43 Peripheral Vascular Disease

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Keypoints

- Peripheral arterial disease is very common, affecting up to 30% of all people with diabetes.
- Amputations are much more common in patients with diabetes and occur 5–8 times more often than in those without the disease.
- Atherosclerosis is common in people with diabetes, and measurement of ankle blood pressure may identify both people with and without diabetes at an early asymptomatic stage.
- People with diabetes have atherosclerotic lesions located more peripherally than people without diabetes and therefore are more commonly inoperable for technical reasons.
- People with diabetes have more complications to surgery, both locally (infections) and systemically (e.g. cardiac, pulmonary) than people without diabetes.
- Treatment of atherosclerosis in diabetes is basically the same as in patients without diabetes.

Introduction

Peripheral vascular disease includes diseases to arteries and veins outside the thoracic region. Because of the limitations of a chapter in a textbook dealing with diabetes, this chapter mainly covers the three most common arterial diseases: peripheral arterial disease (PAD), carotid artery disease and aortic aneurysmatic disease (AAA). Other, rarer manifestations of atherosclerotic disease (e.g. renovascular hypertension, abdominal angina and ischemia of the upper extremity) are mentioned briefly. Special considerations in patients with diabetes are dealt with in relevant sections; for example, infection in an ischemic foot in a patient with diabetes is described in the section on critical limb ischemia.

Atherosclerosis is the main cause of peripheral arterial vascular disease, and the overall pathogenesis is covered in Chapter 39. It is important to appreciate that the pathogenetic mechanisms of clinical atherosclerosis are dual: chronic obstructive and thrombotic. Whereas the chronic obstructive mechanism is the main cause of lower limb ischemia, also in patients with diabetes, it is often preceeded by a thrombotic event; a patient with mild claudication suddenly experiences significantly shortening of walking distance or sudden onset of rest pain. Or, the seemingly healthy person suddenly develops claudication. Of course, a heart attack or stroke in a patient with claudication is also a thrombotic event in a patient with chronic obstructive disease.

In general, patients with diabetes more often develop symptoms of atherosclerotic complications, they do it at a younger age and they are more difficult to treat and have more complications with treatment (especially with invasive treatment).

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Peripheral arterial disease

Peripheral arterial disease is a chronic condition that, like atherosclerosis in other vascular beds, develops over decades. The World Health Organization (WHO) definition includes exercise-related pain and/or ankle brachial index (ABI) <0.9. On average, symptoms from the lower limbs develop 5–10 years later than from the coronary circulation. Acute ischemia may develop because of:

1 Thrombosis in a vessel with pre-existing atherosclerotic plaques and/or stenosis;
2 Embolism (e.g. from mural thrombus in the heart);
3 An arterial lesion upstream; or
4 As a result of trauma.

Diabetes is a major contributor to PAD.

PAD is traditionally divided into four stages (Fontaine):

1 Asymptomatic (ABI <0.9);
2 Functional pain (claudication);
3 Rest pain; and
4 Non-healing ulcers or gangrene.

Incidence

In the most recent population-based studies in Western Europe, the incidence of symptomatic PAD is 3–4% among 60- to 65-year-olds, increasing to 15–20% in persons 85–90 years of age [1–3]. Similar findings have been reported in the USA. Looking at asymptomatic cases where the ABI is <0.9, the incidence is much

higher, and approximately 20% of all persons above 65 years of age, ranging from 10% in persons 60–65 years of age to almost 50% of those aged 85–90 years [1–3]. Critical limb ischemia, defined as ABI <0.4 or rest pain and/or non-healing ulcers, occurs in 1% of persons aged 65 years or older.

Incidence of PAD in people with diabetes

The incidence of PAD in people with diabetes depends on the usual atherosclerosis risk factors and duration of diabetes. There are only few demographic studies studying the general population. Using ABI <0.9 as selection criteria, Lange *et al.* [4] found a prevalence of 26.3% in people with diabetes compared to 15.3% in people without diabetes when screening 6880 Germans above 65 years of age, of whom 1743 had diabetes. Similar findings have been reported by others: 20–30% of those with diabetes have PAD [5,6]. Claudication is twice as common in those with diabetes than those who do not have diabetes.

Pathophysiology

It is outside the scope of this chapter to describe the pathophysiology of PAD in detail (see Chapter 39); however, in brief, the pathophysiology of PAD in those with diabetes is similar to that of a non-diabetic population. The abnormal metabolic state that accompanies diabetes directly contributes to the development of atherosclerosis. Pro-atherogenic changes include increases in vascular inflammation and alterations in multiple cell types. Both mechanisms of atherosclerotic complications are of importance in PAD (gradual narrowing resulting in stenosis and acute thrombosis in existing atherosclerotic lesion). Obviously, the long-term accumulation of lipids in the vessel wall is important and sudden local thrombosis can occur at any time, although in most cases this happens after symptoms (claudication) have developed.

To reach the stage of critical limb-threatening ischemia, advanced atherosclerosis has developed. Often, multiple segments of the arterial tree from the aorta to the foot are affected (stenotic and/or occluded). In people with diabetes, the atherosclerotic lesions are more peripherally located than in people without diabetes. Whereas the iliac and femoral arteries are most commonly stenotic and/or occluded in individuals without diabetes, in those with diabetes, it is most often the crural arteries that are severely affected by atherosclerosis. This poses a challenge for revascularization because the results in general are better the more proximal the reconstruction.

In order to develop ischemic non-healing ulcers, perfusion has to be very poor. The most reliable method for assessment of peripheral perfusion in those with diabetes is measurement of toe pressure. A toe pressure below 20–25 mmHg signals a poor chance of healing of a peripherally located ulcer. The special considerations related to the potentially dramatic course of infection in a diabetic foot are dealt with in Chapter 44.

Asymptomatic stage

The asymptomatic stage of PAD is especially interesting because it is associated with an approximately threefold increased mortality compared to matched controls [7,8]. This excess mortality is caused by accompanying cardiovascular disease (CVD). Asymptomatic PAD can be identified by a very simple test: measurement of ankle blood pressure. This test takes only a few minutes and is expressed as the ABI, where the ankle pressure is divided by the highest of the two arm blood pressures (BPs). In this manner, variations in BP between measurements do not influence the test result. Not only is an ABI <0.9 associated with increased mortality from cardiovascular causes, but also the level of ABI reduction is predictive: the lower the ABI the worse prognosis [7].

Identifying an asymptomatic person with an ABI <0.9 is not a case for evaluation with respect to revascularization of the lower limbs, but a case for serious preventive cardiovascular medicine.

Claudication

Claudication is experienced by the patient as pain in lower limb muscles appearing after walking, most often in the calf, the thigh and more rarely in the buttocks. The walking distance eliciting the pain is very variable, beginning after 10–15 meters in severe cases, whereas other patients will report pain only when walking fast uphill for more than 500 meters for example. It is important for both the patient and the treating physician to understand that claudication, although it may be incapacitating for a few, and troublesome for many, signals severe vascular disease systemically, and that cardiovascular morbidity and mortality is high (elevated 3–4 times compared to matched controls).

Rest pain

Rest pain typically begins at night when the patient is in the horizontal position. The positive effect of gravity on lower limb perfusion is then abolished. The patient typically complains about pain in the toes or feet during the night and most have experienced that standing or sitting up relieves the pain. Many patients will sleep sitting in a chair.

In patients with diabetes, symptomatology may differ because of coincidal peripheral neuropathy. Just like myocardial ischemia can be masked, symptoms from the lower extremity may be missing even though peripheral ischemia exists. This is especially important when a patient with diabetes presents with a small ulcer or wound on the lower limb, even if the patient thinks there is a good explanation for developing the ulcer, such as a relevant trauma. The lack of symptoms to signal peripheral ischemia combined with the risk of escalating infection in a diabetic foot has prompted many diabetologists to recommend routine assessment of peripheral circulation at regular intervals in all people with diabetes.

Non-healing ulcers

Non-healing ulcers often begin after minor trauma (e.g. hitting a toe against a chair or by using shoes that are too small). In some cases the ulcers develop without any trauma and those will often progress to gangrene if not treated. Ischemic ulcers develop on

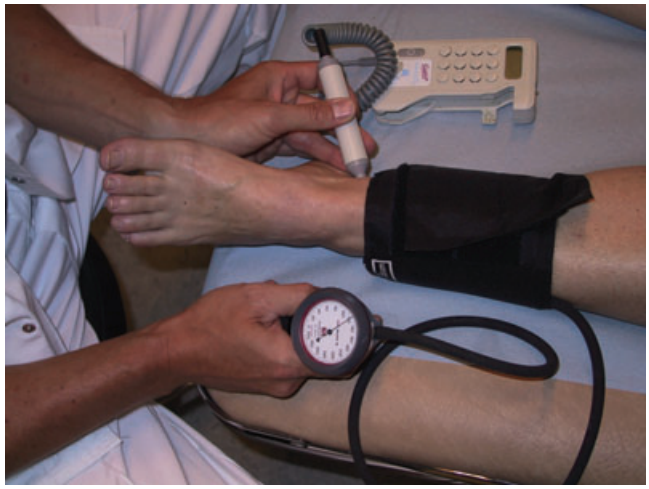

Figure 43.1 Measurement of ankle pressure using Doppler technique.

toes or on the foot, typically at points where shoes are in firm contact. Thus, they are usually easy to discriminate from venous ulcers, which are located at the level of the ankles or lower calf.

Rest pain, non-healing ulcers and/or gangrene are often referred to as critical ischemia. The "diabetic foot" is dealt with in Chapter 44.

Diagnosis

Most often the history and objective findings will ensure the diagnosis, but measurement of ankle blood pressure will quantify the ischemia and can be used to monitor changes in the disease (Figure 43.1). In some patients with diabetes, the media of smaller arteries become calcified making them incompressible. Thus, very high ankle pressures resulting in elevated ABI (>1.3) signals mediasclerosis and should be recognized as a falsely elevated measurement. In fact, ABI >1.3 is associated with a marked increased mortality because media sclerosis is found in patients with diabetes and those with renal failure.

Because small arteries are rarely affected by media sclerosis, measurement of toe pressure is an alternative for assessment of PAD. Use of the strain gauge technique is most commonly used (Figure 43.2). Toe pressure also is useful for prediction of healing of ulcers and amputation wounds.

Prognosis

The risk of amputation is only 1–2% at 5 years. Twenty-five percent of patients with claudication will experience a worsening of their symptoms from the lower legs; however, 75% will be unchanged or improve without revascularization [9]. In contrast the "systemic" risk is huge. Mortality in 5 years will be 15–25% and many more will have non-fatal myocardial infarction (MI) or stroke.

The risk of a patient with diabetes and PAD is much higher than that of the average patient with PAD. The patient with diabetes has an 8 times greater risk of amputation at the level of the transmetatarsal bones or above than the non-diabetic population [10]. In addition to the already severely increased mortality of PAD, patients who additionally have diabetes have a further doubling of their risk of death [10–12].

Figure 43.2 Measurement of toe pressure using strain gauge technique.

Treatment

Treatment of patients with symptoms from the lower limb therefore involves two aspects:

- Treatment of symptoms from the lower limb; and
- Prevention of cardiovascular complications

The former includes lifestyle modification, medical therapy and interventional therapy by either percutaneous transluminal angioplasty (PTA) or open surgery, whereas the latter includes lifestyle modification and preventive medical therapy.

It is beyond the scope of this chapter to detail all aspects of lifestyle modification and preventive medical therapy; however, it is extremely important for the reader to understand that patients with PAD derive as much or greater benefit from lifestyle modification and aggressive preventive medical therapy than any other group of patients (see Chapter 40). Most of the lifestyle changes which are beneficial to the patient with diabetes will benefit the PAD aspect as well, especially smoking cessation, regular exercise, weight loss and dietary changes.

Medical prevention follows the same guidelines as that of other clinical atherosclerotic manifestations such as ischemic heart disease and can be summarized as follows: aggressive statin treatment almost irrespective of cholesterol levels (Heart Protection Study and American Heart Association guidelines), antiplatetet therapy and BP control. In this chapter, only details of lifestyle modification and medical therapy relevant to PTA and surgery are discussed.

Treatment of symptoms from the lower limb

The vast majority of patients should be managed without invasive intervention PTA (and/or surgery). Because the risk of cardiovascular complications (cardiac and cerebral) is much higher than the risk of amputation, the main focus should be on preventive measures in order to halt the atherosclerotic process. The conservative approach with respect to revascularization is especially important for patients with diabetes because of the increased risk of surgical complications and poorer results of revascularization. One exception is patients with critical limb ischemia. Early revascularization before widespread infection can be limb-saving.

Exercise therapy has proven effective for improvement of walking distance, and regular exercise for 3 months can be expected to improve walking distance by 200–250% [13]. Because exercise also reduces cardiovascular morbidity and mortality, it cannot be stressed enough (for both the patient and the physician) that this is extremely important. Because the effect on walking distance is so good, and because it is important for survival, exercise therapy should always be tried before considering interventional treatment. There are only few exceptions where interventional treatment may be considered early on:

1 Patients with very short walking distance, not being able to carry out important daily responsibilities such as their work; and
2 Patients at risk of amputation (rest pain and non-healing ulcers).

The dilemma of explaining to patients that the symptoms they are experiencing from the lower limb are signaling high cardiovascular risk rather than lower limb risk is challenging. First of all, there is (or has been) a general perception that atherosclerosis in the limb is less dangerous than in other locations. The author hopes that the introductory remarks in this chapter have changed this potential misperception for the reader. Medical therapy for claudication includes cilostazol and statins. Treatment with both may be expected to improve walking distance by 30–50% and the latter furthermore reduces the cardiovascular risk. Other drugs have not proven useful in improving walking distance significantly [14].

Interventional treatment

Interventional treatment (endovascular or open surgery) for PAD is indicated when:

- Exercise and other lifestyle modification has failed to improve symptoms to an acceptable state;
- Claudication is incapacitating; or
- Critical limb ischemia is present (rest pain, non-healing ulcers and/or gangrene).

Again, for the patient with diabetes, the indication for revascularization should be considered very carefully in patients only with claudication. The choice between PTA and open surgical management depends on the location and extent of disease. In general, endovascular treatment can be expected to perform well in cases of shorter lesions whereas open surgery is preferred in cases of extensive occlusive disease. Obviously, whenever comparable results can be obtained, PTA is preferred for the simple reason that it is less invasive and associated with less complications than open arterial reconstructions. In patients with severe co-morbidity that might complicate the outcome of open surgery, PTA would be preferred even though theoretically surgery would be the treatment of choice if only patency of the revascularization procedure was considered.

The arterial lesions causing obstruction of blood supply to the lower limb are most often located in the distal abdominal aorta just proximally to the aorta–iliac bifurcation, in the iliac arteries, and in the common and superficial femoral arteries. The arteries in the calf, the anterior and posterior tibial and the peroneal artery, are often involved in those with critical ischemia and with diabetes. In general, when patients with diabetes present with symptoms, they have a more distal involvement with open vessels to the level of the popliteal artery and then occlusive disease of the calf vessels and sometimes also the arteries in the foot. The results of revascularization for patients with diabetes with toe or foot ulcers are worse than the general population partly because reconstructions yield better results with respect to patency when the lesions are more centrally located.

Percutaneus transluminal angioplasty

In principle, PTA can be performed anywhere between the heart and the feet. The more centrally located the lesions being treated, the better the results, especially with PTA. Also, the shorter the stenosis or occlusion, the better the results, and stenting improves patency in most cases. Endovascular-treated common iliac arteries, as an example, remain patent in 60–80% of cases after 5 years and thereafter they may be redilatated. Primary stenting has become the preferred treatment in most cases. Obviously, because complications are rare, and this procedure is associated with the best results, the tendency to offer PTA for iliac artery obstruction is greater than for occlusive disease more peripherally located.

PTA of the superficial femoral artery (Figure 43.3) may relieve symptoms, but the results depend on the extent of disease. The longer the lesion, the greater the risk of early reocclusion. Stenting appears to improve patency, at least for longer lesions (Table 43.1) [15]. When the indication for PTA is claudication, patency is better than if the indication is critical ischemia. This difference relates to the more extensive nature of the disease in the case of critical limb ischemia and may also relate to poor run-off vessels. The 3-year patency is 48%, which may be improved to 64% if stenting is added. In case of critical limb ischemia, the results at

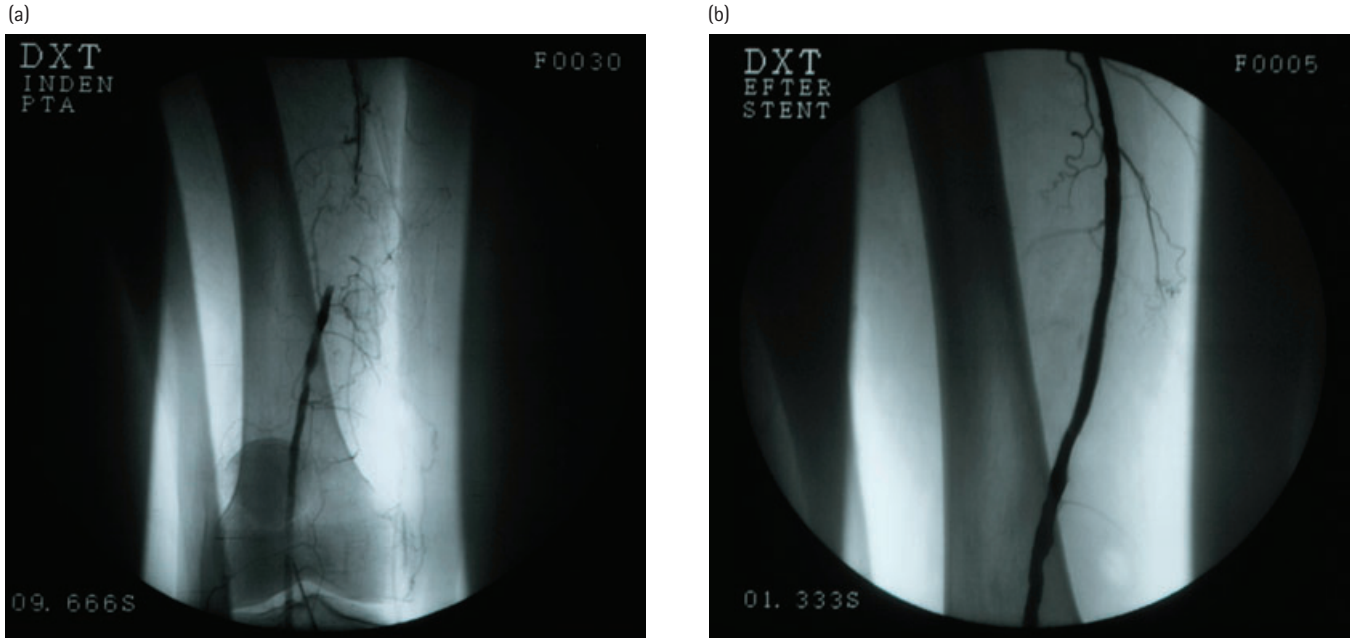

Figure 43.3 Short occlusion of the superficial femoral artery (a) treated with PTA and stenting (b).

Table 43.1 Pooled patency of vascular reconstructions (TASC*II).

	1 year	3 year	5 year	10 year
Endovascular				
Iliac artery	86%	82%	71%	
Fem-pop stenosis PTA	77%	61%	55%	
Fem-pop occl. PTA	65%	48%	42%	
Fem-pop stenosis PTA + stent	75%	66%		
Fem-pop occl. PTA + stent	73%	64%		
Open surgery				
Aorto-bifemoral bypass			90%	80%
Fem-fem cross-over			75%	
Fem-pop vein			80%†	
Fem-pop PTFE†			30–75%†	

fem, femoral; pop, popliteal; PTA, percutaneous transluminal angioplasty; PTFE, polytetrafluoroethylene.
* Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC).
† Secondary patency.

3 years show a patency of 30% without stenting and 63% with stenting (Table 43.1) [15]. PTA of crural vessels is also feasible; however, the long-term results are not good. Data on limb salvage with PTA of crural vessels alone are scarce. Adjunctive medical therapy to improve patency following PTA and stenting, with anticoagulation and/or antiplatelet therapy, has been tested only in a few trials. Antiplatelet drugs improve patency, and the combination of aspirin and clopidogrel may be beneficial [16].

Open surgical revascularization

Open surgical revascularization still dominates as the treatment of choice in cases of critical limb ischemia, because of the extensive nature of the atherosclerotic lesions in these patients. For claudication, open surgical treatment is rarely performed, while for extensive disease of the distal aorta and iliac arteries, the aorto-bifemoral bypass remains the procedure with the best long-term outcome. In addition, femoral–femoral cross-over bypass may be performed for unilateral iliac artery occlusion. Also, endarterectomy, as described below, may be an option for treatment of claudication. Only one trial has compared open surgery with endovascular treatment of critical limb ischemia, the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial [17]. The primary efficacy outcome measure was amputation-free survival, but because approximately two-thirds of the endpoints were deaths, only one-third of the endpoints really determined which procedure was best. Within 6 months postoperatively, there was no difference in the primary endpoint, but thereafter bypass patients seemed to do better [17].

In general, two surgical techniques are used: endarterectomy and bypass. Endarterectomy is performed by separating the intima from the media, and in this manner the atherosclerotic lesion can be removed. Endarterectomy can be used in cases with severe occlusive lesions of limited anatomic extension, in the external iliac or in the common femoral artery. The advantage of this technique is that it can often be performed without the use of artificial graft material and patency is excellent. Bypass is preferred when the obstructive and/or occlusive lesions are extensive (e.g. total superficial femoral artery occlusion or multiple serial lesions warranting a femoral–crural bypass) (Figure 43.4). Bypass surgery can be performed with artificial materials or with auto-

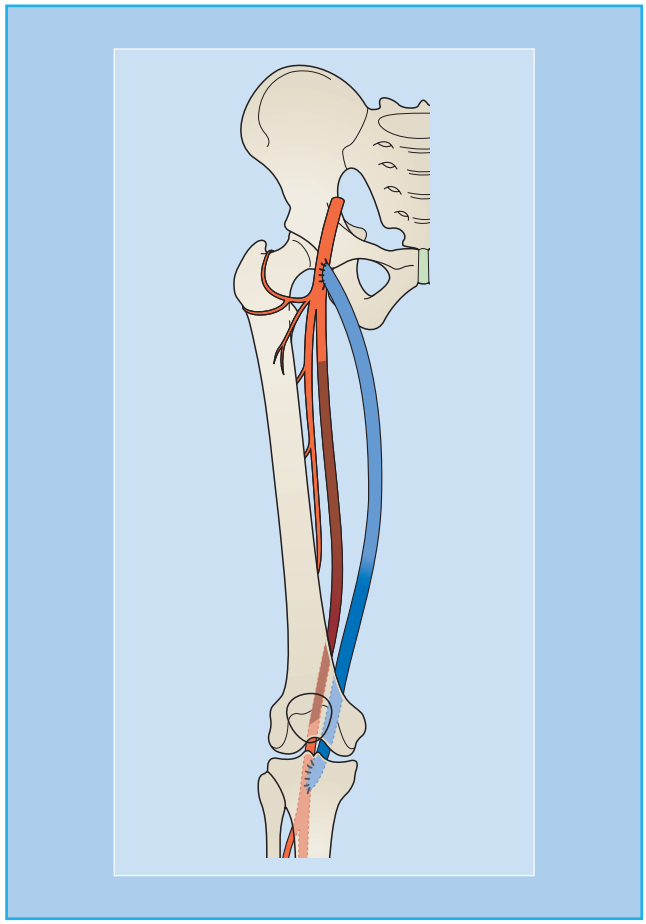

Figure 43.4 Long superficial femoral artery occlusion treated with femoro-popliteal bypass.

logous veins. For bypass of aortic or iliac artery origin, artificial grafts are almost always used. This is because there is no easily removable vein with similar dimensions that can be used in these locations. Also, Dacron or polytetrafluoroethylene (PTFE) grafts perform very well in the aorto-iliac–femoral region. For peripheral bypasses, typically originating from the common femoral artery, autologous vein grafts are preferred for two reasons: they last longer (much better patency) (Table 43.1) and they carry less risk of infection. For longer bypasses, such as from the common femoral to the popliteal artery below the knee, a saphenous bypass is performed leaving the vein *in situ*. This means that the vein is left in its original anatomic location; however, the proximal and distal ends are anatomized to the arterial system. The venous valves are cut with a knife mounted on a catheter and side branches are occluded. In this manner, the vein retains its nervous innervations and native vascularization.

Complications of endovascular treatment

Complications relate mainly to the site of puncture and the risk of peripheral embolization. "Systemic" cardiovascular complications are rare. Hematoma in the groin access point is common; however, it only rarely requires any action to be taken. Development of an iatrogenic pseudo-aneurysm is seen in 0.5–1% of cases and can easily be treated with ultrasound-guided compression or ultrasound-guided thrombin injection.

Complications of open surgical treatment

These can be divided into local and systemic categories. The former relate to the actual incisions and dissections including wound healing and infections. Whereas complications from accidental damage to other organs and/or structures are very rare, wound healing problems and infections are unfortunately quite common. In particular, surgery on the lower limb involving the groin and peripheral incisions have wound complications in 10–20% of cases (e.g. hematoma, lymph oozing or necrosis of the wound) [18]. Infections are seen in 3–5% of cases, approximately one-third involving the vascular reconstruction. Infection of the vascular reconstruction is more frequent when using artificial graft material [18].

Systemic complications to open surgical revascularization relate to the surgical trauma and to the stress response. In vascular reconstructions involving the aorta and other central arteries, the cardiopulmonary complication rate is considerable. Implantation of an aorto-bifemoral bypass graft is associated with a 30-day mortality of 2–5% and a rate of "general" complications of 10–15% (e.g. pulmonary, cardiac, renal, prolonged stay at the intensive care unit, stroke and deep venous thrombosis) [18]. Systemic complications to peripheral revascularizations occur less frequently; however, they are considerable. When the indication is claudication, the morbidity with respect to general complications is low, 2–4%; however, in cases of critical ischemia and peripheral bypass surgery, the morbidity increases to 10% with a 30-day mortality of 3–5%. This difference in morbidity is a reflection of the more advanced level of generalized atherosclerotic disease in patients with critical ischemia. In patients with diabetes, complications are more common especially with open surgery. A doubling of risk should be expected.

Results of endovascular and open surgical reconstructions

These are summarized in Table 43.1. In general, when treating more centrally located arterial obstruction, the long-term results are better. In addition, treating patients with claudication results in better long-term outcome than operating on patients with limb-threatening ischemia. This difference relates to the generally poorer condition of the peripheral circulation in cases of critical ischemia with better run-off vessels in the patient with claudication.

In peripheral reconstructions, vein grafts perform better. It may seem unrewarding to treat patients with critical limb ischemia with a peripheral bypass using an artificial graft when there is only a 50% chance of being patent at 1 year; however, if the alternative is amputation and/or very poor quality of life (i.e. severe rest pain), 1 year with a functioning graft may very well be worthwhile for both the patient and surgeon. Limb salvage as a result is almost always better than patency of the reconstruction

Table 43.2 Separation of threatened from viable extremeties.

Category	Description/prognosis	Findings		Doppler signals	
		Sensory loss	Muscle weakness	Arterial	Venous
Viable	Not immediately threatened	None	None	Audible	Audible
Threatened					
a. Marginal	Salvageable if promptly treated	Minimal (toes) or none	None	(Often) inaudible	Audible
b. Immediate	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	(Usually) inaudible	Audible
Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

because in many cases, once the ischemic limbs with tissue loss have healed, the "need" for amputation becomes less. Patients with diabetes typically have poorer outcome of vascular reconstructions, with patency rates that are inferior to those without diabetes. Patients with diabetes have more complications to treatment, not only infections but also systemic complications are more common.

Acute lower limb ischemia

This condition is most often caused by thrombosis in existing atherosclerosis (i.e. a patient with previous symptoms of chronic PAD). Another common cause is thrombosis of a popliteal aneurysm. Embolism remains a common cause, although not as often as in the past because of better anticoagulant therapy for patients with atrial fibrillation. Eighty percent of emboli are of cardiac origin; however, aneurysms of the aorta or peripheral aneurysms may give rise to peripheral emboli.

Other causes include trauma and iatrogenic lesions (e.g. from arteriography with puncture of the femoral artery). Aortic dissection may cause lower limb ischemia as well as acute deep venous thrombosis (phlegmasia coerulae dolens). Incidence in Western Europe is 300–400 per million per year.

Pathophysiology

Thrombosis is caused by plaque rupture and subsequent thrombosis. Distal to the acute occlusion, arterial flow is slow and when combined with a hypercoagulable condition, it may lead to further thrombosis. The degree of ischemia depends on the location and the degree of collateral development. Therefore, thrombosis is often better tolerated than embolism because patients with existing atherosclerosis most often has developed collaterals.

Emboli will typically occlude an artery at a bifurcation; in the lower limbs, at the aortic bifurcation (saddle embolus), iliac artery and femoral artery bifurcation. Sixty percent of cardiac emboli will end in the lower limbs, 15% in the arms and the rest in the brain and other organs. Microemboli, typically from aneurysms, affect small peripheral arteries, and are thus the cause of "blue toe" syndrome.

Symptoms

Acute ischemia is characterized by pallor, pain, pulselessness, paresthesia and paresis (the 5 P's). Symptoms may begin dramatically and in some cases the late signs of ischemia, paresthesia and paresis occur within a few hours. More often, symptoms begin with pain and paresthesia and later sensory and muscular paresis. Acute ischemia is traditionally divided into three classes (Table 43.2).

Diagnosis

Diagnosis is often easy with typical clinical signs. ABI will be low, if measurable at all. Imaging with either duplex ultrasound, magnetic resonance angiography (MRA) or digital subtraction angiography (DSA) is possible but may delay treatment. In cases of thrombosis, it is most often desirable to perform arteriography with subsequent thrombolysis in order to visualize the underlying pathology causing the thrombosis.

Prognosis

If revascularization is possible before irreversible ischemia has occurred, the limb can be salvaged and normal function regained. Co-morbidity is high in cases of acute ischemia; when acute revascularization is needed the procedure-related mortality is 10–20% because of release of toxic substances from ischemic tissue combined with existing cardiac disease.

Treatment

Thrombosis in existing atherosclerotic lesions may be treated by endovascular or open surgery. The former is preferred if revascularization is not imminent. By catheter-directed intra-arterial thrombolysis, the underlying atherosclerotic lesions will be exposed and may in some cases be treated by PTA and/or stenting. In other cases, bypass surgery may be needed. Inoperable cases may be converted into operable cases by thrombolysis because distal thrombosis most often makes surgery (and PTA) useless when there are no run-off vessels. Another advantage of thrombolysis is that emergency surgery is converted into a less urgent intervention. Emboli can be treated by embolectomy by inserting a balloon catheter, either in the femoral or popliteal artery, and retracting the emboli after inflating the balloon (Figure 43.5). Some cases of embolism may also be treated by thrombolysis.

Prevention

Arterial emboli have a high recurrence rate and the underlying case should be treated, if possible; corrective treatment for atrial

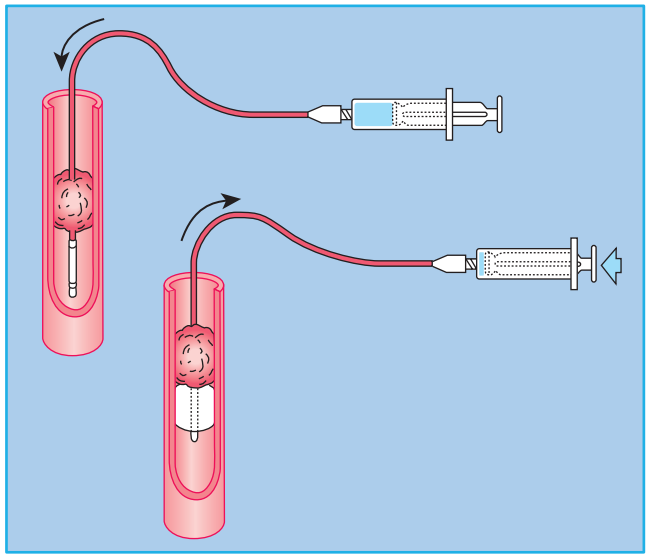

Figure 43.5 Embolectomy performed with a balloon catheter.

fibrillation and resection or exclusion of aneurysms. If the source of embolism cannot be eliminated, anticoagulation must be considered.

Atherosclerosis of renal and mesenteric arteries

Renal artery obstruction

Renal artery obstruction can cause severe hypertension and renal failure but interventional treatment may improve both conditions. Today, open surgical management is only rarely performed because endovascular management is much less invasive and feasible in the majority of cases. Open surgery, thrombo-endarterectomy or bypass, is performed when renal artery disease is combined with other pathology such as aortic occlusion or AAA.

Mesenteric artery occlusive disease

Mesenteric artery occlusive disease may cause abdominal angina. Just like atherosclerotic lesions in other locations, many cases are asymptomatic and probably do not need intervention with regard to the obstructive disease, but lifestyle changes and medical preventive treatment are indicated. Patients with classic symptoms – post-prandial pain occurring 10–20 minutes after a meal and weight loss – often benefit from revascularization; however, many patients have less obvious symptoms, and the mere occurrence of a lesion on one of the three main vessels supplying blood to the gastrointestinal tract (celiac trunk, superior and inferior mesenteric artery) does not warrant interventional treatment. In general, a single lesion in one of the three arteries is seldom thought to cause ischemia. Diagnosis is possible by ultrasound of the suprarenal vessels in most cases, otherwise computed tomography arteriography (CTA), MRA or DSA may be needed. Interventional treatment today is mainly balloon angioplasty and stenting. Long occlusions of the superior mesenteric artery and/or occlusive mesenteric disease combined with other pathology of the aorta may be treated by open surgery (e.g. aorto-mesenteric bypass).

Ischemia of the arms

Atherosclerosis and ischemia of the arm are much less common than in the lower limb. The most common location for development of atherosclerosis in the arteries supplying the upper extremity is in the brachiocephalic trunk and subclavian arteries central for the origin of the vertebral arteries. Rarely, occlusive lesions are located more peripherally in the subclavian or axillary arteries. Takayasu vasculitis may also cause upper extremity ischemia.

Typical symptoms of chronic arm ischemia

Theses include "claudication"; i.e. pain when using the arm. In typical cases pain is encountered when performing tasks with the arms elevated, such as hanging laundry, or other physical use of the arm. Critical ischemia with rest pain or gangrene is rare but may occur. Diagnosis is easy with lack of pulses at palpation. Measurement of bilateral BP and ultrasound may locate and quantitate the stenotic lesion. If BP cannot be measured by auscultation, a Doppler device may be used as for measurement of ankle BP. Additionally, or in case of severe ischemia, finger pressure measurement by strain gauge technique may be used. Upper arm angiography by CT, MRA or DSA may be supplemental.

The prognosis is often good because development of critical ischemia and the necessity for amputation is rare. Patients with finger gangrene should be investigated for vasculitis.

Treatment of upper extremity atherosclerosis is similar to that of atherosclerosis in other vascular distributions: risk factor reduction by lifestyle changes and preventive medications for all, and revascularization in some. In fact, only rarely is interventional treatment indicated, but in cases of incapacitating functional pain and/or critical ischemia, revascularization should be considered. Endovascular treatment dominates because of its less invasive nature for lesions near the origin of the brachiocephalic trunk and subclavian arteries. For lesions that cannot be treated by endovascular techniques, such as long lesions or lesions that cannot be crossed by a guide wire, bypass surgery is indicated (carotid–subclavian bypass). Peripheral bypass of the upper extremity (e.g. at the level of the brachial artery) is rare and patency is poor.

Acute arm ischemia

This is most often caused by embolization, but alternatively can be caused by thrombosis in an existing stenosis such as of the subclavian artery. Whereas the former may be treated easily by embolectomy via a small incision in the cubital fossa, the latter may be more complex to treat, perhaps requiring intra-arterial thrombolysis before vascular reconstruction. Embolism is most often of cardiac origin, either from atrial fibrillation, mural thrombus in the heart or valve disease. Vascular causes include a subclavian aneurysm or stenosis. Microemboli may occur periph-

erally and present as gangrene of one or more fingers. Extravascular causes include a cervical rib. Obviously, eradication of the embolic source is crucial, if possible. Treatment of the peripheral ischemia may include thrombolysis, but in most cases collaterals develop and amputation does not become necessary.

Aortic aneurysmal disease (abdominal aortic aneurysm)

This section focuses on abdominal aortic aneurysms (AAA) because thoracic aortic aneurysms are not considered part of peripheral vascular disease. The main difference between those with and without diabetes with respect to treatment of aneurysms is that patients with diabetes are more prone to complications after surgery; however, because of the nature of preventive surgery for aneurysms, this only rarely causes changes in management once the risk of surgery has been weighed against non-surgical treatment.

Aneurysm of the aorta is a common condition in the elderly, especially in the infra-renal aorta. An artery by definition becomes aneurysmal when the diameter locally increases more than 50% compared to the "normal" diameter proximal or distal to this site. In case of the infra-renal aorta, an aneurysm is present when the diameter exceeds 30 mm.

The prevalence of AAA is approximately 5% in men over 70 years of age; however, only a minority of them will have a size that mandates surgery (diameter >5–6 cm). In patients with other atherosclerotic manifestations, such as PAD or carotid disease, the incidence of AAA is 2–3 times greater than in persons without. Also, there is a 2:1 ratio of AAA occurring in men:women. Finally, the tendency to develop AAA is partly inherited, as the risk for a male with a father or brother with AAA is approximately 20%. People with diabetes seem to have a slightly lower incidence of AAA; approximately 80% of the prevalence of those without diabetes [19].

Pathophysiology

Arteries enlarge with age, and the diameter of the infra-renal aorta is normally below 20 mm in a 70-year-old male. If the wall weakens locally, an aneurysm develops. A true aneurysm develops when all three layers in the arterial wall are involved and dilate as in the case of the typical infra-renal AAA. False aneurysms or pseudo-aneurysms develop after iatrogenic trauma, such as PTA or other transfemoral procedures, and at arterial anastomotic sites. Finally, dissection occurs when a rupture of the intima allows blood to enter between the layers of the artery wall.

Aortic aneurysms may rupture, leading to almost certain death. It is estimated that 80–90% of patients with ruptured AAA die before they get to hospital. Ruptured AAA causes an estimated 2–3% of all deaths among men, whereas the number for women is 1%.

In most AAA there is an atherosclerotic degeneration of the vessel wall that dilates; however, it is unclear why atherosclerosis in some patients results in occlusive disease and in others in aneurysm development. Accelerated breakdown of elastin has a role in AAA development. Simultaneous presence of both occlusive and aneurysmal disease is common in many patients. Inflammatory aneurysms are present in 5–10% of AAA where the aortic wall is thickened as part of perianeurysmal or retroperitoneal fibrosis.

Symptoms from AAA

Symptoms are rare and so most cases are asymptomatic. Diagnosis is often made coincidentally, as when a patient complains of slight upper gastric pain and has an ultrasound of the gallbladder, which discloses the AAA. Also typically, a patient may complain of back pain and have a lumbar X-ray where the AAA is discovered. Whether the patient's pain was really related to the AAA or to gallstones or to the back is often difficult to ascertain.

Some patients will sense a pulsation in the abdomen, while large aneurysms may cause discomfort or compress surrounding organs, mainly the gastrointestinal tract. The main risk is rupture which, when intraperitoneal, most often leads to immediate death. If rupture is into the retroperitoneal space, a hematoma may be contained and the patient may survive for hours. Rupture and development of a hematoma lead to pain in the abdomen and/or back. Chronic rupture is rare because almost all cases will be fatal within hours.

Aneurysms may cause peripheral embolization, causing a cyanotic or gangrenous toe as the first symptom.

Diagnosis

Diagnosis of AAA is easy. Ultrasound is very accurate in making the diagnosis and estimating the diameter of the aneurysm (Figure 43.6). In the few cases where ultrasound is inconclusive, a primary CT scan may be necessary. Otherwise, CT or MR scanning is only performed when the size of the AAA dictates to an extent that intervention should be considered. Arteriography is rarely performed for AAA; however, in cases of both AAA and symptoms of PAD, an arteriogram may be warranted for planning of the revascularization procedure. A patient with acute abdominal pain in pre-shock should always be suspected of ruptured AAA.

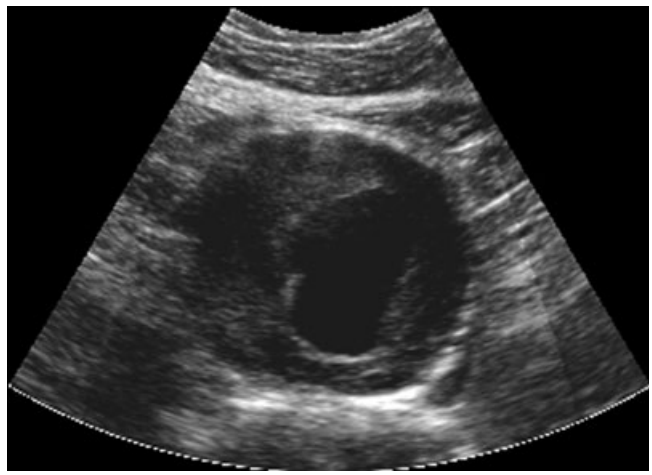

Figure 43.6 Ultrasound image of abdominal aortic aneurysm. Notice the presence of large thrombus inside the aneurysm sac.

Prognosis

The risk of rupture relates to the size of the aneurysm. When the diameter exceeds 6 cm, the annual risk of rupture is 10–20%, whereas the risk of rupture in case of an AAA with a diameter of 3–4 cm is less than 1%. Aneurysms tend to expand; small aneurysms dilate 1–2 mm/year whereas larger aneurysms may expand 2–3 times faster. Smoking and hypertension seem to increase the rate of growth. Rupture is associated with 90% mortality – the survival for those who reach the hospital and have immediate surgery is approximately 50–60%. Concommitent coronary disease is responsible for a 50–100% increased mortality of aneurysm patients even when aneurysm mortality is disregarded.

Treatment

Treatment of AAA involves, in addition to surgery for some, the same preventive treatment that is given to other patients with atherosclerotic manifestations: lifestyle changes and medical therapy with platelet inhibitors, statins and BP control.

Treatment of ruptured AAA is always interventional (open surgical or endovascular) unless the patient's overall condition is considered too poor to attempt rescue. In some cases, a fatal AAA may be a dignified death; for example, in an elderly patient with both end-stage renal failure and heart failure. Symptomatic non-ruptured aneurysms should be treated acutely or subacutely because of the risk of imminent rupture.

Treatment of large asymptomatic AAA reduces AAA mortality [20], and those with asymptomatic AAA should be offered elective interventional treatment if the risk of rupture exceeds the risk of the procedure, and if the patient is fit for the procedure and expected to have some good quality years remaining. Because any procedure for treatment of AAA either carries a considerable perioperative risk or involves a very long postoperative period with potential reinterventions, the decision to offer interventional treatment is not always easy and almost always a decision is made with the patients and their families.

The choice between treatment modalities is made keeping these facts in mind: open surgery is a well-proven procedure with known risks and long-term results, including an overall 3–5% perioperative mortality, but limited AAA morbidity after the procedure. Endovascular aneurysm repair (EVAR) has been shown to have lower perioperative morbidity: 1.5% for EVAR compared to 4.5% for open surgery [21–23]. Because the long-term results of EVAR are unknown (5–10 years), continuous surveillance with annual CT or ultrasound is necessary. Until recently, the number of reinterventions because of either migration or failure of the implanted device, both leading to endo-leak (blood re-entering the excluded aneurysm sac which is thereby again at risk of rupture) were considerable; however, recent data show improvement and is 10–15% at 3 years [23].

As an example of choice of treatment modality, a 65-year-old man with a 6-cm AAA and no other known co-morbidity should be offered treatment, preferentially open surgery, because his perioperative risk will be low (i.e. 2–3%), whereas the annual risk of rupture is approximately 10%. At the other end of the spectrum is the 80-year-old man with previous coronary artery bypass graft surgery and with a similar-sized AAA of 6 cm. His risk with open surgery includes >10% 30-day mortality in addition to a considerable risk of other complications. Endovascular treatment could be a good alternative for this patient if he is expected to live at least 3–5 years.

EVAR has been thought to be a treatment alternative for patients unfit for open surgery. The EVAR-2 trial tested this hypothesis and patients found unfit for open repair were randomized to either conservative management or EVAR. Survival was not improved by EVAR and it was poor in both groups: approximately 50% of patients in both groups were dead at 3 years and only one-quarter of deaths was aneurysm-related [24]. Thus, being found unfit for surgery in this study indicated a poor prognosis in general that EVAR did not affect.

Open surgical treatment with resection of the aneurysm and replacement of the diseased part of aorta with an artificial graft

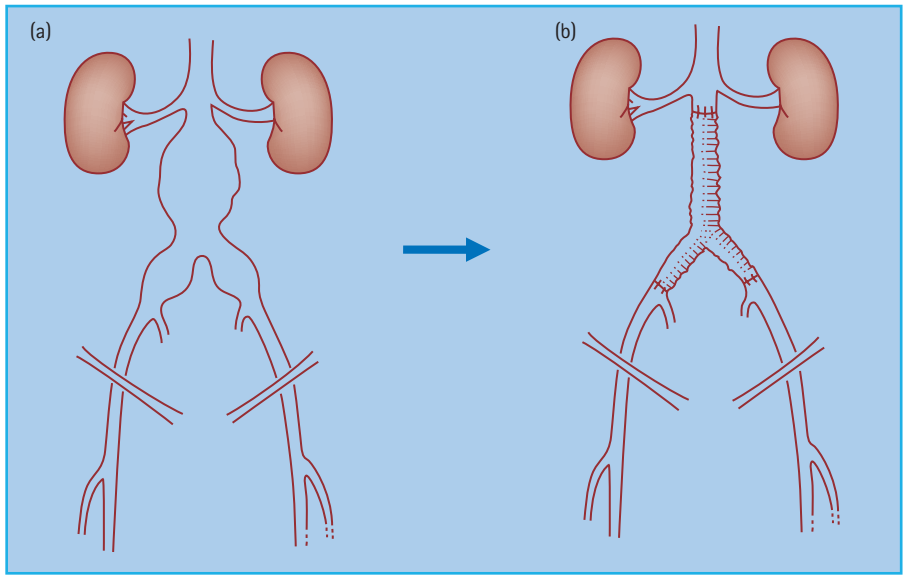

Figure 43.7 Abdominal aortic aneurysm treated by resection and implantation of aorto-bi-iliac bypass graft.

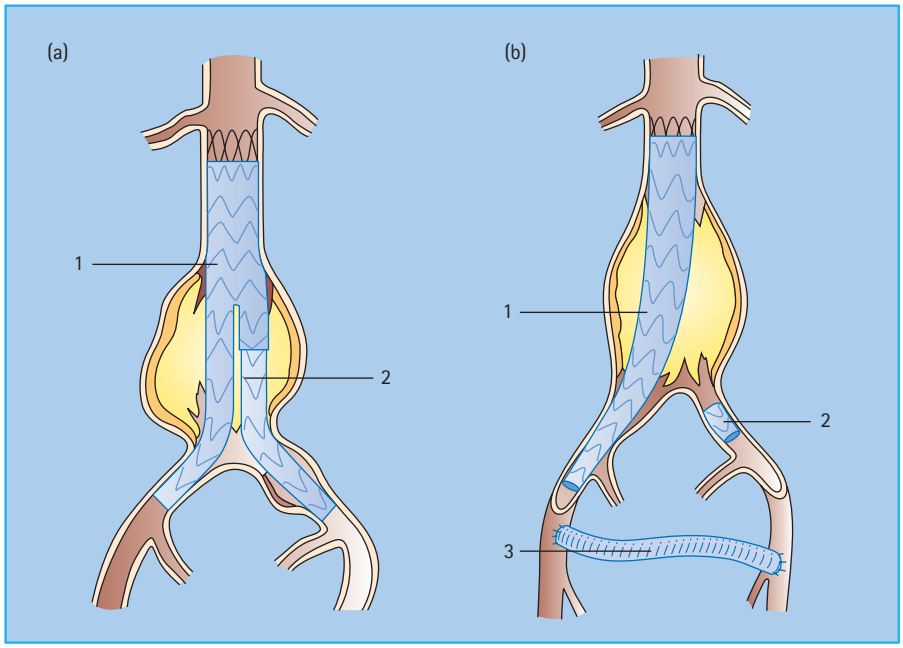

Figure 43.8 Abdominal aortic aneurysm treated by endovascular repair. (A) First the bifurcated graft is inserted via the right femoral artery and fixed by stenting at the proximal and distal end of the graft. The left limb (2) is inserted via the left femoral artery and connected to the main graft. (B) Insertion of an aorto-uni-iliac endograft (1) combined with a femoro-femoral bypass graft (3) is used when one of the iliac arteries (2) cannot be passed.

has been performed for more than 40 years (Figure 43.7). Complications of open surgical repair relate to the considerable surgical trauma of this major procedure. Approximately 10–20% will develop general complications such as cardiac, pulmonary and renal complications in addition to prolonged stay at the intensive care unit and stroke.

Endovascular treatment of AAA involves inserting a collapsed prosthesis via the femoral artery, placing it below the renal arteries, deploying and fixing it (stenting) under X-ray guidance. The technique mostly used today involves inserting a bifurcated graft from one femoral artery and then placing the other limb via the contralateral femoral artery (Figure 43.8). Complications to EVAR are few in the perioperative period, but a considerable number of patients will need reinterventions, which in most cases can be performed by endovascular techniques. These include placement of another proximal stent because of endo-leak and embolization of inferior mesenteric or internal iliac arteries.

Screening

The value of population-based screening for AAA is now well documented. A recent meta-analysis of the four randomized controlled trials found aneurysm-related mortality to be reduced by 43% in people being offered screening [25]. Today, it is recommended in many countries that men older than 65 years and previous smokers undergo ultrasound screening. Family members who are direct descendants of those so affected should also undergo screening.

Peripheral aneurysms

Aneurysms may develop at other locations, popliteal and femoral arteries being the second and third most common locations. More than 50% of patients with peripheral aneurysms also have an AAA. Symptoms are different in the sense that rupture is less common; however, symptoms derived from compression (popliteal vein thrombosis, pain and other symptoms of nerve compression), peripheral embolization or thrombosis of the aneurysm most often bring the patient to medical attention.

Treatment is the same as for AAA: general prevention against atherosclerotic disease and intervention in symptomatic cases. Popliteal aneurysms are generally treated surgically by exclusion and bypass or by resection and replacement by a short graft. Femoral aneurysms are treated by resection and placement of a graft. Endovascular management is possible; however, graft thrombosis and failure of stent graft material have so far made indications unclear. Large asymptomatic peripheral aneurysms should probably be treated by either open or endovascular surgery; however, no documentation is available at this time that such treatment is beneficial.

Aneurysms of visceral or renal arteries may occur but are rare. Treatment is interventional when they are large. Endovascular management is under development, however, its indications are unsettled.

Carotid artery disease

This section focuses on stroke and carotid disease because cerebrovascular disease in general is dealt with in Chapter 42. The relationship to atherosclerosis for many patients with stroke is well documented, although stroke, unlike other ischemic conditions, has other common pathogenetic mechanisms.

It is very important to discriminate between symptomatic disease and asymptomatic cases. Patients with recent cerebrovascular symptoms and an ipsilateral stenosis are comparable with patients with a recent acute coronary event: the risk of a new

thromboembolic event is very high and diagnostic workup and treatment should be started immediately. The pathogenetic mechanism is similar to that of an acute coronary event with plaque rupture and subsequent thrombosis; however, in the case of the carotid, embolization into a cerebral artery is much more common than thrombotic occlusion of the carotid artery itself. Perhaps the larger diameter of the carotid artery explains this difference.

The prevalence of carotid stenosis is high. Among patients with acute cerebrovascular symptoms, an ipsilateral stenosis of greater than 50% diameter reduction is found in 15–20% of cases. In patients with other clinical atherosclerotic manifestations, a carotid stenosis is found in 20–30%.

Pathophysiology and symptoms

See Chapter 42, dealing with cerebrovascular disease.

Prognosis

The risk of stroke is increased in the presence of carotid stenosis. For asymptomatic patients with a carotid stenosis exceeding 60% diameter reduction, the annual risk of ipsilateral stroke is approximately 2%. When carotid stenosis is related to recent ipsilateral cerebral ischemic symptoms (symptomatic stenosis), the risk is much higher, especially just after the first event. The 30-day risk of stroke in patients with previous cerebrovascular symptoms is as high as 10% when an ipsilateral carotid stenosis is present. Thereafter, the risk gradually declines and after a year it is approximately 2–3% annually, similar to asymptomatic carotid stenosis. The 3-year risk of ipsilateral stroke is 25–30% in symptomatic patients with a stenosis greater than 70% diameter reduction.

Diagnosis

Diagnosis of carotid disease should be carried out by duplex ultrasound scanning (Figure 43.9). The accuracy of the method is well documented both for identification and quantification of degree of stenosis. Many surgeons will perform endarterectomy based only on ultrasound examination.

Treatment

Treatment of patients with carotid stenosis is like that of any other condition related to atherosclerosis: treatment of the atherosclerotic disease itself and treatment of local manifestations. Risk factor reduction, including changes in lifestyle, is exactly the same as for patients with other clinical manifestations of atherosclerosis, although there may be regional variation in the choice of antiplatelet agents. Aggressive lipid-lowering reduces both the risk of recurrent stroke and the risk of coronary events especially in this patient group [26–28].

It is important to realize that any intervention for carotid stenosis is performed to prevent future "local" events (stroke). Thus, the risk of the intervention itself should be weighed against the absolute risk of an event. Furthermore, the most common complication of surgery and stenting is ipsilateral stroke, the event that the procedure is supposed to prevent. Most important, the overall risk of the patient should be weighed against the absolute risk reduction derived from the procedure.

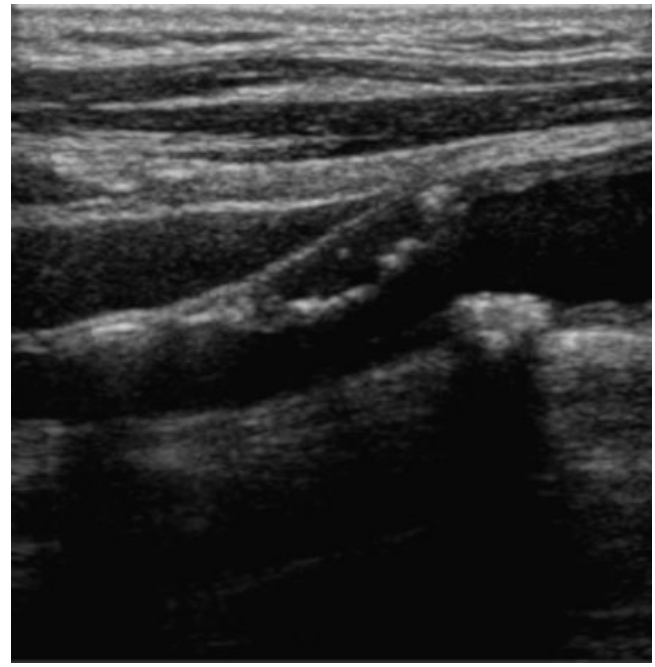

Figure 43.9 B-mode ultrasound image of carotid stenosis. Top part is echolucent indicating high content of lipid/necrotic core; bottom part is echogenic indicating a fibrous plaque.

Symptomatic carotid stenosis

Symptomatic patients with carotid stenosis benefit from endarterectomy when the stenosis is greater than 50–70% diameter reduction and neurologic symptoms are within 6 months of surgery [29,30]. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trialist's Collaborative Group (ECST) trials [29,30] randomized simultaneously, but independently, symptomatic patients with carotid stenosis to best medical treatment or best medical treatment plus endarterectomy. Both trials showed significant benefit (50% relative risk reduction) in patients with greater than 70% stenosis (diameter reduction), whereas the group with 50–69% stenosis had only a marginal effect. Patients with stenoses <50% had no benefit.

Recent reanalysis of the pooled data from these two trials, however, showed that the time interval between onset of neurologic symptoms and surgery was the most important predictive factor of benefit for the patient [31]. The earlier the operation, the greater the benefit. The overall absolute risk reduction of approximately 15% conveyed by endarterectomy could be doubled when patients received surgery within 2 weeks of symptoms. With the knowledge gained during the last 10–15 years concerning the vulnerable plaque and plaque rupture, this finding does not come as a great surprise; however, when these trials were designed, this pathogenetic mechanism of acute ischemia was unknown.

Also, sex, age and degree of stenosis are factors that influence the benefit of surgery [31]. Male sex, older age and severity of stenosis all increase the risk of future stroke in patients with stenosis without any increased risk of the surgical procedure, thus, the overall benefit is greater.

Asymptomatic carotid stenosis

Asymptomatic carotid stenosis is more controversial, although two major trials have shown a small but statistically significant benefit of surgery. First, the Asymptomatic Carotid Atherosclerosis Study (ACAS) trial showed a 50% relative risk reduction of ipsilateral stroke, but the absolute risk reduction was marginal, only 1% per year [32]. Later, the Asymptomatic Carotid Surgery Trial (ACST) reproduced these findings [33]. Taking into consideration that the average annual mortality during the trials were 3–4%, in addition to other ischemic events which were unaffected by the procedure, it may be questioned whether the cost–benefit is reasonable both for the patient and society. The medical treatment offered during these trials was much poorer than that recommended today; thus, the outcomes of these trials may not be reflective of the risk in these patients today. If or when better criteria for selection of patients at higher risk becomes available, selective surgery for high-risk cases of asymptomatic carotid stenosis may yield greater or even much greater benefit.

Technical considerations

Technically, carotid endarterectomy may be performed in two ways: classic endarterectomy (Figure 43.10) or eversion endarterectomy. In the latter, the internal carotid artery is divided from the bifurcation, and endarterectomy is performed by everting the vessel wall, thereby removing the carotid lesion. After the stenosis has been removed, the bifurcation is reconstructed by reanastomosing the internal carotid to the bifurcation.

Carotid endarterectomy may be performed under general or local anesthesia. Classically, general anesthesia has been preferred; however, this has carried the challenge of monitoring cerebral circulation during clamping of the carotid artery. A variety of methods have been used ranging from electroencephalography, stump pressure, distal internal carotid artery pressure, evoked potentials, near-infrared spectroscopy, transcranial Doppler and more. None of these methods have proven ideal, so some surgeons use a shunt on a selective basis, whenever their method for monitoring indicates risk of cerebral ischemia during clamping, whereas others use a shunt routinely. By contrast, performing endarterectomy under local anesthesia gives the surgeon the opportunity to communicate with the patient during clamping. Having the patient awake and responsive during surgery may be the best monitoring of cerebral function during clamping. Also, local anesthesia may carry less cardiac and pulmonary risk. Smaller trials and a recent meta-analysis indicate superiority of local anesthesia [34]; however, recently the General Anesthesia versus Local Anesthesia for carotid surgery (GALA) trial reported its results after randomizing 3529 patients to either universal or local anesthesia for carotid endarterectomy – there was no difference in the risk of perioperative stroke or death [35].

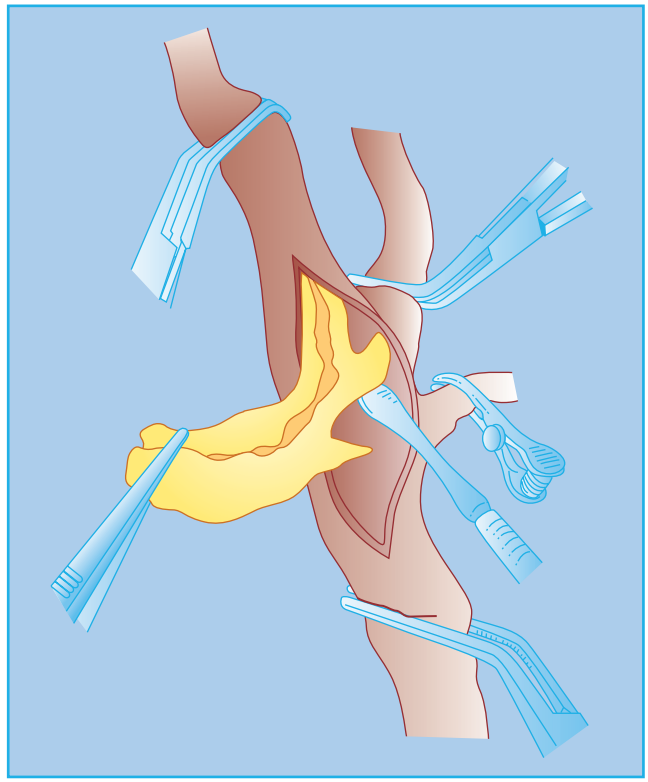

Figure 43.10 Carotid endarterectomy where the intima–media complex is dissected free of the adventitia and removed.

Carotid stenting

This has not yet been proven in randomized clinical trials to prevent ipsilateral ischemic events. Seven randomized controlled trials have been published to compare stenting with endarterectomy; however, they have only focused so far on comparison of perioperative complications. The two most recent trials, the EVA-3S and the SPACE trial, failed to show an advantage of the less invasive carotid stenting method with respect to perioperative events [36,37]. In fact, the EVA-3S trial was stopped early because of excess complications in the stenting group [36]. A recent Cochrane meta-analysis, including all seven randomized controlled trials, favors surgery with respect to the primary outcome of perioperative death and ipsilateral stroke [38]. Nevertheless, it is important to acknowledge that technology does develop rapidly and some of the trials may have used devices and/or technologies that are already outdated. Similarly, there may be differences in trial design, and criticism has been raised specifically as to the training of investigators in some studies. Interestingly, stenting appears to be associated with higher complication rates when performed early after neurologic symptoms and in the elderly – the two strongest indications. Finally, it is important to keep in mind that stenting should be evaluated in

long-term studies, and not only compared with endarterectomy, but also with medical therapy, which has been improved dramatically the last 10–20 years.

Carotid revascularization prior to coronary artery bypass surgery has been practiced in some institutions whereas others have not found it useful. The potential advantage is avoiding cerebral ischemia during the relative hypotension "on pump"; however, the complications of carotid revascularization have outweighed the gains, as evaluated by recent reviews.

It may be questioned whether the evidence for endarterectomy is outdated. Three of the four major trials proving endarterectomy to be of value for symptomatic and asymptomatic surgery were performed when the only fairly constant preventive medication given was aspirin. The last trial randomized 8–10 years ago and only 30% of patients were taking statins. It is stated in the design of these trials that hypertension and hypercholesterolemia were treated when present; however, in that era, the treatment goals for both hypertension and hypercholesterolemia were much more lax than they are now. Also, new drugs have been introduced and their benefit documented since these trials randomized patients (e.g. statins, newer antiplatelet agents, dual antiplatelet therapy and newer antihypertensive drugs). It may be speculated that if these drugs were used systematically, the risk in patients with carotid stenosis would be much less, not least in those with vulnerable plaques. Therefore, new trials are needed to test how today's medical therapy compares with intervention and if the best medical therapy remains inferior to surgery or stenting. New trials are *not* unethical – it is unethical not to undertake new trials.

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