Matters of the Heart

A Review of Peripheral Arterial Disease

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In this article:

1. How does peripheral arterial disease develop?
2. How can its diagnosis be confirmed?
3. What are the treatment options?

Peripheral arterial disease (PAD) generally affects 12% of the population over 60.[1] Although often encountered by primary care physicians, it is still an orphan pathology, often characterized by a one-time evaluation and frequently in conjunction with revascularization.

How prevalent is PAD?

The incidence of PAD increases sharply with age; approximately 20% of patients 70 to 79 are affected, as are a little more than 60% of patients over 85.[2] The risk profile of PAD patients is similar to that of patients who have other forms of atheroscelorsis. Risk factors include hypertension, hypercholesterolemia, cigarette smoking, and diabetes. Males and the elderly are also at higher risk. People over 40, smokers, and people with diabetes are at significantly higher risk for PAD. Diabetes is linked specifically with a progression to acute ischemia and eventual amputation.[2] Although other PAD risk factors (hyperhomocysteinemia, lipoproteins, C-reactive proteins, and blood viscosity) have been identified, their clinical importance, especially with regards to treatment, have yet to be proven.

How does PAD develop?

Most patients with PAD go undiagnosed. Among those who are diagnosed, approximately 75% are asymptomatic. The natural development of PAD

Peripheral Arterial Disease

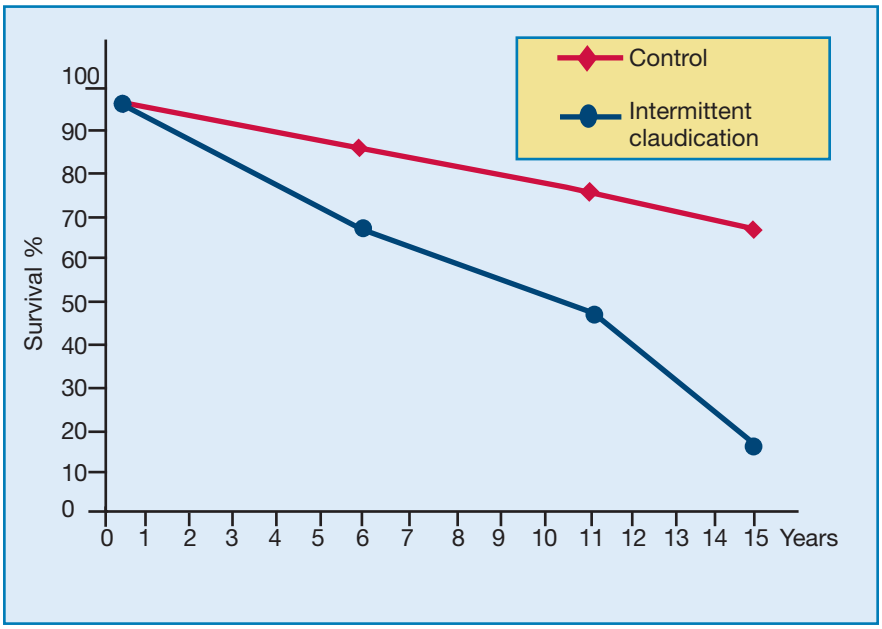

Figure 1. Prognosis of patients with peripheral arterial disease.

is fairly benign. In fact, cohort studies have proven that approximately 75% of patients experience stable or improved symptomatology, while approximately 25% experience symptomatology deterioration over a five-year period. Among this latter group of patients, 5% will require revascularization and 2% will require amputation.[3]

More importantly, since atherosclerosis is a diffused process, a significant number of patients with PAD, whether they are symptomatic or not, will be affected with heart disease and/or cerebral atherosclerosis, even though these patients are often asymptomatic. The concept of complications from systemic atherosclerosis is noteworthy because, even if patients are asymptomatic of PAD, they may still be carriers of a potentially lethal systemic disease (*i.e.*, atherosclerosis), which sharply increases the risk of cardiovascular morbidity/mortality (Figure 1). A new diagnosis of PAD is associated with a 30% mortality rate at five years, primarily due to cardiovascular causes.

Among the few patients who develop acute ischemia, the mortality risk is 20% within six months and the amputation risk is 35% during the same period.[4]

The statistics above are due to the fact that PAD is underdiagnosed and, above all, undertreated. In fact, even though patients suffering from PAD should be undertaking secondary prevention treatment for atherosclerotic disease, numerous studies prove that they are treated with antithrombotics less often and that their risk factors are not as well controlled.[5-7]

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How can PAD diagnosis be confirmed?

If the history and/or examination are consistent with PAD, a para-clinical assessment will confirm the diagnosis. The assessment includes researching risk factors (lipid assessment, glycemia), as well as investigating other sites for atherosclerosis (electrocardiogram, kidney assessment). Tests to measure the ankle/brachial index (ABI), also known as the arm-ankle index, will confirm a PAD diagnosis. The ABI provides a report of the systolic blood pressure (BP) of the lower extremities as compared to the upper extremities. The systolic BP is usually higher in the lower extremities because of gravity. The opposite occurs in PAD patients, as artery blockage lowers the BP in the afflicted extremities. An ABI of ≤ 0.9 indicates a PAD diagnosis, even in asymptomatic patients. Patients with acute ischemia usually register an ABI of < 0.5. The ABI is easily measured at the bedside, with a Doppler ultrasound blood velocity detector. It can also be measured in radiology through a Doppler examination of the lower extremity arteries.

For patients with diabetes, who often present with calcification of the distal arteries, the alternative to measuring the ABI is to monitor their BP through the big toe with a plethysmography, although the BP may be indecipherable at times because the calcified arteries are not constricting.

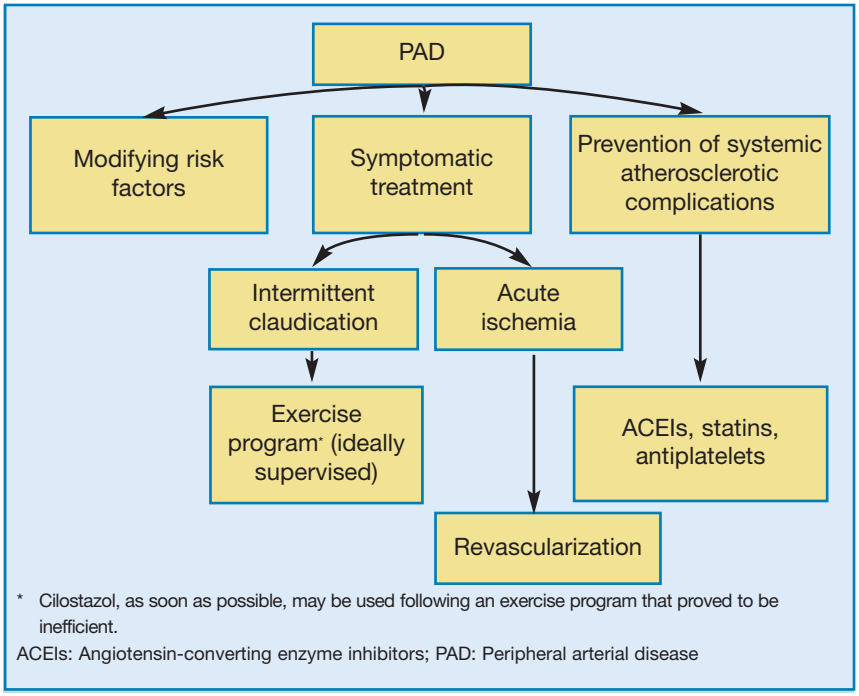

Figure 2. Overall management of PAD.

When revascularization surgery is being considered, it is necessary for the patient to undergo an arteriography. Although the surgery complications are quite low, they may be severe. Risks include iodine allergy, nephrotoxicity to contrast agents, cholesterol embolism, and exsanguination. Indications to proceed with this invasive and costly test must be solid. Angio-computed tomography scans or angio-resonance imaging are currently being used when available, particularly with patients with iodine allergies or subadjacent nephropathy.

What is the treatment?

The main purpose of PAD treatment is to prevent systemic atherosclerotic complications and to relieve the symptoms of the afflicted extremity (Figure 2).

Table 1
Fontaine classification (severity of peripheral arterial disease)

Stage	Symptom
Stage I	Asymptomatic (ABI < 0.9)
Stage II	Intermittent claudication
a	> 200 m
b	< 200 m
Stage III	Pain at rest
Stage IV	Tissular impairment (ulceration or gangrene)

ABI: Ankle/brachial index

Modifying atherosclerotic risk factors

The major objective for treating risk factors is to reduce systemic atherosclerotic complications rather than to alter the natural development of the disease in the afflicted extremity. This being said, it is interesting to note that modifying specific risk factors, such as tobacco use and dyslipidemia, directly influences the natural development of intermittent claudication.[3] Although diabetes treatment is not associated with a reduction in intermittent claudication, it is optimal to treat diabetes, as it lowers the risk of microangiopathy, specifically neuropathy, which could reduce the risk of local complications in PAD patients. All atherosclerotic risk factors for patients suffering from PAD should be treated in compliance with guidelines targeting secondary prevention values.

Pharmacologic therapy should be considered in the treatment of arterial hypertension. Angiotensin-converting enzyme inhibitors (ACEIs) are the recommended treatment for arterial hypertension, as they have proven benefits in the reduction of systemic atherosclerotic complications.[8]

Beta blockers, especially those with cardioselective activity, are not contraindicated for PAD patients in Fontaine stages I and II. Although there is little evidence to support this statement, the use of beta blockers should be limited to patients in a more advanced Fontaine stage (Table 1).

Prevention of systemic atherosclerotic complications

The preventive treatment of systemic atherosclerotic complications is essential in the management of risk factors, as the prognosis of PAD patients is tainted much more with cardiovascular morbidity/mortality than with the progressive symptomatology of the lower extremities. Two major pharmacologic classes have recently been recognized as effective treatment for the prevention of systemic atherosclerotic complications: antiplatelets and ACEIs. The results of recent studies lead us to believe that the use of statins in PAD patients, regardless of the patient's low-density lipoprotein level, would be efficient in the prevention of systemic atherosclerotic complications.[9]

Regarding antiplatelets, a recent study confirms, beyond a reasonable doubt, the efficacy of acetylsalicylic acid (ASA). In fact, a dose of 80 mg administered chronically on a daily basis is just as effective as higher doses.[10]

The adenosine diphosphate inhibitor is another category of antiplatelets used, specifically clopidogrel and ticlopidine. In a large-scale study comparing clopidogrel and ASA for the prevention of systemic atherosclerotic complications in high-risk patients (including PAD patients), clopidogrel showed a marginal higher

efficacy.[11] However, a cost-efficacy study showed that the use of clopidogrel in PAD patients was not cost-effective, especially when used as the first-line treatment.[12]

Current data supports initially treating PAD patients with ASA and administering clopidogrel to all patients who are allergic or intolerant to ASA. For patients who present with a recurrent systemic atherosclerotic event even after taking ASA, clopidogrel could be used as an alternative, even if there is a lack of data supporting this indication.

The use of ticlopidine has declined tremendously because of its medullar toxicity. The use of ASA with an anticoagulant, or ASA with clopidogrel for the prevention of these complications is currently under investigation.

ACEIs, in particular ramipril administered daily at a dose of 10 mg, have also proven to be effective in reducing systemic atherosclerotic complications, despite their antihypertensive effect.[8] Although a study was done on ramipril, there is no reason, at this point, to believe that this atherosclerotic complication-lowering effect is specific to ramipril, but rather that it is an effect brought on by this class of ACEIs. Unless contraindicated, PAD patients should be administered an ACEI, along with an antiplatelet treatment.

There is no current data to justify using an angiotensin receptor antagonist (ARA) or an ACEI/ARA combination to prevent systemic atherosclerotic complications in PAD patients.

Treating intermittent claudication

The symptomatic treatment of intermittent claudication (Fontaine stage II) consists of a physical exercise program based on walking. The actual mechanisms of walking contributing to reducing intermittent claudication are vague, but they are probably associated with an increase in the oxygen extraction capacity rather than the formation of collateral arteries. The exercise program, which has proven to be successful, is supervised. Patients must adhere to, at least, three 45- to 60-minute sessions each week. The program's effectiveness tends to manifest itself after a two-month period, but its benefits abruptly end if the program is stopped. Despite its proven efficacy, the program is restrictive, as it lacks the necessary resources to support it.

In one study, the supervised exercise program was compared to an unsupervised program. Even though the patients in the supervised group did not increase the time spent walking without having pain, they did increase their distance. However those who were in the unsupervised

Take-home message

- PAD may be a sign of potentially lethal atherosclerosis.
- PAD is associated with significant cardiovascular morbidity/mortality.
- ABI can confirm a PAD diagnosis.
- Walking is the recommended symptomatic treatment fo PAD.
- Revascularization should be used for patients with major functional repercussions due to claudication, or for patients suffering from acute ischemia.

program did the same.[13] Therefore, it seems an unsupervised walking program may also serve as first-line treatment for intermittent claudication and should be followed for a minimal period of three to six months.

Several pharmacologic treatments have been used to relieve intermittent claudication. Cilostazol, a phosphodiesterase inhibitor, seems to have higher efficacy than placebo or pentoxyfiline in terms of increasing the distance walked. However, cilostazol treatment is expensive and has yet to be compared to the supervised walking program. Furthermore, it is not yet available on the Canadian market.

Many other medications have been studied in the treatment of intermittent claudication. The results remain moderate and, as with cilostazol, no medication has been compared to the supervised exercise program.

Among natural products, studies have proven that Ginkgo biloba has a beneficial effect on intermittent claudication, but its use should be discouraged because of the lack of Canadian regulations on natural products.

Many other molecules are currently being studied, especially propionyl-L-carnitine, oral prostacyclin and angiogenesis therapy. In brief, there are few pharmacologic treatments actually available to the clinician in the treatment of intermittent claudication.

Revascularization, surgical or via percutaneous transluminal angioplasty (with or without an intravascular stent), should be reserved for patients who present with progressive intermittent claudication despite participation in the walking program and/or therapy with a proven effective pharmacologic treatment. Revascularization should be reserved especially for patients who present with handicapping symptomatologies that interfere with everyday activities. The choice in the type of revascularization is dictated by the site affected and the type of atherosclerotic lesion, as well as by the patient's general health. Regardless of the type of revascularization chosen, an antiplatelet treatment should be administered on a long-term basis. Regular followups should be done in order to trace and prevent the risk of restenosis.

Treatment of acute ischemia

The main objective in the treatment of acute ischemia (Fontaine III and IV stage) is to avoid the loss of the affected extremity by providing surgical revascularization or an emergency percutaneous transluminal angioplasty. There is a pharmacologic treatment available—an analogue of E1 prostaglandin—which is efficient in alleviating pain and delaying amputation. Because of its cost and moderate efficacy, this pharmacologic treatment should be reserved only for patients who represent a very high surgical risk

and for whom amputation is not a reasonable alternative.

Angiogenesis is an interesting therapeutic avenue in the treatment of acute ischemia which is still under study. The treatment of acute ischemia involves: alleviating pain with pain medication, or nonsteroidal and/or opiate anti-inflammatories); treating ischemic ulcers with dressing and gel while also avoiding debridement; and controlling infections, as needed. Ultimately, amputation is the last alternative in the treatment of acute ischemia. CME

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Web sites:

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   www.understandingpad.com
2. American Academy of Family Physicians:
   http://familydoctor.org/handouts/546.html