Management Of Peripheral Arterial Disease: An Overview

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Citation

D Singh. *Management Of Peripheral Arterial Disease: An Overview*. The Internet Journal of Surgery. 2005 Volume 8 Number 1.

Abstract

The management of patients with peripheral arterial occlusive disease (PAD) has to be planned in the context of natural history, epidemiology, and apparent risk factors that predict deterioration. The ankle-brachial index to date has proved to be the most effective, accurate, and practical method of PAD detection. Given that PAD is a powerful indicator of systemic atherosclerosis and (independent of symptoms) is associated with an increased risk of myocardial infarction and stroke, as well as a six times greater likelihood of death, the prevalence and demographic distribution of measurable PAD becomes particularly relevant. Reliable information on interventions to confer symptom relief is much weaker and reflects discrepancies between published reports from centers of excellence and the experience of patients routinely treated in communities around the world. The impact of newer treatment modalities, such as complex endovascular procedures and therapeutic angiogenesis, has been a subject of recent controversy. This review article highlights the management of peripheral arterial disease on the basis of available facts and data's.

INTRODUCTION

Peripheral arterial disease is a common disease in adults and its complications take a great toll in terms of quality of life and treatment costs. As healthcare budgets have taken up more of the economy, and as employers and patients have become concerned about the escalating costs of healthcare, we have entered an era in which individual doctors must become concerned about the costs of a service relative to its benefits. The purpose of this article is to review the literature on the diagnostic and therapeutic procedures for peripheral arterial disease. It emerges that peripheral arterial disease places a great burden on healthcare systems and on society as a whole. Some of these costs, including indirect and intangible costs (i.e. those related to lost productivity, and reduced quality of life, respectively) could be reduced if the condition were to be recognized and correctly treated at an early stage.

Peripheral arterial disease (PAD) comprises those entities that result in obstruction to blood flow in the arteries, exclusive of the coronary and intracranial vessels. Most obstructions are caused by the insidious development of atherosclerotic plaque buildup, and, terminally, by thrombotic occlusion of the remaining lumen. A minority of patients develops peripheral occlusions on the basis of non atherosclerotic etiologies, most commonly embolism from the heart.

At first, patients with chronic PAD experience symptoms of claudication, with muscular pain that develops with ambulation. In the late stages, however, a tissue hypo perfusion progress to pain that occurs even at rest. Ischemic ulceration and gangrene can develop, and major amputation is eventually required in more than one third of these patients.([1]) Alternatively, patients may present with a sudden onset of acute limb ischemia, usually when the occlusion occurs abruptly and without the establishment of preexisting collateral pathways. Mortality is closely linked with the presence of pain at rest or tissue-loss, so-called" critical limb ischemia," with a 1-year mortality rate that approximates 20%in several series. ([2], [3])

Importantly, mortality is greatly increased when patients present with acute limb-threatening symptoms. In-hospital mortality rates have been reported in excess of 20% in this group of surgical patients. ([4], [5]) These rather dismal results have prompted interest in a less invasive strategy for treating the arterial obstruction, namely, pharmacologic thrombolysis.

EPIDEMIOLOGY

Intermittent claudication has been used as a marker of PAD in epidemiological studies to approximate the prevalence of lower extremity PAD in a particular patient population. The estimate is dependent, however, on demographic factors of

the specific population under study, including age, sex, and geographic area. In addition, the methodology used to determine the prevalence of intermittent claudication affects the estimate.(6) For instance, studies based on questionnaires tend to overestimate the prevalence of symptomatic PAD, and patients with complaints that resemble claudication but are un re-lated to the vascular system will be erroneously classified as having PAD. Studies that use an objective method of diagnosis, such as measurement of Doppler systolic ankle pressures, are most accurate. An "ankle-brachial index" can be calculated by dividing the ankle systolic pressure measured with a blood pressure cuff at the malleolar level by the higher of the two brachial pressures. Defining PAD by an ankle-brachial index of < 0.95, one study observed a prevalence of 6.9%in patients aged 45 to 74 years, only 22.0% of whom were symptomatic.(7) The prevalence of intermittent claudication increases dramatically with advancing age, ranging from 0.6%in individuals aged 45 to 54, to 2.5%in those aged 55 to 64, to 8.8% in patients aged 65 to 74.8 The Rotterdam study, a population-based analysis of 7715 patients, documented a prevalence of intermittent claudication ranging from approximately1.0% in those between the ages of 55 to 60 years, to 4.6% in those between the ages of 80 to 85.9 Despite this rather low prevalence of intermittent claudication, fully16.9% of males and 20.5% offer males aged 55 and over had PAD as defined by an ankle-brachial index of < 0.90 in either leg. This observation confirms that the vast majority of patients with significant PAD are asymptomatic. Although the diagnosis of asymptomatic PAD is of lesser clinical significance with respect to the lower extremities, it is a strong marker for future cardiovascular events such as myocardial infarction. (10)

LOWER-EXTREMITY PERIPHERAL ARTERIAL DISEASE

The natural history of lower extremity PAD has been evaluated in a variety of studies, both with regard to the progression of disease in the leg as well as to the long-term morbidity from concurrent generalized athero-sclerotic disease. In the Rochester trial, described later, claudication symptoms were surprisingly benign; the risk of limb-loss was low and was greatly overshadowed by the risk of morbid cardiovascular events and death. Although arteriographic progression of atherosclerotic disease was found in one study in 63%of patients after 5 years,(11) Bloor's classic study of 1961 documented a rate of major amputation of only7% after 5 years and 12% after 10years of follow-up.(12) More recent data corroborate the finding that limb-loss is a relatively rare eventuality in patients with intermittent claudication, with a 5-year risk of major amputation of only 2%.(13) By contrast, limb-loss is much more frequent once the symptoms of rest-pain or tissue-loss become evident (critical limb ischemia). In a prospective study from Italy, the risk of major amputation after only 3 months was 12.2% in patients with rest-pain or ischemic ulceration.3The risk of limb-loss was also found to increase further when patients continued to smoke, (14) as well as inpatients with diabetes. (11) The long-term prospects for patients with lower-extremity PAD must be considered in the context of coexistent generalized atherosclerosis. In an early study from the Cleveland Clinic, some degree of coronary atherosclerosis was present in 90% of patients undergoing routine coronary angiography prior to elective peripheral vascular surgery and 28% of the patients had severe, three-vessel coronary disease.(15)

Long-term survival in patients with lower extremity PAD is greatly diminished as a result of atherosclerotic complications in the coronary and cerebrovascular beds. In the classic study of Criqui, even asymptomatic patients with peripheral atherosclerosis had a risk of mortality that exceeded that of the non diseased population, (10) a finding substantiated by other studies. (16)

The mortality risk was incrementally higher in patients with symptomatic PAD and was further increased in patients with severely symptomatic disease. (10) The cause of death in patients with PAD, however, is rarely a direct result of the lower-extremity arterial disease itself. Approximately 55% of patients die from complications related to coronary artery disease, 10% succumb to complications of cerebro vascular disease, and 25% die of non vascular causes.(13) Less than 10% succumb to vascular events, most commonly a ruptured aortic aneurysm.(13)

DIAGNOSIS

The diagnosis of peripheral arterial occlusive disease begins with taking an accurate history. Intermittent claudication must be differentiated from lower-extremity pain resulting from nonvascular etiologies. True claudication begins after a reproducible length of ambulation and resolves within a few minutes after the patient stops walking, even if he or she remains standing. By contrast, pain from impingement on the nervous structures as a result of spinal stenosis does not resolve after ambulation ceases, and, in fact, maybe worsened by prolonged sitting or standing. The location of the pain is the key to the site of arterial occlusion:

claudication in the calf is typically a result of disease in the superficial femoral artery, whereas claudication in the hip, thigh, and buttock occurs with the narrowing of the aorta and iliac arteries. The most efficient means of objectively documenting the presence and severity of lower-extremity PAD is the measurement of the Doppler ankle-brachial index. Normally, the ankle-brachial index is > 1.0. The index is decreased to 0.50 to 0.90 inpatients with claudication and to lower levels in patients with pain at rest or tissue loss.([17]) The ankle-brachial index may be normal in some patients with mild arterial narrowing; treadmill exercise has been used in these cases to increase the sensitivity of the test. Patients with diabetes mellitus or renal failure may have calcific lower-leg arteries, rendering them incompressible and causing a falsely elevated ankle-brachial index. In these cases, a toe-brachial pressure index can be measured and is more predictive of significant arterial disease.([18]) Contrast arteriography remains the “gold standard” with which all other tests must be compared. Even today, standard arteriography is the most accurate test for all but the occasional patient with such a slow flow in the tibial or foot vessels that digital subtraction imaging fails to demonstrate a patent artery. Arteriography is, however, a semi-invasive modality, and, as such, its use should be confined to those patients for whom a surgical or percutaneous intervention is contemplated. Patients with borderline renal function may experience contrast-induced nephrotoxicity,and in this subgroup the use of alternate contrast agents such as gadolinium or carbon dioxide have been employed.

TREATMENT

The management of patients with lower-extremity PAD is two-pronged: first, the risk factors important in the progression of generalized atherosclerosis are addressed followed by interventions such as pharmacotherapy and endovascular therapy or surgery to relieve the lower-extremity symptoms. Treatment of the patient's lower-extremity symptoms should be chosen on the basis of the severity of the symptoms. Invasive intervention for asymptomatic disease is never appropriate, but the presence of even asymptomatic disease should serve as a marker of generalized atherosclerosis, and therapy should be directed at the primary prevention of systemic complications such as MI and stroke. Similarly, patients with mild or moderate claudication symptoms are best treated with conservative measures such as the institution of an exercise program.

Pharmacotherapy for intermittent claudication can be added as adjunctive treatment to improve walking, although no agent has pro-vided sufficient efficacy to gain widespread acceptance. Although statistically significant differences in such endpoints as the walking distance on a treadmill can be demonstrated in clinical trials, the lack of a robust clinical impact that measures the benefit of these agents has limited their widespread use. Moreover, the use of pharmacotherapy for claudication varies from country to country, with a high rate of use in France and a relatively low rate in the United States.

THROMBOLYTIC THERAPY

Aggressive pharmacotherapy attains great importance in patients with acute limb ischemia resulting from in situ native artery thrombosis or thrombosis of a bypass graft. Early heparin anticoagulation may limit the propagation of thrombus and prevent clinical deterioration, although there is little objective data on which to base this practice.([4]) Retrospective studies suggest that heparin decreases the risk of recurrent embolization in patients with embolic occlusions, and most surgeons continue heparin therapy through the perioperative period, until the patient can be adequately anticoagulated with oral agents.([19,20]) Thrombolytic agents are of value inpatients with acute limb ischemia, and some studies have suggested that their use reduces the high rate of morbidity and mortality associated with immediate surgical intervention.([21,22]) Although thrombolytic therapy does not uniformly obviate the need for an endovascular or open surgical procedure to correct the underlying causative lesion, the use of these agents as initial therapy allows one to defer the more invasive modalities to an elective setting, when the patient can be better prepared for a major intervention.([23])

SURGICAL INTERVENTION

Surgical revascularization is unquestioned as appropriate therapy for patients with chronic critical limb ischemia, directed at the prevention of limb-loss and its accompanying disability. By contrast, surgical intervention is rarely indicated inpatients with intermittent claudication alone, because the risk of major amputation is exceedingly low. Only in the occasional patient whose symptoms interfere with the patient's lifestyle or performance of an occupation will the benefits of surgical revascularization outweigh the risks. There exist two basic choices when surgery is contemplated for chronic lower extremity disease: endarterectomy and bypass grafting.

OPEN SURGICAL PROCEDURES

Endarterectomy is an acceptable option when truly localized

disease is present, for example, the narrowing of the aorta and common iliac arteries alone. [24] Otherwise, patency rates are unsatisfactory, and bypass grafting is more appropriate. The traditional operation for aortoiliac occlusive disease is an aortofemoral bypass, performed with a prosthetic graft because of the large caliber of the vessels. Infrainguinal bypass procedures are best performed with autogenous vein grafts, although the results of prosthetic bypasses are acceptable if the graft does not cross the knee joint.[25] The results of bypass procedures are correlated with the level of the disease; aortofemoral reconstructions are associated with higher patency rates than those for infrainguinal procedures. Nevertheless, with a non diseased saphenous vein of adequate caliber, the long-term patency rate of a bypass to even the infrapopliteal (crural) vessels is quite satisfactory, approximating 70% to 80% at 5 years, irrespective of whether the vein is reversed or left in situ with the valves disrupted.[26,27] Considering the quite dismal results of percutaneous angioplasty and stenting for disease in the crural arteries, autogenous vein bypass to the distal vessels should be considered as first-line therapy in patients with limb-threatening ischemia and distal disease.[27]

PERCUTANEOUS CATHETER INTERVENTIONS

Percutaneous catheter interventions to treat occlusive lesions of the lower extremities, first described by Dotter and Judkins in 1964, [28] are attractive alternatives to open surgical procedures such as endarterectomy and bypass. Procedural indications have been liberalized compared to those for surgical procedures, based on the argument that the minimally invasive nature of percutaneous modalities warrants broadened application. Nevertheless, although devices and results have improved over time, the long-term patency of percutaneous interventions remains inferior to open surgical techniques. Moreover, the use of primary stenting compared to stenting only after inadequate balloon dilation has never been proved to be advantageous.[29,30] Proponents of endovascular therapy cite two contentions to justify continued use of these modalities: first, the decrement in durability is offset by the less invasive nature of endovascular interventions and the resultant decreased morbidity; and second, a patient infrequently experiences clinical or angiographic worsening upon failure of an endovascular intervention, and the interventions can be repeatedly performed after they fail. In a meta-analysis of 2116 patients who underwent aortoiliac percutaneous transluminal angioplasty (PTA) and stent placement, the 30-day mortality rate was less than 1%,[29]and the patency of PTA and stenting for aortoiliac stenoses averaged 86% at 3 years, falling to 62% when aortoiliac occlusions were treated.[30] The results of infrainguinal PTA and stenting were not as good, with 3-year patency rates below 60%.[30] Thus, the available data would suggest that long-term durability is greater with surgical revascularization than with endovascular therapy, but peri procedural complications are lower when percutaneous modalities are employed. The risk-benefit ratio associated with endovascular versus open surgical revascularization can be ascertained only through the performance of well-designed comparative clinical trials. In patients with anatomically appropriate lesions, however, most practitioners preferentially employ endovascular interventions, a practice based on the presumption of lower risks to the patient. Treatment of patients presenting with acute limb ischemia was formerly relegated to open surgical revascularization. Such an approach was associated with a high rate of complications, including major amputation and death. [4, 5]

THE RISK OF MORBIDITY AND MORTALITY IN ACUTE LIMB ISCHEMIA

The acute occlusion of a peripheral artery is a catastrophic event. Whether resulting from in situ thrombosis of a native artery, a bypass graft, or embolization, a series of studies have shown that acute limb ischemia threatens both the patient's limb and life (Table 1). A now classic study by Blaisdell and associates, published over 20 years ago, documented an amputation rate of 25% and a mortality rate of 30%, each following open surgical repair for acute leg ischemia.[4] Despite improvements in operative techniques and postoperative patient care, more recent series continue to verify unacceptably high rates of morbidity. Jivegård and colleagues, in 1988, reported a 20% mortality rate in these patients treated operatively.[5]Even the later prospective studies of selected patients with recent peripheral arterial occlusions observed rates of limb loss and death that exceeded desired targets.[22] Thus, the risk of morbidity and mortality following open surgical intervention remains at an unacceptably high level. What factors explain this finding? Clearly, the baseline medical status of the patients that present with acute peripheral arterial occlusion underlies the observation. Patients are frequently elderly, with a high rate of cardiac and other co morbidities. They are ill-equipped to tolerate the insult of ischemia of an extremity, let alone an invasive surgical intervention to relieve the obstruction. A multivariable analysis of the data from the Rochester series uncovered several variables that were predictive of poor outcome, irrespective of the type of treatment instituted. A

summary of available literature would appear to confirm that individuals who present with acute, limb-threatening ischemia comprise one of the sickest subgroup of patients that the peripheral vascular practitioner is asked to treat. There is some evidence to confirm the impression that a less invasive intervention is better tolerated in this very ill group of patients who develop acute limb ischemia.

Figure 1

Table 1: In-Hospital or 30-Day Rates of Amputation and Death in Selected Series of Patients with Acute peripheral arterial Occlusion Treated with Open Surgical Intervention

Study	Year	Amputation Rate	Mortality Rate
Blaisdell et al	1978	25%	30%
Jivegård et al	1988	NA	20%
Rochester	1994	14%	18%
STILE	1994	45%	6%
TOPAS	1998	2%	5%

NA, Amputation rate not part of the data from this trial.

On the basis of these observations, today many centers employ intra-arterial thrombolytic therapy as the initial intervention, infusing thrombolytic agents directly into the occluding thrombus. Agents such as urokinase, ([31]) alteplase, and reteplase provide a less invasive means of restoring adequate arterial perfusion, addressing the unmasked culprit lesion responsible for the occlusion. An endovascular or open surgical procedure is performed on an elective basis after adequate patient preparation.

In the last decade, studies of the biological mechanisms underlying angiogenesis, i.e. the development of a new vasculature from pre-existing blood vessels, have suggested a new approach to peripheral obstructive artery disease based on the treatment of ischemic tissues with angiogenic growth factors. As demonstrated by experimental studies in animal models, a therapeutic effect can be reached as the newly formed vascular network, functioning as a biologic by-pass, restores a normal blood supply to the ischemic territories. New techniques of gene therapy proved effective in reaching sustained concentrations of angiogenic factors in the target tissues. ([32])

SUMMARY

Acute occlusion of a peripheral artery is a catastrophic event. Whether resulting from in Situ thrombosis of a native artery, a bypass graft, or embolization, acute limb ischemia threatens both the patient's limb and life. Traditionally, open surgical intervention has been the “gold standard” for treatment of these patients. However, the multiplicity and complexity of medical co morbidities account for high rates of perioperative morbidity and mortality. Thus, a minimally invasive alternative to open surgery is desirable, provided that the rate of limb salvage remains similar and other untoward events are infrequent. Catheter-directed thrombolytic therapy has been studied in this regard, offering the potential to restore arterial perfusion without the need for open surgery in many cases. In addition, thrombolysis can clear thrombus from small arteries that are inaccessible to a balloon catheter. Lastly, successful thrombolysis may unmask the lesion responsible for the occlusion and allow a directed, sometimes less invasive treatment.

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