Essentials in the Diagnosis and Management of Peripheral Arterial Disease

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Peripheral arterial disease results from the atherosclerotic involvement of arteries of the upper and lower extremities as well as that of the renal and carotid arteries. In view of the importance of its early recognition we have summarized the clinical manifestations, diagnostic procedures and tests, and the current medical and surgical management including percutaneous revascularization. Algorithms that guide in the diagnostic steps and management decisions have been presented.

Key words: Peripheroarterial disease, Antebrachial index, Atherosclerosis, Coronary artery disease, Diabetes, Hypertension, Smoking, Dyslipidemia, Arteriography.

Peripheral artery disease (PAD) is a term that refers to atherosclerosis when it obstructs the blood supply to the lower and upper extremities. It is a condition similar to coronary artery disease and carotid artery disease. In PAD, fatty deposits build up in the inner linings of the arterial walls and reduce the blood flow. Arteries in the legs, arms, kidneys and neck are the most commonly affected by PAD. People with PAD often have concomitant coronary artery disease (CAD) and cerebrovascular disease and are at higher risk for myocardial infarction (MI) and cerebrovascular accidents (CVA). The clinical manifestations of acute arterial occlusion that result from detachment and embolization of atheromatous debris is not included in this review.

Epidemiology

PAD occurs in more than 70 % of the patients over 70 years of age and its incidence increases with age. Risk factors for the development of PAD are similar to the risk factors for CAD and cerebrovascular disease: cigarette smoking, diabetes, hypercholesterolemia and arterial hypertension. In fact, patients with diabetes and PAD have a poorer outcome than non diabetics(1). Life expectancy of the patients with PAD is shortened. Patients with PAD usually die due to MI or CVA given its close association with CAD and cerebrovascular disease. The mortality from PAD is higher than that of prostate carcinoma in men and breast carcinoma in women.

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Clinical Manifestations

In its early stages, a common symptom is cramping or fatigue in the lower extremities that occurs during exertion and relieved with rest. This is called "intermittent claudication". At least 10 % of those over 70 years of age have intermittent claudication and it is a growing problem due to the increasingly aged population in the United States and Puerto Rico. However, only 50 % of the patients with PAD have intermittent claudication. The severity of symptoms will vary according to many factors such as the presence of collateral circulation, amount or severity of stenosis and vigor of exercise. Pain will be localized according to the level of occlusion. It may be at the buttock, thigh, leg, foot or in combination. The muscles of the calf are the most commonly affected. Cramping in the upper third if the calf is usually due to superficial femoral artery stenosis whereas cramping in the lower third is due to popliteal artery stenosis. Thigh claudication is usually due to occlusion in the common femoral artery and foot claudication due to occlusion of the tibial and peroneal vessels. Isolated foot claudication is rare, but is commonly seen with thromboangiitis obliterans (Buergers's disease). Buttock and hip claudication is usually due to Leriche's syndrome or aortoiliac disease. If bilateral, then it is associated with impotence in men. Leriche's syndrome should be distinguished from pseudoclaudication due to spinal stenosis (which is relieved by leaning forward) and from osteoarthritis of the hip or knee joints.

In vasospastic claudication the peripheral pulses are present and no bruits are heard, however, the patients develop claudication with stress. A subcritical stenotic lesion should be suspected as the cause of these symptoms and those patients need to be carefully examined.

Progressive decrease in limb perfusion can result in ischemic rest pain. This discomfort usually occurs at night and involves the digits and the forefoot. Patients with ischemic rest pain may develop ischemic ulcers and gangrene.

Other manifestations of PAD are: numbness or tingling in the leg, foot, or toes, changes in skin color (pale, bluish, or reddish discoloration), changes in skin temperature, coolness, impotence, infection/sores that do not heal. It is important to know that some patients may have asymptomatic disease. PAD has an adverse effect on the ability to walk and in the quality of life of the patients with it.

Diagnosis

History alone can fail to detect up to 90% of the patients with PAD(2). The physical examination should focus on all the peripheral pulses. Bruits sometimes may be heard, particularly at the carotid, renal and femoral arteries. An abnormal femoral pulse has a high specificity and positive predictive value but the sensitivity is low for large vessel disease. Therefore physical examination may also be unreliable. The best single discriminator is an abnormal posterior tibial pulse. Detection of asymptomatic disease is important for identifying the patients at risk for atherosclerosis at other sites.

Noninvasive tests for the diagnosis of PAD include antebrachial index (ABI), exercise treadmill test, segmental limb pressures, segmental volume plethysmography, ultrasonography and arteriography. Algorithm 1 summarizes the diagnostic work up of patients with suspected PAD.

Antebrachial index. ABI is inexpensive and easy to perform. It is done by dividing the systolic blood pressure at the ankle (posterior tibialis artery) by the systolic blood pressure at the arm (brachial artery). Measurements may be done with a conventional sphygnomanometer or with Doppler ultrasound. ABI provides a measure of the severity of PAD. An ABI less than 0.9 has 95% sensitivity and 100 % specificity for advanced ischemia and is associated with more than 50% stenosis in one or more major vessels. An abnormal ABI also correlates with the presence of CAD and CVA (3,4). Table 1 illustrates the classification of the severity of PAD based on ABI.

If the ABI is normal but the patient is symptomatic the measurements must be done before and after exercise in a treadmill or with active pedal plantar flexion (standing up on toes). A potential source of error when measuring ABI is that calcified vessels may not be compressed normally resulting in falsely elevated Doppler signals.

Table 1. Gradation of Severity of Peripheral Arterial Disease

	Antebrachial index (ABI)
Calcified noncompressible vessel	> 1.3
Normal	1.0 – 1.3
Mild obstruction	0.9- 0.71
Moderate obstruction	0.7 – 0.40
Severe obstruction	< 0.40

An ABI between 0.40 and 0.90 is associated with claudication

Exercise treadmill test. Exercise normally decreases vascular resistance and enhances blood flow to the involved extremity. An arterial stenosis less than 70 % is not of sufficient severity to cause a systolic pressure gradient at rest. With exertion, the same lesion will produce a systolic pressure gradient that will decrease as the patient recovers. ABI measurements must be done at 1 minute intervals for 5 minutes after exertion. Exercise test is useful for the evaluation of patients with symptomatic PAD who have normal ABI. In the exercise treadmill test severe claudication is defined as inability to complete the stress test or systolic blood pressure less than 50 mmHg.

Segmental limb pressures. Once the diagnosis of PAD has been made its level and extent can be assessed using the segmental limb pressures. A 20 mmHg or greater of reduction in blood pressure is considered significant between segments in a particular leg or in comparison with the opposite leg at the same level. The proximal cuff is inflated over systolic blood pressure and is then gradually deflated to determine the systolic blood pressure heard by the Doppler at the foot. This process is repeated for the lower thigh cuff. Positioning the cuff at the thigh will reflect the aortoiliac or superficial femoral artery disease, at the calf will reflect distal superficial femoral artery or popliteal disease, at the ankle will reflect infrapopliteal disease. Normally, the lower extremities have higher blood pressure recordings than upper extremities. If the proximal (thigh) blood pressure is reduced compared with the brachial pressure (thigh brachial index, TBI) less than 1.1 there is a lesion in the aortoiliac territory. If the TBI is > 1.1 in the upper thigh and < 1.1 in the lower thigh then the lesion is in the superficial femoral artery.

In the patient with suspected upper extremity PAD a difference > 10 mmHg between brachial pressures suggest innominate, subclavian, axillary or proximal brachial artery disease.

Segmental volume plethysmography. Plethysmography is the measure of volume change in an organ or limb. It is used in conjunction with segmental limb pressures to assess the level of the obstruction. A standard volume of air is injected into pneumatic cuffs which are placed at various levels along the extremity. Volume changes in the limb segment below the cuff are translated into pulsatile pressure that is detected with a transducer. Pulse volume recordings are then displayed and its contour analyzed. Variations in the contours displayed will determine the severity of the obstruction. This technique is particularly useful for the evaluation of calcified vessels.

Ultrasonography. Is mainly used to depict anatomy, hemodynamics and lesion morphology. Examination begins at the common femoral artery moving distally to the popliteal artery. Color Doppler localizes the areas of stenosis. The main purpose of Doppler is to avoid diagnostic angiography.

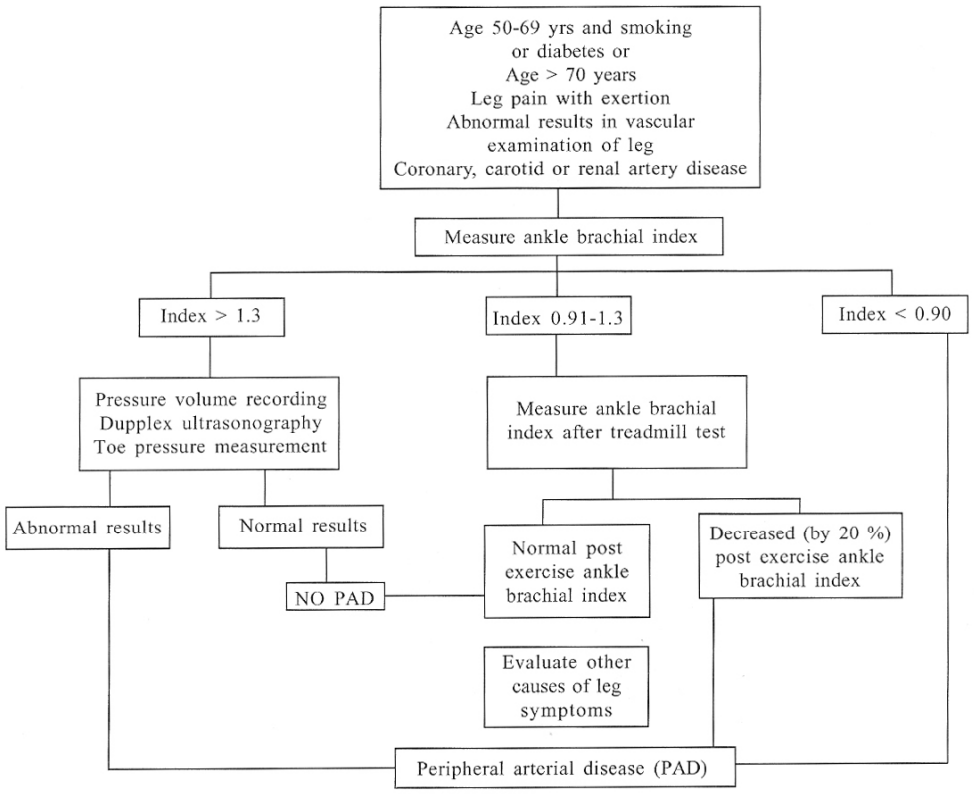
Diagnostic angiography. Angiography is reserved for determination of the exact localization of the obstruction when ultrasonography is not conclusive. Angiography is also used during percutaneous angioplasty to guide the procedure and to evaluate results.

Management

Therapeutic strategies in the management of PAD involve medical, percutaneous and/or surgical interventions. Medical therapy is usually the first line of treatment. Medical management includes: risk factor modification, exercise training for rehabilitation and pharmacologic therapy. Factors to be modified include: cigarette smoking, control of diabetes, hypertension and dyslipidemia. Smoking cessation alone lowers amputation rates and resting limb ischemia (5). Most of the patients with PAD also have CAD, therefore, it is important to adequately control diabetes and hypertension in order to reduce morbidity and mortality from MI or stroke.

There has been concern with the use of beta blockers in the patients with intermittent claudication. To date, it appears that there is no adverse effect with the use of beta

Algorithm 1. Evaluation for the diagnosis of Peripheral Arterial Disease



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blockers in these patients (6,7). The use of angiotensin converting enzyme (ACE) inhibitors has been associated with a reduced mortality in patients without documented CAD but at risk for developing it due to diabetes mellitus or PAD(8). Lipid lowering therapy reduces PAD progression (9,10). Current guidelines for the management of hypercholesterolemia recommend the use of a statin to lower LDL cholesterol below 100 mg/dl in those patients with diabetes, CAD and PAD. Current studies suggest that LDL cholesterol goals will be lowered below 70 mg/dl in the near future.

Exercise rehabilitation reduces symptoms and increases distance to onset of claudication. Exercise sessions must be supervised and must last more than 30 minutes with at least three sessions per week for six months. Exercise improves walking time similar to both angioplasty and antiplatelet therapy(11). The mechanism by which exercise benefits patients with PAD is multiple. Exercise improves endothelial dysfunction by increasing nitric oxide synthase and prostacyclin (12), reduces inflammation and reduces free radicals generation produced by muscle ischemia(13), stimulates vascular angiogenesis(14), improves muscle metabolism(15) and decreases red cell aggregation(16).

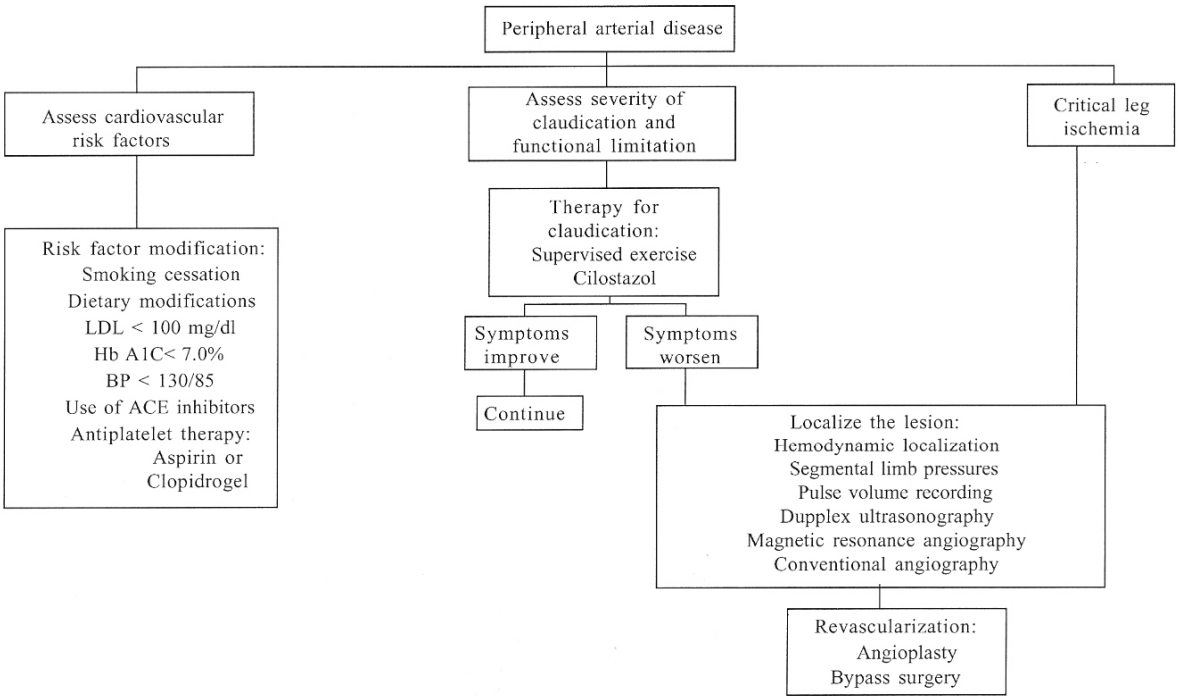
Pharmacologic therapy reduces symptoms and provides relief. Antiplatelet agents include aspirin, dipyridamole, ticlopidine and clopidrogel. Other pharmacologic agents to be discussed are cilostazol and pentoxiphylline.

Aspirin reduces the risk for MI, stroke and vascular death. It also decreases the need for peripheral artery surgery but not the development of claudication (17,18). It is considered the drug of choice due to its important effects in the secondary prevention of associated CAD and lower cost when compared with other antiplatelet agents. The addition of dipyridamole to aspirin increases the pain free walking distance. Ticlopidine has been associated to significant hematologic secondary effects and is therefore not recommended. The use of clopidrogel confers a modest advantage over aspirin (19).

Cilostazol is a phosphodiesterase inhibitor that produces direct arterial vasodilatation and reduces platelet aggregation. Cilostazol may increase pain free walking distance by 50- 67 % and its benefits may be seen as early as 4 weeks. Cilostazol is contraindicated in patients with heart failure of any severity (20).

Pentoxifylline is a rheologic modifier that increases red blood cell deformability, decreases fibrinogen concentration, platelet adhesiveness and blood viscosity. It has been used for a long time for the symptomatic relief

Algorithm 2. Management of Peripheral Arterial Disease



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of claudication. Studies about the efficacy of pentoxifylline have shown conflicting results and its long term benefits are not clear.

Other therapies that have been shown to be ineffective or with nonconclusive data are: estrogen replacement, chelation therapy, vitamin E supplementation, use of vasodilators such as verapamil, antichlamydial therapy, carnitine supplementation, prostaglandin E1, prostacyclin and gluthatione. There is current research with the use of angiogenic growth factors to stimulate the development of collateral arteries. The safety and efficacy of these agents is still debated (21,22).

Current recommendations for the medical management of PAD are summarized in algorithm 2 and include:

1. Aspirin alone or in combination with dipyridamole given indefinitely. Clopidrogel may be superior to aspirin and should be considered as an alternative.
2. Risk factor modification that include diabetes, cholesterol and blood pressure control with the use of diet and medications.
3. Supervised exercise program.
4. Use of cilostazol in patients with disabling claudication, particularly when lifestyle modification alone is not effective and when revascularization cannot be offered or is declined by the patient. Pentoxifylline can be tried but is less effective than cilostazol.
5. If the symptoms worsen with medical therapy then revascularization either percutaneous or surgical should be considered.

Revascularization may be performed percutaneously with angioplasty or may be done with bypass surgery. Percutaneous angioplasty is the therapy of choice and must be considered before surgical intervention. Often a stent is placed to keep the artery open. Surgical therapy is performed particularly for aortoiliac and femoral disease or when a long portion of the artery is affected. A vein from other part of the body or a synthetic blood vessel is used to detour blood around the blocked segment. Surgery may be uncomfortable for the patients and requires longer recovery than angioplasty but its results are good and long lasting.

Conclusion

Peripheral arterial disease goes often unrecognized, underdiagnosed and undertreated. It is associated to coronary and cerebrovascular disease and risk factors for CAD are also associated to PAD. Therapeutic strategies aimed at CAD are also useful for the management of PAD. It is important to recognize PAD in order to avoid the increasingly high morbidity and mortality associated to it. In this review we have summarized the diagnostic modalities and treatment strategies for the managemet of PAD.

Resumen

La enfermedad periferoarterial oclusiva se produce como consecuencia de la acumulación de placas ateroscleróticas en las extremidaes superiores e inferiores así como también en las carótidas y en las arterias renales. La enfermedad periferoarterial oclusiva está asociada a la enfermedad coronariana y cerebrovascular y produce una morbilidad y mortalidad significativa. Es importante su detección a tiempo. Este artículo de revisión provee una guía para el diagnóstico y manejo adecuado de la enfermedad periferoarterial oclusiva.

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