QUALITY CONTROL FOR CAROTID

ENDARTERECTOMY

BY

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The work on which this thesis is based is my own independent work except where acknowledged.

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Dedicated to Christopher M Allsager.

Abstract: Quality Control for Carotid Endarterectomy.

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Introduction.

Carotid endarterectomy has been shown to be beneficial in patients with severe carotid artery stenosis, however the paradox remains that the very operation that is performed to prevent stroke, can indeed cause a stroke.

Aims.

The aims of this study are to assess whether the introduction of a rigorous quality control method could produce a sustained reduction in the intraoperative stroke rate in this unit and whether it was feasible and practical to implement such a programme. The second part of this study will assess the incidence of sustained embolisation in the early post-operative period and investigate whether the antiplatelet agent Dextran 40 can help stop this embolisation, potentially preventing carotid artery thrombosis.

Methods.

A prospective audit of all patients undergoing carotid endarterectomy was performed. The ability to monitor intraoperatively with TCD and perform completion angioscopy was assessed, as was the impact that these quality control techniques had on influencing the surgery. Patients were monitored postoperatively with TCD and any patient who developed sustained embolisation was commenced on an infusion of Dextran 40.

Results.

91% had continuous intraoperative TCD monitoring and 94% underwent successful completion angioscopy, a technical error was identified in 5% of angioscopic assessments. The intraoperative stroke rate was 0% during this study. Postoperative monitoring revealed that 5% of patients develop significant embolisation following CEA, Dextran 40 appeared to stop this embolisation. The overall 30-day any stroke or death rate following CEA has fallen from 6% prior to 1992 to 2.2% in 1998.

Conclusions.

It is possible to implement a quality control programme for CEA and this has been associated with a fall in the overall 30-day death and any stroke rate. We have quantified the number of patients who develop significant embolisation following CEA using TCD and shown that 5% of patients develop significant embolisation following surgery which can be controlled with Dextran 40.

ACKNOWLEDGEMENTS.

PUBLICATIONS ARISING FROM THIS THESIS.

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    Intraoperative stroke During Carotid Endarterectomy.

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    Bell and A.R. Naylor. Eur. J Vasc Endovasc Surg 17, 234 – 240, 1999.

2. Prevention of postoperative thrombotic stroke after carotid

    endarterectomy: The role of transcranial Doppler ultrasound.

    N. Lennard, J.L. Smith, J. Dumville, R. Abbott, D. H. Evans, N.J.M.

    London, P.R.F. Bell A.R. Naylor. J Vasc Surg 1997; 26: 2281 – 2284.

3. Transcranial Doppler Directed Dextran Therapy in the Prevention of

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    Hours.

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4. Reducing the risk of carotid surgery: A 7-Year audit of the role of

    monitoring and quality control assessment.

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CEREBROVASCULAR DISEASE.

CHAPTER ONE

CEREBROVASCULAR DISEASE.

CHAPTER ONE. CEREBROVASCULAR DISEASE.

This chapter will summarise the definition, aetiology, pathology, epidemiology and identify the burden of cerebrovascular disease with particular focus on the United Kingdom.

1.1 Definitions.

Stroke is defined as an acute loss of focal cerebral function (occasionally global when applied to cases of coma or subarachnoid haemorrhage) with symptoms exceeding 24 hours (or leading to death) with no apparent cause other than that of a vascular origin.

A transient ischaemic attack (TIA) is an acute loss of focal cerebral function or monocular visual loss (amaurosis fugax) with symptoms lasting less than 24 hours, and no apparent cause other than that of vascular origin.

1.2 Aetiology of Cerebrovascular Disease.

In 1978 an ad hoc committee of The National advisory council of the National Institute of Neurological and Communicative Disorders and Stroke published a classification and outline of the cerebrovascular diseases which remains a useful basis of classification today[1].

Cerebral Infarction
Transient cerebral ischaemia without infarction.
Intracranial haemorrhage
Vascular malformations and developmental abnormalities
Inflammatory diseases of arteries
Vascular diseases without changes in the brain
Hypertensive encephalopathy
Dural sinus and cerebral venous thrombosis
Strokes of undetermined origin.

80% of all strokes are ischaemic, 20% are haemorrhagic (intracerebral/ subarachnoid) and up to 80% of all ischaemic strokes occur in the carotid territory. The principle aetiologies of ischaemic infarction are detailed in table 1.

Thromboembolism of ICA/MCA	50%
Small vessel disease	25%
Cardiogenic brain embolism	15%
Haematological disease	5%
Non-atheromatous disease	5%

Table 1.1: Aetiology of Carotid Territory Infarction.[2]

<u>Large Vessel Thromboembolism.</u>

As detailed by the table above this is the single commonest cause of ischaemic stroke. Stenoses develop at the origin of the internal carotid artery (ICA) because of the complex haemodynamic phenomena that occur in this region. There is low shear stress, flow stasis and flow separation. These predispose to atherosclerotic plaque formation particularly on the posterolateral wall. If the plaque undergoes acute change such as rupture, ulceration or intraplaque haemorrhage the inner core of the plaque becomes exposed to the flow of blood within the vessel and due to its highly thrombogenic nature predisposes towards the formation of thrombus and the onset of symptoms (Figure 1.1). This may last for a period of a few weeks before resolving and explains the phenomenon of TIA clustering. Recent research suggests that the enzyme matrix metallo-proteinase 9 (MMP 9) levels are significantly raised in unstable plaques or in plaques retrieved from patients with recent onset symptoms, offering the possibility of a potential therapeutic window[3].

ulcer   platelet   platelet
               deposition   emboli
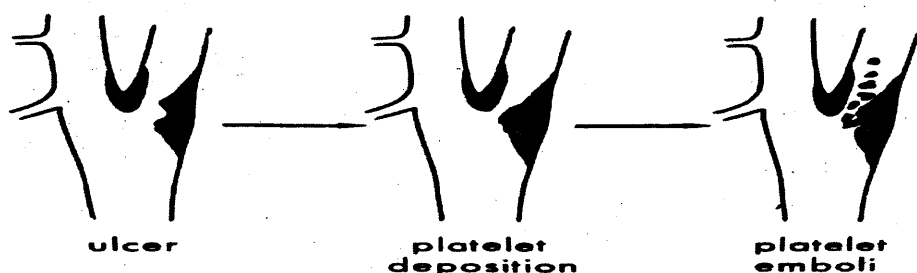
Figure 1.1   Proposed mechanism of ICA thromboembolism.

Small Vessel Disease.

Lacunar infarcts, so called because of the cavity or hole that remains after macrophages have removed infarcted tissue, are produced following occlusion of the deep, penetrating small end-arterioles. The underlying occlusive process may be due to fibrinoid necrosis (associated with hypertensive encephalopathy), lipohyalinosis and microatheroma (associated with chronic hypertension) or microcalcinosis (associated with diabetes).

Cardiogenic Brain Embolism.

Important sources of cardiogenic brain embolism include ventricular mural thrombus (post myocardial infarction, cardiomyopathy), left atrial thrombus (atrial fibrillation) and valvular lesions (vegetations, prostheses, calcified annulus, endocarditis). About 75% of patients who have had a stroke have cardiac failure, atrial fibrillation or an enlarged heart, and there is a two to fivefold increased incidence of stroke in patients with ischaemic heart disease. The embolus may arise from thrombus formed on endocardium overlying an infarct: in two thirds of cases this complication develops within the first 3 weeks after acute myocardial infarction. Other causes of cerebral embolism include infective endocarditis, calcific aortic stenosis, prolapsed mitral valve, atrial myxoma, non-bacterial thrombotic endocarditis in association with cachexia of advanced chronic disease, cardiomyopathy and arrhythmias. Rarely, a thrombotic embolus reaching the heart from the systemic veins may pass through a patent foramen ovale to enter the systemic arterial circulation (paradoxical embolism). Brain damage due to embolism may also complicate cardiac surgery and, more recently, open heart surgery with cardiopulmonary bypass has created new sources of cerebral embolism that include air, fat, particles of silicon and platelet/fibrin emboli from the pump oxygenator.

Haematological Disorders.

Conditions such as myeloma, sickle-cell disease, polycythemia, the oral contraceptive pill and related prothrombotic disorders may predispose towards stroke.

Non-atheromatous disease.

This only accounts for 5% of strokes arising from cerebral ischaemia, causes include collagen vascular disorders such as polyarteritis nodosa (PAN) and systemic lupus erythematosis (SLE), arteritis, migraine, tumours, carotid dissection and fibromuscular dysplasia.

Fibromuscular dysplasia (FMD) is a rare disorder of unknown aetiology that primarily affects the renal and carotid arteries of young women up to middle age. In 60% of cases the disease is bilateral, characteristically affecting the mid-section of the ICA. There is a characteristic angiographic appearance with beading of the artery. There are alternating segments of stenoses and dilatation with possible aneurysm formation. Patients may be asymptomatic or symptomatic with TIA, stroke, arterial wall rupture or dissection. Asymptomatic patients are usually managed conservatively with antiplatelet therapy and Duplex surveillance. The options for treatment of symptomatic individuals include resection with interposition bypass graft, open graduated internal dilatation and more commonly these days percutaneous angioplasty.

There are many types of vasculitis that cause cerebral infarction including arteritis due to micro-organisms and collagen diseases. Polyarteritis nodosa (PAN) affects the CNS in 20% of cases, when the intracranial arteries may have a beaded appearance due to multiple aneurysms. Rupture of these aneurysms is however uncommon, subarachnoid haemorrhage rarely being a presenting feature. Takayasu's arteritis (TA) produces a transmural granulomatous reaction ultimately leading to occlusion through fibrosis. TA predominately affects young females (gender ratio 7F : 1M). Neurological symptoms develop as a consequence of vascular occlusion or via renovascular hypertension. The commonest form, accounting for 65% of cases affects arch vessels and abdominal aorta and its branches. It is characterised by stroke, renovascular hypertension and mesenteric ischaemia. The mainstay of management is corticosteroid therapy which may be combined with other immunosupressive agents such as methotrexate and cyclophosphamide.

In the preantibiotic era acute carotid arteritis sometimes developed in children and young adults with tonsillitis and retropharyngeal inflammation. Arteritis, may also be

caused by various fungal and parasitic diseases, such as, aspergillosis, mucormycosis and cryptococcosis.

Carotid dissection accounts for 2% of all strokes, rising to 20% in young adults. One-fifth of trauma patients with an unexplained neurological deficit will have a dissection and 25% will be bilateral. Carotid dissections are classified as type I if there is irregularity but no significant stenosis on angiography, type II if there is a stenosis > 70% and a 50% dilatation, while type III dissections show complete occlusion. The majority are managed conservatively (systemic heparinisation with subsequent warfarinisation) with the aim being to reduce the incidence of thrombosis and embolization. Surgery tends to be reserved for complex trauma cases (usually type II), but may be indicated in patients with recurrent cerebral events despite medical therapy. Overall carotid dissection carries a 20% mortality and a 30% rate of persisting disability.

Subarachnoid Haemorrhage.

The estimated incidence of subarachnoid haemorrhage is between 10 and 28 cases per 100,000 persons per year[4]. Most of the bleeding into the subarachnoid space results from ruptured aneurysms; only 4 – 5% are from ruptured arteriovenous malformations[4]. Prevention of subarachnoid haemorrhage depends upon identification of risk factors that can be modified or eliminated. Risk factors include age, female gender, hypertension, oral contraceptives, cigarette smoking and alcohol consumption.

1.3 Clinical Presentation.

The term stroke encompasses a wide range of clinical syndromes, each of which may identify the anatomy of the cerebrovascular accident. The Oxfordshire Community Stroke Project (OCSP) has shown that clinical classification based on bedside assessment can reliably predict the vascular pathology and computerized tomography (CT)/autopsy findings following ischaemic stroke.[5]

Patients classified as total anterior circulation infarction (TACI) present with the triad of hemisensory/motor deficit affecting face, arm and leg, homonymous

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hemianopia and higher cortical dysfunction. TACI patients have the largest infarction volumes, occlusion of either the extracranial ICA or intracranial MCA mainstem and a 30 day mortality of 37%. Only 7% are alive and independent at 1 year[5;6]. Patients classified as having partial anterior circulation infarction (PACI) present with one or two of the TACI triad, have focal infarcts on CT and rarely have evidence of major vessel occlusion. The 30 day mortality is 13% and 71% are alive and independent at 1 year[5;6].

Patients classified as posterior circulation infarction (POCI) present with vertebrobasilar symptoms and have infarcts localized to the posterior circulation territory. The 30 day mortality rate is 7% and 80% are independent at 30 days [5].Patients classified as lacunar infarction (LACI) present with symptoms and signs which in pathological studies are associated with disease of the deep perforating arteries (pure motor stroke, pure sensory stroke, sensorimotor stroke and ataxic hemiparesis). LACI patients never have evidence of higher cortical dysfunction and major vessel occlusion is not a feature[5;6].

<u>Typical carotid territory symptoms.</u>

      Hemimotor/hemisensory signs.

      Monocular visual loss (amaurosis fugax).

      Higher cortical dysfunction (dysphasia, visulospatial neglect etc.).

<u>Typical vertebrobasilar symptoms.</u>

      Bilateral blindness.

      Problems with gait or stance.

      Hemi- or bilateral motor/sensory signs.

      Dysarthria.

      Homonymous hemianopia.

      Diplopia, vertigo and nystagmus (provided it is not the only symptom).

Table 1.2   **Carotid and vertebrobasilar symptoms and signs.**

The typical carotid territory and vertebrobasilar territory symptoms are detailed in Table 1.2. The differential diagnosis of carotid territory events includes epilepsy,

tumour, giant aneurysm, hypoglycaemia and migraine. It is not usually possible to differentiate embolic from haemodynamic events although where TIAs are precipitated by a heavy meal, hot bath or exercise, a haemodynamically critical ICA stenosis should be suspected.

The term non-hemispheric is ascribed to patients with isolated syncope (blackout, drop attack), presyncope (faintness), isolated dizziness, isolated double vision (diplopia) and isolated vertigo. These should never be considered carotid or vertebrobasilar unless other more typical symptoms are present and cardiac and inner ear pathology have been excluded.

1.4 Epidemiology.

Mortality.

Stroke accounts for 10 – 12% of all deaths in industrialised countries. Some 88% of stroke deaths are in the over 65s. In 1992 there were 66,300 deaths in England and Wale from stroke, with 2,500 from subarachnoid haemorrhage[7]. Stroke is the third most common cause of death in the United Kingdom after myocardial infarction and cancer[7]. It was for this reason that the Government considered it an important public health issue and included it in *The Health of the Nation* targets[8].

There are noticeable differences in the standardised mortality ratios (SMR) for stroke between countries[9], and between regions of the same country. Japan has the highest cerebrovascular disease mortality rate. The USA, England and Wales have intermediate rates, whereas Poland, Denmark, Sweden and Canada have low rates.

In the UK, SMRs vary considerably from 122 (Northern Region) to 83 (NW Thames) in males and 115 (Mersey) to 84 (NW Thames) in females[10]. The relationship between the prevalence of risk factors and SMRs has not been investigated. Wolfe et al.[11] did however demonstrate that the difference in SMR for stroke in three health authorities of Southern England was due to variations in incidence rather than case-fatality.

In terms of years of life lost as a result of stroke, in England and Wales between 1986 and 1990 an average of 36.6 years of life were lost per 10,000 male population and this varied from 26 in the Oxford region to 48.7 in the Northern region. In females the average range was 29.5 ranging from 21.6 in South West Thames to 42.9 in East Anglia[10].

Incidence.

The incidence is defined as the number of first in-a-lifetime strokes occurring per unit time. Most studies express an incidence rate per 1000 population.

The incidence of TIAs is about 42 per 100,000 per year, about 80% being in the carotid territory[2]. The OCSP study suggests a risk of stroke of 11.6% over the first year following TIA onset, reducing to about 5%[12] annually thereafter. Forty per cent of the strokes following a TIA were in a vascular territory not involved in the original TIA [12].

The incidence of subarachnoid haemorrhage is about 9- 14 per 100,000 per year [13]. Other published estimates are as high as 33 per 100,000 for men and 25 per 100,000 per year in women [14;15]. The case fatality rate is high, 46% within 30 days and 48% at one year [5],[14].

The Oxfordshire Community Stroke Project remains the gold standard for incidence studies of stroke in the UK despite having commenced over 20 years ago when mortality rates were higher and the study area was predominately rural with no ethnic minorities.

The overall incidence of first-in-a-lifetime stroke is 2.4 per 1000 per year. Intracerebral haemorrhage (excluding SAH) accounts for just over 10% of all strokes, the remainder being cerebral infarction [16] [17]. Lacunar stroke syndrome constitutes about 21% of first strokes, and has a crude annual incidence of 0.33 per 1000 per year [16] [18]. These stroke patients have a much lower case-fatality rate (10% at 1 year) and 66% are functionally independent at 1 year. Using the Bamford Classification the following proportion of first strokes can be expected based on several studies [16] [19] (Table 1.3) .

Cerebral Infarction	76%
Partial anterior circulation syndrome	56%
Lacunar syndrome	20%
Total Anterior circulation syndrome	15%
Posterior circulation syndrome	8%
Unclassified	1%
Primary intracerebral haemorrhage	10%
Subarachnoid haemorrhage	4%
Not known	10%

Table 1.3   Incidence of sub-types of stroke.

Stroke rates rise exponentially with age with a 100-fold increase from the 4th decade to the 9th decade of life. Bonita [20] has estimated that the risk of a person of 45 years of age having a stroke within 20 years is very low (about 1 in 30). However, almost one in four men and nearly one in five women aged 45 can expect to have a stroke if they live to their 85th year. Although the life-time risk of having a stroke is higher in men the converse is true for the lifetime risk of dying of a stroke. Thus about 16% of women are likely to die of a stroke compared to 8% of men; this difference is largely attributable to higher mean age at onset of stroke in women and to their greater life expectancy. Typically first events account for 75% of all acute events. The cumulative risk of recurrence over 5 years is high, ranging from about a third to almost half the people who have a stroke.

Since stroke rates increase greatly with age and the number of elderly people is increasing, the burden of stroke on individual families, and the health services is unlikely to fall rapidly. Malmgren et al.[21] estimated that between 1983 and 2023 in England and Wales there will be an absolute increase in the number of patients experiencing first ever stroke of about 30%. There will be an increase in the number of deaths from stroke of about 40% and there will only be an increase of 4 – 8% in the number of disabled long-term survivors. There can be an anticipated increase in the need for acute care and early rehabilitation services over this time period but not in longer term care.

Prevalence of Stroke.

The prevalence is the number of stroke sufferers in the population. There have been very few prevalence surveys of stroke, the prevalence rates being estimated using the incidence and survival data from stroke registers. Hillman et al.[22] have reported findings of a survey in Nottinghamshire of stroke survivors living in the community. They used a postal questionnaire methodology and estimated a total prevalence rate of 46.8 (95% confidence intervals 42.5 – 51.6) per 10,000 population.

Age band	Sex	Rate per 1,000,000	Age band	Sex	Rate per 100,000
20-39	M	98	20-44	M	160
	F	88		F	110
	M&F	93		M&F	140
40-49	M	417	45-54	M	750
	F	235		F	250
	M&F	322		M&F	500
50-59	M	745	55-64	M	2,290
	F	716		F	1,480
	M&F	728		M&F	1,870
60-69	M	1,648	65-74	M	3,860
	F	845		F	1,490
	M&F	1,170		M&F	2,490
70+	M	4,595	75+	M	2,750
	F	1,628		F	3,510
	M&F	3,157		M&F	3,240

Table 1.4   Prevalence rates of stroke from two studies [23].

1.5 Impairment, disability and handicap.

Impairment refers to abnormalities arising at the level of the organism. Impairments are usually the external manifestations of the pathology: the symptoms and signs. Impairments are 'objective' and cover a wide range of states which carry no personal meaning to the patient: hemianopia, sensory loss, muscle weakness, spacticity, pain etc.

Disability refers to changes in the interactions between the patient and the environment. It is the behavioural consequences, which manifest within the patient's environment, or the personally meaningful functions or activities which are no longer executed or are altered. Altered behaviours stretch from continence and turning over in bed to dressing and bathing, interacting with other people and specific work skills. In practical terms, especially in relation to health and social services, disability manifests itself as an increasing dependence upon people and/or environmental adaptations.

Handicap is the most difficult level to define and measure and is the change in social position that arises from illness; it also refers to the social, societal and personal consequences of the disease. It is the roles and expectations that are performed less readily if at all. Table 1.5 details the incidence of impairment and disability, per 100,000 population in the United Kingdom.

1.6 The overall cost of stroke care.

A recent effective Health Care Bulletin [24], stated that stroke care consumes around 4% of NHS expenditure. This estimate includes the cost of inpatient treatment, outpatient follow-up, and general practitioner consultations for stroke. The estimates excluded home nursing costs and costs of prescribed drugs. Based upon 1985 activity data and costs they estimated that the annual cost of inpatient care for stroke was £532 million in England and Wales. Isard and Forbes estimated that the costs of stroke care were £4,626 per discharge [25]. This figure only takes into account the treatment of an acute stroke and does not include the cost of long-term care which may rise to as much as £45,000 in total. Stroke also has major cost implications for

patients and their carers in terms of financial expenditure, lost income and time away from normal activities but limited information is available on the precise scale of these effects in the United Kingdom.

General – SAH, TIAs, stroke – diagnosed.	Cases SAH per year	14
	New cases TIA per year	42
	Carotid territory TIAs	34
	First stroke per year	200
	All acute strokes per year	240
	Stroke survivors alive in community	600
	Presenting for diagnosis	Unknown
Impairment/disability – presentation (i.e. need acute care), all stroke	With reduced consciousness	84
	Severely dependent	140
	Incontinent of urine	106
	Disorientated/unable to communicate	132
	Unable to get out of bed unaided.	168
Impairment/disability at three weeks (i.e. need rehabilitation) all stroke	Needs help dressing	86
	Needs help walking	67
	Needs help with toilet	66
	Communication problems	49
Impairment/disability at six months (i.e. needing long-term support)	Needs help bathing	71
	Needs help walking	22
	Needs help dressing	45
	Difficulty communicating	22
	Confused/demented	39
	Severely disabled	13
Services – at six months	Needs long-term institutional care	23
	Possibly needs speech therapy	24

Table 1.5   Incidence, impairment and disability per 100,000 population (per year where relevant) [23].

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In summary, 10-12% of deaths in the UK are due to stroke and 88% of stroke deaths occur in the over 65s. Although there has been a decline in stroke mortality in this century the reasons remain largely unexplained. The overall incidence of stroke is about 2.4 per 1000 population per year but these data are over 15 years old and estimated in a predominately rural community. One in four men and one in five women aged 45 can expect to have a stroke if they live to 85. Robust estimates of incidence are required especially as over the next 20 years it has been crudely estimated that there will be a 30% increase in stroke incidence as a result of an ageing population.

The overall case fatality rate is 24% at one month, 31% at one year and 55% at five years. Stroke care currently consumes between 4-5% of NHS expenditure. Although this proportion may remain around the same during the next 20 years, there is likely to be a dramatic increase in real terms in total health service costs consumed by stroke care.

The commonest single cause of ischaemic, carotid territory cerebral vascular accident is occlusion of, or embolism from internal carotid artery disease.

Chapter 2.

Management of cerebrovascular disease.

CHAPTER TWO: THE MANAGEMENT OF CEREBROVASCULAR DISEASE.

This chapter will outline the risk factors for stroke and detail the optimal medical management to reduce the incidence of stroke. It will also describe the role of carotid artery surgery, including the indications for surgery and endovascular intervention.

Figure 2.1   Carotid angiogram showing a severe carotid artery stenosis.

2.1 Risk factors for Stroke.

The approach to stroke prevention among patients who have already had their first TIA includes identification and modification of stroke risk factors. Non-modifiable risk factors for stroke include age, sex, race-ethnicity and heredity. Although these risk markers cannot be changed, they nonetheless serve as important identifiers of patients at risk of stroke, for whom an aggressive search for other modifiable risk factors might be particularly important.

Non-modifiable risk factors.

These include age, sex and genetic predisposition.

In the UK the risk of stroke doubles with each successive decade over the age of 55 [26]. In the UK population projections predict an increasingly aged population, at increased risk of stroke. Malmgren and colleagues [21] estimate , however, that this will result in a net increase of only 4% of moderately or severely handicapped individuals. The incidence rates range from 0.2/1000 population per year aged 45-54 to 10/1000 in people aged over 85 [26].

The Framingham study demonstrated an overall 30% increased incidence in men compared with women, which was slightly higher in those aged under 65 [27]. In the Oxfordshire Community Stroke Project, the odds of a male sustaining a first stroke were 26% greater than that of a female [17].

A family history of stroke in any first degree relative was an independent predictor of stroke in women only of a middle class Caucasian cohort, with a relative risk of 2.3 after controlling for age, cholesterol, blood pressure, cigarette smoking and diabetes [28].

Factor	Relative Risk
Male	1.3
Age (55-64 vs. 75+)	5
Family history	2.3
Family history SAH	7

Table 2.1   Non-modifiable risk factors.

Modifiable stroke risk factors.

Modifiable stroke risk factors include hypertension, cardiac disease (particularly atrial fibrillation), diabetes, hypercholesterolaemia, cigarette smoking, excessive use of alcohol and physical inactivity.

Factor	Relative risk	Attributable risk
Hypertension	7	0.46-0.75
Cardiac disease	3	0.11
LVH	4.4	
AF	3-7	0.015 (age 50-59)
		0.24 (age 80-89)
Previous TIA	5-13	0.1
Diabetes mellitus	4.1M	0.18
	5.8F	0.22
Epilepsy	4	
Snoring	3	
Infection	9	
Homocysteinuria	10	
Sickle cell disease	10	
Fibrinogen >3.6g/l	1.8	

Table 2.2   Modifiable risk factors for stroke.

Approximately 4 million people in the UK have a raised diastolic blood pressure between 100-120mmHg . Observational studies have all demonstrated hypertension to be the single most important risk factor for stroke and one which has been shown to be eminently reducible by antihypertensive treatment, in the randomised controlled trial setting. Good blood pressure control remains the cornerstone of managing cerebrovascular disease. It alone will do more to prevent stroke than aspirin, carotid endarterectomy or any other treatment available to us at present.

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Despite increased awareness of the benefits of optimisation of correctable risk factors, evidence suggests that these are not well controlled in most cases [29],[30]. Up to 40% of known hypertensives who are destined to suffer a stroke will not be on any treatment prior to their stroke and only 54% of those on antihypertensive therapy will have one documented diastolic blood pressure reading of <90mmHg. The main stay of controlling high blood pressure include drug therapy, weight loss and reducing salt intake.

Reduction of both systolic and diastolic pressure in hypertensive subjects substantially reduces stroke risk [31],[32]. Reduction of isolated systolic hypertension to <140mmHg in the elderly led to a 42% reduction in stroke risk with no significant decline in overall mortality.

After age, sex and hypertension, cardiac disease is said to be the most important risk factor for stroke. The Framingham Study showed that in the presence of coronary heart disease the relative risk of stroke in men was 2.5, in the presence of congestive cardiac failure it was 2.5 and in the presence of left ventricular hypertrophy it was 4.4 [27].

Atrial fibrillation (AF) affects 2% of the population (0.5% at 50-59 to 8.8% at 80-89) and the Framingham Study has estimated that AF accounts for between 7% and 31% of all strokes in patients under the age of 60 and increases the risk of stroke by a factor of five (1.5% in the fifth decade to 23.5% in eight decade) [33],[34]. Up to 20% of those with AF who suffer a first stroke have a further stroke within one year [35].

The attributable risk of having had a previous TIA is 10%. Estimates of a 13-fold increased risk of stroke for subjects have been observed in the first year after a TIA, and a seven-fold risk for the seven years thereafter [36]. Fifty per cent of TIAs originate from emboli in the region of the carotid artery. Only about 15- 20% of patients with first-time stroke will report a preceding TIA.

Diabetes is a well established stroke risk factor [37]. Death due to cerebrovascular disease is substantially increased in patients with 2 hour blood glucose values above the 97.5 percentile compared with those with values below the 80th percentile [38].

With regard to diabetes mellitus, there is to date, no clear evidence that rigorous control of glycaemia reduces the longterm risk of stroke, however it can substantially reduce the risk of microvascular complications such as retinopathy, neuropathy and nephropathy. The UK Prospective Diabetes Study Group has however shown, that tight control of blood pressure (<150/85mmHg) in type 2 diabetics was associated with a 44% reduction in the risk of stroke as compared to patients randomised to less tight control of their blood pressure (<180/105mmHg) [39].

Lifestyle factors, including cigarette smoking, heavy use of alcohol, and physical inactivity, have all been associated with an increase risk of stroke [40],[41;42].Stopping smoking reduces the risk of further vascular events by about 50% [43].

Premature arteriosclerosis and thromboembolic events are well known complications of homozygous homocysteinuria due to cystathionine beta synthase deficiency which damages vascular endothelial cells. Heterozygosity for homocysteinuria is said to occur in one in 70 of the population and predisposes to premature occlusive arterial disease. Perry et al reported in the British Regional Heart Study, that total homocysteine levels are a strong independent risk factor for stroke [44]. High doses of vitamin B6 treatment could theoretically reduce the risk of thromboembolic disease in these heterozygote subjects.

Greater attention is now being directed towards the treatment of hyperlipidaemia, mainly with a view to preventing myocardial infarction. The most recent lipid-lowering studies leave no doubt that cholesterol reduction reduces the risk of late ischaemic events and that, in addition to reducing the risk of myocardial infarction, a programme of cholesterol reduction will also reduce the risk of late stroke [45],[46]. Meta-analyses of the lipid-lowering trials with statin agents have found significant reductions in stroke risk [47]. A 29% reduced risk of stroke and a 22% reduction in overall mortality were found. Secondary prevention trials showed a 32% reduction in stroke risk and primary trials demonstrated a 20% reduction. Some clinical trials have also demonstrated carotid plaque regression with statins [48],[49].

In 1994 the Medical Research Council and British Heart Foundation joined forces to carry out a randomised study to investigate the effects on mortality and morbidity of

HMG CoA reductase inhibitors (statins) and of antioxidant vitamins in a wide range of people at high risk of coronary heart disease [50]. The study aimed to randomise at least 20,000 patients considered on the basis of their age and past medical history to be at high risk of CHD (Three main risk groups: those with coronary artery disease; with occlusive disease of the non-coronary arteries; or with diabetes) to compare at least 5 years of simvastatin treatment versus placebo. The aim was to provide unequivocal evidence about the net effects of several years of statin therapy on total mortality among high risk patients, as well as to provide reliable assessments of the separate effects on CHD mortality and on specific non-cardiac causes of death. It also aimed to assess the treatments effects on total CHD, on other vascular diseases (e.g. stroke), on the need for vascular surgery, on cancer and on any non-vascular diseases that are sufficiently severe to involve hospital treatment.

The results were published in the Lancet in 2002. A summary of the major findings of the Heart Protection Study are as follows:-

- Cholesterol-lowering with statin treatment reduced the risk of heart attacks and strokes by at least one quarter, as well as reducing the need for arterial surgery, angioplasty and amputations.
- Substantial reductions in these 'major vascular events' were found in a very wide range of high risk patients for whom there had previously been uncertainty about using cholesterol-lowering treatment, including

  Women as well as men;

  People aged over 70 as well as youger people;

  People who have diabetes, narrowing of arteries in their legs or a history of stroke, as well as those who already have heart disease;

  People with blood levels of total cholesterol below 5mmol/l, as well as those considered to have 'high' levels.
- About 5 years of statin treatment typically prevented these major vascular events in:

  100 out of every 1,000 people who have previously had a heart attack

  80 out of every 1,000 people with angina or some other evidence of CHD

70 of every 1,000 patients who had previously had a stroke

70 of every 1,000 patients with occlusive disease in leg or other arteries

70 of every 1,000 people with diabetes

- In addition, continued treatment with a statin prevented further major vascular events and deaths in those people who had already had a heart attack or stroke.

- The benefits of treatment increased throughout the 5-year study period, so more prolonged use of a statin would be expexted to produce even bigger effects.

- The benefits of statins were additional to those of other treatments used to prevent heart attacks or strokes, such as aspirin and blood-pressure lowering drugs.

- The trial showed there was no support for previous concerns about possible adverse effects of lowering cholesterol on particular non-vascular causes of death, on cancers or on strokes due to bleeding.

Based on WHO estimates of the numbers of people with CHD, stroke and diabetes, it can be estimated that the results are relevant to the treatment of some hundreds of millions of people worldwide. If an extra 10 million high risk individuals were to start statin treatment this would save about 50,000 lives each year and would prevent a similar number from suffering non-fatal heart attacks or strokes.

2.2 MEDICAL THERAPY.

Antiplatelet Therapy.

Antiplatelet agents are typically the treatment of choice for prevention of future ischaemic strokes in patients who have experienced a TIA of presumed atherothrombotic origin. Four different antiplatelet agents have shown a benefit in preventing stroke and /or other vascular events in patients with cerebrovascular disease. Aspirin continues to be the most economical and frequently chosen antiplatelet agent for treatment of patients after TIA. Meta analyses suggest that aspirin will reduce the long-term risk of stroke by 25% [51].The greatest controversy regarding the use of aspirin for stroke prevention involves dose selection. At present

there is no compelling evidence than higher or lower doses are more efficacious. The range of acceptable management includes daily doses of aspirin between 30 and 1300mg.

The gastrointestinal toxicity of aspirin is dose related, but even low-dose aspirin (i.e. 50 to 75mg/d) slightly increases the risk of major bleeding, particularly gastrointestinal haemorrhage [52]. Enteric coating reduces gastrointestinal toxicity and appears to inhibit thromboxane synthetase similarly to equal doses of uncoated preparations despite altered pharmacokinetics and dynamics, although this has not been thoroughly studied in elderly stroke-prone patients.

For patients who experience an intial or recurrent TIA while taking aspirin ('aspirin failures'), there is no good evidence that altering the dose of aspirin instead of continuing the original dose will reduce the subsequent risk of stroke [53]. Those that experience TIA or minor ischaemic stroke while taking aspirin appear to have a particularly high risk for subsequent stroke. Most clinicians empirically replace aspirin with another antiplatelet agent in these circumstances. Although such an approach appears sensible, it is not evidenced based.

Alternative antiplatelet agents include ticlopidine, clopidogrel and dipyridamole. Ticlopidine hydrochloride prevents platelet aggregation induced by adenosine diphosphate (ADP). In the Ticlopidine Aspirin Stroke Study (TASS) [54], the efficacy of ticlopidine was compared with aspirin in reducing the incidence of stroke and death from all causes in 3069 patients with a recent TIA (50%), reversible ischaemic neurological deficit (12%), minor stroke (23%), or >1 of these events (15%). The overall risk reduction of fatal and non-fatal stroke by ticlopidine at 3 years was 21%. Ticlopidine also reduced the risk of stroke and all causes of death by 12% compared with aspirin. Although ticlopidine is efficacious in stroke prevention its usefulness is limited by it's side effects including diarrhoea, neutropenia and thrombotic thrombocytopenic purpura. Ticlopidine is typically used in patients who are intolerant to aspirin or who have had an ischaemic event despite taking aspirin. Because the majority of side effects occur within the first 3 months, patients who have tolerated these early months of therapy can generally continue taking the drug.

Clopidogrel is chemically related to ticlopidine and also works by inhibiting platelet aggregation induced by ADP. It does not however have the extensive side-effect profile that ticlopidine possesses. The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial [55] assessed the relative efficacy of clopidogrel and aspirin in reducing the risk of a composite outcome cluster of ischaemic stroke, myocardial infarction, or vascular death. Clopidogrel produced a relative risk reduction of 8.7% of this outcome cluster. Stroke by itself was not a prespecified end point in this trial. Although clopidogrel had a slightly greater efficacy than aspirin in reducing the combined end point of myocardial infarction, stroke, and vascular death, the absolute benefit was small. Compared with aspirin, clopidogrel had a smaller relative risk reduction for stroke than ticlopidine. However, clopidogrel clearly has an advantage over ticlopidine in its side-effect profile. Clopidogrel offers another alternative to aspirin that is particularly useful for patients with intolerance to aspirin. It is also likely to be useful for patients who have an ischaemic event despite aspirin therapy.

The efficacy of the combination of dipyridamole and aspirin has also been assessed. In comparison with aspirin, reductions in stroke risk with the combination therapy of extended-release dipyridamole and aspirin were greater than those reported for clopidogrel however, these agents have not been compared directly. The aspirin and extended-release dipyridamole combination was well tolerated and provides another useful alternative to aspirin for the prevention of stroke [56].

Anticoagulation.

Adjusted-dose oral anticoagulation with warfarin continues to be the therapy of choice for stroke prevention in patients with atrial fibrillation who have had a TIA. The superior efficacy of anticoagulation over aspirin for prevention of stroke in patients with atrial fibrillation and a recent TIA or minor stroke was shown in the European Atrial Fibrillation Trial [57]. In addition considerable data from multiple randomised trials have shown that oral anticoagulation is the treatment of choice for primary stroke prevention in high- risk atrial fibrillation patients. Patients with atrial fibrillation who are at high risk of stroke include persons with a history of hypertension, poor left ventricular function, rheumatic mitral valve disease,

prosthetic heart valves, a prior stroke, TIA, systemic embolism, or age > 75 years [58].
The efficacy of aspirin for the prevention of cardioembolic stroke is considerably less
than warfarin. Aspirin is recommended for patients at high risk of cardioembolism
who have contraindications to oral anticoagulation.

In summary best medical therapy for those patients at high risk of stroke should
include strict control of blood pressure, aspirin therapy, warfarinization of those
patients with atrial fibrillation and a statin to control cholesterol and prevent carotid
plaque progression. If aspirin is contraindicated and warfarinization not indicated
then clopidogrel is the antiplatelet agent of choice.

2.3. SURGICAL MANAGEMENT.

History of surgical intervention.

The first carotid endarterectomy was performed on August 7, 1953, by DeBakey, but
the operation was not reported until 22 years later [59]. The patient was a 53 year old
man with TIAs. The patient did not have recurrence of cerebrovascular disease until
his death from a myocardial infarction 19 years later.

On the 19th May 1954, Eastcott operated on a woman who had a history of 33 TIAs
at St Mary's Hospital, London. She was shown to have a stenosis of the left carotid
bifurcation and underwent resection of the carotid bifurcation with end to end
anastomosis. Eastcott describes in his account of the operation how the patient was
first referred to a neurologist, Dr Denis Brinton. Brinton had previously worked in
Boston and was aware of the work of Fisher on carotid embolic symptoms and
correctly identified the carotid source of this patients symptoms with arteriography.
The Professor of Surgery, Charles Rob was consulted and agreed that surgery
appeared to offer the best hope of a cure. However, it was Eastcott that performed the
surgery, as on the day it was arranged was one during which a distinguished group of
visiting American Surgeons were at St Mary's. Among this group were Wylie and
DeBakey. Wylie had first introduced the technique of thrombo-endarterectomy for
aorto-iliac disease and both he and DeBakey suggested that an endarterectomy would
be appropriate in this situation. Eascott, however, had considerable experimental and

some clinical experience of carotid arterial resection and grafting and therefore preferred this approach. Eastcott describes how the patient lay anaesthetised in an ice water bath until her body temperature fell to 28°C in an attempt at cerebral protection. Clamps were applied, the external carotid artery was ligated a little above its origin, the stenosed segment was resected and the common carotid artery was anastamosed to the internal carotid artery stump. Clamp time was 28 minutes and no heparin was used. The patient was completely relieved of her symptoms and lived for many years, eventually dying of congestive cardiac failure at the age of 86 years. However, this early success was soon to be followed by three early post-operative deaths at St Mary's following carotid resections.
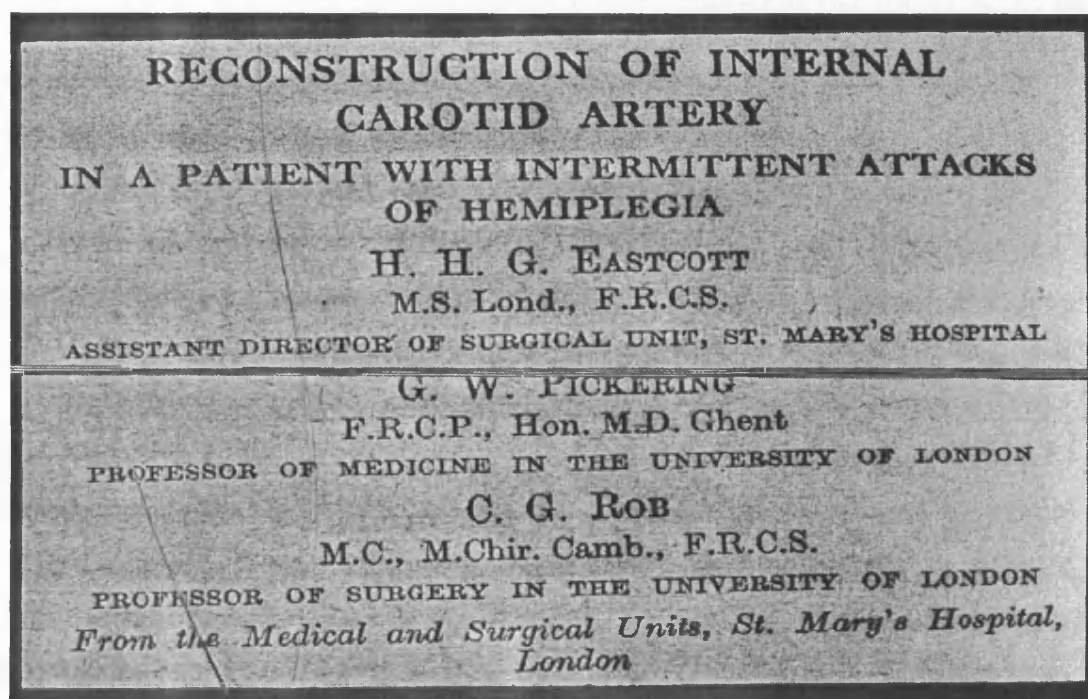
Figure 2.2   **Eastcott's original paper detailing carotid artery reconstruction.**

In 1956, Cooley, Al-Naaman, and Carton performed and published the first report of a carotid endarterectomy [60]. Between the 1950's and 1980's the increasing awareness of the relationship between extracranial carotid disease and stroke led to a dramatic increase in the annual number of operations performed worldwide. However by the early 1980's there was growing concern regarding the paradox that the very

operation undertaken to prevent stroke in the long term could itself cause a stroke in the perioperative period in a small but significant number of patients. This growing concern led to the implementation of two international trials to try and answer the question 'does carotid endarterectomy (CEA) plus best medical therapy confer any additional benefit in terms of long-term stroke reduction over and above that achieved by best medical therapy alone in patients with carotid territory symptoms and a carotid artery stenosis?'

The European Carotid Surgery Trial.

The European Carotid Surgery Trial (ECST) started randomisation in 1981, initially only in the UK but 12 European countries subsequently participated. The trial aimed to answer the following questions in three main categories of carotid stenosis, mild (0-29%), moderate (30-69%) and severe (70-99%).

1. What is the risk of death or stroke in the 30 days following carotid endarterectomy?
2. In patients who survive surgery for 30 days without a stroke, what is the long-term risk of disabling or fatal stroke?
3. What is the risk of stroke in patients treated with medical therapy alone?

The criteria for inclusion were 'Any patient irrespective of age, sex, or race, who, within the 6 months prior to randomisation, had experienced any combination of TIA, amaurosis fugax, retinal infarction, minor ischaemic stroke or non-disabling major ischaemic stroke within the distribution of one or both internal carotid arteries, and who had a stenosing and/or ulcerating lesion of the symptomatic carotid artery at its origin in the neck'.

However an important aspect of inclusion in the trial was an 'uncertainty principle'. A patient who satisfied the entry criteria was only entered into the trial if the neurologist or surgeon were 'substantially uncertain' whether to recommend surgery. This was designed to overcome ethical difficulties, but did mean that not all patients who fulfilled the entry criteria were included in the trial.

Patients were excluded on the following grounds:

1. Patient preference
2. Poor general health
3. Little if any carotid stenosis
4. A lesion thought to be technically inoperable
5. ICA occlusion, or distal stenosis more severe than at the bifurcation
6. Other more likely sources of embolism (recent myocardial infarction, mitral stenosis, atrial fibrillation, etc.) whose TIAs are thought not to be due to atherothromboembolism
7. Vertebrobasilar events
8. Previous carotid endarterectomy of the symptomatic artery.

All patients had baseline blood tests performed along with a selective carotid angiogram prior to randomisation, these were forwarded to a central trial office for the purpose of determining the exact degree of carotid stenosis. The method employed to measure the stenosis involved measuring the lumen at the site of greatest stenosis and comparing this to the estimated diameter of the carotid bulb. Computerised tomographic brain scans were recommended for all patients. Patients were randomised by telephone, all patients received 'best medical therapy' including advice to stop smoking, aspirin, treatment of hypertension and hyperlipidaemia. All operations were performed by the designated trial surgeon, who had to have submitted a track record of previous experience.

Patients taking part in the trial were seen by a collaborating neurologist at 4 months, 1 year, and annually thereafter.

The interim results of this trial were first published in the Lancet in 1991 [61]. At that time it became clear that carotid endarterectomy was of benefit in patients with a recently symptomatic (< 6 months), severe carotid artery stenosis, but was of no value in patients with mild (0 – 30%) stenosis. The position on patients with a moderate carotid artery stenosis remained unclear and recruitment of this group of patients continued after 1991.

The data leading to these conclusions were derived from the results of 2200 patients, of which 1152 were patients either with mild or severe disease. Of these, 60% had

been randomised to surgery and 40% to 'no-surgery'. There were seven deaths within 30 days of operation compared with no deaths in the 'no surgery' group of patients over an identical period of time. Death or disabling stroke occurred in 22 'surgery' patients (3.3%), and if all strokes producing symptoms for more than 7 days are included, the figures rise to 44 patients (7.5%). The number of deaths during follow-up due to other causes were similar in the 'surgery' and 'no surgery' groups (8.3% Vs 8.6%) and similar in the mild and severe stenosis groups.

During the 3 year follow-up period there was an eight-fold reduction in the number of ipsilateral disabling or fatal strokes in severely stenotic patients allocated to surgery compared with 'no surgery' (5/455 Vs 27/323, 2p<0.0001). In patients with mild stenosis there was no difference in the number of ipsilateral ischaemic strokes between the 'surgery' and 'no surgery' groups (1/219 Vs 0/155).

In the severe stenosis group there was a six fold reduction in strokes lasting more than 7 days in the surgery group (9/455 Vs 44/323, 2p<0.0001). In the mild stenosis group there was no stastically significant difference (6/219 Vs 2/155).

The study identified several adverse prognostic factors. In the 'no surgery' group, other than the degree of stenosis the adverse factors were, a history of stroke, residual neurological signs and infarction on the pre-randomisation CT scan. In the surgery group, factors predicting an adverse 30-day outcome were, systolic blood pressure above 160mmHg, and performance of surgery in under 1 hour.

The final results of ECST were published in 1998 including longer follow-up (mean 6.1 years) [62]. This final report changed the indications for carotid endarterectomy outlined in the interim ECST report of 1991. Stroke risk and years of stroke-free survival were statistically modelled taking into account age, sex and degree of carotid stenosis. This narrowed the range of carotid stenosis over which carotid endarterectomy could be considered beneficial. Symptomatic carotid stenosis could be expected to benefit men with a symptomatic stenosis >80%, and women with a stenosis >90%. Surgery was not considered justified in symptomatic patients with moderate (30 – 69%) internal carotid artery stenosis.

	Surgery	No surgery
Deaths/disabling stroke in 30 days	3.3%	0
All strokes in 30 days	7.5%	0
Deaths – other causes in 3 years	8.3%	8.6%
Severe stenosis – disabling stroke/death in 3 years	5/455	27/323
Mild stenosis – disabling stroke/death in 3 years	1/219	0/155
Severe stenosis – strokes longer than 7 days in 3 years	9/455	44/323
Mild stenosis – strokes longer than 7 days in 3 years	6/219	2/155

Table 2.3   **Table comparing the main outcomes in the ECST of surgery Vs no surgery for mild and severe carotid artery stenosis.**

The North American Symptomatic Carotid Endarterectomy Trial [63].

This study was conducted across 50 centres within the United States of America and Canada. The NASCET study was set up following the ECST and essentially had the same aims, using the same three categories of stenosis, mild (0-29%), moderate (30-69%), and severe (70-99%). Importantly, the methodology for determining the degree of stenosis was significantly different, NASCET compared the minimum ICA diameter with the lumen of the normal ICA distal to the stenosis. Accordingly the ECST method overestimates the degree of stenosis compared with the NASCET method.
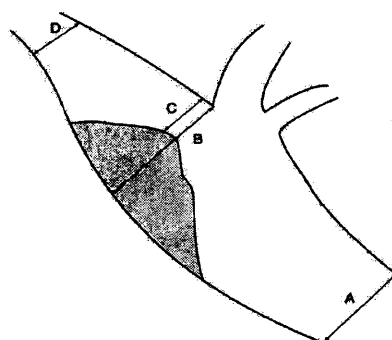
ECST: $\frac{B-C}{B} \times 100\%$

NASCET: $\frac{D-C}{D} \times 100\%$

Figure 2.3   **Comparison of stenosis measurement in ECST and NASCET.**

NASCET established entry criteria for participating centres (a review of the last 50 CEAs conducted within the preceding 24 months had to demonstrate a peri-operative stroke rate of less than 6%). All patients with definite focal retinal and hemispheric events within 30 days of entry were included. The lesion had to be technically suitable for endarterectomy.

Patients were excluded on the following grounds:

1. Mentally incompetent or unwilling to give informed consent
2. No angiographic visualisation of both carotid arteries and their intracranial branches
3. An intracranial stenosis more severe than the surgically accessible lesion
4. Organ failure of kidney, liver or lung, or had cancer likely to cause death within five years
5. Cerebral infarction on either side that deprived the patient of all useful function in the affected territory
6. A cardiac valvular or rhythm disorder likely to be associated with cardioembolic symptoms
7. Had previously undergone an ipsilateral carotid endarterectomy.

All patients underwent bilateral, selective carotid arteriography, CT brain scan and Duplex ultrasonography of the carotid arteries. All angiograms were measured in the central office, by the principle neuroradiologist, using the method detailed previously. Patients were randomised at the Data Management Centre according to computer generated randomisation schedule to either medical care alone or medical care plus surgery. All patients received antiplatelet therapy (1300mg of aspirin per day or a lower dose if side-effects necessitated).

Patients were assessed at 30 days post-operatively by the surgeon. Study neurologists performed medical, neurological and functional status assessments of all patients one month after entry, then every three months for the first year, and every four months thereafter.

The interim results were published in 1991. The conclusion was that CEA was beneficial for patients with a severe symptomatic stenosis. This conclusion was based on the results of 672 patients recruited with severe stenoses. In the 30 day post-operative period 18 surgical patients had cerebrovascular events, 12 were minor, 5 were major (causing a functional deficit persisting for >90 days), and 1 was fatal. One patient died suddenly after surgery giving a rate of 5.8% for all peri-operative stroke/death. The rate for major stroke/death was 2.1% and the mortality rate was 0.6%. In the comparable period the 'no surgery' group had a 3.3% incidence of cerebrovascular events, 8 were minor, 2 were major and 1 was fatal.

The benefits of carotid endarterectomy were expressed according to life-table analysis and showed that the cumulative risk of any ipsilateral stroke at 2 years were 26% in the 'no surgery' group and 9% in the surgery group. Therefore CEA afforded an absolute risk reduction of 17+/- 3.5%. For major or fatal ipsilateral stroke the corresponding estimates were 13.1% and 2.5%, an absolute risk reduction of 10.6 +/-2.6%. CEA also reduced the risk of more minor events such as non-disabling and transient strokes.

As in ECST, the role of surgery in patients with moderate symptomatic stenoses, remained unclear and therefore recruiting to this group continued after publication of the interim results. In 1998 NASCET published it's final results [64]. It split the results for moderate stenosis into 2 groups, <50% and 50 – 69%. Operation was clearly not beneficial for patients with a stenosis of <50%, however, marginal benefit from CEA was reported in patients with stenoses from 50 – 69%. The 5- year rate of any ipsilateral stroke was 15.7% in the 'surgery' group compared with 22.2% in the medical group (p=0.045). This means that 15 patients would have to undergo CEA to prevent one stroke in 5 years. This degree of stenosis corresponds to an ECST stenosis of 70 – 80%, and the marginal benefit of surgery reflects the similar benefit shown for 70 – 79% stenosis in the final ECST results. Patients with NASCET 50 – 69% stenosis, (ECST 70 – 79%) gain a small but significant benefit from CEA. However, this benefit is inextricably linked to the operative risk. Surgeons with a 30-day death/stroke rate > 7.0% should consider whether best medical therapy is a better option in these patients, especially if they are women or have suffered a single ocular event.

Comparison of the ECST and NASCET studies.

For the first time these two large, randomised trials clarified the indications for CEA in symptomatic patients and quantified the expected benefit or lack of benefit for surgery depending on the degree of carotid stenosis. Both trials used the same classification of carotid stenosis into mild, moderate and severe, based on measurements of pre-operative angiograms. However, their methods of determining the degree of stenosis were significantly different. As stated earlier the NASCET study compared the luminal diameter of the stenosis with the first section of normal artery distal to the stenosis, whilst the ECST study compared the luminal diameter of the stenosis with the diameter of the carotid bulb. Since the diameter of the carotid bulb is invariably greater than the diameter of the more distal ICA the ECST patients were estimated to have a greater degree of stenosis than the NASCET patients. A study measuring 700 ECST angiograms by both methods showed that only 48% of patients classified as severe by ECST would have been included in the NASCET severe category [65]. The 70% NASCET stenosis measures over 80% by the ECST method. Similarly the 70% ECST stenosis measures around 60% by the NASCET method. This explains why the final results of the trials show a benefit for patients with > 70% stenosis in NASCET, but a greater degree of stenosis (80% for males and 90% for females) is required before a benefit is shown in ECST.

The method used to determine the degree of stenosis in both trials was biplanar angiography, this remains the gold standard, however, Duplex ultrasound scanning, has overtaken angiography as the most popular way in which to visualise carotid artery stenoses. The main disadvantage of carotid angiography, is that there is a small, but definite morbidity and mortality associated with it. This risk was not included in the analysis of the trials morbidity and mortality, because angiography occurred prior to randomisation. Hankey et al showed that neurological morbidity associated with selective carotid angiography is 3.4% and that the disabling stroke rate is 1.3% [66]. Duplex scanning is non-invasive, and as such is not associated with any significant morbidity. In addition the B-mode pictures are able to give valuable information with regards to the characteristics of the plaque (i.e. plaque ulceration). Duplex criteria for quantifying stenoses vary, and individual vascular laboratories

need to perform their own validation exercise to compare duplex and angiographic measurement.

	NASCET	ECST
Study Population	USA & Canada 50 centres	14 European Countries 80 centres
Imaging technique	Biplanar angiography	Biplanar angiography
Definition of carotid stenosis	Luminal diameter of stenosis Vs Diameter of normal distal ICA	Luminal diameter of stenosis Vs diameter of carotid bulb
Number of patients in severe (>70%) group	328	455
Peri-operative death/disabling stroke rate	2.1%	3.3%
All peri-operative strokes	5.8%	7.5%
Risk reduction over no surgery	8 fold reduction in risk	10 fold reduction in risk

Table 2.4   Methods and results for the severe carotid stenosis groups undergoing surgery in the ECST and NASCET studies.

Asymptomatic carotid artery surgery.

Population studies have shown the prevalence of carotid stenosis greater than 50% (almost all asymptomatic) to rise from 0.5% in people in their 50's to about 10% in those over 80 years of age [67][68]. The risk of stroke in subjects with asymtomatic carotid artery stenosis is about 2% per year, significantly less than those with symptomatic disease [69][70]. Under these circumstances the balance for benefit and harm for prophylactic surgery is much finer.

The value of CEA in reducing the risk of stroke has been demonstrated by the Asymptomatic Carotid Atherosclerosis Study (ACAS) [70] and a subsequent meta-analysis of data from all randomised trials [71]. ACAS randomised subjects with an asymptomatic carotid stenosis > 60% on angiography (equivalent to about 75% stenosis measured by ECST). After a median follow-up of 2.7 years the trial was stopped. The actuarial estimated 5 year risk of stroke was 5.1% after surgery versus 11% in the medical group. This represented an relative risk reduction of 53%, the absolute risk reduction was 5.9% over five years. Although ACAS remains the best published randomised trial to date, there are concerns about its applicability to routine clinical practice. These concerns primarily relate to the fact that the 30-day death/stroke rate was 2.3% (of which 1.2% was due to angiographic stroke), the 5 year risk was projected (the median follow-up was only 2.7 years), there was no benefit in women, CEA did not prevent disabling stroke, there was an inverse relationship between late stroke risk and stenosis severity in medically treated patients and no data on the influence of concurrent risk factors.

The Asymptomatic Carotid Surgery Trial (ACST) is a multi-centred, randomised, European trial comparing CEA and best medical therapy for asymptomatic carotid disease. The published trial results are awaited.

Meta-analysis, has confirmed a definite benefit of CEA in preventing ipsilateral ischaemic stroke and stroke in any location [71]. The benefit is small, corresponding to an absolute risk reduction of 2% over an interval of 3.1 years. Fifty subjects would have to have a CEA to prevent one stroke over a 3 year interval. In the USA, ACAS has led to a large increase in the number of CEAs for asymptomatic disease. In the UK, CEA for asymptomatic disease comprises a relative minority of the overall CEA workload. In Australia it has been calculated that were CEA to be offered to all asymptomatic patients, it would only prevent 3% of strokes and would cost Australia $1.5 million per stroke prevented [72]! Undoubtedly there are asymptomatic patients who would benefit from CEA either because they are at low risk of peri-operative stroke, or more probably because they are at high risk of stroke without operation. Unfortunately there are insufficient data at present, and until high risk groups can be identified, CEA for asymptomatic patients should not be recommended.

Combined carotid and cardiac surgery.

Carotid and coronary artery disease occur concurrently in many patients. Two to eighteen per cent of patients undergoing coronary bypass grafting (CABG) are estimated to have severe carotid disease, although most are asymptomatic. Forty per cent of CEA patients have significant coronary disease. The risk of stroke after CABG is increased with carotid artery disease [73]; 3.8% of patients with unilateral carotid stenosis > 50% suffer a hemispheric stroke. In patients with bilateral carotid stenoses of 80 – 99% the hemispheric stroke rate was 8.3% [73]. These data, showing an increased risk of stroke with significant asymptomatic carotid artery disease, are the rationale for performing CEA either prior to CABG, or as a combined procedure. The presence of a carotid bruit increases the risk of peri-operative stroke fourfold, in those patients undergoing CABG [74]. The combination of age > 60 years combined with stenosis > 75 % is associated with a peri-operative stroke risk of 15% as compared with 0.6% in patients > 60 years undergoing CABG with no stenosis [75].

There is no evidence from randomised trials to guide clinicians as to whether CEA and CABG should be performed as a combined procedure or separately, or even at all. It is suggested that where both lesions are symptomatic a combined procedure is appropriate [76]. Combined procedures may be advocated for symptomatic cardiac disease with severe asymptomatic carotid stenosis, but the situation for symptomatic carotid disease with asymptomatic cardiac lesions is not clear [77]

Operative Stratergy	Stroke (%)	MI (%)	Death (%)
Synchronous CEA +CABG	6.2	4.7	5.6
CEA then CABG	5.3	11.5	9.4
CABG then CEA	10	2.7	3.6

Table 2.5   Summary of meta-analysis of staged versus synchronous CEA and CABG [78].

Emergency carotid endarterectomy and crescedo transient ischaemic attacks.

In the 1960's emergency carotid endarterectomy for acute stroke was associated with major mortality and morbidity, mainly due to haemorrhagic transformation of ischaemic infarction [79] [80]. This led not only to the abandonment of this strategy, but also to the recommendation that any patient suffering a stroke should wait at least 6 weeks before undergoing CEA in order to allow the area of infarction to stabilize. Early CEA (within 2 – 4 weeks) is increasingly being recommended in stroke patients who make a rapid recovery from their neurological deficit so as to reduce the 20% risk of recurrent stroke within the first 6 week period [81]. Although the latter isn't universally accepted as main stream practice, evidence from a recent meta-analysis suggests that early CEA does not increase the operative risk in selected patients [82]. Urgent CEA is recommended in patients with stroke in evolution, stuttering hemiplegia or crescendo TIAs, especially if there is evidence of a critical or unstable carotid lesion.

Crescendo TIAs are defined as recurrent cerebral or retinal ischaemia of increased severity, frequency or duration. In 1981 Metzner et al. published a small series of patients with crescendo TIAs who underwent emergency CEA with no major complications [83], however of the 5 patients treated non-operatively four suffered strokes and one died of cerebral infarction. The published results of emergency carotid surgery are variable with complication rates ranging from no deficits in 12 patients to operative mortalities as high as 20% and neurological deficits in up to 40% of patients in other series [84-90].

Patients with crescendo TIAs have traditionally been treated with heparin whilst waiting for urgent surgery, despite there being no published evidence that this prevents further neurological events. In fact there is evidence to the contrary, in a 4 year study, 29 patients with repetitive TIAs were treated with heparin until carotid surgery was undertaken. There was a mean wait of 5 days for surgery, and whilst on heparin there were 2 carotid occlusions and 13 patients continued to have further TIAs. Post-operatively there was 1 stroke and 1 death due to myocardial infarction [91]. In another study, 20% of patients with neurologically unstable conditions waiting for urgent surgery continued to have TIAs despite intravenous heparin [90].

Endovascular treatment of carotid disease.

Over the last decade there has been increasing interest in treating carotid
atherosclerosis by endovascular means. The internal carotid artery (ICA), is one of
the last major vessels to be considered for angioplasty, primarily because of concerns
over the adverse effects of procedural embolisation. CEA has been accepted as a
means of preventing ischaemic stroke for 45 years but only achieved level 1 evidence
of benefit in 1991[62][63]. Conversely, carotid angioplasty (CA) is a relatively new
treatment method and has not been subjected to the same scrutiny. However an
overview of all published series in 1992 [92] showed that it was both feasible and a
potential alternative to CEA.

Author	Year	Number	Death	Major Stroke	Minor Stroke
Wiggli	1983	2	0	0	0
Brockenheimer	1983	3	0	0	0
Tsai	1986	6	0	0	0
Theron	1987	5	0	0	0
Freitag	1987	11	0	0	0
Mathias	1987	15	0	0	0
Kachel	1987	24	0	0	0
Brown	1990	12	0	0	0
Theron	1990	13	0	0	0
Porta	1991	32	0	0	1
TOTAL		123	0	0	1

**Table 2.6   Overview of published results of carotid angioplasty prior to
1992 (adapted from Brown [92]).**

In 1996 Gil-Peralta and colleagues [93], treated 87 patients with high grade (>70%)
symptomatic carotid artery disease with simple balloon dilatation. A 4.9% death and
disabling stroke rate was recorded, with 3.7% of patients suffering a TIA. They failed

to cross the lesion in 5% of patients. At 4 years over 95% of their patients were free from ipsilateral disabling stroke.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) [94] is a randomised trial investigating the safety and long term efficacy of endovascular techniques in symptomatic carotid disease. Twenty-four centres from around the world randomised 560 patients to two limbs of the trial to compare endovascular therapy against surgery (if patients were fit) and endovascular therapy against best medical therapy (if patients were unfit for surgery). As with ECST patients were only randomised if they were suitable for both forms of treatment or if there was doubt as to the best form of management. The best medical therapy limb of the trial, however, recruited too few patients for any conclusions to be drawn.

Five hundred and four patients with significant, symptomatic carotid stenosis were randomised between endovascular treatment (n=251) and conventional surgery (n=253). Demographics, presenting symptoms and risk factors were similar between the two groups. For endovascular patients, stents were used in 55 (26%) and balloon angioplasty alone in 158 (74%). The 30-day adverse event rates following treatment did not differ significantly between endovascular treatment and surgery (6.4% versus 5.9%, respectively for disabling stroke or death: 10% versus 9.9% for any stroke lasting more than 7 days, or death).

The non-cerebral complications were also similar in both groups except for significantly more cranial nerve palsies after surgery (not surprisingly there were none after endovascular treatment). At 1 year after treatment severe (70 – 79%) ipsilateral carotis stenosis was more common after endovascular treatment (25 [14%] versus 7 [4%], p<0.001). However, at follow-up there was identical freedom from all stroke and death, and ipsilateral stroke and death for both treatments up to 3 years. Criticism of this trial has focused on the randomisation, requiring that cases were deemed suitable for endovascular techniques. Concern has also been raised regarding the number of 30-day strokes following surgery in this trial, being significantly higher than those published from NASCET and ECST.

More recently primary carotid artery stenting has taken over from angioplasty as the endovascular treatment of choice for carotid artery stenosis. The first report of a multicentre prospective protocol based study of carotid artery stenting, the North American Percutaneous Angioplasty Register, was published in 1993 [95]. Interim results were reported on 165 angioplasty procedures in 147 symptomatic nonsurgical patients. The average stenosis was 84% (range, 70% - 99%). Death from all causes occurred in 3% of procedures, and stroke occurred in an additional 6% of procedures.

In 1996, Dietrich et al [96] reported the results of carotid artery stenting in 110 symptomatic patients with a $\geq$ 70% stenoses from a single institution. One procedure failed (0.9%) for technical reasons and was converted to a CEA. Two deaths (1.8%) occurred (one from stroke, one from a cardiac event). Seven strokes (two major [1.8%] and five minor [4.5%]) and five transient neurological events (4.5%) occurred. On the basis of this early experience, the authors concluded that the incidence of periprocedural neurological complications was excessive.

The WALLSTENT trial was a multicentred, prospective randomised trial of carotid artery stenting versus CEA. Patients with a symptomatic carotid artery stenosis of 60 – 99% were randomised to either CEA or stenting, the primary end-point was ipsilateral stroke, procedure- related death or vascular death within 1 year [97]. A total of 219 patients were enrolled, 107 in the stent group and 112 in the CEA group. The primary end-point rate at approximately 1 year was 12.1% in the stent group versus 3.6% for CEA. The rate of any major stroke was 3.7% for the stent group and 0.9% for CEA. The 30-day peri-procedural complication rate (any stroke or death) was 12.1% for the stent group and 4.5% for CEA. Based on these data and a futility analysis, the study was terminated before the planned maximum of 700 patients were enrolled.

The use of distal cerebral protection devices is becoming widespread during stenting. These devices are used to prevent plaque debris entering the cerebral circulation. The stenting and angioplasty with protection in patients at high risk for endarterectomy study (SAPPHIRE) randomised patients to CEA or carotid angioplasty [98],[99;99]. This study was conducted in 29 centres within the United States. Patients included in the trial had either a >80% asymptomatic stenosis or a symptomatic stenosis >50%

combined with one feature that would make them high risk for a carotid endarterectomy. These features included, age >80, congestive heart failure, severe chronic obstructive pulmonary disease, previous carotid endarterectomy, neck iiradiation, radical neck surgery and unusual lesions that were more distal or proximal than normal. Exclusion criteria included stroke within the last 48 hours, presence of thrombus within the artery or total occlusion.

The primary end-point of the trial was the cumulative incidence of death, stroke, or myocardial infarction within 30 days after the procedure or death or ipsilateral stroke between 31 days and 1 year. 747 patients were enrolled in the study but only 334 patients underwent randomisation to carotid stenting with an embolic protection device, or endarterectomy.

In the analysis of patients with symptomatic carotid artery stenosis, the cumulative incidence of the primary end-point at 1 year was 16.8% among those who received a sten, as compared with 16.5% among those who underwent endarterectomy (p=0.95). In the post-procedural period the cumulative incidence of the primary end-point at 30 days among these patients was 2.1% among those who received a stent and 9.3% among those who underwent endarterectomy (p=0.18). For patients with asymptomatic carotid artery stenosis, the cumulative incidence of the primary end-point at 1 year was lower among those who received a stent (9.9%) than among those who underwent enarterectomy (21.5%) (p=0.02). In the periprocedural period, the cumulative incidence of death, myocardial infarction or stroke was 5.4% among those who received a stent, as compared to 10.2% among those who underwent endarterectomy (p=0.2).

The SAPPHIRE trial does appear to have confirmed its hypothesis that carotid artery stenting with distal emboli protection is not inferior to carotid endarterectomy, but certain specifics of the design and enrolment in this trial deserve comment. 747 patients were recruited into the trial yet only 334 patients underwent randomisation to stenting or endarterectomy. Of the remaining 413 patients, 406 were entered into the stent registry and 7 were entered into the surgical registry. Almost 60% of patients within this trial were felt to be too high risk such that endarterctomy could not safely be performed!

More than 20% Of patients in each treatment group were treated for recurrent carotid artery stenosis, the substantial number of patients with stenosis serves to bias the results in favour of stenting for two reasons. Firstly 'redo' endarterctomy is typically associated with higer rates of complications than is the primary operation, and secondly, carotid artery stenting for recurrent disease is inherently less risky when the disease is intimal hyperplasia rather than complex plaque (i.e. there is less risk of embolisation).

The difference between the treatment groups in the composite end-point at 1 year is related to the higher incidence of perioperative (mostly non-Q-wave) myocardial infarction in the endarterectomy group, (8.1% in the endarterectomy group vs 2.5% in the stenting group, p=0.03). Myocardial infarction was not included as an end-point in the large endarterectomy trials. If the conventional end-point of stroke or death at 30 days plus ipsilateral stroke or death from neurological causes within 31 days to 1 year is used there is no significany diference between the 2 treatment groups (5.1 % in the stenting group vs. 7.5% in the endarterectomy group, p=0.4).

Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) is a multicentred, randomised trial to compare carotid stenting and endarterectomy [100]. This trial will randomise 2500 patients with symptomatic stenoses $\geq 50\%$. The primary outcome events for this clinical trial will include, any stroke, myocardial infarction, or death during the 30 day perioperative or periprocedural period, or ipsilateral stroke after 30 days. Secondary goals include :-

- To describe differential efficacy of the two treatments in men and women
- To estimate and contrast the restenosis rates
- To identify subgroups of participants at differential risk for the two procedures
- To evaluate differences in health-related quality of life issues and cost effectiveness.

The results of this trial are still awaited.

Variation in carotid plaque morphology has been shown to change plaque susceptibility to distal embolisation during carotid stenting and subsequent complications [101]. The preoperative Duplex characteristics of a carotid plaque may determine the risk of cerebral complications during carotid endovascular intervention. The ICAROS (Imaging in Carotid Angioplasties and Risk Of Stroke) registry of carotid artery stenting is a mulitcentre international registry of carotid artery stenting designed to determine the criteria for identifying patients at higher or lower risk of periprocedural stroke and restenosis at one year [102]. The aim of the registry is to improve patient selection and consequently reduce the risk of cerebral embolisation during carotid stenting.

At present carotid artery stenting is reserved for a limited subset of patients, including high-risk patients with significant medical co-morbidities, patients with carotid restenosis after previous CEA, anatomically inaccessible lesions above C2 and radiation induced stenoses. The conducting of clinical trials (CREST and others), should provide level I and II evidence, on which to establish a firm, clinical recommendation. Until these data are available during the next few years, carotid artery stenting may be limited to randomised, clinical trials and defined unique subsets of high-risk patients.

2.4 Summary of the management of carotid artery disease.

All patients with extracranial cerebrovascular disease benefit from optimisation of risk factors including, hypertension, hyperlipidaemia, diabetes, and cardiac disease. All patients should be on antiplatelet therapy and atrial fibrillation should be treated appropriately. Large multi-centred randomised trials have established level 1 evidence for the role of CEA in those patients with a severe (>70% NASCET criteria, >80/90% ECST criteria), symptomatic carotid artery stenosis. The data from these trials suggests however that CEA is not indicated in symptomatic patients with a moderate or mild stenosis (<70%). The only possible exception might be a patient with repeated cerebral ischaemic events despite optimal medical therapy.

Patients with asymptomatic carotid stenosis >75% do have a reduced risk of stroke after carotid endarterectomy, but the advantage is only marginal. Fifty operations

would need to be performed in order to prevent 1 stroke. There are no data from randomised trials to support combined CEA and CABG for symptomatic carotid and cardiac disease. Meta-analysis suggests that a combined operation can be performed without excess risk. Patients with crescendo TIAs represent a particularly high risk group in whom urgent surgery is indicated, but is accompanied with high surgical risk.

Chapter 3.

The operative technique of carotid endarterectomy.

CHAPTER THREE: THE OPERATIVE TECHNIQUE OF CAROTID
ENDARTERECTOMY.

In this chapter I will describe the method of carotid endarterectomy used by the surgeons participating in this study. This description will then be used as a basis for discussion of alternative methods of operation and areas of controversy, such as the use of intraluminal shunts, type of anaesthesia and patch angioplasty. The complications that may arise following surgery will be described.

3.1 SURGICAL TECHNIQUE.

In Leicester CEA is performed under light general anaesthetic, using loupe magnification. The patient is positioned supine with the head extended and turned away from the side of the operation, using a rubber head ring. The table is placed in the head up position and rolled laterally slightly away from the surgeon. A sandbag is placed under the shoulder blades to aid head extension.

An incision is made over the anterior border of the sternocleidomastoid muscle, centred over the carotid bifurcation. Dissection is continued deep to the anterior border of the sternocleidomastoid until the carotid sheath is entered. The carotid artery is identified and adequate exposure of the common, internal and external carotid arteries is obtained. The hypoglossal nerve and vagus nerve are sought and preserved. The distal ICA must be exposed 1cm beyond the upper limit of the carotid plaque and this can be facilitated by ligation and division of the small tethering vessels accompanying the hypoglossal nerve and/or division of the digastric muscle. Arterial slings are placed around the common, internal and external carotid arteries and the superior thyroid artery.

The patient is then systemically heparinised using 5000 i.u., given intravenously. A Pruitt-Inahara shunt is then prepared for insertion by testing the inflation and deflation of the retaining balloons and any air bubbles excluded by flushing with saline. Soft clamps are then applied to the CCA, ECA, and ICA and a linear arteriotomy is made from the CCA extending into the ICA beyond the extent of the plaque. The larger end of the shunt is then inserted inserted into the CCA and the

retaining balloon inflated. The blood-flow from the CCA is then vented through the shunt to ensure patency. The smaller end of the shunt is then inserted into the ICA and the retaining balloon inflated. Blood flow is then restored through the shunt. The operation can then be performed without undue haste.

The appropriate plane between the atheroma and the media is entered with a flat-bladed, Watson-Cheyne dissector and the plaque divided from the CCA, it is then removed in a cephalad direction into the ICA, where it is cut transversely using micro-scissors to avoid leaving a flap. An eversion endarterectomy of the proximal portion of the ECA is performed. Figure 3.1 shows the plaque removed at endarterectomy. The proximal and distal endpoints of the endarterectomy are then tacked down with 7/0 prolene interrupted sutures, to prevent dissection when blood flow is restored. The endarterectomy surface is examined carefully under loupe magnification (2.5X) to ensure a smooth surface, free of debris, roughened areas, ulceration or other irregularities.

The arteriotomy is then closed using a patch angioplasty (prosthetic or long saphenous vein) with a running suture of 6/0 prolene. When the closure is within 1cm of completion the shunt is clamped, the internal carotid balloon deflated and the distal limb of the shunt removed, the ICA is clamped quickly behind it. The procedure is then repeated for the CCA and then the vessel flushed with normal saline. An angioscope is then inserted to examine the endarterectomy zone prior to restoration of blood flow, allowing removal of residual thrombus or suture repair of intimal flaps. On removal of the angioscope the vessels are back-bled once more, the final few sutures of the closure are performed and the clamps are removed in the following order, ECA, CCA, ICA. This ensures that any remaining debris is swept up into the external carotid distribution.

Post-operatively the patient is awoken in theatre and transferred to a high dependency unit for further monitoring.
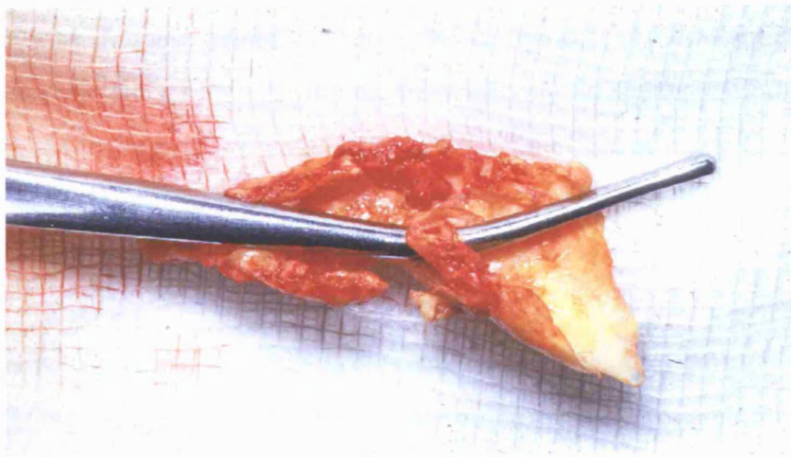
Figure 3.1   **Plaque removed at carotid endarterectomy.**

3.2 CONTROVERSIES CONCERNING CAROTID ENDARTERECTOMY.

Anaesthesia.

CEA may be performed under either general or local anaesthesia, and there is some evidence that the cardiac risk of surgery maybe reduced with the latter [103], despite greater blood pressure lability and higher catecholamines levels that might be expected to increase cardiac risk. Although it has been suggested that peri-operative β-blockade may protect the myocardium this view has not been widely accepted. Other criticisms of LA surgery include the potential for hurried and technically inadequate surgery, patient and surgeon stress and an unsatisfactory environment for training junior surgeons. Experience with the technique indicates that none of these are true.

An ideal anaesthetic will allow maintenance of normal PaO2 and PaCO2 tensions and control of arterial pressure, and preservation of cerebral autoregulation. Previous work indicates that anaesthetic agents can have both beneficial and adverse effects on cerebral perfusion and oxygenation. Thus, barbiturates reduce cerebral metabolic rate and cerebral oedema, whilst propofol may protect against certain biochemical effects of reperfusion and offer greater haemodynamic stability on emergence from

anaesthesia. The widely used inhalational, volatile anaesthetic agents (isoflurane, halothane) may increase cerebral blood flow but suppress cerebral autoregulation and increase cerebral lactate concentration, whilst all volatile agents and nitrous oxide may increase intracranial pressure. Thus, the overall effect of many GA agents upon cerebral metabolism is unpredictable despite allowing control of PaO_2, $PaCO_2$ and blood pressure.

In contrast LA (superficial and deep cervical plexus blockade) preserves autoregulation and improves cerebral oxygenation during carotid clamping which induces a reflex rise in systemic blood pressure [104]. This may explain the findings of a meta-analysis suggesting that neurological complications, cardiac events and death following CEA are reduced by at least 50% when LA is used [103]. These end-points are currently being evaluated in a randomised trial (GALA Trial). Finally LA allows continuous and highly reliable intra-operative monitoring (awake testing) of the cerebral ischaemia, allowing a selective shunting policy.

Superficial and deep cervical plexus blockade, with additional intra-operative infiltration, is safe and effective. It also provides a period of post-operative analgesia. Some patients may be unsuitable for loco-regional anaesthesia (previous stroke with dysphasia, hemiplegia or marked anxiety) and for these GA is preferred. Some surgeons dislike the idea of performing such precise operation on an awake, mobile patient and prefer the more controlled conditions produced by general anaesthesia.

There is no doubt that CEA under LA is the undisputed 'gold-standard for determining who requires a shunt following carotid clamping. LA will not, however, prevent operative strokes due to thrombo-embolism. Non-randomised studies suggest a possible benefit for CEA under LA regarding a reduction in operation related strokes and overall cardiovascular morbidity. However, this has never been corroborated in any randomised trial. The GALA trial is currently underway in the UK and will be the largest randomised study of its kind. It will be better placed to evaluate health economics, patient acceptability, and outcomes (stroke, cardiovascular) than any systematic review of non-randomised and usually retrospective trials. Until GALA is published, there is no systematic evidence that anaesthetic technique influences outcome.

Patch angioplasty versus direct closure.

Patch angioplasty following CEA may reduce the rate of early ICA thrombosis (reduced thrombogenicity of the endarterectomy site, improved ICA diameter) and late restenosis (neointimal hyperplasia) and thus improve both early and long-term stroke rates. However, patching increases the carotid clamp time and the risk of patch related complications (rupture, false aneurysm, sepsis). Opponents of patching cite the 1% risk of vein patch 'blow-out, which usually occurs on the 5-7th postoperative day [105], and the 1% risk of prosthetic patch infection [106].

At least six randomised trials of obligatory patching or obligatory primary repair have been performed and the Cochrane Stroke Review Group has subjected these trials to a meta-analysis [107] (Table 3.1). All trials found that patching reduced the incidence of ipsilateral peri-operative stroke and the meta-analysis indicated a 66% reduction in the relative odds, in the setting of overall stroke rate of 2.7% for the two groups. This was highly significant. Similarly there was an 83% reduction in the odds of peri-operative ICA occlusion together with a trend suggesting that 30 day combined stroke and death rates were reduced. Of equal importance was the finding that patching was associated with significant reductions in ipsilateral stroke or combined stroke and death during long-term follow-up. There were also fewer ICA occlusions or re-stenoses of > 50%. It appears that patching could prevent 30 ipsilateral strokes and 24 deaths/1000 operations within 30 days of surgery. Furthermore, an additional 28 strokes and 75 deaths may be prevented in the subsequent 3 years. This meta-analysis compared routine patching with primary closure, no trial has been performed to compare routine patching with selective patching.

Surprisingly, support for patching is not universal. Some surgeons favour selective patching based on data that suggests complications following direct repair are greater when the diameter of the ICA is 5mm or less, particularly in women, in whom the mean diameter of the ICA (4.9±0.6 mm) is 8-15% less than in men (5.3±0.7 mm) [108;109]. With this protocol approximately 50% of patients will need a patch. There is

no randomised trial to support this view although a non-randomised study reported a lower incidence of residual/recurrent ICA stenosis when selective patching was applied in this way [110].

30 Day Outcomes.

	Routine patching	Primary closure	Odds ratio of increased risk with primary closure
Ipsilateral stroke	1.3%	3.9%	2.9 (95%CI 1.3 – 6.7)
All strokes	1.6%	4.2 %	2.6 (95%CI 1.1 – 6.7)
Carotid thrombosis	0.3%	3.9%	5.9 (95%CI 2.2 – 17)

Long Term Outcomes.

	Routine patching	Primary closure	Odds ratio of increased risk with primary closure
Ipsilateral stroke	1.6%	4.4%	2.6 (95%CI 1.1 – 6.3)
All strokes	2.2%	5.9%	2.6 (95%CI 1.2 – 5.9)
50-100% restenosis	4.5%	13%	3.1 (95%CI 1.9 – 5.3)

Table 3.1 **Systematic review of six randomised trials comparing patch versus primary closure of the arteriotomy [107].**

Further uncertainty remains regarding which material should be used. Autologous long saphenous vein (LSV), Dacron, Polytetrafluoroethylene (PTFE) and autologous cervical vein have been proposed as suitable.

For the three materials most widely used (LSV, Dacron, PTFE) there are insufficient data upon which to make firm conclusions as to the best choice. The putative advantages of vein patches include low thrombogenicity, better handling characteristics, good haemostasis and superior resistance to infection. However, early vein patch rupture or suture line disruption with haemorrhage or false aneurysm formation may occur (0 – 4%), particularly when the external jugular vein or LSV from the ankle are taken. Patch rupture carries a high mortality.

Proponents of synthetic patches highlight their easy availability, mechanical integrity and higher resistance to aneurysm formation. However, risks of patch sepsis are increased. In a recent randomised trial of 276 patients, Hayes observed that there was no difference in the magnitude of post-operative embolisation (a marker of increased predispotion to thrombosis) between vein and Dacron patched patients [111].

The Cochrane meta-analysis [107] showed similar outcomes for PTFE and vein. An alternative analysis of six studies indicated a trend to reduced peri-operative stroke rate when vein was preferred to Dacron or PTFE. When the combined data for all synthetic patches were compared to LSV, there was no difference in the incidence of early post-operative ICA occlusion or the development of a > 50% stenosis within 1 year [108].

Shunting.

Shunt use during CEA has attracted considerable debate with three approaches to surgery evolving. Some surgeons use a shunt for all patients, believing that the risk of intra-operative stroke is reduced and that additional time is available, particularly when a patch is required or if a trainee is performing the surgery. Conversely others never use a shunt, suggesting that they may cause platelet and air emboli, intimal damage, late restenosis and arterial dissection. In addition shunts may kink, dislodge and reduce access to the operative field. Finally, some surgeons deploy shunts selectively when intra-operative monitoring demonstrates evidence of cerebral ischaemia following carotid clamping.

Counsell et al have reviewed the trials of routine shunting versus no shunting [112]. These demonstrate trends suggesting fewer strokes and stroke-related deaths and lower 30-day mortality in patients who have a shunt. However, the number of outcome events was small and the trials varied in randomisation methods, risk stratification, surgical technique and the frequency of patching. Thus there is no conclusive evidence to support either routine shunting or non-shunting.

If selective shunting is to be employed then a reliable method of detecting intra-operative ischaemia is required. Many techniques have been examined in the search

for a suitable method of monitoring, these include physiological tests reflecting cerebral perfusion (electroencephalography, somatosensory evoked potentials), direct assessments of cerebral blood flow (stump pressure, transcranial Doppler ultrasound, cerebral oximetry), or direct neurological testing (awake testing during LA surgery). The relative merits of these methods will be summarised in detail in the following chapter. With the exception of awake testing during LA surgery which should be regarded as the gold standard, none is perfect. At present it is clear that awake testing is the only reliable method that accurately identifies patients for selective shunting.

The most commonly used shunts are the Javid shunt (which permits higher flow rates) and the double-ballooned Pruitt-Inahara shunt, which is more flexible. A randomised trial investigating the in vivo haemodynamic performance and neurological outcome of these two types of shunt was reported by Wilkinson et al [113]. They concluded that whilst the Javid shunt performed much better than the Pruitt shunt haemodynamically, it gave rise to significantly more prolonged embolisation events upon restoration of internal carotid artery flow. The increased incidence of emboli in the Javid group could potentially lead to an increased incidence of thromboembolic stroke.

Shunting is one of the single-issue subjects (along with patching and anaesthesia) that have dominated discussions about the performance of CEA over the last five decades. No data (randomised or otherwise) has conclusively shown that any one shunt is preferable. There is, however, a growing concensus that a policy of never shunting anyone is inappropriate. In the absence of level I evidence, advocates of each policy must accept the limitations and benefits of each shunt strategy.

Shunts are employed to protect against haemodynamic stroke. Haemodynamic failure accounts for about 20% of all intraoperative strokes [114]. The majority of the remaining intraoperative strokes (and most of the postoperative ones) are thromboembolic. About 3% of shunts malfunction [115]. This is usually due to undetected impaction of the shunt lumen against the distal carotid wall or a vessel coil. Unless some monitoring modality is available this will go unnoticed and lend further support to the notion that intraoperative strokes occur despite using a shunt.

Anticoagulation and heparin reversal during CEA.

Anticoagulation with heparin during CEA is not universal, and amongst those surgeons that routinely heparinise there is great variation in the dose used. Some surgeons use up to 15,000 i.u. There is no evidence to suggest that dose variations influence stroke rates or death rates, although 2 reports indicate that heparin reversal with protamine increases peri-operative stroke rates [116][117]. In these studies there were no strokes in the non-reversed groups compared to rates of 2.6% (5/193) and 6.5 % (2/31) in those patients given protamine. If real, this effect may be due to increased platelet adhesiveness and thrombosis at the endarterectomy site. This possible benefit was achieved at the expense of more frequent re-exploration for haematoma and increased drainage volumes following surgery.

The value of these reports is uncertain as only one study [116] was randomised, and variations in shunt use and patch angioplasty in both studies may have influenced the results. Indeed in one study [112] all strokes occurred in non-patched patients, whilst in the other the frequency of primary closure was 50% higher in the group given protamine [116]. Given these variables the true impact of heparin reversal in the pathogenesis of post-CEA stroke remains unclear.

3.3 COMPLICATIONS FOLLOWING CAROTID ENDARTERECTOMY.

Carotid endarterectomy is the most frequently performed noncardiac vascular procedure in the world. Randomised prospective clinical trials have clearly shown that CEA is a highly beneficial treatment modality compared with best medical therapy for patients with symptomatic, high grade, ipsilateral carotid artery stenosis [63][62]. However carotid endarterectomy itself has intraoperative and postoperative risks. The complication rate after CEA should be maintained at an extremely low rate by surgeons to keep the beneficial effects of CEA over best medical therapy. Perioperative complications of carotid endarterectomy include stroke, myocardial infarction and death and postoperative complications are cranial nerve injuries, wound haematoma, hypertension, hypotension, hyperperfusion syndrome, intracerebral haemorrhage, seizures and recurrent stenosis. Of these, cranial nerve injuries and recurrent stenosis are the only ones not directly related to the early post-operative care of patients following CEA.

The risk of death and/or major stroke, in the randomised trials, after carotid endarterectomy is 2 – 4%, although this rises to 5.5 – 7.5% if all minor strokes are included [63] [62]. In addition CT scan evidence suggests that up to 12 % of all patients suffer silent cerebral infarction during the operation [118]. Certain patients appear to be at higher risk of operative stroke, including those with a history of crescendo TIAs or recent stroke, CT evidence of infarction, a residual neurological deficit, complex ulcerated plaque on preoperative angiogram or Duplex scanning and contralateral occlusion [61] [63]. Operating predominantly on patients who are at high risk of stroke may result in a higher rate of complications than those quoted for the trials.

Two thirds of strokes are thought to occur during surgery, of which 80% are thought to be embolic in origin and 20% haemodynamic [114]. Haemodynamic strokes may occur as a consequence of inadequate collateral cerebral blood supply during carotid clamping, a critical reduction in boundary zone perfusion pressure secondary to intracranial occlusive disease or as a consequence of shunt complications (occlusion, kinking, malposition or spasm) [119].

Embolic strokes account for the majority of infarcts during surgery. Emboli may arise from atheromatous debris from the carotid plaque during carotid dissection or mobilisation. Shunt insertion may dislodge plaque distally which embolises to the barin once flow is restored through the shunt. Embolisation may arise from technical defects such as intimal flaps, these may be clamp induced, shunt induced or arise from the endarterectomy zone itself or the distal endpoint.

Thrombotic strokes may be caused by a combination of embolisation from the initial clot formation and haemodynamic factors when the thrombus eventually occludes the artery. Various causes of vessel thrombosis have been published including, perioperative hypotension, uncorrected internal carotid artery kink or loop, a hypoplastic internal carotid artery, and peri-shunt thrombosis. Causes of platelet-fibrin thrombus include a rare idiopathic predisposition or heparin induced platelet antibody, or more commonly endarterectomy surface irregularity or an intimal flap.

One of the most important risk factors after CEA is hypertension. Poorly controlled hypertension increases the risk of post-operative complications, including neck

haematoma and hyperperfusion syndrome. Pre-operative hypertension has been found to be the single most important determinant for development of post-operative hypertension [120]. Towne and Bernhard reported that the incidence of pre-operative hypertension in patients who developed post-operative hypertension was 79.6%, compared with 57.4% in patients who did not develop this complication [120]. Moreover, they found a significantly increased incidence of neurological deficit and operative mortality rate in the group who developed post-operative hypertension. Bove at al. [121] reported a 19% incidence of post-operative hypertension after carotid endarterectomy and noted a 10% incidence of fixed neurological deficits in these patients. Caplan et al. [122] reported an increased risk of intracerebral haemorrhage after carotid endarterectomy when uncontrolled hypertension persisted.

About 21% of normotensive patients may have increased blood pressure after CEA [120 123]. The particular peak of rise is highest in the first 48 hours following surgery. The pathophysiology of this usually 'episodic' hypertension might be related to surgically induced abnormalities of carotid baroreceptor sensitivity. Unstable blood pressure occurs in 73.5% of patients during the first 24 hours after CEA. Postoperative hypotension (systolic blood pressure < 120mmHg) occurs in approximately 5% of patients, responds well to fluids and low dose phenylephrine infusion, and usually resolves in 24 to 48 hours. Patients with significant hypotension should undergo serial ECGs and cardiac enzyme studies to rule out myocardial infarction.

Postendarterectomy hyperperfusion syndrome occurs in patients with high grade stenosis and long-standing hypoperfusion and leads to paralysis or severe impairment of cerebral autoregulation. In the pre-operative state, a condition of chronic relative hypoperfusion exists in the hemisphere distal to the high grade stenosis. Small blood vessels in this region remain maximally dilated to ensure adequate blood flow. This chronic vasodilatation is thought to result in loss of autoregulation. After correction of the stenosis, blood flow at a normal or elevated perfusion pressure is restored to the previously hypoperfused hemisphere. In the absence of autoregulation, sufficient vasoconstriction to protect the capillary bed is not possible, and breakthrough perfusion pressure results in oedema and haemorrhage. The profound increase in

cerebral blood flow may cause a severe unilateral headache that is characteristically improved by upright posture.

The most catastrophic event that can occur secondary to hyperperfusion is intracerebral haemorrhage. The Mayo Clinic published data on 2362 consecutive carotid endarterectomies which showed that intracerebral haemorrhage occurred in 0.6% of patients within 2 weeks after surgery [124]. Haemorrhages were large and often fatal (60%) or associated with poor outcome (25%). Risk factors for developing intracerebral haemorrhage include advanced age, association with hypertension, presence of high grade stenosis, poor collateral flow and slow flow in the middle cerebral artery territory on angiography. Strict control of blood pressure in patients who are at risk of hyperperfusion can prevent or limit the severity of hyperperfusion syndrome.

Seizures following carotid endarterectomy are uncommon. Nielson et al. [125] reported that seizures developed in 5 of 158 patients (3%) who were haemodynamically compromised 5 to 7 days after CEA. Seizures occurring in the absence of post-operative cerebral infarction or postendarterectomy intracerebral haemorrhage are usually attributed to cerebral hyperperfusion syndrome and the early stages of hypertensive encephalopathy. Brain oedema due to hyperperfusion is an important cause of seizures [126]. Seizures can be treated with intravenous diazepam and dexamethasone may be used to reduce cerebral oedema, although there is no evidence that this is effective.

Wound haematomas are relatively common following CEA. In the NASCET study 5.5% of patients had documented wound haematomas [63]. The majority are relatively small, cause little discomfort and do not require surgical evacuation. Larger haematomas or those that expand precipitously require emergency treatment. If there is no loss of the airway, the patient should undergo emergency evacuation of the haematoma in theatre. If the airway has been compromised, emergency evacuation of the haematoma on the ward may be required if intubation cannot be achieved. Meticulous attention to haemostasis during closure of the wound after carotid endarterectomy is the most important factor in reducing the incidence of this complication.

Several cranial and cervical nerves are at risk during CEA and post-operative nerve dysfunction may occur in 3 – 27% of patients. The majority recover within 12 months although 7% are permanent. Even when temporary, such injuries may cause disability, particularly when the recurrent laryngeal or XII nerves are involved. Such lesions assume greater importance when proceeding to contralateral CEA, since bilateral palsies of either nerve may result in upper airway obstruction, and difficulties with speech and swallowing. Neck haematoma, re-exploration for bleeding, shunting, patch closure, a trainee surgeon and a high carotid lesion all increase the risk of nerve palsy. Nerve transection should be rare given sound anatomical knowledge, although neuropraxia may result from stretching or retraction. Thus adequate exposure of the carotid artery, careful deployment of self-retaining retractors and cautious use of diathermy are important in preventing nerve injuries.

Late post-operative complications include infection of artificial patch material (which may be a cause of patch rupture) and carotid artery restenosis. Restenosis tends to occur within the first year as a result of myointimal hyperplasia. It is a relatively benign condition, usually being asymptomatic. It may be treated if symptomatic with balloon angioplasty.

Carotid endarterectomy depends on the highest standards of surgical and perioperative care if a successful outcome is to be guaranteed. The causes of stroke in the peri-operative period are many and various, but detecting and preventing these complications appears to be the key to reducing peri-operative morbidity and mortality. Two main strategies have been developed to achieve this, the application of intra-operative monitoring methods to detect ischaemia and embolisation, and the use of completion quality control methods to detect technical errors that can cause peri-operative thrombosis and embolism. These quality control and monitoring methods will be described and evaluated in the next chapter.

Chapter 4.

Methods of reducing operative risk.

CHAPTER FOUR: METHODS OF REDUCING OPERATIVE RISK.

This chapter will discuss in detail the aetiology of stroke following carotid endarterectomy, monitoring methods that are available and the principles underlying the role of monitoring. I shall also describe the role of quality control assessment and the various means available.

4.1 AETIOLOGY OF STROKE FOLLOWING CAROTID ENDARTERECTOMY.

Strokes following carotid endarterectomy may be subdivided into intra-operative and post-operative. With an intra-operative stroke the patient recovers from general anaesthesia with a new neurological deficit. In the case of a post-operative stroke, the patient suffers a stroke some time after a normal recovery from general anaesthesia. The table overleaf (Table 4.1) details the various causes of intra and post-operative stroke. Two thirds of strokes are thought to occur during surgery, of which 80% are thought to be embolic in origin [114].

4.2 MONITORING METHODS.

The aim of intra-operative monitoring during carotid endarterectomy is to identify disorders of cerebral function and blood supply. The ideal method would detect all conditions known to be associated with adverse clinical consequences, be safe, easy to use and simple to interpret. A number of methods have been developed, but as yet, no single method has proved to be superior.

Awake testing.

The simplest, most effective and least expensive means of monitoring cerebral function is direct assessment of the awake patient during local anaesthetic carotid endarterectomy. A combination of deep and superficial cervical plexus blockade is given using a long acting local anaesthetic such as bupivacaine. Top up injections of local anaesthetic may be given, this is usually required around the carotid sheath.

Intra-operative Stroke	Post-operative stroke
Embolism	**Embolism**
Spontaneous embolisation (unstable plaque)	Particulate emboli from endarterectomy zone
Particulate emboli during dissection	Particulate emboli following external carotid artery thrombosis.
Particulate emboli dislodged by shunt	
Major air embolism through shunt malfunction.	
Particulate embolisation from endarterectomy zone	
Thrombosis	**Thrombosis**
Peri-shunt thrombosis	Secondary to technical error
On-table carotid thrombosis	Secondary to hypotension
	Secondary to siphon disease
	Secondary to coagulation disorder
Miscellaneous	**Miscellaneous**
Haemodynamic failure (no shunt used)	Hypertensive encephalopathy
Haemodynamic failure (shunt malfunction)	Primary intracerebral haemorrhage
	Haemorrhagic transformation of infarct
	Hyperperfusion syndrome

Table 4.1   **Causes of perioperative stroke.**

A trial clamping of the internal carotid artery is then performed. Most patients with clamp intolerance demonstrate the effects of ischaemia within 1 – 3 minutes by a decreasing level of consciousness, motor weakness or inability to perform mental tasks (e.g. count from 100 backwards). However neurological signs can develop later in the procedure so the patient's neurological status needs to be regularly reviewed, every 3 – 5 minutes. If signs of ischaemia occur a shunt is then inserted.

This is a very sensitive method of detecting clamp ischaemia and the need for shunting. It will not however, prevent thromboembolic complications. Some patients do not tolerate the procedure under local anaesthetic.

Internal Carotid Artery Stump Pressure.

This technique was first described by Michel and colleagues in 1966 and involves the direct puncture of the common carotid artery with a needle connected to a pressure transducer, the more proximal common carotid artery and external carotid artery are occluded by clamps [127]. The mean pressure in the artery should reflect collateral perfusion from both the vertebrobasilar and contralateral carotid arteries. The early studies showed a greater number of adverse neurological outcomes in patients with a stump pressure of less than 25 mmHg who were not shunted [128]. Initial recommendations were that shunts should be inserted with stump pressures below this threshold, however, further experience saw the threshold rise to 50 mmHg, and some authors recommended a threshold of 70 mmHg [129].

The ability of stump pressures to predict ischaemia reliably has been questioned. Kelly and colleagues noted that 6% of patients demonstrated ischaemic EEG changes despite having a stump pressure in excess of 50 mmHg [130]. In 125 patients undergoing CEA under local anaesthesia 24 lost consciousness within 1 minute of carotid artery occlusion even though a third of these had stump pressures in excess of 50 mmHg. In another study, comparing stump pressure to cerebral blood flow, Mackay and colleagues found that 24% of patients with stump pressures greater than 50mmHg had cerebral blood flow of less than 18ml/min/100g, which is considered the lowest level of hypoperfusion tolerable [131].

The reliability of carotid stump pressure measurements are further affected by anaesthetic agents, systemic blood pressure and arterial partial pressures of oxygen and carbon dioxide. Furthermore, the method does not take into account the presence of a MCA stenosis distal to the circle of Willis, which could cause a lower perfusion pressure in that territory than that indicated by the carotid stump pressure [132].

Intra-operative measurement of cerebral blood flow.

The most commonly applied method of measuring cerebral blood flow involves the intra-arterial injection of an inert radioactive gas, xenon 133. The time taken for beta emissions to washout from the brain is measured by an extracranial collimated

sodium iodide scintillation counter focused on the head and face area of the motor cortex. The calculation of cerebral blood flow is based on the Kety-Schmidt analysis of distribution volume and characteristics of an inert gas. The initial slope or 'fast component' of the washout curve relates directly to the regional blood flow. Injections are made prior to clamping to establish a baseline and again immediately after internal carotid clamping to obtain the washout curve [133].

Sundt and colleagues found a high correlation between EEG findings and cerebral blood flow values. CBF values less than 10ml/min/100g were invariably associated with ischaemic changes on the EEG. Ischaemic changes were usually associated with CBF below 15ml/min/100g and to allow a margin of safety, they recommended shunting all patients with CBF of 18ml/min/100g or less [134]. However, further studies by Morawetz and colleagues failed to demonstrate a correlation between CBF of less than 10ml/min/100g and the development of postoperative neurological deficits. In their study of 129 carotid endarterectomies, 22 patients had a CBF of less than 13ml/min/100g and 8 had a CBF of less than 9ml/min/100g, none were shunted, no patients developed any neurological complication. Five neurological complications did however develop in patients with CBF of greater than 20ml/min/100g [135]. The average time of clamping in this study was 20 to 30 minutes, this correlates with primate studies that indicate a CBF of less than 10ml/min/100g can be tolerated for 20 to 30 minutes without permanent neurological deficit [136].

The measurement of CBF using xenon 133 washout requires expensive equipment, the presence of a technician and can pose a radiation hazard. All of these factors contribute towards the limited availability of this monitoring method.

Electroencephalogram (EEG).

The electroencephalogram measures the electrical activity of the brain. Multiple cup electrodes filled with conductive jelly are attached to the scalp at intervals and in particular over the vulnerable watershed areas of the cerebral arteries. There are usually two electrodes connected to one input of a differential amplifier, the output is the difference in voltage of the two electrodes. The scalp recorded EEG is an indicator of the summated post-synaptic potentials arising from

cortical neurons in the vicinity of the recording electrodes. The amplitude of the EEG output is an index of the amount of electrical activity present and the frequency of the output indicates the type of activity. The EEG can be composed of predominantly slower frequencies (delta, theta), or faster frequencies (alpha, beta). In general cortical ischaemia will produce smaller amplitude and slower frequencies.

It has been suggested that the EEG is most useful for detecting ischaemia as a result of carotid cross clamping. In a series of 105 consecutive procedures Ivanovic and colleagues described three patterns of EEG response to clamping of the internal carotid artery:

1.   Mild or no power reduction.

2.   Marked power reduction, characterised by reduction of EEG spectral power by more than 50% in one or two frequency bands.

3.   Global power reduction, reflecting a 50% reduction of EEG spectral power in all frequency bands.

The authors recommended that all patients with a global power reduction should be shunted. Insertion of a shunt caused a gradual reversal of the power reduction which was complete within 5 minutes [137].

Intra-operatively normal EEG readings can be affected by various anaesthetic agents. Barbiturates produce slowing, reduction in amplitude and with higher doses can produce burst suppression patterns and/or isoelectric EEG. This dose dependent depression of cerebral activity can mimic the effects of cerebral ischaemia. The volatile halogenated agents produce alterations of frequency content at lower concentrations and reductions in amplitude at higher concentrations, which, again may mimic cerebral ischaemia. Narcotic agents have a similar effect [138]. Physiological changes such as severe hypotension, hypothermia, hypo- and hypercarbia can all effect the EEG and must be excluded when changes occur [133].

Caution is advised when using EEG to monitor patients with prior strokes. These patients may have cortical tissue in the 'ischaemic penumbra', electrically silent but viable, which may be pushed into infarction by cross-clamping. Since the tissue was

electrically silent at the time of operation it is not possible to monitor this tissue using EEG [133]. A further draw back is that EEG may not detect ischaemia of the internal capsule [133].

Somatosensory Evoked Potentials.

Somatosensory evoked potential recording involves the electrical stimulation of a peripheral nerve (e.g. the median nerve) and recording the resultant afferent volley of electrical activity at different points along its path and ultimately on the scalp overlying the relevant somatosensory receiving area in the cerebral cortex. Since this neuronal activity is dependent on cerebral blood flow it has been proposed that somatosensory evoked potentials (SEPS) may be a sensitive and simple method of monitoring cerebral ischaemia. The technique was first applied to CEA by Markand in 1984 [139].

The critical parameters are the absolute latencies, which represent the time that the ascending volley takes to traverse various portions of the pathway to the cortex. In general cerebral ischaemia produces longer latency, smaller amplitude cortical responses [133]. The criteria for shunting is a 50% reduction in amplitude of the primary cortical wave and prolongation of the central conduction time by 1ms [119].

The rate at which these stimuli can be delivered is limited by the properties of the cortex, therefore the information obtained is intermittent every 20 to 200 seconds. The cortical components of the SEPS are preferentially attenuated by anaesthetics and analgesics, especially the volatile halogenated anaesthetic agents used during carotid endarterectomy [133]. SEPS does however produce information regarding the function of the internal capsule unlike EEGs.

The most devastating effects of cerebral ischaemia are motor paralysis. SEPS only provides an indirect assessment of the motor pathways, assuming that insults to motor pathways will be reflected in changes in conduction along sensory pathways [133].

Reflected Near-infrared Light Spectroscopy (Transcerebral Oximetry).

Transcerebral oximetry involves the use of a near-infrared light souce and two photodetectors placed on the scalp. Near-infrared light at wavelengths of between 650nm and 1100nm is transmitted into the scalp and cortex, this is reflected by the underlying tissues in a parabolic curve. The first photodetector, placed 10mm from the light source receives light reflected and attenuated predominantly through scalp, skull and a superficial area of the brain. The second photodetector, placed 27mm from the light source receives light attenuated by the scalp, skull and a larger and deeper section of brain tissue. Near-infrared light penetrates human tissue to a depth of several centimetres and is attenuated by the chromophores – oxyhaemoglobin, deoxyhaemoglobin and carboxyhaemoglobin. The ratio of deoxyhaemoglobin to oxyhaemoglobin is calculated to provide a reading for intracerebral blood oxygenation, and the signal from the superficial structures is subtracted from that of the deeper structures to calculate the oxygen saturation of the blood in the brain. The technique was originally described for use over the frontal lobes [140]. More recently this technique has been adapted to provide more meaningful results for CEA over the parietal lobe and the territory of the middle cerebral artery [141]. This has involved increasing the source detector distances to 30 and 40mm respectively; the authors inserted a shunt if the cerebral oxygenation fell by more than 10% on clamping [141].

This technique has the advantage that it allows continuous monitoring of cerebral oxygenation, however, it only provides an indirect measure of both neuronal function and cerebral blood supply. Oxygenation is sampled over one superficial segment of brain tissue, which may not be representative of other more important deeper areas (e.g. the internal capsule). Transcerebral oximetry like the other monitoring methods mentioned above is not able to detect cerebral embolisation.

Transcranial Doppler Ultrasonography.

Transcranial Doppler Sonography (TCD) uses a low frequency ultrasound beam to penetrate the skull at its thinnest points to isonate the cerebral arteries. When used for monitoring patients during CEA, the transtemporal window is used and the middle cerebral artery is isonated. The middle cerebral artery supplies blood to the motor

and sensory cortex of the brain, and can be regarded as the direct intracranial continuation of the internal carotid artery.

TCD utilises the Doppler principle to measure the velocity of blood flow within the MCA and with the use of fast Fourier spectral analysis produces a real-time, visual display on a video monitor of the blood velocity waveform, which is easy to interpret. The MCA velocity is a reliable indicator of blood flow although it should be stressed that it is not an actual measure of blood flow as the diameter of the MCA being isonated is unknown and may vary. This method is used to assess the adequacy of cerebral collateral blood supply at clamping, the adequacy of shunted blood flow and the blood flow in the MCA once the clamp is removed and normal circulation is established through the endarterectomised internal carotid artery [142] [143]. Halsey found that a decline in MCAV to less than 40% of the original MCAV carried a mild risk of ischaemia, falls to less than 15% of baseline correlated with a severe risk of ischaemia [142]. However, a disadvantage of substituting TCD, a purely haemodynamic method for direct measures of cerebral ischaemia is that some patients with recent infarction or other foci of cerebral ischaemia may have no tolerance to any reduction in MCA blood flow. These patients would be missed by TCD but detected by direct measures of cerebral ischaemia (e.g. awake testing).

The most important advantage of this technique of monitoring, is that TCD can also detect cerebral embolisation and since this is thought to be the most important cause of intra-operative neurological defects [114] [144], this gives TCD an important advantage over other monitoring methods.

TCD does however have some disadvantages. Approximately 10% of patients do not have an accessible transtemporal window and as such cannot be monitored. Although TCD provides a direct measurement of cerebral blood flow it does not assess neuronal function. The cost of a TCD monitor is expensive, and as with EEG, SSEP and xenon 133 washout a technician is required. Despite these disadvantages, the combination of real-time visualisation of cerebral blood velocity and the ability to detect embolisation has led to this method of monitoring becoming increasingly popular.
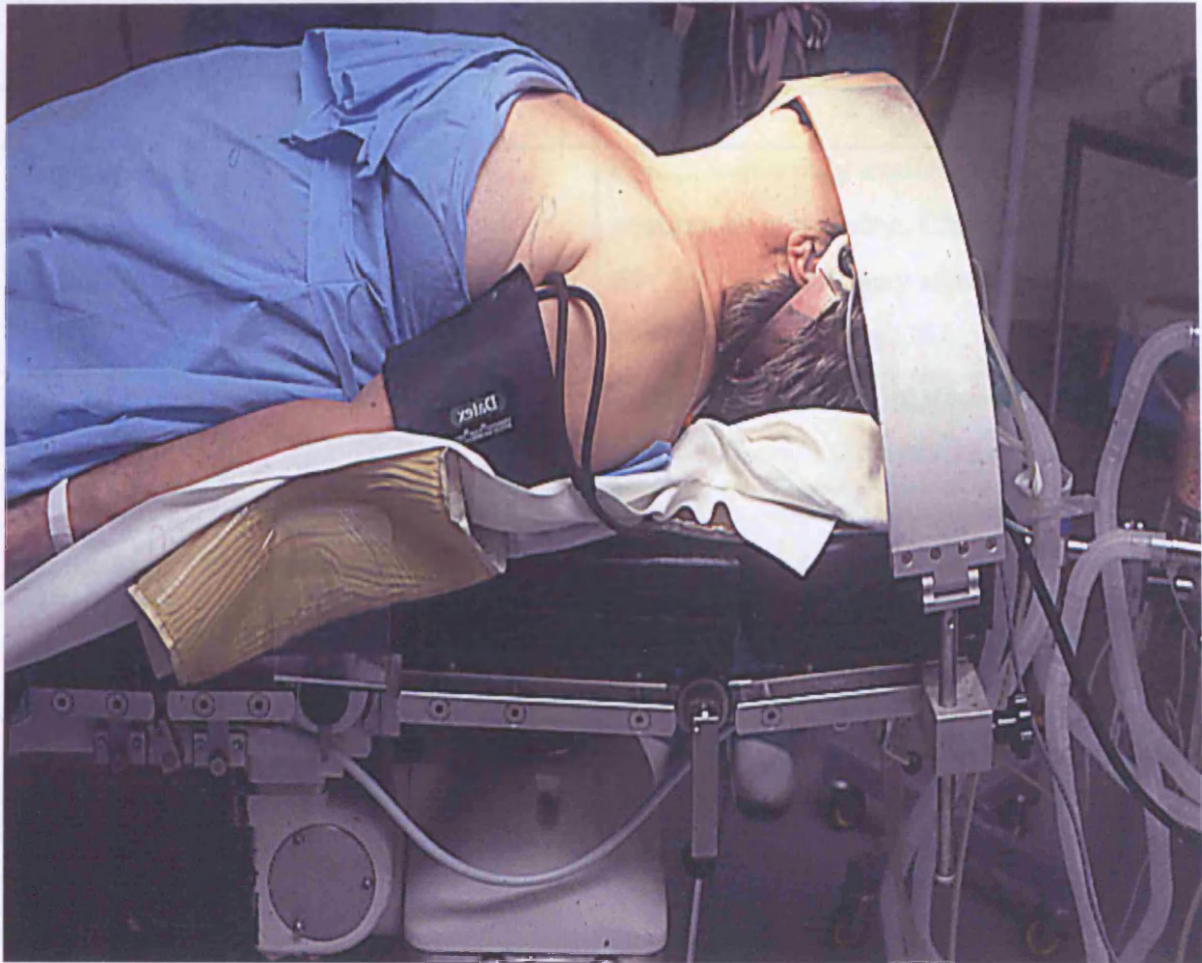
Figure 3.1 **Patient positioned on the operating table with TCD monitoring in place.**

The table overleaf (Table 4.2) summarises the cerebral monitoring methods available, and the suggested criteria for selective shunt insertion during carotid endarterectomy. It also details the advantages and disadvantages for each monitoring method.

Methods of cerebral monitoring and criteria for selective shunt insertion.

Technique	Suggested Criteria	Comments
Stump Pressure	<50mmHg	Cheap, universally available. No continuous monitoring. Changes in BP, $PaCO_2$, PaO_2 may affect circle of Willis flow during CEA.
Cerebral blood flow washout	<18-20ml/100g/min	Limited availability, expensive, radiation hazard. Technician required.
Near-infrared spectroscopy	Decrease in cerebral O2 saturation >10%	Expensive, research tool, uncertain contribution of extracranial perfusion.
Awake testing	Altered neurological function.	Cheap, reliable and continuous monitoring. Patient compliance.
EEG	Decreased amplitude, slowing, loss of fast activity	Continuous. Technician required. Assesses superficial cortex> deeper tissue. Affeted by GA and previous stroke.
SSEP	> 50% decrease in amplitude or >1ms increase in central conduction time.	Moderate cost. Technician required. Affected by GA/analgesics. Assesses internal capsule viability.
TCD	>50% - >70% decrease in MCAV	10% Patients have no window, expensive, technician required. Detects embolisation.

Table 4.2   Methods of cerebral monitoring and criteria for selective shunt insertion.

4.3 QUALITY CONTROL METHODS.

It has been estimated that 65% of perioperative strokes may be related to technical error resulting from defects in surgical technique [144]. Given that in effect CEA is a prophylactic operation, and that potential benefit is directly related to complication rates, knowing the importance of technical error, it is surprising that there is no

commonly accepted method of quality control. One problem is the many different types of technical errors that can occur, and result in a neurological deficit. No one method of quality control can detect all of these potential defects.

Technical Error	Comments
Embolism during operation	
Air embolism	Shunt malfunction/restoration of blood flow
Particulate embolisation	Dissection, shunt insertion, postoperative
Intimal flaps	
Clamp induced	Clamp applied across plaque
Residual	At endarterectomy zone
Shunt induced	Shunt raises flap on insertion
Suture stenosis	
Distal arteriotomy closure	
Toe of patch angioplasty	
Uncorrected ICA kink	
Thrombus formation	
Idiopathic	
Heparin dependent	Heparin induced antibody
Wall irregularity	At endarterectomy zone
Intimal flap	
Perishunt thrombosis	Proximal/distal to shunt
Haemodynamic errors	
Carotid clamping	Inadequate collateral cerebral circulation
Shunt occlusion or kinking	Often unrecognised by surgeon
Shunt malfunction	Inadequate blood supply through the shunt
Intracranial stenosis/thrombosis	
Shunt induced arterial spasm	
Intracranial haemorrhage	
Hyperperfusion	
Intracranial anuerysms	May rupture secondary to hypertension

Table 4.3   Technical errors resulting in peri-operative morbidity and mortality.

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The ideal quality control method would detect all technical errors, be safe and easy to use and interpret and be readily absorbed into the operative routine. A number of different quality control methods have been applied to CEA and the advantages and the disadvantages associated with these methods will now be discussed.

Angiography.

In 1967 Blaisdell conducted intraoperative angiography during 100 patients undergoing CEA. He detected technical defects in 26 cases [145]. Further studies have confirmed the usefulness of this technique and there is evidence to show a reduction in peri-operative morbidity and mortality as a result of the use of this technique [146]. However, difficulties in obtaining reliable intra-operative images of the carotid bifurcation and an associated morbidity /mortality with the technique has prevented its widespread use [66].

Continuous Wave Doppler.

Continuous wave Doppler (CWD) consists of a hand-held ultrasound probe applied to the surface of the artery after restoration of blood flow, and enables an assessment of blood flow velocity across the endarterectomy site [147]. CWD can be used independently by the surgeon, to indicate a residual stenosis, or vessel occlusion. It is simple to apply, however, unless the angle of insonation is standardised, and specific velocity readings taken, interpretation consisits of a subjective assessment of the auditory signal. An increase in audible tone is taken to indicate a stenosis, while the absence of a signal indicates occlusion. This method does not, however, provide any information regarding the structure of the abnormality and will not demonstrate the presence of intimal flaps.

B-Mode Ultrasound/Duplex.

B-Mode ultrasound (BMU) consists of a hand-held probe applied to the surface of the artery, once again after restoration of blood flow. The probe is much larger than the CWD probe but provides a real-time Grey-scale image of the artery and

endarterectomy site. It enables the detection of abnormalities such as arterial kinks and intimal flaps. The tecnique is more complex than CWD and may require a second operator to adjust the controls to obtain satisfactory images and experience is needed to correctly interpret the images [148].

Duplex combines the B-Mode images with velocity measurements to provide a combined assessment of the structural components of a defect and its effect on blood flow [149]. Colour duplex provides a colour-coded image of the blood flow velocity in combination with a grey-scale image [150]. Both of these methods provide a comprehensive assessment of the operated artery but consist of expensive equipment that requires considerable expertise both to obtain accurate images and to interpret them correctly.

Angioscopy.

An angioscope is a flexible fibreoptic telescope that can be inserted into the lumen of the artery after completion of the endarterectomy and prior to final restoration of blood flow. Pressurised saline irrigation through an integrated irrigation port simulates blood flow and serves to illustrate abnormalities such as thrombus or intimal flaps. This allows for detected abnormalities to be corrected prior to restoring blood flow, however, it will provide no information regarding blood flow through the endarterectomised artery such as residual stenosis or arterial kinks [151].

The figure overleaf (Figure 4.2) shows the view obtained through the angioscope, visualising the distal intimal flap which has been tacked down and the Dacron patch used to close the arteriotomy.
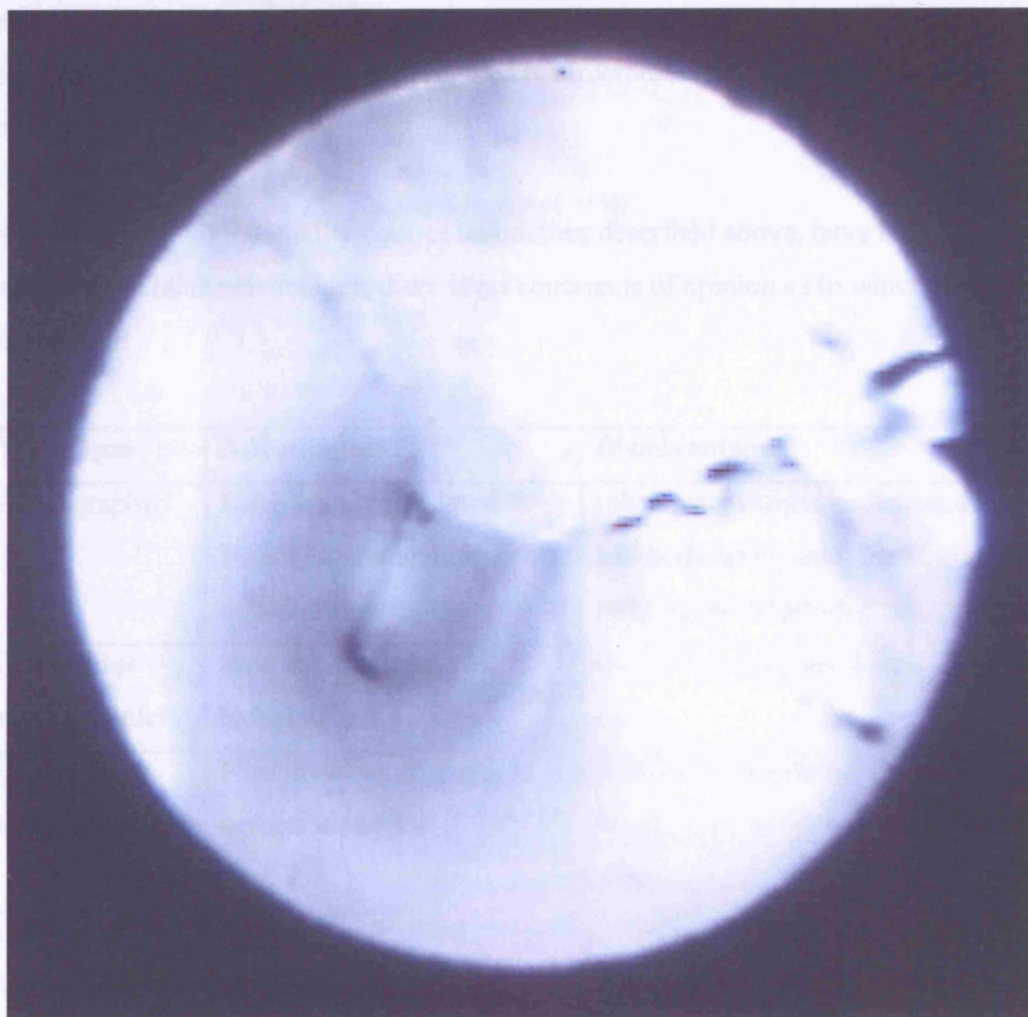
Figure 4.2   Normal angioscopic assessment.

<u>**Transcranial Doppler Ultrasonography.**</u>

Although TCD has been thought of as a monitoring tool it also has an application as a continuous method of quality control detecting errors of surgical technique whilst the operation is in progress. TCD has the ability to detect significant embolisation during various stages of the operation. If significant emboli are detected during the dissection phase of the procedure, suggesting an extremely fragile plaque, surgical technique can be altered to reduce the incidence of embolisation or the ICA can be clamped early to prevent emboli travelling to the cerebral circulation. Significant embolisation following restoration of blood flow has been shown to be associated with on-going carotid artery thrombosis [152], this may prompt early re-exploration of the carotid artery or pharmacological intervention. TCD is also able to detect

abnormalities of blood flow such as kinking or occlusion of the shunt. TCD does not however provide information with regards to structural errors, such as intimal flaps or residual stenosis.

As can be seen all the quality control techniques described above, have both advantages and disadvantages, there is no concensus of opinion as to which method is superior.

Technique	Advantages	Disadvantages
Angiography	Established technique. Direct anatomical images of blood flow.	Inadequate images/radiation. No haemodynamic data. Requires technicians. Morbidity/mortality
Continuous wave Doppler	Simple technique. No technicians.	Subjective analysis. Gross defects only.
B-Mode Ultrasound	Non-invasive. Structural defects identified.	Technical help, large probe. Image interpretation. No haemodynamic data.
Duplex Ultrasound	Haemodynamic and structural data.	Technical help needed. Image interpretation, probe size. Expensive.
Colour Duplex	As above	As above. More expensive.
Angioscopy	Direct images, easy to interpret. Correct defects prior to restoring flow.	Applied before restoration of flow. No haemodynamic data.
TCD	Identifies embolisation and blood flow abnormalities.	No structural defects identified. Requires technician. Expensive.

Table 4.4   The advantages and disadvantages of several methods of quality control.

4.4 QUALITY CONTROL AND MONITORING METHODS USED IN THIS STUDY.

As described above there are multiple monitoring and quality control techniques available to the carotid surgeon, however there is no superior method that is universally applied. Between 1992 and 1994 a study was undertaken in this unit by Gaunt et al [153] to compare the application of angioscopy, BMU, CWD, and TCD as quality control methods during carotid endarterectomy. It should be noted that colour Duplex assessment was not used in this study.

A prospective study was performed of 100 consecutive patients undergoing carotid endarterectomy for severe, ipsilateral, symptomatic, carotid artery stenosis. The aims were threefold:

1. To compare the ability of the techniques to detect technical error.
2. To assess the feasibility of applying each technique for routine use.
3. To assess whether applying these methods provided useful information as to the cause of perioperative neurological complications.

The findings of this study will be summarised here. Of the techniques employed to detect completion defects, angioscopy had significant advantages over BMU and CWD. Angioscopy proved to be a simple technique to perform enabling the surgeon to operate independently of technicians and the magnified images of the arterial lumen viewed on colour monitors required little specialised knowledge for interpretation. Angioscopy proved to be a sensitive technique for the detection of intimal flaps and fragments of intraluminal thrombus. A major advantage of angioscopy was that defects were detected and corrected prior to restoration of flow, avoiding the need to reopen the artery, and preventing distal embolisation.

	CCA	ICA
Intimal Flap	0	4
Major Thrombus	2	6
Minor Thrombus	4	11
Stenosis	0	0

Table 4.5   Defects detected by angioscopy [153].

Angioscopy enabled a full assessment in 98% of patients compared to only 76% with BMU and 91% with CWD. The low percentage achieved with BMU was due to the large dimensions of the probe and poor penetration of artificial patch material. The low number of adequate examinations achieved with BMU would severely limit its routine application. It should be noted however, that the B-mode probe used in this study was a standard shape and produced black on white images, there are now available colour 'L' shaped probes which can give much better results.

Difficulty in examing the distal end-point was also experienced with CWD in 9% of cases and difficulty with signal interpretation occurred. No intimal flaps or luminal thrombus were detected with either BMU or CWD, however these monitoring techniques proved more sensitive than angioscopy at detecting stenoses. B-mode apparently identified 2 minor (<30%) stenoses and 2 major stenoses (>30%). The 2 major stenoses were re-explored but no correctable defect was found and post-operative duplex scans at 6 weeks and 6 months were normal. The 2 minor stenoses were not re-explored and post-operative duplex scanning failed to confirm the presence of minor stenoses.

With CWD 4 major stenoses were identified, however this was not confirmed with B-mode imaging and the arteries were not re-explored. Post-operative Duplex scanning did not confirm the presence of an abnormality in any of these cases. CWD also identified an arterial kink in one patient, this was confirmed with B-mode imaging, however in the context of the operation, the surgeon felt this wasn't significant and the artery was not re-explored. Post-operative Duplex scanning confirmed the presence of an arterial kink causing a stenosis of 30% at the junction

of the distal patch, this was not a significant flow limiting lesion. Duplex scan at 6 months did not show any progression of the stenosis.

The post-operative Duplex scan at 6 weeks identified a number of defects which were either not detected intra-operatively or developed post-operatively. These consisted of 2 arterial kinks, a 75% stenosis due to intimal hyperplasia at the distal endpoint and 2 asymptomatic carotid artery thromboses. No new defects developed between 6 weeks and 6 months. Gaunt concluded after careful review of the intra-operative recordings of angioscopic and B-mode images and the CWD velocity profiles that these defects developed post-operatively. This would suggest that although completion quality control techniques are useful in detecting technical errors that may occur during CEA, these techniques do not ensure the elimination of all arterial defects, as some may develop in the post-operative period. These techniques are therefore useful at preventing intra-operative stroke but will not eradicate all late post-operative strokes.

TCD also played an important role in detecting technical errors in 41 patients in this study. TCD monitoring detected particulate embolisation during the dissection of the carotid artery in 23 patients. Early warning of this phenomena enabled modification of surgical technique and in persistent cases, early distal ICA clamping to avoid further distal embolisation. TCD monitoring also identified shunt kinking/malfunction in 13 patients and identified rupture of the distal retaining balloon of the Pruitt-Inahara shunt in 2 patients.

In 6 patients TCD detected unexpected particulate embolisation in the early post-operative phase. In 3 cases the embolisation was minor, self-limiting and asymptomatic, however in 3 cases embolisation was persistent and preceeded progression on to carotid artery thrombosis and the development of serious neurological deficits. In all three cases re-exploration of the carotid artery revealed a mass of platelet thrombus adherent to the endarterectomy zone. No technical errors were detected in any of these cases by angioscopy, BMU or CWD. TCD monitoring may therefore have a significant role to play in the prevention of post-operative stroke by the early detection of incipient carotid artery thrombosis.

Gaunt concluded from his study that the combination of continuous TCD monitoring with angioscopy yielded the highest detection of technical errors. Angioscopy was the most accurate of the completion techniques and the easiest to routinely apply. TCD not only has a role as a continuous quality control measure, detecting errors of operative technique as they occur during the operation, but its ability to identify carotid artery thrombosis in the early post-operative period, prior to the development of neurological signs, enabling early surgical re-exploration is an important new clinical technique.

The important clinical question raised by Gaunt's study was whether the increased detection and correction of technical errors by angioscopy and TCD would lead to a reduced peri-operative morbidity and mortality for CEA. There have been numerous studies of quality control techniques in the past, which, although they have shown an increased detection of surgical defects, correction of these have not reduced the overall morbidity and mortality for CEA. Lane compared B-mode ultrasound assessment of CEA with no assessment in 380 operations. Although BMU detected a significant number of technical defects, which were corrected intra-operatively, there was no statistical significant effect on the overall post-operative morbidity and mortality in the two groups[154].

The aims, therefore, of this thesis were to assess if the routine application of TCD monitoring combined with completion angioscopy can reduced the incidence of intra-operative stroke and furthermore, to assess whether the introduction of more prolonged post-operative monitoring with TCD, can significantly reduce the incidence of post-operative stroke.

Chapter 5.

Transcranial Doppler ultrasonography.

CHAPTER FIVE: TRANSCRANIAL DOPPLER ULTRASONOGRAPHY.

This chapter will describe the principles underlying the use of transcranial Doppler ultrasonography including the history and development of TCD, examination techniques, TCD as applied to CEA and the detection of cerebral emboli using TCD.

5.1 THE DOPPLER PRINCIPLE.

The Doppler principle was first described by the Austrian physicist, Christian Doppler, in 1842. It details the relationship between the velocity of objects and the frequencies of transmitted and reflected sound waves [155].

In brief, if sound waves of a given frequency are transmitted towards a moving object the frequency of the reflected waves depends to a certain extent on the direction of movement of the object. If the object is moving towards the source of the transmitted waves, the reflected waves will have a higher frequency. If the object is moving away the reflected waves will have a lower frequency. The degree of frequency shift depends on the velocity of the moving object and therefore the velocity of that object can be calculated if the frequency shift is known. An example of the Doppler effect is the change of the pitch of sound emitted from a rapidly moving vehicle as it passes a stationary observer. Sound waves are regions of high and low pressure in the air and they travel at fixed velocity. The separation between the high and low pressure regions depends on the wavelength and therefore on the frequency. If the object that is emitting the sound wave is moving forward, the interval between the high pressure waves comes closer together, reducing the wavelength and increasing the frequency. Conversely as a source moves away, the interval between the high pressure waves increases with a corresponding increase in the wavelength and a decrease in frequency.

When the principle of Doppler ultrasound is applied to the detection of blood flow the frequency of the ultrasound is reflected and changed by moving red

blood cells and is in proportion to the blood velocity according to the Doppler equation:

$$\Delta f = 2fv \cos\theta/c$$

Where f is the transmitted ultrasound frequency; Δf is the shift in ultrasound frequency; v is the velocity of the blood and θ is the angle between the ultrasound beam and the blood vessel. C is the velocity of sound in the tissues.

Unfortunately it is not possible to measure the angle between the ultrasound beam and the blood vessel when using TCD, however the most often insonated artery, the middle cerebral artery runs perpendicular to the surface of the skull for a considerable distance from its origin. Insonating the artery from the posterior temporal window, the angle of insonation is seldom greater than 30° which means that the measured velocity is at least 87% of the true velocity. Absolute values for velocities measured by TCD have an inbuilt error, which must be taken into account when analysing MCA velocity data.

It should be stressed that TCD measures the velocity of blood flow and not the volume of blood flow. This is because the diameter of the artery cannot be determined accurately enough to enable calculation of absolute flow in millilitres. Although some authors have found a good correlation between measures of cerebral blood flow and TCD velocity values, an individual value can only be considered an indicator of the amount of blood flow and not an absolute measure [143].

In the clinical situation this 'indication' of blood flow can be used to detect large falls in cerebral blood flow known to be associated with neurological damage. A MCA velocity of less than 10 – 15 cm/sec during carotid clamping has been associated with a flattening of the EEG in some cases, and therefore has led to recommendations that the MCA velocity should be maintained above this level [156]. However due to the reasons explained above the values for MCA velocity can be inaccurate and Halsey suggested that the percentage fall in MCAV on carotid clamping is a more reliable indicator of ischaemia. It was found that if the

MCAV fell to less than 40% of its preclamp value this was associated with mild cerebral ischaemia and falls to less than 15% caused severe ischaemia [142].

5.2 TCD EXAMINATION TECHNIQUES.

Transcranial Doppler sonography exploits three areas of the skull where the bone is relatively thin and therefore provides less of a barrier to the penetration of ultrasonic waves. These areas are known as acoustic windows and are located as follows; the transtemporal window [157], the transorbital window [156] and the transoccipital window [158]. The transtemporal window is the most commonly used and is located over the temporal bone just superior to the zygomatic arch. The transtemporal window is used to insonate the middle cerebral artery and therefore is the site used for monitoring during CEA.

Although radiological studies have shown that the transtemporal area is consistently radiolucent area of the skull, insonation is still impossible in approximately 10% of subjects due to hyperostosis [159]. This predominantly occurs in post-menopausal women and is due to a localised increase in the density of the inner table of the skull.

The transtemporal window is divided into three regions, posterior, middle and anterior, moving from the area just infront of the ear and above the zygomatic arch forwards. The posterior transtemporal region is the one most commonly used, but if no window is located there, the other regions should be investigated. The probe is placed on the posterior temporal area with some aqueous ultrasound coupling gel between the probe and the skin. The acoustic intensity is set to 100% of its maximum and the sample volume depth set to 55mm and the probe angled slightly forwards and upwards. From this position, slight alterations in depth and angle are made until a Doppler signal is obtained. The angle and position is further adjusted to obtain the maximum MCA velocity possible (see explanation above). For positive identification of the MCA the following criteria should be satisfied [160].

1. With the probe on the posterior temporal window the probe should be angled slightly anterior and superior.

2. The Doppler spectral signal obtained should have a positive deflection (indicating blood flow towards the probe). The systolic upstroke should be steep (except in cases of severe flow limiting proximal stenosis) and the time-averaged mean velocity should be in the region of 55+/-12cm/sec.

3. On increasing the depth (55 – 64mm), the signal should bifurcate, with a negative deflecting signal becoming visible in addition to the positive deflection. This indicates the point of the bifurcation of the internal carotid artery into the anterior (negative deflection) cerebral artery and the middle (positive deflection) cerebral artery. Increasing the depth further and angling the probe more anteriorly should yield a predominantly negative deflection indicating insonation of the anterior cerebral artery alone (65 – 70mm).

4. On decreasing the depth, the MCA signal should be detectable to at least 45mm although the angle of the probe may need to be adjusted to take account of any bends in the artery. Only the MCA is detectable at these shallow depths, because it runs outward towards the skull for 16 – 20mm of its course before bifurcating.

5. Having identified the MCA and ACA the probe should now be angled posteriorly and the depth increased to 60 – 70mm in order to identify the posterior cerebral artery.

It is probably safe to say that the only criterion which does not vary is the fact that blood flow in the MCA should always be towards the probe. However anatomical variations and altered directions of blood flow due to disease can make positive vessel identification very difficult.

A very severe ipsilateral carotid stenosis or occlusion can reduce flow in to such an extent that the direction of blood flow in the ACA is reversed providing collateral blood supply. In such a case the bi-directional signal at the bifurcation is never seen, giving the impression that the MCA can be traced to a much greater depth than would normally be expected.

Alternatively, in cases of reduced ipsilateral carotid blood flow, the amount of blood flowing through the PCA may be dramatically increased. In such a patient the MCA waveform is detectable but the systolic upstroke is damped and the velocity reduced so that it does not represent a typical MCA waveform. The PCA signal is the strongest with a steep systolic upstroke and a higher blood flow velocity and therefore closely mimics the MCA and can lead to monitoring of the wrong artery. The probe however will be noted to be angled posteriorly, and if angled more posteriorly still, no other signals will be detected.
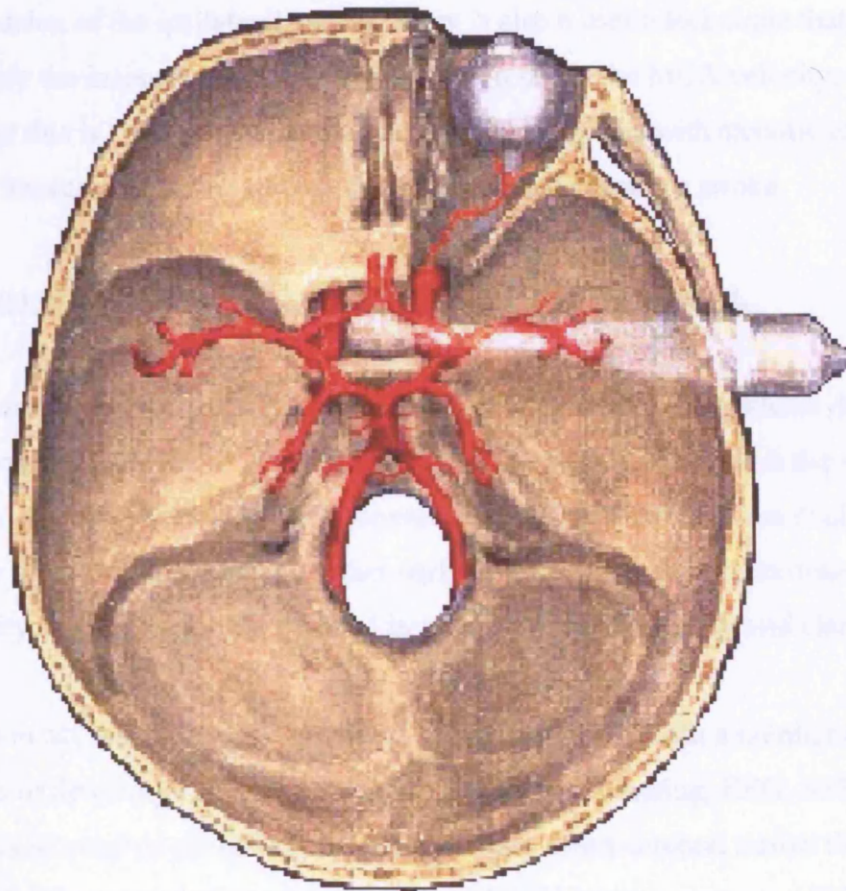
Figure 5.1   TCD probe insonating the MCA through the transtemporal window.

If the MCA has been correctly identified and is being continuously monitored during CEA the velocity should fall when the ipsilateral carotid artery is clamped. The degree of fall will be determined by the adequacy of the collateral vessels to increase the blood supply to compensate for the loss of carotid supply. However the velocity should never fall to zero as there is usually some collateral

supply even if it is inadequate to prevent ischaemia. If the velocity does fall to zero it is likely that the ICA has been insonated by mistake. This is because the ICA is below the circle of Willis and therefore below the collateral blood supply. If the velocity increases it is highly probable that the PCA has been insonated. Blood flow in the PCA increases on carotid clamping to compensate for the reduced supply from the carotid artery. The blood flow in the ACA also increases but is usually a weaker signal than the posterior.

Compression of the ipsilateral carotid artery is also a useful technique that helps to identify the insonated artery as it will cause a fall in the MCA velocity. However this is not a suitable technique for use in patients with stenotic carotid disease because of the risk of dislodging plaque and causing a stroke.

Detection of intra-operative ischaemia using TCD monitoring.

Padayachee was the first to describe the use of TCD to monitor patients during carotid endarterectomy [161]. This study of 19 patients concentrated on the variation in MCAV at different stages of the operation and in particular on the decline in velocity upon carotid clamping. Other early investigators also concentrated on the ability of TCD to predict cerebral ischaemia at the time of carotid clamping.

The fall in MCAV at the time of clamping was correlated with a number of other methods of detecting cerebral ischaemia such as awake testing, EEG, SSEP, measures of cerebral perfusion and more recently mean cerebral transit time [119]. Although it has already been described that MCAV is not a measure of blood flow several investigators found a good correlation between these methods and low MCAV values indicating ischaemia. Several investigators found that a MCAV between 10 – 15cm/sec correlated with a decrease in frequency and amplitude of waveforms during EEG monitoring indicating cerebral ischaemia [156]. However, Halsey found the relative decline in MCAV more reliable at correlating with ischaemia detected on EEG. A decline in MCAV to less than 40% of the original value carried a mild risk of ischaemia, less than 15 % correlated with a severe risk of ischaemia [142].

A disadvantage, however, of substituting TCD, a purely haemodynamic method, for direct measurements of cerebral ischaemia, is that some patients with a recent infarction or other foci of cerebral ischaemia may have no tolerance to any reduction in MCA blood flow. These patients would be detected by direct measurements of cerebral ischaemia, but missed by TCD, which would merely indicate an MCAV adequate to prevent ischaemia in the majority of subjects.

In our study all patients were shunted, therefore TCD had a limited role to play in the detection of cerebral ischaemia, although it has proved useful at detecting shunt malfunction which was not otherwise apparent. Our main indication for the use of TCD, is the detection of cerebral emboli, which will be described in the next section.

Doppler Ultrasound detection of cerebral emboli.

Intravascular microemboli were first detected with Doppler ultrasound on the vena cava and aorta of sheep and swine following decompression from exposures to hyperbaric air [162-164]. Decompression venous gas emboli in the peripheral veins and in the pulmonary artery were later confirmed in human experimental divers [165] and this information was used for the development of safer decompression tables for divers.

With the introduction of TCD and the monitoring of the middle cerebral artery during carotid endarterectomy and pulmonary bypass, aeroembolism was again detected but now in the intracranial arteries. During the course of monitoring carotid enarterectomies it became apparent that signals identical to the qualities of gas bubbles were occurring during dissection before arteriotomy as well as during pre-operative and post-operative evaluation of patients [166]. It was clear that these signals were not arising from bubbles because there was no possibility that air was spontaneously entering into the arteries. It was concluded the signals were caused by particulate emboli. Spencer, who did much of this early work identifying air and particulate emboli, described the criteria used in his research for identifying emboli within the cardiovascular system

1. They are short transients, less than 0.1 sec ranging from 3 to 60 dB above the background Doppler blood velocity spectrum.
2. They are unidirectional within either the advancing or receding velocity spectrum.
3. Their duration in the velocity spectrum is inversely proportional to their velocity.
4. They are random in occurrence in the cardiac cycle.
5. They usually change frequency/velocity as they pass through the sample volume.
6. They sound to the ear like harmonic chirps, whistles or clicks, depending on their velocity.
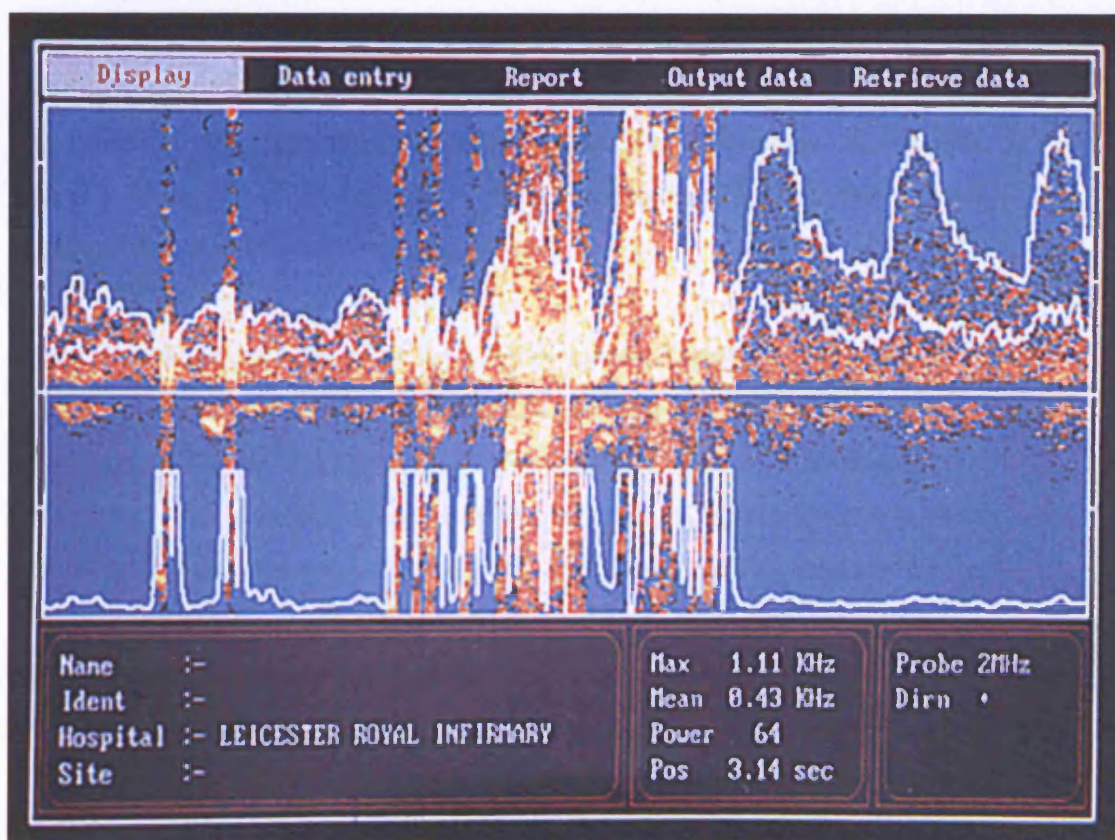
Figure 5.2   **Multiple emboli within a Doppler blood velocity spectrum.**

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5.3 THE CLINICAL RELEVANCE OF TCD DETECTED EMBOLI DURING CAROTID ENDARTERECTOMY.

Emboli are commonly detected during CEA, however the clinical relevance of the embolisation was unclear, as not all patients with emboli suffered ischaemic injury.

Naylor prospectively monitored 30 consecutive patients undergoing CEA and detected intra-operative embolisation in 15 of them [143]. Embolisation was observed in one patient during carotid mobilisation, in one patient during carotid clamping, in 12 immediately following shunt insertion and in eight following final clamp release and restoration of flow. There was however no evidence that this embolisation led to neurological deficits.

Jansen prospectively monitored 130 operations and detected 75 episodes of embolisation in 55 patients [167]. In 54 patients embolisation was not associated with post-operative neurological deficits or intra-operative EEG abnormalities. One patient suffered massive embolisation after clamp release and suffered an intra-operative stroke which resolved post-operatively.

These studies were not designed specifically to investigate clinical outcome or the clinical relevance of TCD detected embolisation. Gaunt conducted a study specifically designed to determine the clinical importance of TCD detected emolisation [153]. This prospective study of 100 patients, confirmed that intra-operative embolisation was common, affecting 92% of his patients. The majority of these emboli, however, were of no clinical significance. In particular, intra-operative emboli were not associated with silent CT infarction or visual field deficits. Apart from one patient with gross air embolisation following shunt complications, there was no evidence that air emboli were associated with any clinical sequelae.

This study did however identify two stages during CEA when clinically significant embolisation did occur. More than 10 particulate emboli occurring during the initial dissection phase was associated with deterioration in post-operative cognitive function, while persistent particulate embolisation during the recovery phase was a predictor of incipient carotid thrombosis and the development of major neurological

deficits. He concluded that early intervention based on the TCD evidence of embolisation had the potential to avoid adverse clinical consequences related to these events.

PART 2.

Chapter 6.

The prevention of intra-operative stroke.

CHAPTER SIX: THE PREVENTION OF INTRA-OPERATIVE STROKE.

6.1 INTRODUCTION.

Riles has shown that despite a surgeon's best efforts, inadvertent technical error remains one of the most important factors predisposing to thromboembolic and haemodynamic stroke during CEA [168]. However, while virtually every vascular surgeon would probably perform some form of completion assessment following femoro-distal bypass, surprisingly few adopt a similar strategy during CEA.

In 1992, Gaunt undertook a study in this unit to assess various methods of quality control. His study found that for this unit the combination of TCD monitoring combined with completion angioscopy yielded the biggest detection of technical errors. During this study period the incidence of intra-operative strokes fell from 4% to 1% [154].

The aim of the first study in this thesis was to assess whether this policy of quality control can be continually implemented and have a sustained effect in reducing the intraoperative stroke rate.

6.2 MATERIALS AND METHODS.

Between March 1995 and 31 December 1996, 252 patients (median age 68 years) underwent either carotid endarterectomy (n = 243) or saphenous vein carotid bypass (n = 9) for the correction of severe (>70%) internal carotid artery stenotic disease. Patients who underwent surgery for carotid body tumour, aneurysm, fibromuscular dysplasia or Takayasu disease were excluded.

Clinical presentation included stroke in 96 patients (38%), TIA/amaurosis fugax in 129 patients (51%), whilst 27 patients (11%) were asymptomatic. Unilateral stenoses were present in 161 (64%), bilateral ICA stenoses in 50 (20%), while 41 (16%) had a contralateral occlusion.

Carotid endarterectomy was performed via a longitudinal arteriotomy in a standardised manner throughout the period of the study by one of three consultants in vascular surgery, or by a higher surgical trainee under consultant supervision. The procedure was performed under normotensive, normocarbic general anaesthesia. All patients were systemically heparinised using 5000iu heparin intravenously. Routine shunting was employed in all patients (Pruitt-Inahara). The proximal and distal intimal flaps were tacked down using 7:0 prolene (Ethicon) and all arteriotomies were closed with a Dacron patch (Vascutek).

Following completion of the procedure and recovery from anaesthesia, the patient was examined neurologically and transferred to the High Dependency Unit for 6 hours of postoperative transcranial Doppler monitoring (see following chapter). Any new neurological deficit apparent upon recovery from anaesthesia was recorded and the patient assessed by a neurologist. Post-operative neurological complications (i.e. those that developed following a normal recovery from anaesthesia and up to 30 days thereafter) were also documented. The protocol required that all patients who recovered from anaesthesia with a new neurological deficit be investigated immediately with colour Duplex and TCD. The decision to re-operate thereafter was left to the discretion of the surgeon. All neurological deficits that developed during the post-operative period were investigated by colour Duplex, TCD and CT scan.

Continuous TCD monitoring of blood flow velocity (time averaged mean) in the ipsilateral middle cerebral artery was performed using a 2MHz pulsed wave probe, via the transtemporal window, secured with an elasticated headband connected to a Scimed PC842 transcranial system. The probe was protected from displacement by a detachable, semi-circular metal head-guard attached to the operating table. Recording commenced immediately following induction of anaesthesia and continued until the surgical drapes were removed. Data were recorded onto digital audiotape enabling off-line analysis with particular emphasis on the number and character (air vs. particulate) of emboli detected throughout the procedure.

During the procedure a research fellow experienced in TCD or technician was on hand to supervise minor readjustments of the probe position and generally advise the surgeon of unexpected phenomena. In general, the aim was to keep the MCA velocity ≥15cm/s throughout the procedure, preferably ≥20cm/s.

Following endarterectomy and prior to closure of the patch, the shunt was removed, the carotid vessels were flushed and irrigated with heparinised saline and then re-clamped. A 5mm segment of the arteriotomy adjacent to the origin of the external carotid artery was left unsutured and through this an angioscopic assessment was made of the distal ICA, proximal CCA, ECA orifice and the endarterectomy zone. Following this the final few sutures to complete the patch closure were inserted and flow restored.
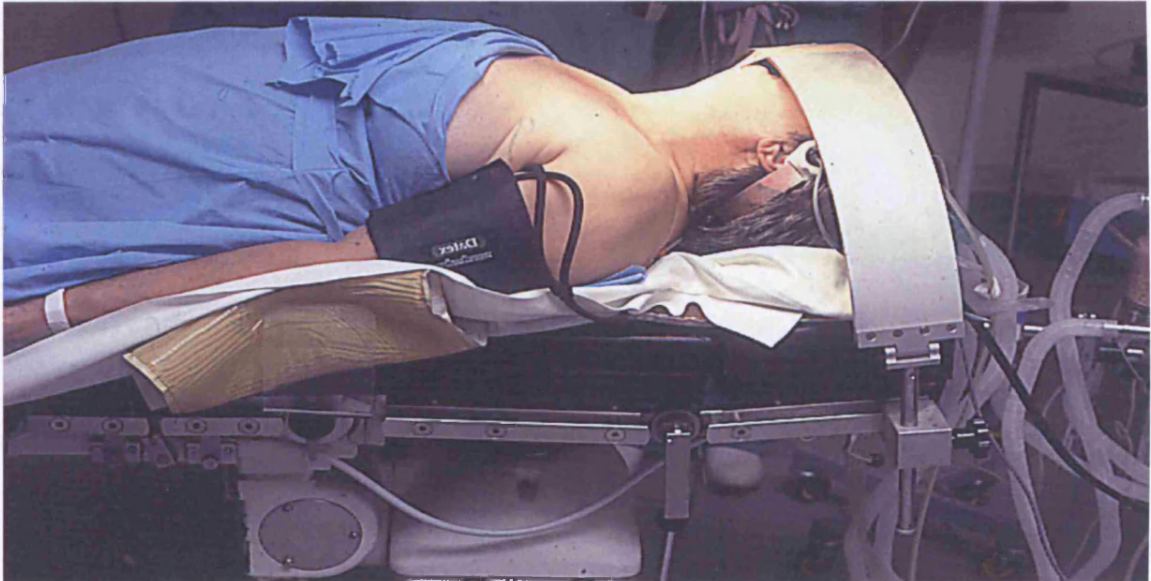
Figure 6.1   Patient positioned on the operating table.

During the initial few months of this study a 2.8mm flexible multi-fibre angioscope was used. Although there were no major problems with the view provided the main problem was the angioscope developed repeated fibre breakage and it quickly became unusable. In March 1995 the angioscope was replaced with a more robust 5mm diameter flexible hysteroscope. A standardised operation note required the surgeon to record any abnormal findings within the endarterectomy zone. The policy of the unit was to remove any fragments of thrombus and repair any intimal flap > 3mm. When necessary an estimate of

luminal sizing of an abnormality was based on comparison with the 2mm diameter head of the forceps that could be passed down the instrument channel of the scope. If any abnormality required correction, the endarterectomy zone was routinely re-examined to confirm there was no residual abnormality.
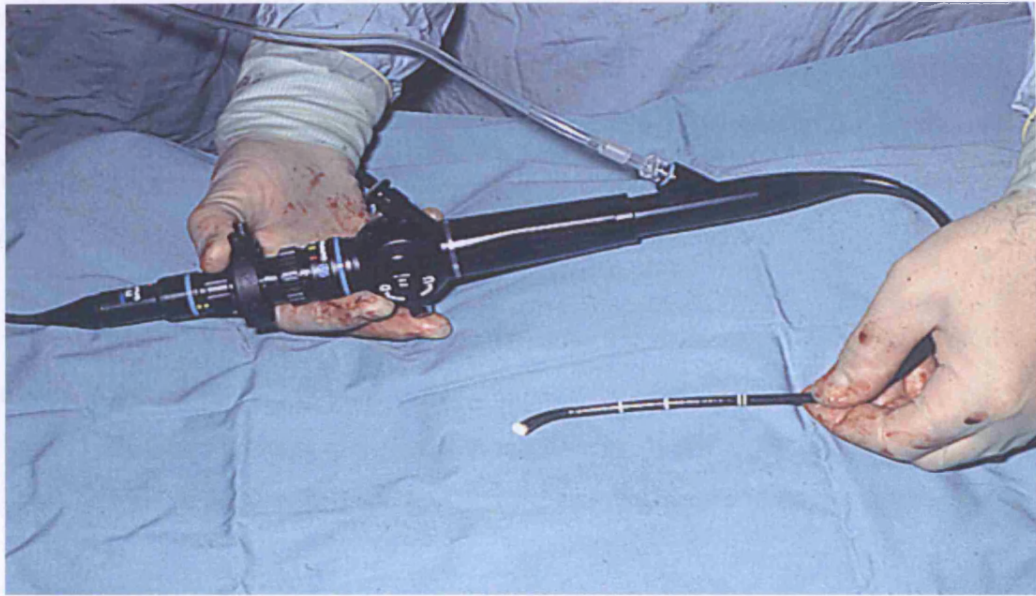
Figure 6.2   The angioscope.

From October 1995 owards we introduced a policy of postoperative TCD monitoring, where ipsilateral MCAV data were recorded for 10 minutes every 30 minutes for 6 hours following restoration of flow. Any patient who had ≥ 25 emboli detected during any 10 minute period of monitoring was commenced on an incremental infusion of Dextran 40, starting at a rate of 20ml/h. If the rate of embolisation did not diminish, the infusion was gradually increased by 5ml/h every 10 minutes to a maximum of 40ml/h. Once the Dextran infusion rate was stabilised, it was then continued at that dose for a further 12 hours.

All patients were discharged home on aspirin therapy (150mg daily), usually on the 3rd to 5th postoperative day, and all were reviewed 4-6 weeks later in the vascular clinic.

6.3 RESULTS.

Ability to monitor.

Continuous intra-operative TCD monitoring was achieved in 91% of patients undergoing CEA in this study. Technical failures (insonating the wrong artery, irretrievable dislodgement of the probe, equipment failure) fell from 3% in the initial pilot study to 0.4% in this study. The only residual barrier to routine TCD monitoring remained an inaccessible cranial window (affecting 6% of patients in this study) and insufficient TCD machines to monitor more than two procedures at any one time (2.8%).

A successful angioscopic assessment was performed in 94% of patients in this study. The principal reasons for not performing angioscopy were equipment failure in three patients (1.2%), two theatres requiring the angioscope at the same time (1.2%), while eight of the nine patients who were undergoing carotid bypass were not angioscoped.

Transcranial Doppler monitoring.			
Successful TCD monitoring	No TCD window	Simultaneous CEAs	Technical Failure
229 (90.8%)	15 (6%)	7 (2.8%)	1 (0.4%)
Completion angioscopy			
Successful angioscopy	Equipment failure	Simultaneous CEAs	Other reason
238 (94.4%)	3 (1.2%)	3 (1.2%)	8 (3.2%)

Table 6.1   Ability to undertake TCD monitoring and completion angioscopy.

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Prevention of inadvertent technical error.

During this study, 94% of patients underwent a normal angioscopic assessment. Six patients underwent repair of an intimal flap, while six were noted to have residual luminal thrombus which was remove prior to restoration of flow.

Normal angioscopy	Intimal flap >3mm	Luminal thrombus
226 (95%)	6 (2.5%)	6 (2.5%)

Table 6.2   Angioscopy findings prior to restoration of flow.
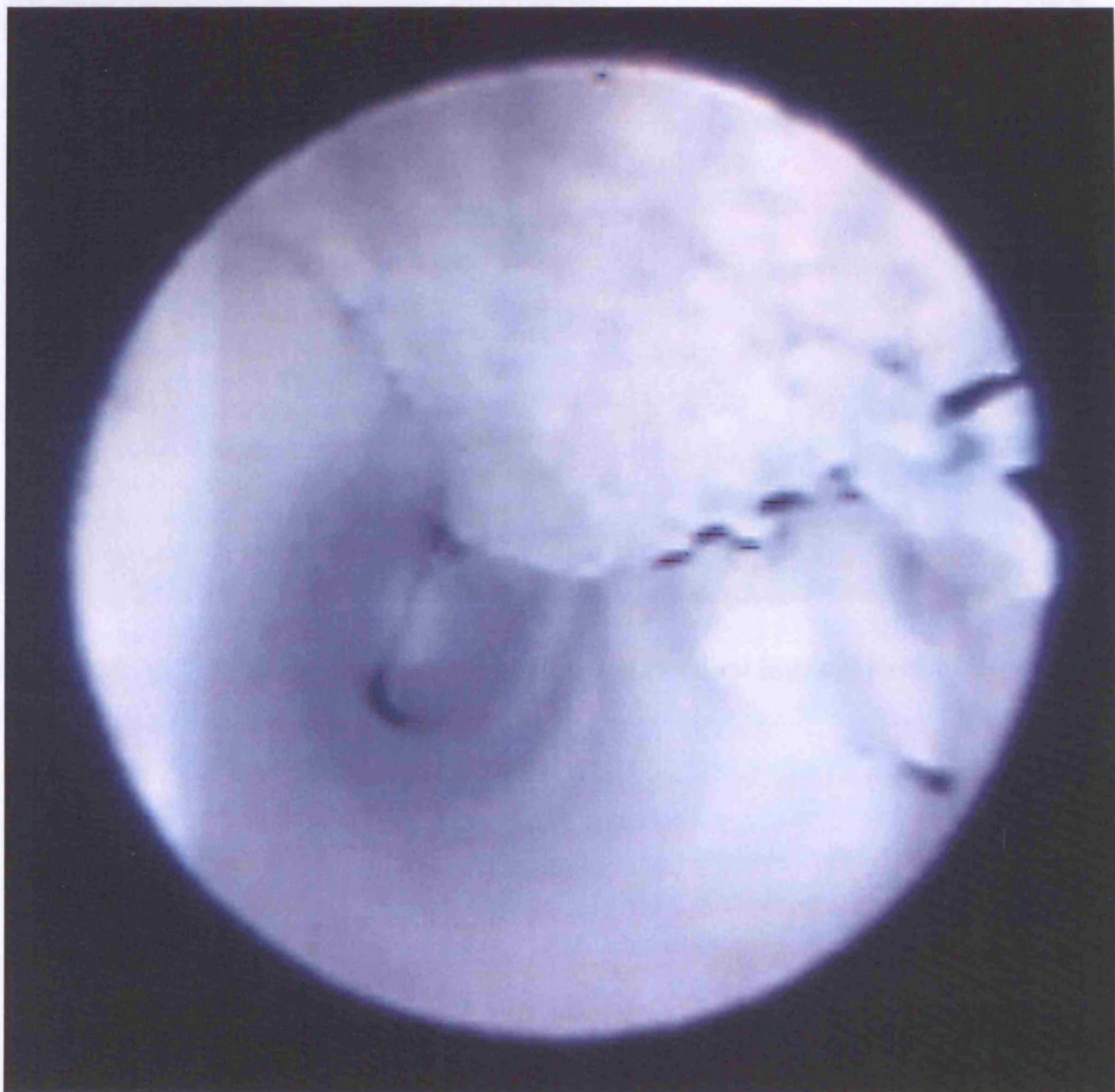
Figure 6.3   Normal angioscopic assessment.
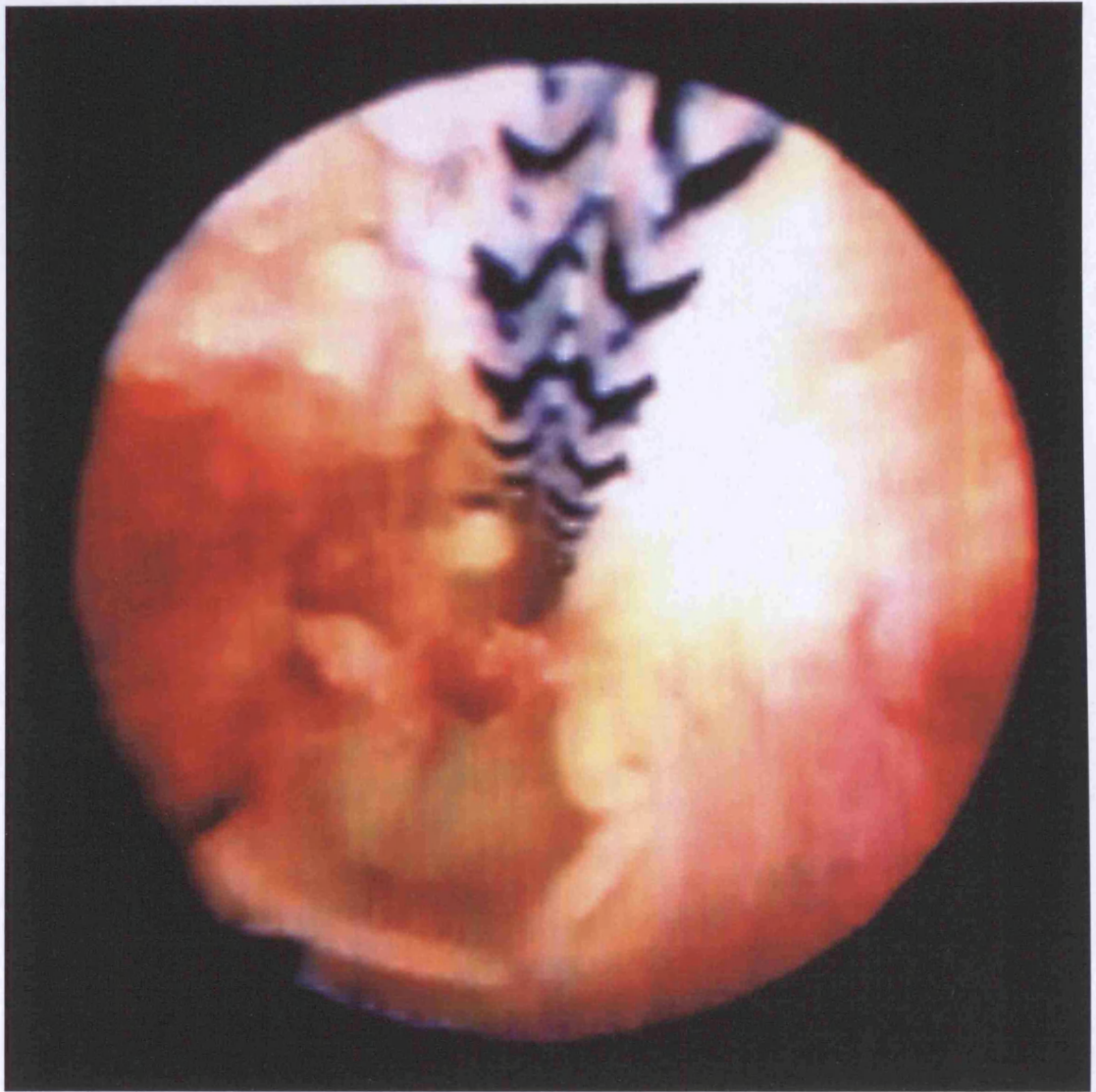
Figure 6.4   **Angioscopic assessment showing residual luminal thrombus.**
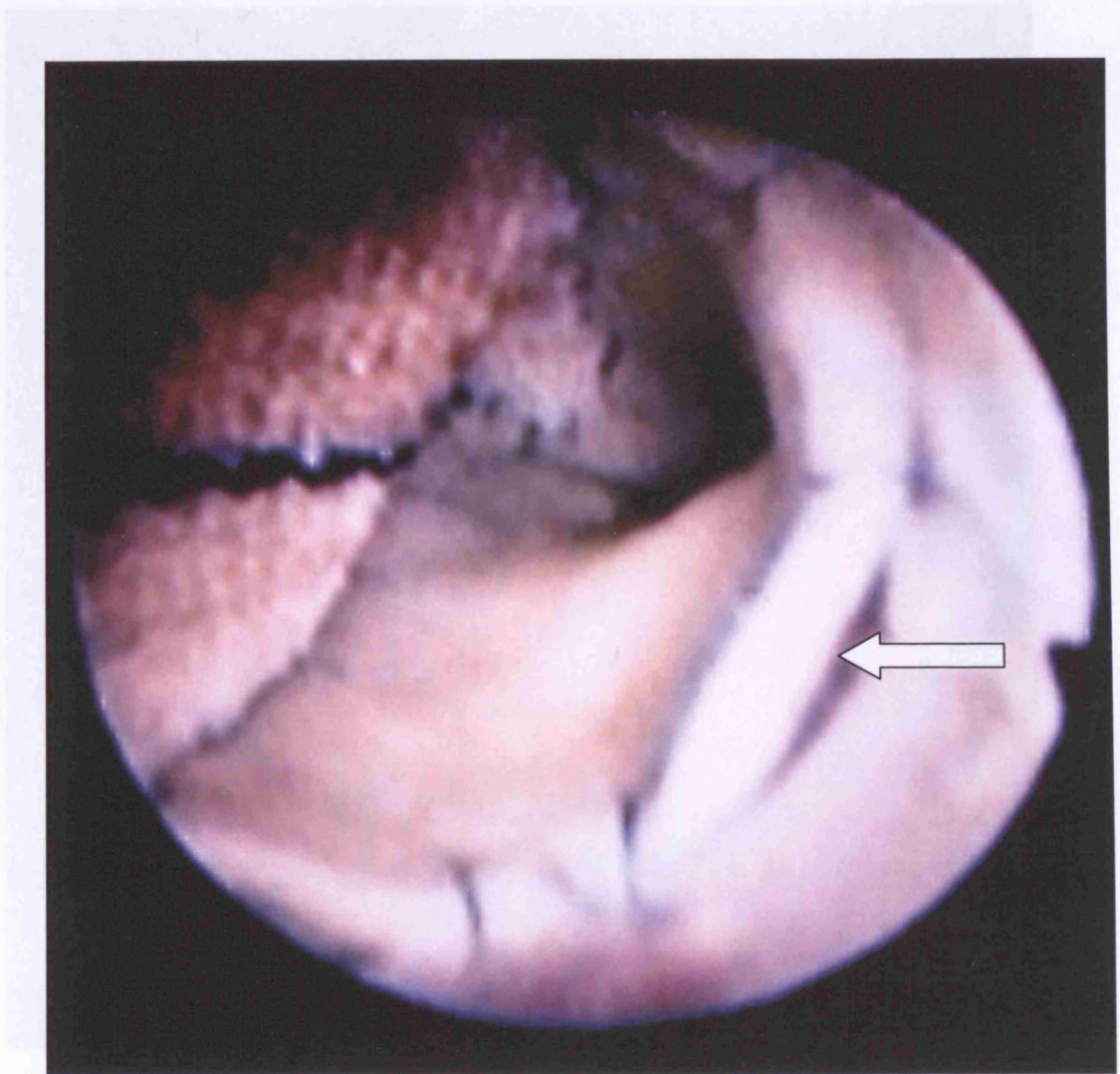
Figure 6.5   Angioscopic assessment showing elevation of the distal intimal step during irrigation with heparinised saline. This could become a nidus for platelet thrombus deposition and secondary embolisation.
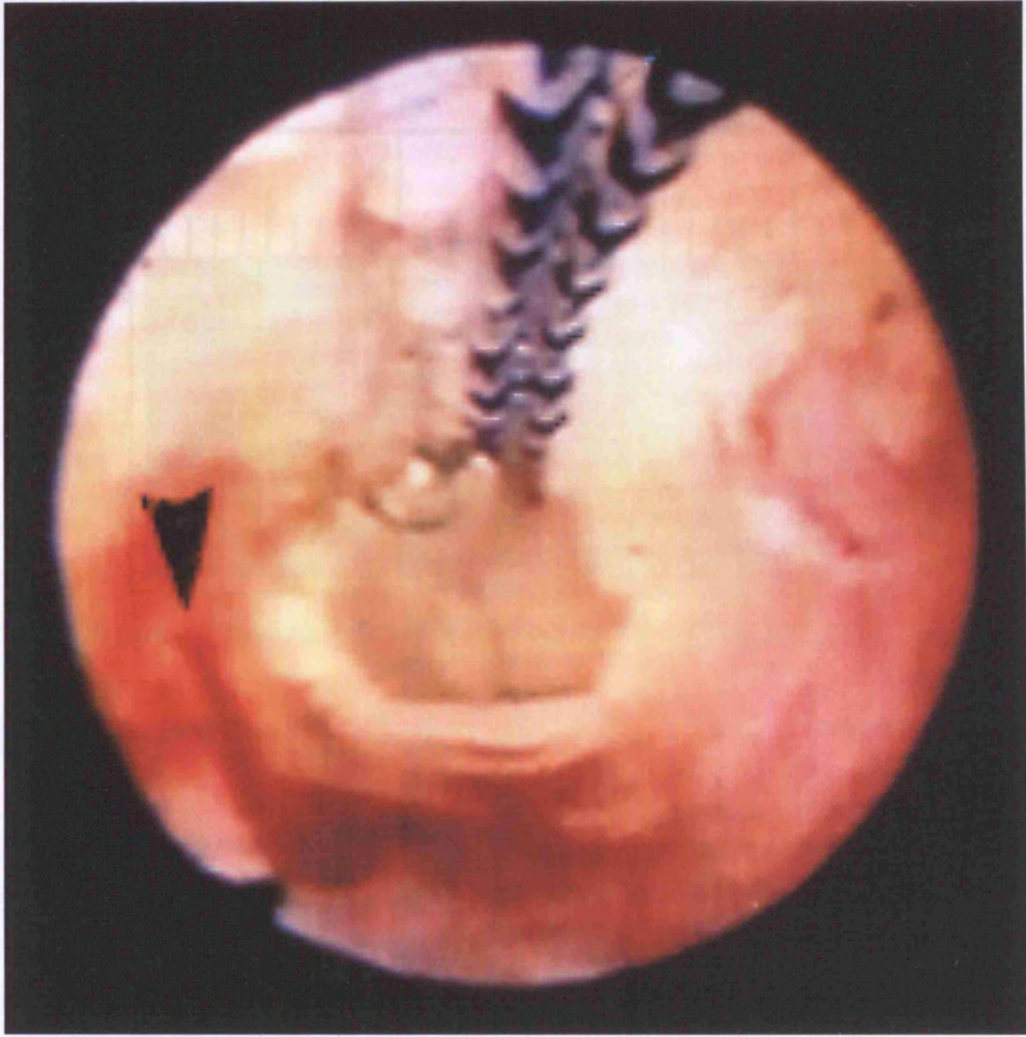
Figure 6.6 Angioscopic view of bleeding from the vasa vasorum. This may be the source of thrombus accumulation.
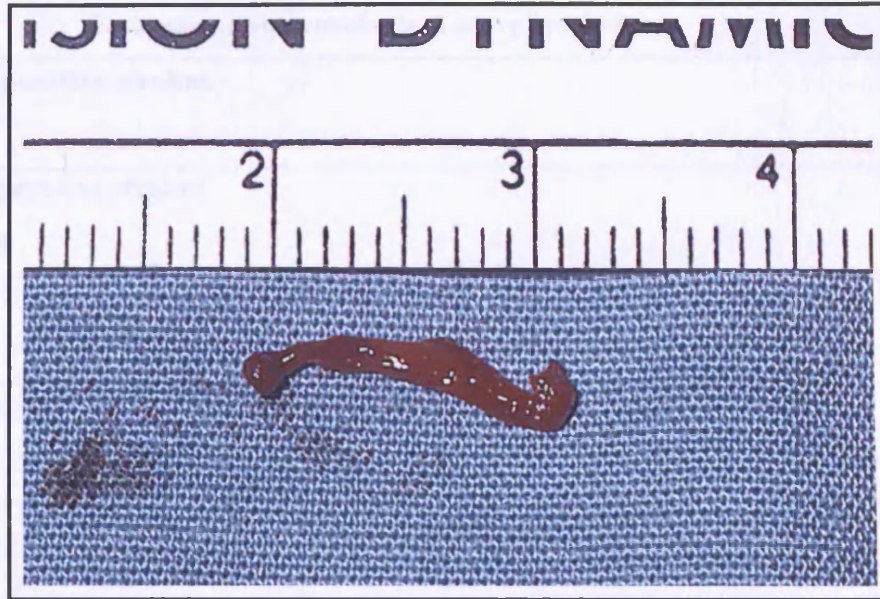
Figure 6.7 Residual thrombus removed from endarterectomy zone.

Impact on neurological morbidity.

In this study, no patient recovered from anaesthesia with a new neurological deficit, giving an intra-operative stroke rate of 0%. However, seven patients died or suffered a stroke in the 30-day postoperative period to give an overall death and disabling stroke rate of 1.6% and a death/any stroke rate of 2.8%. Table 6.3 details the perioperative neurological complications during this study.

The commonest cause of early morbidity was intracranial haemorrhage which was proven on CT scan in three patients. Two of these patients did not have an accessible TCD window, but blood pressure control had been normal throughout. Haemorrhage occurred on days 3 and days 7 post-operatively. The remaining patient underwent routine peri-operative TCD monitoring and angioscopic assessment, was discharged home on day 5 but suffered a fatal intracranial haemorrhage on day 23.

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Table 6.3   Peri-operative neurological complications.

(i) Intra-operative strokes.

None

(ii) Post-operative strokes

and deaths

Deaths (n=3)	Disabling stroke (n=1)	Non-disabling stroke (n=3)
Intracranial haemorrhage*	Unknown *#	External carotid thrombosis*
Intracranial haemorrhage*		Hyperperfusion stroke*
Intracranial haemorrhage		Postop MI/embolus

* Strokes which occurred prior to introducing a policy of 6 hours postoperative monitoring.

#Stroke apparent following weaning from ventilator.

Of the remaining four post-operative strokes, one underwent an uneventful CEA but had to return to theatre 2 hours later for evacuation of a neck haematoma. Immediately following this he became hypoxic and required continuing ventilation, following which he awoke with an ipsilateral monoparesis. Extracranial and transcranial Duplex studies were normal but a CT scan revealed a focal MCA territory infarct. This stroke occurred prior to the implementation of our policy of routine post-operative TCD monitoring so that we do not know if he had TCD evidence of ongoing post-operative embolisation.

Three non-disabling strokes (with full recovery within 72 hours) occurred in the post-operative period. The first followed thrombosis of the external carotid artery 5 hours post-operatively. At re-exploration, there was a tongue of thrombus extending into the ICA, which was acting as a source of embolism. This stroke again occurred prior to our implementing the post-operative TCD monitoring policy. A second patient was readmitted on day 7 with a classical hyperperfusion syndrome stroke (blood pressure 240/160, MCAV 140 cm/sec, normal Duplex, no intracranial occlusions on TCD and diffuse oedema on CT scan). The remaining patient was readmitted on day 9 with an ECG and enzyme proven myocardial infarct (normal

Duplex and TCD, focal MCA territory infarct on CT scan). In this patient we cannot reliably differentiate between a carotid or cardiac source for her focal embolism, but cardiogenic embolism was probably the likely cause.

In summary, the incidence of intra-operative stroke was 0%, the number of post-operative strokes and deaths was 7 (2.8%), however 5 out of 7 of these neurological complications occurred prior to the introduction of the post-operative TCD monitoring policy and of the remaining 2 patients, one suffered a fatal intracranial haemorrhage on day 23 and the other was readmitted on day 9 with a postoperative MI and a non-disabling MCA territory infarct.

6.4 DISCUSSION.

Following publication of the ECST/NASCET trials, the number of patients requiring CEA increased dramatically. Both the proven benefit over best medical therapy alone in patients with severe symptomatic stenoses and the heightened awareness that the trials created have led to the increase in referrals to surgeons. However the paradox remains that the very operation that is performed to prevent stroke can indeed cause a stroke. The margins for error are small and success depends on individual operators obtaining low morbidity and mortality rates consistently.

In order to develop a strategy for reducing the risk of stroke following CEA it is important to audit underlying patterns of peri-operative stroke with respect to timing and causation and thereafter to use this data to design and implement a systematic approach to prevention and/or early intervention.

Peri-operative strokes can be divided into two sub-groups. Intra-operative strokes (IOS) are apparent immediately following recovery from anaesthesia and must be attributable to some adverse event during the operation. Post-operative strokes (POS) can occur at any time after recovery from anaesthesia and usually follow thromboembolisation, hyperperfusion or haemorrhage.

Evidence suggests that the majority of peri-operative strokes occur intra-operatively [114], that patients presenting with a history of stroke, a residual neurological deficit, crescendo TIAs or those with haemodynamic compromise or ipsilateral CT scan infarction are at particular risk of IOS. The principle underlying cause of IOS is usually inadvertent technical error [144]. Awareness of this fact has led to the subsequent conclusion that patients at the highest risk of suffering an IOS are probably more vulnerable to the effects of hypoperfusion or microembolisation so that the margin for technical error is further reduced or possibly non-existent [119]. The fact that despite his/her best efforts the surgeon may be inadvertently responsible for causing and IOS is a difficult, but important concept to accept. Although most vascular surgeons are obsessive at undertaking some form of quality control assessment following femoro-distal bypass, few have adopted a similar strategy for carotid endarterectomy.

In 1992, Gaunt undertook a study in this unit to evaluate the role of quality control assessment in reducing the unit's rate of IOS, which had previously been 4%. That study concluded that (for us) a combination of TCD monitoring and completion angioscopy provided the highest yield in detecting technical error and determining the cause of perioperative morbidity and mortality. By the end of that study the IOS rate had fallen from 4% to 1%. However, although this study corroborated our own suspicions that experienced surgeons could be responsible for technical error, there remained a degree of scepticism as to whether quality control assessment could ever reduce the rate of IOS long-term and whether it was feasible or practical to implement such a programme. One aim of this thesis was to address this issue.

The answer to the question as to whether quality control assessment was associated with a sustained reduction in the rate of IOS appears to be yes. The rate of IOS that was 4% prior to Gaunt's study, fell to 1% during his study, and was further reduced to 0% during this latest study period. During this period of time the only consistent operative or technical factor that could have altered our IOS rate was the introduction of routine quality control assessment, and any counter argument that the improvement merely reflected increasing experience is unlikely, given that 50% of the CEAs were performed by vascular trainees rotating through the department.

The largest single factor in preventing IOS, although impossible to prove in the absence of a randomised trial, has been the identification and removal of residual luminal thrombus (2.5% cases in this trial) which accumulates on the highly thrombogenic endarterectomised surface during patch closure. The thrombus usually forms at the site of entry of the vasa vasorum into the endarterectomy zone.

The principle advantage of angioscopy is that it can be performed prior to restoration of flow so that intraluminal abnormalities, especially residual thrombus, can be corrected immediately, preventing propagation distally once blood flow is restored. Angioscopy is easy to use with no requirement for technical support. In our own unit the theatre staff set up the monitors and the surgeon performs the angiosopic assessment, which in this study was successful in 94% of patients. The original angiosope was, however, particularly prone to fibre breakage and poor image quality, but this problem was rectified by the introduction of a more robust flexible hysteroscope. Image quality with the latter is excellent and the scope does not need to be advanced up the ICA to visualise the distal endpoint of the endarterectomy, which could have been a potential problem with smaller calibre arteries. Moreover, the instrument channel allows grasping forceps to remove adherent thrombus under direct vision if necessary. This practice is however cumbersome and we now remove the thrombus by suction aspiration followed by repeat angioscopy.

Some surgeons, however, remained concerned that the angioscopic assessment will unnecessarily prolong the clamp time predisposing towards haemodynamic stroke. This study appears to show that this concern is unfounded. It appears that undetected residual luminal thrombus is more likely to cause an IOS than prolonging the carotid clamp time by a few minutes whilst angioscopic assessment is being performed.

Transcranial Doppler monitoring, in contrast to angioscopy, does require significant technical imput. Surgeons cite the need for technical support, inaccessible windows, delays to starting the operation, equipment getting in the way, bulky head-probe systems, probe dislodgement and scepticism that TCD rarely significantly alters outcome as reasons not to employ this technique. This study shows that we

were able to achieve continuous monitoring in 91% of our patients, suggesting that, with experience, most of these irritating problems diminish. The semi-circular head-probe protection system used in this unit, rarely interferes with the operative field and as technicians become more experienced, the incidence of inaccessible cranial windows fell to about 6%, while the time taken to insonate the artery correctly rapidly improves.

Gaunt's study provided evidence to support the role of TCD monitoring as a continuous quality control technique, detecting errors of surgical technique during the operation and detecting persistent particulate embolisation in the immediate post-operative period, an indication of incipient carotid artery thrombosis. Potentially harmful particulate embolisation, from an unstable carotid plaque, during the initial dissection phase of the operation can be detected by TCD. If the embolisation persists, the carotid artery may be clamped early in order to prevent an intraoperative complication. With increasing experience of TCD we have found that it has been possible to modify our surgical technique to reduce the number of emboli detected during the operation by 40%. During Gaunt's study in 1992, the median number of particulate emboli detected during CEA was 21 (95% CI 16 – 29), by 1995, the median number of particulate emboli had fallen to 9 per procedure (95% CI 7 – 14, ρ =0.00081) [169] (see Table overleaf). TCD provides an ideal quality control method when training junior surgeons, dissection of the carotid artery must proceed with great care to avoid embolisation from an unstable plaque. TCD provides clear audible evidence of embolisation warning the surgeon how careful he or she must be.

Operative phase	Group 1 (n=75)	Group 2 (n=75)	P value
Dissection	10 (4-14)	2 (1-5)	0.019
Shunt opening	7 (5-9)	4 (3-5)	0.003
During shunting	7 (4-11)	4 (2-7)	0.138
ECA flow restoration	8 (5-12)	4 (3-7)	0.078
ICA flow restoration	19 (14-27)	16 (12-21)	0.75
Skin closure	111(19 – 231)	Sample too small	N/A
Duration of shower	1.2 (0.9-6.4)s	1.5 (0.8-2.2)s	0.60
Total particulate	21 (16-29)	9 (7-14)	0.0008
Total gaseous	18 (14-24)	15 (11-19)	0.13
Total emboli	43 (33-55)	25 (19-31)	0.002

Table 6.4 **Experience with transcranial Doppler reduces the incidence of particulate embolisation during CEA. Group 1 monitored between 1992-1993, Group 2 monitored in 1995. Values are median (95 per cent confidence interval)** [170].

There are certain obvious criticisms that can be aimed at this study which need to be addressed. This was a purely observational study. A natural history study has not been carried out, we do not know that patients with identified technical errors would necessarily go on to suffer an intraoperative stroke. Ideally, in order to prove that the identification and correction of technical errors was solely responsible for the reduction in intraoperative stroke rate, a randomised trial should have been carried out. This would have involved implementing the monitoring policy as described, and then randomising those patients found to have a technical error to either correction of the technical error or not. This would have placed the surgeon in an ethically dangerous position, knowingly completing an operation that was technically flawed. Permission for such a study would not have been granted from the local Medical Ethics Committee, particularly in the light of the findings of Gaunt's Study, which had shown a drop in the intraoperative stroke rate following correction of these technical errors. Because of this it is not possible to state

categorically that the reduction in intraoperative stroke rate, was solely due to the identification and correction of these technical errors.

Analysis of this study should, ideally, include multiple regression analysis of the various risk factors for stroke, in order to assess whether the reduction in intra-operative stroke, between the two groups (those operated on prior to 1992 when no quality control assessment was in place, and those operated on after the introduction of the quality control programme) was significant. Unfortunately, all the data required to analyse this, is not available for the patients operated on prior to 1992. We are therefore not able to categorically say the fall in the intra-operative stroke rate is significant, it is however, encouraging that the intra-operative rate of stroke has remained low (1% during Gaunt's study; 0% in this current study).

Finally it should be noted from the results, that 2.8% of patients in this study did not undergo intraoperative TCD monitoring, and that 1.2% of patients did not have completion angioscopy, due to concurrently running operating lists and simultaneous CEAs. None of these patients developed a stroke. Following the completion of this study, operating lists have been reorganised, such that there are no longer any simultaneous operating sessions. This means that are ability to implement the quality control programme has improved.

6.5 SUMMARY.

In summary Gaunt's study was implemented because of the 4% intraoperative stroke rate, during CEA, prior to 1992. His study suggested that inadvertent technical error was probably the commonest underlying cause and that, a combination of TCD monitoring and completion angioscopy provided the maximum yield in terms of identifying these. During that study there was a fall in the IOS rate from 4% to 1%.

This observational, follow-up study has shown that the continued implementation of a rigorous quality control programme has sustained, and further decreased the intra-operative stroke rate to 0%. This quality control programme however, did not

reduce the rate of post-operative stroke, which has remained stable at almost 3%. The prevention of post-operative stroke became the aim of our next study.

Chapter 7.

Prevention of postoperative thrombotic stroke.

CHAPTER SEVEN: PREVENTION OF POST-OPERATIVE THROMBOTIC STROKE.

7.1 INTRODUCTION.

In the preceding chapter it has been shown how a policy of quality control assessment (TCD monitoring plus completion angioscopy) was associated with a fall in the intra-operative stroke rate of this unit from 4% to 0%. However, despite this protocol change there was no change in the rate of post-operative internal carotid artery thrombotic stroke, which remained constant at 3%.

Following a review of complications, between January of 1992 and August 1995, nine of 300 patients (3%) had a stroke as a result of documented occlusion of either the cervical ICA (n=7), the cervical ECA (n=1), or the ICA siphon (n=1). All underwent either re-exploration (n=8) or autopsy (n=1). Eight of the nine became symptomatic within 6 post-operative hours. In terms of underlying cause, thrombosis followed false aneursym formation caused by excessive endarterectomy in one patient (operation in 1992), whereas in a second patient occlusion of the carotid siphon at the site of a severe stenosis precipitated total ICA occlusion. A third patient had occlusion of her external carotid artery and had a tongue of embolising thrombus protruding into the ICA on re-exploration. In each of the remaining six cases, there was a large platelet rich thrombus found within the endarterectomy zone, which otherwise showed no evidence of technical error at exploration. In no patient was the thrombus primarily adherent to the patch angioplasty. Overall, four of the nine patients either died (n=2) or had a major disabling stroke (n=2), whereas four had a less severe stroke but with a residual deficit. Only one patient (external carotid artery occlusion with ICA embolisation) made a complete recovery within 7 days of onset.

Post-operative thrombotic stroke is thus an unpredictable and devastating complication, and there does not seem to be any consistent method of identifying those at risk of platelet rich thrombus forming within the endarterectomy zone, in the absence of technical error. There is evidence to suggest that platelets adhere to the exposed collagen of the endarterectomy zone within minutes of restoring carotid

blood flow [171] and that the maximal rate of adherence appears to be 1 hour after clamp release [172].

Previous work by Gaunt [152], suggested that post-operative ICA thrombosis was preceded by a phase of asymptomatic microparticulate embolisation, which could be detected by TCD ultrasound. It was predicted and subsequently demonstrated that a TCD diagnosis of embolisation could be used to permit early therapeutic or surgical intervention to prevent ICA thrombosis [152]. This work has subsequently been corroborated by Levi [173], who has shown that 60% of patients who have greater than 50 embolic signals detected per hour in the early post-operative period go on to have a stroke.

Initially we tried a routine policy of Dextran 40 therapy for all patients undergoing carotid endarterectomy. This policy had to be abandoned however, because of an increase in the number of bleeding complications and congestive cardiac failure secondary to Dextran 40. Within 2 weeks of abandoning this policy a further patient suffered a post-operative thrombotic stroke.

In an attempt to prevent this devastating complication, we made a further protocol change, based on a TCD diagnosis of ongoing embolisation. The aims were first to determine the overall incidence of post-operative embolisation: second, to see whether the rate of embolisation was altered by the administration of the antiplatelet agent dextran-40: and third to see whether such a policy altered our overall post-operative ICA thrombotic stroke rate.

Figure 7.1   Platelets adhering to endarterectomy zone.

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7.2 MATERIALS AND METHODS.

Between September 12th, 1995, and August 13th, 1996, 133 patients underwent CEA for correction of a severe (>70%) stenosis of the ICA. Of these, 100 were serially monitored for 6 hours after the operation using a modified TCD system that was specially designed for this project. The remaining 33 patients were not included in this study because of an inaccessible cranial window for TCD (n=12), refusal to give informed consent (n=1), or because two CEAs were performed simultaneously and only one modified TCD was available for post-operative monitoring (n=20). Ethical permission for this study was given by the Leicestershire Ethical Committee.

Table 7.1 gives details of the patient demographics.

Age	Range 44 – 84 years (Median 70 years)
Male:Female	65:35
TIA/Amaurosis	64
CVA	31
Asymptomatic	5
Treated hypertension	61
Ischaemic heart disease	36
Diabetic	8
Ipsilateral stenosis 70 – 79%	27
80 – 89%	33
90 – 99%	39
Contralateral occlusion	18

Table 7.1   Patient demographics.

The median age of the study group was 70 years (range, 44 to 84 years). Thirty-five were female, and 65 were male. Sixty-four had had a transient ischaemic attack or amaurosis fugax, 31 had had an established stroke in the MCA territory and only five were clinically asymptomatic prior to surgery. Treated hypertension was a risk factor in 61% of the patients, 36% had a history of ischaemic heart disease, and 8% were diabetic. An ipsilateral >70% stenosis was present in 99% of patients (70% to 79%, n=27; 80 to 89%, n=33; 90% to 99%, n=39). The remaining patient had a 65%, symptomatic stenosis with a contra-lateral occlusion. Overall, 18% of the study group had a contra-lateral occlusion or contra-lateral stenosis of >70%.

Aspirin therapy was not stopped before surgery. CEA was performed as previously described, under general anaesthetic and systemic heparinisation, with routine shunting and patch closure and with completion angioscopy. Continuous intra-operative TCD monitoring of blood flow velocity in the ipsilateral middle cerebral artery was performed using a 2MHz pulsed wave probe via the transtemporal window. The probe was secured with an elasticated headband and connected to a Scimed PC842 TCD system (Scimed, Bristol UK). During the operation, one of the research fellows experienced in TCD was present to supervise minor revisions in probe position and advise the surgeon of any unexpected phenomena. The surgeon was thereafter permitted to take whatever action he thought appropriate to correct the situation. For example, embolisation during the carotid dissection phase warned of unstable carotid plaques and permitted early ICA clamping, whereas shunt malfunction (kinking, sustained embolisation, low flow) was immediately identified and steps taken to correct it (exclusion of kinking, deflation of distal Pruitt shunt balloon, or augmentation of blood pressure to improve flow). In general we aimed to keep MCA velocity at 15cm/sec or greater throughout the procedure, preferably 20cm/sec or greater.

Patients recovered from anaesthesia in the operating theatre and were then transferred through to the high dependency unit or recovery area of theatre, with the TCD probe still in position. The patients were then monitored for a further 6 hours post-operatively. In theory, unregulated continued exposure to ultrasound could be potentially harmful, causing cranial heating and headache. To reduce the theoretical risk of continuous exposure to ultrasound waves, an integrated TCD system that

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could be programmed to automatically switch itself on for 10 minutes, every 30 minutes was developed by the Department of Medical Physics at Leicester Royal Infirmary. The system was programmed to automatically boot-up at the same preset focussing depth, gain setting and power rating on each occasion. All waveform data were recorded onto digital audio-tape for off-line analysis of embolic signals. In a study previously carried out by another research fellow in this unit, it had been shown that all emboli detected during the early post-operative period were exclusively particulate [174]. Accordingly, for the purposes of this study any emboli detected during the 6 hour post-operative period were assumed to be non-gaseous. Post-operative monitoring continued for 6 hours, during which any loss of signal was corrected by adjustments to the probe position by one of the research fellows experienced in TCD.

If a patient was found to have 25 or more emboli during any 10-minute period of monitoring, he or she was commenced on an incremental intravenous infusion of Dextran-40, initially at 20mls/hr. The threshold of 25 emboli was derived from previous work carried out in the department by Gaunt [152] [153]. If the rate of embolisation did not diminish, the infusion rate was gradually increased by 5ml/hr every 10 minutes up to a maximum of 40ml/hr. Patients were not routinely tested for Dextran hypersensitivity in this study. Once the Dextran infusion rate was stabilised, it was then continued at that rate for a further 12 hours. If, however, embolisation persisted despite incremental Dextran therapy, the protocol required that the carotid bifurcation be examined by Duplex if possible, or else the patient was considered for surgical re-exploration.

Any new neurological deficit persisting for more than 24 hours within the first 30 days after surgery was classified as a stroke and the severity scored at 30 days by a neurologist using the Oxfordshire Handicap Scale (OHS). The OHS scale is a modified version of the Rankin Score and takes into account the disability associated with dysphasia/aphasia. A stroke score of 0-2 was classified as non-disabling whilst a score of 3-5 was deemed disabling. Any patient suffering a peri-operative stroke was investigated by CT head scan, Duplex ultrasound plus TCD examination of the extra- and intra-cranial circulation. Patients suffering a fatal stroke underwent autopsy.

7.3 RESULTS.

No patient in this series was found to have any neurological deficit upon recovery from anaesthesia.

Number of emboli.

The table below summarises the number of patients in whom emboli were detected during the 6-hour period of monitoring. Fifty-two patients had no emboli detected at any time during the post-operative period, whereas 48% had one or more emboli detected. Overall, 23% had fewer than 10 emboli, 17% had between 11 and 50, 3% had between 51 and 100 emboli. Only 5% of patients had more than 100 emboli detected during the 6-hour period of monitoring.

No. of emboli	No. of patients	%
0	52	52
1 to 10	23	23
11 to 25	10	10
26 to 50	7	7
51 to 75	2	2
76 to 100	1	1
>100	5	5

Table 7.2   Incidence of post-operative embolisation.

Timing of emboli.

The figure overleaf shows that the onset of embolisation occurred primarily within the first two post-operative hours. Nineteen patients began to embolise during the first post-operative hour, whereas a further 24 began to embolise during the second post-operative hour. Thereafter, the chances of any patient beginning to embolise were very small, with only 5% of patients developing embolisation during the third post-operative hour. Of most practical importance was the observation that if embolisation had not begun by the end of the third post-operative hour, it did not begin to do so therafter. However, 10% of patients in whom embolisation had begun

in the first three post-operative hours had more than 10 emboli detected during the fourth to the sixth post-operative hours, including one patient who had sustained embolisation that required Dextran therapy.
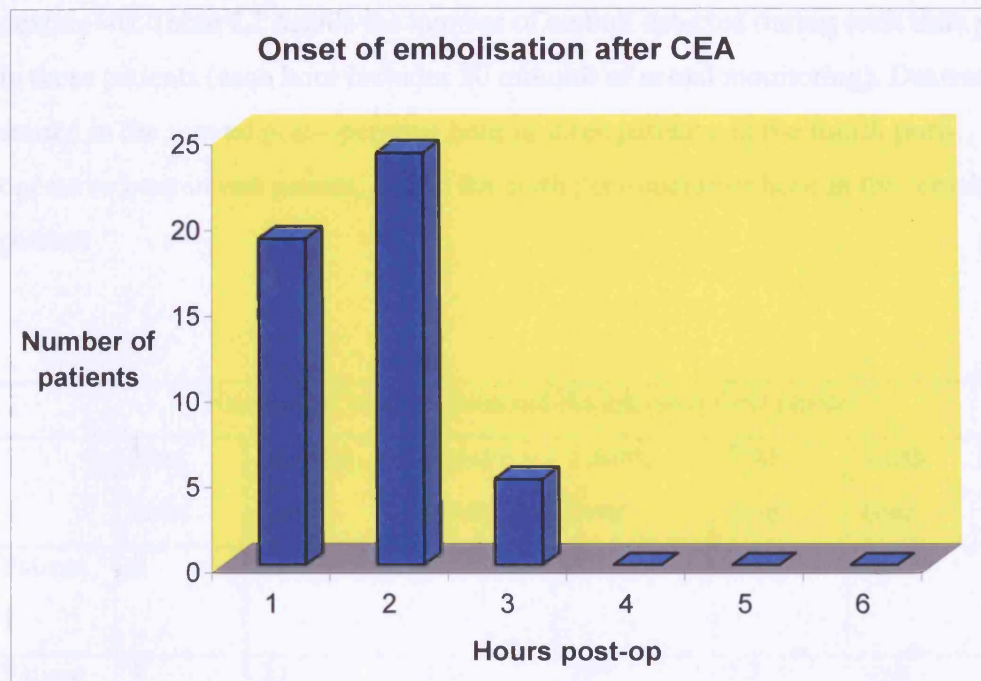
Figure 7.2 **Onset of embolisation.**

Onset of embolisation	Number of patients	Mean Rank
No Emboli	52	26.5
1st Hour	19	79.82
2nd Hour	24	73.73
3rd Hour	5	71.50
4th Hour	0	
5th Hour	0	
6th Hour	0	

Table 7. 3 **Kruskal-Wallis Test P value <0.001**

Intervention with Dextran-40.

Five patients had more than 25 emboli detected during any one 10-minute period of monitoring and were accordingly commenced on an incremental infusion of dextran-40. Table 7.2 details the number of emboli detected during each time period in these patients (each hour includes 20 minutes of actual monitoring). Dextran was started in the second post-operative hour in three patients, in the fourth post-operative hour in one patient, and in the sixth post-operative hour in the remaining patient.

	Number of emboli detected during each time period						
	First hour	Second hour	Third hour	Fourth hour	Fifth hour	Sixth hour	Total
Patient 1	0	15	0	1	6	101*	123
Patient 2	8	21	13	69*	14	108	233
Patient 3	0	71*	63	4	2	1	141
Patient 4	0	238*	16	27	14	12	297
Patient 5	0	317*	63	44	35	17	476

Table 7.4   **Effect of Dextran 40 on embolus count.**

*****Time period when Dextran was started.**

Figure 7.3 illustrates the effect of the dextran infusion on the ensuing embolus count rate. Note that in the hour before the dextran was started, the embolus count was 0 in three patients, thirteen in a fourth and six in the fifth. Thereafter the embolus count increased dramatically. However, after the institution of dextran therapy there was an immediate decline in the rate of embolisation. In one patient, (patient 2) an

initial fall was followed by a secondary rise in the rate of embolisation, necessitating serial increases in the infusion rate to 40ml/hr. Thereafter the rate of embolisation rapidly fell to zero. In this series none of the patients who received dextran-40 had any post-operative problems related to bleeding, cardiac failure or renal failure, which can be associated with dextran-40.
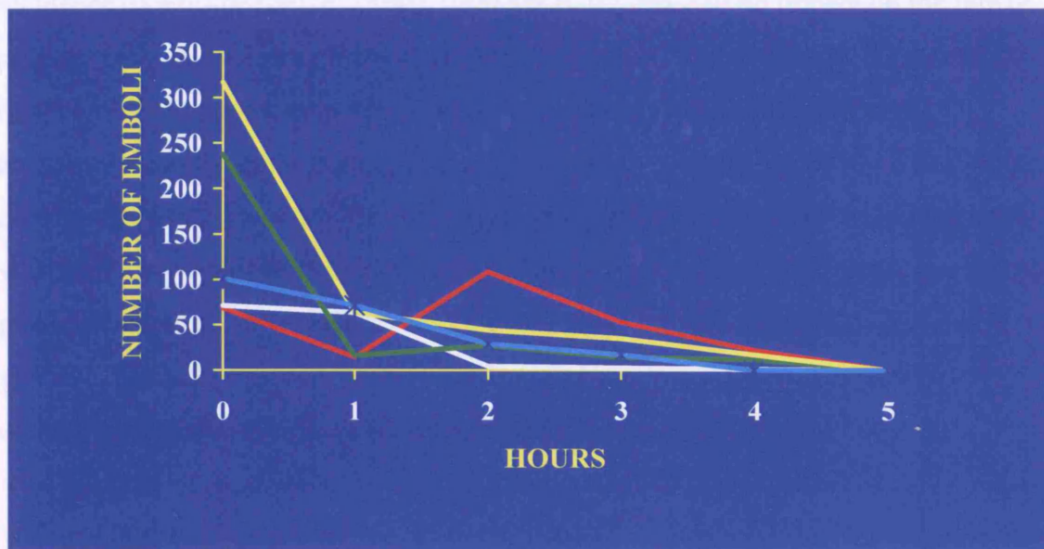
Figure 7.3   **Effect of Dextran infusion on embolus count.**

Dextran was started at time 0. In one patient (red line) the rate of embolisation increased after an initial fall, necessitating further increase in dose. Thereafter, rate of embolisation diminished, and eventually ceased in all patients. The effect of the Dextran infusion on embolisation was tested for significance using the Spearman's rank test, the correlation coefficient was -.822, giving a p value at 0.01.

Neurological complications.

None of the 100 patients recovered from anaesthesia with a new neurological deficit, and none suffered any post-operative neurological morbidity, giving an overall peri-operative neurological complication rate of 0%.

DISCUSSION.

Post-operative carotid artery thrombosis complicates up to 3% of carotid endarterectomies, often with devastating consequences. It usually manifests itself within 6 hours of the operation. In the previous chapter I have described how the introduction of a rigorous quality control programme significantly reduced the incidence of intra-operative strokes from 4% to 0% but had no impact on the rate of post-operative stroke, which remained constant at 3%. Gaunt's study [153] identified a small group of patients who developed asymptomatic persistent particulate embolisation in the early post-operative period and subsequently went on to develop carotid artery thrombosis. This finding has been confirmed by other investigators [173] who have shown that 60% of these patients with high embolic load in the immediate post-operative period will go on to thrombose their carotid artery. Significantly if you re-explore the thrombosed artery a friable platelet thrombus is found at the endarterectomy site but no evidence of underlying technical error.

We hypothesized that the introduction of an antiplatelet agent could help reduce the incidence of post-operative carotid artery thrombosis. Initially, the unit introduced a routine policy of post-operative Dextran therapy which, while abolishing all post-operative thromboses, was unfortunately associated with an increased incidence of neck haematomas and one death due to multiorgan failure. In the light of this we then implemented a policy of selective Dextran therapy in potentially high-risk patients guided by TCD evidence of sustained post-operative embolisation.

This study has firstly quantified the number of patients who develop post-operative embolisation following CEA. It has shown that although 48% of patients will have 1 or more embolus following the procedure, only a very small proportion, 5%, develop significant embolisation, predictive of progression on to carotid artery thrombosis. We have also shown that intervention with Dextran reduced, and subsequently stopped the embolisation in all patients in whom it was used. An important point to note was that in one patient, the rate of the Dextran infusion had to be increased in order to control the embolisation. This means that continued monitoring is required once the Dextran has been started in order to titrate the correct dose of Dextran required to control the emboli.

Significantly, this study also found that the rate of embolisation was maximal in the first two post-operative hours, and that if a patient had not begun to embolise by the end of the third post-operative hour, he or she is unlikely to do so thereafter ($p < 0.001$). This may be of most practical importance, as sustaining a monitoring policy such as this requires considerable imput from technical support staff. It may be possible to stop monitoring after 3 hours in those patients who have had no embolisation (52%), and only continue for a more prolonged period in those who have already started to embolise.

Ideally this study would have been randomised, with those patients who developed persistent particulate embolisation randomised to receive Dextran 40, or observed. This protocol would however have been unlikely to gain ethical approval in light of the fact that 60% of patients who have greater than 50 embolic signals detected per hour go on to suffer a stroke [173]. An alternative protocol would have been to randomise those patients who develop persistent particulate embolisation to receive either Dextran 40 or another antiplatelet agent, such as aspirin or clopidogrel. Such a study would however, require much larger numbers of patients to take part in it, as only 5% of patients in this study developed significant embolisation requiring intervention. Comparison of different antiplatelet agents in diminishing embolisation in the post-operative period, presents an opportunity for further research in the future.

Of most significance, this study showed that the introduction of routine postoperative TCD monitoring combined with selective Dextran therapy has reduced the incidence of postoperative stroke. No patient in this series of 100 patients undergoing CEA had any perioperative neurological complication at all. If this reduction in postoperative complications could be sustained the potential clinical benefit is significant. However, the resources required to continue this monitoring policy are considerable and not readily available, particularly in smaller units and in those units where fewer CEAs are performed. The cost-benefit ratio needs to be assessed. However, if as is suggested by these results the monitoring period could safely be reduced to 3 hours rather than 6 hours the burden of providing such an intense monitoring service may be reduced. The aim of the next

study was to assess if 3 hours of postoperative monitoring was as effective as 6 hours and continued to provide a significant reduction in the postoperative stroke rate.

Chapter 8.

Prevention of postoperative stroke – 3 hours monitoring.

CHAPTER EIGHT: THREE HOUR POSTOPERATIVE MONITORING.

8.1 INTRODUCTION.

In the previous chapter I have described how a policy of selective Dextran therapy in potentially high-risk patients, guided by TCD evidence of sustained postoperative embolisation was adopted into our unit. All CEAs were monitored for six hours, Dextran was used in 5% of patients and embolisation ceased in all and no patients suffered a carotid artery thrombosis. The six hours of postoperative monitoring posed considerable logistical problems and it would be clearly preferable to reduce this to a minimum in low risk patients. The pilot study showed that only 52% of patients embolised following CEA, and significantly that all patients destined to embolise would do so within the first 3 postoperative hours. Only 5% of patients developed significant embolisation requiring Dextran therapy. We therefore undertook a further prospective study to see whether adoption of a 3- hour monitoring policy was associated with any increase in the incidence of postoperative carotid thrombosis.

8.2 MATERIALS AND METHODS.

Between 20th August 1996 and 4th December 1997, 192 patients underwent either CEA (n=186) or carotid bypass (n=6) in the Vascular Unit at Leicester Royal Infirmary for the correction of a severe internal carotid artery stenosis. Fifty-three patients presented with a stroke (32%), 90 suffered a TIA or amaurosis fugax (54%), while 23 were asymptomatic (14%). A unilateral stenosis was present in 102 (61%), bilateral severe ICA stenosis was present in 35 (21%) while 29 (17%) had a contralateral occlusion. A history of previous myocardial infarction was present in 35 patients (21%), 53 (32%) were on treatment for angina, 101 (61%) were on treatment for hypertension, while 23 (14%) were diabetic. Table 8.1 overleaf, details the patient's demographics. All patients were on aspirin therapy, which was continued through their hospital stay. Permission for this study was given by the Leicestershire Ethics Committee.

TIA/Amaurosis	54%
CVA	32%
Asymptomatic	14%
Previous MI	21%
Treated ischaemic heart disease	32%
Treated hypertension	61%
Diabetic	14%
Bilateral severe stenosis	21%
Unilateral severe stenosis	61%
Contralateral occlusion	14%

Table 8.1   Patient demographics.

Endarterectomy was performed in the same manner throughout the study by a consultant vascular surgeon or higher surgical trainee under supervision using normocarbic, normotensive general anaesthesia and systemic (5000iu) heparinisation. All were routinely shunted (Pruitt-Inahara), the proximal and distal intimal steps were tacked down with 7:0 prolene (Ethicon) and all arteriotomies were closed with a Dacron patch (Vascutek). A small number of patients underwent a carotid bypass with reversed saphenous vein for the correction of very high disease, gross distal kinking or the presence of an excessively thinned arterial wall following endarterectomy.

Following endarterectomy and prior to final closure of the patch, the shunt was removed, the carotid vessels flushed with heparinised saline and then reclamped. A 5mm segment of the arteriotomy adjacent to the origin of the external carotid artery was used for angioscopic assessment using a 5mm diameter flexible hysteroscope (Olympus 1078-48). The policy of the unit was to remove any fragments of thrombus and repair any intimal flap>3mm. If any abnormality required correction,

the endarterectomy zone was routinely re-examined to confirm there was no residual abnormality.

Following recovery from anaesthesia, the patient was examined neurologically and transferred to the High Dependency Unit for further monitoring. Any new neurological deficit apparent upon recovery from anaesthesia was recorded and the patient assessed by a neurologist. Postoperative complications were similarly documented. Our protocol required us to investigate all patients awakening from anaesthesia with a new neurological deficit by colour Duplex and TCD. The decisison to re-operate remained at the discretion of the surgeon. All neurological deficits occurring in the postoperative period were investigated by colour duplex, TCD, CT scan or re-exploration and all patients were assessed by a consultant neurologist.

Patients were monitored continuously from induction of anaesthesia with TCD using a 2MHz pulsed wave probe insonating the ipsilateral MCA. Data were recorded onto digital audio tape for off-line analysis with particular emphasis on the number and character (air or particulate) of emboli.

Postoperatively ipsilateral MCAV data were recorded for 10 minutes every 30 minutes following restoration of flow. Any patient who had $\geq$ 25 emboli detected during any 10 minute period of monitoring or any patient in who emboli caused distortion of the MCA waveform (suggesting a large embolus) was commenced on an intravenous infusion of Dextran 40, starting at a rate of 20ml/hr. If the rate of embolisation did not diminish the infusion was gradually increased at increments of 5ml/hr every 10 minutes to a maximum of 40ml/hr. Patients receiving Dextran were monitored by TCD for 6 hours after restoration of flow. Once the Dextran infusion rate was stabilised, it was continued at that dose for a further 12 hours. If the patient did not have any emboli detected during the first three hours of postoperative monitoring then TCD surveillance was discontinued.

All patients were discharged home on aspirin therapy on the third to fifth postoperative day, and all were reviewed in the vascular clinic 6 weeks later.

Any new neurological deficit persisting for more than 24 hours within the first 30 days after surgery was classified as a stroke and the severity scored at 30 days by a neurologist using the Oxfordshire Handicap Scale (OHS). The OHS scale is a modified version of the Rankin Score and takes into account the disability associated with dysphasia/aphasia. A stroke score of 0-2 was classified as non-disabling whilst a score of 3-5 was deemed disabling. Any patient suffering a perioperative stroke was investigated by CT head scan, Duplex ultrasound plus TCD examination of the extra- and intra-cranial circulation. Patients suffering a fatal stroke underwent autopsy.

8.3 RESULTS.

Twenty-six of the 192 patients in the study period were not monitored in the early postoperative period because of inaccessible window, technical problems or because a simultaneous CEA was being performed elsewhere which required the presence of monitoring staff.

Numbers and timing of emboli.

Seventy-six patients (46%) had no emboli detected during the first 3 hours of postoperative monitoring, while 79 (48%) had 1 – 25 emboli, 7 (4%) had 26 - 50 emboli and 4 (2%) had ≥ 50 emboli detected. Of the 90 patients found to have one or more emboli, 43 (48%) had their first embolus detected within the first postoperative hour, 43 (48%) started to embolise in the second hour while only 4 (4%) had their first embolus detected in the third hour. Thus overall 95% of patients destined to embolise did so within the first 2 postoperative hours.

Dextran 40 therapy.

Nine patients (5%) were commenced on postoperative Dextran 40 therapy. Figure 8.2 illustrates the effect of Dextran on the ensuing embolus count. In the majority of patients the embolus count fell rapidly but in three patients, the rate of infusion had to be progressively increased either because the embolus count rate failed to diminish (n=1) or because the embolus rate actually increased (n=2). However, all

patients ceased embolising whilst on the Dextran therapy. One of the nine required monitoring for 8 hours overall, while a further 4 were monitored for a total of four hours. Thus overall, 97% of the 166 patients were monitored for only 3 hours, 2% for 4 hours and 1% for >4 hours.
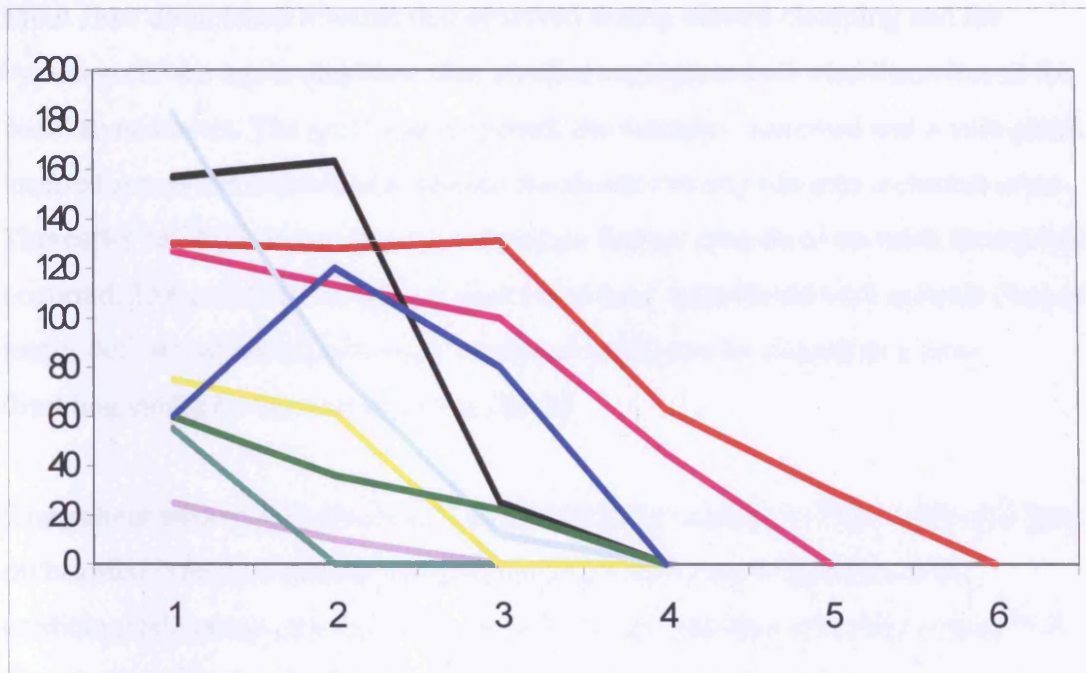
Figure 8.1   Effect of Dextran therapy. The three patients who required an increase in their dose of Dextran are shown by the red, blue and black lines. The remainder all stabilised on a base infusion rate of 20ml/h.

Again the effect of the Dextran infusion on embolisation was tested for significance using the Spearman's rank test. The correlation coefficient was -.518, showing a significance at the level of 0.01.

Operative morbidity and mortality.

One patient (0.6%) recovered from anaesthesia with a new neurological deficit. He had a contralateral occlusion and underwent a vein bypass for disease extending up to the base of the skull. During carotid clamping there was no MCA flow on TCD indicating inadequate collateralisation. Good MCA flow signals were obtained following restoration of flow but after 2 minutes, there were increasing embolic

signals and MCA velocity began to fall rapidly despite having commenced an on-table Dextran infusion. On-table angiography revealed thrombus within the mid-portion of the graft. The shunt was re-inserted, the thrombus removed and the graftotomy closed primarily after no obvious technical error was identified. Five minutes after secondary restoration of flow, profuse embolisation again recurred, MCA flow diminished towards that observed during carotid clamping and the bypass graft was again reopened after another angiogram indicated thrombus at the distal anastomosis. The graft was reopened, the thrombus removed and a vein patch inserted across the anastomosis despite the absence of any obvious technical error. Thereafter MCA flow was maintained and no further episode of on-table thrombosis occurred. The patient subsequently recovered from anaesthesia with aphasia (but no motor deficit), which significantly improved for him to be classed as a non-disabling stroke by the neurologist at day 30.

One patient who underwent an emergency CEA for crescendo TIAs suffered a fatal myocardial infarction on day 3 despite having undergone full preoperative cardiological assessment to give an overall 30-day operative mortality rate of 0.6%. One further patient suffered a disabling stroke on day 22 following a CT proven intracerebral haemorrhage. Neither of these two patients had received Dextran therapy in the postoperative period. One further patient received Dextran in the immediate postoperative period, which controlled his embolisation. However, on the fifth postoperative day he developed a monoplegia of his arm. Duplex scanning revealed diffuse irregularity of the distal endarterectomy/ICA and TCD revealed profuse cerebral embolisation. Dextran was recommenced at 50ml/hr and this rapidly controlled the embolisation and he went on to make a full neurological recovery (stroke grade 0 at 30 days by neurologist).

Thus the overall death and disabling stroke rate was 1.2%, while the death/any stroke rate was 2.4%.

8.4 DISCUSSION.

In 1995 we implemented a protocol whereupon Dextran was given to patients with sustained embolisation ($\geq$ 25 emboli in a 10 minute period) during a 6 hour phase of

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postoperative TCD monitoring, and who were therefore considered high risk of progression on to carotid artery thrombosis. In that study, 5% of patients required Dextran therapy and embolisation ceased in all patients. More importantly, no patient suffered a carotid thrombosis in that series. However, implementing a routine policy of 6 hours of TCD monitoring after carotid endarterectomy posed important logistical problems, not least manpower. We therefore undertook a second study, which took advantage of an observation that was made during the original work. It was noted that >95% of patients who were destined to embolise would do so within the first 3 postoperative hours. We therefore hypothesised that it may be feasible to reduce the postoperative monitoring to 3 hours without significantly increasing the risk of postoperative thrombosis.

The findings of this latest study appear to support this hypothesis. The vast majority of patients (96%) who are destined to have any emboli will start within 2 hours but very few (5%) will require intervention with Dextran. No patient in this series suffered a stroke due to carotid thrombosis within 30 days of surgery. These findings suggest that 90-95% of low risk patients require only 2-3 hours of monitoring while 5-10% of higher risk patients may require longer periods of assessment. Our evidence suggests however that only 1% will require prolonged monitoring beyond 4 hours.

This study has also shown that no single dose of Dextran will guarantee control of postoperative embolisation. In this series, three of nine patients (33%) required progressive increments in their Dextran therapy in order to control the embolisation and this is in accordance with our experience in the initial study. This therefore suggests that implementation of a routine policy of postoperative Dextran therapy will probably reduce the overall risk of postoperative carotid thrombosis, but it will almost certainly not abolish it. Moreover, this study is the first to demonstrate that certain patients may start to re-embolise after some days have passed. This particular patient was high risk for re-exploration, which might otherwise have dislodged the luminal thrombus. His initially high rate of embolisation on day 5 settled rapidly with the high dose Dextran and a check duplex scan at 30 days showed no evidence of any residual stenosis or thrombus.

In summary, until there is a more effective method for identifying those at highest risk of suffering a postoperative carotid thrombosis it would seem reasonable to monitor all patients for 2-3 hours postoperatively with TCD. The few, perhaps 5% with sustained embolisation will require Dextran therapy, the dose of which can then be modified according to the embolus count. Hopefully in the future it may be possible to modify the perioperative antiplatelet therapy in these patients so that the need for postoperative monitoring can be rendered obsolete.

Chapter 9.

Prospective Audit of Results.

CHAPTER NINE: PROSPECTIVE AUDIT OF RESULTS.

9.1 INTRODUCTION.

In the preceeding chapters I have described how the application of a rigorous quality control policy, routinely employed during carotid endarterectomy has maintained a reduction in the rate of intraoperative stroke and postoperative thrombotic stroke. The final, logical step in this study was to observe how these methods combine to affect the overall stroke rate of this procedure in this unit.

This chapter comprises data recorded from 500 patients all undergoing carotid endarterectomy. Of these 500 patients, 292 were personally monitored by myself, the remaining 208 patients were monitored by technical support staff and clinicians based at the Leicester Royal Infirmary during that time.

9.2 MATERIALS AND METHODS.

Between October 1995 and January 1999, 500 consecutive patients were entered into a prospective audit of outcome after CEA. Permission for this study was granted by the Leicestershire Area Ethics Committee.

Preoperative assessment

Patients were assessed in a single visit clinic where risk factor management and Duplex assessment was performed. Angiography was undertaken in <5% [175]. Aspirin (75-150 mg daily) was continued throughout the operative period. Duplex scanning was repeated within 24 hours of surgery and all patients had their TCD window marked. Two hundred and seventy five (55%) presented with TIA /amaurosis fugax, 146 (29%) with a stroke, while 79 (16%) were asymptomatic. Seventy asymptomatic patients (88%) had bilateral severe disease or a severe stenosis and contralateral occlusion. One hundred and twenty three (25%) had a history of myocardial infarction and 158 (32%) were on anti-anginal therapy. 310

patients (62%) were on treatment for hypertension and 74 (15%) were diabetic. A unilateral stenosis ≥ 70% was present in 317 patients (63%), 95 (19%) had bilateral stenoses ≥70%, while 88 (18%) had a stenosis ≥70% and contralateral occlusion.

TIA/Amaurosis	55%
CVA	29%
Asymptomatic	16%
Previous MI	25%
Treated angina	32%
Treated hypertension	62%
Diabetic	15%
Unilateral severe stenosis	63%
Bilateral severe stenosis	19%
Contralateral occlusion	18%

Table 9.1   Patient demographics.

Operative technique.

The basic technique of CEA (general anaesthesia, systemic heparinisation, loupe magnification, routine shunting (Pruitt-Inahara), patching (collagen impregnated Dacron (n=361) or groin saphenous vein (n=115)) and distal intimal tacking) has remained unchanged since 1988. This series of 500 CEAs comprises CEA (n=476) or carotid venous bypass (n=24) with 243 procedures being performed by a consultant and 257 by a vascular higher surgical trainee (HST) under supervision.

Intraoperative monitoring.

TCD monitoring was commenced after induction of anaesthesia using a fixed 2 MHz head probe (Scimed PC2-64B, Fishponds, Bristol, UK), which was protected by a semi-circular flat plate headguard. The surgeon and anaesthetist aimed to ensure that mean blood flow velocity in the middle cerebral artery (MCAV) was > 15 cm/sec at all times. The threshold of 15cm/sec was chosen because Halsey has shown this to correlate with loss of cerebral electrical activity [142]. If the MCAV was <15cm/sec following shunt insertion, the shunt was repositioned to exclude abutment against the distal ICA lumen. If the MCAV was still <15cm/sec, the blood pressure was therapeutically elevated by the anaesthetist. Any occasion where TCD significantly altered operative decision-making was recorded. All MCAV data were recorded on to digital audio tape for off-line analysis. Prior to complete patch closure, a 5mm space was retained adjacent to the orifice of the external carotid artery. The shunt was removed and all vessels back vented and irrigated with heparinised saline. The lumen of the endarterectomy zone was then inspected with a flexible hysteroscope (Olympus 1070-48,). Our policy for revision following angioscopy has remained unchanged since Gaunt's study and is to repair all intimal flaps > 3mm and remove any residual thrombi from the lumen.

Postoperative monitoring.

Following recovery from anaesthesia, the patient was transferred to the recovery area of theatre or the high dependency unit for a 3-hour period of TCD monitoring. All TCD data were recorded on to digital audio tape for off line analysis. Previous work in this department has demonstrated that emboli detected in the post-operative period are exclusively particulate [174] and that 3hrs monitoring was as effective as six hours. Dextran 40 was administered to any patient who had (i) ≥ 25 emboli in any 10 minute period or (ii) emboli that distorted the MCA waveform, which suggested that they were large. The threshold of ≥ 25 emboli per 10 minute period was based on the findings of Gaunt's original study [153]. Intravenous Dextran was administered as a 20ml bolus and then 20 mls/hr, increased stepwise every 10 minutes to a maximum of 40 mls/hr if there was no reduction in the rate of embolisation. Once the rate of embolisation stabilised or reduced, Dextran was continued at that dose for a further 12 hours.

Postoperative assessment.

Any new neurological deficit persisting for more than 24 hours within the first 30 days after surgery was classified as a stroke and the severity scored at 30 days by a neurologist using the Oxfordshire Handicap Scale (OHS). The OHS scale is a modified version of the Rankin Score and takes into account the disability associated with dysphasia/aphasia. A stroke score of 0-2 was classified as non-disabling whilst a score of 3-5 was deemed disabling. Any patient suffering a perioperative stroke was investigated by CT head scan, Duplex ultrasound plus TCD examination of the extra- and intra-cranial circulation. Patients suffering a fatal stroke underwent autopsy. As part of an internal quality audit, the latter 223 CEAs in this series were all evaluated preoperatively and again at 24 hours and 30 days following surgery by a neurologist. Prior to this, only those patients suffering a neurological defecit during or following surgery were examined by a neurologist.

9.3 RESULTS.

Intraoperative TCD.

Intraoperative TCD monitoring was achieved in 451 patients (90%). Thirty-seven patients (7%) had no cranial window, four (1%) were not monitored because two CEAs were performed simultaneously in adjacent theatres and there was insufficient equipment/staff. In eight patients (2%), there was either technical equipment failure or the wrong artery was insonated (most commonly the posterior cerebral artery).

It was difficult to objectively audit occasions when TCD altered operative/anaesthetic practice. Surgeons adjusted their technique if there was spontaneous embolisation during dissection and the outcome of this was impossible to audit reliably. Similarly, transient shunt kinking was immediately recognised and corrected. However, TCD was of particular benefit in eight (1.8%) patients. TCD identified one on-table cardiac arrest following electro-mechanical dissociation (normal ECG, zero MCAV) and it guided management during one case of anaphylactic shock when the systolic BP was only 26 mm Hg. In two patients, the external carotid artery was preferentially shunted, as the MCAV was < 10 cm/sec

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when the shunt was inserted into the internal carotid artery (ICA). In three other patients, MCAV was < 10 cm/sec following shunt insertion. In each, repositioning of the distal shunt limb or partial deflation of the distal shunt balloon increased MCAV to > 20 cm/sec. We assume that in these situations, the distal shunt lumen impinged on the distal ICA wall. Finally, TCD diagnosed one case of on-table thrombosis as the neck was being closed. (see later).

Completion angioscopy.

Nineteen patients (4%) did not undergo angioscopy because of equipment failure or because a reversed saphenous vein bypass had been performed. Following a minor protocol change during the study, all bypass patients now undergo angioscopy. Of the 481 undergoing angioscopy, 445 (93%) underwent a normal study, 21 (4%) had fragments of luminal thrombus removed, the source of which was bleeding from the vasa vasorum on to the highly thrombogenic endarterectomy surface. The thrombus was removed by suction aspiration and repeated irrigation with heparinised saline prior to repeat angioscopy. The distal anastomosis was revised in only 15 patients (3%) to correct either a distal intimal flap or an elevated distal intimal step. The median time taken to perform angioscopy was specifically audited in the last 80 CEAs in this series and was 51 seconds (95% CI 35 – 67s)

Postoperative TCD monitoring.

Four hundred and fifty one patients (91%) underwent 3 hours of TCD monitoring postoperatively. Overall, 313 (69.4%) had 1 or more emboli detected within 3 hours of surgery but 93% had <50 emboli detected in total. Of those destined to embolise, 179 (57%) started to embolise within the first hour, 122 (39%) in the second hour and 12 (4%) in the third hour. Twenty-two patients (4.9%) had >25 emboli/10 minute period (n=19) or large emboli which distorted the MCA waveform (n=3) and received adjuvant Dextran. Following Dextran therapy, the median embolus count fell rapidly (table 9.2). However, the dose of Dextran had to be increased in 7/22 patients (32%) in order to control the rate of embolisation. All patients destined to receive Dextran had started to embolise within the first two post-operative hours. No carotid thrombosis and no embolic stroke occurred in any of the 287 patients

with no emboli detected in the post-operative period. In addition, no carotid thrombosis occurred in any of the patients receiving Dextran. However, two patients receiving Dextran suffered a focal embolic stroke in the postoperative period (Table 9.3).

Number of emboli detected in 3 hours	Number of patients	(%)
none detected	187	41.5
1 – 20 emboli	195	43.2
21 – 50 emboli	37	8.2
51 – 100 emboli	16	3.5
101 – 200 emboli	6	1.3
201 – 300 emboli	4	1.0
300 + emboli	6	1.3

Table 9.2   Incidence of embolisation in the early postoperative period following carotid endarterectomy.

9.4 30-DAY COMPLICATIONS.

Intraoperative stroke.

One patient (0.2%) recovered from anaesthesia with a non-disabling stroke (case 9, table 3) having undergone a vein bypass to the skull base. He had zero MCAV during clamping indicating negligible collateral flow via the circle of Willis. Profuse embolisation started within minutes of flow restoration, MCAV fell rapidly to 3 cm/sec and a diagnosis of on-table thrombosis was made. Angiography revealed thrombus in the mid- section of the graft and this was removed (no evidence of underlying technical error). Despite intravenous heparin and Dextran, the graft re-occluded within minutes of flow restoration (thrombus in the distal graft) and a patch was placed across the distal anastomosis. Despite two episodes of on-table thrombosis and > 750 emboli, the patient recovered from anaesthesia with a dysphasic stroke but no motor/sensory deficit. (OHS 2 at 30 days). In the absence of TCD, the neurological deficit would only have become apparent when attempts were made to awaken the patient and the outcome would almost certainly have been far worse because of his negligible collateral circulation.

Postoperative complications.

Ten patients (2%) died (n=6) or suffered a non-fatal stroke (n=4) within 30 days of surgery having made an uneventful recovery from anaesthesia. None of the deaths followed thrombo-embolic events in the carotid territory. The commonest cause of death was intracranial haemorrhage (n=2,) or cardiac pathology (n=3) but none of these patients received adjuvant Dextran therapy.

case	DEATHS aetiology	timing	DISABLING CVA aetiology	timing	NON-DISABLING CVA aetiology	timing
1	ICH	day 3				
2	MI	day 3				
3	cardiac failure	day 5				
4	Brainstem CVA	day 7				
5	ICH	day 7				
6	cardiac failure	day 14				
7			MCA embolism	<6 hrs (*)		
8			ICH	day 23		
9					ICA thrombosis	on-table D
10					MCA embolism	day 5 D
11					cardiac embolism	day 9

(*) It is assumed that this stroke occurred during the phase of sustained embolisation while the patient was re-intubated and treated for severe cardiac failure. Because of this, therapeutic doses of dextran could not be administered.

(ICH = intracranial haemorrhage, MI = myocardial infarction, CVA = cerebrovascular accident)

D indicates a patient that received Dextran 40

Table 9.3   Aetiology and timing of perioperative complications.

Two of the four postoperative non-fatal strokes were disabling while two were non-disabling. One disabling stroke followed a CT proven intracranial haemorrhage (ICH) on day 23 (no Dextran given). The remainder suffered a CT documented carotid territory embolic stroke. The first developed profound cardiac failure following recovery and required immediate re-intubation and inotropic support. Within one hour there was evidence of sustained embolisation but only a small dose of Dextran was administered because of his cardiac failure. Accordingly, the rate of embolisation was uncontrolled and a hemiparetic stroke was apparent upon extubation (OHS score 3 on day 30). The second patient was discharged home on

day 3 but was readmitted on day 9 with a minor stroke. Duplex and TCD were normal and there was no evidence of ongoing embolisation but serial ECGs and cardiac enzymes indicated that she had suffered a recent myocardial infarction. A CT scan confirmed a focal infarct and it was suspected that this was cardio-embolic in origin. The third embolic stroke occurred in a 72 year old male who received Dextran in the early post-operative period. Embolisation was rapidly controlled with Dextran and no emboli were evident when TCD was repeated 24 hours postoperatively. On the fifth day he suffered an upper limb monoparesis and TCD again revealed profuse embolisation. In view of the inevitable neck oedema and the fact that his initial endarterectomy had extended high, he was treated with high dose Dextran (50mls/hour). This immediately controlled his embolisation. He made a rapid recovery thereafter and was discharged home on day 9 (OHS score 1 on day 30).

The table overleaf (Table 9.4) summarises the results from our series of 500 patients relative to presentation, degree of stenosis, the grade of operating surgeon, whether the assessor was a neurologist or surgeon, age and gender.

Overall the death and/or disabling stroke rate in this study was 1.6%. The death and/or any stroke rate was 2.2%, despite the fact that > 50% of the CEAs were performed by trainees under supervision. The incidence of ipsilateral carotid territory thrombo-embolic stroke was 0.8% (on-table carotid thrombosis n = 1, postoperative embolic stroke n = 3). If the potential cardiac embolic stroke is excluded, the rate of ipsilateral carotid territory embolic stroke was only 0.6%.

Parameter	Number	Death and/or Disabling Stroke	Death and/or Any Stroke
Presentation			
TIA/AFX	275	1.8%	2.18%
Stroke	146	2.05%	2.73%
Asymptomatic	79	0.0%	0.0%
Degree of stenosis			
unilateral	317	0.9%	1.6%
bilateral	95	2.1%	3.15%
contralateral occlusion	88	2.27%	3.4%
Operator			
consultant	243	1.65%	2.5%
supervised HST	257	1.56%	1.95%
Patient Assessor			
surgeon	277	1.44%	2.17%
neurologist	223	1.80%	2.24%
Gender			
Male	329	1.2%	1.8%
Female	171	2.3%	2.9%
Age			
Age <75 years	385	0.8%	1.6%
Age >75 years	115	4.3%	4.3%
Overall	**500**	**1.6%**	**2.2%**

Table 9.4   30-day operative risk following CEA.

9.5 DISCUSSION.

Prior to 1992, the 30-day risk of death/stroke after CEA in our unit was 6% with the majority, being apparent upon recovery from anaesthesia. Despite being within international guidelines, we were motivated to see if the risk could be reduced. This was the impetus underlying the current research programme. The operative technique (routine shunting, patching, tacking) has remained constant since 1988 and we are not aware of any scientific evidence that mitigates towards changing practice. Indeed, the role of the shunt and carotid patch has so dominated debate

that, for some, it has assumed the convenient role of 'scape goat' should problems arise, thereby absolving the surgeon from responsibility. We chose to evaluate the role of monitoring, partly because there was evidence that implementation of such a protocol might improve outcome [176] [177]. Our hypothesis was that implementation of a monitoring programme should reduce the operative risk by preventing technical error and was based on the following observations; firstly, intraoperative stroke has to be attributable to a specific event and, second, the majority of strokes follow technical error [144] to which high risk patients have little or no reserve [178].

When planning the study, we were aware that previous attempts to see if monitoring positively influenced outcome were largely unsuccessful. However, in retrospect, this probably reflected a failure to ask the right questions [179]. Firstly, most have been designed to identify clamp ischaemia so as to develop criteria for shunting even though haemodynamic failure is a relatively rare cause of stroke [114] [180]. Few have been developed to prevent thrombo-embolism. Second, there remains the flawed assumption that a single monitoring modality is superior to all others. Thirdly, despite awareness that technical error is the commonest factor underlying operative stroke, few surgeons include any form of QC assessment within their monitoring protocol. Thus, is it reasonable to blame EEG, SEP, TCD or awake testing for failing to prevent a stroke due to embolisation of luminal thrombus if no effort was made to remove this prior to restoration of flow? The rationale underlying monitoring and QC assessment is simple; the prevention of operative stroke is preferable to its treatment, i.e. once a stroke has occurred there may be little that one can do.

Advantages of the latest study include its prospective design, large numbers, standardised operative technique throughout, independent neurological assessment and the fact that it was preceded by discrete phases wherein a single change was made to the protocol followed by a further period of audit. To date, it is the largest series reporting the roles of TCD and angioscopy and the natural history of postoperative embolisation and progression on to carotid thrombosis. It has also highlighted the important but different causes of intra versus postoperative stroke, which is essential when designing a global monitoring protocol.

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In our original study, we observed that (for us) the combination of TCD plus angioscopy offered the maximum yield in terms of identifying technical error [154]. Prior to 1992, intraoperative stroke was our principal problem. However, since introducing a policy of angioscopy and TCD, only 2/800 CEAs (0.25%) have been complicated by intraoperative stroke and both followed on-table thrombosis. Despite being a non-randomised observational study, the large numbers involved suggest a positive causal relationship. The choice of TCD and angioscopy reflects their compatible roles as monitoring and QC techniques. The role of TCD is to (i) warn of particulate embolisation from unstable plaques during dissection thereby enabling modification of surgical technique [169], (ii) to ensure that MCAV is always >15cm/sec thereby minimising the risks of haemodynamic injury, particularly in the ischaemic penumbra [181] and (iii) to ensure optimal shunt function. There seems little point in using a shunt if one does not also ensure it is working. This and other studies suggest that shunt malfunction occurs in 1-3% of CEAs [115], and may have contributed towards the misconception that shunts cause as many strokes as they prevent! Finally, TCD is currently the only method capable of diagnosing on-table thrombosis, which was responsible for the single intraoperative stroke in this series. In the absence of TCD, the ensuing deficit would undoubtedly have been far worse. Once the learning curve has been mastered, TCD is unobtrusive and of considerable value training junior surgeons the skills reuquired for carotid surgery, and contributes towards reducing the incidence of particulate embolisation during the procedure [169].

The principle role of angioscopy is the identification and removal of luminal thrombus in 4% prior to flow restoration. Some of these thrombi have been surprisingly large, and resistant to blind irrigation with heparinised saline. There has previously been scepticism as to the source of these thrombi but this study has shown that they originate from the vasa vasorum (figure 6.6). Although completion Duplex and angiographic evaluation are alternatives to angioscopy, they can only be performed once flow has been restored, by which time any luminal thrombus may already have embolised to the brain. On a practical note, multifibre angioscopes are too fragile and the flexible hysteroscope is preferable. It usually only requires insertion into the endarterectomy zone as the distal views are otherwise quite excellent. In particular, there is no need to advance the scope over the intimal steps

and no patient in our overall experience of 800+ patients has suffered an intra-operative stroke due to a minute or two of added clamp time.

While we were pleased to note that the risk of intraoperative stroke was virtually abolished following the introduction of TCD and angioscopy, we were concerned to note that it had no impact on the risk of postoperative thrombotic stroke. By 1995, this was the single commonest cause of morbidity and mortality in our practice. In the past it had been assumed that thrombosis invariably followed surgeon error but when our patients were re-explored, we consistently found that all had a white/red friable platelet thrombus adherent to the endarterectomy zone with no evidence of underlying technical error [171]. Research suggests that platelets adhere to the endarterectomy zone within minutes of flow restoration [180]. However, evidence from three continents has now clearly shown that postoperative carotid thrombosis is preceded by a period of sustained or increasing embolisation [154] [152] [115] [173] [182] [183]. In particular, Levi demonstrated that up to 60% of patients with sustained embolisation would progress onto a stroke [173] and this is in accordance with our own experience [154]. In this latest series of 500 patients, 42% had no emboli detected in the first three postoperative hours and none suffered an ipsilateral carotid territory stroke within 30 days. However, 58% of patients had one or more emboli detected but, in 89%, the early phase of embolisation was rapidly self-limiting and fell to zero without therapeutic intervention and none suffered an ipsilateral embolic stroke. Only 22 (5%) of patients developed sustained rates of embolisation (>25 in 10 minutes) and were considered to have at least a 50% risk of progressing onto thrombotic stroke based on previous experience [154] [173]. Each received Dextran, and embolisation ceased in all but one, although the dose had to be increased in 32%. No patient in this series suffered a carotid thrombosis and none had to be re-explored. However two patients receiving Dextran suffered focal embolic strokes (Table 9.3). Finally, no patient destined to suffer an intracranial haemorrhage or major cardiac event received any Dextran in the post-operative period.

For us, the easiest aspect of the programme to implement has been the intra-operative TCD and angioscopy and we are convinced that this has contributed towards the significant decline in intraoperative stroke from 4% to 0.2%. What has been more difficult to implement has been the early postoperative TCD monitoring.

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In this respect, the key questions for the future include (i) why are certain patients destined to suffer a postoperative thrombo-embolic stroke despite the absence of technical error, (ii) does this susceptibility reflect ineffective (or absent) pre-operative anti-platelet therapy and (iii) are there any other agents superior to Dextran in controlling postoperative embolisation and progression on to thrombosis? In this series, two patients suffered an embolic stroke despite adjuvant Dextran therapy. In one, we were unable to administer an optimal dose of Dextran because of severe cardiac failure. Agents such as Rheopro (a monoclonal antibody that binds to glycoprotein IIa/IIIb receptors and inhibits platelet aggregation), or S-Nitrosoglutathione (a nitric oxide donor that appears to have relative platelet specificity)[184], may be useful alternatives in this difficult situation but neither have been evaluated in large scale studies. The second is the only case in our experience where sustained embolisation recurred some days after surgery and such a rare phenomenon may be impossible to anticipate and prevent. Ideally, however, it would be preferable not to have to monitor any patients postoperatively. Preliminary research in our unit suggests that the platelets of patients destined to suffer sustained embolisation have increased sensitivity to ADP stimulation [185], which offers the potential for preoperative pharmacological intervention and the avoidance of any postoperative TCD monitoring in the future.

In summary, the introduction of an integrated programme of monitoring has been associated with a 60% reduction in the 30-day risk following CEA since 1992. The incidence of thrombo-embolic stroke has fallen to <1% and intracranial haemorrhage and cardiac pathology now account for >50% of all perioperative complications. This sustained improvement is not simply a reflection of increasing experience as the majority of cases were performed by trainees and if, anything, we are now operating on higher risk patients than we were in the early 1990s when patients with mild and moderate stenoses were randomised in the European Carotid Surgery Trial. However, critics might argue that while our non-randomised trial results are impressive, similarly good results are achievable without any monitoring or quality control assessment [186]. Unfortunately, large community based studies do not support this statement [187], [188], [189], [190] and CEA is once again under critical worldwide review because of concerns that the results of the randomised trials (which used selected surgeons) may not be generalisable into routine clinical

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practice. Moreover, the overall operative risk in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) was 6.5% [168], i.e. identical to our own experience prior to implementing the monitoring and QC programme. Current evidence suggests that 93% of CEAs in the USA are now performed in non-NASCET centres with a mortality rate that is not only higher than that reported in NASCET but directly proportional to surgeon experience and annual workload [189] [190]. Data from Europe suggests a similar trend [191]. In this era of individual accountability, it is imperative that all surgeons quote their own results rather than those of the international trials to justify clinical practice. Unless steps are taken to ensure that the results of CEA are at least equal to that reported in the ECST and NASCET, the operation could once again fall into disrepute.

Chapter Ten.

Conclusions and prospects for future research.

CHAPTER 10: CONCLUSIONS AND PROSPECTS FOR FUTURE RESEARCH.

The European Carotid Surgery Trial and The North American Symptomatic Carotid Endarterectomy Trial studies were published showing that carotid endarterectomy was significantly better than medical therapy alone at preventing disabling strokes in patients with severe, symptomatic carotid artery stenosis. This has led to a dramatic increase in the number of patients referred for surgery, however, the authors of both studies emphasised that the benefit of carotid endarterectomy was dependent on a low rate of perioperative neurological deficits. Therefore the detection and elimination of perioperative complications became paramount.

Several large retrospective studies have identified a wide range of different mechanisms by which perioperative strokes could occur. The two main strategies that developed to reduce perioperative strokes were intraoperative monitoring and completion quality control.

In a previous study carried out in this centre, where a comparison of a variety of quality control techniques was made, across a cohort of patients, it was concluded that a combination of transcranial Doppler monitoring and completion angioscopy provided the highest yield in detecting technical error and determining the cause of perioperative morbidity and mortality. Transcranial Doppler was also particularly useful in detecting clinically significant embolisation during the dissection phase of the surgery and the early postoperative period.

The question that arose from this earlier work, was whether the routine application of continuous intraoperative transcranial Doppler monitoring and completion angioscopy during carotid endarterectomy would significantly reduce perioperative morbidity and mortality?

The studies reported in this thesis have shown that the continued implementation of a rigorous quality control programme, is not only possible, but has sustained and further decreased the intraoperative stroke rate in this unit to 0.2%. The intraoperative stroke rate prior to the introduction of this programme had been 4%. Although we cannot, categorically attribute the fall in stroke rate to the quality

control programme, due to a lack of a randomized trial. The fact that intraoperative stroke rate has remained persistently low in the last 500 patients suggests a positive causal relationship. The introduction of this quality control programme did not however reduce the postoperative stroke rate, which had remained consistently at 3%.

Gaunt, amongst others, has identified a period of sustained embolisation in the early postoperative phase, which provided an early warning of incipient carotid artery thrombosis. It was hypothesised that intervention at this stage could help reduce the number of patients suffering a postoperative stroke following carotid endarterectomy. The aim, therefore, of the second part of this study was to evaluate the role of routine postoperative transcranial Doppler monitoring in combination with selective Dextran therapy, at reducing the rate of postoperative embolisation and possibly the postoperative stroke rate.

In Chapter seven I have described how this study first quantified the number of patients who develop sustained embolisation following carotid endarterectomy. I have shown, that although 48% of patients had ≥ 1 embolus following the procedure, only a very small proportion, (5%), develop significant embolisation, predictive of progression on to carotid artery thrombosis. We have also shown that intervention with Dextran 40 reduced and subsequently stopped high-grade embolisation in most of the patients in whom it was used. However, this study has shown that in some patints the dose of Dextran required to stop embolisation may need alteration. Most significantly this study showed that the introduction of a routine policy of postoperative transcranial Doppler monitoring combined with selective Dextran 40 therapy reduced the incidence of postoperative stroke.

The study also showed that the rate of embolisation was maximal in the first two postoperative hours and that if a patient had not begun to embolise by the end of the third postoperative hours, he or she was unlikely to do so thereafter. This led us to carry out a further study to see whether adoption of a three-hour, postoperative transcranial Doppler monitoring policy would be as effective as a six-hour monitoring period at maintaining a sustained reduction in the rate of postoperative stroke.

Thes second study confirmed that only a small number of patients developed significant embolisation in the early postoperative period (5%), and that once again Dextran was effective at both stopping embolisation, although dose adjustment was again required in certain patients.Once again, the postoperative stroke rate remained low.

Finally a prospective audit of 500 consecutive patients, has shown that it is both possible to implement this policy of intraoperative transcranial Doppler monitoring, completion angioscopy and postoperative transcranial Doppler directed Dextran therapy routinely. Implementation of this policy has led to a sustained reduction in both the intraoperative and postoperative stroke rate producing an overall death and disabling stroke rate of 1.6% and a death or any stroke rate of 2.2%.

The studies included in this thesis are clearly open to critiscism in terms of the methodology used. Firstly in terms of prevention of intraoperative stroke, using a quality control programme, there is no evidence that correcting the technical errors detected by the programme prevented an intraoperative stroke. Ideally, a sequential cohort study (natural history study followed by further study with intervention), or a randomised trial comparing intervention to no intervention should have been carried out. It was felt that it would not be ethical to carry out such a study, as the surgeon would be knowingly completing a operation that was technically flawed.

In terms of prevention of postoperative stroke, again an ideal trial would have randomized those patients with sustained postoperative embolisation (5%), to receive Dextran therapy or nothing. Again, this was felt to be unethical, in light of evidence that 60% of these patients go on to have a stroke [173].

The final audit of 500 patients, revealed a death or any stroke rate of 2.2%, this is a 60% reduction from the death or any stroke rate of 6% prior to 1992. Ideally this reduction should be subjected to multiple regression analysis in order to test it's significance. Unfortunately due to incomplete data collection on patients prior to 1992 this has not been possible, therefore although the reduction in 30-day morbidity and mortality appears sizeable, it's significance cannot be proven.

This study has however raised further questions. Firstly, although Dextran 40 is effective at stopping postoperative embolisation, it may also cause serious side-effects, namely, congestive cardiac failure and renal failure which may be life-threatening. This could limit the application of Dextran 40 and requires a period of labour-intensive postoperative monitoring to ensure it is only given to those patients with sustained embolisation in the early post-operative period. Further research is required to see if other therapeutic options, with fewer side-effects, may be used to reduce and stop postoperative embolisation.

Secondly this study has identified that only a small group of patients develop sustained embolisation following carotid endarterectomy. Further research is planned to study this group of patients more, in order to try and identify a clotting abnormality, predisposing towards platelets adhering to the endarterectomy zone. If this is the case it may be possible to identify these patients prior to surgery therefore allowing a targeted postoperative monitoring policy or indeed an alternative therapeutic option.

It must be mentioned that since this study has been performed, the incidence of carotid artery stenting has increased significantly and is likely to expand further over the next few years. The publication of the SAPPHIRE Trial [99], earlier this year, has suggested that in high-risk patients, in the presence of cerebral protection systems for emboli, stenting may be as safe as carotid endarterectomy. No postoperative monitoring was performed for emboli following carotid artery stenting in this trial, but this may be an interesting area for further investigation using TCD. Is embolisation a significant problem following carotid artery stenting? If so, is this embolisation clinically significant, and will it respond to antiplatelet therapy, such as Dextran 40?

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