Clinical Vascular Disease

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editor

CLINICAL VASCULAR DISEASE

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CARDIOVASCULAR CLINICS

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Preface

Vascular diseases are common, and in our aging population will be even more common in the future. Although relatively little attention was devoted to vascular disorders in medical school curricula and graduate training programs in the past, there has been an increased clinical awareness and interest in this subject in recent years because of the availability of noninvasive diagnostic methods and the development of new modalities of treatment.

One of the fascinating aspects of vascular diseases is the diagnostic challenge often presented by these disorders. Whereas the clinical features of many vascular disorders, such as occlusive peripheral arterial disease, are straightforward and readily explained, the protean manifestations of other vascular conditions, such as pulmonary embolism and aortic dissection, can present severe diagnostic challenges that require great clinical acumen. Usually, the symptoms and signs of vascular disease are due to a primary vascular disease, but on occasion, they can be due to involvement of a part of the vascular system by a nonvascular process; indeed, the vascular finding may be the clinical clue to an otherwise occult lesion or disease.

Though most vascular diseases, other than aneurysm and thromboembolism, are not life-threatening, their complications and associated disability can often be prevented or controlled if they are recognized and managed properly.

This issue of CARDIOVASCULAR CLINICS presents the practical diagnostic and therapeutic principles that we hope will assist the clinician in dealing with these increasingly frequent disorders. The subjects presented—occlusive peripheral, cerebral, and renal arterial disease; aneurysmal disease; vasospastic disorders; the arteritides; venous and arterial thromboembolism; edema and ulceration of the lower extremities; and antithrombotic therapy—were selected and organized to provide the reader with an up-to-date and relevant resource to aid in the recognition and management of a majority of the common vascular diseases and their complications.

John A. Spittell, Jr., M.D.
Guest Editor

Editor's Commentary

Vascular disease continues to rank as an important cause of morbidity and mortality. This issue of CARDIOVASCULAR CLINICS provides a wide ranging examination of virtually all the common and uncommon vascular disorders encountered clinically—including peripheral, carotid, and renal arterial diseases; aneurysms; acute and chronic venous disorders; pulmonary embolism; vasculitides; leg ulcers; lymphedema; and other causes of edema. Clinical diagnosis and management are stressed throughout the various chapters. The contributing authors have provided unusual expertise and clinical insight. I am extremely grateful to each of them for their exemplary contributions, and I am particularly indebted to John A. Spittell, Jr., M.D. who provided the guidance needed to bring this volume to fruition.

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of Occlusive Arterial Disease

Jay D. Coffman, M.D.

INTERMITTENT CLAUDICATION

Patients who have intermittent claudication without ischemic rest symptoms or signs and are not disabled from their occupation should be treated conservatively. In several studies,[1-4] the majority of patients either did not have a progression of symptoms or improved with time. In a study from the Mayo Clinic,[1] 93 percent of patients with intermittent claudication from superficial femoral artery disease and without diabetes mellitus either had no progression of symptoms (69 percent) or improved (24 percent). Imparato and coworkers[4] found that 79 percent of their patients remained stable or improved over a mean period of 2.5 years, regardless of the initial severity of symptoms. The immediate success rate of surgical bypass operations for femoral artery disease is 80 to 90 percent in the best medical centers, but drops to 70 percent in five years.

There is some evidence that restoration of blood flow to an extremity with an obstructed artery may lead to progression of arteriosclerosis distally. In 42 patients, Morris and coworkers[5] demonstrated by angiography that the arteriosclerosis process progressed significantly faster in operated limbs than in nonoperated limbs. It may be that the increased pressure and flow following surgery causes acceleration of the disease in the distal vessels.

Another determining factor in choosing the type of therapy for patients with intermittent claudication is their life expectancy. In several studies,[6-8] the mortality has been 20 to 30 percent in 5 years, 40 to 72 percent in 10 years, and approximately 74 percent in 15 years. There is an overall 10-year reduction in survival for patients with obstructive vascular disease. The prognosis for survival depends strongly on the presence of coronary artery disease and diabetes mellitus. Surprisingly, the concurrence of hypertension or cerebrovascular disease does not appear to affect life expectancy. In one study,[7] the 14 patients with both coronary artery disease and diabetes mellitus had died within a five-year period. In another investigation, all patients with diabetes mellitus had died within eight years.[6] Unfortunately, these studies concerning life expectancy and concurrent diseases involved patients who had undergone vascular surgery; the effect of the latter cannot be taken into account.

Thus, the decision for conservative therapy in the patient with intermittent claudication is based on the unusually good prognosis for symptoms of the disease, the success rate of surgery, and an estimate of life expectancy; the presence of coronary artery disease or diabetes mellitus are additional weighty factors. Surgery is necessary or becomes so in some patients (Fig. 1). A definite indication for surgery is ischemia of the feet manifested by symptoms of rest pain, numbness or paresthesias, or signs of rubor (cold, reddish cyanosis), ulcers, or gangrene.

Patients with progressive disease, indicated by an increase in symptoms over a six-month or longer period, should also be offered surgery. If the symptoms are interfering with the
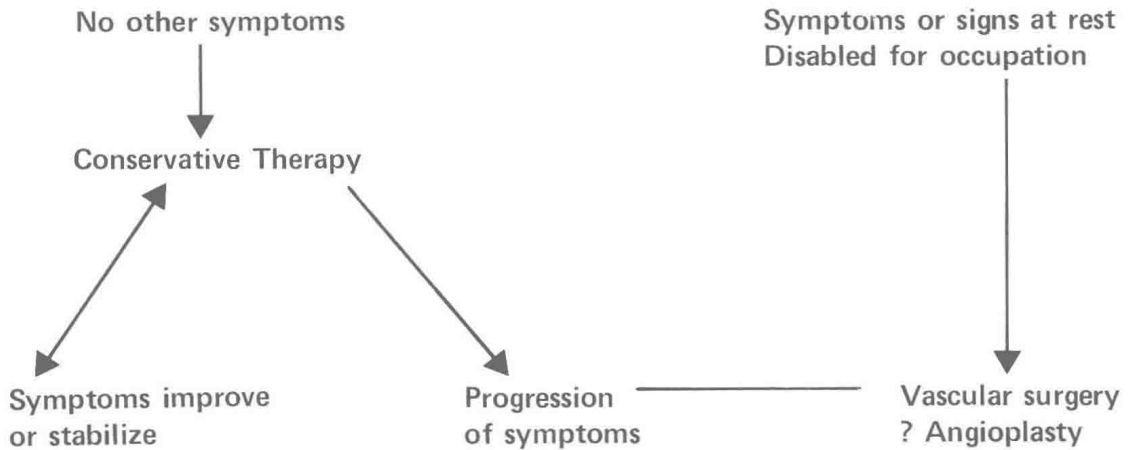
INTERMITTENT CLAUDICATION

No other symptoms

Symptoms or signs at rest
Disabled for occupation

Conservative Therapy

Symptoms improve
or stabilize

Progression
of symptoms

Vascular surgery
? Angioplasty

Figure 1. Treatment of arteriosclerosis obliterans.

patient's employment or seriously limiting the patient's life-style, surgery is necessary to continue a productive life. It is especially important to follow a conservative approach in patients with a recent onset of intermittent claudication, because they sometimes improve remarkably in a few months. If angioplasty proves to be a successful means of restoring blood flow, the indications for an invasive approach will be widened. However, even if surgery or angioplasty is performed, the underlying disease process is still present and medical treatment should be instituted.

General Measures

General measures (Table 1) are very important in the care of patients with obstructive arterial disease. Because of their simplicity, these measures are often neglected by the physician, or their importance underestimated by the patients. The nature of the disease and the fact that it is not life-threatening should be carefully explained to the patient. Many patients fear the loss of limbs but do not express this fear to the physician. The patient should be reassured that the disease is usually not progressive, but if worsening of symptoms should occur, then surgery can be considered. They should be instructed to watch for progression of symptoms or the development of ischemic symptoms or signs of the feet at rest. They must be told that cuts or bruises may take much longer to heal because of decreased circulation. Trauma, ulcers, or discolored skin areas must be reported immediately. In a study by Weis and Fairbairn,[9] 62 percent of amputations resulted from mechanical, chemical, or thermal trauma as the initiating event. Patients should keep the feet clean, warm, and dry at all times and wear only correctly fitting shoes. Toenails should be cut straight across to avoid ingrown nails and infections.

Table 1. Modalities of conservative treatment of arteriosclerosis obliterans

Definite value	Probable value	No proven value
General measures	Control of:	Fibrinolytic therapy
Stop smoking	Diabetes mellitus	(except acute occlusions)
Exercise regimens	Hypertension	Anticoagulant therapy
	Hyperlipidemia	Vasodilators

Since the limb musculature can only do a certain amount of work because of limited blood flow, climbing stairs or hills shortens the patient's walking distance. Similarly, carrying excess body weight or bundles will decrease walking time to onset of intermittent claudication. If patients are obese, they should be placed on a weight-reduction diet. A slower walking pace or even a cane may enable the patient to traverse necessary distances. If these points are carefully explained, patients often learn to tolerate their limitations very well.

Risk Factors

Besides general measures, medical management of patients with arteriosclerosis obliterans can be approached from the point of view of risk factors. The most important risk factors are diabetes mellitus, hypertension, hyperlipoproteinemia, and tobacco smoking. Family history is also a high risk factor, but it cannot be "treated." Two of the risk factors mentioned are present in at least 60 to 70 percent of patients and only 1 percent of patients have no risk factor.[10]

Diabetes Mellitus

Patients with diabetes mellitus often develop extensive arteriosclerosis at a young age, and the disease is more rapidly progressive than in patients without diabetes. The reasons for this relationship are unknown. Not all diabetic patients have hyperlipoproteinemia and, therefore, it is not the sole cause. In the past, ischemic disease in diabetic patients was blamed on small-vessel disease. Small-vessel lesions showing endothelial hyperplasia and periodic acid-Schiff (PAS) staining material in the arteriolar walls were described.[11,12] However, studies using the electron microscope have found no small-vessel lesions except a thickened capillary basement membrane.[13,14] The abnormal basement membrane has been shown to be more permeable to ions and large molecules and may help explain the retinopathy and nephropathy of diabetes, but its effect on muscle blood flow or nutrition is not known.[15,16] It has also been shown that the vascular reactivity to vasodilator drugs injected intra-arterially is normal in diabetic patients, and this is further evidence against a small-vessel lesion.[17]

The distribution of severe involvement of blood vessels in patients with diabetes mellitus is different from that in patients with intermittent claudication without diabetes. Diabetic patients have less aortoiliac disease, an equal involvement of the superficial femoral arteries, and a greater amount of disease of the vessels between the knee and the ankle.[14,18] In a study of the vasculature of the foot,[18] patients without diabetes showed more arteriosclerosis than patients with diabetes.

Diabetes mellitus has been reported in 7 to 30 percent of patients with obstructive arterial disease; the percentages probably vary with the number of patients included with aortoiliac disease. It is common enough that all patients with arteriosclerosis obliterans should have a glucose tolerance test. The seriousness of diabetes mellitus in prognosis is also reflected in the fact that the amputation rate over a five-year period is four times greater in diabetic patients than in nondiabetic patients with vascular disease.[1] It has not yet been shown that strict control of diabetes mellitus will prevent progression of the arteriosclerosis, but recent studies with improved metabolic control of patients indicate that other complications of diabetes may be prevented.[19] Such studies are necessary in diabetic patients with peripheral vascular disease but, until available, it appears most logical to treat the diabetes intensively.

Hypertension

Patients with hypertension have a greater incidence of atherosclerosis and its complications. Peripheral vascular disease occurs twice as frequently as coronary artery disease in hypertensive patients.[10] This may be due to the hemodynamic stress of the higher blood pressure in

the lower extremities. One theory blames arteriosclerosis on the constant trauma of pressure, streaming, and turbulence of blood flow at angulations, branching, and bifurcations of arteries, leading to intimal damage and proliferation, and finally ending in plaque formation and fatty infiltration of the intima.[20]

Hypertension has been reported in 29 to 39 percent of patients with obstructive arterial disease. The control of hypertension has been shown to prevent strokes,[21] but no data are yet available regarding prevention of peripheral vascular disease. It is noteworthy, however, that propranolol has been reported to aggravate the symptom of intermittent claudication, or the symptom may appear for the first time with use of this drug.[22]

Hyperlipoproteinemia

Many studies have related hyperlipoproteinemia with obstructive vascular disease. Patients with familial type II hypercholesterolemia develop arteriosclerosis and its complications at an early age, often in the third decade. The majority of patients with arteriosclerosis obliterans and hyperlipoproteinemia are type IV or II; most studies have found type IV to be most common.[10,23] In type IV, the vascular disease is often more severe, but these patients tend to be older and have a high incidence of diabetes mellitus. The rare type III patients have more peripheral vascular disease than coronary artery or cerebral vascular disease. The incidence of hyperlipoproteinemia has varied from 31 to 57 percent in different studies.

In animal studies, treatment by diet and drugs to reduce cholesterol levels after induction of atherosclerosis has been shown to cause regression of lesions.[24] However, there are few such human studies. Levy and associates[25] reported that angina pectoris and intermittent claudication improved or even disappeared in patients with type III hyperlipoproteinemia treated by diet and clofibrate. Zelis and coworkers[26] studied a group of type III patients and found that their peak reactive hyperemia calf blood flow increased in as short a time as three months after treatment with an appropriate diet and clofibrate. Because the lesions in the arteries in these patients may be a foamy cell type, it is easier to envision their regression. Ost and Stenson[27] treated a group of hypercholesterolemic patients with diet and nicotinic acid. They reported that 19 of 31 patients improved their walking tolerance. However, repeat angiography after 3.5 years showed that 55 percent progressed, 35 percent remained unchanged, and only 10 percent regressed. The three patients who showed regression did have an improvement in their walking tolerance. Knight and associates[28] performed angiography before and after an average of 4.3 years following partial ileal bypass in hypercholesterolemic patients. Their nine patients remained stable by repeat angiography. Blankenhorn and coworkers[29] quantitated early atherosclerotic lesions of the femoral arteries by digital imaging angiography in 25 patients with severe hypercholesterolemia. After one year of intensive treatment, angiography was repeated. Progression occurred in 13 patients, 3 did not change, and 9 showed lesion regression. The 9 patients who demonstrated regression of their lesions had attained significantly lower levels of cholesterol than the other 16 patients. In this study, hypertension was also treated and it would be difficult to dissociate the effects of the two variables. Until more data are available, it appears reasonable to treat hyperlipidemia in patients who have arteriosclerosis obliterans.

Tobacco Smoking

Cigarette smoking is highly correlated with intermittent claudication, as shown by the Framingham study.[30] By multivariant analysis, cigarette smoking was second to no other risk factor; this was true for both men and women. The rate of occurrence of intermittent claudication was twice as great among smokers than nonsmokers, and the risk tended to increase with the intensity of the habit. In studies of obstructive arterial disease, 73 to 90 percent of patients are tobacco smokers.

How tobacco smoking induces or aggravates arteriosclerosis obliterans is not known. It has been shown that carbon monoxide increases the entry of cholesterol into the arterial endothelium in animals.[31] In some studies, tobacco smoking has been shown to raise blood lipids as well as increase platelet adhesiveness.[32] It has definite effects on peripheral blood flow, but the pathogenetic importance of this alteration is unknown. Smoking cigarettes decreases cutaneous blood flow of the feet significantly in normal subjects and usually in patients with obstructive arterial disease.[33] It has also been demonstrated to decrease reactive hyperemia blood flow in patients with obstructive arterial disease, meaning that it can affect stress-induced blood flow requirements. The decrease in cutaneous blood flow evidently occurs via the sympathetic nervous system, because it is markedly attenuated by reserpine or guanethidine administration.[34] Nicotine is a known stimulant of the sympathetic nervous system. Furthermore, patients do not show tachyphylaxis to tobacco; a decrease in blood flow occurs even in habitual smokers. The smoking of lettuce cigarettes or sham smoking does not decrease blood flow; so it is probably the nicotine in cigarettes that is the active agent. Chewing tobacco and cigar or pipe smoking can also affect the circulation.

Patients should not be promised relief of their symptoms if they stop smoking, for they may lose their motivation if the claudication does not improve. Cigarette smoking in normal subjects increases muscle blood flow, but in patients with obstructive arterial disease, muscle blood flow is unchanged.[35] The mechanism responsible for the increase in muscle blood flow with smoking is uncertain, but it may be partially due to the rise in systemic blood pressure.

Clinical studies strongly support the fact that patients must stop smoking. A study from the Mayo Clinic[36] has shown that 11 percent of patients with arteriosclerosis obliterans who continued to smoke required amputation of their limbs during a five-year period, whereas no amputations were necessary in patients who stopped smoking. Even after surgical bypass of obstructed arteries is performed, patients must give up smoking. Studies have shown that there are more occlusions of bypass grafts or of endarterectomies if patients continue smoking compared with those who quit after surgery.[37,38] In one study,[37] 25 percent of aortofemoral grafts occluded in patients who smoked more than five cigarettes per day compared with 10 percent in those who smoked fewer than five cigarettes per day; femoropopliteal grafts fared worse, as 40 percent occluded in smokers compared with 10 percent in nonsmokers. The frequency of graft occlusions rose with an increasing number of cigarettes smoked per day. If patients stopped smoking, they reverted to the normal rate of graft occlusion. In these studies, there was no significant difference in rate of graft occlusion if the results were analyzed for sex or age. One investigator[37] concluded that patients should not be offered vascular surgery if they refuse to stop smoking.

Exercise

There is general agreement in the literature that exercise regimens increase walking distance in patients with intermittent claudication. However, the mechanism underlying the improvement is not clear. In such patients, several studies[39-44] have demonstrated an increase in maximal walking distance after exercise training periods of a few months. In a small group of patients,[43] an increase in postexercise ankle blood pressure was found. However, other studies[39,41,44] failed to show an increase in muscle blood flow in the affected leg after ischemic exercise or at rest. Muscle metabolic function has also been reported to be improved in patients on exercise regimens.[44] In animal studies, rats with occluded femoral arteries have a greater exercise capacity than normal rats when the former group has had exercise training.[45] In dogs with acutely or chronically ligated femoral arteries, exercise induced by electrical stimulation of muscles increased collateral blood flow and decreased vascular resistance.[46] Arterial dilatation above the area of exercising muscle has been attributed to a wave of relaxation traveling centrally along the smooth muscle fibers of the vessel wall, the impulse being carried by the muscle fibers themselves. There is, therefore, evidence for an increased collat-

eral circulation with exercise. However, the possibility still exists that the improvement with exercise occurs by use of muscles not involved in the ischemic area or by better muscle coordination.

Exercise as a preventive measure may also be of value because it increases high-density lipoproteins in humans. In rabbits fed high cholesterol diets, exercised animals had less atherosclerosis than nonexercised controls.[47]

Successful exercise regimens have included supervised programs daily, every other day, or weekly; but it is important that the patient exercise daily. Exercise periods vary from 30 minutes to 1 hour. There has been no standard exercise except that the upright position is recommended. Heel raising, knee bends, energetic walking, stair climbing, running, jumping, dancing, playing ball, and skipping rope have been employed. It is important only that the patient exercises for 30 minutes to 1 hour each day in addition to normal activity. During this period, the patient should exercise as long as possible with the pain, rest until asymptomatic, and then exercise again. Exercises should be individualized according to the patient's capabilities and other diagnoses. Improvement often occurs within three months.

Buerger's exercises have been recommended for patients with ischemic rest pain. Supposedly the increased ischemia induced by elevation of the limb above heart level for a brief period leads to an increased blood flow during the ensuing dependency phase. Neither Buerger's exercises nor exercise of the involved extremity increases muscle blood flow as measured by a radioisotope method in the gastrocnemius muscle.[48]

Fibrinolytic Therapy

Dissolution of thrombi by thrombolytic agents, streptokinase or urokinase, has great appeal for restoring blood flow to a limb with an obstructed artery because its success would avoid surgical intervention. In 1967, a review of the results of streptokinase therapy in several European centers showed that only 34 percent of patients with acute occlusions had complete lysis of their lesions.[49] In a later report, Amery and associates[50] had a similar overall success rate if only the patients who left the hospital without amputation had reappearance of arterial pulses distal to the occlusion and had no serious complications were considered as successes. Evidently, lesions are lysed more frequently in smaller arteries than in larger vessels. Whether intravenous or intra-arterial administration of the fibrinolytic agent is the best route is not known. Thrombolytic therapy has also been attempted in patients with chronic occlusions.[51] The success rate is much less and the best results are obtained in those patients with the most recent occlusions. For some reason, proximal short stenotic lesions have responded more favorably in patients with chronic occlusions.

The place of thrombolytic therapy in occlusive arterial disease is not settled. Whether intra-arterial infusions directly adjacent to the thrombi may be more successful, as shown in coronary artery thrombosis, has not been studied. Thrombolytic therapy cannot be undertaken lightly because the incidence of minor and major bleeding is significant, and febrile reactions may be encountered with streptokinase. Defibrination therapy with ancrod derived from snake venom and other enzymes also has been used in the therapy of ischemic vascular disease. Results are inconclusive in patients with severe foot ischemia,[52] and intermittent claudication is not improved.[53]

Anticoagulant and Antiplatelet Therapy

Chronic anticoagulant therapy has been used in the treatment of arteriosclerosis obliterans but has not been popular in this country. Theoretically, it might prevent thrombosis in diseased areas of blood vessels or grafts, and extension of existing thrombi. Heparin may change large serum lipoproteins to a smaller nonatherogenic class.[54] However, there are no studies which compare anticoagulated patients with an adequate control group. In a study by Till-