LOWER EXTREMITY ARTERIAL DISEASE
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LOWER EXTREMITY ARTERIAL DISEASE

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The morbidity of peripheral arterial disease and its associated co-morbidities are becoming increasingly recognized by physicians and scientists in the 21st century. Drs. Caralis and Bakris' volume on *Lower Extremity Arterial Disease* is an up-to-date and clinically relevant contribution to the field of arterial disorders that brings together the numerous pathophysiologic, diagnostic, and therapeutic advances in the evaluation of atherosclerosis and peripheral arterial diseases involving the lower extremities.

The editors have carefully organized their volume into sections that detail the epidemiology of arterial disorders as it relates to smoking, diabetes, and hypertension as risk factors. There is ample coverage of diagnostic testing for claudication and lower extremity arterial disease using both noninvasive and arteriographic techniques. A superb chapter on the pathogenesis of arteriosclerosis using a translational approach segues the sections on diagnosis and epidemiology with those on treatment and special patient populations.

The editors have four chapters devoted to the management of claudication and lower extremity arterial disease: nonpharmacological (exercise), medical therapy, angioplasty, and endovascular stent placement and revascularization. These comprehensive chapters are very clinically oriented and help the reader to understand when nonsurgical versus surgical management should be considered.

The chapters in *Lower Extremity Arterial Disease* have been written by several well-known authors who have provided comprehensive, scientifically sound, and clinically appropriate information. As series editor of Clinical Hypertension and Vascular Diseases, I am delighted by this timely and excellent book and know that *Lower Extremity Arterial Disease* will become a highly useful textbook for all physicians interested in arteriosclerosis, diabetes, vascular medicine, interventional radiology, and general and vascular surgery.

*William B. White, MD*

*Series Editor*
Arterial diseases are the leading causes of morbidity and mortality in all industrialized countries, and their incidence is increasing in non-industrial countries. Among the industrialized countries, the United States in particular is in the midst of an epidemic of obesity and diabetes. One in four Americans meets the criteria for obesity and the number keeps growing.

Lower Extremity Arterial Disease (LEAD) is a common disease entity for men older than 40 and women older than 50 years of age. The prevalence of LEAD continues to increase with age, from less than 3% in the population younger than the age of 60 to more than 20% at age 75 and older. The majority of patients older than 75 with LEAD are asymptomatic. Prevention of arterial disease is key to reducing morbidity and mortality. LEAD is associated with specific risk factors, namely hypertriglyceridemia, homocysteinemia, very low HDL cholesterol, physical inactivity, and above all cigarette smoking and diabetes mellitus, alone or in tandem.

LEAD, symptomatic or not, particularly when it coexists with Coronary Artery Disease (CAD) (Chapter 9), calls for polypharmacy. Polypharmacy should no longer have a bad connotation in treating patients with LEAD and CAD. In patients with metabolic syndrome and LEAD, a short-acting statin in the evening and triglyceride-reducing fenofibrate during breakfast can improve time to claudication significantly, improve endothelial function, improve the lipid profile, and at the same time decrease the probability of a coronary event. Fenofibrate and rosvastatin or simvastatin should be given twelve hours apart to avoid an overlap of their half-lives. In treating LEAD, aggressive risk factor modification should be implemented, which includes: smoking cessation, euglycemic control of diabetes, ideal control of both systolic and diastolic pressure, dramatic improvement of the lipid profile, low calorie Mediterranean diet rich in antioxidants, and, equally important, exercise therapy, either community based or supervised (Chapter 11).

Percutaneous interventions with balloon angioplasty, bare metal stents, and the more preferable for the femoral and infrafemoral arteries, drug-diluting stents, offer dramatic improvement of the stenosed or occluded lumen (Chapter 12). Blood flow is restored and great symptomatic relief is achieved. Arterial grafting techniques have also pro-
vided tremendous advances in reinstituting peripheral blood flow with the lowest possible periprocedural complication rate. Today's therapeutic armamentarium also includes the most promising approach for advanced and distal disease (i.e., therapeutic angiogenesis). The vascular growth factors can be administered intra-arterially or intramuscularly in the ischemic muscle. Therapeutic angiogenesis combined with the other current therapeutic options and aggressive risk-factor modification can remarkably improve claudication, prevent limb loss, and prolong life (Chapters 10 and 13).

The presence of LEAD, as defined by an ankle brachial index (ABI) of less than one, adversely influences the prognosis of coronary heart disease. The lower the ABI (the lowest in either ankle), the worse the prognosis. The morbidity and mortality from coronary artery bypass grafting is higher in patients with LEAD. The same increased morbidity and mortality also occurs during or after percutaneous coronary interventions, short or long term. LEAD differs from other peripheral arterial diseases by its specific medical therapy as well; the drug currently approved by the Food and Drug Administration to treat the symptoms of claudication, the phosphodiesterase III inhibitor Cilostazol, has no effect on other arterial beds like the renal or the carotid systems (Chapter 10).

Intermittent claudication can be caused by an abdominal aortic aneurysm (AAA), which is a totally different disease entity with different pathophysiology and distinct genetic mechanisms. AAAs cannot be stopped from increasing in diameter with either blood pressure control or antilipid therapy.

Lower Extremity Arterial Disease provides a comprehensive state-of-the-art review of LEAD. A detailed review of its cardinal symptom, intermittent claudication, is presented in Chapter 1. The book provides a thorough and detailed description of noninvasive and accurate assessment of LEAD with special emphasis on the ABI and its diagnostic and prognostic significance. Modern diagnostic methods, such as vascular flow patterns and magnetic resonance angiography, are eloquently presented for the educational benefit of the clinician in Chapter 2. The known risk factors for LEAD and CAD—smoking, diabetes mellitus, dislipidemia, systemic hypertension, and physical inactivity—are presented in the chapters on epidemiology and risk factors (Chapters 3–8).

The question "What do claudiants die from?" is reviewed and analyzed in the chapter on LEAD coexisting with CAD. The presence of LEAD increases significantly the probability of coexisting CAD. In patients who cannot exercise much because of claudication or in asymptomatic patients with LEAD, the preferred approach to diagnose coex-
isting CAD is dual isotope pharmacological stress testing either with adenosine IV or dipyridomole IV. Adenosine should not be given if bronchial asthma, hypotension, or profound bradycardia is present. Alternatively, dobutamine can be utilized as a pharmacologic stressor. Dobutamine should not be used in patients with LEAD and atrial fibrillation; dobutamine remarkably accelerates atrioventricular conduction. Dobutamine should be avoided as a pharmacologic stressor if blood pressure is elevated; it may precipitate a hypertensive crisis. If the clinical index of suspicion is high, then the cardiovascular physician may recommend coronary angiography (luminography is a more accurate term). Overall, single photon emission computed tomographic images of the myocardium are preferable because they can accurately assess myocardium at risk in patients with LEAD.

In morbidly obese patients (those weighing more than 350 lbs) with LEAD, neither myocardial perfusion studies nor coronary angiography can be performed for technical reasons. These patients can be evaluated with contrast echocardiography (Chapter 9). The management of patients with LEAD and CAD is the same as in every patient who has myocardial ischemia, silent or symptomatic.

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INTRODUCTION

Legend has it that the term claudication was given after the Roman Emperor Claudius, who would walk for a short distance, then stop and stand before he would start walking again. Etymologically, claudication is derived from the Latin verb claudicare, which means to limp. In 1858, Jean Martin Charcot described pain in the lower extremities resulting from arterial insufficiency. Intermittent claudication can inhibit walking, and cause limping due to ischemia of the lower extremity unilaterally or bilaterally. The most common cause of lower extremity ischemia is peripheral arterial disease of the major arteries supplying the legs and feet. Lower extremity ischemia may also progress to severe limb-threatening ischemia with symptoms and physical signs at rest as well. A detailed complete history should be obtained from every patient, middle-aged and the elderly, before the diagnosis of claudication is made. Vascular claudication under the age of 45 years is rare.

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Frequent symptoms of lower extremity arterial disease (LEAD) are pressure, tightness, squeezing sensation, burning, and frank pain precipitated by leg exercise and relieved by rest. Intermittent claudication also may be present as fatigue in working skeletal muscles. Continuous pain must be differentiated from intermittent pain, because continuous pain may be a result of a sudden arterial occlusion with or without pre-existing stenosis. Extremely severe ischemia or ischemic neuropathy, ulceration, or gangrene can also cause continuous pain.

Persistent pain of an extremity may have a different etiology other than arterial occlusive disease, from an atheromatous process or embolization. Connective tissue diseases with arteritis can cause persistent leg pain (1). Venous insufficiency, severe anemia, muscle phosphorylase deficiency, muscular dystrophy, radiation fibrosis, and retroperitoneal fibrosis have been associated with painful lower extremities (1,2). Ergot toxicity and cyclist's lesion may cause pain in the legs during exercise (2–4). (Ergotamine toxicity can also cause mitral valve disease [3] and coronary spasm.) Extra-arterial causes of persistent pain are phlebitis with or without phlebothrombosis and lymphangiitis. Intermittent tightness or pain in a muscle group is more characteristic of intermittent claudication, and is generally associated with exertion. Rarely, claudicants may report worsening of the claudication when treated with β-blockers (5,6). In general though, β-blockers are safe in LEAD. If there is a definite indication for their use, they should be administered. They can cause reduction of the cardiac output and blockade of β2-adrenoreceptor mediated skeletal muscle vasodilatation. The latter effect results in unopposed β-adrenoreceptor vasoconstriction. β-Blocking agents with β1-selectivity (cardioselective) should be used instead in order to avoid the effects of peripheral vasoconstriction.

Intermittent claudication typically occurs with walking and is relieved with rest or standing. Location of the symptoms can be the hip, unilaterally or bilaterally, the thighs, the calf most frequently, and the foot. Claudication of the foot caused by ischemia is less common. It may exist independently of claudication of the calf when the occlusive lesions are diffuse and involve small arterial branches of the infrapopliteal arteries distally (4) such as in diabetic patients. A clinical clue to the diagnosis of frank claudication of the foot is its common association with more proximal arterial occlusions and calf pain. Claudication of the foot is usually manifested as pain or ache or a catch or a cramp in the forefoot precipitated by walking. More observant patients also report a more cold foot at night, ipsilaterally. Prognostically, claudication of the foot, as uncommon as it may be, indicates severe and diffuse atherosclerotic disease that frequently progresses to ischemic pain at rest. The posterior tibial pulse is virtually always absent (8–11).
Intermittent claudication is a clinical diagnosis. Usually lower extremity ischemia is caused by flow-limiting atherosclerotic plaques. Intermittent claudication is the presenting symptomatology in half of the patients with chronic lower extremity ischemia. The other one-third to half of patients with documented peripheral arterial occlusive disease are asymptomatic or silent (8). Other symptoms and physical findings indicating more severe ischemia are pain at rest, pale and cold extremity(s), ischemic ulcers, peripheral cyanosis, and gangrene (12).

Less frequently, peripheral symptoms may appear episodically as a result of an otherwise silent dissection of the aorta (4). Coarctation of the aorta, thoracic, or abdominal, is another cause of intermittent claudication (4, 13). Episodic claudication can also be caused by distal embolization of a mural thrombus from the left cardiac ventricle or the left atrium, and less commonly from a left atrial or left ventricular myxoma. Because of its many clinical presentations cardiac myxoma has been described as the great simulator (14). The importance of atrial fibrillation as a cause of embolism is well known (15). Increasingly, recognized sources of emboli utilizing trans esophageal echocardiography are left atrial thrombi in patients with large left atria, atrial septal aneurysms, or fibrillating atria. Embolization from the heart can precipitate a dramatic symptomatology. Claudication can be a result of an aortic aneurysm or from an arterial aneurysm situated proximally to the site of the symptoms. An aneurysmal dilatation (16) or a significant ectasia can cause hemodynamically important limitation of blood flow and be the source of distal emboli as well. The prevalence of abdominal aortic aneurysms in older men varies from 0.4 to 5.4%. In carotid artery disease the prevalence of abdominal aortic aneurysms can be as high as 25.7% (17). Atherosclerosis can be a generalized disease.

The symptoms of claudication is a result of LEAD confirmed by ABIs or duplex scanning can be classified on a scale of I–IV, a grading classification of the Canadian Heart Association that parallels that of angina pectoris.

**Claudication, Class I** is hemodynamically significant LEAD diagnosed, either by physical examination, by arterial flow studies, or by ankle brachial indices but without symptoms.

**Claudication, Class II** is symptomatology precipitated by moderate exertion, e.g., walking fast or for a long distance or uphill and relieved by rest, usually standing.

**Claudication, Class III** is characterized by symptoms precipitated by walking on a straight level and for a short distance, the equivalent of one to two city blocks, approximately 50–100 m.

**Claudication, Class IV** is ischemic pain of one or both lower extremities occurring even at rest.
Many patients with LEAD may deny the specific symptomology of claudication, but tend to walk very slowly even on a straight level. Limb ischemia can be significant as evidenced by physical findings of diminished pulses, atrophic skin changes, elevation blanching, dependent rubor, and delayed venous filling time. Yet, it can be painless, a condition pathophysiologically analogous to silent myocardial ischemia. Silent limb ischemia and silent myocardial ischemia can frequently co-exist with a higher prevalence in elderly men and women.

In 1962, the widely used WHO/Rose questionnaire (Table 1) on intermittent claudication was developed for use in epidemiological surveys. However, several population studies have shown that it is only moderately sensitive (60 to 68%), although highly specific (90 to 100%). Reasons for the moderate if not poor sensitivity and high specificity were determined following its application to 586 claudicants and to 61 subjects with other causes of leg pain. The results showed two important findings: (1) over half of the false negatives were produced by one question alone, and (2) only three questions were required to maintain the specificity of the questionnaire. This knowledge, in conjunction with the pretesting of additional questions, enabled a new questionnaire to be constructed, the Edinburgh Claudication Questionnaire (Table 2). This questionnaire was tested on 300 subjects aged over 55 years attending their general practitioner, and found to be 91.3% (95% CI 88.1 to 94.5%) sensitive and 99.3% (95%CI 98.9 to 100%) specific in comparison to the diagnosis of intermittent claudication made by a physician. The repeatability of the questionnaire after six months was excellent ($\kappa = 0.76, p < 0.001$) (18).

The physician taking the history should bear in mind, as he unravels his detective work, the various risk factors and disease entities that predispose to or aggravate LEAD. Common risk factors for peripheral arterial disease are cigarette smoking, diabetes mellitus, hypertension, hyperlipidemia (particularly hypertriglyceridemia), aging, sedentary life, and obesity. Less commonly one may detect a history of gout (with hyperuricemia), homocysteinemia high sensitivity C-reactive protein, and thrombophilic states as predisposing factors for claudication. A hypertensive patient, who has none of the mentioned risk factors and complains of claudication, may have an abdominal aortic aneurysm (16). The risk factors for LEAD have been well documented in the literature (16,19–32). Among some less known risk factors for intermittent claudication include an elevated hematocrit (2), hostile personality (25), and a decreased forced vital capacity (28). The best single discriminator for LEAD is a decreased or absent posterior tibial pulse (33).
Chapter 1 / Claudication

Table 1
The WHO/Rose Questionnaire on Intermittent Claudication

| (a) Do you get a pain in either leg on walking? | 1. □ Yes 2. □ No |
| (b) Does this pain ever begin when you are standing still or sitting? | 1. □ Yes 2. □ No |
| (c) Do you get this pain in your calf (or calves)? | 1. □ Yes 2. □ No |
| (d) Do you get it when you walk uphill or hurry? | 1. □ Yes 2. □ No |
| (e) Do you get it when you walk at an ordinary pace on the level? | 1. □ Yes 2. □ No |
| (f) Does the pain ever disappear while you are still walking? | 1. □ Yes 2. □ No |
| (g) What do you do if you get it when you are walking? | 1. Stop 2. Slow down 3. Continue at same pace |
| (h) What happens to it if you stand still? | 1. Usually continues more than 10 minutes 2. Usually disappears in 10 minutes or less |

Definition of positive classification requires all of the following responses: “Yes” to (a) and (d); “No” to (b) and (f); “stop” or “slow down” to (g); and “usually disappears in 10 minutes or less” to (h). Grade 1 = “no” to (e) and Grade 2 = “yes” to (e) (18).

How prevalent is intermittent claudication? Intermittent claudication is present in about 4.5% of individuals over 60 years of age, compared with 2% of patients under 60 years of age (34,35). The odds ratio for claudication in men is three times higher than in women. Diabetic patients are at five times greater risk than nondiabetic individuals. Six percent of men and 3% of women between the ages of 55–74 years have claudication (36). In the diabetic patient, peripheral arteriosclerosis is 11 to 40 times higher than in the nondiabetics (36). Diabetic men with intermittent claudication have double the risk for stroke. Congestive heart failure may be three times higher when both conditions co-exist, diabetics and claudication, compared with either alone. In LEAD gangrene among diabetic and nondiabetic patients was found to be 31% and 5%, respectively (37). In the Framingham (Massachusetts) Heart Study (28), 5209 men and women aged 35–94 years were followed for cardiovascular events. For men 35–54 years old, the prevalence of peripheral arterial disease was 7.4%; for women it was 8.2%. In the ensuing two decades, the prevalence for men was 12.5% for the sixth decade of life and 11.6% for the seventh decade, whereas for women it was 14.4% and 9.4%, respectively. In the age group 75–94 years, the prevalence decreased in men to 7.1% and 5.0% in women (28). Smoking, more than any other risk
Table 2
The Edinburgh Claudication Questionnaire

(1) Do you get a pain or discomfort in your leg(s)?
   Yes ☐
   No ☐
   I am able to walk ☐

If you answered “yes” to question (1) - please answer the following questions. Otherwise you need not continue.

(2) Does this pain ever begin when you are standing still or sitting?
   ☐ Yes ☐ No

(3) Do you get it if you walk uphill or hurry?
   ☐ Yes ☐ No

(4) Do you get it when you walk at an ordinary pace on the level?
   ☐ Yes ☐ No

(5) What happens to it if you stand still?
   Usually continues more than 10 minutes ☐
   Usually disappears in 10 minutes or less ☐

(6) Where do you get this pain or discomfort? Mark the spaces(s) with “x” on the diagram below

Front

Back

Definition of positive classification requires all of the following responses: “Yes” to (1), “No” to (2), “Yes” to (4). If these criteria are fulfilled, a definite claudicant is one who indicates pain in the calf, regardless of whether pain is also marked in other sites; a diagnosis of atypical claudication is made if pain is indicated in the thigh or buttock, in the absence of any calf pain. Subjects should not be considered to have claudication if pain is indicated in the hamstrings, feet, shins, joints, or appears to radiate, in the absence of any pain in the calf (18).

factor, can accelerate peripheral arterial disease and increase its severity (30). The physician, as in all disease entities, should expand in a detailed fashion into all of the patient's past and present health aspects, family history, occupational history, detailed past medical history, operations, and medications.
A large percentage of claudicants (more than 65%) suffer from severe coronary artery disease, silent or symptomatic (38-42). A truly investigative approach should be taken, in order to detect in the history, or in the symptomatology or in the patient's habits, clues for coronary artery disease. A patient may have significant coronary artery disease and LEAD as well, but may not experience effort angina because claudication may stop the patient first. In a study of 25 patients (42) with intermittent claudication, eight were found to also have carotid artery obstruction. It is interesting to note here that in 1914 Ramsey Hunt termed cerebral intermittent claudication the brain ischemia resulting from partial carotid artery occlusion (43,44). If peripheral arterial disease co-exists with carotid disease, the probability of the same LEAD having coronary artery disease as well is 85%. Three-hundred-twelve patients with LEAD were followed for 8- to 11- years (45). Sixty-nine percent died during the follow-up and 68% of the deaths were cardiac. The 5-year mortality of claudicants is 29%. In a Japanese study (46), 30% of claudicants died within 5 years and 60% of them died from cardiac or cerebrovascular disease. In claudicants, by far, the leading cause of death is cardiac.

Within 5 years from the onset of claudication, 55% of all patients will experience an improvement of their symptomatology or their symptoms will stabilize. In 14% of claudicants the ischemic process will progress. The amputation rate is 4% in 5 years. More than 80% of patients avoid ischemic complications or amputation for 5 or more years. Up to 15% of those who continue to smoke will undergo amputation within 5 years. Diabetics who smoke cigarettes have an amputation rate of about 25% within 9 years (47-49). In a landmark study by Criqui et al. (50), patients with LEAD were followed for 10 years; 62% of men and 33.3% of women died during the follow-up, as compared with 16.9% of men and 11.6% of women without peripheral arterial disease (50). Today, with our powerful therapeutic armamentarium ranging from regional thrombolysis, angiogenesis, drug eluting stents, balloon angioplasty directional and/or rotational atherectomy, and other endovascular strategies or bypass surgery, amputation should be preventable. Sadly, it is not.

CLAUDICATION IN THE ELDERLY

In the elderly, the symptoms of pain, pressure, or tightness, may be modified and more ill defined; actually they may be minimal to absent. Similarly, asymptomatic coronary heart disease with silent myocardial infarction and silent ischemia is more prevalent in the elderly. Epidemiologic studies estimate the prevalence of claudication to be as high as 10%
in patients between 65 and 70 years of age, up from 4.5% for the age group 60–64 years of age (46). The true prevalence of significant LEAD may be much higher as a result of underreporting of the specific symptomatology of claudication by the elderly. In a study of more than 500 patients older than 70 years of age, there was a much higher prevalence of intermittent claudication than in younger patients (48). The evaluation of the elderly for LEAD should rely more on meticulous physical examination and other objective data and less on the patient’s complaints. Peripheral and coronary artery disease can co-exist more frequently and more silently in the elderly. The physician is challenged to identify patients at risk for gangrene, which is more prevalent in older patients, even though ischemic symptoms may be unimpressive or lacking. A detailed physical examination of the cardiovascular system in order to detect signs of peripheral ischemia should be an integral part of the physical examination of individuals over the age of 60 years. Today’s medicine, in addition to an ever improving transcatheter therapeutic technologies, possesses risk factor modification methods to render gangrene and amputation preventable. Gangrene and amputation should be considered as a defeat for the physician(s) who have cared for the patient. The number of amputations should start declining in patients with LEAD. This has been the trend for the number of myocardial infarctions annually in the United States, downward for the past three decades, mainly as a result of aggressive risk factors modification and other therapeutic interventions.

Claudication is a clinical, easy to make diagnosis. Claudication of the upper extremities, although much less frequent than that of the lower extremities, is also a clinical diagnosis. The extremities should be examined carefully. Examination of the peripheral arterial system should include an evaluation of the volume and character of the arterial pulses of the carotids and of the arteries of the upper extremities: the subclavian, the brachial, the radial, and the ulnar. Physical examination should definitely encompass the abdominal aorta for abnormal pulsations, ectasias and/or bruits, and the arteries of the lower extremities: femoral, popliteal, dorsalis pedis, and posterior tibialis. The pulse volume can be graded on a scale of 0 to 4. In addition to palpation, physical examination of the peripheral arterial system should include auscultation over the carotids, auscultation over the subclavian arteries above, and below the mid-clavicular area. A bruit over the subclavian artery and disappearance of the radial pulse with compression of the subclavian artery is evidence for subclavian syndrome. On occasion, a bruit may be heard by auscultation deep in the axilla. The bruit, a composite of low frequency sounds, is better appreciated when the examiner is using the bell of the stethoscope.
Auscultation for abdominal and femoral bruises is a must in evaluating any patient.

The clinician should grade the pallor and check for elevation blanching by raising the lower extremity 30–40 degrees above the horizontal level. The examiner should press with his or her index finger to occlude capillary inflow and then, time in seconds, the return of color. Color return time of 15–20 seconds indicates moderate ischemia (50). In severe ischemia, it takes more than 40 seconds for the baseline color to return. The venous filling time (in seconds) is another useful bedside index and should be measured. Elevation and dependency tests give a rough but reliable estimate of the degree of ischemia of the lower extremities. If more objective data are desired the systolic blood pressure index can be determined (51). Ankle-to-arm systolic pressure ratios below 0.97 and 0.90 were found to be a highly probable sign of LEAD (51). The fall in ankle systolic pressure after exercise may serve as an objective indicator of the severity of hemodynamically important LEAD. This simple evaluation can become a standard test; a fall in the leg pressure that occurs after 1 minute of walk at a speed of 4 mph at 10% elevation (52) indicates hemodynamically significant LEAD. In a study of 150 patients with peripheral arterial disease and claudication the ankle mean pressure was 58 mmHg; in patients with rest pain it was 33 mmHg and in patients with chronic ulceration, it was 20 mmHg (53,54).

With electromagnetic flowmetry and Doppler ultrasound (55) it is possible to confirm and quantitate patient complaints, follow the disease progression, and document improvement following pharmacotherapy, exercise therapy, percutaneous endovascular interventions or arterial reconstructive interventions. Limb scintigraphy with thallium-201 presents advantages and great potential for clinical applications (56).

Peripheral arterial occlusion can be the initial manifestation of cardiac or systemic disease. At times, patients with chronic stable claudication may experience abrupt shortening of the distance at which claudication occurs, and this may be the only symptomatic evidence of an acute arterial occlusion either by embolization of by thrombus formation on a pre-existing arterial stenosis. The situation is not chronic and stable any more, but acute and unstable. As ischemia becomes more severe, the patient with chronic peripheral arterial disease develops ischemic pain at rest. The pathophysiologic mechanisms and the clinical presentation parallel the evolution of chronic stable angina pectoris to unstable angina and acute coronary syndromes.

When limb ischemia becomes more severe, rest pain appears usually in the toes or the foot and can become nocturnal. The patient with rest pain at night finds some relief by sitting up on the side of the bed with
the feet in a dependent position. A reverse Trendelenburg position can be helpful. Ischemic ulceration, usually but not always, a result of trauma to the ischemic limb can be a cause of severe pain. The ischemic ulcer has a discrete edge covered with eschar and its base is pale.

In the young, two congenital lesions are noteworthy: (1) entrapment of the popliteal artery, causing calf claudication with walking but not with running, and (2) adventitial cystic disease of the popliteal or femoral arteries (62–65). Both warrant surgical repair.

Differential Diagnosis

Epidemiologically, claudication caused by peripheral arterial disease affects primarily patients over the age of 40 years. Buerger's disease or thromboangitis obliterans is primarily a disease of younger men. It was first described by Leo Buerger in 1908 (57–59). Most patients with Buerger's disease are smokers. Smokers may present with peripheral vasospasm, cold fingers and toes. Cyanosis can be observed upon exposure to cold. Smokers, both men and women, (61) with peripheral vasospasm (Raynaud's phenomenon) frequently have coronary spasm with chest pain or other angina equivalent symptoms at rest, particularly in the morning hours. When observed in a hospital setting, an electrocardiogram (ECG) should be taken during chest pain; the ECG may show ST elevation and much less frequently ST segment depression. The ECG is normal between the attacks of coronary spasm. Men with Buerger's disease may also have a history of phlebitis, usually superficial. They typically seek medical attention for claudication of the arch or the calf. Physical examination is remarkable for diminished pulses of the small arteries. Frequently, the upper extremity is also involved. The etiology of Buerger's disease may relate to an autoimmune process (58,60) rather than atherosclerosis.

The differential diagnosis of claudication should also include occupational diseases with recurrent blunt trauma. Claudication can be iatrogenic in etiology, particularly among patients who suffer from migraine attacks and consume high doses of ergot containing preparations. Ergotamine derivatives can cause coronary spasm, peripheral vasospasm, and claudication (4). Arteritis associated with collagen vascular disorders, temporal arteritis (4), and Takayasu's disease (70,71) can also be causes of claudication. Infrequently, claudication can be the presenting symptom of congenital arterial narrowing or of fibromuscular hyperplasia (4). Popliteal artery aneurysm, almost always related to atherosclerosis, is another surgical disease that causes claudication, rest pain, skin ischemia, and gangrene. Ultrasonography is the most useful
diagnostic tool (66) for popliteal aneurysm. Thoracic outlet compression may be symptomatic or may present with intermittent ischemic symptoms of the arm and forearm, peripheral vasospasm and at times severe ischemia of the hand and of the fingers depending on the site of the arterial occlusion (67–69). The cause of the distal ischemia in the thoracic outlet syndrome is distal embolization from compression of the subclavian artery. Anatomically, the thoracic outlet syndrome is caused by compression of the subclavian artery by a cervical rib or by an abnormal first rib that can be palpated in the supraclavicular fossa.

Occlusive arterial disease of the upper extremity, a rare entity, can cause arm claudication and may be associated with other ischemic symptoms. Ischemia of the upper extremity should be of particular interest to the cardiologist in view of the increasing utilization of the internal mammary arteries as coronary arterial grafts.

**PSEUDOCLAUDICATION**

Approximately half a century after Charcot described ischemic pain in the lower extremities, Dejerine in 1911 described a syndrome he called *intermittent claudication of the spinal cord* (72–74). This neurogenic intermittent claudication is known as pseudoclaudication. In 1954, Verbiest reported in detail symptoms caused by the developmental narrowing of the lumbar vertebral canal (72). Later, a number of cases of neurospinal compression were reported (73–75). Pseudoclaudication or neurogenic claudication is bilateral or unilateral and consists of discomfort or pain in the buttocks, thighs, legs, and calves precipitated by walking uphill, on a straight level, or worse by walking downhill. Standing can also cause symptoms in neurogenic claudication. The discomfort or weakness or frank pain is relieved by sitting or by lying down (76). Bending forward or adopting a flexed position can alleviate the symptoms of neurogenic claudication (75). Leaning against a wall or bending forward can also improve the symptoms of pseudoclaudication. Prolonged standing has been associated with severe discomfort in neurogenic claudication, but not in vascular claudication. Walking downhill can precipitate pain in neurogenic claudication, but not in vascular claudication (77). In advanced cases of neurogenic claudication there is pain both in the standing and in the supine positions. Physical examination of the peripheral pulses is usually normal. By contrast in vascular claudication, the peripheral pulses are diminished or absent, there are bruits and physical findings of peripheral ischemia. The electromyogram is abnormal in neurogenic claudication and normal in vascular claudication. Patients with neurogenic claudication often complain of leg weak-
ness and may actually fall down (76). This weakness is best evoked by attempts to walk on the heels or on the toes. Any position that tends to cause the canal to become narrower will aggravate pseudoclaudication. Bending forward opens up the canal and relieves the symptoms (76,77). A lordotic position hyperextends the spine and produces radicular pain. Probably the best finding on physical examination is to provoke the symptoms by having the patient stand up or walk for a few minutes and notice if they adopt a flexed position. Standing up for several minutes will cause the patient to bend forward and lean on the nearest back support. Continued walking for several minutes induces leg distress. In about 43% of patients with neurogenic claudication, the deep tendon reflexes are reduced at the ankle level and in 18% of patients there is a reduction at the knee level. In neurogenic claudication rechecking the deep tendon reflexes of the lower extremities after walking for several minutes or standing for several minutes will show a reduction as compared with sitting (76).

Neurogenic claudication and vascular claudication are not mutually exclusive and can co-exist in about 9% of patients with either diagnosis. Vascular changes in the lower extremities may co-exist, because of the older age group in which vascular and neurogenic claudication occur. In one study (72), up to 42% of patients with pseudocludication were found to have absent pedal pulses. The etiology of neurogenic claudication is lumbar stenosis (78,79). In the nineteenth century, medical reports were published describing a narrow spinal canal syndrome in achondroplastic dwarfs. Other rare congenital causes of pseudocludication are Morquio’s syndrome dysplasia, hypochondroplasia, and Down’s syndrome. Apart from discogenic disease acquired causes are Paget’s disease, systemic amyloidosis (80), hypertrophied ligamentum flavum, and calcium pyrophosphate crystal deposition (81). Syphilitic arteritis of the cord (Dejerius syndrome) in years past and the Foix Alajouanine syndrome are two very rare causes of neurogenic intermittent claudication (90). Degenerative joint and ligament hypertrophy is the leading cause of lumbar stenosis. The ligamentum flavum which normally does not exceed 4 mm in thickness may measure 7–8 mm. Spinal stenosis, which is the anatomic cause of neurogenic claudication, can be either congenital with a congenitally narrow spinal canal or more frequently acquired. The diameter of the canal is narrowed by the hypertrophic skeletal changes. In the middle-aged or the elderly patient who can have both neurogenic and vascular complications, the correct diagnosis, because of the variance in the presenting symptomatology and physical signs, has to be confirmed by basic laboratory evaluation. The plain radiographs of
the lumbar spine show dense bony structures and the presence of degenerative disease. Further evaluation consists of co-axial tomography and preterably magnetic resonance imaging (MRI) \((82,83)\). Myelography is an important test \((82)\), but is less frequently indicated even when laminectomy is being considered by the consulting surgeon. Computed tomography and MRI are complementary tests for the preoperative elevation \((82,83)\). Plain X-ray films are of far less value in evaluating the lumbar spine; they are more useful for the cervical spine. Pseudoclaudication, which was not widely appreciated in the past \((84,85)\), is now part of the differential diagnosis of intermittent claudication.

Wilson \((87)\) divided patients with this condition into two groups: (1) In the larger group, symptoms occurred during any activity or position involving extension of the lumbar spine that he termed postural cauda equina claudication, and (2) a smaller group of patients, with symptoms of the affected extremities after exercise that he described as ischemic cauda equina claudication.

According to Blau et al. \((88,89)\), the vascular factor is more important. In exercised animals, vessels inside the canal are dilated and if the canal is narrow increased blood supply is prevented, thus leading to ischemia of the cord and the nerve roots. However, this explanation is not shared by others \((90)\). It does not explain why neurogenic claudication occurs in the lordotic position at rest. Pseudoclaudication can be caused by other orthopedic conditions of the hips, knees, and other joints.

**VASOSPASTIC CLAUDICATION**

Vasospasm occurring in the digital circulation is also known as Raynaud’s phenomenon. Raynaud’s phenomenon is caused by abnormal vascular reactivity precipitated by exposure to cold or by emotional stress. Peripheral vasospasm was first described by the French clinician, Maurice Raynaud in 1862 \((91)\). Usually in peripheral vasospasm there are three phases: first, the main arterial branches of the digits constrict causing a marked reduction of the blood flow to the tissues; the skin of the digits becomes pale and the patient complains of numbness, pain or paresthesias. The second phase is the cyanotic phase; the digits appear blue, purple or even black in extreme cases. The cyanotic phase continues until the blood flow is re-established as the arterial branches open up again. The cyanotic color is caused by deoxygenated hemoglobin in the post arteriolar capillaries. The third and final phase, is the post-ischemic hyperemia; the increased blood flow to the skin gives a blushed coloration. Many years ago, Allen and Brown \((92)\) described the minimal requisites for the diagnosis of Raynaud’s disease or syndrome.
It should be noted that several patients do not exhibit the classical color changes. They may complain only of cold and numb fingers or toes; thumbs are usually spared.

As with claudication caused by atherosclerosis, Raynaud's phenomenon is a clinical diagnosis. No practical laboratory test exists to diagnose peripheral vasospasm. The physician should elicit the symptoms by taking a detailed history. Color charts can also be used. The patient is asked to identify the color of the skin during a typical episode by choosing colors from actual photographs of Raynaud's attacks. Patients with peripheral vasospasm are classified as having primary or secondary Raynaud's phenomenon. In primary Raynaud's phenomenon, the patient has symmetrical attacks in the absence of digital pitting, ulceration, or gangrene. The nailfold capillaries are normal and screening tests for connective tissue disease, like erythrocyte sedimentation rate, antinuclear antibodies, immunoglobulin electrophoresis, etc. are normal. The prognosis of primary vasospasm is usually benign, provided the appropriate protective measures from direct exposure to cold are taken. The situation is different in secondary Raynaud's phenomenon. The most common cause of secondary Raynaud's phenomenon is an underlying collagen vascular disease. Several conditions are associated with Raynaud's (91-97). CREST consists of Calcinosis, Raynaud's phenomenon, Esophageal changes, Sclerodatly, and Telangiectasias. Raynaud's phenomenon may precede a connective tissue disorder for years (94). The prognosis in secondary Raynaud's phenomenon depends on the underlying connective tissue disease. The most common cause of secondary Raynaud's phenomenon is scleroderma. Approximately 90% of patients with scleroderma have Raynaud's phenomenon and it can be the first clinical expression of the disease. Peripheral vasospasm has also been associated with systemic lupus erythematosus in about 30 to 40% of patients. Approximately 20% of patients with dermatomyositis describe Raynaud's phenomenon. An association of Raynaud's phenomenon with Sjogren's syndrome has been described. The existence of Raynaud's phenomenon in collagen vascular diseases may adversely influence their prognosis. In lupus erythematosus, for example, the presence of Raynaud's symptomatology has been associated with pulmonary hypertension. Any kind of vasculitis or vascular injury can be subsequently associated with Raynaud's phenomenon. Raynaud's symptoms in patients with giant cell arteritis (polyarteritis nodosa) can evolve to cutaneous gangrene (93-96).

Hyperviscosity states like cryoglobulinemia have been associated with Raynaud's phenomenon: from reversible vasospasm to frank pur-
pura. Certain pharmacologic agents can cause or aggravate Raynaud’s phenomenon. The most notorious for that toxicant is nicotine. Smoking can cause both coronary and peripheral vasoconstriction and has been associated with coronary spasm in men and women (61). Cocaine is another cause of both coronary and peripheral vasospasm. Ergotamine derivatives can also produce both coronary and peripheral vasospasm. Raynaud’s phenomenon occurs in about 30% of cases following chemotherapy with Vinca alkaloids and bleomycin. β-Blockers have also been reported to cause Raynaud’s phenomenon, but very rarely as have certain sympathomimetic agents used as over-the-counter cold preparations.

The pathophysiology of peripheral vasospasm is unclear. The author of this chapter would like to propose the hypothesis that it is a result of endothelial dysfunction. In the late 1920s, Sir Thomas Lewis hypothesized that Raynaud’s disease is a result of a local vascular fault (99), but after all these years, the fault has not been adequately defined. An attractive hypothesis is an imbalance of the endothelial function, involving endothelin (100–106). Endothelin (107) that is produced by the endothelial cells is a potent vasoconstrictor, whereas nitric oxide, an endothelium-derived relaxing factor (EDRF), is a potent vasodilator (104). Prostacycline and prostaglandins also produced by the endothelial cells normally counteract thromboxene, which is a potent platelet derived-vasoconstrictor. A parallel mechanism leading to peripheral vasospasm can be increased sensitivity to α-adenoceptor agonists (102).

Individuals with primary Raynaud’s phenomenon are more likely to respond well to therapy than individuals with secondary Raynaud’s phenomenon. Many patients with mild Raynaud’s phenomenon are minimally disabled, but often frightened by the cutaneous color changes. The majority of patients do not need pharmacologic intervention. Protection of the upper and lower extremities from direct exposure to cold is a practical approach. Although Raynaud’s phenomenon is more severe during the winter, recurrent attacks do occur in any season upon a sudden cold stimulus. Often a rapidly changing temperature is more likely to precipitate peripheral vasospasm than exposure to a lower, but constant temperature. A central body chill is as likely to provoke an attack of Raynaud’s as is a direct cold exposure to the hands. In a number of patients, emotional stress is a major precipitating factor. All known aggravating factors should be avoided and by all means smoking. Ketanserin has been tried in the treatment of Raynaud’s phenomenon occurring with scleroderma (109).
Calcium channel blockers (CCBs) are the most widely used pharmacologic agents for the treatment of peripheral vasospasm (110–112). Sympatholytic agents have also been used in the treatment of Raynaud's phenomenon. Topical nitroglycerin ointment can be applied with a nocturnal nitrate-free interval to avoid nitrate tolerance.

The treatment of claudication due to LEAD is multifaceted: aggressive risk factor modification, regression therapy of the atheromas, pharmacotherapy, exercise therapy, endovascular transcatheter therapeutic interventions, angiogenesis, and vascular graft procedures.

In any patient with documented LEAD, risk assessment for cerebrovascular, and coronary heart disease of utmost importance.

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