PERIPHERAL VASCULAR DISEASE

Thromboembolism and Antithrombotic Therapy in Peripheral Arterial Disease

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Atherosclerosis complicated by thromboembolism is the main cause of obstructive arterial disease in the legs. Two studies from West Germany suggest that antiplatelet drugs may slow the progress of atherosclerosis in leg arteries and prevent occlusive thrombosis under some circumstances. The same agents may also reduce the risk of rethrombosis after successful vascular repair in the femoropopliteal region; in one trial, aspirin decreased the incidence of reocclusion after thromboendarterectomy and, in another, the combination of aspirin and dipyridamole was effective after bypass with synthetic material. Antithrombotic drugs are used in most centers after percutaneous transluminal angioplasty, but there is no definite evidence for their need. Thus, it appears that in contrast to cardiac and cerebrovascular disease, few efforts have been made to determine the true value of antithrombotic therapy in peripheral arterial disease.

The management of acute thromboembolism in the legs requires a multidisciplinary approach. Depending on the type (embolic or thrombotic), length and localization of the arterial occlusion, surgical (embolectomy, thromboendarterectomy, peripheral bypass surgery) or nonsurgical (systemic fibrinolysis or local thrombolytic therapy with or without balloon angioplasty) treatment is preferred. The importance of nonsurgical therapeutic approaches may become even greater in elderly patients with a poor operative risk. This review discusses the available therapeutic modalities in acute and chronic peripheral thromboembolic arterial disease.

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The most common cause of obstructive arterial disease in the lower limbs is slowly progressive atherosclerosis, often complicated by thrombosis. Other types of degenerative or inflammatory arteriopathy that may also impede the blood supply to the legs are less frequent (Table 1). In this review, we focus on the problems of secondary prevention and treatment of peripheral arterial disease due to thrombosis on atheromatous lesions. In addition, the management and prevention of arterial embolism will be discussed.

Antithrombotic Drugs in the Secondary Prevention of Atherosclerosis and Thrombosis in the Leg Arteries

The importance of platelets and platelet-derived substances and the role of fibrin in arterial thrombogenesis is emphasized in another review (1) in this symposium. From these concepts, both anticoagulant and antiplatelet drugs could theoretically slow down the course of the thrombotic components in the progression of occlusive arterial disease. However, the preventive potential of antithrombotic drugs has been tested far less in peripheral arterial disease than in ischemic coronary and cerebral disease. The relatively benign evolution of atherosclerosis in the legs largely accounts for this neglect. The reduced life expectancy in these patients is mainly due to excess cardiac mortality; the risk of a leg amputation is relatively low and the threat remote. In addition, the capricious natural history of the arterial lesions and the clinical symptoms require strictly controlled studies to distinguish between spontaneous evolution and drug effects.

Oral anticoagulants. Thrombosis is only the final step of a long evolution. Therefore, long-term oral anticoagulation is unlikely to represent a spectacular advance in the prevention or progression of peripheral arterial occlusive disease. In fact, a few trials (2–4) have shown a favorable trend, but their design and size do not allow a definite conclusion. A prospective study (5) was performed in The Netherlands in patients suffering from intermittent claudication. All the selected patients were initially on oral anticoagulant therapy for at least 6 months. They were then randomly assigned to switch to placebo or to continue the vitamin K antagonist. The trial was stopped prematurely.

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Table 1. Etiology of Peripheral Arterial Occlusive Disease in the Legs

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Degenerative arteriopathy</td>
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<tr>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Mönckeberg’s medial sclerosis</td>
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<tr>
<td>Medial cystic degeneration</td>
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<tr>
<td>Fibromuscular dysplasia</td>
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<tr>
<td>Inflammatory arteriopathy</td>
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<tr>
<td>Thromboangiitis obliterans (Buerger’s disease)</td>
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<tr>
<td>Arteritis associated with connective tissue disease</td>
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<tr>
<td>Systemic giant cell arteritis</td>
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<tr>
<td>Takayasu’s disease</td>
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<tr>
<td>Arterial thrombosis</td>
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<tr>
<td>Idiopathic or immunologic (lupus anticoagulant or heparin-induced thrombocytopenia)</td>
</tr>
<tr>
<td>Peripheral arterial embolism</td>
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<tr>
<td>Arterial trauma</td>
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<tr>
<td>Drug-induced or spontaneous arterial spasm</td>
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because of a significantly greater number of deaths in the placebo group. These favorable results were apparently not confirmed in a second controlled but still unpublished Dutch trial (6), which showed no benefit of anticoagulants on walking distance until claudication, ankle systolic pressure, ischemic symptoms or amputation rate.

**Antiplatelet agents.** To date, only few data are available to suggest a beneficial effect of antiplatelet drugs on the progression of atherosclerosis and the occurrence of its thrombotic complications in patients with obstructive peripheral arterial disease. Three hundred patients with a stenosis of the femoral artery were randomized by Schoop et al. (7) to receive daily either 1 g of aspirin, 1 g of aspirin combined with 225 mg of dipyridamole or placebo; they were followed up for 4 years. The occlusion rate was lower in the two groups treated with the active drugs, but the combination was not superior to the administration of aspirin alone. In addition, antiplatelet therapy did not prevent femoral artery thrombosis in diabetic and hypertensive patients. Recently, Hess et al. (8) reported a placebo-controlled, double-blind, 2 year trial in 199 patients with arteriographically studied evolution of peripheral atherosclerosis. Progression of the disease was most pronounced in the placebo group, less so in the aspirin-treated group (1 g daily) and least of all in the aspirin-dipyridamole–treated group (1 g, 225 mg daily). In contrast with the results of Schoop et al. (7), patients who smoked and those with hypertension benefited most from active treatment.

Retrospective data accumulated from several (published and unpublished) double-blind studies on the effect of ketanserin in patients with intermittent claudication seem to suggest a decrease in cardiovascular complications with this novel serotonin antagonist. An international multicenter trial is currently studying this hypothesis prospectively on a large scale.

**Antithrombotic Drugs in the Prevention of Thrombosis After Peripheral Arterial Surgery and Percutaneous Transluminal Angioplasty**

**Prevention after thromboendarterectomy.** Bollinger and Brunner (9) recently reported the final results of a prospective study of 120 patients who were followed up for 2 years after a successful endarterectomy in the femoropopliteal region. All patients received warfarin for the initial 2 postoperative weeks. They were then randomized into three treatment groups for prophylaxis of reocclusion: aspirin (1 g daily), aspirin-dipyridamole (1 g, 225 mg daily) or an oral anticoagulant (warfarin). The cumulative patency rate at 2 years was 84% for the aspirin group, 76% for the aspirin-dipyridamole group and only 58% for the warfarin-treated patients. Both antiplatelet regimens were significantly superior to warfarin, but the level of hypocoagulability induced by warfarin was probably insufficient. However, endarterectomy in the femoropopliteal region has largely been abandoned by most surgeons in favor of bypass surgery.

**Prevention after bypass surgery.** Because Dacron grafts in the aortoiliac region have a high long-term patency rate, demonstration of a beneficial effect of antithrombotic agents would require a huge number of patients. For reconstruction to the popliteal, tibial or peroneal arteries, autologous veins, human umbilical veins or polytetrafluoroethylene prostheses (PTFE grafts) are used. Thrombosis of these bypass grafts during the first postoperative month is generally a result of defective surgical technique or a precarious runoff. Late occlusion, in contrast, is related to excessive proliferation of the neointima along the inner wall of the graft followed by thrombosis. To prevent this complication, some surgeons prescribe an oral anticoagulant for the first postoperative months. In some patients with very precarious runoff, life-long warfarin treatment is recommended. However, this practice is based on personal clinical experience rather than on controlled trials. One study (10) suggests that the combination of aspirin and dipyridamole reduces (p < 0.05) the risk of occlusion of prosthetic femoropopliteal grafts.

**Prevention after percutaneous transluminal angioplasty.** In a large majority of centers that practice balloon catheter peripheral angioplasty, either anticoagulants or antiplatelet agents are administered to reduce the number of early reocclusions. Intake of antiplatelet drugs can be started 1 or 2 days before the actual procedure. This usage dates from the very first days of the technique and is based on the expectation that any lesion inflicted to the intima will induce a rapid adhesion of platelets followed by thrombus formation. To our knowledge, no clinical trial has addressed the role of antithrombotic treatment in the prevention of early reocclusion after angioplasty in the peripheral arteries. Even if this tradition of early antithrombotic prophylaxis...
appears acceptable, the value of a long-term antithrombotic strategy needs assessment.

Management of Acute Arterial Thromboembolism in the Legs

Irrespective of whether an acute arterial occlusion is due to thrombosis or embolism, a number of urgent measures are to be taken. The ischemic leg is placed in a position of about 15° dependency to avoid further impairment of capillary perfusion. Direct heating of the cold leg and mechanical trauma are avoided. Heparin treatment is initiated at a therapeutic dosage to prevent extension of thrombosis or recurrent embolism. Further therapeutic measures will depend on whether the acute occlusion is caused by embolism in a healthy artery or thromboembolism in an atheromatous artery. A proposal of a decision-making pathway in acute thromboembolism of leg arteries is presented in Figure 1.

Arterial embolism in healthy arteries. This is the predominant type in young patients with atrial fibrillation. The embolus is removed with the Fogarty catheter, usually under local anesthesia. The success rate in terms of limb salvage is about 90% (11), the best results being obtained in patients subjected to early embolectomy (that is, within 8 hours). Leg edema may occur after successful revascularization as a result of transudation of fluid across the capillary membrane, the permeability of which is increased by hypoxia. This complication may induce a compartment syndrome and lead to further damage of the muscle, nerves and vessels. Fasciotomy may be required. Anticoagulation is continued after embolectomy unless the source of the embolus is discovered and eradicated.

Thromboembolism in atheromatous arteries. Most of the acute arterial thromboses and many of the emboli are superimposed on atheromatous plaques in an already impaired arterial circulation. The same general measures are taken and, in many cases, the Fogarty procedure just described (11) will be tried without delay. However, the short- and long-term success rate of thromboembolectomy in these conditions is considerably lower than that for an arterial embolus in a healthy artery. If the Fogarty procedure fails or is not advisable, localized endarterectomy with thrombectomy or vascular reconstruction may be attempted depending on the arteriographic findings.

Thrombolytic therapy. If a surgical intervention is considered impractical for technical reasons (multiple emboli in an already compromised circulation) or because of the poor general condition of the patient, systemic or local thrombolytic therapy can be considered followed by antithrombotic therapy. The ability to restore blood flow in acutely occluded arteries by systemic administration of thrombolytic agents in various treatment schemes has been amply demonstrated in the past two decades (12-14). The success rate seems to depend on the delay between the acute event and the initiation of therapy, although this point is not established in all series. Hemorrhagic complications due to the systemic lytic state induced by streptokinase or urokinase are not uncommon. A more fibrin-specific thrombolytic agent like tissue-type plasminogen activator has only recently been introduced for clot-selective thrombolysis in a variety of thromboembolic conditions (15), including acutely or subacutely thrombosed peripheral arteries and bypass grafts (16). This new agent may represent an attractive alternative to both conventional systemic and local thrombolytic therapy.

Local thrombolysis with low dose streptokinase has been used in the last few years in patients with poor general condition or in subjects with difficult surgical access. The method was initially proposed by Dotter et al. (17), who infused streptokinase in a dose of 5,000 IU/h through a catheter placed in the immediate vicinity of the clot. The procedure was later modified (18) so that the catheter was passed into the proximal part of the occluding thrombus. Hess et al. (19) reduced the duration of infusion to a maximum of 5 hours, thereby avoiding significant activation of
the fibrinolytic system and reducing the risk of hemorrhagic complications. Recanalization was obtained in about 70% of the cases, and was sustained for 1 year in 50%. The technique is applied for progressive lysis of occluded bypass grafts as well, and less recent thrombi may still be dissolved (Fig. 2).

"Blue toe" syndrome. A number of patients present with recurrent pain and ischemia in the toes or fingers, even though the blood supply through the large arteries appears intact as shown by normal peripheral pulses and systolic pressures. This so-called blue toe (or blue finger) syndrome may be due to obstruction of the microcirculation in patients with essential or secondary thrombocythemia. The platelets of these patients aggregate spontaneously in vitro (20). Usually, the symptoms respond to symptomatic treatment with aspirin, and skin perfusion improves quickly. The underlying cause of the thrombocytosis needs investigation and adequate treatment. Similar but more lasting symptoms of distal ischemia are occasionally caused by peripheral microembolization of atherosclerotic debris or cholesterol emboli originating from ulcerated lesions in proximal arteries. Here, too, antiplatelet drugs may help temporarily, but vascular repair without further delay is usually indicated.

Iatrogenic acute arterial occlusion. The daily use of intraarterial catheters for diagnostic or therapeutic procedures and for monitoring purposes accounts for an increasing number of acute arterial occlusions. Early thrombectomy is the treatment of choice for this complication in adults (21); in many children, infusion of heparin appears to be sufficient (22). Prophylaxis with antithrombotic drugs, if indicated, can normally be stopped after a few days.

Management of Chronic Ischemia of the Legs

Prevention. Secondary prevention of atherosclerosis in patients with obstructive disease of the leg arteries is not restricted to the discussion on the usefulness of antithrombotic drugs; reducing the risk factors is probably a more important issue. Thus, for decades, patients with peripheral arterial disease have been exhorted to abstain from smoking, to follow an appropriate diet and to have hypertension and diabetes controlled. Other therapeutic measures including vascular surgery and angioplasty are, to a large extent, palliative; that is, they try to relieve symptoms or, at very best, extend the viability of the leg.

Drug treatment. Daily physical exercise has been shown to markedly increase the walking distance in patients with claudication (23). On the other hand, drug treatment of chronic leg ischemia remains a highly controversial issue. Since the case against vasodilating agents was presented (24,25), new randomized, placebo-controlled, double-blind trials with different agents have been published (26-28). With these substances, characteristics other than vasodilation are stressed (for example, improvement in blood rheology or cell oxygenation). Also, antithrombotic drugs were tested for their ability to relieve symptoms of chronic ischemia. For instance, in a Japanese trial (29) the antiplatelet agent ticlopidine appeared to significantly decrease the number and extent of ischemic ulcers due to atherosclerosis and thromboangiitis obliterans. Recently, ketanserin was suggested to improve substantially the walking distance and the calf blood flow in patients with claudication (30), but these data have not been confirmed (31).
Patients with (severely) handicapping claudication and those with more advanced stages of ischemia should undergo arteriography to select for each of them the optimal treatment modality. A very brief review is given here.

Reconstructive vascular surgery. Many of the patients who undergo vascular surgery have multisegmental arterial occlusive disease. The proximal lesion is repaired first either by aortoiliac endarterectomy or, more commonly, by aortofemoral bypass grafting. The operative mortality of aortoiliac surgery is low (32,33). Surgical repair of a femoropopliteal occlusion is normally attempted rather than tofemoral bypass grafting. The operative mortality of aortofemoral bypass surgery depend on the extent of the arterial disease (distal runoff) and the material used for the graft. A higher patency rate is obtained with autologous veins (75% at 5 years) than with synthetic materials (35,36). Distal bypasses to the tibial arteries have a 5 year patency rate of 55% and a limb salvage rate of 73% if autologous veins can be used (37,38). In poor risk patients and other selected cases, alternative surgical procedures such as a profundaplasty or so-called extraanatomic bypasses may be preferred.

Percutaneous transluminal angioplasty. The technique originally proposed by Dotter and Judkins (39) became popular after the development of the modified Gruntzig double lumen catheter (40). Short isolated lesions are the ideal indication for a balloon procedure. The immediate success rate is greater than 90% in the iliac and more than 80% in the femoropopliteal region; late patency rates of approximately 85 and 75%, respectively, have been published (35,41,42). The most common complications are local hematoma at the puncture site and distal embolization, which rarely requires urgent surgical intervention. The method may have a theoretical advantage in younger patients in whom vascular surgery can be postponed for a number of years. For longer lesions, a combination of local thrombolysis with low dose streptokinase and percutaneous transluminal angioplasty can be used, as already described.

Miscellaneous procedures. The value of lumbar sympathectomy in patients with obstructive arterial disease of the legs remains disputed, even though this intervention has been practiced for almost six decades. In some centers, it is still used in conjunction with aortofemoral grafting to improve the distal perfusion. Others advocate it to (temporarily?) augment skin perfusion in patients with severe ischemia in whom vascular repair appears impractical; they hope in this way to relieve rest pain and accelerate healing of small skin ulcers. However, unequivocal evidence that sympathectomy is effective in these two conditions is scarce.

Systemic thrombolytic therapy with streptokinase has also been used in patients with chronic arterial obstruction, severe ischemia and poor operative prognosis (14,43). At present, the practice of local thrombolysis combined with angioplasty is increasing, but no properly controlled study comparing the two types of streptokinase administration is yet available (44). Other proteases such as brinase (45), ancorod (46) and hyaluronidase (47) have been injected into patients with severe ischemia without convincing results. Data on the infusion of prostaglandin E1 (48) and prostacyclin (49,50) are conflicting. In a controlled study (51), relief of rest pain was noted.

Many years ago Lassen et al. (52) reported a successful attempt to treat patients with gangrenous foot ulcers by increasing the systemic arterial pressure with sodium chloride and mineralocorticoids. However, increasing the blood pressure in aged atherosclerotic patients is not devoid of risk, and this therapy has been restricted to ischemic ulcers in young patients with Buergers disease (53).

References


