THERAPEUTIC INTERVENTIONS

The management of cerebral aneurysms

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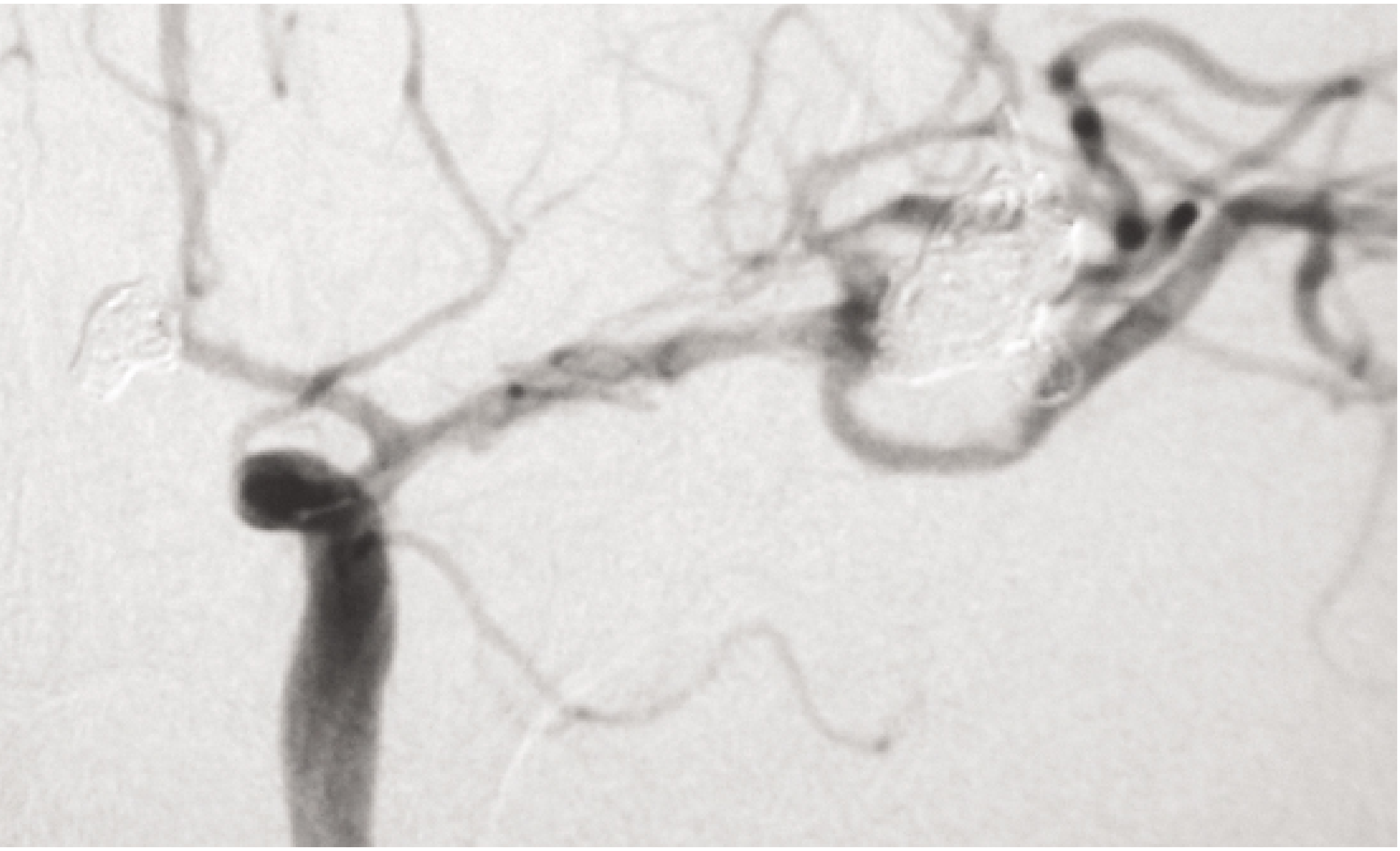

t of ruptured ms: life after ISAT

BACKGROUND

Aneurysmal subarachnoid haemorrhage (SAH) is devastating for many young and middle aged patients. Mortality and disability have altered little over the past 20 years (Hop *et al.* 1997). Moreover, about one-quarter of patients do not even survive long enough to reach hospital. Of those that do, about one-third rebleed in the first three weeks with a subsequent mortality of 60–80% (Alvord *et al.* 1972; Kassell *et al.* 1990; Brilstra *et al.* 2000; Roos *et al.* 2000). The first concern after resuscitation is therefore to secure the aneurysm, and so prevent rebleeding. This also allows more aggressive treatment of the complications of SAH such as vasospasm. Since Dandy first surgically clipped an aneurysm in the 1930s, clipping has until recently been the accepted method of isolating the aneurysm from the parent artery. Although clipping was never subjected to a randomised trial, it has been calculated that it reduces the mortality compared to the natural history by 10% (Brilstra *et al.* 2002).

There have been many attempts to find a less invasive way of treating aneurysms but none proved effective until the introduction of coiling. Pushable non-attached coils had been used occasionally, typically for aneurysms that were not amenable to surgical clipping, but the breakthrough came with the Guglielmi detachable coils (GDC) – coils that had a controlled detachment and could be delivered when the coil was in a safe position within the aneurysm (Guglielmi *et al.* 1991). Coiling is done via the endovascular route, avoiding the complications of craniotomy. The advantages were immediately obvious to some clinicians but others felt uncomfortable that the new technique was likely to be less durable than surgery – despite apparent occlusion of the aneurysm, might rebleeding become a problem in later years?

ISAT – THE INTERNATIONAL SUBARACHNOID ANEURYSM TRIAL

In 1995 Molyneux and Kerr from Oxford set up the ISAT trial, an international randomised controlled trial (RCT) of clipping vs. coiling (ISAT 2002). In 2002, it was stopped slightly early when the probability of coiling being safer than surgery went beyond $P = 0.001$. But despite this apparently clear-cut result the trial has generated much heated discussion and vigorous debate as to how aneurysmal subarachnoid haemorrhage should now be managed (Lasjaunias 2002).

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The fact is that ISAT showed that one year after SAH, treatment by coiling rather than clipping of ruptured cerebral aneurysms resulted in a 22.6% relative reduction in death and disability with an absolute risk reduction of 6.9% (further follow up has increased this latter figure to 8%). This result caught many neuroscience units unprepared, understaffed and ill-equipped. So perhaps it should come as no surprise that some in the neurosciences community have been strongly critical of this trial. As Sackett (Sackett 1979) pointed out, each field of medicine goes through a cycle of controversy:

> *Although there continues to be debate about whether RCTs are needed, appropriate, too pure, irrelevant, impossible, elitist, each field of health and health care goes through its own natural history of this debate. A review of public and individual patient based research into the big killers heart disease, cancer, stroke shows a repetitive sobering recognition of the harm and waste that attends best intentions but inferior evidence followed by biting the bullet and doing the conceptually easy but logistically tough RCTs.*

RESPONSE TO THE CRITICISMS OF ISAT

Criticisms of the trial methodology

- The surgical centres that participated had neurosurgeons that were not vascular specialists (Kirkpatrick *et al*. 2003)

  No Results from the so-called superior specialized centres were all from observational studies reported by surgeons involved in the assessment of their own patients. Rothwell *et al*. have shown that such studies typically report much lower complication rates than those using independent neurological assessment (Sellar & Whittle in press). Nearly all the main contributing centres in ISAT were large neuroscience units admitting around 120 SAH patients a year. High volume is one of the prerequisites of obtaining good outcome surgical figures, and in California at least the in hospital mortality was rather higher than in the ISAT centres (Bardach *et al*. 2002).
- The results are not generalisable, the trial only randomised good grade, small anterior circulation aneurysms (Sackett 1979).

  No The trial is applicable to about two-thirds of patients admitted to hospital who are in good grade, and who have small anterior circulation aneurysms (Sellar *et al*. 2003). In many centres posterior circulation aneurysms are already managed by coiling as first choice treatment.
- The result is marginal and no better than the natural history

  No The combined morbidity and mortality of coiling was 23% relatively better than surgery which in turn is 10% better than the natural history (Brilstra *et al*. 2002).
- The long-term efficacy (durability) of coiling is not established but it is for clipping (Lasjaunias *et al*. 2002)

  Yes But ISAT started in 1995 so there are up to 8 years of follow up and currently the re-bleed rate is 0.16%/year. The long-term re-bleed risk would have to be 6% to upset the trial findings. But longer follow up is important and is under way.
- The trial was unethical because observational studies had already shown the superiority of coiling so many patients who should have been coiled were randomised to surgery (Lasjaunias 2002)

  No Firstly, observational studies provide poor scientific evidence. Secondly, patients who were randomised were only those where there was clinical equipoise in the clinicians' mind, i.e. they genuinely felt both treatments could be equally good for the particular individual case. This meant that some ISAT centres who became more convinced of the merits of coiling by the end of the trial were only randomising 3% of their patients (e.g. Edinburgh). The point of equipoise moves as experience is gained (perhaps no RCT should logically ever reach statistical significance if the clinicians participating are properly shifting their point of equipoise in line with their ongoing experience).

Concern about the impact of the trial

- Patients will all be considered suitable candidates for coiling whereas each patient requires careful consideration by a multidisciplinary team including a neurosurgeon (Lasjaunias 2002).

No ISAT has actually improved communication between surgeons and interventionists.

- Specialist neurosurgical units with expertise in neurovascular disease will be disbanded (Kirkpatrick *et al.* 2003)

  No There will be an increase in demand for specialist neurosurgical expertise, but this may have to be in fewer centres to maintain critical mass and experience.

- Training in the surgical skills required for clipping will become impossible.

  No It will occur in the specialist neurovascular centres.

Response to ISAT in the USA

It is likely that over time a consensus will accept the findings of the trial. Indeed the American Society of Neuroradiologists has recently issued a 'Position Statement'. They concluded that all patients who have had an aneurysmal subarachnoid haemorrhage should have a consult with an interventional neuroradiologist and offered treatment by coiling of those aneurysms that are suitable (Derdeyn *et al.* 2003).

One point not yet teased out of ISAT is the psychological impact of craniotomy. It is no surprise that the common neurosurgical outcome scales, such as the Glasgow Outcome Scale used in ISAT, have little or no psychological or mental test component. The patient who has a good 'surgical' outcome is one who is independent in their day-to-day activities, but psychologically and intellectually they may be far from normal. In fact, patients who are coiled are far more likely to get back to work within a year than those who are clipped (Johnston *et al.* 2000), and further ISAT analyses will explore this issue.

WHICH PATIENTS DOES ISAT NOT INFORM US ABOUT?

Some of the criticisms of ISAT do need to be taken more seriously and one is the question of how to manage the sort of aneurysms that were not randomised in sufficient numbers for ISAT to be informative:

Basilar tip aneurysms (Fig. 1)

The lack of randomization of these patients into ISAT was because neurosurgeons had quickly realized that coiling was superior to clipping which was so often followed by a stormy post-operative course. It didn't need a randomised trial for a widespread change in practice. Observational data have been published supporting this stance (Leusseveld *et al.* 2002).

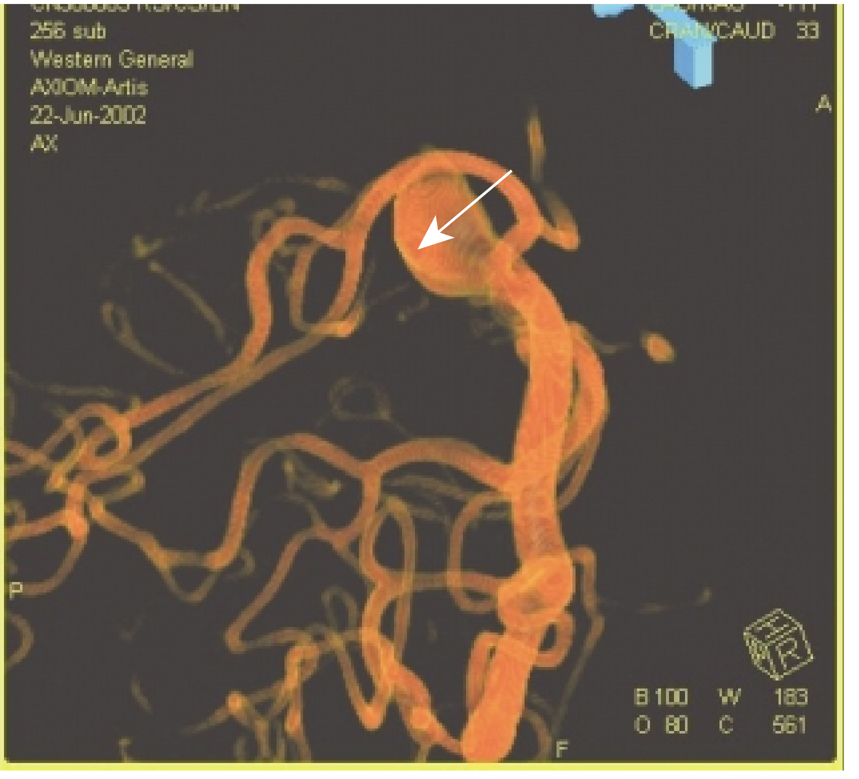

Figure 1 3D catheter angiogram showing a basilar tip aneurysm (arrow). Despite often being broad-necked these aneurysms are usually more straightforward to coil than to clip.

Posterior inferior cerebellar artery (PICA) aneurysms

These account for just 0.5% of all ruptured aneurysms and only 33 were randomised into ISAT. These aneurysms are unusual because they do not arise at an arterial bifurcation but typically about 1–2 mm distal to the origin of the PICA, from the wall of the vessel itself. They are also usually wide-necked (Fig. 2) . Endovascular treatment is often compromised by the angioarchitecture, and complete coiling of the aneurysm is impossible without compromising blood flow down the distal PICA. We have documented 43 consecutive cases, all but one of which were treated by coiling. Despite only coiling 40% completely, no rebleeds have so far been encountered over a 10 years follow up, and so coiling appears to offer protection even when only partial. However, 10% of patients did require recoiling due to aneurysm regrowth and clearly all incompletely occluded aneurysms need to be followed up meticulously.

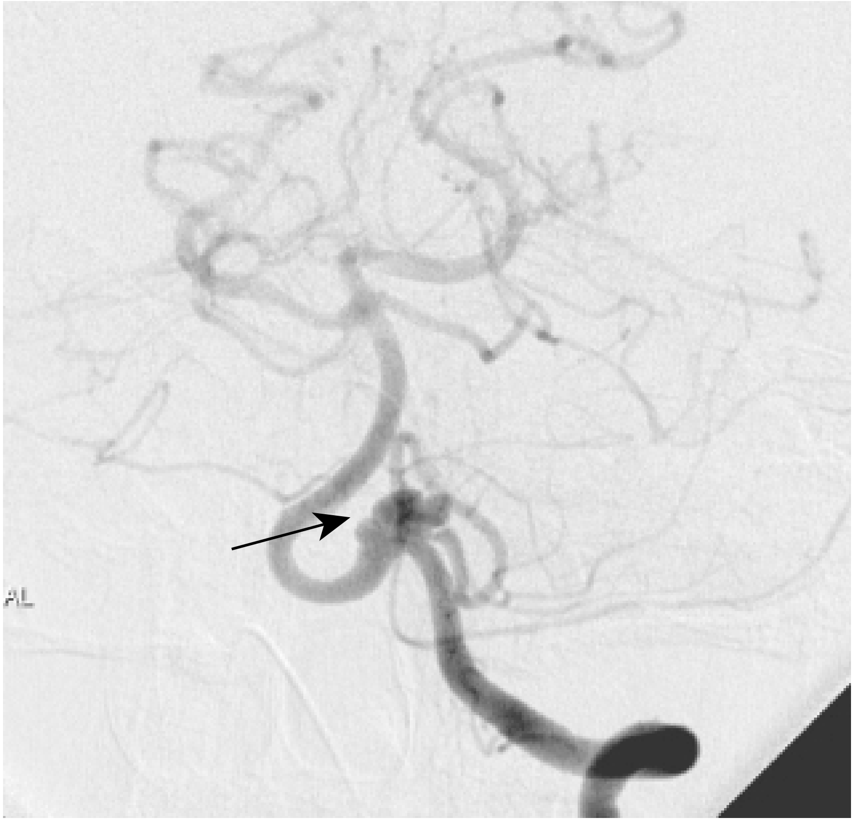

Figure 2 A dissecting PICA aneurysm (arrow) – note the narrowing of the artery just proximal to the aneurysm neck. A broad necked aneurysm like this requires either parent vessel occlusion, or stenting, with coiling.

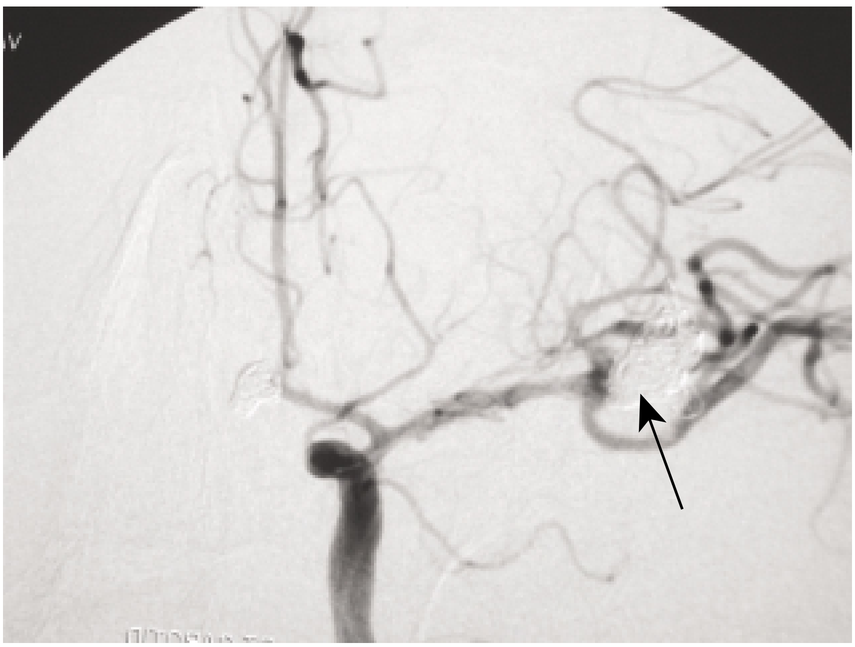

Figure 3 An MCA aneurysm with a broad neck successfully coiled (arrow).

Middle cerebral artery (MCA) aneurysms

These aneurysms were under-represented in ISAT: only 259 were randomised. In fact they are often technically difficult to coil (Figs 3 and 4) and the risks of complications greater. Occlusion of the dominant MCA has a mortality of over 50%. Again we have analysed our own prospective series of 100 aneurysms. The complication rate is slightly above our overall figures but these aneurysms often are wide-necked (Fig. 4) or incorporate important branch vessels (Fig. 3) and require skilful surgical or endovascular treatment (Soh *et al*. 2003).

Giant aneurysms

These represent about 5% of all cerebral aneurysms (Choi & David 2003). Initially it was felt that the lamellated thrombus that frequently lines their lumen offered some protection from haemorrhage, but presentation with rupture is unfortunately common. Other presentations are as a mass lesion with progressive neurological deficit. Giant cavernous sinus aneurysms often present with severe orbital pain and ocular movement problems. Occasionally they compress the pituitary and mimic an adenoma (a nasty shock for the unwary pituitary surgeon!).

There is a 50% mortality in the first two years after presentation. Drake and Peerless found in their small series of 31 giant aneurysms that only one patient was alive at five years (Peerless 1990). These aneurysms present a formidable management challenge both for surgeons and interventionists. The aneurysms frequently have broad necks and incorporate important branch vessels. Moreover, the neck is often atheromatous and calcified making clipping difficult. Unfavourable anatomy may mean that bypass surgery is required. Endovascular treatment, placing coils in the sac of the aneurysm, has had poor results (Malisch *et al*. 1997). In many cases the coils migrate into the clot and the aneurysm recurs. Remodelling with a balloon may well be necessary because of the broad neck, or a stent may be required to protect the parent artery. In a good review, the best outcomes were achieved in those patients who could tolerate balloon occlusion of the parent artery (Choi & David 2003).

Poor grade subarachnoid haemorrhage

There is no evidence that surgery is effective in this group of patients, and there is only limited observational data on the efficacy of coiling. Van Loon found improved outcomes with early coiling in these poor grade SAH patients (van Loon *et al.* 2002). Our own experience has been less encouraging (Ross *et al.* 2002). No significant improvement was found in our coiled group. Our own policy is to wait until the patient is in a stable cardiac and respiratory state before coiling.

THE ROLE OF MULTIDISCIPLINARY TEAMS

The best outcome from ISAT, after the furore has calmed down, will be for neurovascular centres to get themselves organized and work out the best way of treating their own patient population. There is no doubt that considerable reorganization of services will have to take place. More than at any previous time, multidisciplinary teams must be established to take on this task. There has never been a greater need for expert neurosurgical skills and the centres of excellence should be preserved where possible, but there may be a need to concentrate the necessary skills in fewer centres. Up to 20% of aneurysms cannot be coiled even if the best interventional expertise is available. Complex aneurysms often require bypass procedures. And neurosurgeons have an unrivalled experience in the management of many complications of SAH such as vasospasm and hydocephalus.

These teams should consist not only of neurosurgeons and neuroradiologists but also anaesthetists, neurologists, and nurses. One-quarter of patients admitted to hospital with SAH who die do so from medical complications. Many of these problems are cardiorespiratory in nature and require the skills of an intensive care team.

But why have a neurologist in the team? There has been a move away from the traditionally demarcated roles of surgeons and neurologists. Neurologists have become increasingly active in the management of acute stroke, even in the UK. There is a new breed of neurologist interested in all the components and ramifications of acute neurology, including stroke and SAH management. Already in the U.K. many SAH patients are admitted initially under neurology services, as most have been for years in Holland. Many of the complications of SAH are related to brain ischaemia, an area where neurologists have expertise and much to offer. The long-term rehabilitation and support of SAH survivors involves the support services used by other stroke patients, and we need the independence and disinterested participation of neurologists to allow us to progress with the research that needs to be done to answer the many unanswered questions in this field.

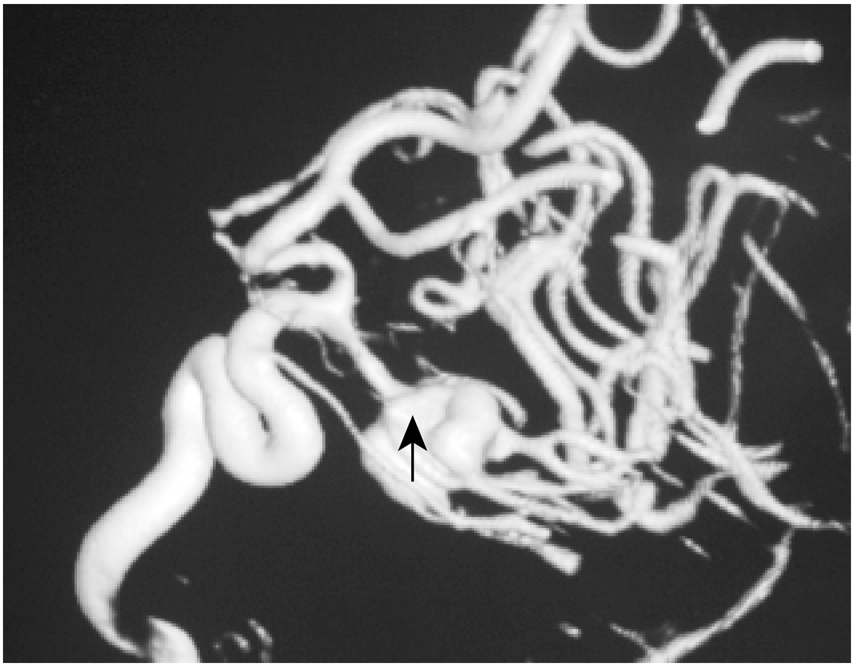

Figure 4 A large MCA aneurysm (arrow) with several branch vessels arising from the sac.

If neuroradiologists are going to share the clinical care, or even take overall responsibility for some patients with acute cerebrovascular disease, their training will have to ensure they have the appropriate clinical skills. An ideal training programme would include clinical posts in acute medicine, intensive care, neurology and neurosurgery as well as in neuroradiology and interventional neuroradiology.

TECHNICAL ADVANCES

Since ISAT started there have been many technical advances. Not least the new angiographic equipment available over the past 2–3 years has made a significant impact on the safety of coiling. We have recently reviewed the advantages of 3D catheter angiography, the most valuable being the ability to sort out the complex relationship between the aneurysm, its parent vessel and its branches (Fig. 5) (Soh & Sellar 2003).

New coils

The first development was the three-dimensional coil (Fig. 6) designed to reduce the frequency of coil compaction. The GDC 3D coil

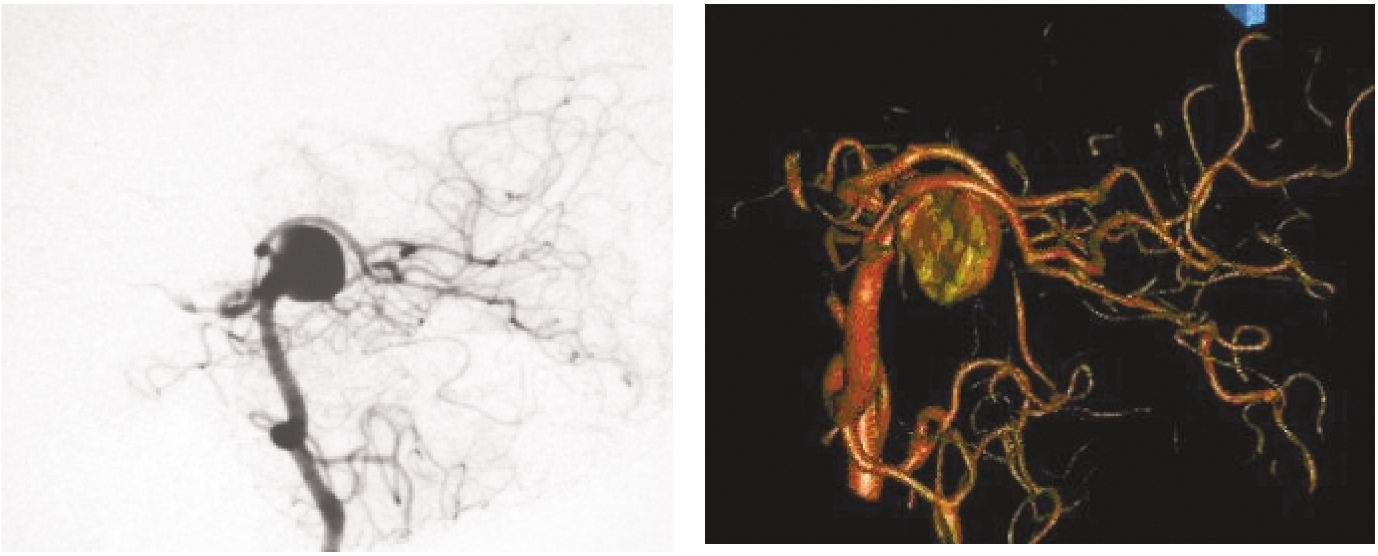

Figure 5 Compared with 2D catheter angiography (left) 3D catheter angiography (right) unravels the complex relationship between the basilar tip aneurysm, the parent basilar artery and its branch vessels.

(Boston Scientific, Freemont, CA, U.S.A) has an omega design with small loops and larger loops. This has the disadvantage that the smaller loops may prevent subsequent coils from passing out of the basket formed, which could lead to compartmentalization and ears and lobules of aneurysm left uncoiled. However, it does work well for broad-necked aneurysms where the structure results in the coils folding back into the aneurysm rather than prolapsing into the parent vessel. Subsequent 3D coils devised by Micrus and Cordis (Johnson & Johnson, Miami, FL, USA) are wound so as to coat the aneurysm wall and can be used like Russian dolls to pack the centre of the aneurysm. But these coils, particularly the longer lengths, are more likely to prolapse out of a wide aneurysm neck. The latest in coil technology aims to heal the aneurysm as well as pack it. Three systems are currently available: the matrix coil (Boston Scientific, Boston, MA, USA), the cerecyte coil (Micrus Corp., Sunnyvale, CA, USA) and the hydrogel system (Microvention, Aliso Viejo, CA, USA). The matrix coil is coated with two different sugars – lactose and galactose – which stimulate an intense fibrotic reaction. The hydrogel coil is more straightforward to pack and works by absorbing water into the coating to increase the diameter of the coil threefold. The hydrogel coating has fissures that also help stimulate the healing process. The latest coil of the three, the cerecyte, has the sugars inside the coil and has the advantage of handling like a conventional coil.

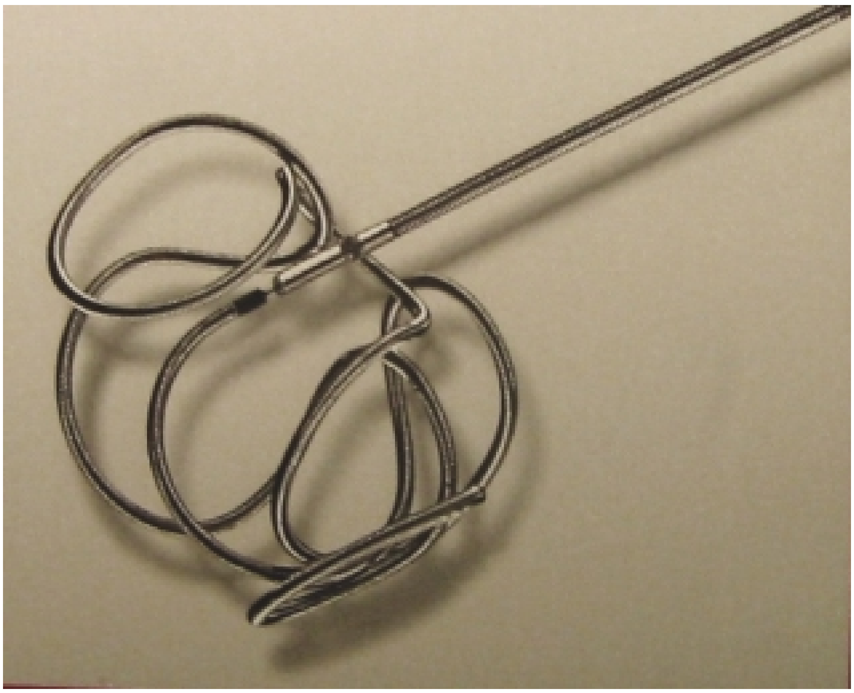

Figure 6 3D GDC coil (Boston Scientific).

Wide necked and complicated aneurysms

These pose considerable problems to the neurointerventionist. The neck may be so wide that 3D coils prolapse out into the parent vessel lumen. Several techniques are now available to solve this problem. If the aneurysm is a terminal artery aneurysm, e.g. basilar tip or carotid bifurcation, then the Trispan (Boston Scientific) device is very effective This consists of three loops of coil that come out of a central stem, like petals. This is deployed in the aneurysm and then pulled down into the neck to prevent subsequent coils from prolapsing through the neck. If the aneurysm is a side-wall aneurysm then the Trispan can seldom be successfully deployed but the aneurysmal neck can be protected using a balloon – the so called remodelling technique to prevent coils protruding into the parent vessel lumen. (Fig. 7).

Finally the latest devices to be used for these aneurysms are thin nitinol stents that are placed across their neck (Fig. 8). These are strong enough to prevent coils from compressing them but thin enough not to block crucial small vessels such as the perforators (Szikora *et al*. 1994). They are also useful in treating aneurysms with diseased parent vessels, e.g. mycotic or dissecting aneurysms

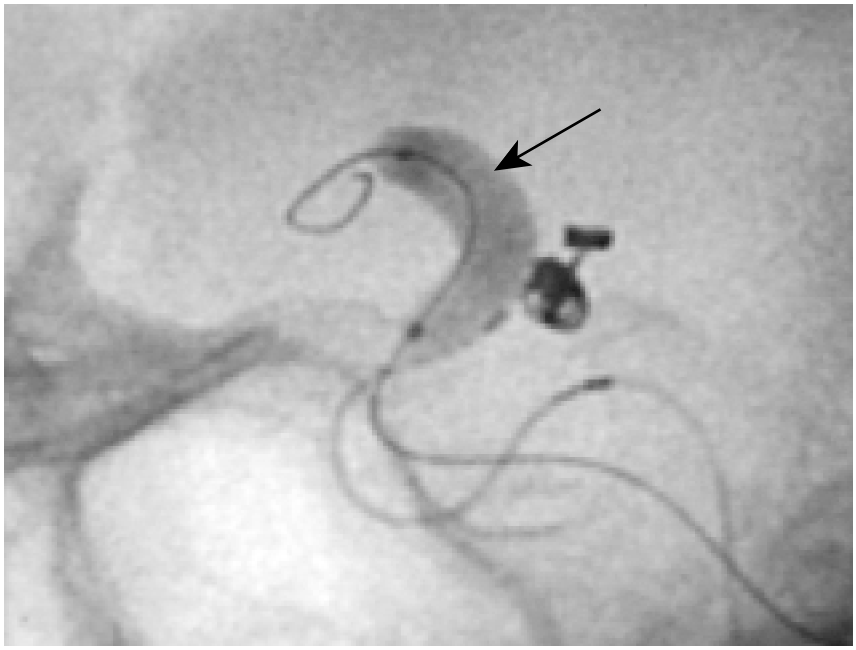

Figure 7 A balloon (arrow) placed in the parent vessel (carotid siphon) prevents the coils protruding from a wide necked aneurysm.

Onyx (MTI)

This material is an ethylene vinyl alcohol copolymer that is dissolved in dimethyl sulfoxide (DMSO) when it is injected into an aneurysm. The DMSO diffuses into the blood and the copolymer precipitates into the aneurysm lumen. In order to prevent the Onyx from refluxing out of the aneurysm the neck is protected with a balloon with or without a stent until the material has precipitated or set. Early reports are encouraging when it is realized that many of the cases that this technique is reserved for are the most difficult aneurysms, or aneurysms that have recurred. Molyneux reported 22 patients, 100% occlusion was achieved in 20 (Molyneux 2002). Interestingly three patients had parent vessel occlusion on follow up, although to date this has not resulted in any clinical deterioration. Two patients did have permanent neurological sequelae from embolic phenomena, not surprisingly, as obtaining a complete seal of the aneurysm is difficult. This is not a technique for the part-time interventionist.

Figure 8 A stent for protecting the parent vessel lumen.

COMPLICATIONS OF COILING

Technical complications include rupture of the aneurysm, occlusion of the parent vessel with thrombus, and distal embolization.

Rupture

Rupture during coiling occurs in approximately 3% of ruptured aneurysms (Croft & Kalmes

2002). There are a number of reasons for this, not all of which are due to operator incompetence! The aneurysm wall is sometimes wafer thin and any coil, however carefully placed, will result in rupture. It is usually complex anatomy that increases the risk of rupture. A tortuous proximal vessel will result in poor distal control of the microwire and catheter, and the wire may then jump forward through the aneurysm wall. Fragile aneurysms are often small or have dissected parent arteries, adding to the difficulties. Occasionally rupture is due to overpacking an aneurysm but this is rare. Rupture is not always fatal, indeed in up to 70% of ruptures the patient survives neurologically intact.

Thrombosis

Thrombosis of an artery occurs in a number of different situations; if looked for carefully it occurs in up to 28% of cases (Pelz *et al*. 1998), although persisting neurological deficits only occur in 5%. Proximal occlusion of a parent artery may occur due to clot forming on coils bulging out of the aneurysm neck. This can be treated with tissue plasminogen activator, which can result in haemorrhage from an unprotected aneurysm that has led many to use abciximab (Reopro) either intravenously, or intra-arterially into the clot. Theoretically and in practice the clot already formed around the site of aneurysm rupture is not affected by Reopro (Qureshi *et al*. 2000). Having opened the vessel we typically wait 15 min to see if re-occlusion is going to occur and if it does then we attempt to remodel the coils with a balloon.

Distal occlusion

Distal occlusion poses an interesting problem. It is usually embolic from the catheter, the aneurysm, the coils, or proximal arterial disease. What to do is aided by CT perfusion imaging. If the perfusion in the affected area is over 20 mLs/100 g/min then increasing the blood pressure by 10–20 mmHg is probably safer than using thrombolytic agents since this suggests potentially adequate collateral flow. Occasionally clot is resistant to these therapeutic measures and more drastic action is required. Large clots can be retrieved with mechanical devices such as a goose -necked snare or the Merci retriever (Fig. 9) (Concentric Medical, Mountain View, CA, USA). If all these modes of attack fail it may be possible to angioplasty soft clot.

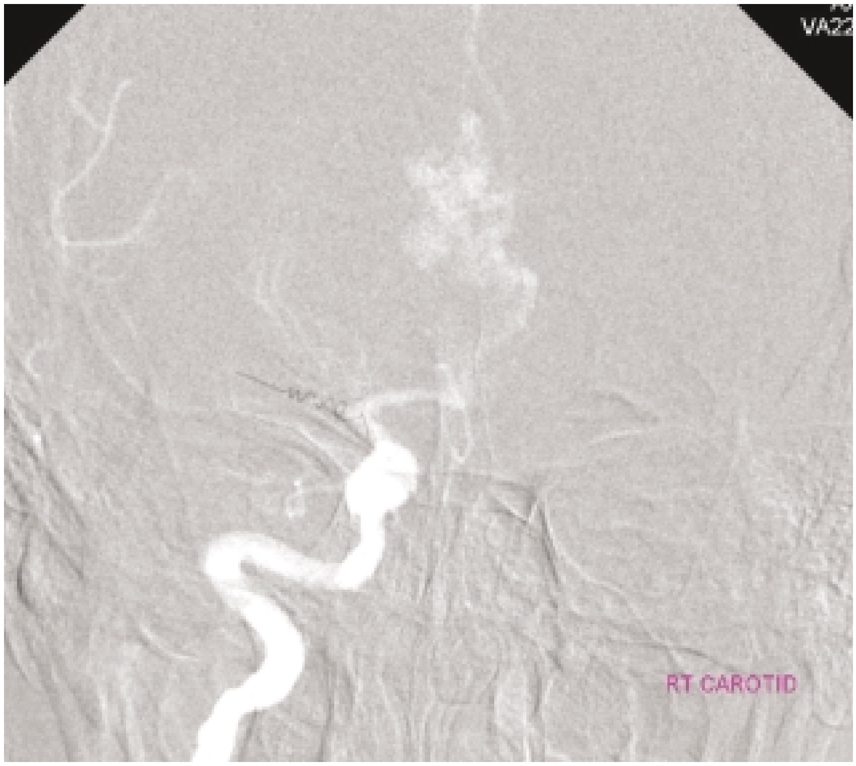

Figure 9 The Merci Clot retriever (Concentric Medical), arrow. This has a corkscrew action and embeds into the clot. A proximal balloon prevents forward flow and debris embolizing distally

CONCLUSIONS

- The ISAT trial should result in about 80% of all ruptured aneurysms that get to hospital being coiled.
- Specialist neurovascular surgery is still needed but will be concentrated in fewer centres.
- Management of subarachnoid haemorrhage is a team event requiring neurological support and input.
- Recent developments in interventional management of aneurysms include stents and liquid embolic agents.
- Complications of coiling include rupture, thrombosis and distal arterial occlusion – overall there is a 5% stroke risk.
- ISAT has been a landmark for neurosurgery and neuroradiology, the first well conducted randomised controlled trial encompassing both fields. Its legacy will hopefully be to have set up a group of clinicians in different specialties who are keen to go on to tackle the next set of important questions in the management of SAH.

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