Intermittent claudication is a symptom complex associated with atherosclerosis of the aorta and lower extremities. It is a clinical marker of systemic atherosclerosis, and therefore, management cannot be considered isolated from treatment of underlying risk factors of atherosclerosis. The focus of the management is twofold. The first is to reduce morbidity and mortality from cardiovascular events, including myocardial infarction and stroke. The second focus is to improve the functional status of patients who have impairment of daily activities secondary to symptoms of claudication through pharmacologic and rehabilitative means, that is, exercise. Exercise is the cornerstone of therapy. A conservative approach is favored in patients who have mild and moderate symptoms of claudication. Intervention with percutaneous techniques or surgery is generally reserved for patients who have severe impairment of lifestyle or threatened tissue.

(Key words: atherosclerosis, intermittent claudication)

Atherosclerosis has become increasingly recognized in the community as a significant cause of morbidity and mortality. It is a systemic disease that is most frequently associated with fatal and nonfatal myocardial infarction, stroke, and disease of the aorta and lower extremities.

Intermittent claudication is a symptom complex associated with impaired inflow most often associated with atherosclerosis involving the aorta and large arteries of the lower extremities. Its diagnosis and treatment cannot be considered isolated given the close association with cardiovascular and cerebrovascular disease. For the purpose of this discussion, however, the focus is on the natural history, medical evaluation, and management of the patient who presents with intermittent claudication.

Definition

The word “claudication” stems from the Latin, claudicatio, meaning “to limp.” It is a symptom complex that generally occurs in the lower extremities. Historically, it is described as cramping or fatigue within a muscle group that is associated with a predictable distance of walking. Resting provides relief that occurs after a few minutes. Symptoms again recur after the same predictable amount of exercise.

The time to onset of symptoms and the location of the symptoms are directly related to the degree and location of inflow stenosis. The time of onset of symptoms may be shortened by the grade of incline and speed of ambulation. Significant aortoiliac stenosis typically results in hip, buttock, or thigh symptoms, whereas superficial femoral or popliteal stenosis results in calf muscle discomfort.

Fontaine and Rutherford are both accepted classification systems for peripheral artery disease.1,1p395 Each scale grades peripheral artery disease from asymptomatic to gangrene or major tissue loss (Tables 1 and 2). These classification systems can be applied when evaluating the baseline status and progression or improvement of disease symptoms.

When evaluating patients with leg complaints, it is important to recognize that there are several causes for leg pain and fatigue with ambulation. Historical factors that are inconsistent with the aforementioned description of symptoms should cause the clinician to consider other potential etiologies for leg pain. Patients who obtain little or no relief of their symptoms after resting for 5 minutes or less and either have to sit or lean and reposition their legs may have an alternate reason for their leg symptoms. Other historical clues that may lead to an alternative diagnosis for leg symptoms include variable distances of walking from one day to the next or from morning to evening, pain brought on by prolonged standing, and ease of leg discomfort by use of a cart or cane to lean on while walking. Table 3 lists common causes of nonarterial leg pain with associated symptoms that help to differentiate them from arterial claudication.

It is important to keep in mind that leg symptoms in an aging population may be confounding, so that more than one pathologic entity may be present and accounting for different symptoms. For example, both osteoarthritis and peripheral artery stenosis may be present in the same patient. Therefore, the patient may present with two separate leg complaints, one typical of osteoarthritis and one typical of claudication. In this situation, the noninvasive vascular laboratory testing may be a useful adjunct to identify the most significant debilitating culprit for the patient.

Epidemiology and natural history

The incidence of symptomatic and asymptomatic atherosclerotic disease increases in the population proportionately with age. In the general population of patients aged 65 years and older, atherosclerotic cardiovascular disease is considered to be present to some degree, regardless of the presence or absence of other risk factors associated with arteriosclerosis obliterans (ASO). It has been projected that by the year 2040, 21.8% of the population will be 65 years of age or older.2 These are impressive numbers that illustrate the scale of the problem that physicians face.

Population-based studies have used the screening ankle brachial index (ABI) together with either patient interview or standardized questionnaires such as the SF-36 or Walking Impairment Questionnaire (WIQ). Questionnaires focus on the overall functional status of patients in everyday activities and also contain subjective pain-rating scales. The ABI is determined by dividing the ankle pressure by the higher of the two systolic brachial pressures. When obtaining the ankle pressure, typically a pencil-probe Doppler scan is used and the systolic pressure is...
measured by each, the dorsalis pedis artery and posterior tibial artery. The higher pressure of the two is then used to make the final calculation (Figure 1).

Large-vessel peripheral arterial disease (PAD) manifested by asymptomatic disease with an ABI of less than 0.9 or symptomatic disease with a history of claudication is present in approximately 28% of the general population older than 55 years. Five percent of this population will have symptoms of intermittent claudication; the remainder will be symptom free. Nine percent of the patients who are asymptomatic at baseline will have symptoms of intermittent claudication develop in 5 years.3

Those presenting with intermittent claudication typically have the condition remain stable for 5 years. Only a small number will require amputation (4%). One quarter of this same group will have either worsening claudication or require lower extremity revascularization. In those patients who present with intermittent claudication, the cardiovascular event rate, both fatal and nonfatal, is about 5% to 6% per year.4

Pathophysiology
The progression of the atherosclerotic plaque and its hemodynamic impact on the vessel lumen, development of collateral circulation, and the metabolic milieu of the affected skeletal muscle are intimately interactive.

In the nonexercising limb, the skeletal muscle is a high-resistive vascular bed that has low oxygen requirements for resting metabolism. Exercise results in a decreased vascular resistance to accommodate the metabolic requirements and increased flow. As a result of the inflow impairment, however, the flow cannot meet the metabolic demands of the exercising muscle, thus resulting in discomfort and fatigue.

Clinical evaluation of intermittent claudication
A history that is consistent with intermittent claudication has been discussed previously. The physical examination of any patient who presents with this history must include a thorough vascular examination. This should always include:
- Bilateral arm blood pressure measurements;
- Auscultation and palpation of the carotid arteries, subclavian arteries, and femoral arteries;
- Approximation of the size of the abdominal aorta; and
- Assessment for epigastric (renal artery) bruits.

Palpation of brachial, radial, popliteal, dorsalis pedis, and posterior pulses is also performed.

Different grading systems are used when describing the presence, absence, and intensity of pulses. The TransAtlantic Inter-Society Consensus (TASC) group

<table>
<thead>
<tr>
<th>Stage</th>
<th>History</th>
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<tbody>
<tr>
<td>I</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>IIa</td>
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</tr>
<tr>
<td>IIb</td>
<td>Moderate-severe claudication</td>
</tr>
<tr>
<td>III</td>
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</tr>
<tr>
<td>IV</td>
<td>Tissue loss or ulceration</td>
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<table>
<thead>
<tr>
<th>Grade</th>
<th>Category</th>
<th>History</th>
</tr>
</thead>
<tbody>
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<td>0</td>
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<tr>
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</tr>
<tr>
<td>I</td>
<td>2</td>
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<tr>
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<td>Severe claudication</td>
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<tr>
<td>II</td>
<td>4</td>
<td>Ischemic rest pain</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>Tissue ulceration (minor)</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>Tissue loss/gangrene</td>
</tr>
</tbody>
</table>


Table 1
Fontaine Classification System for Peripheral Artery Disease

<table>
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<tbody>
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</tbody>
</table>


Table 2
Rutherford’s Classification of Peripheral Arterial Disease*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Category</th>
<th>History</th>
</tr>
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</tr>
</tbody>
</table>


Table 3
Claudication Versus Other Causes of Leg Pain

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Location of pain</th>
<th>Associated with exercise</th>
<th>Relieving factors</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Intermittent claudication</td>
<td>Calf, hip, buttock, or thigh</td>
<td>Always</td>
<td>Stopping</td>
<td>Lasts minutes</td>
</tr>
<tr>
<td>☐ Lumbar stenosis</td>
<td>Calf, hip, buttock, or thighs</td>
<td>Also standing</td>
<td>Spine flexion</td>
<td>Back history</td>
</tr>
<tr>
<td>☐ Herniated disc</td>
<td>Radiates down leg</td>
<td>Variable</td>
<td>Variable, NSAIDs</td>
<td>Back history</td>
</tr>
<tr>
<td>☐ Osteoarthritis</td>
<td>Hips, knees, ankles</td>
<td>Variable</td>
<td>NSAIDs/acetaminophen</td>
<td>History of arthritis/age and obesity</td>
</tr>
</tbody>
</table>
for the management of PAD grades pulses as absent, diminished, or normal as grade 0, or grade 1, grade 2, respectively.\(^1\text{p 561}\)

Pulse findings should coincide with the location of pain on ambulation and should be supported by the noninvasive studies that are obtained.

Skin and foot care, especially in the diabetic population, also needs to be assessed. Foot deformities such as hammer toes, pes planus, weight-bearing callous formation, and bunion deformities are commonly encountered. These deformities may predispose to ulcer formation, especially if the patient has evidence of peripheral neuropathy. Inspection for interdigital cracks and heel fissures as well as sensory neurologic examination including vibratory and pinprick testing should be performed on every patient.

The diagnostic evaluation of intermittent claudication should be thought of in two separate categories. These include physiologic or functional assessment and anatomic assessment (Figure 2). Segmental pressures, segmental plethysmography, or pulse volume recordings (PVR), Doppler waveform analysis, exercise testing, and reactive hyperemia testing are all methods to physiologically assess limb perfusion. Typically, segmental pressures are used together with plethysmography or Doppler waveform analysis or both, depending on the practice of the noninvasive vascular laboratory.

The clinician must consider, when reviewing segmental pressures in diabetic patients, that there is a predilection to early development of calcified vessels. Calcification within a vessel wall causes diminished compressibility and, therefore, elevated pressure measurements. This can be misleading if not recognized. An alternative to measurement of ankle pressures in this group is the measurement of toe pressures. Toe pressures have been demonstrated to be more accurate in the assessment of patients with calcified vessels as the distal pedal vessels are typically spared. This small vessel sparing does not, however, overcome the proximal segmental pressure dilemma in these patients. It is for this reason that complementary parameters such as plethysmographic tracings (PVRs) frequently accompany segmental limb pressure measurement.

Exercise testing is not only useful to clarify an ambiguous history, but also to gather a baseline functional test of the patient’s walking distance until claudication. It is important to recognize that a patient with a history of intermittent claudication may, indeed, have a completely normal study finding at rest and a significant drop in ankle pressures with exercise. It is always important to assess exercise tolerance of the patient with claudication before initiating therapy.

Reactive hyperemia is another modality of obtaining a functional assessment of the patient’s lower extremity perfusion. It has limited utility from a clinical perspective, in that patients who would be tested in such a fashion are likely not limited by claudication secondary to a sedentary lifestyle.

The second category of diagnostic evaluation is the anatomic assessment. These studies should be obtained if intervention is being considered. The “gold standard” continues to be arteriography. Other methods that are being used include duplex ultrasonography, magnetic resonance imaging with magnetic resonance arteriography, and spiral computed tomography (CT). Of these alternative methods of imaging, duplex ultrasonography has been most widely reviewed.

The greatest degree of accuracy can be obtained in the femoropopliteal vessels with a greater than 50% stenosis.\(^3\) Magnetic resonance arteriography and spiral CT have more limited availability; computer reconstruction artifact and patient movement artifact make them difficult studies to perform.

Assessing risk factors

When patients present with intermittent claudication, management is already considered “secondary prevention.” It is critical, therefore, to document cardiovascular risk factors and treat them aggressively.

Age and gender are certainly not risk factors that can be modified; however, when atherosclerotic disease is diagnosed in a patient younger than 50 years, the clinician should consider additional screening for elevated Lp(a) lipoprotein and plasma homocysteine. Both are markers for premature and familial tendencies for progressive atherosclerosis.\(^6\text{-}7\)

Diabetes is a powerful risk factor for progressive systemic atherosclerosis. It has been shown to increase the risk of major amputation by as much as 16% when compared with nondiabetic individuals with ASO.\(^8\)

The effects of smoking on progression of peripheral atherosclerosis, although not well understood, are well documented. The rate of progression of ASO, recurrence and failure of revascularization procedures, amputation rates, and cardiovascular morbidity and mortality are all impressively increased in a smoking population.\(^9\)

Hypertension is defined as a blood pressure of 140/90 mm Hg recorded two or more times after the initial visit.\(^10\) This condition, together with hyperlipidemia, is the most undertreated of the conditions despite both being well-established risk factors for atherosclerotic heart disease, stroke, and peripheral vascular disease.\(^11\text{-}12\)
Treatment

Patients who have no evidence of limb-threatening ischemia or severe debilitating claudication should be treated conservatively.\textsuperscript{13-15} Conservative management comprises aggressive risk factor modification, a walking program, and pharmacologic agents as needed (Figure 3).

The goal of treatment of patients with intermittent claudication is twofold:
- to identify, treat, and prevent or delay progression of atherosclerotic disease as a systemic entity, and
- to improve functional status and exercise tolerance.

Lifestyle changes are probably the most difficult to achieve. School and community programs, media outlets, and patient and physician education are all ways to promote awareness and primary and secondary prevention. Public education programs are a large undertaking with a very important role in our society, but despite what may be viewed as good community awareness, the average person does not follow the guidelines for a healthy lifestyle.

Smoking cessation is of paramount importance. Many community hospitals have programs that assist patients in kicking the habit. Certainly, however, a very important factor in initiating this lifestyle change is physician communication and support. Different methods of cessation have been studied with variable rates of success. Behavioral modification techniques, the use of nicotine-containing gums and patches, and most recently, the use of bupropion hydrochloride as an agent to improve attempts at smoking cessation are available and should be discussed with the patients in the office.

The management of the diabetic patient with intermittent claudication includes an ongoing assessment of glycemic control, education, and close monitoring of skin care and foot deformities. Patient awareness of his/her own level of neuropathy and instruction for appropriate footwear and daily maintenance including cleansing and inspection may curtail a tendency for ulceration.

Maintaining a blood pressure below 140/90 mm Hg has been associated with a significant reduction of cardiovascular morbidity. Initial blood pressure measurements should be done in both upper extremities and the higher of the two used for clinical management. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC VI) outlines a management approach that can and should be adhered to in order to maintain the goal of less than 140/90 mm Hg in all patients without exception to age.

The National Cholesterol Education Program\textsuperscript{16} recommends that a fasting lipid profile be measured in all patients older than 20 years at least once every 5 years. Among patients with established atherosclerotic disease, the target for treatment is the low-density-lipoprotein (LDL) cholesterol level. When lowered to levels of less than 100 mg/dL in this population of patients, LDL cholesterol is associated with a decreased risk of cardiovascular events.

The use of antiplatelet therapy is associated with a decreased morbidity and mortality from cardiovascular events. Although it is not proven to primarily reduce cardiovascular events, the use of aspirin, 75 mg/d to 325 mg/d, as secondary prevention is the most widely used and studied antiplatelet therapy. It has been demonstrated to reduce the risk of vascular death by about one sixth.\textsuperscript{17} In 1996, the CAPRIE investigators\textsuperscript{18} demonstrated in a large-scale, randomized, blinded trial that the effectiveness of clopidogrel bisulfate, a thienopyridine derivative similar to ticlopidine, was more effective than 325 mg of aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or vascular death. Three subgroups were identified in this trial: those with myocardial infarction, those with stroke, and those with PAD. Analysis demonstrated a 23.8% risk reduction of peripheral arterial events; however, the actual effect of clopidogrel on the functional status of patients with intermittent claudication is not yet understood. The safety profile of this medication is comparable to that of aspirin; however, the cost of long-term clopidogrel therapy may be prohibitive to patient compliance/adherence. Therefore, this medication is generally not used as a first-line agent for secondary prevention of car-
dovascular events or for the initial treatment of claudication.

Currently, only two medications are approved by the US Food and Drug Administration for use in patients with intermittent claudication. Pentoxifylline is a well-known hemorrhagic agent that has had approval since 1984. Cilostazol, approved in 1999, is a phosphodiesterase III inhibitor. From findings of studies comparing pentoxifylline versus cilostazol versus placebo, it appears that the clinical efficacy of cilostazol is superior to that of pentoxifylline. Cilostazol has been demonstrated to significantly improve maximal pain-free walking distance by as high as 40% without any significant change in ABL. Further investigations to study the effects of cilostazol on intermittent claudication as well as other cardiovascular events are ongoing.

Cilostazol, as a phosphodiesterase inhibitor, has been contraindicated for use in patients with documented or subjective evidence of congestive heart failure. When considering prescribing this medication, the clinician should review the package insert for further information.

The cornerstone of conservative therapy to improve patients’ functional status is an exercise program. Such a program, however, is frequently prescribed incorrectly. As recommended by the TASC group, the sessions for walking should take place three times a week for 1 hour. Patients are instructed to walk until they have a mild to moderate amount of pain. At that point, they are instructed to rest until the pain subsides, then resume walking. Generally, the pace should be 1.5 mph to 2.0 mph. The workload is increased as tolerated, either by increasing grade or speed.

Hiatt and colleagues demonstrated that a supervised walking program as aforedescribed can improve symptom-free walking distance up to 123% from baseline after 12 weeks. Furthermore, in their study, despite no appreciable change in ABL, there was a 30% increase in peak oxygen consumption, likely reflecting either improved muscle oxygen delivery or improved skeletal muscle oxidative metabolism.

The limitations of enrolling patients with intermittent claudication in a supervised exercise program for 1 hour three times a week are recognized. Many cardiac rehabilitation centers, however, have the facilities to accommodate such a program. Availability of such facilities is obviously going to vary among institutions. Nonetheless, with a motivated, educated patient, a walking program can be carried out successfully on an independent basis.

Some advocate endovascular techniques for the percutaneous treatment of patients with intermittent claudication; however, this topic is controversial. Generally, intervention of any kind—percutaneous or surgical—is reserved for those patients with significant lifestyle impairment or for tissue salvage.

Comment
Intermittent claudication is an entity that must be recognized in the community. Not only does this symptom complex cause significant disability, but it is also a marker for systemic atherosclerosis. The management of patients with intermittent claudication is typically conservative, yet it should be aggressive as it carries a significant implication for the future health of our patients and society. Aggressive medical therapy of intermittent claudication includes modification of risk factors and lifestyle, exercise, and education, as well as pharmacologic treatment.

References