Continuing Medical Education

Peripheral Arterial Disease: Diagnostic Evaluation and Current Therapeutic Options

New treatments offer an improved prognosis for PAD.

Goals and Objectives

After reading this article, the podiatrist should be able to:

1) Verbalize a definition of peripheral arterial disease

2) Understand the risk factors associated with peripheral arterial disease

3) Identify the objective methods used to confirm the diagnosis of peripheral arterial disease

4) Appreciate the importance of risk factor intervention as primary therapy of peripheral arterial disease

5) Develop a strategy for treatment of peripheral arterial disease using medical, endovascular, and surgical modalities.

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*Following this article, an answer sheet and full set of instructions are provided (p. 190).—**Editor***

By Michael R. Jaff, DO

Peripheral arterial disease (PAD) is defined as occlusive arterial disease of the lower extremities that reduces arterial flow during exercise or, in advanced stages, at rest. The presentation of PAD is varied, and may appear as asymptomatic arterial disease with abnormal non-invasive tests; symptomatic disease presenting as either classic or atypical intermittent claudication (IC); and critical limb ischemia (CLI), manifesting as ischemic rest pain, non-healing ischemic ulcers, or gangrene. Prompt recognition of this disorder is critical to avoid progressive deterioration in physical function, limb loss, and premature death from myocardial infarction or stroke. The podiatrist plays an important role in this process, and must understand the prevalence and natural history, presenting symptoms and signs, objective diagnostic tests, importance of risk factor intervention, and therapeutic alternatives.

Epidemiology

The prevalence of PAD depends on how one defines the disease. Given the inaccuracy of physical examination, using pulse examination as the sole criterion will grossly overestimate the true prevalence. In contrast, an historical query for the presence of intermittent claudication underestimates the prevalence of PAD. Epidemiological studies have wide-ranging prevalence rates from 1.6% to 12%, while other studies using objective disease detection with non-invasive tests have prevalence rates varing from 3.8% to 33%.(1) Non-invasive methods for disease definition in epidemiological surveys have usually

Continued on page 182

PAD...

included statistically validated claudication questionnaires. The Edinburgh Claudication Questionnaire (a modification of the World Health Organization/Rose claudication questionnaire), when compared with the independent assessment by two physicians of 300 patients over age 55, demonstrated a sensitivity of 91% and specificity of 99% for the diagnosis of intermittent claudication.[1]

The ankle-brachial index (ABI), which is a comparison of the systolic blood pressure in the dorsalis pedis and posterior tibial arteries of the limb to the brachial artery of the arm using a hand-held Doppler, has been validated against angiographically confirmed PAD and found to be 95% sensitive and almost 100% specific.[2] In clinical practice, this is the most simple, inexpensive, reliable and reproducible method of identifying patients with PAD.

The age-adjusted prevalence of PAD, as defined by an ankle-brachial index < 0.9 is 12%1. PAD prevalence rates defined by non-invasive testing are reported to be 2.5% at age 40 to 59 years, 8.3% at age 60 to 69 years, and 18.8% at age 70 to 79 years.[3]

Diagnosis of Peripheral Arterial Disease

Classic ("Rose") intermittent claudication, the most common symptom of PAD, is characterized by exertional discomfort in a major muscle group in a limb, which develops with exercise and is promptly relieved with rest. A significant proportion of patients with symptomatic PAD will not describe classic symptoms, making the diagnosis more difficult. More than 50 percent of patients with PAD are either asymptomatic or have atypical symptoms, one-third have classic symptoms of intermittent claudication, and 10 percent of patients develop critical limb ischemia.[4] The spectrum of PAD is not a continuum. Patients commonly present with CLI without having experienced prior symptoms (the classic example is the patient with diabetes mellitus who sustains minor trauma to a foot after wearing ill-fitting shoes and develops gangrene, never having experienced claudication in the past).

The first objective test which must be performed in patients either at risk for PAD, or with symptoms and physical findings of PAD is the ankle-brachial index (ABI). The ABI is a safe, simple, highly accurate, and reproducible method of determining * The presence and severity of PAD * The cardiovascular risk of myocardial infarction, stroke, and vascular death.

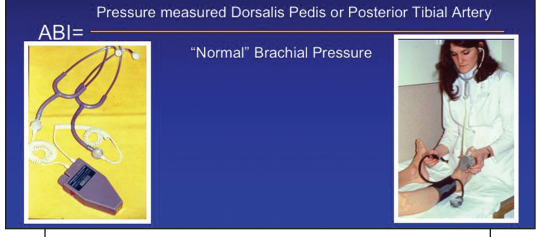
This test is easily performed in the podiatric specialist's office. It requires

* Routine sphygmomanometer
* Hand held, continuous wave Doppler
* Acoustic Gel.

In patients with symptoms suggestive of PAD, physical findings increasing the likelihood of PAD, or in patients at high risk for PAD, the ABI is the ideal office-based objective evaluation.

A sphygmomanometer is placed on the upper arm, and the systolic pressure is measured using a hand-held Doppler device. This process is repeated on the contralateral upper arm. The higher of the two pressures is used as the denominator of the ABI calculation. Following this, the sphygmomanometer is placed on the lower leg, just above the ankle. Again utilizing the hand-held Doppler, an arterial Doppler signal is obtained in the dorsalis pedis artery, the cuff inflated until the arterial Doppler signal disappears, and then the cuff is gradually deflated. When the arterial Doppler signal returns, this represents the arterial pressure in the dorsalis pedis artery. The Doppler device is then positioned posterior to the medial malleolus, and the arterial Doppler signal of the posterior tibial artery is obtained. Using the identical method as described for the dorsalis pedis artery, the pressure is then determined in the posterior tibial artery.

Figure 1



The higher of the two ankle pressures (either the dorsalis pedis or posterior tibial artery) is used as the numerator of the ABI calculation.

The process is repeated on the contralateral limb.

A normal ABI is defined as a resting measurement > 0.90. Any value < 0.90 represents the presence of PAD. Obviously, the lower the ABI, the more severe the PAD. Patients with ABI values > 0.70 may be asymptomatic, or have very mild symptoms of intermittent claudication. ABI values between 0.40 and 0.70 represent patients with mild to moderate intermittent claudication. Values < 0.40 suggest the most advanced stages of PAD, with ischemic rest pain, non-healing ulcerations, and gangrene occurring with frequency.

The ABI provides information about the presence or absence of PAD, along with the severity and risk of co-morbid atherosclerotic events. If the clinician, however, desires more detailed information concerning the location of arterial occlusive disease, whether disease is represented by stenoses or occlusions, the length of atherosclerotic disease, and the status of the 'run-off' arteries, other diagnostic tests such as segmental limb pressures, pulse volume recordings, Doppler segmental waveforms, and arterial duplex ultrasonography should be considered.

The ABI is a highly accurate method of determining the presence of PAD and its severity. However, if the ankle vessel is calcified, commonly seen in patients with diabetes mellitus or end-stage renal disease, an accurate ankle pressure cannot be obtained. The pressure in these calcified arteries is often > 200-250 mmHg. If not recognized as artifactually high, the physician may falsely conclude that arterial circulation is adequate, or even normal, in these patients. In this scenario, other tests available in the vascular diagnostic laboratory are necessary, including photoplethysmography, digital pressures, arterial duplex ultrasonography, and even assessments of wound healing potential utilizing transcutaneous oximetry (TcP02).

Patients with classic historical symptoms of PAD may have a normal physical examination and ABI. In this

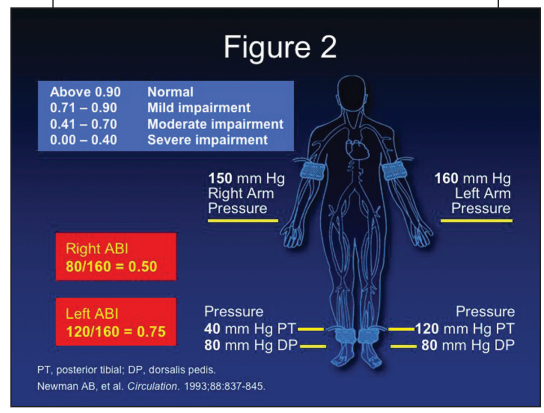
Continued on page 183

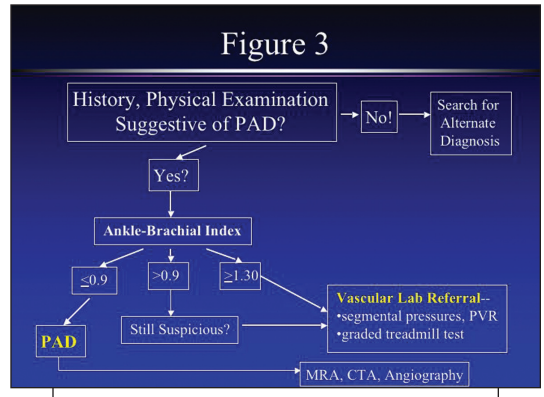
scenario, the astute clinician must pursue an exercise physiologic study performed in the vascular diagnostic laboratory. Patients have resting pressures measured, and are then placed on a treadmill at a constant speed and constant grade of incline. The patient is asked to report initial symptoms of limb discomfort, and then terminate the exercise when the discomfort is limiting. After exercise, pressures are again measured. A significant decrease in post-exercise pressures confirms the diagnosis of PAD, and also characterizes the functional limitation of the symptoms.

With the use of sequential limb blood pressure cuffs and commercially available equipment, segmental limb arterial blood pressures may be obtained. Each pressure measurement is compared to its proximal cuff, and to the cuff on the contralateral limb. For example, the pressure obtained in the proximal thigh cuff is normally > 30 mmHg higher than the brachial pressure. If this is not found, this would suggest the presence of inflow aorto-iliac artery disease. Each cuff pressure should be no lower than 20 mmHg than the pressure cuff proximal to that level. Disease localization occurs one segment proximal to the cuff with the lower pressure. Therefore, if the pressure in the lower thigh cuff is 40 mmHg lower than the high thigh cuff, this would suggest superficial femoral artery occlusive disease.

Pulse volume recordings (PVR's) are plethysmographic tests which provide qualitative information. Simply put, a blood pressure cuff is inflated to a level that does not interrupt arterial flow (usually ~ 60-65 mmHg). As each arterial pulse passes through the segment of artery beneath the cuff, the volume of blood causes distention of the artery. This is sensed by the cuff, which then transmits the volume change to a recorder, providing a waveform. In the normal setting, this waveform is similar in appearance to an intra-arterial pressure waveform. As the arterial circulation worsens, the PVR looses the dicrotic notch, lowers in amplitude, and widens. These tests require a highly trained technologist, as well as a physician who understands the subtleties of waveform interpretation.

Segmental arterial Doppler waveforms may also be performed, and are easier to interpret. Using a bidirectional Doppler probe, Doppler waveforms are obtained at each arterial level. Normal Doppler waveforms are triphasic. Mild to moderate PAD are represented by biphasic Doppler waveforms. Severe PAD results in monophasic and ultimately, flat waveforms. Segmental Doppler waveforms are easy to perform, and require little training to interpret. In the scenario of non-compressible arteries, however, Doppler waveforms lose accuracy.





Arterial duplex ultrasonography is a highly accurate examination, which may be performed from the aortic bifurcation to the ankles. Utilizing currently available Duplex ultrasound scanners, arteries are visualized, often with color imaging, and Doppler velocities are obtained. A doubling in the peak systolic velocity suggests a 50-99% stenosis. Arterial duplex ultrasonography requires a highly skilled technologist. In addition, a complete examination of both lower extremities is time-consuming. In patients who are in need of revascularization, this examination is as accurate as arteriography in predicting the optimal revascularization method.

In patients who are being considered for revascularization, duplex ultrasound scanning, magnetic resonance angiogram (MRA), and more recently computer tomographic angiography (CTA) are valuable in localizing arterial disease. Duplex ultrasonography can be used for direct visualization of arteries and is especially useful after revascularization (surgical bypass grafts or stent placement). MRA is considered one of the most significant advances in diagnostic techniques in the past 10 years, as blood flow imaging is possible without the administration of radiocontrast media. Studies have demonstrated the MRA technique is accurate and comparable to angiography. Both of these tests are noninvasive and thus pose no significant risk for anaphylaxis or nephrotoxicity. CTA is emerging as a very useful test to plan revascularization strategies. This technique requires the administration of intravenous contrast. Angiography should be reserved for those patients in whom revascularization is mandatory.

Risk factors for the Development of PAD

The risk of developing PAD can be predicted by age and well-defined atherosclerotic risk factors, including tobacco use, diabetes mellitus, hypercholesterolemia and hypertension. The Framingham Heart Study data has defined age, sex, serum cholesterol level, hypertension, tobacco use, diabetes mellitus, and coronary heart disease as factors associated with an increased risk for PAD and intermittent claudication.[5] This "risk factor profile" is useful in determining populations and patients at risk.

Age

The prevalence of PAD increases sharply with age, from 3% in patients < 60 years of age to 20% in patient >75 years of age.[4] Data from subjects in the Framingham study revealed that the prevalence of PAD

Continued on page 184

increased 10-fold from men aged 30-44 to men aged 65-74 and almost 20-fold in women from the younger to older age-groups.[6] In the Rotterdam and San Diego epidemiological studies, prevalence rates increased with advancing age both for IC and for PAD defined with the use of objective tests.[7,8]

Hypertension

The role of hypertension as a major risk factor for the development and progression of PAD is well demonstrated in the Framingham Offspring Study and the German Epidemiological Trial on Ankle Brachial Index (GET ABI study).[9,10] No studies are available, however, to evaluate whether antihypertensive therapy directly alters the progression of symptomatic PAD. The Appropriate Blood Pressure Control in Diabetes (ABCD) Study demonstrated a marked reduction in cardiovascular events in normotensive PAD patients with diabetes when treated with an intensive blood pressure-lowering strategy as compared to standard antihypertensive therapy.[11] In the most recent guidelines from the Joint National Committee on the Detection, Evaluation, and Treatment of hypertension, PAD is considered equivalent in risk to ischemic heart disease, therefore supporting aggressive blood pressure control.[12]

Tobacco Use

The single most important modifiable risk factor for the development of atherosclerotic disease is tobacco use. The amount and duration of tobacco use correlate directly with the development and progression of PAD. Smoking increased the risk of intermittent claudication by 8 to 10-fold in the Reykjavik Study and cessation of tobacco use resulted in a 50% reduction in rates of intermittent claudication over a 20-year period among Icelandic men.[13] The best evidence for a causal role of tobacco use in atherosclerotic PAD is an improvement in outcome with tobacco cessation. Tobacco cessation results in improved ankle pressure and exercise tolerance in patients with intermittent claudication as early as 10 months after tobacco cessation.[14] Tobacco cessation also has a major impact on the long-term risk of complications, including progression of PAD, myocardial infarction and mortality. In a study by Jonason et al., the rate of development of rest pain in intermittent claudication patients was 0% in non-smokers and 16% in smokers, while 10 year rates of myocardial infarction were 11% and 53%, 10 year cumulative rates of cardiac death were 6% and 43% and 10-year survival rates 82% and 46% among non-smokers and smokers respectively.[15] From the limb standpoint, tobacco cessation is associated with improved post-operative graft patency rates.[16]

Diabetes Mellitus

PAD is prevalent in patients with diabetes mellitus. A survey of patients with diabetes 50 years of age or older demonstrated a prevalence of PAD of 29%.[17] In the Rotterdam study, diabetes was present in 11.9% and 16% of male and female patients respectively, with abnormal ABI, versus 6.7% and 6.3% for those without PAD.[18] In the Cardiovascular Health Study, diabetes was associated with a 3.8-fold increased prevalence of PAD in patients over age 65.[19] In a Veterans Administration patient population with intermittent claudication, diabetes was the major independent predictor of death.[20]

Hyperlipidemia

The Lipid Research Clinics (LRC) Prevalence Study confirmed the association of dyslipoproteinemia (specifically low HDL-cholesterol and elevated LDL-cholesterol) with symptoms and signs of PAD.[21] In the National Cholesterol Education Program Adult Treatment Panel III report on detection, evaluation and treatment of high blood cholesterol in adults, PAD (regardless of diagnostic methods) is considered a coronary artery risk equivalent.[22] Lipid-lowering agents, most commonly HMG-CoA reductase inhibitors ("statins") are thought to benefit PAD patients by decreasing risk for coronary events and by potentially reversing atherosclerotic lesions. Data from the Scandinavian Simvastatin Survival Study (4S) of 4,444 patients with known cardiovascular disease revealed that use of simvastatin reduced episodes of new or worsening IC by 38%.[23] In familial hypercholesterolemic patients treated with simvastatin for 2 years, the intima-media thickness in the femoral artery decreased by a mean of 0.283 mm. This suggests atherosclerotic disease reversal with statin treatment in high-risk hypercholesterolemic patients.[24]

Hyperhomocyteinemia

Multiple prospective and case controlled studies have suggested that an elevated plasma homocysteine concentration is an independent risk factor for atherothrombotic vascular disease in the coronary, cerebral, and peripheral vasculature. In a meta-analysis of 27 studies, a modest increase in homocysteine was independently associated with an increased risk of CAD, cerebrovascular disease and PAD.[25] In a prospective study of patients with symptomatic PAD, for each 1.0 mol/L increase in the plasma homocysteine level, there was a 3.6% increase in the risk of all-cause mortality at three years and a 5.6% increase in the risk of cardiovascular-related death.

C-Reactive Protein

C-reactive protein (CRP) has recently emerged as a novel risk factor associated with risk of systemic atherosclerosis. CRP together with the total cholesterol-HDL-C ratio were the strongest independent predictors of development of symptomatic PAD in a study by Ridker PM, et al. CRP in the same study provided additive prognostic information over standard lipid measures.[26]

Natural History of Peripheral Arterial Disease

The impact of peripheral arterial disease on limb and life is quite different, and has implications on management strategies. Weitz, et al., defined the 5-year outcomes (on both limb and life) of PAD on patients over age 55 with IC. The majority of patients have no progression of limb symptoms over the subsequent five years after initial presentation. Of the remaining, 27% demonstrate progression of symptoms, while the need for revascularization or limb loss occurs in a minority (<10%) of patients.[1]

Despite the relatively stable prognosis for the affected limb, there is a marked risk of cardiovascular morbidity and mortality over 5-years

Continued on page 185

after diagnosis of intermittent claudication. The rate of nonfatal cardiovascular events (myocardial infarction and stroke) is 20%, with 5-year mortality rates of 30 %.[27] At the time of diagnosis of IC, at least 10% of patients with PAD have concomitant cerebrovascular disease, and 28% have coronary heart disease.

The overall mortality rate in patients with intermittent claudication is 30% at 5 years, 50% at 10 years, and 70% at 15 years. The mortality of patients with intermittent claudication is approximately 2.5-fold that of an age-matched general population.[34] The majority of these deaths are caused by coronary artery disease, cerebrovascular disease, and other vascular diseases (i.e. abdominal aortic aneurysm, mesenteric ischemia).[28] Subjects with asymptomatic PAD appear to have the same risk of cardiovascular events and death seen in patients with intermittent claudication.

For patients with critical limb ischemia, the outcomes are significantly worse. In addition to the marked increase in rates of limb loss, 20% of these patients die within 6 months. The annual mortality rate in patients with CLI is 25%. Virtually all patients who present with gangrene and/or ischemic rest pain are dead within 10 years. [34, 29]

Severity of PAD can be defined based on ABI values. An abnormal ABI is a potent predictor of cardiovascular events and premature mortality. In the Heart Outcomes Prevention Evaluation (HOPE) study, an abnormal ABI was a strong predictor of cardiovascular morbidity and mortality during 4.5 years of follow-up, even in patients without symptoms suggestive of PAD.[30]

These findings have prompted the American Diabetes Association to recommend screening ABI in all diabetic patients over age 50, and in diabetic patients < 50 with other PAD risk factors (e.g., smoking, hypertension, hyperlipidemia, or duration of diabetes >10 years).[31]

The Management of PAD

The goals of therapy for patients with PAD are to prevent systemic atherosclerotic disease progression and clinical cardiovascular events, prevent limb loss, and improve functional status of patients with intermittent claudication. Patients with PAD must be approached with the same intensity for secondary cardiovascular disease prevention and risk factor modification as recommended for patients with coronary artery or carotid artery disease. In 2001, a multidisciplinary task force of the American College of Cardiology and American Heart Association published recommendations for risk factor modification in patients with atherosclerotic cardiovascular disease.[32] In these guidelines, all patients diagnosed with PAD must receive aggressive therapy to prevent subsequent atherosclerotic disease and clinical events. Secondary prevention strategies include:

Regular aerobic exercise reduces cardiovascular risk (by lowering cholesterol, blood pressure, and improving glycemic control) and produces symptomatic improvement in patients with PAD.

1. Tobacco cessation
2. Physical activity
3. Dietary modification
4. Weight maintenance/ reduction with target BMI 18.5-24.9 kg/m2 and waist circumference <35 in women and <42 inches for men.
5. Blood pressure control
6. Modification of elevated total and LDL-cholesterol levels
7. Anti-platelet therapy.
8. ACE inhibitor therapy
9. Glycemic control in patients with diabetes mellitus Modification of risk factors requires knowledge, patience, and perseverance by the clinician, as most patients find this aspect of their care very challenging with limited short-term rewards.

Anti-platelet Therapy

Anti-platelet agents are recommended to prevent associated cardiovascular morbidity and mortality. Platelet activation is increased in patients with PAD, suggesting an underlying prothrombotic state.[33] Until recently, however, the use of aspirin in patients with PAD was not based on direct evidence, but only on analogous data in coronary and cerebral atherosclerosis, where anti-platelet therapy has documented clear efficacy.

A meta-analysis of anti-platelet treatment in patients after peripheral arterial bypass surgery, albeit demonstrating a non-significant effect on cardiovascular outcomes and survival, revealed a mildly positive effect on the patency of peripheral arterial bypass grafts.[34]

The Antithrombotic Trialists' Collaboration summarized the results from 287 studies involving 135,000 patients randomized to anti-platelet therapy or placebo. This meta-analysis also evaluated 77,000 patients treated with different anti-latelet regimens. In the subset of patients treated with anti-platelet therapy for PAD (N=9214), anti-platelet therapy demonstrated a 23% reduction in serious vascular events, with similar benefits among patients with intermittent claudication and those patients undergoing lower extremity revascularization.[35]

Ticlopidine, a thienopyridine derivative which blocks the activation of platelets by adenosine diphosphate (ADP), has demonstrated significant benefit in patients with PAD. Enthusiasm for this drug has been tempered, however, by the substantial risk of thrombocytopenia, neutropenia (which occurs in 2.3 % of treated patients), and thrombotic thrombocytopenic purpura (which occurs in 1 in 2000-4000 patients).[36] We do not recommend the routine use of ticlopidine in patients with PAD.

Clopidogrel (Plavix), a second thienopyridine derivative, has an action similar to ticlopidine without the serious hematological side effects. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) Study, a multicenter, multinational, prospective randomized trial, evaluated aspirin versus clopidogrel in over 19,000 patients with recent stroke, MI, or symp-

Continued on page 186

tomatic PAD. Clopidogrel was associated with a modest yet significant reduction in the primary composite endpoint of MI, ischemic stroke, and vascular death when compared with aspirin. In a subgroup analysis of 6,452 patients enrolled in CAPRIE due to PAD, clopidogrel offered a relative risk reduction of 24% over aspirin.

Clopidogrel is well-tolerated, with no increase in adverse events or discontinuation when compared to aspirin. Clopidogrel has been associated with a low risk of adverse hematologic effects. The estimated risk of thrombotic thrombocytopenic purpura is 4 per million patients, a level that does not warrant routine hematologic monitoring.[37] Clopidogrel is the only anti-platelet agent approved by the United States Food and Drug Administration (FDA) specifically for the reduction of cardiovascular events in patients with PAD.[38]

The combined effect of aspirin plus clopidogrel has been demonstrated in patients with acute coronary syndromes.[39] Currently enrolling trials will address combination therapy in PAD; however, this recommendation cannot be made at present.

We recommend anti-platelet therapy in every eligible patient with PAD. If the economic issues of long-term clopidogrel are manageable, this agent is superior to aspirin in reducing the risk of major cardiovascular events and vascular death.

Exercise Therapy

Patients with intermittent claudication have marked impairment in exercise performance and overall functional capacity. Reduced walking capacity is associated with impairment in the performance of activities of daily living and in general quality of life. Their peak oxygen consumption measured during graded treadmill exercise is 50 % of age-matched subjects with normal peripheral arterial circulation, indicating a level of impairment similar to patients with debilitating congestive heart failure.[23]

Regular aerobic exercise reduces cardiovascular risk (by lowering cholesterol, blood pressure, and improving glycemic control) and produces symptomatic improvement in patients with PAD. The beneficial effects of exercise may be explained by several mechanisms, including improvements in endothelial vasodilator function, skeletal muscle metabolism, blood viscosity and inflammatory responses. Exercise training also improves oxygen extraction and walking efficiency by decreasing oxygen consumption for the same workload.[40]

In a meta-analysis of randomized trials of exercise in patients with intermittent claudication, exercise therapy significantly improved pain-free walking time by 180% and maximal walking time by 150% over 6 months. When compared to percutaneous revascularization, supervised exercise produced significant improvements in walking time at six months, and did not differ significantly from surgical treatment.[41]

Revascularization attempts are warranted in patients with symptom-limiting intermittent claudication or in those patients who progress to ischemic rest pain with or without ulceration.

We recommend a supervised exercise program which encompasses specific factors. Supervised exercise therapy is the most effective symptomatic therapy for patients with IC. Supervised exercise therapy includes 6-month programs, with sessions three times per week, walking as the main form of exercise, and sessions lasting 60 minutes. The main factors limiting success of exercise therapy include lack of patient motivation and compliance, and the economic obstacles for reimbursement in the United States. Available data analyzing the implementation of supervised exercise in patients with PAD are pessimistic. In the United Kingdom, regular walking exercise was not followed by almost 50% of patients with intermittent claudication.[42]

Pharmacologic Treatment of Peripheral Arterial Disease

Pentoxifylline (Trental®), a methylxanthine derivative, improves red cell deformability, lowers fibrinogen levels, and retards platelet aggregation. It is the first medication approved by the FDA (in 1984) for the treatment of patients with IC.[1] A recent review of all available trials concluded that the actual improvement in walking distance attributable to pentoxifylline is unpredictable, may not be clinically important compared with the effects of placebo, and does not justify the added expense for most patients.[43] Based on current evidence we do not recommend the routine use of pentoxifylline in patients with PAD.

Cilostazol, a phosphodiesterase III inhibitor, was the second oral agent approved for the treatment of mild to moderate intermittent claudication in 1999. In addition to its antiplatelet properties, cilostazol promotes vasodilatation, increases plasma HDL and decreases plasma triglycerides, and potentially inhibits smooth muscle cell accumulation after percutaneous coronary intervention.[1] The true mechanism whereby cilostazol improves pain-free walking distance is unknown.

Cilostazol increases pain-free and maximal walking distances by 40-70% and 65-83% respectively after 12-24 weeks when used at the recommended dose of 100 mg orally twice daily. Treatment with cilostazol is also associated with improvements in health-related quality of life.[44]

In the pivotal prospective, multicenter, 24-week randomized trial comparing cilostazol to pentoxifylline and placebo in 698 patients with intermittent claudication, the improvement seen with cilostazol (a mean percent increase of 54% from baseline) was significantly greater than that seen with either pentoxifylline (a 30% mean percent increase) or placebo. Side effects, such as headache, palpitations, and diarrhea, were more common in the cilostazol group, but discontinuation rates were similar between cilostazol and pentoxifylline (16% vs. 19%).[45]

Chronic use of phosphodi-

Continued on page 187

esterase III inhibitors in patients with congestive heart failure has been associated with an increase in mortality due to a proarrhythmic effect. Therefore, cilostazol must not be prescribed to patients with intermittent claudication who have congestive heart failure.[46] The safety data from eight phase 3 clinical trials involving 2,702 patients and from postmarketing surveillance in the United States representing 70,430 patient-years of exposure did not reveal increased cardiovascular morbidity or mortality risk in patients receiving cilostazol.[47]

Cilostazol should be taken one-half hour before or two hours after food, as high-fat meals markedly increase its absorption. Diltiazem, grapefruit juice or omeprazole can increase serum concentration of cilostazol if they are taken concurrently. Cilostazol can be safely administered with aspirin or clopidogrel without any further increase in bleeding time.[48] We recommend the use of cilostazol as initial therapy for patients with mild to moderate intermittent claudication.

Revascularization for Peripheral Arterial Disease

Revascularization for peripheral arterial disease cannot occur on the basis of angiographic or non-invasive physiologic test results alone. The finding of a stenosis or short segment occlusion of these vessels does not indicate the need for revascularization. It is the clinical symptomatology of the patient, coupled with the presence of atherosclerotic risk factors, other co-morbid medical conditions, and the results of non-invasive tests that allows for appropriate decisions concerning the need for revascularization. It is unlikely that a patient presenting with mild symptoms will require revascularization. Risk factor modification, enrollment in a supervised exercise program[49] or an experimental trial of pharmacotherapy for intermittent claudication[50] seems more appropriate.

Revascularization attempts are warranted in patients with symptom-limiting intermittent claudication or in those patients who progress to ischemic rest pain with or without ulceration. Endovascular therapy, first proposed more than 35 years ago by Dotter and Judkins[51] for the treatment of diseased coronary arteries, revolutionized the management of certain patients with peripheral arterial disease (PAD). This approach, however, with its reliance on techniques such as angioplasty, stents, stent-grafts, and various mechanical devices, was not viewed by the practicing interventionist as a viable option for individuals with PAD until the 1980's. Since then, interest has rapidly grown and endovascular therapy has now become a primary option in the treatment of PAD.[52]

While the technology and devices available for endovascular therapy in PAD have become increasingly more sophisticated and reliable, a review of the data reveals that endovascular therapy is not risk-free. Early experience with angioplasty for PAD in 352 patients (453 angioplasties) resulted in 59 complications in 53 patients[53] The advent of endovascular stents led to improved patency, but not a significant reduction in adverse events, including access site complications. In a series of patients with iliac artery atherosclerosis for whom 147 iliac artery stents in 98 limbs were deployed, there were 29 (19.4%) complications.[54]

Vascular surgical procedures are classically reserved for patients with critical limb ischemia (ischemic rest pain, non-healing ischemic ulcers, gangrene). These patients have multilevel arterial disease, and require bypass procedures to targets below the knee. The autogenous saphenous vein is the ideal conduit to use for such procedures, and if performed by skilled and experienced surgeons, limb salvage and patency rates are quite acceptable.[55]

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Continued on page 188

Continuing Medical Education

PAD...

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Dr. Jaff. is currently the Director of Vascular Medicine and the Vascular Diagnostic Laboratory and Associate Program Director in Internal Medicine at Lenox Hill Hospital in New York City. He is president of the Society for Vascular Medicine and Biology, and serves as a member of the Board of Directors for the Intersocietal Commission for the Accreditation of Vascular Laboratories. He is a member of the editorial board of several journals including Vascular Medicine, Angiology, Catheterization and Cardiovascular Interventions, the Journal of Vascular Surgery, Annals of Internal Medicine, and the Journal of Endovascular Therapy.

EXAMINATION

Continuing Medical Education

See answer sheet on page 191.

1) The most common symptomatic manifestation of peripheral arterial disease is
   A) Ischemic ulceration
   B) Classic "Rose" intermittent claudication
   C) Atypical exertional limb symptoms
   D) Gangrene

2) Peripheral arterial disease affects what percent of adults over age 60 in the United States?
   A) 1%
   B) 8%
   C) 15%
   D) 50%

3) The ankle-brachial index
   A) Has a 15% risk of invoking significant limb pain during the examination.
   B) Carries sensitivity and specificity rates of ~80%.
   C) Requires an advanced degree in physiology to accurately perform
   D) Requires a sphygmomanometer, acoustic gel, and Doppler.

4) A 57 y.o. female presents with bilateral buttocks numbness with walking 50 yards. These symptoms have been noticeable for the past 3 years, and have progressively worsened over the past 6 months. When the patient stops and stands, the numbness resolves within 5 minutes. She does not experience similar symptoms at rest, or with standing. Her right arm blood pressure is 170 mmHg; left arm blood pressure 200 mmHg. The pressure via hand-held continuous wave Doppler of the right dorsalis pedis artery is 140 mmHg, posterior tibial artery 130 mmHg; left dorsalis pedis artery 110 mmHg, posterior tibial artery 90 mmHg. Which of the following is a true statement:
   A) Based on the history and Doppler pressures, the symptoms are clearly non-vascular in nature.
   B) The right leg ankle-brachial index is 0.65.
   C) The left leg ankle-brachial index is 0.65.
   D) The patient has right subclavian artery disease.

5) Which of the following is not a component of an effective exercise program for intermittent claudication?
   A) Six month duration
   B) Supervision by an exercise physiologist/physical therapist
   C) Each session lasts 10 minutes
   D) 3 sessions per week.

6) Clopidogrel has demonstrated a significant reduction in myocardial infarction, stroke, and vascular death in patients with intermittent claudication and peripheral arterial disease when compared to similar patients treated with aspirin. Cilostazol has demonstrated
   A) Antiplatelet effects which exceed that of aspirin and clopidogrel
   B) A reduction in stroke when compared to aspirin therapy
   C) An improvement in pain-free walking distance to a statistically significant degree over placebo and pentoxifylline.
   D) Similar impact on pain-free walking distance when compared to clopidogrel.

7) A patient presents with a painless ulcer on the plantar aspect of the left foot. The patient is unsure as to how the ulcer formed, and does not know the duration of the ulcer. The patient has no history of exercise-induced limb discomfort, and has never been told of peripheral arterial disease in the past. The ulcer is located on the plantar aspect of left second metatarsal head. The base of the ulcer has extensive yellow exudate, and there is a large amount of surrounding callus formation. The patient has no pinprick or light touch sensation, proprioception, or vibratory sensation of the feet. The first step in the management of this patient is
   A) Schedule the patient for an arteriogram
   B) Perform an ankle-brachial index at the bedside
   C) Debride the ulcer
   D) Order transcutaneous oximetry

8) When performing an ankle-brachial index, if a systolic Doppler pressure exceeds 250 mmHg, one can presume that
   A) The patient's circulation is abnormal
   B) The Doppler is malfunctioning
   C) You are performing the test incorrectly
   D) The patient's circulation is normal.

9) A patient with hypertension and hyperlipidemia describes a history classic for intermittent claudication of the right lower extremity. There are no rest symptoms or ulcerations. Both pedal pulses are easily palpable. The ankle-brachial index is normal. Your next step is
   A) Prescribe custom orthotic devices for plantar fasciitis
   B) Either refer the patient for a treadmill challenge test or perform toe raises in your office followed by repeat ABI determination.
   C) Order an MRI of the lumbosacral spine looking for lumbar canal stenosis
   D) Order an MRA of the lower extremity arteries.

10) Which of the following diagnostic tests will not help plan revascularization in a patient with ischemic rest pain of the foot?
   A) Magnetic resonance arteriography
   B) Arterial duplex ultrasonography
   C) Transcutaneous oximetry
   D) Computed Tomographic Angiography

11) The most important modifiable risk factor for the development of peripheral arterial disease is
   A) Male sex
   B) Hypertension
   C) Age
   D) Tobacco Use

12) In the Cardiovascular Health Study, diabetes was associated with a ___-fold increased prevalence of PAD in patients over age 65.
   A) 2.0
   B) 3.8
   C) 5.0
   D) 7.0

13) Patients with asymptomatic PAD have mortality rates which are _____ to those patients with intermittent claudication?
   A) Similar

Continued on page 190

Continuing Medical Education

EXAMINATION

(cont'd)

B) Lower than
C) Higher than
D) Unknown

14) Secondary prevention strategies in patients with PAD include all of the following EXCEPT
A) Tobacco Cessation
B) Weight loss
C) Use of wool socks
D) Reduction in LDL-cholesterol

15) The CAPRIE study demonstrated superiority of what agent over aspirin in preventing recurrent heart attacks, strokes, or dying from vascular disease?
A) Persantine
B) Inderal
C) Trental
D) Clopidogrel (Plavix)

16) Cilostazol is a phosphodiesterase III inhibitor whose mechanism of action includes all of the following EXCEPT
A) Increased dilation of arteries
B) Promotes platelet aggregation and adhesion
C) Reduction in triglycerides and elevation of HDL-cholesterol
D) Inhibition of smooth muscle cells in coronary arteries after angioplasty

17) Which of the following instructions for use of cilostazol is correct?
A) Take immediately after eating
B) Avoid spicy foods
C) Avoid diltiazem or omeprazole
D) Take each dose with grapefruit juice

18) Indications for revascularization in patients with PAD include all of the following EXCEPT
A) Limb discomfort after walking 1.0 miles
B) Rest pain that awakens a patient from sleep
C) Gangrene
D) Non-healing ulceration on the toe

19) Which of the following treatment strategies is most appropriate?
A) Surgical bypass in a patient with 10 block intermittent claudication
B) Percutaneous transluminal angioplasty in a patient with 10 block intermittent claudication
C) Risk factor modification, antiplatelet therapy, exercise in a patient with 10 block intermittent claudication
D) Pentoxifylline in a patient with 10 block intermittent claudication

20) Complication rates of patients who undergo iliac artery intervention occur in what % of cases?
A) 0.5
B) 10
C) 20
D) 50

See answer sheet on page 191.

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Peripheral Arterial Disease
(Jaff)

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1.	A	B	C	D	11.	A	B	C	D
2.	A	B	C	D	12.	A	B	C	D
3.	A	B	C	D	13.	A	B	C	D
4.	A	B	C	D	14.	A	B	C	D
5.	A	B	C	D	15.	A	B	C	D
6.	A	B	C	D	16.	A	B	C	D
7.	A	B	C	D	17.	A	B	C	D
8.	A	B	C	D	18.	A	B	C	D
9.	A	B	C	D	19.	A	B	C	D
10.	A	B	C	D	20.	A	B	C	D

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