is not recommended in that it has not proved to be cost-effective.[19] Clinicians, however, should be alert to symptoms of PAD in persons at increased risk (persons older than 50 years, smokers, diabetics) and should evaluate patients who have clinical evidence of vascular disease. Two epidemiologic studies have shown that a low ankle-brachial index is an independent predictor of all-cause and cardiovascular mortality.[20,21] In a substudy of the Systolic Hypertension in the Elderly Program (SHEP) trial,[21] an ankle-brachial index ≤ 0.9 predicted all-cause mortality with a relative risk ratio of 3.8. Similarly, in a study of women older than 65 years, an ankle-brachial index of < 0.9 predicted all-cause mortality with a relative risk ratio of 3.1.[20] These findings have prompted the suggestion that ankle-brachial index measurements be included as an integral part of the physical examination in patients older than 55 years of age and in those who appear at risk for development of atherosclerosis.[22] Screening for hypertension and hypercholesterolemia should be conducted, and appropriate counseling should be given regarding the use of tobacco, physical activity, and nutritional risk factors for atherosclerotic disease.

Approaches to Treatment

In managing PAD, it is critically important to deal with the high risk of developing severe and often fatal cardiovascular complications. The first priority is to aggressively modify risk factors that enhance the progression of atherosclerosis and atherosclerotic complications. It is also important, however, to relieve the symptoms of intermittent claudication. Unlike risk reduction, symptomatic improvement is apparent to the patient, often within a matter of weeks or a few months, and can enhance a patient's quality of life considerably.

Lifestyle Modification

Any lifestyle change that reduces the risk factors for PAD is beneficial. Intervention programs include

Table 3. Approaches to Treatment of Peripheral Arterial Disease and Intermittent Claudication.

Life-style modification
Smoking cessation
Diet for weight loss and lipid altering
Supervised and unsupervised exercise programs
Pharmacotherapy
Risk-reducing agents
Antiplatelet drugs: aspirin, ticlopidine, clopidogrel, cilostazol*
Lipid-altering drugs: fibrates, niacin, statins (simvastatin, lovastatin, pravastatin, atorvastatin), bile acid sequestrants
Agents under study
Propionyl-L-carnitine, prostaglandin drugs, angiogenic growth factors, L-arginine
Drugs for treatment of intermittent claudication
Cilostazol
Pentoxifylline
Invasive therapy
Endovascular procedures
Surgical procedures

*Cilostazol, in addition to antiplatelet activity, improves vasodilation, increases HDL-cholesterol levels, and decreases plasma triglyceride levels.

cessation of or decrease in smoking, dietary modifications for weight loss and lowering lipid levels, and a combination of supervised and unsupervised exercise (Table 3).

Smoking Cessation

Stopping or decreasing smoking undoubtedly reduces the progression of PAD. In fact, patients who stop smoking have a twofold increase in their 5-year survival rate compared with those who continue to smoke.[23]

Diet

Dietary management to decrease weight and control serum lipid levels is also beneficial. The National Cholesterol Education Project (NCEP) guidelines recommend that patients with objective evidence of PAD receive dietary and pharmacologic therapy to achieve LDL cholesterol < 100 mg/dL.[24]

Exercise

Physical training and exercise therapy are recommended for patients with intermittent claudication. Regular exercise coupled with risk factor modification, especially smoking cessation, is the cornerstone of conservative therapy for intermittent claudication.[25,26] Various studies have shown significant improvement in pain-free walking distance and maximum walking distance in patients who followed a supervised exercise program for 6 months or longer.[26,27] A recent study in older patients with PAD showed that exercise rehabilitation lowered total cholesterol and LDL-cholesterol levels, is associated with a decline in systolic blood pressure, and significantly increased both pain-free walking distance and maximum walking distance as assessed by treadmill exercise performance.[28] A recently published meta-analysis of randomized, controlled trials of exercise therapy showed an improvement in pain-free walking distance of 179%, while maximum walking distance increased by an average of 122%.[29]

Because the main factor limiting success of exercise therapy is lack of patient motivation, and because exercise might not always be supervised in real life, improvement might not be as dramatic in unsupervised settings. The most effective programs are supervised, involve walking exercise, and are of at least 3 to 6 months' duration. Maintenance of regular exercise, either independent or supervised, should be continued indefinitely, or the benefit might inevitably be lost.

Pharmacotherapy

Antiplatelet and lipid-lowering therapies are effective in decreasing the risk of cardiovascular morbidity and improving long-term survival. Some agents can also improve symptoms of claudication. Emerging therapies, such as carnitine and propionyl-L-carnitine, prostaglandins, angiogenic growth factors, and L-arginine, are under investigation and could have potential benefit (Table 3). It should be noted that exercise therapy is a recommended adjunct to pharmacotherapy.

Antiplatelet Agents

Aspirin, dipyridamole, ticlopidine, and clopidogrel are the agents commonly referred to as antiplatelet drugs, although cilostazol could also fall into this category. Aspirin, ticlopidine, clopidogrel, and picotamide appear to prevent ischemic events. In clinical trials, however, these agents have not been shown to improve intermittent claudication, as measured by pain-free walking distance or maximum walking distance. Cilostazol is of proven benefit and pentoxifylline of questionable benefit in the treatment of intermittent claudication.[30–32] In fact,

only these drugs are approved by the FDA for treatment of this condition.

Pentoxifylline, a methylxanthine derivative, was until recently the only drug approved by the FDA for relief of intermittent claudication symptoms. It improves red-cell deformability, lowers fibrinogen levels, and retards platelet aggregation. Early small trials of pentoxifylline showed improvement in maximum walking distance in patients with intermittent claudication.[33] More recently, with the completion of larger trials, pentoxifylline has come to be considered minimally effective in improving intermittent claudication.[31]

Cilostazol, a phosphodiesterase III inhibitor, is a new treatment option for intermittent claudication approved by the FDA in 1999. In addition to its antiplatelet properties, cilostazol improves vasodilation, increases plasma HDL-cholesterol levels, and decreases plasma triglyceride levels.[15,34] Cilostazol and its active metabolites have a long half-life of approximately 10 to13 hours and achieve good serum concentration (C_{max} for cilostazol approximately 1,200 ng/mL at 3 hours), with steady state reached in a few days.

Eight phase III placebo-controlled trials have shown the efficacy of cilostazol.[30–32,34–37] In these studies comparing cilostazol with placebo, patients receiving 100 mg or 50 mg of cilostazol twice a day showed a significant increase in treadmill walking distance.[30,36] Patients on cilostazol also experienced improved functional status in physical performance and community walking ability.[35] In a double-blind study comparing cilostazol with placebo, maximum walking distance increased 41% with cilostazol.[30] The withdrawal of cilostazol in one study resulted in worsening symptoms of intermittent claudication, establishing the benefit of treatment with the agent.[31] In comparison, the effects of pentoxifylline, like those of placebo, remained essentially unchanged after withdrawal.[31] Therapy with cilostazol resulted in improvements in the lipid profile, with significant increases in HDL-cholesterol levels of about 10% ($P < .001$) and significant decreases in triglyceride levels of about 15% ($P < .001$), with greater effects found in patients with higher baseline triglyceride levels.[34]

Cilostazol was well tolerated, even in patients with renal or mild hepatic impairment; the main side effects were headache, diarrhea, and palpitations.[36,38,39] The standard cilostazol dosage of 100 mg twice a day provides the most efficacy, but patients who experience side effects might benefit from reducing the initial dosage to 50 mg twice a day.[36] Cilostazol is contraindicated in patients with congestive heart failure, although it has not been shown in any clinical trial to precipitate or worsen this disease. The contraindication is based on the finding that other phosphodiesterase III inhibitors increased the morbidity and mortality of patients with class III or IV congestive heart failure (New York Heart Association), which these drugs were intended to treat.[40] There has been no increased mortality associated with cilostazol. Although cilostazol is six to seven times more expensive than generic pentoxifylline, its proven benefit makes it a superior drug for treatment of intermittent claudication.

Aspirin has no effect on intermittent claudication symptoms but is useful in reducing cardiovascular events in the population of patients with PAD.[41] A drawback is that aspirin, even in relatively low doses (<325 mg/d), has been associated with gastrointestinal intolerance.[42]

Ticlopidine blocks the activation of platelets by adenosine diphosphate (ADP) and has been shown to reduce the risk of stroke and myocardial infarction in patients with intermittent claudication.[43] Ticlopidine, however, is associated with thrombotic thrombocytopenic purpura[44] and neutropenia and has not been approved for treatment of intermittent claudication.

Clopidogrel, a new thienopyridine derivative, has an action similar to ticlopidine and is indicated for secondary prevention of ischemic events in patients who have had a recent myocardial infarction, stroke, or symptomatic PAD. In a recent study (CAPRIE),[45] clopidogrel, when compared with aspirin, resulted in a 23.8% relative risk reduction of ischemic stroke, myocardial infarction, or other vascular death in the PAD group. Like ticlopidine, clopidogrel has been shown to be associated with an increased risk of thrombotic thrombocytopenic purpura.[46] Clopidogrel is not indicated for the treatment of intermittent claudication.

Lipid-Altering Agents

In PAD, the major lipid risk factors for peripheral atherosclerosis are elevated LDL cholesterol, decreased HDL cholesterol, and increased triglyceride levels. Clinical trials have shown that lipid modification is associated with stabilization or regression of femoral atherosclerosis.[47] Colestipol-

niacin therapy was shown to be effective in reducing progression of atherosclerotic disease,[48] and other lipid-altering drugs, such as cholestyramine, are also recommended.[2,49] More recently, statins have become the primary intervention. Simvastatin was found to reduce the incidence of carotid bruits and cerebrovascular events, as well as new-onset or worsening angina pectoris and intermittent claudication, and to improve survival.[36,50]

Emerging Agents

Several new agents are under study and have shown modest benefit in the PAD population. Patients with PAD develop metabolic abnormalities in skeletal muscles of the lower extremities, resulting in changes in carnitine metabolism and accumulation of acylcarnitines.

Propionyl-L-carnitine has been shown to improve exercise and quality of life in patients with intermittent claudication.[51]

Prostaglandin drugs (PG), such as PGE_1 and PGI_2, show promise in the treatment of intermittent claudication.[5] In an open-label study comparing pentoxifylline, PGE_1, and exercise treatment in PAD patients, a 30% increase in maximum walking distance was obtained with exercise or pentoxifylline compared with a 149% increase with intravenous PGE_1; disease progression was also reduced with PGE_1.[52] Recent trials using a PGI_2 analog that is orally active (Beraprost) failed to show a statistically significant improvement in walking distance compared with placebo; the oral prostacyclin was also found to be poorly tolerated at higher doses secondary to side effects.[36,53]

Angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), are mitogenic agents for development of new collateral channels in models of peripheral ischemia. Recent studies using gene transfer of naked DNA encoding for VEGF have shown promise in angiogenesis in patients with critical limb ischemia.[54] Phase I and phase II trials are in progress evaluating these agents for treatment of claudication and critical leg ischemia.

L-Arginine has been shown to induce nitric oxide formation and improve endothelial-dependent vasodilation in patients with atherosclerosis. Small studies have shown improvement in pain-free walking distance and maximum walking distance after treatment of intermittent claudication with this compound,[55] and an L-arginine-enriched food bar has been recommended as nutritional therapy for PAD.[56]

Invasive Therapies

For most patients with PAD, the primary care physician should feel comfortable in the management of their vascular issues. Arteriography is not necessary in the diagnostic evaluation of patients with PAD and is indicated only when the condition necessitates definitive revascularization, either endovascular or surgical. Referral to a vascular care specialist is indicated for patients with lifestyle-limiting claudication (refractory to exercise and pharmacotherapy) or evidence of critical limb ischemia (eg, rest pain or tissue loss, including ulcers or gangrene). To help define the anatomy when performing an arteriographic examination, noninvasive arterial studies, including ankle-brachial indexes and arterial imaging with duplex ultrasonography, may be added to guide the operator in planning a diagnostic strategy. As in all invasive procedures, substantial cardiovascular morbidity and mortality exist in addition to the expense. In each case, therefore, the risk-benefit ratio must be weighed.

Conclusions

The primary goals of therapy for PAD and intermittent claudication are to relieve symptoms (in the case of intermittent claudication) and to reduce progression of the disease and development of cardiovascular complications. Risk-factor modification is key. Improvements in walking ability can increase a patient's overall mobility and have a positive impact on cardiovascular outcome. Invasive measures should be considered if medical treatment fails, if the patient's mobility is severely limited by claudication, or if there is critical limb ischemia.

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