Review Article

Treatment of the critically ischaemic lower limb

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Introduction

Peripheral arterial occlusive disease (PAOD) causes symptoms of intermittent claudication or rest pain in 1.5% of men under the age of 50 and 5% of men over 50,¹ though other studies have shown that perhaps only one third of people with PAOD are symptomatic,² and that intermittent claudication progresses to rest pain or gangrene in only 15–20% of patients¹ (though other authors have put this figure as high as 50%³). This is more likely to occur in the presence of risk factors of smoking, diabetes, hypertension, hyperlipidaemia and distal arterial disease. Five thousand new patients a year are referred to limb-fitting centres in the UK after amputation for vascular disease,⁴ although this probably represents only half of all amputees. The Second European Consensus Document on Chronic Critical Leg Ischaemia gives an estimated amputation rate of 140/million/year for the UK,⁵ though suggesting that only 25% of patients with PAOD undergo amputation.

Traditionally, staging of critical leg ischaemia was by the Fontaine classification,⁶ though the Second European Consensus Document suggests that this should be altered to define chronic critical leg ischaemia as either persistently recurring ischaemic rest pain requiring regular adequate analgesia for more than 2 weeks, with an ankle systolic pressure ≤ 50 mmHg and/or a toe systolic pressure of ≤ 30 mmHg; or ulceration or gangrene of the foot or toes with an ankle systolic pressure of ≤ 50 mmHg or a toe systolic pressure of ≤ 30 mmHg.⁵ The toe systolic pressure must be used in diabetes, where calcified arterial walls can give misleadingly high readings at the ankle.

Acute ischaemia

Acute ischaemia of the extremity may be due to arterial occlusion from spontaneous thrombosis, embolus, arterial bypass graft thrombosis, trauma

or spasm.⁷ The presence of occlusion or stenosis can be determined noninvasively with the use of duplex Doppler ultrasonography, though most patients will require arteriography prior to thrombolytic or surgical therapy. Management of an acutely occluded peripheral artery remains difficult, and acute non-traumatic lower limb ischaemia caused by embolism or thrombosis is accompanied by a 25% mortality and 20–40% major amputation rate.⁸ Traditionally balloon embolectomy has been used in acute non-traumatic lower limb ischaemia, but it can be difficult to distinguish preoperatively between an embolus with propagated thrombus from thrombosis of an atherosclerotic vessel, and the use of a balloon in such a vessel may cause intimal damage and worsen the prognosis.⁹ Moreover, surgery may not be successful in patients with emboli in smaller vessels.¹⁰

For these reasons dissolution of the offending thrombus seemed an attractive proposition, and the concept of thrombolysis has advanced considerably with the development of various thrombolytic agents and improved techniques in interventional radiology. Thrombolysis is most successful in acute ischaemic events,^{11,12} though several authors have demonstrated effective lysis in occlusions several months old.^{13–15} However, patients presenting with rapidly advancing ischaemia and neurological loss are best treated by surgery as these limbs may not be able to withstand a further period of ischaemia,¹⁶ and limbs in which irreversible changes have set in must not be revascularized as complications such as renal failure¹⁷ can be precipitated. Streptokinase was the first drug to gain widespread use, usually given as an initial loading dose to overcome plasma streptococcal antibodies from previous exposure to streptococci,¹⁸ followed by a maintenance infusion of 5,000 units/hour given intra-arterially. The intra-arterial route also offers the advantage of access for angioplasty of an underlying stenosis, which may be necessary in up to one third of cases.¹⁹ Newer thrombolytic drugs such as tissue plasminogen activator, urokinase and anistreplase have since been introduced, and other

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forms of administration such as pulsed spray catheters, which could reduce the time to lysis, have also increased the usefulness of thrombolysis. Thrombolysis has also been used as an adjunct to surgical embolectomy with promising results,^{20–23} though this requires further trials. There is still no consensus as to which patients are best suited to thrombolysis nor an optimum drug or method of administration. However, there seems no doubt that thrombolysis will be increasingly used in the management of acute peripheral limb ischaemia.

Chronic ischaemia

Patients with rest pain and/or gangrenous changes need urgent referral for investigation. However, the same is not true of intermittent claudication, where patients should probably not be referred until 6 months after the onset of symptoms, unless progressive, as most claudicants develop sufficient collateral supply to render them asymptomatic. Once referred, a full history and clinical examination should be undertaken, and routine investigations performed including a full blood count with white cell and platelet count, urea, creatinine and electrolytes, and blood sugar. An electrocardiogram should also be performed. Plasma lipids and plasma viscosity may also be required. For diabetic patients, glycosylated haemoglobin, urine analysis and assessment of peripheral neuropathy are also necessary. Ankle-brachial indexes should also be carried out, though the toe pressure should be used in diabetics. If a vascular laboratory is available, segmental arterial pressures and waveform analysis are very useful prior to arteriography and, if the ankle-brachial index is normal, the patient should be walked on a treadmill until he develops pain, and the Doppler pressures repeated. Arteriography is then required, with intra-arterial digital subtraction arteriography the investigation of choice. This should show the vessels down to the foot and ideally include the contralateral leg.

General management

Patients without rest pain or gangrenous changes should be encouraged to undertake gentle exercise,²⁴ and, if appropriate, told to stop smoking. Long-term anti-platelet agents such as aspirin should be given as there is a 25% reduction in the risk of myocardial infarction, stroke and pulmonary embolism.²⁵ If confined to bed, low-dose heparin should be given to reduce the incidence of deep vein thrombosis and the leg left dependent, though care must be taken to prevent oedema of the lower limb. Diseases such as untreated hypertension or diabetes must be adequately controlled.

Treatment with beta-blockers should be avoided as they may cause peripheral vasoconstriction. However, in critical limb ischaemia, control of hypertension should be delayed if possible because of the reduction in perfusion to the limb and consideration should be given to stopping or reducing anti-hypertensive medication in well-controlled hypertensives for a short period, with a view to increasing systemic arterial pressure and hence blood flow to the limb, as this may improve healing of ischaemic ulcers.²⁶

Prior to consideration of surgery, patients should also be investigated for evidence of any coronary or carotid disease which may require management, though, unless symptomatic, management of the ischaemic limb will usually take precedence.

Specific treatment

Angiography should be performed on all patients thought suitable for surgical or radiological intervention. This enables accurate localization of the site of stenosis or occlusion, and allows appropriate management decisions. In general, patients with chronic limb ischaemia rarely have one localized lesion, and in cases of multiple lesions, proximal blocks should be treated before distal unless it is thought that angioplasty of a single distal block would allow healing of an ischaemic ulcer prior to bypass surgery. It has been proposed that reconstruction should be attempted if there is a greater than 25% chance of saving a limb for the patient for at least 1 year⁵ and, as the mortality from amputation is between 12 and 20%,^{27,28} and survival rates of 50–60% at 3 years,^{29,30} reconstruction should be tried in almost all cases.

Surgical management

This has been the mainstay of management of the chronic ischaemic limb and is still widely used, especially for aorto-iliac disease, where very high long-term patency rates are reported. In a patient unfit for major surgery with an aortic occlusion or in cases of failure of a previous aorta to lower limb reconstruction, extra-anatomic bypass may be considered. Axillary artery to one or both femoral arteries bypasses have been used, though thoracic aorta to femoral artery bypass is a simple technique which gives good haemodynamic results and better late results than axillo-femoral or bifemoral bypass.³¹ Iliac lesions alone are now probably best managed with percutaneous transluminal angioplasty (PTA) of the lesion followed by the insertion of a stent, as this procedure has no increase in complication rate over PTA alone and long-term results are promising.³² If there is an extensive iliac

block thought unsuitable for PTA and the patient is unfit for an aortobifemoral graft, a femoro-femoral or (preferably) ilio-femoral crossover graft should be performed. For femoral artery occlusions with above knee anastomoses, synthetic grafts give good results with long-term patency rates only slightly less than vein grafts, such that the Second Consensus Document on Critical Limb Ischaemia states that synthetic grafts should be used in preference to vein, which should be reserved for coronary artery grafting or later distal bypass grafting.⁵ However, below the knee, femoropopliteal or distal grafts do very poorly using synthetic material and vein should be used, either reversed or *in situ*.³³ The latter method has gained in popularity, although there is currently no evidence that the results achieved are superior.³⁴

Graft failure can be early (less than 30 days) or late. The former is usually due to an incorrect choice of operation (for example, a distal bypass graft with untreated inflow obstruction) or technical failure at operation. This should be avoided by on-table arteriography at completion. Late failure is usually due to thrombosis, intimal hyperplasia or progression of disease. Graft surveillance should be performed to prevent failure, especially due to stenosis of a vein graft which is amenable to treatment by PTA, and Duplex imaging at 1, 3, 6 and 12 months, and then annually has been recommended.⁵ When occlusion has occurred, arteriography should be performed, following which the graft should be reopened by thrombolysis or surgery, and the cause of the occlusion treated if possible.

Radiological management

Transluminal balloon dilatation of stenoses in vessels is very successful, with good long-term patency rates in larger vessels.³⁵ The results of recanalizing occlusions have been much less impressive, and those longer than 3 cm are likely to reocclude.³⁶ It has also been found that percutaneous dilatation of elastic vascular stenoses is ineffective, especially at the anastomosis between synthetic graft and native vessel. However, for relatively localized stenoses, PTA is the treatment of choice, and can give good results down to³⁷ and below³⁸ the femoral-popliteal segment. Newer recanalization techniques are currently being evaluated such as the use of laser or atherectomy catheters (e.g. the Tracwright (Kensey), the Simpson Athero-Cath, and the transluminal extraction catheter), though these have not gained widespread use, at least in the UK. PTA can also be carried out at the same time as surgery, for example, to treat an iliac stenosis to restore inflow prior to a femoropopliteal bypass graft. There has also been much work on the use of thrombolytic therapy together

with balloon angioplasty, especially in late graft thrombosis, where thrombolysis offers the advantage of lysing both graft and distal thrombus, revealing any underlying distal obstruction which may then be amenable to treatment. Thrombolysis is also often technically easier and more successful than surgical re-exploration of grafts, with better results achieved in saphenous vein than synthetic grafts.^{39,40} Enclosed thrombolysis following balloon angioplasty has also been suggested⁴¹ as a means of removing fibrin from the newly dilated segment, improving patency rates.

Chemical sympathectomy has been used in an attempt to improve skin blood flow; however, there is no evidence that it improves outcome, and should not be used.

Pharmacological treatment

The traditional conservative management of chronic limb ischaemia in hospital was the use of dextran 40 or 70 to reduce plasma viscosity, given as an infusion for 48 h. Naftidrofuryl oxalate (Praxilene) increases intracellular ATP and decreases lactic acid levels in ischaemia, and is usually given as 200 mg twice daily as an infusion over a minimum of 90 minutes for 7 to 10 days. It can be administered in low molecular weight dextran. Intravenous heparin can also be given, with the advantage of also decreasing the risk of venous and arterial thromboses. These can be administered to a patient with rest pain or ischaemic changes on admission to hospital while full investigation is performed. There has been much recent interest in the use of prostanooids PGI₂ or PGE₁ or the stable prostacyclin analogue iloprost, usually given intravenously or intra-arterially for 3–4 days. However, the apparent success of earlier trials has not in general been proved in double-blind randomized studies. Longer-term use (3–4 weeks) of iloprost reduces analgesia requirements and improves ulcer healing,^{42,43} and increases the chance of survival with a viable limb at 6 months.^{44,45} It would, therefore, seem appropriate to use this in all patients thought unsuitable for any form of revascularization procedure. Various oral medications are licensed for use in chronic limb ischaemia including naftidrofuryl (Praxilene), oxpentifylline (Trental) and inositol nicotinate (Hexopal), though evidence for their effectiveness is limited, and they should not be used instead of revascularization.

Summary

Medical therapy of PAOD is only indicated in patients unsuitable for vascular reconstruction or angioplasty. The approach includes early detection of subjects at risk, avoidance of known risk factors,

and appropriate management of diseases such as diabetes and hypertension. Vasodilators are of little use orally, though some drugs may have a part to play for short-term management and iloprost should be considered for patients unsuitable for revascularization. The ankle systolic or toe pressure should be used as a measure of disease and, if reduced, arteriography should be performed. This

should not be limited to those thought fit for major surgery, as angioplasty or thrombolytic therapy may be appropriate, and aortoiliac disease may be treated by extra-anatomic bypass if not suitable for major surgery. Arterial reconstruction is associated with a reduction in both mortality and amputation, and should be attempted if a greater than 25% chance of limb salvage could be expected.

References

- Dormandy, J., Mahir, M., Ascady, G. *et al.* Fate of the patient with chronic leg ischaemia. *J Cardiovasc Surg* 1989, **30**: 50–57.
- Widmer, L.K., Greensher, A. & Kannel, W.B. Occlusion of peripheral arteries: a study of 6400 working subjects. *Circulation* 1964, **30**: 836–842.
- Fowl, R.J., Gewirtz, R.J., Love, M.C. & Kempczinski, R.F. Natural history of claudicants with critical hemodynamic indices. *Ann Vasc Surg* 1992, **6**: 31–33.
- DHSS Statistics and Research Division. *Amputation Statistics for England, Wales and Northern Ireland*. Department of Health and Social Security, London, 1976–86.
- Andreani, D., Bell, P., Bollinger, A. *et al.* Chronic critical limb ischaemia. *Circulation* 1991, **84** (Suppl.IV): 1–26.
- Fontaine, R., Kieny, R., Gangloff, J.-M. *et al.* Long-term results of restorative arterial surgery in obstructive diseases of the arteries. *J Cardiovasc Surg* 1964, **4**: 463–472.
- Lavanier, G.L., Sacks, D. & Robinson, M.L. Acute limb ischaemia. *Emerg Med Clin North Am* 1992, **10**: 103–119.
- Lusby, R.J. & Wylie, E.J. Acute lower limb ischaemia: pathogenesis and management. *World J Surg* 1983, **7**: 340–346.
- Jamieson, C.W. Is it important to differentiate between acute and acute on chronic ischaemia? In: Greenhalgh, R.M., Jamieson, C.W. & Nicolaidis, A.N. (eds) *Limb Salvage and Amputation for Vascular Disease*. W.B. Saunders, London, 1988, pp. 105–112.
- Abbott, W.M., McCabe, C., Maloney, R.D. & Wirthlin, L.S. Embolism of the popliteal artery. *Surg Gynecol Obstet* 1984, **159**: 533–536.
- Hess, H., Mietaschk, A. & Bruckl, R. Peripheral arterial occlusions: a six year experience with local low dose thrombolytic therapy. *Radiology* 1987, **163**: 753–758.
- Movak, K.T., Jewell, E.R. & Persson, A.V. The role of thrombolytic therapy in surgical practice. *Br J Surg* 1989, **76**: 298–304.
- Poliwode, H., Alexaner, K., Buhl, V., Holsten, D. & Wagner, H.H. Treatment of chronic arterial occlusions with streptokinase. *N Engl J Med* 1969, **280**: 689–692.
- Verstraete, M., Vermeylen, J. & Donati, M.B. The effect of streptokinase infusion on chronic arterial occlusions and stenoses. *Ann Intern Med* 1971, **74**: 377–382.
- Hess, H., Ingrisch, H., Mietaschka, A. & Rath, H. Local thrombolytic therapy of peripheral arterial occlusions. *N Engl J Med* 1982, **307**: 1627–1630.
- Walker, W.J. & Giddings, A.E.B. A protocol for the safe treatment of acute lower limb ischaemia with intra-arterial streptokinase and surgery. *Br J Surg* 1988, **75**: 1189–1192.
- Lang, E.K. Streptokinase therapy: complications of intra-arterial use. *Radiology* 1985, **154**: 75–77.
- Verstraete, M., Vermeylen, J., Amery, A. & Vermeylen, C. Thrombolytic therapy with streptokinase using a standard dose scheme. *Br Med J* 1966, **i**: 454–456.
- Barr, H., Lancashire, M.J.R., Torrie, E.P.H. & Galland, R.B. Intra-arterial thrombolytic therapy in the management of acute and chronic limb ischaemia. *Br J Surg* 1991, **78**: 284–287.
- Comerota, A.J., White, J.V. & Grosh, J.D. Intraoperative, intra-arterial thrombolytic therapy for salvage of limbs in patients with distal arterial thrombosis. *Surg Gynecol Obstet* 1989, **169**: 283–289.
- Parent, N.E., Bernhard, V.M., Pabst, T.S. *et al.* Fibrinolytic treatment of residual thrombosis after catheter embolectomy for severe lower limb ischaemia. *J Vasc Surg* 1989, **9**: 153–161.
- Beard, J.D., Nyamekye, I., Earnshaw, J.J., Scott, D.J.A. & Thompson, J.F. Intraoperative streptokinase: a useful adjunct to balloon-catheter embolectomy. *Br J Surg* 1993, **80**: 21–24.
- Meryerovitz, M.E., Goldhaber, S.Z., Reagan, K. *et al.* Recombinant tissue-type plasminogen activator vs. urokinase in peripheral arterial and graft occlusions: a randomised trial. *Radiology* 1990, **175**: 75–78.
- Spacil, J., Hlavova, A., Linhard, J. & Prerovsky, I. The effect of slow walking on the subcutaneous blood flow in the legs in patients with ischaemic disease of lower limbs. *Vasa* 1976, **5**: 323–328.
- Antiplatelet trialists collaboration: Final report of a second cycle. *Br Med J* (in press).
- Lassen, N.A. & Larsen, O. Conservative treatment of gangrene using mineralocorticoid-induced hypertension. *Lancet* 1968, **i**: 606–609.
- Barber, G.G., McPhail, N.V., Scobie, T.K., Brennan, M.C. & Ellis, C.C. A prospective study of lower limb amputations. *Can J Surg* 1983, **26**: 339–341.
- Jamieson, M.G. & Ruckley, C.V. Amputation for peripheral vascular disease in a General Surgical Unit. *J R Coll Surg Edin* 1983, **28**: 46–50.
- Couch, N.P., David, J.K., Tilney, N.L. & Crane, C. Natural history of the leg amputee. *Am J Surg* 1977, **133**: 469–473.
- Huston, C.C., Bivins, B.A., Ernst, C.B., Griffin, W.O., Jr. Morbid implications of above knee amputations. *Arch Surg* 1980, **115**: 165–167.
- Branchereau, A., Magnan, P.E., Moracchini, P., Espinoza, H. & Mathieu, J.P. Use of descending thoracic aorta for lower limb revascularisation. *Eur J Vasc Surg* 1992, **6**: 255–262.
- Shields, D.A., Sarin, S., Shami, S.K., Scurr, J.H. & Coleridge Smith, P.D. Intravascular stenting. *Vasc Med Rev* (in press).
- Rutherford, R.B., Jones, D.N., Bergentz, S.E. *et al.* Factors affecting the potency of infrainguinal bypass. *J Vasc Surg* 1988, **8**: 236–246.
- Moody, A.P., Edwards, P.R. & Harris, P.L. In situ versus reversed femoropopliteal vein grafts: long-term follow-up of a prospective, randomized trial. *Br J Surg* 1992, **79**: 750–752.
- Kadir, S., White, R.L., Kaufman, S.L. *et al.* Long-term results of aortoiliac angioplasty. *Surgery* 1983, **94**: 10–14.
- Gallino, A., Mahler, F., Probst, P. & Nachbur, B. Percutaneous transluminal angioplasty of the lower limbs – 5 year follow-up. *Circulation* 1984, **70**: 619–623.
- Morgenstern, H.R., Getrajdman, G.I., Laffey, K.J., Bixon, A. & Martin, E.C. To talk occlusions of the femoral popliteal artery: high technical success rate of conventional balloon angioplasty. *Radiology* 1989, **172**: 937–940.

38. Buckenham, T.M., Loh, A., Dormandy, J.A. & Taylor, R.S. Infrapopliteal angioplasty for limb salvage. *Eur J Vasc Surg* 1993, **7**: 21–25.
39. Lebolt, S.A., Tisnado, J. & Cho, S.-R. Treatment of peripheral arterial obstruction with streptokinase: results in arterial versus graft occlusions. *Am J Roentgenol* 1988, **151**: 589–592.
40. Kakkasseril, J.S., Cranley, J.J., Arbaugh, J.J., Roeder-sheimer, R. & Welling, R.E. Efficacy of low dose streptokinase in acute arterial occlusion and graft thrombosis. *Arch Surg* 1985, **120**: 427–429.
41. Tonnesen, K.H., Holstein, P. & Anderson, E. Femoropopliteal artery occlusions treated by percutaneous transluminal angioplasty and enclosed thrombolysis. *Eur J Vasc Surg* 1991, **5**: 429–434.
42. Balzer, K., Bechara, G., Bisler, H. *et al.* Placebo-kontrollierte, doppel-blinde Multicenterstudie zur Wirksamkeit von Iloprost bei der Behandlung ischämischer Ruheschmerzen von Patienten mit peripheren arterieller Durchblutungsstörungen. *Vasa* 1987, **20** (Suppl): 379–381.
43. Norgren, L., Alwmark, A., Ängqvist, K.A. *et al.* A stable prostacyclin analogue (iloprost) in the treatment of ischaemic ulcers of the lower limb: a Scandinavian–Polish placebo-controlled, randomised multicenter study. *Eur J Vasc Surg* 1990, **120**: 1477–1482.
44. Belcher, G. Effects of iloprost and factors affecting outcome in patients with severe inoperable lower limb ischaemia. UK Severe Limb Ischaemia Study Group. *Agents Actions* 1992, **37** (Suppl): 354–360.
45. UK Severe Limb Ischaemia Study Group. Treatment of limb threatening ischaemia with intravenous iloprost: a randomised double-blind placebo controlled study. *Eur J Vasc Surg* 1991, **5**: 511–516.