THE ASSESSMENT OF THE CEREBRAL CIRCULATON FOLLOWING STROKE

ANTHONY ROBERT KENTON

Submitted to the University of Leicester
for the degree of
Doctor of Medicine

1997

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

ACKNOWLEDGEMENTS

My sincere gratitude goes to the following:

Dr RJ Abbott for his moral and academic support and friendship both before and during my research post
Dr IF Pye, Dr P Critchley, Dr PAH Millac and Dr M Lawden for their academic and financial support

Dr AR Moody for his interpretation of the MR scans

All the staff in the MRI suite for the assistance in performing the scans which was invaluable and for their sense of humour

Dr ME Ardron for allowing me to study his patients

Mr NA Taub for his invaluable help with the statistical analysis

All concerned in the vascular studies unit for the use of the scanner and for performing many of the carotid ultrasound scans

Louise for all her support

STATEMENT OF ORIGINALITY

All the transcranial colour-coded sonography scans were performed by myself.

The carotid ultrasound scans were mainly performed by the technicians in the vascular studies department at the Leicester Royal Infirmary.

The magnetic resonance imaging scans were interpreted by Dr AR Moody.

The statistical analysis was performed by myself with the assistance of Mr NA Taub.

CONTENTS

Acknowledgements ii

Statement of originality iii

Contents iv

List of figures ix

INTRODUCTION 1

CHAPTER 1 CEREBRAL INFARCTION 5

1.1 Anatomy of the Cerebral Circulation 6

1.1.1 Internal carotid artery 6

1.1.2 Anterior cerebral artery 7

1.1.3 Middle cerebral artery 7

1.1.4 Posterior cerebral artery 8

1.1.5 Variations in the cerebral circulation 8

1.2 Epidemiology of Stroke 10

1.2.1 Definition 10

1.2.2 Incidence 10

1.3 Pathophysiology of Stroke 12

1.3.1 Vascular processes involved in cerebral infarction 12

1.3.2 Pathophysiology of cellular infarction 12

1.4 Treatment of Ischaemic Stroke 20

1.4.1 Thrombolysis 20

1.4.2 Neuroprotection 22

1.4.3 Other treatments 22

1.5 Prevention of Stroke 23

1.5.1 Primary prevention 23

1.5.2 Secondary prevention 24

1.6 Imaging Techniques in Acute Stroke 28

1.6.1 Computed tomography 28

1.6.2 Magnetic resonance imaging 29
1.6.3 Diffusion MRI 30
1.6.4 Perfusion MRI 31
1.6.5 MR spectroscopy 32
1.6.6 Positron emission tomography 33
1.6.7 Transcranial Doppler ultrasound 33

CHAPTER 2 PATIENTS AND METHODS 35
2.1 Patients 36
2.1.1 Inclusion and exclusion criteria 36
2.1.2 Patient details 39
2.2 Methods 40
2.2.1 Transcranial Doppler 40
2.2.2 Transcranial colour-coded sonography 46
2.2.3 General limitations of TCD and TCCS 56
2.2.4 Normal values for MCA velocity 59
2.2.5 Carotid ultrasound 64

CHAPTER 3 A COMPARISON OF TCCS AND MRA IN ACUTE STROKE 65
3.1 Background 66
3.1.1 MRA techniques 66
3.1.2 MRA in intracranial abnormalities 67
3.1.3.MRA and TCD 68
3.1.4 TCD and intra-arterial angiography 68
3.2 Aims of the Study 70
3.3 Subjects and Methods 71
3.4 Results 72
3.4.1 Patient details 72

3.4.2 TCCS and MRA 72

3.5 Discussion **83**

CHAPTER 4 MIDDLE CEREBRAL ARTERY VELOCITY AS A PROGNOSTIC INDICATOR IN ACUTE STROKE **86**

4.1 Background **87**

4.1.1 Stroke severity and outcome 88

4.1.2 Investigations and outcome 90

4.1.3 Patient profile and outcome 92

4.1.4 The use of scales in the assessment of outcome 94

4.1.5 Prognostic scales 100

4.1.6 Classification of stroke sub-type 102

4.1.7 The assessment of outcome 105

5.1.8 Transcranial Doppler studies of outcome 108

4.2 Aims of the Study **110**

4.3 Subjects and Methods **111**

4.3.1 Patient selection 111

4.3.2 TCCS 111

4.3.3 Clinical assessment 111

4.3.4 Assessment of outcome 112

4.3.5 Statistical methods 112

4.4 Results **113**

4.4.1 MCA velocity 113

4.4.2 Initial clinical assessment 113

4.4.3 3 month assessment 117

4.4.4 Clinical outcome and MCA velocity 117

4.4.5 Clinical outcome and initial clinical assessment 120

4.4.6 Comparison of MCA velocity and clinical assessment 123

4.5 Discussion **125**

CHAPTER 5 RECANALISATION OF THE MIDDLE CEREBRAL ARTERY: INCIDENCE, TIME COURSE AND THE EFFECT ON CLINICAL OUTCOME **130**

5.1 Background **131**

5.1.1 Historical perspective 131

5.1.2 Imaging studies in reperfusion 132

5.1.3 Summary of previous studies 138

5.2 Aims of the Study **139**

5.3 Subjects and Methods **140**

5.4 Results **141**

5.4.1 Patient details 141

5.4.2 Investigations 142

5.4.3 Time to recanalisation 143

5.4.4 Transcranial colour-coded sonography 144

5.4.5 Clinical outcome 149

5.4.6 Clinical outcome and time to recanalisation 150

5.5 Discussion **151**

CHAPTER 6 THE RELATIONSHIP BETWEEN VASCULAR PATHOLOGY AND STROKE TYPE **156**

6.1 Background **157**

6.1.1 Clinical manifestations of vessel disease 157

6.1.2 Middle cerebral artery-mainstem 158

6.1.3 Middle cerebral artery-main branches 159

6.1.4 Middle cerebral artery-cortical branches 160

6.1.5 Lacunar syndromes 162

6.1.6 Transcranial ultrasound studies 164

6.2 Aims of the Study **165**

6.3 Subjects and Methods **166**

6.4 Results 167
6.4.1 Total anterior circulation syndrome 167
6.4.2 Partial anterior circulation syndrome 170
6.4.3 Lacunar syndrome 172
6.5 Discussion 174

CHAPTER 7 CONCLUSIONS 177
7.1 TCD versus TCCS 178
7.2 TCCS and MRA 179
7.3 Prognosis and MCA Velocity 180
7.4 MCA Recanalisation 181
7.5 Vascular Pathology 182
7.6 Future Role of TCCS 183

APPENDIX 184

BIBLIOGRAPHY 188

LIST OF FIGURES

Chapter 2

1. The Diasonics ultrasound scanner 48

2. TCCS of the basal cerebral arteries 52

3. Doppler waveform of the MCA 55

4. Mean velocity calculation 55

Chapter 3

1. MRA of the basal cerebral arteries 77

2. MRA of MCA occlusion 77

3. Colour duplex ultrasound of internal carotid artery occlusion 78

4. MRI of MCA territory infarction 78

5. Spectral Doppler display of MCA branch occlusion 79

6. MRA of MCA mainstem attenuation 80

7. MRA of MCA branch occlusion 80

8. TCCS showing filling of the MCA via ACA collateral flow 81

9. MRI showing infarction in an MCA branch vessel territory 82

Chapter 4

1. Spectral Doppler display of MCA 114

Chapter 5

1. TCCS of proximal MCA occlusion 145

2. Spectral Doppler display demonstrating hyperaemic flow in the MCA 146

3. TCCS of the basal cerebral arteries showing MCA recanalisation 146

4. Spectral Doppler display of ACA 148

Chapter 6

3. MRI of cerebral haemorrhage 169

5. MRI of a patient with a PACI 171

7. MRI demonstrating a lacunar infarction 173

INTRODUCTION

INTRODUCTION

The diagnosis of many medical conditions relies mainly on the history and physical examination, with only a few diagnoses being made on the results of investigations. However, special investigations often allow the underlying pathological processes to be better understood. This research project is concerned with the non-invasive imaging of the cerebral circulation following stroke. Cerebrovascular disease has traditionally lagged behind cardiac disease and cancer (the other two most common fatal disorders in the developed world) in terms of research, political and public interest. This now seems to be changing as stroke is enjoying a higher profile. It has been singled out as one of the target diseases in The Health of the Nation, it has been the focus of some of the largest randomised controlled trials (so called 'mega-trials') ever conducted and new imaging techniques have allowed the pathophysiology to be studied in minute detail. In particular, computed tomography (CT) and magnetic resonance imaging (MRI) have contributed to the better understanding of the disease process. In most circumstances, they have replaced older, invasive techniques, such as angiography.

Transcranial Doppler (TCD) ultrasound was first reported in 1982 (Aaslid et al. 1982) while the newer technique of transcranial colour-coded sonography (TCCS) was first described in 1990 (Bogdahn et al. 1990). Both TCD and TCCS are used routinely in many European countries (especially Germany, Italy and France) as well as the USA but have not found a niche in the UK. This probably reflects the scepticism that TCD does not offer the physician a useful tool in the routine clinical setting (Bornstein and Norris, 1994). However, TCD has been employed in the UK for the monitoring of patients undergoing carotid endarterectomy (observing the number and type of emboli in the middle cerebral artery) and in patients with subarachnoid haemorrhage (determining the timing of vasospasm) and there have been several papers published on these topics. However, TCD has rarely been used in the setting of acute stroke in this country. TCCS is used even less than TCD and in the UK there have not been any publications on the use of TCCS outside this

centre, although there have been several papers published on the use of TCCS from European and American centres.

Improvements in MRI have resulted in new MR techniques becoming available in the research and clinical setting. Diffusion-weighted imaging (DWI) and perfusion MRI allow the degree of tissue ischaemia and the cerebral blood flow to be measured, while MR angiography is able to image the intra and extracranial vessels. Perfusion MRI is a measure of the brain's microcirculation while MRA and TCCS reflect the changes occurring in the major cerebral arteries. By repeating these measurements over a period of time, the natural history of the circulatory changes following stroke can be elucidated.

A large number of trials assessing the efficacy of thrombolysis in acute stroke were being conducted during the time that this study was being performed. They were based on the assumption that early reperfusion of ischaemic tissue would lead to a better clinical outcome. TCCS and the novel MR techniques described above may be invaluable investigations in this setting. The patency of the cerebral vessels can be assessed with TCCS and MRA, the degree of ischaemia can be measured with DWI and overall cerebral blood flow measured using perfusion MRI. These techniques were not used in these trials. This was mainly because all the trials imposed either a 3 or 6 hour time window within which the patients had to have a CT scan and be randomised. This did not leave sufficient time for other tests to be performed. Additionally, these novel techniques are not routinely available in many centres. The results of the thrombolysis trials were disappointing, with only one trial showing that thrombolysis was effective in reducing morbidity and mortality (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). Better patient selection may have led to more favourable results in the other trials. Patients could only be selected according to clinical assessment and the results of investigations. CT scanning was obligatory in all studies in order to differentiate cerebral haemorrhage from infarction. However, CT scans are usually normal if performed within a few hours of stroke. It was suggested that one possible method of identifying patients that would benefit from thrombolysis would be to perform novel MR imaging, such as DWI and perfusion MRI, prior to treatment (Baron et al. 1995). This is impractical in everyday clinical practice due to the availability and

cost of MRI. It would seem essential that, if further thrombolytic trials are to be conducted, more sophisticated investigations will have to be carried out. TCCS offers a non-invasive, rapid and relatively cheap method of imaging the cerebral circulation.

This purpose of this research project is to assess the cerebral circulation following stroke using TCCS. It is hoped that this technique can be used to identify the underlying vascular pathology in stroke, to follow up the changes in the cerebral circulation over time and to identify whether these changes can be used as a guide to prognosis. TCCS may prove to be an invaluable investigation in the assessment of the acute stroke patient and may help identify a sub group of patients who may benefit from, an otherwise, potentially harmful treatment.

CHAPTER 1

CEREBRAL INFARCTION

1.1 ANATOMY OF THE CEREBRAL CIRCULATION

The cerebral circulation is divided into the anterior and posterior circulation. The anterior circulation is supplied by the carotid vessels and the posterior circulation is supplied by the vertebrobasilar system. The two systems join to form the circle of Willis.

1.1.1 Internal Carotid Artery

The internal carotid artery (ICA) originates from the common carotid artery at the level of C3-C5. It courses superomedially to enter the petrous portion of the temporal bone just anterior to the jugular foramen in the skull. It travels through this bone in the carotid canal, initially running vertically, then making an anterior curve to run more horizontally. After emerging from the apex of the petrous bone, the ICA crosses over the foramen lacerum to enter the cavernous sinus. Here, the vessel runs medially towards the posterior clinoid process of the sella turcica and then turns sharply anteroinferiorly. It then turns sharply again this time superiorly, running adjacent to the anterior clinoid process. These two sharp bends form an 'S' shape and are known as the carotid siphon. Two small branches are given off in the cavernous sinus: the meningohypophyseal trunk and the lateral main stem artery. The latter artery can form anastomoses with the external carotid artery system. The ICA leaves the cavernous sinus by piercing the dura mater and entering the subarachnoid space. It immediately gives off the ophthalmic artery which runs anterolaterally into the optic canal and towards the orbit. The ICA then runs superiorly in the supraclinoid region. Here, the second major branch of the ICA is formed: the posterior communicating artery (PCoA). This vessel runs posteromedially towards the tentorial incisura. The origin of the PCoA is a common site of both nonaneurysmal dilatations of the vessel, called an infundibulum, and true aneurysms. The final supraclinoid branch of the ICA is the anterior choroidal artery. This vessel runs around the uncus of the temporal lobe before entering the lateral ventricle.

The terminal ICA then splits into two major branches: the anterior and middle cerebral arteries.

1.1.2 Anterior Cerebral Artery

The anterior cerebral artery (ACA) can be divided into two segments: A1 and A2. The A1 segment lies between the ICA bifurcation and the anterior communicating artery (ACoA) and the A2 segment lies distal to the ACoA. The A1 segment arises just above the anterior clinoid process and then runs medially and forwards and crosses over the optic chiasm. Just distal to the chiasm, it enters the interhemispheric fissure to join the ACoA. The average length of the A1 segment is 13 mm and it has an average diameter of 2.6 mm (Perlmutter and Rhoton, 1976). The proximal part of the A1 segment is rich in small perforating branches known as lenticulostriate arteries. These vessels supply the anterior and posterior limbs of the internal capsule, hypothalamus and pallidum (Perlmutter and Rhoton, 1978).

The ACoA is a short artery (average length: 3.3 mm, average diameter: 1.4 mm) which joins the two ACAs in the interhemispheric fissure (Perlmutter and Rhoton, 1976). Its perforating branches supply the corpus callosum and anterior hypothalamus.

The A2 portion of the ACA runs sharply anterosuperiorly towards the callosal genu. It gives off several cortical branches, including callosomarginal, pericallosal and orbitofrontal arteries. The callosomarginal artery travels parallel to the pericallosal artery and gives rise to two or three major cortical vessels supplying the medial aspects of both the frontal and parietal lobes. In 18-60% of hemispheres, the callosomarginal artery is absent.

1.1.3 Middle Cerebral Artery

The middle cerebral artery (MCA) is the largest of the intracerebral vessels and supplies 80% of the cortical blood flow. It runs for 18-26 mm as a single stem or trunk before giving off the penetrating lenticulostriate branches. The trunk then divides into either two (78%), three (12%) or multiple (10%) branches. The MCA can be divided into four segments according to its course over major brain landmarks (Gibo et al. 1981). The M1 segment consists of the entire MCA mainstem up to and sometimes including the initial short segments of the post-bi or-trifurcation. The branches then turn to form a right angle (the genu) and are known

as the M2 segment. This courses over the surface of the insula and terminates at the circular sulcus. Most of the cortical branches arise from the M2 portion. The M3 portion runs from the circular sulcus to the lateral surface of the Sylvian fissure. The M4 segment starts as the branch vessels leave the Sylvian fissure and includes the entire remainder of the courses of the vessels.

There are twelve superficial, cortical subdivisions of the MCA which supply wedge shaped areas of cortex. These branches do not tend to form collaterals with each other. However, as the branches become finer, they eventually form anastomoses with terminal pial vessels of the ACA and PCA in the hemispheric border zones.

1.1.4 Posterior Cerebral Artery

The posterior cerebral arteries (PCA) are the major source of blood supply to the midbrain, thalamus, occipital lobes, inferior and medial temporal lobes and posterior inferior parietal lobes. The two PCAs are formed from the terminal branching of the basilar artery. The PCA curves laterally around the midbrain and is termed the P1 segment until it meets the posterior communicating artery (PCoA). The P1 segment gives off thalamoperforating vessels which supply the medial portions of the midbrain and the posteromedial thalamus. The P2 portion runs through the ambient cistern around the midbrain. It gives off thalamogeniculate and posterior choroidal arteries. Then the PCA gives off four cortical branches: anterior temporal, posterior temporal, parieto-occipital and calcarine arteries. These supply the hippocampus, medial temporal lobe, occipital lobe and medial inferior parietal lobe.

1.1.5 Variations In The Cerebral Circulation

Variations in the anatomy of the classic circle of Willis are common and may be found in up to 80% of brains (Riggs and Rupp, 1963). The ACoA has been reported as being absent (0.2-2%), hypoplastic (1-37%), duplicated (10-43%) or plexiform (6-9%) (Sawada and Kazui, 1995). The lack of a properly functioning ACoA can lead to an impairment of interhemispheric collateral flow. The ACA can be affected in similar ways to the ACoA, although less frequently.

Anomalies of the MCA are rare, occurring in less than 3% of the population (Saver and Biller, 1995). The most common abnormality is duplication of the MCA with the second vessel arising from the ICA. The MCA is absent in 0.3% of the population.

The PCA can exist in a foetal form in around 10% of people (Hoyt et al. 1974). In this case, the P1 segment becomes hypoplastic and smaller than the PCoA. The PCoA itself can be absent or hypoplastic on one or both sides.

The left vertebral artery tends to be slightly larger than the right artery and in 10% of people, one vessel is hypoplastic. The point at which the two vertebral arteries combine to form the basilar artery varies greatly and both vessels can have a very tortuous course.

1.2 EPIDEMIOLOGY OF STROKE

Stroke is the third commonest cause of death in the UK (behind ischaemic heart disease and cancer) and the leading cause of physical disability. It imparts a huge financial burden on the state and it has recently been singled out as a priority in The Health of the Nation (Secretary of State for Health, 1991).

1.2.1 Definition

Stroke has been defined by The World Health Organisation as a clinical syndrome that is characterised by the rapid onset of focal and/or global signs and/or symptoms of loss of cerebral function lasting more than 24 hours or leading to death that has no other cause other than a vascular origin (Hatano, 1976). This definition encompasses cerebral ischaemia, subarachnoid haemorrhage (SAH) and primary intracerebral haemorrhage (PICH). It does, however, exclude SAH which presents with only a headache i.e. no focal signs. The majority of this thesis will concentrate on ischaemic stroke rather than on SAH and PICH.

1.2.2 Incidence

Incidence studies have been difficult to conduct for several reasons. Hospital based surveys will be biased as not all stroke patients are admitted to hospital, neither do all stroke patients, even when in hospital, have a computed tomography (CT) scan so there may be error in the diagnosis, especially when trying to differentiate between stroke sub-types or mechanisms (i.e. infarction from haemorrhage).

In the Oxford Community Stroke Project (OCSP), the incidence was calculated for all hospital and community stroke patients. This gave a figure of 2/1000 per year for first ever stroke (Bamford et al. 1988). If applied nationally, there will be over 100000 people suffering a stroke every year; equivalent to one person every 5 minutes. Although stroke is more common in the elderly, about one quarter of all strokes occur in the under 65 year age group with a further quarter in the 65-74 age group.

The mortality of stroke would seem to be an easy parameter to measure but even this can be inaccurate. The diagnosis of stroke is not always made correctly,

although CT scanning has helped markedly. The rate of post mortem examinations is low in the elderly and coupled with a tendency to ascribe sudden death in the elderly as secondary to a stroke can lead to errors. However, about 64 000 deaths per year are recorded as being due to stroke (The Secretary of State for Health, 1992). Nearly 8% of these are in the under 65 age group.

As the elderly population increases in size, the incidence of stroke may be expected to increase. However, in recent years stroke mortality in the UK has, in fact, fallen. It is not yet clear whether this reflects a decrease in the incidence of stroke or whether it is due to better survival following the stroke. If it is due to improved survival, it is unlikely to be due to new treatments (as there have been none employed in routine clinical practice) nor is it likely to be due to the development of acute stroke units (as these are a relatively recent development). There may be a change in the type of stroke that is occurring e.g. more people may be suffering from lacunar strokes than before although this information is not available due to the lack of accurate, comprehensive stroke registers. Thus, at the present time, it is not yet understood why stroke mortality is falling in this country.

There have been few reliable studies looking at stroke incidence with time, although the Rochester, Minnesota stroke study does provide some evidence of changing incidence rates with time. In the 1950's and 1960's, stroke incidence did fall, but this decline seems to have levelled off and may even be increasing (Broderick et al. 1989). Other studies have shown stroke incidence to be increasing in Denmark and Sweden (Terent, 1988; Jorgensen et al. 1992) but decreasing in Japan (Ueda et al. 1981).

One explanation that is often put forward for a decreasing incidence of stroke, is the better control of risk factors and, in particular, hypertension (Whisnant, 1984). However, others have argued that the better control of hypertension cannot account for all of the decline (Bonita and Beaglehole, 1989). Similarly, the increase in the numbers of carotid endarterectomy cannot explain the decline in incidence fully as only about a fifth of strokes are preceded by a TIA. Thus, like the decrease in stroke mortality, the exact mechanisms are unknown. It may well be that a combination of factors, including better control of blood pressure, carotid endarterectomies and changes in reporting stroke incidence, all contribute to the changes seen with time.

1.3 PATHOPHYSIOLOGY OF STROKE

The complex events which eventually lead to cerebral infarction can be divided into two processes. Firstly, the vascular event that leads to a decrease in cerebral blood flow and secondly, the consequent alterations in cellular chemistry which result in cellular infarction.

1.3.1 VASCULAR PROCESSES INVOLVED IN CEREBRAL INFARCTION

95% of all ischaemic strokes are due to thromboembolic phenomena. The remaining 5% are due to the rare, 'small print' causes listed in table 1.

Table 1. Rare causes of cerebral infarction

inflammatory	**arterial dissection**	**trauma**
rheumatoid arthritis	infective arterial disease	penetrating injury
polyarteritis nodosa	trauma	cervical rib
systemic lupus erythematosus	atheroma	epileptic seizure
antiphospholipid syndrome		carotid compression
sarcoidosis	**metabolic**	
giant cell arteritis	mitochondrial cytopathy	**congenital**
irradiation	hypoglycaemia	Marfan's syndrome
inflammatory bowel disease	Fabry's disease	pseudoxanthoma elasticum
coeliac disease	homocystinuria	fibromuscular dysplasia
infections		Ehlers-Danlos syndrome

Atheroma

This is the commonest cause of thromboembolism leading to cerebral infarction. It is almost universal in the elderly age group and has a predilection for certain sites. Large and medium sized vessels are most often affected especially at sites of arterial branching and confluence (Fisher, 1954). Other areas, in particular, the cerebral vessels distal to the circle of Willis, are only rarely sites of significant atheroma

formation. Atheroma develops over several years to form plaques of fibrolipid material. Platelets adhere to the plaques and this in turn can lead to luminal narrowing or occlusion. Alternatively, part of the plaque can embolise and obstruct a distal, narrower vessel. Thus, emboli from the internal carotid artery tend to travel and lodge in either the ophthalmic artery or the anterior cerebral circulation (MCA and ACA).

Causes of Atheroma

Atheroma is likely to develop following endothelial injury in genetically predisposed people. Through population based studies, there have emerged clear risk factors for the development of atheroma and its clinical consequences e.g. ischaemic stroke, myocardial infarction.

age this is the strongest risk factor for ischaemic stroke (Bamford et al. 1988)

sex there is a slight excess of ischaemic stroke in men (but much less than that of ischaemic heart disease). This excess, however, is not found in the very young or old (Lerner and Kannel, 1986).

hypertension increasing diastolic blood pressure in the range of 70-110 mmHg leads to an increased risk of ischaemic stroke- the risk of an event doubling for every 7.5 mmHg rise (Collins and MacMahon, 1994). Raised systolic blood pressure, even if it associated with a 'normal' diastolic pressure is associated with an increase in the risk of ischaemic stroke (Kannel et al. 1981; Shaper et al. 1991; Keli et al. 1992).

smoking there is a 1.5-2 times increase in the risk of ischaemic stroke in smokers compared to non-smokers (Donnan et al. 1993b). However, the risk is less apparent in the elderly.

diabetes leads to doubling of the risk of ischaemic stroke (Manson et al. 1991; Burchfiel et al. 1994).

lipids unlike the case with ischaemic heart disease, where there is a strong link between raised cholesterol and low-density-lipoprotein-cholesterol and decreased high-density-lipoprotein-cholesterol levels and myocardial infarction, the relationship between abnormal blood lipids and ischaemic stroke remains unclear. In a recent study, there was little if any association between raised cholesterol levels and all strokes (Prospective Studies Collaboration, 1995). Lowering plasma cholesterol levels does not seem to decrease the risk of ischaemic stroke (Hebert et al. 1995).

fibrinogen has a strong positive association with ischaemic stroke. However, there are many confounding variable such as age, sex, hypertension, smoking, diabetes, social class and stress. It is difficult to measure fibrinogen in a standard way, there are no randomised controlled trials of fibrinogen and so the link with ischaemic stroke remains unclear (Ernst and Resch, 1993).

There are several other factors which may be risk factors for ischaemic stroke, although at the present time there is no proven causal relationship. For example: raised factor VII coagulant activity (Meade et al. 1993), lack of physical exercise (Gloag, 1992), obesity (Folsom et al. 1994), alcohol (van Gijn et al. 1993), race (Howard et al. 1994).

Cardiac Embolism

Cardiac embolism accounts for approximately 20% of all ischaemic stroke (Cerebral Embolism Task Force. 1989; Broderick et al. 1992). Emboli can lodge in various intracerebral vessels ranging from the MCA trunk causing massive infarction to a small peripheral branch which may be asymptomatic (Caplan, 1993). Atrial fibrillation (AF) is the commonest cause of cardioembolic stroke accounting for up to 20% of all cases (Sandercock et al. 1992). Non-rheumatic AF (the commonest cause of AF in the Western world) carries a 5% risk of ischaemic stroke per annum (Hart and Halperin, 1994). It is probably the sole cause of ischaemic stroke in certain patients (Aberg, 1969; Friedman et al. 1968). However, AF may not always be causal as it often co-exists with other risk factors for ischaemic stroke such as

hypertension. Additionally, only about 10-15% of patients with AF have detectable thrombus in the left atrium, although the number will probably increase as better methods of detection evolve (Daniel, 1993). Within the AF population, patients at high risk of ischaemic stroke are those with rheumatic AF, the elderly, those with co-existing hypertension and diabetes and those patients with left ventricular dysfunction (Atrial Fibrillation Investigators. 1994; van Latum et al. 1995; Bonita and Beaglehole, 1989).

Other causes of cardiac embolism are:

Prosthetic heart valves

Mitral valves and, in particular, mechanical (as opposed to tissue) valves are prone to form thrombus from which emboli can arise (De Bono, 1982). If properly anticoagulated, the risk of ischaemic stroke with all valve types is approximately 2% per annum (Bloomfield et al. 1991; Hammermeister et al. 1993).

Infective endocarditis

Infected vegetations formed on the valves can embolise and result in stroke. About 20-25% of patients with infective endocarditis will have a stroke. Haemorrhagic transformation of the infarct is common in these patients.

Cardiomyopathies

The dilated type of cardiomyopathy is particularly associated with mural thrombus formation and embolism (Fuster et al. 1981).

Cardiac tumours

Although the commonest cardiac tumour - myxoma, is most often found in the left atrium, it is still a very rare cause of embolus formation.

Other

paradoxical emboli: emboli from the venous system can pass into the cerebral circulation most commonly via a patent foramen ovale or an atrial septal defect.

marantic endocarditis: debilitated patients, especially those with cancer or disseminated intravascular coagulation, can develop small fibrin/platelet vegetations on their heart valves.

mitral valve prolapse: uncomplicated cases are now not regarded as sources of cerebral emboli (Marini et al. 1993; Orencia et al. 1995).

Small Vessel Disease

Disease of the small vessels of the cerebral circulation may account for up to 25% of all cases of ischaemic stroke (Bamford et al. 1987; Hankey and Warlow, 1991). The vessels most often affected are those between 40 and 800μm in diameter e.g. lenticulostriate arteries and the thalamoperforating arteries (Bamford and Warlow, 1988; Orgogozo and Bogousslavsky, 1989). The pathological process behind small vessel disease has been termed variously, lipohyalinosis, fibrinoid necrosis, hyalinosis and angionecrosis (Fisher, 1991). Although pathological evidence is not as widely available as that for major strokes, due to the lower mortality rate, it seems that the muscle in the walls of small vessels is replaced with collagen. The vessels become tortuous and eventually the blood flow is decreased leading to cerebral ischaemia.

Patients with small vessel disease tend to develop lacunar strokes. There is a low incidence of large vessel disease and less frequent sources of emboli than those patients with large cortical infarctions (Mast et al. 1994; Hankey and Warlow, 1991; Tegeler et al. 1991b).

1.3.2 PATHOPHYSIOLOGY OF CELLULAR INFARCTION

The brain is completely dependent on glucose for its energy supply. Glucose is broken down in a series of steps in the glycolytic and tricarboxylic acid cycle to yield adenosine triphosphate (ATP). In the absence of oxygen, glucose is metabolised anaerobically. This, however, leads to a much smaller yield of ATP and also the accumulation of lactic acid. This in turn leads to a build up of calcium in the cell as the mitochondria lose their ability to sequester calcium (Siesjo, 1992).

In the resting state the cerebral blood flow (CBF) is approximately 55 ml/100 g/minute (Leenders et al. 1990). Total CBF is about 800 ml/min in the resting state which is 20% of the total cardiac output (Kety, 1950). The cerebral metabolic rate of oxygen (CMRO2) is approximately 3.4 ml/100g/min in the resting state.

CBF is usually kept at a constant level due to autoregulation (Powers, 1991). As the arterial blood pressure drops, the cerebral resistance vessels (arterioles) constrict, thereby increasing the cerebral pressure and so restoring CBF. Similarly, if the arterial pressure increases, the arterioles dilate in order to keep the CBF constant. However, autoregulation becomes ineffective if the arterial pressure falls below 40-50 mmHg (Harper, 1966). Any subsequent reductions in arterial pressure are mirrored by a fall in CBF. As CBF falls, the amount of oxygen extracted from the blood, the oxygen extraction fraction (OEF), increases in order to maintain CMRO2 - the so called 'misery perfusion' (Baron et al. 1981). If the CBF falls still further, to less than 20-25 ml/100g/min, the OEF is already maximal and so the tissues become ischaemic with a fall in CMRO2 and an impairment of cellular metabolism (Powers et al. 1984; Pulsinelli, 1992).

The Ischaemic Penumbra

When CMRO2 is low due to a decrease in CBF, there is a decrease in the electrical activity of the brain (Heiss et al. 1976; Heiss, 1992). If CBF falls to below 15 ml/100g/min, the EEG flattens and evoked potentials are lost. Irreversible cell damage occurs when the CBF reaches approximately 10 ml/100g/min (Siesjo,

1992). If low CBF persists, the neuronal cells start to metabolise glucose anaerobically, with a subsequent accumulation of lactic acid. Cellular metabolism becomes impaired, K+ ions start to leak out of the cell and Na+ ions and water enter the cells causing cytotoxic oedema. Calcium also enters the cells triggering a series of steps leading to mitochondrial failure and cellular death (Harris et al. 1981; Siesjo, 1992).

The concept of ischaemic thresholds has lead to the development of the idea of an ischaemic penumbra (Astrup et al. 1981). This is the brain tissue which is ischaemic and non-functioning (i.e. CMRO2 is low) but has not yet reached the threshold for cellular death. Thus, the penumbra is dependent on the degree and duration of the ischaemia and may represent brain tissue which is potentially salvageable. The length of time that tissue remains salvageable is unknown and depends on many factors including the amount of collateral blood flow to the ischaemic area. Recent positron emission tomography (PET) studies have shown that areas of ischaemic tissue following a stroke may remain viable for up to 17 hours (Marchal et al. 1996a). This has profound implications for the treatment of ischaemic stroke, especially when considering thrombolytic treatment.

Reperfusion

The concept of the ischaemic penumbra has lead to the idea of a therapeutic time window. This is the period of time during which treatment will be able to salvage the ischaemic tissue and return it to a normal level of function. Thrombolysis has been used successfully in the treatment of myocardial infarction (ISIS-3 Third International Study of Infarct Survival Collaborative Group. 1992) up to 24 hours after the onset of symptoms. However, we know that neuronal tissue is more sensitive to ischaemia than cardiac muscle. Animal testing allows the cerebral vessels to be clamped and then reopened at various time intervals. Following this, the brain can be examined histologically for signs of ischaemia and infarction. From these studies it has been shown that after a period of approximately 60 minutes, irreversible neuronal damage occurs (Minematsu et al. 1992a; Minematsu et al. 1992b). This has lead to the belief that reperfusion and hence thrombolytic therapy

has to be administered within a very short time interval from the onset of symptoms if it is to be effective. In reality, the situation is more complex. A critical factor may be the presence of collateral circulation. Even if a major cerebral artery is occluded, the area it supplies may remain viable for a longer period than expected due to the presence of collateral vessels from either the contralateral hemisphere or from another major cerebral artery.

Another complicating factor is the metabolic effects of reperfusion. It is known that if tissue has become ischaemic and then the blood supply is returned, further damage can occur- the so called 'reperfusion injury'. This is due to a complex series of metabolic steps which lead to the production of free radicals such as superoxide ions (0_2^-) during anaerobic metabolism. Ischaemic cells have high levels of intracellular calcium and adenosine monophosphate (AMP) due to adenosine triphosphate dephosphorylation. Calcium and AMP lead to oxidation of xanthine dehydrogenase to xanthine oxidase. When the cell is reperfused, xanthine oxidase catalyses the conversion of hypoxanthine to xanthine urate using oxygen as an electron acceptor. This results in the formation of the superoxide ion which is highly destructive as it reacts and damages proteins, nucleic acids and lipids. Damage to the cell membranes results in changes in its permeability. This leads to release of inflammatory mediators which, in turn, lead to disruption of the microvasculature and damage to the blood-brain barrier.

1.4 TREATMENT OF ISCHAEMIC STROKE

Over the last few years there has been a tremendous increase in research into new treatments for ischaemic stroke. This has been triggered by a better understanding of the pathophysiology of cerebral infarction and better methods of investigating stroke generally. The most exciting treatments studied have centred around thrombolysis and neuroprotection.

Thrombolysis will be discussed first and in most detail as the assessment of patients with new imaging techniques may prove to be an important part of the treatment strategy.

1.4.1 Thrombolysis

The success of thrombolysis in the treatment of myocardial infarction, as well as a better understanding of the pathophysiology of cerebral ischaemia, has lead to a number of trials of thrombolysis in acute ischaemic stroke. The concept behind the use of thrombolysis was based on the ischaemic penumbra and is as follows: if a stroke was caused by arterial occlusion (such as the MCA) then the tissue supplied by that vessel would stay in a potentially salvageable state for a period of time (the therapeutic window). If thrombolytic treatment was given and the blood supply to this area was returned within this time, then the tissue would return to its normal functioning state. This would lead to a decrease in the amount of infarcted brain tissue and a good clinical outcome. However, thrombolysis increases the risk of haemorrhage generally, and of intracerebral haemorrhage in particular. Also, the exact length of the therapeutic window and the precise effect of reperfusion injury to the brain is unknown in humans.

At the time of writing this thesis there had been 5 major randomised double blind placebo controlled trials assessing the safety and efficacy of thrombolytic agents in ischaemic stroke. The results were, on the whole, disappointing, and only one trial has lead to the introduction of a thrombolytic agent in the clinical setting of ischaemic stroke (NINDS) (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. 1995). Three trials (Multicentre Acute Stroke

Trial-Italy (MAST-I) (Multicentre Acute Stroke Trial-Italy (MAST-I) Group, 1995), Multicentre Acute Stroke Trial-Europe (MAST-E) (The MAST group. 1993), Australian Streptokinase trial (ASK) (Donnan et al. 1996) used streptokinase as the thrombolytic agent, while the remaining two trials NINDS and the European Collaborative Acute Stroke Study (ECASS) (Hacke et al. 1995) employed recombinant tissue plasminogen activator (t-PA).

All the trials except the NINDS trial were terminated early due to a worse outcome in the treated group compared to placebo (Donnan et al. 1995; Hommel et al. 1995). In the NINDS trial, patients were given intravenous t-PA (0.9 mg/kg body weight) within 3 hours of ischaemic stroke. A computed tomography (CT) scan was performed prior to treatment to exclude cerebral haemorrhage. Assessment of the patients showed that, although there was no evidence of an early (24 hour) recovery, patients had a better outcome at 3 months as assessed on various stroke disability scales.

In all the trials there was, not unexpectedly, a higher rate of haemorrhagic transformation (HT) in the treated group as compared to placebo. This seemed to offset the benefits that other patients gained from thrombolysis. Risk factors for HT include CT evidence of oedema and large areas of hypoperfusion (Ueda et al. 1994). Subgroup analysis of the ECASS showed that patients treated within 3 hours had a better 3 month outcome than the placebo group (Hacke et al. 1995). However, there was a higher early death rate in the treated group. Again this reflects the higher rate of HT. It was concluded that if a patient survives the early stages of treatment then they will go on to have a better outcome than the untreated group.

Thus, selection of patients for these trials is obviously of the utmost importance. Generally, the trials excluded patients who had very minor neurological deficits and those with major deficits. The rationale behind this was that patients with only a minor deficit are more likely to a have lacunar stroke i.e. small vessel disease and not an occlusion in one of the major cerebral arteries. They are therefore unlikely to benefit from thrombolysis. Additionally, these patients tend to have a good prognosis anyway. Patients with severe neurological deficits have a poor prognosis anyway and are most at risk of HT. It has been argued that if the patients could be better selected, then there could be a reduction in the early death rate of the treated

group and thus an overall benefit for the treatment group. It seems likely that the best method of selecting the most appropriate patients for treatment is by using more sophisticated imaging techniques. Additionally, it may also be possible to identify patients who would still benefit from treatment outside the arbitrary 3 or 6 hour time window that has been set in the trials.

1.4.2 Neuroprotection

Ischaemia leads to an increase in intracellular calcium which, in turn, leads to the release of excitatory amino acids such as glutamate and aspartate. These amino acids can stimulate certain receptor sites such as the *N*-methyl-D-aspartate (NMDA) site causing further calcium influx and cellular damage. NMDA receptor antagonists, such as selfotel, were developed and used in clinical trials to prevent this release of excitatory amino acids. However, many had severe side effects including psychosis, and none are currently in routine clinical use.

Lubeluzole, a nitrous oxide modulator, in a recent trial, reduced the 28 day mortality of ischaemic stroke from 18% (placebo) to 6% (treated) (Diener et al. 1996). However, higher doses of lubeluzole actually led to an increased risk of death when compared to placebo.

Other trials of neuroprotective agents such as anti-ICAM-1 and GABA agonists are currently being performed. So far, there have been no trials looking at combining treatments such as thrombolysis and neuroprotection and these may be the basis of future trials.

1.4.3 Other treatments

There are still many other treatments for ischaemic stroke that are widely practised. The recent International Stroke Trial (IST) highlighted the tremendous variability between different countries in their approach to ischaemic stroke (Ricci, 1995). Many countries still routinely use drugs which, after meta analysis of the randomised trials, have been shown to have no benefit in the treatment of ischaemic stroke. Examples are steroids, haemodilution, calcium channel blockers and glycerol.

1.5 PREVENTION OF STROKE

Strategies for the prevention of stroke, as with any disease, can be divided into primary and secondary prevention. Primary prevention refers to therapies that will prevent the disease from occurring. These therapies are aimed at reducing the risk factors for a particular disease e.g. stopping smoking and are often aimed at the population at large.

Secondary prevention is concerned with reducing the risk of a recurrence of the disease and is therefore aimed at a smaller population but one which generally has a high risk of the disease.

1.5.1 PRIMARY PREVENTION

The main risk factors for stroke are hypertension, age, smoking, diabetes, male sex and raised blood lipids. These are also the main risk factors for ischaemic heart disease (IHD) and merely reflect the common underlying pathology of atheroma. Modifying these risk factors therefore, should also have a beneficial effect on IHD. As stroke and IHD account for about two thirds of all deaths in the UK, primary prevention of these diseases could have a dramatic impact on the health of the nation. Primary prevention can either be targeted at a large population who, overall, have only a small risk or at a few people with a very high risk of the disease. For example, lowering the whole population's blood pressure by 2-3 mmHg will reduce the incidence of stroke in the population by 10% (Ebrahim, 1990). In terms of overall benefit, the first approach is the most successful as it prevents the larger number of events. However, the second approach gives the greater benefit on an individual basis.

Atrial fibrillation

A meta-analysis of 5 trials of warfarin in the primary prevention of stroke in patients with atrial fibrillation (AF) has shown a decrease in the risk of stroke of 68% (Atrial Fibrillation Investigators. 1994). The annual rate of stroke in the control patients

(untreated) was 4.5% and in the treated patients it was 1.4%. There was a higher reduction in women (84%) than in men (60%). The annual rate of major haemorrhage was only slightly increased in the treated patients: 1.3% (treated) and 1.0% (untreated). The effect of aspirin was also investigated in the meta-analysis. The results were not as consistent as those for warfarin and may have reflected the differing doses used in the trials (75 mg and 325 mg). However, the overall risk reduction on aspirin was 36%. It was noted that patients under the age of 65 years without risk factors (hypertension, previous stroke or TIA, diabetes) had a low risk of stroke without treatment (1.0%) and may not need treatment.

1.5.2 SECONDARY PREVENTION

The strategies for secondary prevention involve both pharmacological intervention (antiplatelet and anticoagulant drugs) and surgical interventions (carotid endarterectomy) as well as general measures such as blood pressure control.

Medical prevention

Aspirin

Aspirin reduces the risk of deep vein thrombosis and pulmonary embolism in high risk patients such as those undergoing surgery (Antiplatelet Trialists' Collaboration, 1994a). It also reduces the risk of recurrent myocardial infarction, ischaemic stroke and vascular death (Antiplatelet Trialists' Collaboration, 1994b). By analysing data from several randomised controlled trials, it has been shown that aspirin will reduce the 3 year risk of MI, stroke and vascular death from 22% to 18%. Ischaemic stroke is reduced from 12.2% to 9.7%. There is an increase in haemorrhagic strokes in the treated group of 0.2% to an annual risk of 0.6%. Although the trials only followed patients for 2-3 years, it is generally accepted that antiplatelet therapy should continue for life.

Aspirin has also been extensively investigated in the setting of patients with transient ischaemic attacks (TIA) due to carotid stenosis. The results will be discussed in the section on surgical prevention.

At the time of writing, two large randomised trials investigating the use of aspirin in the setting of acute stroke had just finished and preliminary data were becoming available. The International Stroke Trial (IST) (International Stroke Trial Pilot Study Collaberative Group. 1996) and the Chinese Acute Stroke Trial (CAST) recruited over 30 000 patients between them. The IST compared heparin (high and low doses or 'avoid') and aspirin (300 mg or 'avoid') in suspected ischaemic stroke within 24 hours of onset. Aspirin reduced the risk of ischaemic stroke as expected. However, there was an increase in the number of haemorrhages both intracranial and extracranial when either low or high dose heparin was added. Thus, aspirin should be given to all suspected ischaemic stroke patients as soon as possible following a stroke and heparin should be avoided. The CAST studied aspirin (160 mg) versus placebo. Preliminary results showed that in hospital deaths were significantly reduced, but there was no difference in the two groups in death or dependency at 6 months.

Subgroup analysis of the MAST-I showed that aspirin given within 6 hours of stroke onset decreases 6 month mortality by 40%, but does not affect long term disability (Multicentre Acute Stroke Trial-Italy (MAST-I) Group, 1995).

Anticoagulation

Two large multicentre randomised trials are currently assessing aspirin treatment with anticoagulation in patients with ischaemic stroke who are not in AF: Stroke Prevention in Recurrent Ischaemia Trial (SPIRIT) and Warfarin Aspirin Recurrent Stroke Study (WARRS). At the time of writing, there were no published results available.

However, anticoagulation has been assessed mainly in the setting of patients in AF as these have a high risk of embolic stroke. In the European Atrial Fibrillation Trial (EAFT), warfarin reduced the risk of recurrent stroke in patients with non-rheumatic AF by 66% from 12% to 4% per year (European Atrial Fibrillation Trial Study Group, 1993). The annual rate of major haemorrhage was relatively low (2.8%) and in particular, there were no documented cases of intracerebral bleeds. Overall, 90 vascular events, mainly strokes, are prevented if 1000 people are treated with warfarin for one year. The dose of warfarin used to treat patients was later analysed

(European Atrial Fibrillation Trial Study Group, 1995). It was found that patients with an International Normalised Ratio (INR) of between 2 and 4 had the lowest rate of vascular events. An INR below 2 lead to an increase in recurrent ischaemic stroke and an INR above 5 lead to a high risk of bleeding complications.

Surgical Prevention

The operation of carotid endarterectomy (CEA) in the setting of secondary prevention of stroke and vascular events has been studied in two large trials: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) (North American Symptomatic Carotid Endarterectomy Trial Collaborators. 1991; European Carotid Surgery Trialist's Collaborative Group. 1991). In both of these trials CEA reduced the risk of stroke in patients with severe carotid stenosis. The risk reduction was dependent on the severity of the stenosis. A complicating factor in the trials was that the measurement of carotid stenosis was different in the two groups so that a stenosis of 70% in the NASCET was equivalent to 82% in the ECST. Operating on a patient with a 70% (NASCET) or greater stenosis reduces the risk of stroke to that of a patient without a carotid stenosis. However, the operation of CEA is not without risk itself. Perioperative stroke rates vary widely in published data (Rothwell et al. 1996) but probably lie between 3 and 10% in most centres (Warlow et al. 1996). They are dependent not only on the experience of the surgeon but also on the type of patient: the risk of perioperative stroke is increased in female patients, older patients, patients with contralateral carotid occlusion, cortical TIA's as opposed to amaurosis fugax and those patients with CT evidence of infarction. In patients with a 70% or greater carotid stenosis, the risk of perioperative death or stroke is less than the risk of future stroke. However, for patients with a stenosis of less than 70%, the perioperative stroke rate outweighs any benefit this may give the patient. Thus, CEA is performed on patients with a 70% or greater carotid stenosis, whereas patients with lesser degrees of stenosis are treated with aspirin.

Carotid angioplasty

There has been recent interest in the procedure of percutaneous transluminal balloon angioplasty in the treatment of carotid stenosis (Brown et al. 1990). Potential advantages include the avoidance of a general anaesthetic and surgical complications and a shorter hospital stay. However, potential dangers include rupture of the artery, dissection of the artery, embolisation of a disrupted plaque and causing a low flow infarction. Although a major trial is currently assessing angioplasty (CAVATAS), it is generally not used in routine clinical practice.

General Measures

It is uncertain at the moment whether a reduction in blood pressure in patients with a prior history of stroke or TIA will lead to a lowering of their risk of a recurrent event. Although there seems to be a trend towards a lower risk, the differences between treated and untreated groups are not statistically different (McMahon and Rodgers, 1994).

There is no strong evidence to support the idea that a reduction in cholesterol levels will lead to a lowering of the risk of ischaemic stroke. However, a reduction in cholesterol will lead to a reduction in cardiac deaths (from which stroke survivors are at a high risk) and so cholesterol reduction is usually advocated.

Stopping smoking, reducing high alcohol and fat consumption and increasing exercise are all probably beneficial. Although, like lowering cholesterol levels, there is no good evidence from trials that these measures will reduce the risk of further strokes, they are all good lifestyle strategies and should be encouraged.

1.6 IMAGING TECHNIQUES IN ACUTE STROKE

Imaging techniques in neurology have changed greatly in the last few years. This has been especially the case in cerebrovascular medicine. The advent of computerised tomography (CT) scanning in the 1970's allowed the neurologist, for the first time, to obtain detailed anatomical pictures of the brain. This was then surpassed by the invention of magnetic resonance imaging (MRI). Recently, MRI has developed so that there are new ways of imaging the brain: MR angiography, diffusion weighted imaging, perfusion MRI and MR spectroscopy. Advances in ultrasound has produced the ability to measure intracranial blood flow velocity with transcranial Doppler (TCD) and most recently to image the brain parenchyma and vessels using duplex transcranial colour-coded sonography (TCCS).

Positron emission tomography (PET) enables the metabolic function of the brain to be measured.

Although intra-arterial angiography still has a definite role to play in the imaging of the cerebral vasculature, it is becoming less prevalent due to advances in MR and ultrasound technology.

1.6.1 Computed Tomography

CT scanning was the first noninvasive technique for imaging the brain parenchyma. As technology has progressed so to have the quality of CT scans. CT scanning changed the way in which stroke patients were investigated as it was the first method available to safely differentiate cerebral infarction from haemorrhage. It is widely used in clinical practice following suspected stroke. CT is not as reliable as MRI in detecting abnormalities in the early stages of acute cerebral infarction. In one study (Fieschi et al. 1989) CT was abnormal in 13 out of 80 patients studied within 6 hours. Follow up studies showed abnormalities in a further 43 patients. Another study, however, had a higher success rate in the acute stages of stroke: 35 out of 44 cases were identified within 6 hours of stroke onset (Bozzao et al. 1989a). The hallmark sign of infarction on CT is an area of low density However, the earliest

signs are usually a hyperdense vessel if there is thrombus in the artery, subtle loss of the grey/white matter interface and effacement of the sulci.

A limitation of CT is that very small infarctions, usually lacunar infarctions, can be missed and will only be imaged using MRI (Lenzi et al. 1991). Additionally, CT is less able than MRI to image the brainstem due to bony artefacts (Bonafe et al. 1985).

CT scanning is a relatively rapid procedure and is not as sensitive to patient movement as MRI, thus making it easier to perform in the early stages of stroke. The size of the infarction measured by CT does not correlate well with clinical prognosis, although the site of infarction is often more important (Knopman and Rubens, 1986).

The main indications for performing a CT scan in a stroke patient are to firstly differentiate infarction from haemorrhage and then, in cases of infarction, to identify the vascular territory. Even the first generation scanners were found to be 100% accurate in differentiating intracerebral haemorrhage from infarction (Paxton and Ambrose, 1974).

1.6.2 Magnetic resonance imaging

Standard T1 and T2 MRI can be used to image areas of infarction. Initial experimental studies showed that some scans become abnormal within a couple of hours of infarction and that ischaemia over 6 hours was routinely imaged (Spetzler et al. 1983). Thus, MRI is more sensitive than CT in detecting ischaemia in the early stages of acute cerebral infarction, especially within the first few hours. There is also some evidence to suggest that the size of the infarct on early MRI scans is a good indicator of outcome (Saunders et al. 1995a).

The early changes of ischaemia are prolongation of both the T1 and T2 relaxation times. This appears as an area of high signal on T2. In chronic infarcts, T2 remains prolonged as does T1, which leads to an area of low signal on T1. MRI has better resolution than CT and is therefore the technique of choice for imaging lacunar infarctions. These are best imaged on T2 and appear as areas of high signal.

MRI is less able to distinguish infarction from haemorrhage in the early stages as both pathologies appear as high signal on T2 and low signal on T1 (Kertsez et al. 1987). However, MRI is useful in the subacute stages of haemorrhage when CT changes of infarction and haemorrhage are similar.

1.6.3 Diffusion MRI

Diffusion MRI was introduced in 1986 by Le Bihan (LeBihan et al. 1986). It is based on the diffusion pattern of water. In animal models, when brain tissue becomes ischaemic, the diffusion of water drops (Moseley et al. 1990). The drop has been seen as early as 14 minutes following occlusion of the middle cerebral artery (Hossmann and Hoehn-Berlage, 1995). It continues to decrease for one hour, plateaus for several hours and then starts to rise again and eventually reaches and rises above baseline values at approximately 48-72 hours. The exact pathophysiological mechanisms responsible for the changes in water diffusion are not known. However, it is probably related to changes in cellular energy. As ischaemia persists, the Na+/K+ pumps start to fail. This leads to an influx of water and cytotoxic oedema and possibly a reduction in water. Quantitative values can be calculated for the diffusion of water and are expressed as the apparent diffusion coefficient of water (ADC). This can be calculated for different areas of the brain. It has been shown that the ADC is at its lowest at the centre of the ischaemic area (the core) and slowly normalises towards areas of non ischaemic tissue. Although it is not known, there may be threshold values of the ADC that represent infarcted (irreversibly damaged) tissue and reversible ischaemic (penumbral) tissue. The ADC and volume of abnormal tissue on DWI may be a guide to clinical outcome and final infarct volume (Back et al. 1994; Welch et al. 1995) and may reflect the degree of metabolic changes during the ischaemic period (Wick et al. 1994).

In animal studies, very early reperfusion can lead to the ADC returning to normal values in all areas supplied by the artery . However, if reperfusion occurs one or two hours post occlusion, the ADC only returns to normal in certain more peripheral areas of the tissue, indicating some permanent tissue damage (Minematsu et al. 1992b).

In human studies, the ADC falls by 20-50% within the first few hours of stroke and DW images show abnormalities earlier than conventional T2 imaging (Sorensen et al. 1996; Warach et al. 1996; Warach et al. 1992a). After 12-24 hours, the ADC rises and reaches normal levels at 5-10 days (Warach et al. 1995). The chronic infarct has a high (2-3 times normal) ADC. This allows differentiation between new and old infarcts (Marks et al. 1996). The ADC is a quantitative value which does not depend on the field strength of the magnet and can be used in comparative studies in different hospitals or on different scanners. Diffusion MRI can take up to 20 minutes to perform. However, new scanners with echo planar imaging facilities can cut the time taken to about a second. This is especially important in imaging acute stroke patients as diffusion scans are degraded significantly by motion.

1.6.4 Perfusion MRI

This MRI technique is based on cerebral blood flow. There are two ways in which perfusion MRI can be performed: by inducing changes in the magnetic susceptibility or by tagging inflowing arterial spins. The first technique generally employs a paramagnetic contrast agent such as gadolinium to induce the change. Using gadolinium, changes in signal due to relative changes in cerebral blood volume and cerebral blood flow, can be calculated. Although this can be performed using T1 images (Kent et al. 1989), better sensitivity can be obtained with T2* weighted images. Arterial spin labelling has the advantage that it is completely non-invasive. By tagging inflowing blood with a single inversion pulse, images can be taken of the target tissue before and after the blood has flowed to the tissue. Subtracting one image from the other will yield a measure of cerebral blood flow (Edelman et al. 1994). Echo planar imaging has lead to the acquisition time being reduced so that perfusion studies are more feasible in humans. In one such study, perfusion MRI showed deficits in patients who had MRA proven vessel occlusion or stenosis (Warach et al. 1992b). Interest has arisen in the possibility of combining diffusion MRI and perfusion MRI in order to image the ischaemic penumbra (Moseley et al. 1993; Rother et al. 1996; Maeda et al. 1993; Quast et al. 1993). In a study on gerbils, the ADC was normal until the cerebral blood flow reached 15-20

ml/100g/min (Busza et al. 1992). At levels below this, the ADC fell, indicating failure of cellular metabolism. Thus, tissue which has decreased perfusion but a normal ADC, may be penumbral tissue (i.e. it will return to normal function if perfusion is normalised). Tissue which has decreased perfusion but a raised ADC may already be infarcted and therefore not be salvageable.

1.6.5 MR Spectroscopy

Many different nuclei such as proton (1H), phosphorus (31P), sodium (23Na), and carbon (13C) can be used to as the basis of MR spectroscopy. However, for technical reasons, studies on human stroke have concentrated on the 31P and 1H nuclei. Of these two, proton spectroscopy gives the better resolution and higher sensitivity. In normal brain there are characteristic proton spectra: the largest resonance originates from N-Acetyl Aspartate (NAA) which is found in neurones. Other large signals are due to various trimethylamines (including choline) and creatine plus phosphocreatine (Baker et al. 1991). Lactate, in normal brain only yields a small signal.

In ischaemic conditions, as the brain switches to anaerobic glycolysis, lactate is produced. This leads to a sharp rise in the lactate signal (Gillard et al. 1996). Lactate levels can return to normal levels if the ischaemia is not prolonged. However, if ischaemia is prolonged then even if perfusion is returned, the mitochondria may not be able to metabolise glucose aerobically, and so the lactate levels will rise even further as anaerobic glycolysis continues. It has been suggested that areas of ischaemia in which lactate is high but in which NAA is normal represent the ischaemic penumbra and that the lactate level can be used as a predictor of outcome following stroke (Graham et al. 1995). Reperfusion in these cases should lead to limited tissue loss. Spectroscopic studies in human stroke have shown a continuing fall in NAA several days after the stroke (Saunders et al. 1995b). This may reflect the fact that the final infarct volume depends not only on the initial insult e.g. arterial occlusion but also on the state of the collateral circulation.

1.6.6 Positron Emission Tomography

PET is the only method in which various metabolic parameters can be measured. It gives quantitative values of the cerebral metabolic rate of oxygen (CMRO2), the oxygen extraction fraction (OEF), and cerebral blood flow (CBF) (Heiss and Podreka, 1993). In acute stroke, PET has been used to assess the relationship between the degree of metabolic dysfunction and clinical outcome and infarct size (Marchal et al. 1993). Tissue with a very low CMRO2 (<1.4 ml/100 g/min) within the first few hours following stroke was imaged as infarcted tissue using CT one month later. In addition, areas of tissue which had a CBF of <12 ml/100g/min also developed into infarcted tissue. Clinical outcome was assessed in the same study. Patients could be divided into three groups according to PET findings. Group one had large areas of hypoperfusion and a corresponding low CMRO2. These patients fared poorly. Another group of patients had a raised CBF with either a normal CMRO2 or a slightly decreased CMRO2. These findings were thought to be due to spontaneous reperfusion of the vessel; these patients had an excellent prognosis. The third group consisted of patients with a low CBF but a normal CMRO2 as a result of an increased OEF. This was thought to represent the existence of good collateral vessels which limited the amount of necrosis. These patients had a variable course. From a clinical point of view, patients in the first and second group should not be included in trials of thrombolysis. In the first group, reperfusion may lead to haemorrhagic transformation and further oedema. In the second group, the patients have a good prognosis without treatment and so they should not be exposed to possible harmful therapeutic intervention such as thrombolysis. It is third group that may have the most to gain from thrombolysis.

1.6.7 Transcranial Doppler Ultrasound

TCD has been used to study cerebrovascular disease in a number of ways. The accuracy of TCD has been assessed by comparing it to conventional angiography in patients with acute stroke, serial TCD examinations have been performed to establish the changes in blood flow velocity with time and to assess the prognostic implications.

TCD has been shown to be an accurate means of imaging the cerebral vessels when compared with intraarterial angiography (Zanette et al. 1989). TCD examination showed no flow in the MCA in cases of angiographically proven occlusion of the ICA in its intracranial course or occlusion of the MCA. In addition, occlusion of more than three MCA branch vessels on angiography led to a marked decrease in the MCA flow velocity when compared to the contralateral hemisphere.

Follow up studies on acute stroke patients have shown that patients with MCA occlusion or very low MCA velocity tend to have large CT abnormalities and a worse prognosis than patients with normal MCA velocity (Kushner et al. 1991). The effect of recanalisation of an occluded MCA has also been studied. The results, however, are not consistent, with some authors reporting a benefit with early recanalisation (Ringelstein et al. 1992) while other authors have not shown such a relationship (Grosset and Lees, 1992).

CHAPTER 2

PATIENTS AND METHODS

2.1 PATIENTS

2.1.1 INCLUSION AND EXCLUSION CRITERIA

Patients were eligible for the study if they met the following 2 inclusion criteria:

(i) suspected cerebral infarction in the carotid territory

(ii) investigations able to be completed within 24 hours of stroke onset

The diagnosis of acute cerebral infarction is usually suspected from the history. Examination of the patient will often reveal the characteristic findings of focal weakness, sensory loss or loss of higher cortical function. However, there are many other pathological conditions which can give rise to a similar history and clinical findings. The main differential diagnosis of acute cerebral infarction is that of an intracerebral haemorrhage. This can only reliably be distinguished by imaging the brain. Similarly, cerebral tumours and other space occupying lesions can give rise to diagnostic difficulties. Since inclusion in the study preceded imaging, some of the patients studied did not ultimately turn out to have cerebral infarction.

Patients were selected if it was thought that the lesion was in the carotid territory. This was chosen for the following reasons:

(i) it is generally more difficult to diagnose vertibrobasilar (VB) stroke than carotid artery stroke from the history and examination. It was thus assumed that many patients would be entered into the study and scanned who would subsequently be excluded if the diagnosis was incorrect

(ii) performing TCCS on patients with VB stroke is practically more difficult. The patients have to kept on their side with their necks flexed in order to obtain adequate images of the vertebral and basilar arteries. This is very difficult in the acute stage of stroke when many of these patients will be restless. As all the TCCS scans were performed by the author on his own, it would have proved very difficult to maintain the position of the patient for the duration of the scan.

Exclusion criteria were therefore as follows:

(i) inability to obtain informed consent from either the patient or next of kin

(ii) patient not co-operative to undergo investigations

(iii) contraindication to any investigation

(iv) inability to complete investigations within 24 hours from stroke onset

Informed consent

Before any patient was entered into the study, informed consent had to be obtained. This was taken from either the patient themselves or their next of kin. Many of the patients who had suffered a mild stroke were able to give consent themselves. However, this was not always possible with patients who exhibited major neurological deficits especially those with dysphasia. In those patients in whom it was felt that the patient was not able to fully understand the study details, the next of kin were contacted. If they were not in the hospital , they were telephoned and a brief overview of the study was given. They were then invited to discuss the study more fully in hospital with the author before a decision was made. If this was declined, then the patient was not entered into the study. If the next of kin accepted the offer, a full explanation of the study was given to them before any tests were performed. Both patient and next of kin were given a comprehensive information sheet that they were asked to read before giving consent (see Appendix).

Patient co-operation

Certain patients were excluded from the study if it was thought that they were not co-operative to undergo the various imaging techniques. This group included those patients that were too ill to be imaged such as those requiring ventilatory support, experiencing seizures, cardiovascularly unstable etc. Patients who were very restless were also excluded as it was thought that adequate images would not be obtained from these patients.

24 hour time window

Since the investigations had to be completed within 24 hours of stroke onset in order for the patient to be included in the study, not all patients who arrived in hospital and were assessed within 24 hours were actually admitted into the study if it was not possible to organise the appropriate investigations before the 24 hour time limit elapsed. It was envisaged that one of the main reasons for exclusion would be the 24 hour time limit for investigation. This deadline was particularly difficult to overcome as the ultrasound scanner was in virtual constant use during the day for routine and emergency clinical work. In order to obtain scanning time, a visit to the emergency admission ward (ward 33) of the Leicester Royal Infirmary was made every day in the early morning so that the scanner could be used before the unit opened at 9 a.m. If a patient was identified who fulfilled the entry criteria, informed consent was requested. When this was obtained, the patients were taken to the vascular studies unit where the scanner was situated. Patients had to be transferred on to a trolley, as the beds were too wide to fit into the scanning room. TCCS was performed in the usual manner and then all patients additionally underwent a carotid ultrasound scan which was generally performed by one of three vascular technicians.

2.1.2 PATIENT DETAILS

119 patients were entered into the study. 30 patients were excluded for the following reasons: 21 patients lacked an adequate acoustic window, 2 patients had cerebral tumours, 3 patients refused consent, 4 patients deteriorated and were too ill to undergo scanning. 75 patients had a cerebral infarction and 14 patients had cerebral haemorrhage on either CT or MRI.

The temporal window was used to insonate the basal cerebral arteries and the vessels were then interrogated with pulsed-wave Doppler. The mean and peak velocities were recorded for each MCA. In order to assess the side to side asymmetry in MCA velocity, the asymmetry index (AI) was calculated. An AI of ± 20% was taken to be abnormal (Zanette et al. 1989). The lower limit of normal for

the mean MCA velocity was set at 40 cm/s. This figure was derived from a previous study (Martin et al. 1994) in the same department on 29 healthy subjects over the age of 60 years which yielded data on 53 MCA's (in 5 hemispheres the MCA could not be insonated due to lack of a suitable acoustic window). In that study the mean MCA velocity ±2 standard deviations was 58 cm/s ±18.

All patients were studied in the vascular studies unit of the Leicester Royal Infirmary, using the Diasonics 'Spectra' scanner described in the following section.

2.2 METHODS

2.2.1 TRANSCRANIAL DOPPLER

The first report of transcranial Doppler (TCD) was made by Aaslid in 1982 (Aaslid et al. 1982). Since then, TCD has been widely used in a number of clinical and research fields. Although it is commonly used as a diagnostic tool in the United States of America and in many European countries, it has yet to gain widespread use in the UK. The main advantages of TCD are its noninvasive nature, portability and low cost which make it one of the easiest and cheapest methods of studying cerebral haemodynamics.

Historical Perspective

Christian Andreas Doppler

Doppler was born in Salzburg on 29th November 1803. His education was mainly in mathematics and physics and he studied both in Salzburg and Vienna. After marrying at the age of 32 he took up the post of Supplementary Professor of Higher Mathematics at the Technical Institute in Prague. 5 years later, in 1841, he became the full Professor of Mathematics and Practical Geometry at the Institute. It was in the following year that he presented his most famous paper, 'On the colored light of the double stars and certain other stars of the heavens' at the Royal Bohemian Society of the Sciences in Prague. His work was largely based upon theories proposed by the English astronomer Bradley (1693-1762). Bradley, who went on to become the Astronomer Royal after the death of Edmund Halley in 1742, had realised that the displacement of observed stars was too great to be accounted for by parallax. He proposed that the position of a light source is dependent upon the velocity and direction of the observer relative to the source.

A Dutch reformed minister, Christoph Buys Ballot, was a fierce critic of Doppler's work and set out to disprove Doppler's theory. In order to do this, a light source travelling at extremely high speed had to be found. This was not possible at the time, so Buys Ballot decided to test the theory using sound waves instead. The sound

source used was a horn player and the high speed was generated by placing this man on a train travelling along the recently opened Amsterdam-Utrecht railway. Speeds of up to 40 mph were generated and when the train passed the station the note of the horn was heard to rise by almost half a note and then fall by the same amount as the train receded. The experiments were repeated using more horn players and musically trained observers but the results were the same. Doppler's theory was proved correct.

Since then, the Doppler theory has been used extensively in many different aspects of science. Examples of its application are: the 'big bang' theory of the origin of the universe which is partly based upon the observed red shift of stars, the calculation of the speed of planetary motion and rotation, the tracking of satellites in space and the estimation of a car's speed by the police.

The Doppler Principle

When considering the measurement of blood flow velocities using the Doppler principle, the 'source' and the 'observer' are one and the same i.e. the transducer. The frequency shift is produced by the movement of blood cells within the blood vessel either towards or away from the transducer.

A transducer produces a wave which travels through the medium at a particular frequency and speed. When it meets a column of blood travelling at a different speed, the frequency that is met by the blood will be different

Let f_0 = frequency of the transmitted wave

f_1 = frequency of the transmitted wave that is encountered by the moving blood

v = velocity of the blood

c = velocity of the transmitted wave

then $f_1 = f_0 (1 + v/c)$ **(1)**

Thus, if the blood is flowing towards the transducer, the frequency of the transmitted wave will appear to be higher (its wavelength will have decreased) when it encounters the blood.

Once this wave has reached the blood, it is reflected back to the transducer which now acts as a receiver. The frequency of the wave will change because the new source (the blood cells) is travelling towards the receiver.

Let f_2 = the new frequency of the wave that is transmitted by the moving blood

λ_1 = the wavelength that is transmitted from the blood cells

λ_2 = the wavelength that is received by the transducer

if $f_2 = c/\lambda_2$ **(2)**

then $f_2 = f_1/(1-v/c)$ **(3)**

By combining the equations **(1)** and **(2)** we have

$$f_2 = f_0\,(1+v/c)/(1-v/c) \quad \textbf{(4)}$$

In transcranial blood flow measurements, the velocity of the transmitted wave is 1,540 m/s and the velocity of the blood is around 1 m/s or less. Thus the above equation can be simplified to

$$f_2 = f_0\,(1+2v/c) \quad \textbf{(5)}$$

the Doppler shift frequency is the difference between the transmitted frequency and the received frequency

let f = the Doppler shift frequency

then $f = f_2 - f_0 = 2.f_0.v/c$ **(6)**

Thus, for practical purposes, the Doppler shift is proportional to the emitted frequency and velocity.

All the above calculations are based on the assumption that the blood is flowing directly towards the emitted waves. This is rarely the case in clinical practice as there is an angle, θ, that exists between the line of insonation and the line in which the blood is moving in. This angle is known as the angle of insonation. The component of the velocity that produces the Doppler shift is that part which travels along the line of insonation. If the blood is travelling perpendicular to the line of insonation, then the Doppler shift will be zero. The relationship between the Doppler shift frequency and the angle of insonation is expressed in the following formula

$$f = 2f_0.v.\cos\theta/c \qquad (7)$$

Rearranging (7), we have an equation to calculate the perceived velocity of the blood:

$$v = c.f/2\cos\theta.f_0 \qquad (8)$$

Thus, the velocity of the moving target (the blood flow velocity) will always be equal to or less than the true velocity, if angle correction is not made. As the angle increases so does the error. At 30°, the error will be 13.5% (cos 30 = 0.87) and at 60°, the error will be 50% (cos 60 = 0.5). In practical terms, the angle of insonation is unknown when using TCD. Thus, it is important to keep the angle of insonation as low as possible to minimise the error in calculating the velocity.

TCD Instrumentation

TCD utilises a transducer which acts both as the transmitter of waves and as the receiver of these waves. Short bursts of waves are produced and these travel through the medium (i.e. skull bone, brain parenchyma etc.) and then they reach the moving column of blood. The blood will reflect some of these waves back towards the transducer and these will be picked up. The waves will then be converted to electrical signals and amplified. There is a finite time taken for the transmitted pulse to travel to the target and then be reflected back to the transducer. This is the pulse

transit time and by varying this parameter, the depth of insonation can be varied. Thus, by having a long pulse transit time, the depth of insonation will be increased. This is the principle of range gating. This can also be used to select the sample volume i.e. the volume from which reflected signals are to be received. TCD generally employs large sample volumes such as 1 cm in order to maximise the probability of receiving a signal from the target.

Spectral Analysis

The received signal is processed in order to obtain a display. Firstly, the signal is filtered in order to reduce the low frequency 'wall thumps' due to arterial pulsation. The signal is analysed by fast Fourier transform (FFT). This is based on a mathematical formula and is usually performed by a microprocessor. The signal is thus converted to a spectral display which is seen on a monitor screen. The display consists of discrete lines ranging in number from 32 to 256. The intensity of each spectral line is represented by a grey-scale.

Aliasing

Because the transducer acts both as the transmitter and receiver of the pulsed wave, it can only sample the reflected waves once during the pulse sequence. The pulse-repetition frequency (PRF) is the frequency at which pulses of ultrasound waves are transmitted. This can be varied by the operator. If the insonation depth is large, then the PRF has to be low. This is because the pulse transit time will be large and so the reflected waves will take a long time to reach the transducer; if the PRF was high then the reflected wave would have had time to reach the transducer and be analysed before the next pulse is produced. Many TCD machines will automatically lower the PRF when the depth of insonation is increased. The PRF also determines the maximum Doppler shift that can be measured. This frequency is half that of the PRF and is termed the Nyquist frequency. If the Nyquist frequency is exceeded, then a 'wrap around' effect is produced when the spectral display is produced. This effect is termed aliasing. In this situation, the PRF is usually decreased by the operator in order to obtain a normal waveform pattern on the display.

Blood Flow Velocity

The measurement of velocity of a single target has been outlined above. The aim of TCD is to measure the velocity of the blood flowing in a vessel. The targets that act as reflectors of the ultrasound waves are the red blood cells themselves. However, not all red blood cells travel at the same velocity within a vessel. The cells closest to the vessel wall travel more slowly than those cells in the middle of the vessel (laminar flow). In addition, blood flow becomes disrupted at bends in the vessel and at bifurcations. In a given sample volume, the ultrasound waves will be reflected by all the cells in that volume. These cells will have a range of velocities and insonation angles and so the resulting frequency shift will consist of a range of values. This is termed intrinsic spectral broadening. By summing the effects of each component of the Doppler spectrum, it is possible to determine the intensity weighted, time averaged mean blood flow velocity.

The maximum frequency shift occurs when the blood flow velocity is at its greatest. This is termed the peak systolic velocity. The time averaged maximum or mean velocity is calculated by averaging the maximum envelope over a cardiac cycle.

2.2.2 TRANSCRANIAL COLOUR-CODED SONOGRAPHY

TCCS employs both B-mode ultrasound and a colour-coded ultrasound facility in order to create an image. As with TCD, the velocity of a moving target can be measured using pulsed waves and the velocities represented on a spectral display.

B-Mode Display

The components of a B-mode imaging system consist of a transducer, pulser, receiver, memory and image display. The pulser produces short bursts of electric voltage which cause the transducer to produce a short burst of ultrasonic energy. The pulses are usually less than 1 μs long. The receiver modifies the returning signal in several ways. It amplifies the signal so that it can be processed further. It also compensates for the fact that signals from deeper structures will be lower than those from more superficial structures. The receiver also acts as a filter to reject low signal 'noise'. The image is constructed by using the pulse-echo principle. By knowing the exact time it has taken for a wave to be reflected back to the receiver, the exact distance from the receiver can then be calculated.

Colour Flow Imaging

Colour flow imaging (CFI) allows the real time superposition of motion information which has been colour-coded onto a B-mode image. The colour display is coded in two ways. Firstly, the direction of blood flow is coded. This is traditionally coded red if the flow is towards the transducer and blue if the flow is away from the transducer. The display is also coded according to the Doppler shift frequency (and hence velocity) of the moving target i.e. the blood flow. Typically, high velocity towards the transducer is seen as orange/yellow and high velocity in the opposite direction is seen as light blue/green.

The spectral Doppler display is produced in virtually the same manner as for TCD. The pulsed waves can be generated in the same probe as that which generates the pulse echo for the B-mode imaging.

Transducers

There are several different types of transducers available for CFI. However, in transcranial work, the most commonly used transducer is a phased array transducer. These have a small head and a wide field of view and are also used in cardiac imaging. The field of view can be increased further if the scanning head is curved i.e. a curved phased array transducer. The transducer consists of a line of elements, usually between 32 and 64, which are arranged in either a straight or curved manner. A 'wave' is created by each element generating a pulse in sequence and then receiving that pulse.

Although these transducers have a wide angle of view, they have poorer image quality than linear array transducers. This is because some of the ultrasound energy is lost as it is not transmitted in the same direction as the main ultrasound beam.

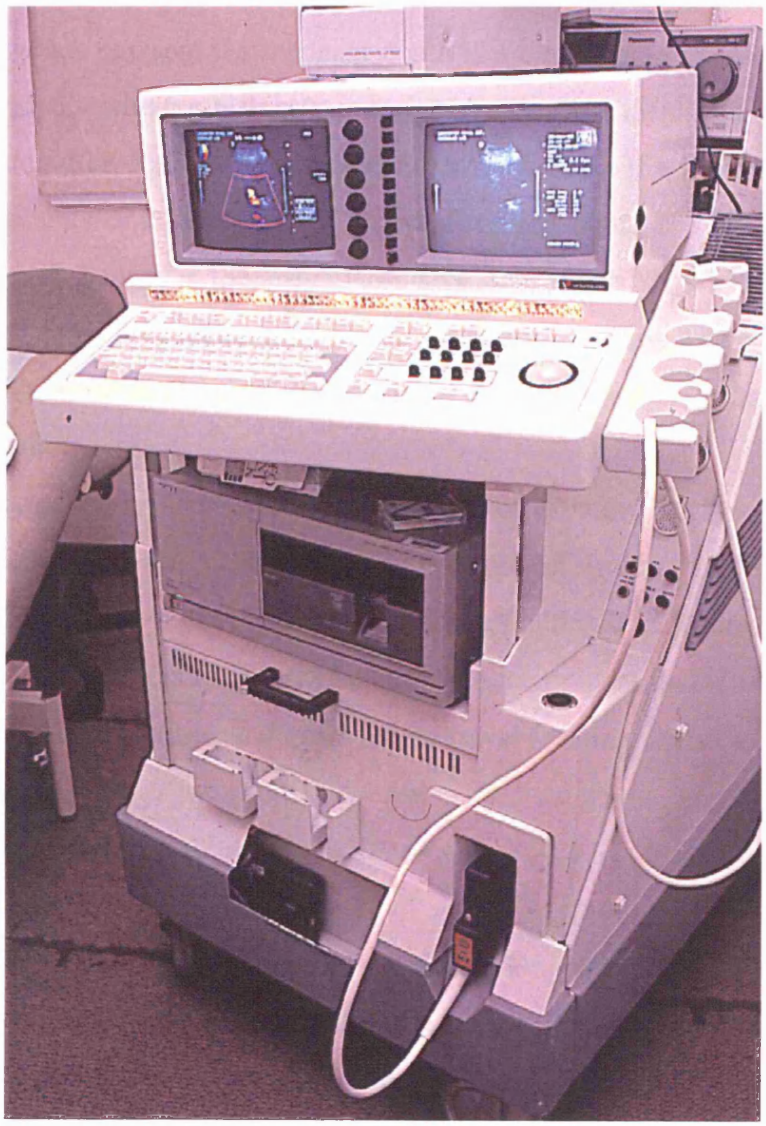
Performing the scan

All the scans performed in this study were carried out on a 'Spectra' series scanner (Diasonics Inc., Milpitas, California) (Figure 1). It was located in the vascular studies department in the surgical wing of The Leicester Royal Infirmary NHS Trust. The transducer had a curved phased array design with a radius of 20 mm and a scanning angle of 70°. The frequency of the pulsed wave to generate the B-mode was 2 MHz. The colour flow Doppler frequency was 2.25 MHz and the pulsed wave spectral Doppler frequency was 2 MHz.

B-Mode Imaging

B-mode imaging was started as soon as the transcranial probe was plugged into the front socket of the system. In practice, the B-mode image did not provide very much information as the images were very homogenous. Therefore, colour flow imaging was initiated as soon as possible.

Figure 1. The Diasonics master series scanner located in the vascular studies unit at the Leicester Royal Infirmary.



Colour Doppler Imaging

As soon as the colour Doppler control was activated, a colour-coded signal was superimposed on to the B-mode image. The depth of imaging could be altered using the depth switch which changed the scanning depth in 1 cm increments. A rectangle appeared in the display within which colour-coded signals were displayed. The size of the rectangle could be changed manually using a trackerball. If a large area was selected, large amounts of information had to be processed. Thus, the images were produced slowly and changes in the image were seen only after a short delay. If the scanning area was small, the images were produced almost instantly. The number of frames that could be processed were 3.4 per second for the largest areas and 27 per second for the smallest areas.

The colour gain could be adjusted manually and this increased the brightness of the colour Doppler signals. However, all signals were increased so that if the gain was set too high, a very 'noisy' picture was produced. As the depth of insonation was increased, the machine automatically increased the gain to compensate for the loss in signal that occurs when the ultrasound beam has to travel for long distances through a medium.

Spectral Doppler

The spectral display was activated by use of the pulsed Doppler facility. If this was selected, a spectral display was produced on one screen (generally the right hand screen) and the B-mode and colour coded images were displayed on the other screen.

The sample volume had a default setting of 5.4 mm. Although this setting was used most often, the size could be varied from 1.5 to 20 mm. The sample volume was displayed as two small parallel lines, the width of which corresponded to the volume. The vessel was interrogated by placing the sample volume over the vessel by means of a trackerball. Once the sample volume was in position, the angle correction facility was used. By turning a knob by the side of the screen, a small indicator could be rotated around until it lay along the long axis of the target vessel. This compensated for the angle of insonation and the angle was displayed on the monitor.

The pulse repetition frequency (PRF) was adjusted so that aliasing did not occur. The PRF could be adjusted manually for both colour imaging and spectral Doppler display. For spectral interrogation, the PRF could be varied between 1.4 kHz and 22.2 kHz depending on the velocity of the blood flow in the vessel under study. The PRF of the colour display could be varied between 100 Hz and 5 kHz and was generally kept between 1.5 and 3 kHz.

As with most scanning systems, a high pass filter (HPF) was available on the Spectra. The HPF is a filtering system whereby low frequency signals can be rejected. This is often useful to employ as many low frequency signals arise from vessel wall motion (wall thump) and their inclusion in the display gives rise to a 'noisy' image. However, it must be used with caution as by filtering out all low frequency signals, low blood flow velocities can also be missed. The HPF was usually set at 25-50 Hz for colour imaging and between 50-100 Hz for pulsed-wave Doppler interrogation.

Both the colour display and the spectral display could be inverted. This meant that, for colour imaging, all vessels with flow towards the probe were coded in blue instead of red and for blood flow away from the probe the vessels were coded in red. Inverting the spectral Doppler display meant that for blood flow towards the probe the deflection was negative and vice versa. Because no blood flow measurements could be made when there was a negative deflection in the display, these vessels had to be inverted before measurements were attempted.

All colour and spectral Doppler displays could be frozen and the scanner kept a record of previous imaging frames. Thus, all frames from a short series of cardiac cycles could be studied in detail and at the examiners leisure. A zoom facility enabled a chosen area to be enlarged which again aided vessel identification. In order to produce hard copies of the scans, both a colour printer (for the colour-coded B-mode images) and a monochrome printer (for the spectral Doppler display) were connected to the scanner. A 'text' button allowed formal text to be printed on screen which could then be incorporated on the hard copy for labelling. Additionally, an arrow could be placed anywhere in the display which was useful in identifying vessels when making hard copies.

Examination Technique

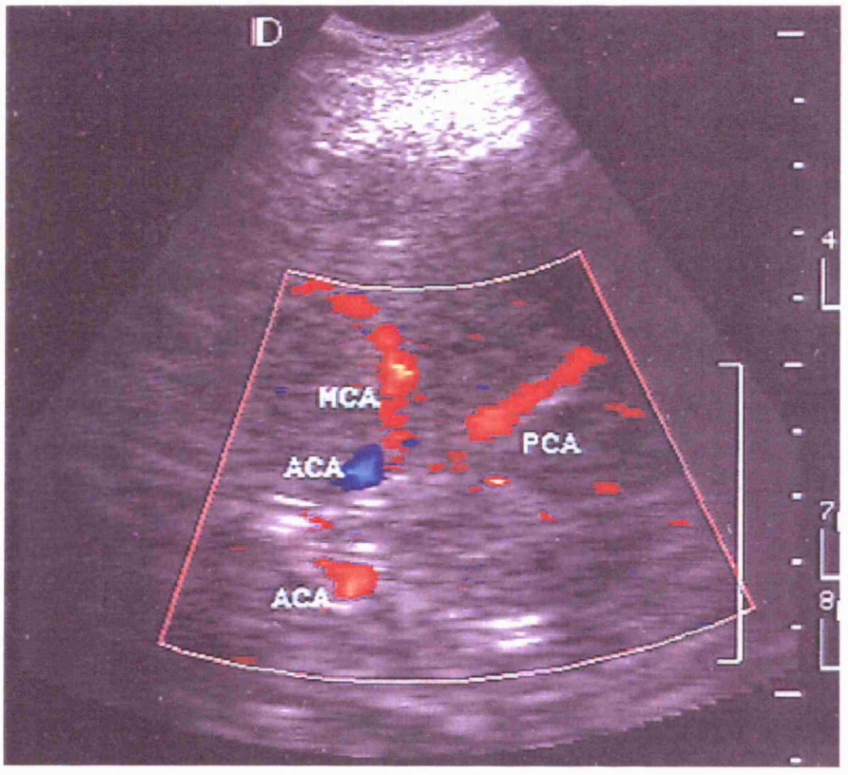
The majority of the examinations took place in the vascular studies unit where the scanner was situated. Subjects were studied in the supine position for imaging of the MCA, PCA and ACA. Generally, patients arrived at the unit by trolley and so were left on the trolley for the scan. The subjects were asked to lie as still as possible with their head turned to one side. Most subjects managed to lie completely flat, but in others their heads had to be propped up with extra pillows. In order to obtain good contact between the probe head and the skin, a large amount of ultrasound gel was used. The probe was then placed above the zygomatic arch and tilted slightly anteriorly. With the B-mode display on, the main feature that could be observed was the mid brain. This was represented by a small butterfly echolucent area at about 6-7 cm depth.

Generally, the B-mode display was not used for diagnostic purposes as the vessels could not be imaged well without the colour display. The colour imaging facility was then employed and a systematic search for the cerebral vessels was made. As with many examination techniques, the presumed normal side was always examined first in order to establish the anatomy before the symptomatic hemisphere was imaged.

Middle cerebral artery

The MCA is generally the most easily imaged vessel although this is obviously not the case in many stroke patients who have MCA occlusion. The MCA is found by angling the probe slightly superiorly and anteriorly. The MCA appeared in red as the blood flow was towards the probe (Figure 2). It could be seen originating at the terminal ICA and running in an antero-lateral direction. In the normal subject, the MCA could be imaged from its origin for a variable length (2-3 cm) until it divided. The finer branches of the MCA were rarely seen in much detail. The MCA originates at a depth of approximately 5.5-6.5 cm and can usually be imaged to a depth of 3 cm.

Figure 2. **The basal cerebral arteries in a normal subject imaged with TCCS. The middle cerebral artery (MCA) is seen colour-coded in red, the anterior cerebral artery (ACA) is seen in blue and the posterior cerebral artery (PCA) is seen in red.**



Anterior cerebral artery

The ACA originates at the termination of the ICA. It then travels antero-medially before joining the anterior communicating artery (ACoA). It is best imaged by following the MCA to its origin and then angling the probe slightly superiorly (Figure 2). The origin of the ACA is usually at a depth of 6-6.5 cm and can be imaged along its course for about 1-2 cm. The ACA was rarely imaged after it joined the ACoA as the A2 segment runs almost perpendicular to the ultrasound beam. As blood flow in the ACA is away from the probe, it was coded in blue. Care had to be taken not to confuse the terminal ICA with the ACA as the former can sometimes be coded in blue as well. However, the ACA runs in a more superior plane and has a higher frequency spectral Doppler display.

Posterior cerebral artery

The PCA was best imaged with the probe angled posteriorly in the horizontal plane. The two segments of the PCA (P1 and P2) could usually be imaged. The P1 segment curves around the midbrain and is colour-coded in red. It then starts to run posteriorly and as it curves it runs perpendicular to the ultrasound beam and is often difficult to image. The P2 segment runs in a postero-medial direction and is coded in blue. The PCA was usually seen running at a depth of 6-6.5 cm.

Occasionally the posterior communicating arteries could be imaged. They run between the PCA 1 and the terminal ICA. It is a small artery with a low flow in healthy subjects. It runs almost perpendicular to the ultrasound beam. Its low flow and large angle of insonation mean that it is only rarely imaged in normal subjects.

Pulsed Doppler Interrogation

All vessels that were imaged were interrogated with pulsed wave Doppler at a frequency of 2 MHz. The sample volume was usually left at the default setting of 5.4 mm. Using the trackerball, the sample volume was placed over the target vessel. It was generally placed at the most proximal part of the vessel or at that part of the vessel which ran most closely to the line of insonation. This minimised errors due to angle correction which was employed in all scans.

Once the sample volume was in the correct position, the display was switched to Doppler recordings. This froze the colour screen. After several cycles had been recorded, the spectral display was frozen (Figure 3). Using the memory facility, several cycles could be analysed in succession. The peak systolic velocity was measured by placing a marker at the maximum velocity on the Doppler display. The machine then automatically calculated the value. In order to calculate the mean velocity, the maximum velocity envelope was traced out by means of the trackerball. The velocity was then calculated by the scanner (Figure 4).

Figure 3. Spectral Doppler display of the middle cerebral artery in a normal subject. Peak velocity is 128.2 cm/s.

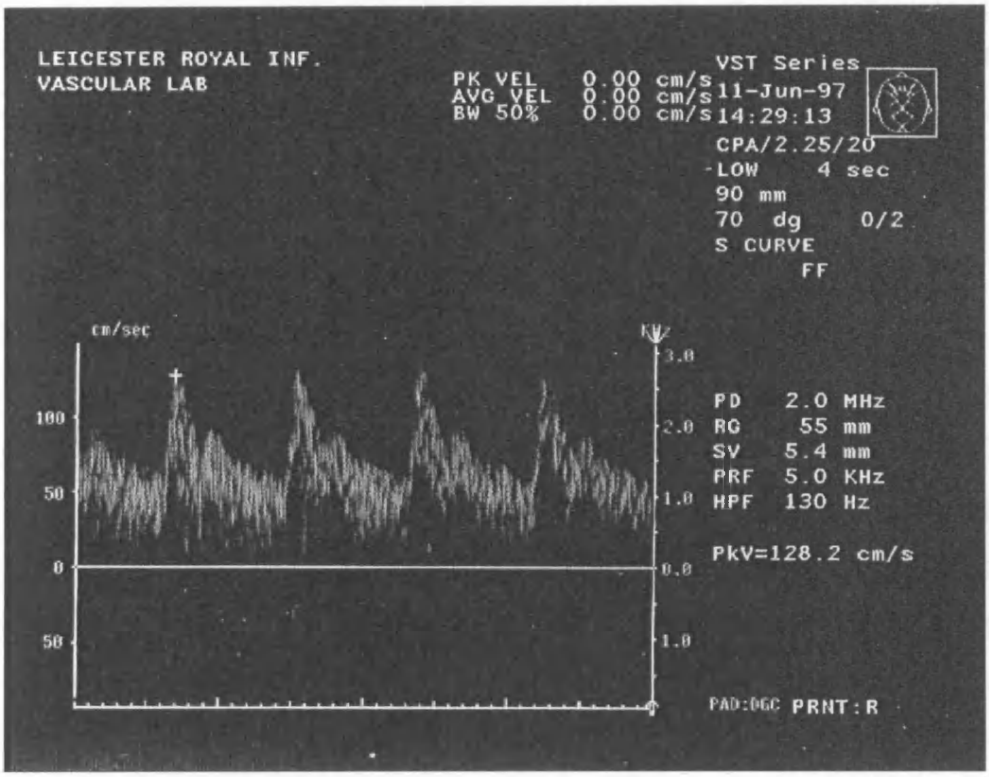
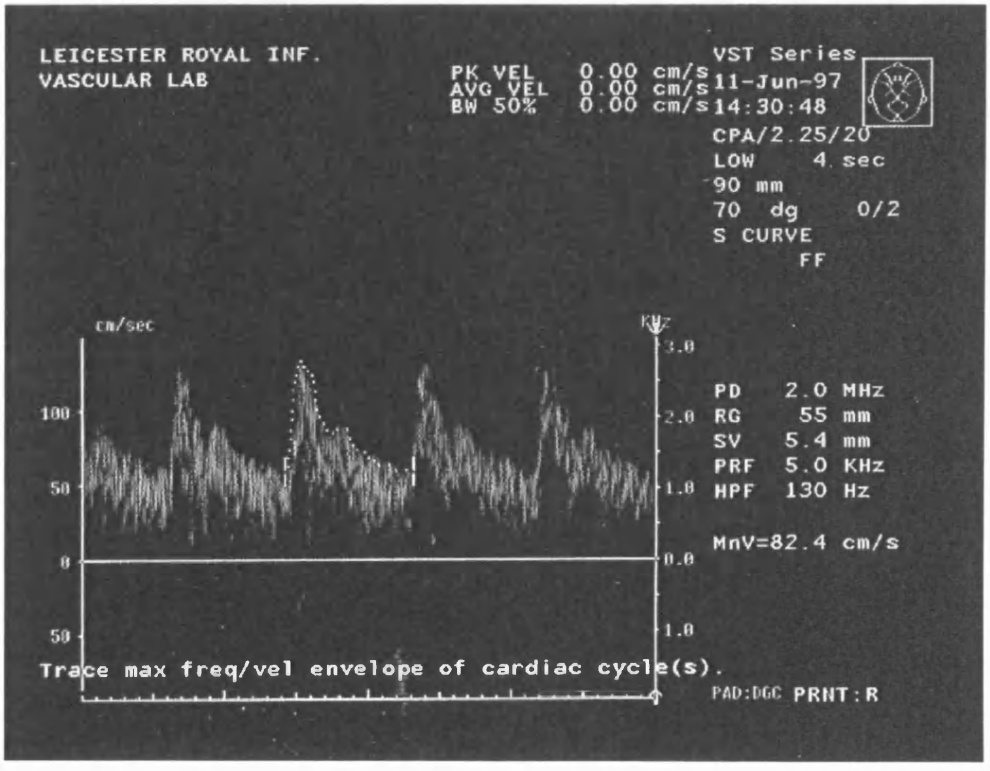


Figure 4. The mean velocity is calculated by manually tracing around the maximum velocity envelope. Mean velocity is 82.4 cm/s.



2.2.3 GENERAL LIMITATIONS OF TCD AND TCCS

Both TCD and TCCS have certain limitations that are common to both systems. Additionally, they have limitations peculiar to themselves and consequently, in some situations one technique is to be preferred over the other.

The acoustic window

White described the acoustic characteristics of the skull and divided the skull into 3 layers (White et al. 1978): an inner and outer layer of ivory bone and a middle layer of cancellous bone. It is the cancellous layer that proves to be the greatest barrier to ultrasound penetration due to its porous nature and arrangement of its spicules. Cancellous bone tends to cause ultrasound waves to scatter. In the temporal region, all three bony layers are at their thinnest and so penetration of ultrasound is at its highest. However, even by utilising the temporal window, 80% of the total ultrasound power may be lost. In order to maximise the penetration, lower frequency ultrasound is used in transcranial imaging (2-2.5 MHz). The power of the system can be increased although this may give rise to excessive 'noise' and may have safety implications.

The acoustic window therefore relies on the temporal bone being thin at that point. Unfortunately, hyperostosis (thickening of the inner table of the skull) tends to affect the frontal and temporal bones. It is especially common in the elderly population and is commoner in females. In an autopsy survey, hyperostosis was seen in 50% of the females over the age of 60 years (Gegick et al. 1973). Additionally, subjects of Afro-Caribbean and Oriental origin also tend to have hyperostosis and therefore often lack a suitable acoustic window. This caused failure of TCD in 30% of black women over the age of 50 years in one study (Halsey, 1990). Although the failure rate is generally between 10 and 15%, some TCD studies have estimated it to be as low as 5% (von Reutern and von Budingen, 1993) and as high as 35% (Kaps et al. 1990). TCCS studies generally report a higher failure rate, approaching 20-25% but again this is dependent upon the study population.

Operator dependency

Both TCD and TCCS, like all other ultrasound techniques, are operator dependent. Studies have shown good intraobserver variability when performing TCCS. Baumgartner studied 20 healthy subjects on 3 separate occasions within 10 days. Correlation coefficient was between 0.80 and 0.94 for the peak systolic velocity in the basal cerebral arteries (Baumgartner et al. 1994). Interobserver reliability has also been assessed for TCCS. Schöning and co-workers examined 27 normal subjects with TCCS and recorded blood flow velocities in the MCA, ACA and PCA (Schoning et al. 1993). Correlation coefficients for peak systolic and mean velocity were as follows: MCA, 0.68 and 0.70, ACA, 0.75 and 0.56, PCA, 0.63 and 0.56. Another study showed slightly worse interobserver reliability but studied fewer subjects (Martin, 1994).

Sample volume

TCD uses large sample volumes. This is because there is a better chance of obtaining a signal with large volumes. However, large sample volumes can lead to inaccuracies in velocity measurement if neighbouring vessels are included in the volume. With TCCS the sample volume can be decreased because the search for the vessel is not made using pulsed wave Doppler. Instead, the vessel is identified using the colour imaging display and then the vessel is interrogated with Doppler facility.

Vessel Identification

One of the main limitations that is especially evident with TCD, is that of mistaken vessel identification. In order to positively identify vessels using TCD, several parameters have to be taken into account. These include the depth of insonation, the direction of blood flow and various compression tests. Essentially, the search for a vessel is made in a 'blind' fashion. Once a frequency shift has been picked up, the depth of insonation has to be altered in order to 'track' that vessel. With TCCS, the vessels are colour-coded making identification much quicker and more accurate.

Particular difficulty is encountered with TCD when patients have anatomical variations in the circle of Willis or when collateral pathways exist.

Safety of Transcranial Ultrasound

Ultrasound has been used extensively in many areas of medicine. It has become part of the routine assessment of the foetus and it is probably due to its use in obstetrics that its safety has been scrutinised.

Ultrasound energy produces heat and can cause cavitation. The latter effect is caused by the production of bubbles. These bubbles oscillate with the pressure changes induced by the ultrasound. If oscillation increases, the bubbles can collapse and produce a shock wave which has the potential for tissue damage. However, this has not been demonstrated in transcranial imaging.

Ultrasound energy is partly converted to thermal energy and this causes warming of the insonated tissue. Low frequency ultrasound penetrates tissue deeper than higher frequencies and so leads to warming of deeper structures. Conversely, high frequency ultrasound leads to superficial warming. Bone in particular, heats up faster than soft tissue as it absorbs much more of the ultrasound beam. The spatial peak temporal average intensity ($I\text{-}_{SPTA}$) is the maximum value of the temporal average ultrasound in the acoustic field and is measured in mW/cm^2. There have been no reports of significant biological effects in mammalian tissues exposed to unfocused ultrasound with intensities below 100 mW/cm^2 or to focused ultrasound below 1 mW/cm^2 (American Institute of Ultrasound in Medicine, 1988).

In general, all transcranial examinations should be performed with low output settings and high receiver gain. The time spent with the transducer in contact with tissue should be kept to the minimum time necessary for the examination (European Federation of Societies for Ultrasound in Medicine and Biology. 1990).

2.2.4 NORMAL VALUES FOR MCA VELOCITY

Due to its angle correction, TCCS should be able to produce a more accurate estimation of blood flow velocity. There have been several studies reporting reference data for normal subjects using TCCS. They have generally shown that the velocities in all vessels are higher than previously measured with TCD. Reference values for the major cerebral arteries according to age and sex are given in table 1

Table 1. Reference values for middle cerebral artery velocity.

artery	velocity	female 20-39	male 20-39	female 40-59	male 40-59	female >60	male >60
MCA	vp^1	117±18	108±18	107±14	97±17	96±20	76±18
	vp^2	115±5	108±5	112±8	99±5	88±6	94±6
	vm	77±4	70±4	78±5	66±4	57±5	58±4
ACA	vp^1	90±19	82±17	83±16	73±18	82±23	62±17
	vp^2	90±5	91±7	96±8	82±6	78±10	80±5
	vm	57±7	58±4	66±5	56±5	51±7	51±7
PCA	vp^1	72±12	65±13	65±12	62±10	65±13	47±8
	vp^2	71±4	71±4	77±5	63±3	69±9	67±5
	vm	48±3	46±3	54±4	43±3	42±5	42±3

vm: mean velocity, vp^1: peak systolic velocity (Baumgartner et al. 1995), vp^2: peak systolic velocity (Martin et al. 1994)

Determinants of blood flow velocity

From the above values, it can be seen that velocities vary with both age and sex. However, many other factors also influence blood flow velocities.

Age

Many transcranial Doppler studies have shown a decrease in blood flow velocity with age (Ley-Pozo and Ringelstein, 1990; Ackerstaff et al. 1990; Brass et al. 1989; Grolimund and Seiler, 1988; Ameriso et al. 1990; Vriens et al. 1989) with a marked drop in velocities in the over 60 years age group. A decrease in cerebral perfusion and blood flow has been demonstrated by PET (Leenders et al. 1990). The loss of elastic tissue in the vessel wall with age may partly explain these findings since this loss will lead to dilatation of the vessel and a drop in velocity.

Sex

Cerebral blood flow has been reported as being slightly higher in females (Gur et al. 1987). This difference has been detected in TCCS studies (Martin et al. 1994; Baumgartner et al. 1995) as well as TCD studies (Grolimund and Seiler, 1988) but tends to be less marked in the those over 60 years of age. It has been hypothesised that the higher velocities seen in premenopausal women, is due to the lowering of the haematocrit by oestrogen (Grolimund and Seiler, 1988).

Blood Pressure

High blood pressure has been associated with higher systolic flow velocities in otherwise healthy subjects(Zwiebel, 1992). High blood pressure may also cause greater flow velocities due to constriction of the vessel (Lindegaard et al. 1987).

Haematocrit

Haematocrit and cerebral blood flow velocity are inversely proportional (Ameriso et al. 1990) and a similar relationship is also seen with haematocrit and cerebral blood flow (Brass et al. 1988). Sickle cell disease causes an increase in MCA velocity whereas polycythaemia causes a decrease in blood flow velocity (Brass et al. 1991).

Carbon dioxide

Carbon dioxide (CO_2) has a potent effect on cerebral blood flow. Hypercapnia will result in arteriolar dilatation, a fall in peripheral resistance and an increase in cerebral blood flow. A fall in the partial pressure of CO_2 will have the opposite effect. Measurements of blood flow velocity are made proximally to the resistance vessels and it is assumed that the diameter of the major basal arteries remains constant (Lindegaard et al. 1987). Thus, changes in blood flow velocity due to changes in the partial pressure of CO_2 should reflect changes in cerebral blood flow (Aaslid et al. 1989). Studies have shown a near linear increase in blood flow velocities with changes in CO_2 within the physiological range (Kirkham et al. 1986).

Monitoring CO_2 concentration is essential when the resting state of the subject is likely to have changed (e.g. before and after an operation). However, it is not usually monitored for intra or interindividual measurements as the changes are minor (De Witt et al. 1993).

Cardiac output

Changes in cardiac output should not affect cerebral blood flow if autoregulation is intact. However, changes in blood flow velocities have been noted in healthy subjects performing physical exercise (Hellstrom and Wahlgren, 1993). MCA velocity increases in mild to moderate exercise and decreases in vigorous exercise even in the presence of increasing heart rate and blood pressure. The rise in velocities with moderate exertion is thought to reflect a rise in systolic blood pressure. The subsequent fall in velocity may be related to a fall in CO_2 secondary to hyperventilation.

Fibrinogen

Fibrinogen levels and blood flow velocities are inversely proportional (Ameriso et al. 1990). Increased fibrinogen levels are associated with high blood viscosity and this will in turn lead to a high resistance and low velocity (Ameriso et al. 1990).

Vessel diameter

Changes in vessel diameter will result in changes in velocities. There has been a wide range of reported vessel diameters in normal subjects and may explain the range in blood flow velocities seen in healthy subjects (Lindegaard et al. 1987).

Cognitive activity

It has been shown that cognitive activity can influence blood flow velocities. Mental tasks, especially those that involve verbalisation, can lead to an increase in MCA velocity of up to 20% and have been used for the investigation of cerebral dominance (Markus and Boland, 1992). The blood flow velocities in the posterior circulation rise with visual stimulation (Aaslid, 1987).

Velocity Ratios

Velocities in the cerebral vessels can be expressed in absolute terms or as ratios of the velocity in one vessel compared to that in another. Ratios can either compare the velocity in one vessel with the velocity in the same vessel on the opposite side, or comparison can be made between two different vessels on the same side.

The ratio of MCA to ACA is approximately 1.3 in healthy subjects (Adams et al. 1992). In cerebrovascular disease, the ratio can fall below unity indicating that blood flow is greater in the ACA than in the MCA (Mattle et al. 1988). The ratio is lowered most in proximal disease of the MCA and is less marked in disease of the branches of the MCA. This has been used as a guide to the detection of disease in the MCA in patients who have had an acute ischaemic stroke (Kaps et al. 1990). The reasons for the fall in the MCA:ACA ratio are twofold. Firstly, the velocity of the MCA will fall in cases of distal occlusion and secondly, there will be shunting of blood via the leptomeningeal vessels to the ACA.

This ratio will also be affected if there is collateral flow in the anterior communicating artery. This may occur in cases of ICA occlusion where the blood flow to the ipsilateral hemisphere is maintained by retrograde filling of the ACA. In

this case the MCA velocity may still be in the normal range but the ACA velocity will be markedly increased.

Ratios have been devised to study the side to side asymmetry in certain vessels. The relative flow velocity (RFV) is simply the ratio of velocity in one vessel compared with the corresponding contralateral vessel. Because it takes into account both hemispheres, systemic variations, such as those due to cardiac output, should be cancelled out. It should therefore give an estimate of blood flow asymmetry. From studies on healthy subjects, the limit for normal side to side variations in velocity in the MCA is approximately 20% (Adams et al. 1992; Martin, 1994). The ACA tends to be more variable than the MCA in terms of its anatomy and consequently the RFV is greater at 35% (Martin, 1994).

Zanette devised another measure of side to side asymmetry: the asymmetry index (Zanette et al. 1989). This is expressed in the following formula:

$$AI = \frac{(MV_1 - MV_2)}{(MV_1 + MV_2)/2} \times 100\%$$

where MV_1 and MV_2 are the mean blood flow velocities in the ipsilateral and paired contralateral vessel respectively. It has been used mainly in the quantification of abnormal flow following acute cerebral infarction (Ni et al. 1994; Kushner et al. 1991).

2.2.5 CAROTID ULTRASOUND

As with transcranial ultrasound, there are several different types of machines available for performing carotid ultrasound. Generally, they employ pulsed-wave Doppler with a B-mode image (duplex systems) although some have colour flow imaging as well.

All the carotid ultrasound scans performed in this study were done so using the same machine as that used for transcranial imaging (Spectra system, Diasonics Inc., Milpitas, California). The probes used were either of 5 MHz or 10 MHz frequency according to the size of the patient.

Patients were examined in a semi-supine position. Initially the colour flow facility was switched off so that the B-mode image could be examined in detail. It is from this image that abnormalities of the vessel wall can be seen most clearly. Next the colour imaging was used in order to identify any areas of abnormal flow. Stenotic areas usually appeared as short sections of turbulent flow with aliasing. Pulsed-wave Doppler was employed to measure the Doppler shift frequency and hence determine the blood flow velocity in the target vessel. As with TCCS, compensation for the angle of insonation was made.

Intra-arterial angiography is the gold standard for imaging the carotid vessels and measuring the amount of stenosis. However, it does carry a definite risk of stroke and death which is greatest in those with acute cerebral infarction (Hankey et al. 1990). Non-invasive methods such as ultrasound have become more widespread and, with colour flow imaging, the results are comparable to angiography (Tegeler et al. 1991a).

The Doppler shift frequency varies according to the diameter of the vessel: as the vessel becomes more stenosed, the frequency shift, and hence velocity, will rise until the vessel is completely occluded and then no Doppler shift frequency will be detectable (Bluth et al. 1988). The findings were therefore expressed as a percentage reduction in diameter and for the purposes of this study were divided into 5 groups: normal (0%), mild (1-29%), moderate (30-69%), severe (70-99%) and occluded (100%).

CHAPTER 3

A COMPARISON OF TRANSCRANIAL COLOUR-CODED SONOGRAPHY AND MAGNETIC RESONANCE ANGIOGRAPHY IN ACUTE STROKE

3.1 BACKGROUND

The gold standard for the imaging of the cerebral vasculature is intra-arterial angiography. It provides clear anatomical detail and can also provide information on the collateral circulation. However, it involves arterial puncture and the injection of a potentially allergenic contrast medium. The risk of angiography in patients prior to carotid endarterectomy has been estimated to be 4% for transient neurological problems, 1% for stroke and 0.1% for death (Hankey et al. 1990). The figures are higher in patients with acute stroke. This has led to the decrease in the use of angiography in the assessment of the acute stroke patient. The use of digital subtraction angiography (DSA) enables smaller amounts of contrast medium to be injected and gives good anatomical detail. DSA can be performed by intravenous injection which decreases the neurological complications. However, it requires larger volumes of contrast media so that the risk of systemic reactions is increased. Additionally, intravenous DSA does not provide accurate anatomical information in up to 20% of studies (Turner and Murie, 1989).

Magnetic resonance angiography (MRA) is a non-invasive method of studying the cerebral vasculature. It has been used in a wide range of vascular abnormalities including carotid stenosis (Carriero et al. 1995), arteriovenous malformations (Turski et al. 1993), aneurysms (Huston et al. 1991) and venous thrombosis (Padayachee et al. 1991).

3.1.1 MRA Techniques

There are two basic MRA techniques: time of flight (TOF) and phase contrast (PC). Both techniques rely on the signal differences between flowing blood and stationary tissue and aim to enhance the former while suppressing the latter. In the TOF method, stationary tissue is partially saturated with repeated radiofrequency (RF) pulses. Blood flowing into the tissue is unsaturated and when it enters the saturated acquisition slice (2D) or volume (3D), it produces flow-related enhancement. This leads to a 'bright blood' or 'white blood' image, where flowing blood is seen as

white against a black or dark background tissue (Edelman, 1993). In order to produce angiogram-like pictures, the source images have to undergo volumetric post-processing methods. The most commonly used method is maximum intensity projection (MIP) which is based on a ray tracing algorithm. This allows the image to be viewed from different angles. 2D TOF is sensitive to low velocity blood flow and so is used to image veins or the carotid bifurcation. However, 2D TOF images can be severely degraded by motion. 3D TOF allows very thin slices to be imaged and is therefore used to image the cranial arteries. It is less motion sensitive than 2D TOF and the acquisition time is shorter.

PC MRA is based on velocity induced-phase shifts of moving spins in the presence of a magnetic gradient. Using complex phase subtraction and specially calibrated acquisitions, the difference in signal intensity between flowing blood and stationary tissue is proportional to the velocity of the flowing blood. Quantitative flow information can be derived from this method (Dumoulin et al. 1989). PC MRA is very sensitive to slow flowing blood and produces better background suppression than TOF techniques. However, it is very motion sensitive and acquisition and post processing times are longer than for TOF MRA (although these times may shorten with newer high gradient field systems).

3.1.2 MRA in Intracranial Abnormalities

In order to evaluate the ability of MRA to detect intracranial abnormalities, Stock performed both MRA and intra-arterial DSA in 50 non-consecutive patients (Stock et al. 1995). He used a 3D TOF technique and post-processing was carried out using a MIP algorithm. MRA had a 100% sensitivity and 100% specificity for detecting arteriovenous malformations, aneurysms with a diameter of more than 3 mm, intracranial vessel displacement and extracranial-intracranial bypass. MRA had a sensitivity of 100% and specificity of 95% for the detection of vessel occlusion, 50% and 98% for aneurysms smaller than 3 mm and a sensitivity and specificity of 86% for vessel stenosis. With regard to vessel occlusion, MRA gave two false positive results: one patient had collateral flow via the anterior cerebral artery and the other patient had retrograde flow due to an extracranial-intracranial bypass. It

was concluded that MRA was sensitive and specific in a range of intracranial abnormalities except in the case of small aneurysms.

3D TOF MRA has been shown to agree exactly with conventional angiography in identifying patients with MCA stenosis and MCA occlusion (Sawada et al. 1994).

MRA has also been evaluated in acute ischaemic stroke (Warach et al. 1992b). 34 patients were investigated within 48 hours of stroke: abnormal vessels seen on MRA corresponded well with abnormalities on T2 weighted images and on perfusion MRI. Following ischaemic stroke, MRA can detect abnormalities before T2 weighted images become abnormal (Warach et al. 1992a). The authors concluded that the combination of MRA with other MRI techniques would provide the clinician with a powerful non-invasive tool in the assessment of cerebral ischaemia.

MRA has also proved to be a useful tool in screening patients with sickle cell anaemia at risk of stroke (Seibert et al. 1993).

3.1.3 MRA and TCD

There have been some small studies in which MRA and TCD have been performed in patients with intracranial abnormalities. An interesting study compared the ability of each of these methods with intra-arterial DSA to assess MCA stenosis (Rother et al. 1994). The authors found that MRA identified all patients with DSA and TCD confirmed MCA stenosis. However, DSA did not detect 5 cases of TCD and MRA diagnosed stenosis. The authors concluded that the combination of TCD and MRA was more sensitive than DSA in the diagnosis of MCA stenosis and so DSA could no longer be considered the 'gold standard' investigation. This has yet to gain wide acceptance in the imaging of intracranial vessels but it is now common practice to image the extracranial carotid vessels with a combination of MRA and duplex ultrasound instead of intra-arterial angiography.

3.1.4 TCD and Intra-arterial Angiography

TCD and intra-arterial DSA have been performed together in several studies. Zanette studied 48 patients with these techniques within 6 hours of stroke onset

(Zanette et al. 1989). There was good agreement between TCD and DSA: in patients with DSA confirmed carotid siphon occlusion or occlusion of the proximal part of the MCA, TCD failed to detect a Doppler shift frequency. In patients with occlusion of 3 or more MCA branch vessels, TCD revealed significantly lower velocities in the ipsilateral MCA compared to the contralateral MCA. There was no such asymmetry seen in cases of less than 3 MCA branch vessel occlusions. Other studies have confirmed the high sensitivity of TCD in detecting intracranial vessel abnormalities. The sensitivity and specificity of detecting MCA mainstem occlusion has been reported as 91% and 99% respectively (Ley-Pozo and Ringelstein, 1990). Using a mean velocity cut off point of 80 cm/s, Rorick was able to detect 83% of DSA confirmed MCA stenoses in a group of 65 stroke patients (Rorick et al. 1994). Other authors have claimed higher rates for the detection of MCA stenosis: Ley-Pozo reported a sensitivity of 86% and a specificity of 99% (Ley-Pozo and Ringelstein, 1990) and Camerlingo reported a sensitivity of 92% (Camerlingo et al. 1993). In all these studies, TCD has been shown to have a high specificity and sensitivity for the detection of intracranial stenosis and occlusion.

3.2 AIMS OF THE STUDY

At the time of writing, there were no reports of the sensitivity or specificity of TCCS to detect intracranial abnormalities in stroke. Although a few studies have employed TCCS in the setting of stroke, none have evaluated this technique against an established imaging method. The imaging technique of choice in order to validate TCCS is intra-arterial DSA. However, due to its invasive nature and associated complications, it was not thought ethical to expose patients to DSA. Therefore, MRA was used in order to assess the cerebral vasculature.

The aims of this study were:

(i) to assess the feasibility of performing MRA in the setting of acute stroke

(ii) to assess the ability of TCCS to detect abnormalities in the basal cerebral arteries following stroke

(iii) to determine the changes in MCA velocity in MRA confirmed cases of vessel occlusion and stenosis.

3.3 SUBJECTS AND METHODS

44 patients were entered into the study (21 male, 23 female; age range: 40-88 years, median: 74.8 years). T2 weighted axial magnetic resonance images of the brain were taken at the same time as the MRA in order to differentiate ischaemic from haemorrhagic stroke and to exclude other causes of acute neurological deficit.

TCCS was performed in the usual manner. The mean MCA velocity was measured in all basal cerebral arteries and the asymmetry index was calculated. An occluded vessel was inferred by lack of signal on the colour display despite visualisation of at least 2 other vessels and lack of any signal when interrogated with pulsed-wave Doppler.

Mean time from symptom onset to TCCS was 15.4 hours (range: 4-24 hours). TCCS was performed within 4 hours of MRA (range: 15 minutes to 4 hours, median 2 hours).

MRA was performed on a 1T Magnetom system (Siemens, Erlangen, Germany) employing a circularly polarised transmit-receive head coil with 26 cm inner diameter. 3D Time of Flight images were obtained using a FISP 3D sequence, in the majority of cases utilising magnetisation transfer and TONE to improve contrast between flowing blood and background tissue (TR36, TE10, flip angle 20, acquisition 1, field of view 230×230, matrix 256×256, slab thickness 50 mm, time of acquisition 9 minutes 52 seconds. Using MTC and TONE, a 192×256 matrix in conjunction with a TR of 42 ms gave a total acquisition time of 8 minutes 30 seconds). Post-processing employed maximum intensity projection (MIP) to produce angiographic like images. These were viewed in 12 projections rotated about a side to side axis through the imaging volume. The source data and targeted MIPs were employed if there were equivocal results from the full MIP data set. The MRA results were assessed by a consultant radiologist, Dr A. Moody. The vessels were classified into 3 groups according to their MRA appearances: normal, attenuated and absent. MRA was performed blinded to the results of the clinical examination and TCCS. TCCS was performed blinded to the result of MRA and MRI but not to the clinical state of the patient.

3.4 RESULTS

3.4.1 Patient details

14 patients were excluded from the study: 5 patients lacked a suitable acoustic window for TCCS, 4 patients were too restless to obtain adequate MRA scans, 3 patients had primary intracerebral haemorrhages and 2 patients had intracerebral gliomas.

The remaining 30 patients had definite acute cerebral infarction diagnosed by MRI.

A summary of the results are given in Tables 1 and 2; the mean MCA velocities according to MRA findings are given in Table 3.

3.4.2 TCCS and MRA

Of the patients presenting with cerebral infarction, 10 were found to have normal AIs in the MCA (i.e. ±20%). Average mean MCA blood flow velocities were 53.4 cm/s (range: 34-88.8 cm/s) in the symptomatic vessel and 55.5 cm/s (range: 35.6-88.6 cm/s) in the asymptomatic vessel. There was no significant difference between these velocities. 8 of these patients had normal MRA scans (Figure 1). T2 weighted MRI scans of these 8 patients were normal in 2 patients, revealed scattered high signal areas, indicative of small vessel disease, in 2 patients, a small high signal area in the internal capsule in 2 patients and a small high signal area in the parietal lobe in 2 patients. MRA in the remaining 2 patients with a normal AI, revealed MCA branch vessel attenuation on the symptomatic side; T2 weighted MRI was normal in 1 patient and revealed small vessel disease in the other patient.

In 10 patients no colour-coded or spectral Doppler signal could be detected from the MCA despite obtaining adequate signals from both anterior cerebral artery (ACA) and posterior cerebral artery (PCA). Mainstem MCA occlusion was therefore diagnosed. The AI of all these patients was -200%. The average mean MCA velocity in the asymptomatic vessel was 41.1 cm/s (range: 34.3-48.4 cm/s). All 10 patients had absent MCAs on the symptomatic side on MRA (Figure 2). In addition, 1 patient had an occlusion of the ipsilateral internal carotid artery (ICA)

(tandem lesion), confirmed by colour-coded duplex ultrasonography (Figure 3). In 7 of the patients with MCA occlusion, velocities in the symptomatic ACA were significantly greater than the contralateral hemisphere (AI>+27%) (Zanette et al. 1995). MRA failed to show any differences between the ACAs in these patients. T2 weighted MRI scans revealed large MCA territory infarctions in 8 patients (Figure 4), a basal ganglia infarction in 1 patient and scattered high signal areas in 1 patient.

9 patients were found on TCCS to have a reduced AI (range: -20.1% to -78.9%, mean: -44.8%) (Figure 5). The average MCA velocity was 30.5 cm/s (range: 21.1-44.2 cm/s) on the symptomatic side and 48.5 cm/s (range: 30.5-69.4) on the asymptomatic side; the difference in the average velocity in the 2 groups was statistically significant ($p<0.006$, Student's t-Test). MRA revealed 2 patients to have marked attenuation of the proximal segment of the MCA (Figure 6) and MRI scans showed a parietal lobe infarction in 1 patient and a haemorrhagic parietal lobe infarction in the other. 4 patients had evidence of M2 branch vessel occlusion on the symptomatic side (Figure 7). One patient also had an occluded ICA diagnosed by colour-coded duplex ultrasonography and TCCS showed retrograde filling of the ipsilateral ACA combined with a high flow velocity in the anterior communicating artery indicating interhemispheric collateral flow (Figure 8). MRI scans showed high signal areas consistent with infarction in MCA branch vessel territory in all patients (Figure 9). The remaining 3 patients with a reduced AI had M2 branch vessel attenuation on MRA; MRI was normal in 1 patient and showed evidence of a small parietal lobe and basal ganglia infarction in 2 patients.

1 patient presented with a high AI (+73.5%); mean MCA velocity 55.4 cm/s. MRA indicated MCA branch attenuation on the symptomatic hemisphere and MRI revealed a parietal lobe infarction.

Table 1. Middle cerebral artery velocity, asymmetry index and MRA findings in patients with acute cerebral infarction.

pt	mean MCA velocity cm/s		AI (%)	MRA findings	site of infarction on MRI
	sym	asym			
1	0	41.0	-200	MCA occlusion	par-temp
2	0	42.5	-200	MCA occlusion	bg
3	0	48.4	-200	MCA occlusion	par-temp
4	0	43.3	-200	MCA occlusion	par-temp
5	0	36.8	-200	MCA occlusion	par-temp, bg
6	0	34.3	-200	MCA occlusion	par-temp
7	0	44.8	-200	MCA occlusion	par-temp-frontal
8	0	43.8	-200	MCA occlusion	par-temp-frontal
9	0	35.6	-200	MCA occlusion	small hs in occ,par
10	0	40.6	-200	MCA occlusion	par-temp-frontal
11	21.1	48.6	-78.9	branch occlusion	fronto-par
12	30.4	68.5	-77.3	mainstem attenuation	par
13	24.8	49.0	-67.2	mainstem attenuation	par
14	41.0	69.4	-51.4	branch occlusion	int cap, occ
15	21.7	30.5	-33.7	branch attenuation	par
16	21.6	29.3	-30.3	branch attenuation	bg
17	38.5	48.9	-23.8	branch attenuation	normal
18	44.2	54.2	-20.3	branch occlusion	par
19	31.3	38.3	-20.1	branch occlusion	par
20	49.9	59.3	-17.2	normal	small vessel disease
21	48.8	56.8	-15.1	branch attenuation	small vessel disease
22	51.5	60.3	-7.9	normal	normal
23	34.0	35.6	-4.6	branch attenuation	normal
24	55.3	56.8	-2.6	normal	int cap
25	88.8	88.6	0.2	normal	normal
26	45.9	44.8	2.4	normal	par
27	54.1	52.3	3.4	normal	small vessel disease
28	52.3	50.4	3.7	normal	par
29	53.7	49.7	7.7	normal	int cap
30	55.4	25.6	73.5	branch attenuation	par

AI: asymmetry index, MCA: middle cerebral artery, MRA: magnetic resonance angiography, MRI: magnetic resonance imaging, pt: patient, par: parietal lobe, temp: temporal lobe, occ: occipital lobe, bg: basal ganglia, int cap: internal capsule, sym: symptomatic, asym: asymptomatic.

Table 2. Clinical details

pt	age	sex	risk factors	clinical details
1	77	f	BP	HP, HH, FP
2	72	f	BP, TIA	HP, FP
3	84	f	TIA	HP, HH, FP
4	75	f	BP, SMO	HP, HH, DP, FP
5	76	f	IHD	HP, HH, DP, FP
6	76	f	BP	HP, HH, DP, FP
7	73	m	BP, IHD, DM	HP, HH, DP, FP
8	75	m	IHD	HP, HH, DP ,FP
9	65	m	IHD	HP, HH, FP
10	76	f	BP, IHD	HP, HH, FP,
11	88	m	TIA	HP, HH, FP, DP
12	61	f		DP
13	86	f		HP, HH, FP
14	71	f		HP, HH, FP, DP
15	81	m	BP, TIA, IHD	HP, FP
16	84	f	IHD	HP, FP
17	76	f	BP, TIA, DM, IHD	HP, FP,
18	80	f	TIA	HP, FP
19	79	f		HP, HH, FP
20	84	m		FP
21	79	m		HP, FP
22	83	f		HP, FP
23	72	f	BP	HP
24	57	f		HP
25	57	m		FP
26	71	f		HP, FP
27	78	m	SMO	HP, FP
28	48	m	BP	HP, FP
29	68	m	TIA, SMO	HP
30	60	m		HP, FP

HP: hemiparesis, HH: homonymous hemianopia, FP: facial palsy, DP: dysphasia, BP: hypertension, TIA: transient ischaemic attack, IHD: ischaemic heart disease, SMO: smoker, DM: diabetic

Table 3. Values of Symptomatic Mean MCA Velocity in Patients According to MRA Findings.

	mainstem attenuation	branch occlusion	branch attenuation	normal	reference value*
n	2	4	6	8	53
mean velocity (cm/s)	27.6	34.4	36.7	56.4	58.0
95% CI	±5.5	±10.2	±11.1	±9.3	±3.0
range	24.8-30.4	21.1-44.2	21.6-55.4	45.9-88.8	n/a

MCA: middle cerebral artery, MRA: magnetic resonance angiography, n/a: not available, * from Martin et al 1994.

Figure 1. **Magnetic resonance angiography in a patient demonstrating normal basal arteries.**

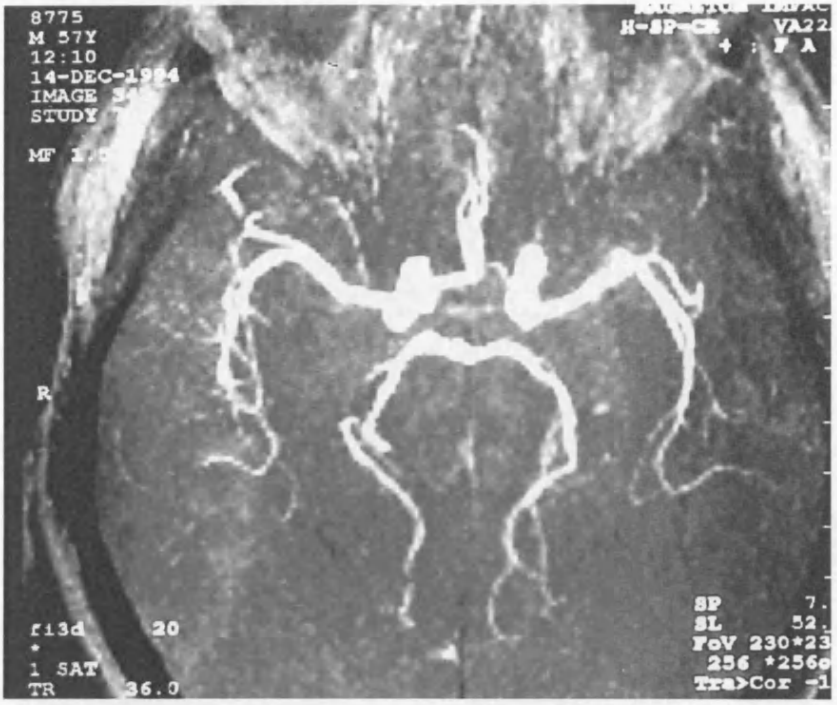


Figure 2. **Magnetic resonance angiography in a patient with occlusion of the proximal segment of the middle cerebral artery (arrow).**

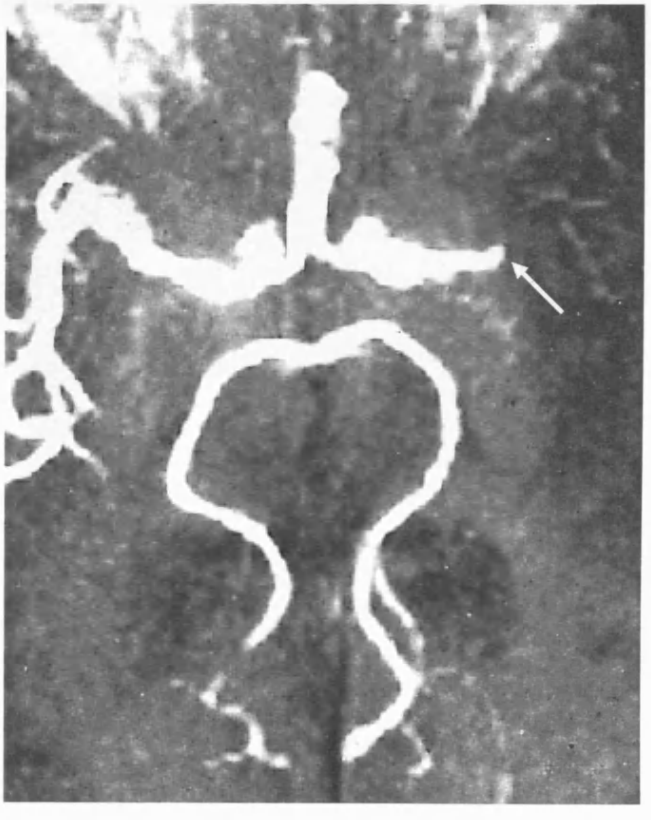


Figure 3. **Occlusion of the internal carotid artery demonstrated by colour duplex ultrasound. The common carotid artery fills normally (red) and then comes to an abrupt stop at the site of the occlusion (arrow).**

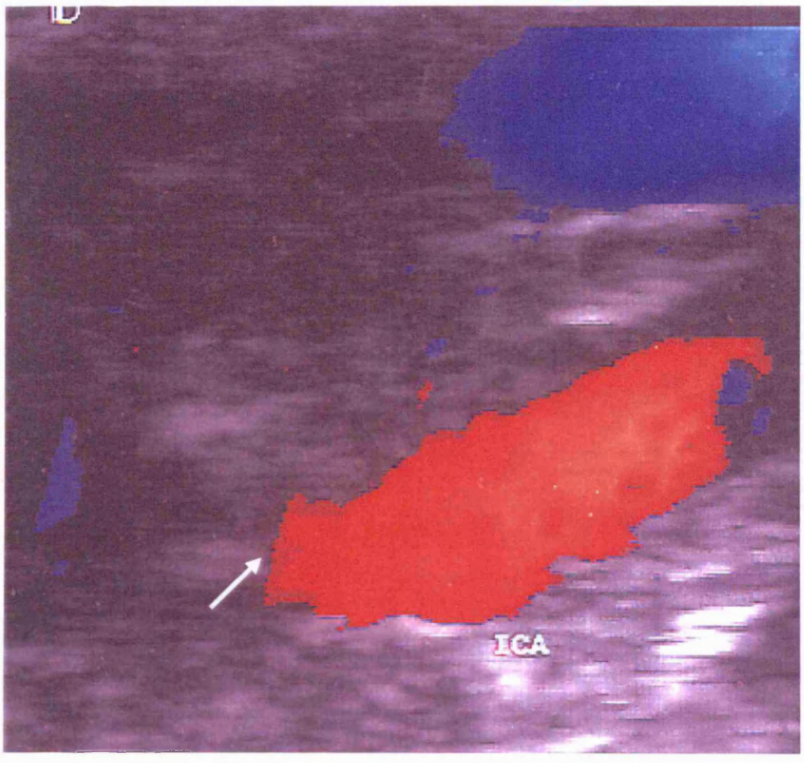


Figure 4. **T2 weighted magnetic resonance image of a large middle cerebral artery territory infarction.**

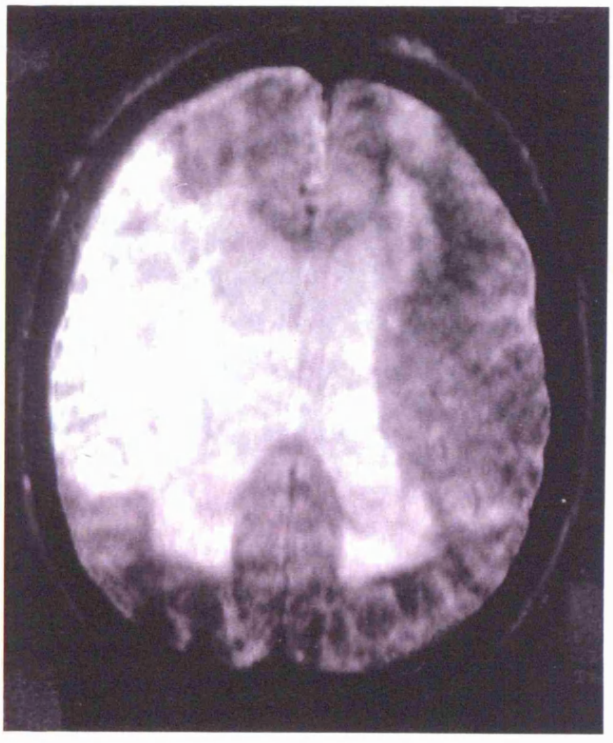
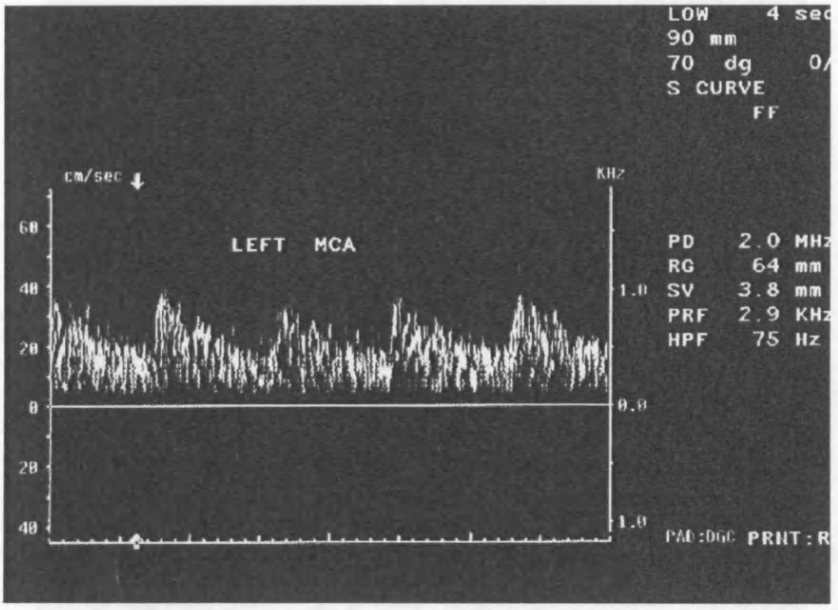


Figure 5. **Spectral Doppler display of the left and right middle cerebral artery of a patient with left middle cerebral artery branch occlusion on MRA. The mean velocity in the left MCA is much lower than that of the right MCA resulting in a low asymmetry index. Note the different scales used in each display.**



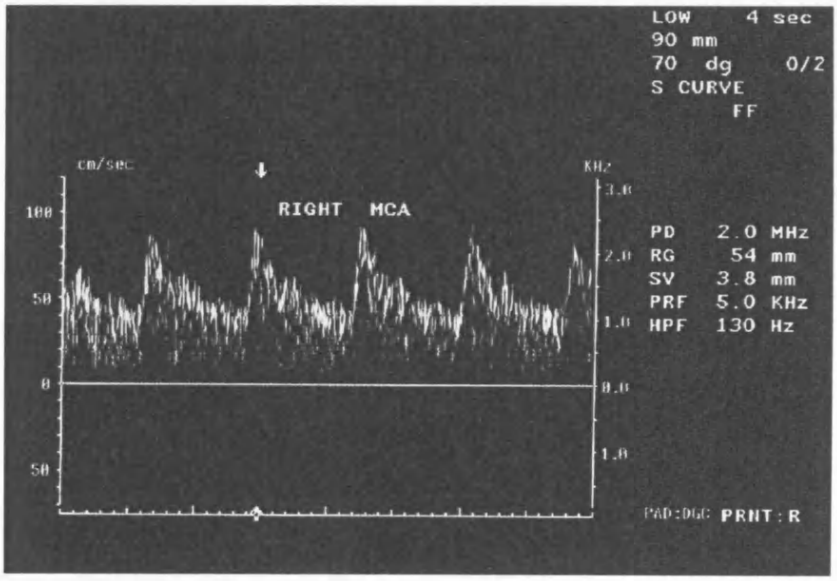


Figure 6. Attenuation of the mainstem of the right middle cerebral artery demonstrated by magnetic resonance angiography (arrow).

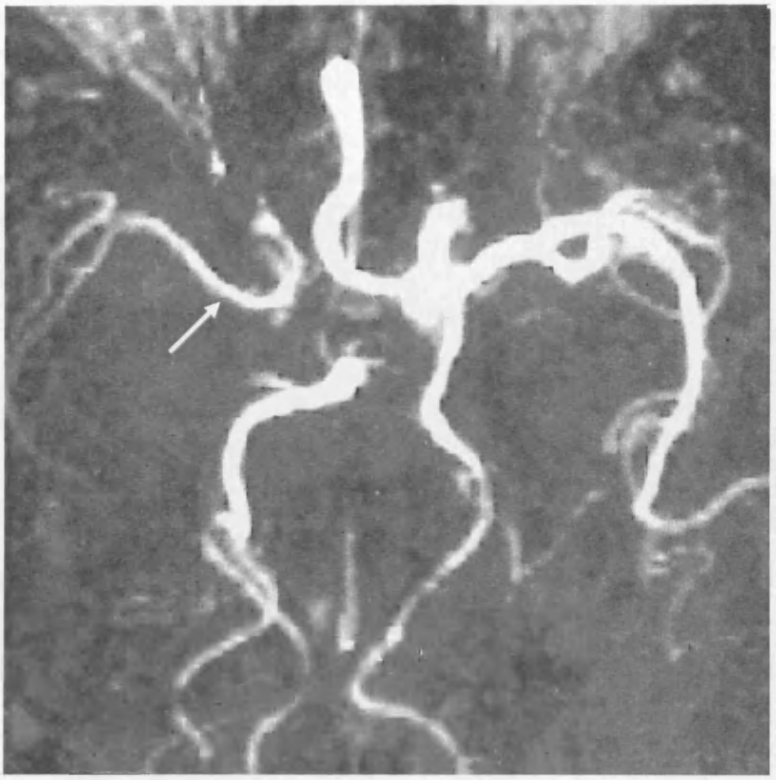


Figure 7. MRA showing occlusion of a number of branches of the left middle cerebral artery (arrow).

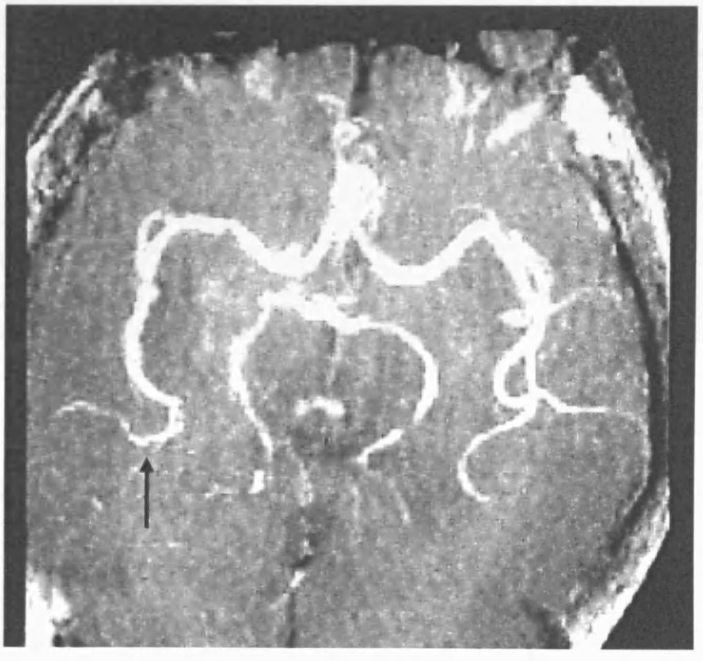
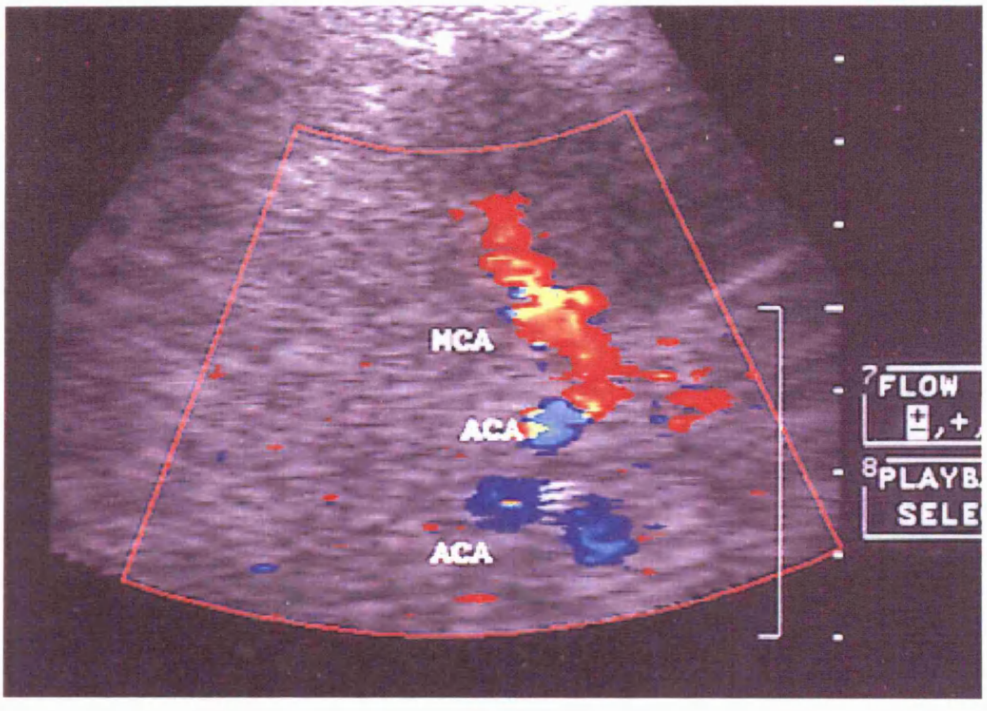
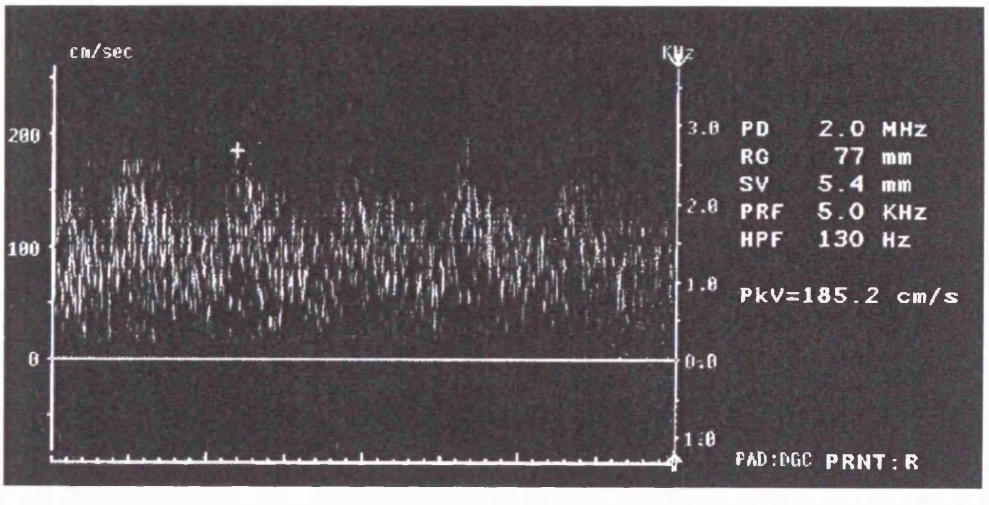


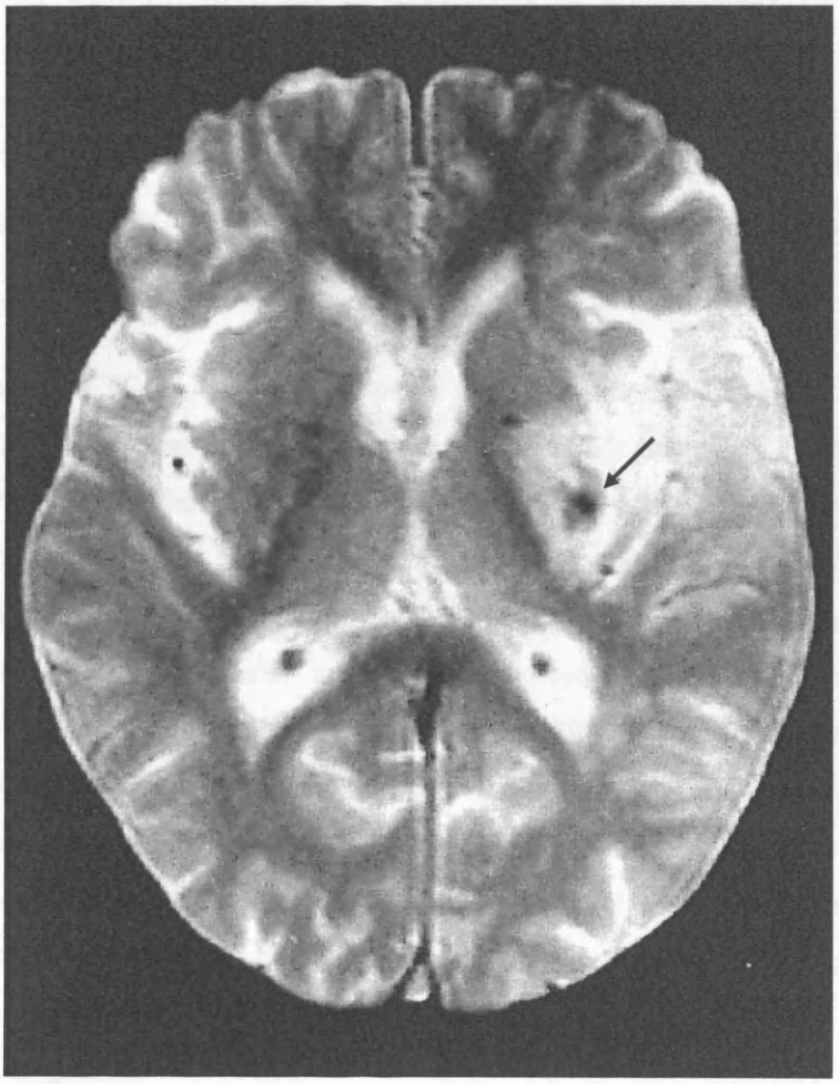
Figure 8. **Collateral flow from the contralateral internal carotid artery via the anterior cerebral artery (ACA). Both the middle cerebral artery (MCA) and the ACA are seen in red. The ipsilateral ACA is normally colour coded in blue because the flow is away from the transducer. However, in this patient the contralateral internal carotid artery was supplying the ipsilateral MCA via the anterior communicating artery causing flow reversal in the ipsilateral ACA.**





Spectral Doppler display of the anterior communicating artery. There is marked turbulence and a very high blood flow velocity (peak velocity = 185 cm/s) typical of a collateral vessel.

Figure 9. **Infarction caused by occlusion of branch vessels of the middle cerebral artery demonstrated on a T2 weighted magnetic resonance image. There is also a small haemorrhage adjacent to the infarction (arrow).**



3.5 DISCUSSION

One of the main limitations of TCD has been the number of patients that lack a suitable acoustic window, which has been estimated at approximately 10-15% (Wada et al. 1990). This is slightly less than for TCCS (von Reutern and von Budingen, 1993) which, due to the B-mode imaging, lacks the penetration of conventional TCD. The failure rate increases with age and is also higher in females due to the higher prevalence of temporal hyperostosis. In our study population, the majority of the patients were over 65 years old (34 out of 43) and the failure rate was 16.3%.

Another limitation of TCCS is the lack of spatial resolution compared to MRA. It is not always possible to visualise the M2 branches of the MCA using TCCS. This is due to the slower flow in these branches compared to the M1 portion. Therefore, as it is not usually known exactly how many M2 branches there are, it is not possible to make a certain diagnosis of M2 branch occlusion with TCCS. A previous study comparing TCD and intra-arterial angiography showed that multiple branch occlusion was associated with a low AI (Zanette et al. 1989). This was confirmed in our study as all 4 patients with branch occlusion had low AI's. In addition, these patients had low absolute MCA velocities in the symptomatic hemisphere. The low velocity resulting from the distal obstruction is due to 'damped' flow velocity and is also seen in other vessels such as the common carotid artery proximal to occlusion of the ICA.

There was exact agreement between the 2 techniques for diagnosing MCA mainstem occlusion. However, this finding can only be reported with confidence with TCCS if the other vessels can be clearly identified. Otherwise, failure to identify the MCA may be a result of poor ultrasound penetration. This highlights another area in which TCCS is superior to conventional TCD: with the B-mode facility and colour-coding of TCCS, the major vessels can usually be identified rapidly and with more certainty than with TCD and so the lack of an MCA signal is apparent immediately. This reduces the lengthy 'search' required with TCD to image the ACA and PCA in order to make a definite diagnosis of MCA occlusion. An associated finding in acute MCA occlusion is raised blood flow velocity in the ipsilateral anterior cerebral artery

(ACA). This is due to a shunting of blood from the occluded MCA to the patent ACA and has been reported in previous studies (Kaps et al. 1990; Mattle et al. 1988; Zanette et al. 1989). This finding was present in 7 of our patients with MCA mainstem occlusion.

In our study group, many of the patients were restless following the event and the quality of the MRA was consequently reduced. This can make interpretation of the finer branches of the MCA difficult and may lead to an overestimation of the number of attenuated MCA branch vessels present. In addition, some patients with acute stroke have very low absolute MCA velocities and this may give rise to reduced flow related enhancement with this time of flight technique and thus an overestimation of the number of MCA branch occlusions.

Although MRA in this study was able to give detailed anatomical information, it did not provide any quantitative data regarding blood flow velocity. The use of phase contrast techniques (Dumoulin et al. 1989) may, however, provide flow information that not only relates to the direction of flow, but may also give true quantitative flow velocity data.

There was a significant difference between the mean MCA velocities in the patients with normal MR angiograms and the 12 patients with attenuated or occluded MCA branch vessels on MRA (Table 2). 8 out of these 12 patients had a mean MCA velocity outside the normal reference range (i.e.<40 cm/s). The lower velocities in patients with an abnormal MRA probably reflected the presence of distal flow disturbances in the MCA. The mean MCA velocity in patients with a normal MRA was 56.4 cm/s and none of these patients had a mean MCA velocity under 40 cm/s. The value of 56.4 cm/s agrees closely with reference data for healthy subjects over 60 years of age (mean MCA velocity: 58 cm/s; 95% CI: 55-61 cm/s) (Martin et al. 1994). All patients with a normal MRA had either a hemiparesis or a facial palsy and none had evidence of higher cortical dysfunction. The normal MCA velocities recorded in this group is in keeping with the presumed small vessel pathology underlying such lacunar infarctions (Horowitz et al. 1992) and agrees with previous studies (Naylor et al. 1993).

An AI of less than -20% had a specificity of 100% and a sensitivity of 86% in identifying patients with an abnormal MRA. For a mean MCA velocity of less than

40 cm/s, the specificity was 82% and the sensitivity was 100%. Thus, mean MCA velocities above 40 cm/s or an AI greater than -20% are strong predictors of a normal MRA. The AI missed 3 patients who had an abnormal MRA; in each case the abnormality was a small degree of branch attenuation without vessel occlusion.

TCCS is a useful tool in the assessment of the acute stroke patient. The equipment is portable and can therefore be used as a bedside investigation. This may prove advantageous in certain patient groups such as those too ill to undergo conventional neuroimaging. TCCS can be easily repeated and may prove useful in monitoring patients response to therapeutic intervention. The scans can be performed rapidly: the cerebral vessels being imaged within minutes if there is an adequate acoustic window. This may have implications for the assessment of patients undergoing treatment which has to be performed within a strict time limit. TCCS can be performed early in the clinical course of the stroke and, like MRA, may show flow abnormalities which are not yet apparent on either CT or standard T1 and T2 MR imaging. However, there is quite a substantial failure rate due to the lack of a suitable acoustic window, especially in elderly females. This is a particular problem in cerebrovascular disease as most of the patients are elderly.

MRA is more able to demonstrate the anatomy of the circle of Willis, especially the finer branches of the basal cerebral arteries. MRA has the advantage that it is not limited by the availability of an acoustic window, which precluded TCCS on 5 patients. However, in our study, there were 4 patients who had to be excluded because, once in the MR scanner, they could not keep still enough for adequate imaging. MRA is also limited by the possible generation of artefacts in the processing technique (Tsuruda et al. 1992). These include the overestimation of stenosis, mistaking stenosis for occlusion, vessel overlap, misinterpreting stationary bright areas for blood and the poor visualisation of small vessels (Baumgartner et al. 1995).

We have shown that TCCS can reliably identify proximal MCA occlusion. MRA can identify attenuation and occlusion of distal MCA branches which cannot be imaged satisfactorily with TCCS. However, the latter findings can be inferred if mean MCA velocity is below the threshold value of 40 cm/s or if the AI is less than -20%.

CHAPTER 4

MIDDLE CEREBRAL ARTERY VELOCITY AS A PROGNOSTIC INDICATOR IN THE ACUTE STAGES OF ISCHAEMIC STROKE

Chapter 4

4.1 BACKGROUND

Patients who have ischaemic cerebrovascular disease exhibit a very wide range of clinical manifestations. Some patients with cerebrovascular disease are asymptomatic; the disease only becoming evident after certain investigations have been performed e.g. a CT scan. Conversely, patients can present with infarctions of large parts of the cerebral cortex and a high risk of death. Thus, the definition of a stroke encompasses a large spectrum of clinical entities and so the prognosis of stroke is also highly variable.

When a patient has a stroke, it is important to have a guide to their prognosis, not only for the benefit of the patient and family who obviously want to know, as soon as possible, what the chances of recovery are, but also for the benefit of the carers who need this information in order to target treatment and resources appropriately. It seems obvious that a 52 year old who walks into the outpatient department with a mild weakness of their arm and no other symptoms has a much higher chance of being self caring in 3 months time than a 90 year old patient who is admitted to casualty unconscious and not responding to any stimuli. In this scenario, prognosis has been calculated based on 2 measures: age and severity of the stroke. It would seem rational that young patients have a better outcome than older patients and that patients are more likely to do well if they have a 'mild' stroke as opposed to a 'severe' stroke. However, there may be many factors that contribute to a 'severe' stroke that do not necessarily affect prognosis.

Since stroke is a common disease, it is possible to obtain large amounts of data regarding outcome. By looking at outcome at a certain period following the stroke, a number of factors that influence the prognosis of stroke have been identified. These factors can be divided into (i) measurements of neurological disability (amount of limb weakness, higher mental impairment etc.), (ii) investigations (pyrexia, blood pressure, infarct size on CT etc.), (iii) personal details (age, sex, past medical history etc.).

4.1.1 Stroke severity and outcome

Many factors contribute to a stroke being classified as 'severe'. However, not all of these factors may have prognostic significance. There have been many studies that have looked at certain clinical features of stroke in relation to outcome.

Severity of weakness

Several studies have shown that patients with a severe hemiparesis have a worse outcome than those with milder deficits (Jimenez and Morgan, 1979; Feigenson et al. 1977; Stern et al. 1971; Wade et al. 1984c; Kotila et al. 1984). However, another study by Wade did not show any correlation between the severity of the weakness on admission and functional outcome at 13 months (Wade et al. 1985). One explanation for the discrepancies observed is related to the outcome measures used in these studies. Wade used functional outcome as a measure, whereas Feigenson used function at discharge, Kotila measured function at 3 months and Stern used improvement in function. In a more recent study, Olsen (Olsen, 1990) found that arm and leg weakness were good measures of functional outcome at discharge. Only 10% of patients with severe weakness of a limb (MRC grade ≤ 2) regained functional independence compared to 50% of those with less severe weakness (MRC grade >3). Chambers found that the severity of leg weakness was a major determinant of functional outcome at 3 months but was less important in the outcome at 2 years (Chambers et al. 1987). Although the above trials have not all been conducted in the same manner, most agree that the severity of limb weakness is associated with functional outcome.

Incontinence

Incontinence has been assessed in several studies. It is easy to measure and, as it can be classified in simple categories, assessment of incontinence does not require any special training (unlike the assessment of e.g. visual field defects). Urinary incontinence has been shown to be highly predictive of a poor outcome in several studies (Anderson et al. 1974; Jimenez and Morgan, 1979; Wade et al. 1985; Wade et al. 1983; Bourestom, 1967; Lehmann et al. 1975). Indeed, as it seems to be such an important prognostic indicator, Gladman and co-workers compared the ability of

urinary incontinence and another simple clinical assessment of stroke severity (whether the patient was 'alert' or 'drowsy or comatose') to predict stroke outcome with 5 established multivariate models for outcome prediction (Gladman et al. 1992). They found that the simple classification of patients according to continence and conscious level was as good or better than all but one of the multivariate models. Similarly, a large study by Taub found that urinary incontinence at 24 hours was as good as more complex models at predicting outcome (Taub et al. 1994). Functional outcome was assessed in 392 patients at 3 months: incontinence had a sensitivity of 60% and a specificity of 78% in predicting moderate/severe disability.

Faecal incontinence has not been studied as extensively as urinary incontinence. However, 3 studies have all shown it to be associated with a poor outcome (Jimenez and Morgan, 1979; Anderson et al. 1974; Bourestom, 1967).

Loss of consciousness

Impairment of consciousness at the onset of symptoms has been found to be associated with a poor outcome in several studies (Howard et al. 1986; Chambers et al. 1987; Azzimondi et al. 1995). Similarly, the longer the patient remains drowsy, the worse the outcome. A study by Kotila (Kotila et al. 1984), however, did not find an association with drowsiness and 3 month functional outcome although there was an association at 1 year. This study did, however, include patients who had suffered with sub arachnoid haemorrhage and intracerebral bleeds as well as ischaemic stroke. In the study by Gladman mentioned above, the other variable assessed along with incontinence was impairment of consciousness. This had a specificity of 59% and a sensitivity of 76% at predicting death at 3 months. Because conscious level seems to be an important factor in predicting recovery, it is often incorporated into predictive models.

Other neurological deficits

Although impairment of consciousness and severity of the hemiparesis are important determinants of prognosis following stroke, other factors have been identified which may also affect outcome.

visuo-spatial deficits

Several studies have shown that marked impairment of visuo-spatial awareness has a negative effect on outcome (Bourestom and Howard, 1968; Wade et al. 1984a; Denes et al. 1982; Feigenson et al. 1977). However, some of these studies were performed 3-4 weeks after the stroke. The assessment of visuo-spatial awareness in these studies was based on several rather complex tests that may well have been too complex to perform in the acute stages of stroke. Visuo-spatial deficit is not usually used as a predictor of stroke outcome because of the complexity of the tests.

aphasia

In one study of 122 patients, Oder (Oder et al. 1988) found that aphasia was not an independent predictor of functional outcome, death, recurrent stroke or ability to return to work. Another study has also confirmed this finding (Feigenson et al. 1977).

conjugate eye deviation

This has been shown to adversely affect prognosis following stroke irrespective of whether the patient has a hemianopia or not (Kelley and Kovacs, 1986).

4.1.2 Investigations and outcome

Many investigations are performed on patients with stroke. In the following section, only the more common tests will be discussed as the role of more advanced imaging techniques such as SPECT, PET and MRI will be dealt with elsewhere.

glucose

There have several studies evaluating the significance of hyperglycaemia in acute stroke. Two studies have shown that a raised glucose concentration in the acute stages of cerebral infarction is not an independent predictor of a poor outcome. In the first study (Woo et al. 1990), a poor outcome was associated with patients who had a raised glucose level due to stress hyperglycaemia but diabetic patients with raised glucose levels did not have a poor outcome. Matchar found that hyperglycaemia had no association with either mortality or functional outcome at 3

or 6 months (Matchar et al. 1992) although another study found that a non-fasting glucose concentration of above 130 mg was an indicator of poor outcome (Chamorro et al. 1995).

pyrexia

Azzimondi studied 183 acute stroke patients, 43% of whom had a pyrexia within 1 week of the ictus (Azzimondi et al. 1995). After taking into account impairment of conscious level (which was a predictor of poor outcome), the presence of a pyrexia was associated with a higher risk of death at 1 month. The presence of infection was also associated with a poor outcome in another study (Chamorro et al. 1995).

Other factors

An abnormal ECG has been associated with a poor outcome in some studies (Wade et al. 1984c; Howard et al. 1986; Sacco et al. 1991). This may well reflect the existence of ischaemic heart disease in these patients who probably have a worse prognosis than those patients without co-existing heart disease.

A high haematocrit, after adjustments were made to take into account age and other prognostic variables, was not an independent predictor of outcome (Ozaita et al. 1987). A raised erythrocyte sedimentation rate was found to be an independent predictor of stroke outcome and this was thought possibly to be due to a prothrombotic state in these patients (Chamorro et al. 1995).

4.1.3 Patient profile and outcome

Many variables have been studied, none more so than age. However, even if strong predictors of outcome are identified, these parameters cannot be altered.

Age

Age has probably been studied the most out of any other parameter. It is predictable that younger patients should have a better prognosis than older patients if all other variables are the same and there have been many studies that have confirmed this hypothesis (Bamford et al. 1990a; Nakayama et al. 1994; Chambers et al. 1987; Howard et al. 1986; Kotila et al. 1984; Woo et al. 1992; Chamorro et al. 1995; Azzimondi et al. 1995). However, a study by Wade (Wade et al. 1984b) in which 162 patients were assessed at 6 months following stroke found no association between the initial severity of the stroke or the functional outcome and age, although increasing age was associated with a longer hospital stay. However, another study by the same author (Wade et al. 1984c) found that age was one of three variables that identified 92% of the patients who died at 2 years post stroke. The other 2 variables were the ability to walk and co-existing cardiovascular disease. Another study which challenges the view of a strict association between age and outcome was performed by Nakayama (Nakayama et al. 1994). 515 patients with ischaemic stroke were followed up at 3 months and assessed with the Barthel Index (BI) as a measure of disability and the Scandinavian Stroke Scale (SSS) as a measure of neurological dysfunction. He found an association between age and initial BI and SSS. Increasing age was also associated with a poorer BI at discharge but not a poorer SSS at discharge. Nor was age associated with 3 month mortality or hospital stay. The conclusion from this study was that age did not influence the neurological deficit as much as it influenced the functional outcome i.e. older patients find it more difficult to perform activities of daily living than younger patients do given the same amount of neurological deficit. Feigenson conducted a retrospective study on 248 patients admitted to a stroke rehabilitation ward (Feigenson et al. 1977). Age was not associated with functional outcome or length of stay in hospital.

Sex

In several studies, there has not been an association between sex and outcome (Kaste and Waltimo, 1976; Kaplan and Hier, 1982; Wade et al. 1984a; Drake, Jr. et al. 1973).

Race

There have been very few studies looking specifically at ethnic origin and outcome. One study looked at differences in 1 month outcome in different racial groups in New York (Sacco et al. 1991). It was found that the 1 month mortality was lower in Hispanics than it was in Blacks and Whites. Additionally, the 1 year recurrent stroke and death rates were significantly lower in Hispanics (21.4%) compared to Whites (34.8%) and Blacks (31.1%). These findings were explained by differences in the incidence of stroke risk factors in the different groups.

4.1.4 THE USE OF SCALES IN THE ASSESSMENT OF STROKE

Over the last few years, there has been an increase in the number of stroke scales that have been published and used in the assessment of the acute stroke patient. These scales have usually been devised in order to quantify changes in a patient's neurological condition as a result of intervention. Although stroke scales vary in their content, there are several characteristics that should be common to all scales: they should be valid, reliable, specific, sensitive and easy to use (Lyden and Lau, 1991).

Validity

This refers to the concept that the measurement used accurately describes the underlying phenomenon (Nunnally, 1978; Asplund, 1987). Validity is often divided into 3 types: criterion, content and construct validity. Criterion validity is a measure of whether the stroke scale can be used to estimate the current clinical status of the patient (concurrent validity) and predict the future health of the patient (predictive validity). Concurrent validation often requires the correlation of the scale with another scale or other measure of status. The size of the infarct on brain imaging has been used to assess concurrent validity. However, the size of the infarct on CT does not always correlate well with the degree of weakness (Knopman and Rubens, 1986).

Content validation refers to the extent to which the scale includes all the relevant parameters of what is being measured (Cote et al. 1989). It relies mainly on expert opinion and reviews of the literature and not on statistical methods (Nunnally, 1978).

Construct validity is a measure of how much a new test and an established test measure the same construct (Lyden and Lau, 1991) and is usually demonstrated by the use of correlation coefficients (Nunnally, 1978). It is assumed that the parameters measured in a scale, such as limb weakness and dysphasia, give information about a single underlying construct (Feinstein et al. 1986). Thus, the

importance of construct validation in stroke scales is questionable because neurological deficit does not truly represent a single construct.

Reliability

This parameter refers to the amount of variability in scoring. A reliable test is one in which the variance (in scoring) is low (Nunnally, 1978). Reliability includes interrater and intrarater reproducibility as well as internal homogeneity (consistency among scale items). Providing good training in how to perform the assessment should decrease intrarater and interrater variation. This can also be achieved by decreasing the number of grades in a particular assessment. However, this can lead to a decrease in the specificity of the test. Observer reliability is best measured by using the kappa statistic.

Specificity

Specificity is a measure of the relevance of the scale. If a scale is looking particularly at one type of stroke, then the deficits assessed should all be deficits that are encountered in that stroke syndrome. For example, if a scale has been devised to assess posterior circulation strokes, then it should not include an assessment of dysphasia but rather, it should include an assessment of co-ordination, diplopia etc. Thus, a universal scale to assess all types of stroke is not possible as it would necessarily include too many non-specific tests. Tests included in the scale should include those that reflect the patient's prognosis (Adams et al. 1989). Tests that are good predictors of clinical outcome should be included as long as they are reliable, valid and easy to use.

Sensitivity

Sensitivity refers to the ability of the test to detect a change in the patient's condition. For a given deficit, the assessment should include all the possible outcomes e.g. in the assessment of limb weakness, the range should be from normal power to complete paralysis. The more grades there are in a particular category, the more sensitive the test becomes. However, the increase in sensitivity is at the expense of reliability. The assessment is therefore a compromise between having

enough grades to pick up a change in the patient's condition but not so many as to make the test unreliable.

Ease of Use

The assessment should be easy to perform. It should not be necessary to use special materials in the assessment. The tests should also be able to be completed quickly (e.g. within 10 minutes); this may be particularly important if the tests are to be used in conjunction with treatments that have to be given within a narrow time window.

Stroke scales commonly used in studies

There are numerous stroke scales in use. Three of the most commonly used scales will be discussed: the National Institute of Health stroke scale, the Canadian stroke scale and the Scandinavian stroke scale.

The National Institute of Health Stroke Scale

The National Institute of Health stroke scale (NIH) was devised in order to assess the effect of dextran and naloxone in acute stroke (Brott et al. 1989a). The scale is a 15 item assessment based on 5 previously used scales: the Toronto Stroke Scale, the Oxbury Initial Severity Scale, the Cincinnati Stroke Scale, the Edinburgh-2 Coma Scale and the Boston Diagnostic Aphasia Examination. The total score can range from 0-36. The test procedures are well described so that it should be easy to perform. The scale was slightly modified (Table 1) by excluding 'plantar response' and 'pupillary reflexes' (Goldstein et al. 1989). This 13 point score has a range of 0-31. The interrater reliability of the modified scale was good with a mean kappa score of 0.66 (Goldstein et al. 1989). However, kappa scores did vary according to the item being tested: loss of consciousness commands: 1.0, language: 0.79, limb ataxia: -0.16. In a further study, ataxia was once again found to have a low kappa value and its inclusion in the NIH scale was questioned (Lyden et al. 1994). The intrarater reliability of the NIH scale is good, with a kappa value of 0.66-0.77 (Brott et al. 1989a). In the same study, there were no statistically significant differences between

the intrarater reliability of a consultant neurologist, a neurology houseman or a neurology nurse. Concurrent validity was assessed by means of a Spearman rank correlation with infarct volume on day 7 (r = 0.74) (Brott et al. 1989b). The sensitivity of the scale is good (Wityk et al. 1994) so it is able to detect small changes in the patient's neurological condition. In a recent study, the predictive accuracy of the NIH scale was assessed (Muir et al. 1996). 373 patients were studied and outcome was evaluated at 3 months. The NIH scale had a sensitivity of 71% at predicting poor outcome and a specificity of 90%. It added significantly to the predictive power of the Canadian Neurological Scale and the Guy's prognostic score.

The NIH scale was chosen as the 'gold standard' stroke scale in this study as one of the main aims of the study was to assess the ability of the MCA velocity to predict outcome and to assess whether it added to anything to a standard stroke scale. The NIH scale has been shown to be a very good predictor of outcome and may be superior to other stroke scales. Additionally, the NIH stroke scale is sensitive to small changes in neurological condition. Thus, it can be used over time to assess improvement or deterioration in a patients condition which may have implications for the long term outcome.

The Canadian Neurological Scale

The Canadian Neurological Scale (CNS) was devised on the basis of a literature review and on clinical experience (Cote et al. 1986). The scale was developed so that it could be performed by non-physicians and so it is relatively simple to perform. Because of this, tests of visual field defects and gaze palsies were not included in the scale and so two important prognostic signs have been excluded. The scale has been tested for inter and intrarater reliability in 34 patients (Cote et al. 1986) and both parameters were found to be satisfactory. Content validity was established by the selection of items and their weights by a group of neurologists. Criterion validity was established by comparison with a neurological examination and a four item global neurological assessment (Cote et al. 1988). The CNS was

modified in 1989 and this scale was also evaluated (Cote et al. 1989). It had good inter and intrareliability especially for arm weakness which was probably due to the fact that there are only 2 grades of weakness. Predictive validity was assessed and the scale was shown to be good a predicting mortality, recurrent stroke and dependence at 6 months (Cote et al. 1989; Censori et al. 1993).

The Scandinavian Stroke Scale

This scale was originally devised to measure the effect of haemodilution in acute stroke (Scandinavian Stroke Study Group. 1985). The scale consists of a long term and a prognostic scale. Concurrent validity was assessed by comparing the scale to a standard neurological examination. Predictive validity was established in a study of 373 acute stroke patients: the initial SSS score was a good predictor of 3 month neurological and functional outcome (Cote et al. 1989; Scandinavian Stroke Study Group. 1988). Interobserver reliability was found to be good. There is no good information regarding the construct or content validity of the scale. The scale is easy to use and can be completed within 10 minutes.

Table 1. The National Institute of Health Stroke Scale

Test	Scale	Score
level of consciousness (LOC)	alert, keenly responsive	0
	drowsy but arousable	1
	requires repeated stimulation to attend	2
	reflex responses, totally unresponsive	3
LOC questions (age, month)	both correct	0
	1 correct	1
	none correct	2
LOC commands (open/close eyes and hand)	obeys both	0
	obeys one	1
	obeys neither	2
eye movements	normal	0
	partial gaze palsy	1
	forced deviation	2
visual fields	normal	0
	partial hemianopia	1
	complete hemianopia	2
facial palsy	normal	0
	minor	1
	partial	2
	complete	3
motor arm	holds limb at 90° for 10 seconds	0
	holds limb at 90° for less than 10 seconds	1
	some effort against gravity	2
	no effort against gravity	3
motor leg	holds limb at 30° for 5 seconds	0
	holds limb at 30° for less than 5 seconds	1
	some effort against gravity	2
	no effort against gravity	3
limb ataxia (out of proportion to limb weakness)	absent	0
	present in 1 limb	1
	present in 2 limbs	2
sensation (hemisensory loss to pin prick)	normal	0
	mild to moderate loss	1
	severe to total loss	2
neglect	none	0
	visual, tactile, auditory	1
	profound inattention to >1 modality	2
dysarthria	none	0
	slurs but can be understood	1
	unintelligible	2
language	normal	0
	mild to moderate	1
	severe	2
	mute	3

4.1.5 PROGNOSTIC SCALES

The studies outlined above have identified a number of parameters which are associated with outcome. In order to produce a model for predicting outcome, some of those parameters must be included. However, as with most predictive models, there is a limit to the number of variables that can be usefully included. If too many variables are used, the model becomes too complicated to use and often the addition of some variables does not contribute significantly to the predictive power of the model.

The Guys Predictive Model

This model was devised by Allen by prospectively studying 148 consecutive stroke patients (Allen, 1984). Patients were assessed clinically and their outcome assessed at 2 and 6 months. Two outcome groups were established: good (full recovery, mild symptoms and/or disability but able to perform activities of daily living with or without aids, able to walk without aid, able to live independently) and poor (moderate to severely disabled, not able to live alone, needs help to walk, dependent, dead). Multivariate analysis was used to identify parameters that had a high predictive value of outcome. These parameters were then given a score according to how important they were at predicting outcome. These scores were added together and subtracted from a constant. The resulting Guy's prognostic score (GPS) can be matched to a graph and the percentage likelihood of functional independence can be calculated.

The prognostic variables used in the model are: age, complete limb paralysis, the combination of higher cerebral dysfunction with a hemiplegia and a hemianopia, drowsiness or coma, loss of consciousness at onset. The presence of an uncomplicated hemiparesis leads to the addition (not subtraction) of a score. The model is given in Table 2.

Table 2. The Guy's Prognostic Score

constant	+ 40
complete limb paralysis	- 12
higher cerebral dysfunction, hemiplegia, hemianopia	- 11
drowsiness or coma	- 10
loss of consciousness at onset	- 9
age (years)	- age × 0.4
uncomplicated hemiparesis	+ 8

Although the model looks complicated at first, the only real calculation that has to be performed is the multiplication the patient's age by 0.4. For example a 78 year old patient who has dysphasia (higher cerebral dysfunction), hemiplegia and a hemianopia, is drowsy and has no movement of his limb will have a GPS of: 40 - 12 - 11 - 10 -(78 × 0.4) = -24.2. A 78 year old patient how presents just with weakness of a limb and no other features (i.e. an uncomplicated hemiparesis) will have a GPS of: 40 - (78 × 0.4) + 8 = +16.8.

In his study, Allen found that the model had an overall predictive value of 89%. The analysis of outcome at 2 months was very similar to that at 6 months as very few patients moved from one outcome group to the other in that interval. In a validation study, the score was found to have a sensitivity of 0.72 and a specificity of 0.63 at predicting a bad outcome as measured on the Barthel Index (Gompertz et al. 1994). The authors proposed a modification to the scoring system that simplified the calculation of the score.

4.1.6 CLASSIFICATION OF STROKE SUB-TYPE

A widely used classification of stroke sub-type is that used in the Oxford Community Stroke Project (Bamford et al. 1988; Bamford et al. 1991). This classifies patients into 4 stroke types: total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) and posterior circulation syndrome (POCS). If the stroke is caused by an infarction, the word 'syndrome' is usually replaced with 'infarction' thus giving the abbreviations TACI, PACI, LACI, POCI. The findings in each group are given table 3. The classification is a clinical one based on the findings of a neurological examination. However, the sub-types of stroke reflect the site and size of the lesion.

Table 3. The OCSP Classification of Stroke Sub-type.

Type	Clinical findings
TACI	unilateral weakness and/or sensory deficit affecting the face, arm and leg *plus* new disturbance of higher cerebral function (e.g. dysphasia, dyslexia, visuo-spatial disorder) *plus* homonymous hemianopia or quadrantinopia
PACI	any 2 of the above new disturbance of higher cerebral function alone pure motor/sensory deficit less extensive than for LACI (e.g. monoparesis)
LACI	pure motor stroke pure sensory stroke sensorimotor stroke ataxic hemiparesis
POCI	ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit bilateral motor/or sensory deficit disorder of conjugate eye movement cerebellar dysfunction without ipsilateral long tract deficit isolated hemianopia or cortical blindness

LACI

LACI is usually caused by the occlusion of a single deep perforating artery. This is represented pathologically by a 'lacune' and radiologically by a small deep infarct (Donnan et al. 1993a). Most lacunes occur in the region of the lentiform nucleus and are clinically 'silent'. Lacunar strokes are usually caused by lesions in the internal capsule and pons: areas in which a small lesion can cause a large neurological deficit due to the high density of eloquent tracts. One of the hallmarks of a LACI is the absence of higher cortical dysfunction such as dysphasia, neglect etc., the absence of visual field defects and the absence of drowsiness following the stroke.

TACI

This stroke type occurs most often as a result of occlusion of the MCA mainstem, ICA or both. Infarction occurs in both the deep and superficial territories of the MCA and leads to a large volume infarction on CT scanning. However, occasionally PCA territory ischaemia can produce a clinical picture similar to a TACI although generally the hemiparesis is mild compared to the hemianopia and dysphasia (Wardlaw et al. 1996).

PACI

A PACI is usually caused by small or medium sized infarctions in the MCA territory or large subcortical infarcts (Wardlaw et al. 1996). Angiographical findings vary from complete occlusion of the MCA or ICA to normal findings (Olsen et al. 1985). Difficulties can arise in distinguishing a PACI from a TACI if the patient is not co-operative and there is uncertainty about the presence of higher cortical dysfunction or hemianopia. Generally, in these cases, the deficit is considered not to be present and the stroke is classified as a PACI. The exception is when the patient is drowsy. If this is considered to be due to the stroke itself, then the infarction is likely to be large and so a TACI is diagnosed.

POCI

This type of stroke arises from lesions in the vertebro-basilar system. This sub group is the most heterogeneous and comprises are variety of CT findings and angiographical lesions.

The OCSP Classification and Outcome

Patients in the OCSP have been prospectively followed up for up to 6 years and various reports on the mortality and morbidity have been published (Dennis et al. 1993; Bamford et al. 1990a; Burn et al. 1994; Bamford et al. 1990b; Bamford et al. 1988). The outcome of 543 patients with cerebral infarction has been reported for 1 month, 6 months and 1 year (Bamford et al. 1991). Patient outcome was classified as dead, dependent and independent. The percentage of patients who were dead or dependent at 1 and 6 months for each stroke subtype is as follows: TACI: 95%, 95%; PACI: 43%, 44%; LACI: 38%, 33%, POCI: 38%, 32%. The main causes of death were complications due to immobility (71% and 58% in PACI and TACI respectively) and cardiac disease (67% in LACI). Thus, the overall outlook for patients with TACI is poor with the majority of deaths being due to the stroke and its secondary complications. The prognosis for patients with a lacunar infarction is much better but there is a mortality rate of 10% at 1 year which is mainly due to cardiac disease (Bamford et al. 1987).

4.1.7 THE ASSESSMENT OF OUTCOME

Stroke outcome can be assessed in a variety of ways which are based around the concept of impairment, disability and handicap. These terms have been extensively described and defined in the World Health Organisation document, The International Classification of Impairments, Disabilities and Handicaps (ICIDH) (World Health Organisation. 1980). Impairment is defined as a loss or abnormality of psychological, physiological or anatomical structure or function, whether or not due to a disease, provided that it is exteriorized. Disability is defined as any restriction or lack resulting from an impairment of the ability to perform an activity in a manner or within the range considered normal for a person in his or her environment. Disability is not only dependent upon the impairment but also upon the training, expectation and skills of the individual. Handicap is defined as the disadvantage for a given individual, often (although not always) resulting from an impairment or disability that limits or prevents the fulfilment of a role that is normal, depending on age, sex and social and cultural factors, for that individual. This is a complex definition which is often difficult to assess as it encompasses many factors such as the expectations of family, the community and work colleagues as well as financial status and level of previous achievement.

Impairment, disability and handicap are linked. In the context of stroke, the impairment may be 'leg weakness', the disability then may be 'difficulty in walking' and the handicap will be 'loss of independence'. Another example could be 'dysphasia', 'difficulty with speaking' and 'loss of communication'.

In the context of stroke, impairment, disability and handicap can be assessed in different ways. Impairment is usually assessed by the amount of neurological dysfunction. This can be measured on one of the stroke scales described above. Disability can be measured by assessing the ability of the patient to perform various basic activities of daily living (ADL). The most commonly used assessment scale of disability is the Barthel Index (BI) (Mahoney and Barthel, 1965) which will be described below. Handicap is not often measured in stroke outcome as it very complex but a basic assessment can be made using the Oxford Handicap Scale

(modified Rankin scale) (Bamford et al. 1989). The scale was modified from the original scale (Rankin, 1957) by replacing the word 'disability' with 'handicap' and introducing the term 'lifestyle' into the original scale.

The Barthel Index

This widely used assessment of ADL was first published as a 10 point scale with a scoring system ranging from 0-100. It was later modified so that the scoring was from 0 to 20 (Wade and Collin, 1988). The BI covers a wide range of daily activities including washing, feeding, transferring, dressing etc. (see table 4). The BI has been used in many studies as a measure of disability and has been extensively validated (Wade and Hewer, 1987) and has also been shown to be reliable (Collin et al. 1988; Wolfe et al. 1991). The reliability of the BI, measured by using telephone interviews, has also been shown to be good (Korner-Bitensky and Wood-Dauphinee, 1995; Shinar et al. 1987). One criticism of the scale is that it has maximum and minimum scores and so introduces a 'floor' and 'ceiling' effect (Wellwood et al. 1995). A modification of the scale has been proposed in order to increase its sensitivity (Shah et al. 1989) although this has not been generally accepted.

Table 4. The Barthel Index.

Item	Assessment	score
feeding	independent	10
	need help	5
	dependent	0
transfers (bed to chair)	independent	15
	needs major help	10
	needs minor help	5
	dependent	0
grooming (washing face, shaving, hair)	independent	10
	needs some help	5
	dependent	0
toilet use	independent	10
	needs some help	5
	dependent	0
bathing (bath or shower)	independent	5
	dependent	0
mobility (walking or wheelchair 50 yards)	independent (can use aids)	15
	needs help	10
	independent with wheelchair	5
	dependent	0
stairs	independent	10
	needs some help	5
	dependent	0
dressing	independent	10
	needs help	5
	dependent	0
bowels	continent	10
	occasional incontinence (<1/week)	5
	incontinent	0
bladder	continent	10
	occasional incontinence (<1/week)	5
	incontinent	0

4.1.8 TRANSCRANIAL DOPPLER STUDIES OF OUTCOME

Although there have been several TCD studies in the setting of acute cerebral infarction, not many have assessed the relationship between middle cerebral artery (MCA) velocity and outcome. One of the first studies that did investigate the relationship was performed by Halsey (Halsey, Jr. 1988). In this small study, 15 patients with presumed MCA territory stroke were investigated within 12 hours of symptom onset. 8 patients had an MCA velocity of < 30 cm/s: 7 still had total paralysis of the arm at 6 months and 1 patient made a full recovery. 7 patients had a velocity of > 30 cm/s: 2 made a full recovery, 3 made a partial recovery and 2 remained hemiplegic. Although the numbers were small in this study, the results were statistically significant. The author concluded that a velocity of 30 cm/s may be used to identify patients with a good or poor prognosis in the early stages of stroke. One criticism of the study is that the outcome measure, arm paralysis, is not a true reflection of the functional outcome of the patient as a whole.

Kushner found that the MCA velocity in 42 acute stroke patients was highly predictive of the size of infarction on CT scanning both at 1 week and at 1 - 3 months (Kushner et al. 1991). Although all the patients were assessed clinically using the Canadian Neurological Score, the results of these clinical findings were not published in the paper. Although the size of the infarction on CT may be a reflection of the amount of tissue damaged following stroke, it does not follow that it reflects the actual clinical outcome.

Ni studied 31 patients within 48 hours of stroke onset (Ni et al. 1994). Clinical assessment was made using the Hemispheric Stroke Scale (HSS) (Adams et al. 1987) which is a measure of neurological deficit rather than functional outcome or disability. Patients were divided into a poor and a good outcome group according to their HSS score. A significantly reduced MCA velocity on the symptomatic side compared to the contralateral hemisphere was found in patients with a poor outcome: sensitivity: 83%, specificity: 85%. An absolute MCA velocity of <40 cm/s was also found to be predictive of a poor outcome with a sensitivity of 72% and a specificity of 92%. The combination of a MCA velocity of <40 cm/s with a

significant reduction in the side to side asymmetry resulted in a sensitivity of 67% and a specificity of 100% and a positive predictive value of 100%. The authors proposed that MCA velocity could be used as a prognostic indicator in MCA territory infarction. Unfortunately, the authors did not investigate the relationship between the initial HSS score and outcome to see whether MCA velocity added to the prognostic ability of the score.

The association between MCA velocity and outcome was investigated by Hedera in patients with internal carotid artery occlusion (ICA) (Hedera et al. 1992). 31 patients were examined within 48 hours of stroke onset and 25 of these patients were followed up at 1 month. The neurological assessment was made on a scale devised by Bartko and Danisova which has rarely been used in subsequent studies and so it has not been thoroughly validated (Bartko and Danisova, 1977). They found that velocities less than 31.2 cm/s (Doppler shift frequency of 800 Hz) were indicative of a poor outcome and patients with an MCA velocity of less than 23.4 cm/s (Doppler shift frequency of 600 Hz) were in a particularly bad prognostic group. In addition, patients with a velocity of greater than 31.2 cm/s were more likely to improve clinically as measured on the scoring system: sensitivity: 0.87, specificity: 0.60. The authors did not comment on the presence of collateral pathways in these patients so that the reason for a low MCA velocity may have been due to either distal MCA branch occlusions or poor collateral flow from the contralateral ICA.

4.2 AIMS OF THE STUDY

The clinician has many ways of predicting the outcome of stroke, either by using clinical assessments or by the use of special investigations. The use of TCD in the prognosis of stroke has not been investigated in much detail and there have not been any studies published on the use of TCCS in acute stroke. Most TCD studies have focused attention on the prognosis in patients with MCA occlusion. The aims of this study are as follows

(i) to establish whether MCA velocity can be used as a prognostic indicator in acute cerebral infarction.

(ii) to establish whether MCA velocity adds any prognostic information in addition to that gained from simple clinical assessments.

4.3 SUBJECTS AND METHODS

4.3.1 Patient selection

119 patients were entered into the study. 44 patients were excluded for the following reasons: 21 patients lacked an adequate acoustic window, 14 patients were shown to a have cerebral haemorrhage, 2 patients had cerebral tumours, 3 patients refused consent, 4 patients deteriorated and were too ill to undergo scanning.

4.3.2 TCCS

TCCS was performed in the manner already described. The mean MCA, ACA and PCA velocity was measured in both hemispheres. The asymmetry index (AI) was calculated for each vessel.

4.3.3 Clinical Assessment

All patients were examined at the same time as the TCCS scan. Patients had a full neurological examination performed.

The GPS was calculated for each patient. This prognostic model was chosen as it has good prognostic power. It is also one of the few scores that takes into account age which is known to be a good prognostic indicator.

The test items on the NIH stroke scale were assessed and the score calculated. The change in neurological status was calculated by subtracting the NIH score at 1 week from the score at day 1. A difference in 4 points or more on the scale was taken to be indicative of a clinically important change, either improvement or deterioration (Haley, Jr. et al. 1992; Brott et al. 1992).

Stroke sub-type was classified according to the OCSP. The OCSP is one of the most frequently used classifications of stroke sub-type. It is reliable and is an accurate predictor of outcome.

An appointment to return to the hospital for a clinical assessment was sent to all patients at 3 months. Patients who could not attend for their appointment were contacted by telephone so that a verbal assessment could be made.

4.3.4 Assessment of Outcome

Patients were assessed using the Barthel Index (BI) at 3 months as a measure of disability. The information was generally collected from the patient but in cases where the patient was not able to provide the information, the spouse or carer was interviewed. The BI is one of the most widely used disability scales and has been validated in several studies.

Patients were divided into 2 outcome groups according to their level of dependence: good and poor. The good outcome patients consisted of patients who had made a full recovery and had no symptoms and patients with some residual deficits that did not stop the patient from being self caring and living independently. The poor outcome group consisted of patients who were dependent on others for their activities of daily living and as such had a restricted lifestyle.

4.3.5 Statistical Methods

The main outcome measure, independence vs. death and dependence, was treated as a binary outcome. The dependent variables such as MCA velocity, AI, NIH score, GPS were continuous variables. The three categories of MCA velocity and AI ('zero', 'low' and 'normal') were treated as ordered variables. The OCSP classification was treated as categorical data. Multiple linear logistic regression analysis was employed and the odds ratio (with 95% confidence intervals) and p value were then calculated. When two variables were being assessed, the likelihood ratio test was employed.

Analysis was performed on a commercially available statistical package for personal computers (SPSS for windows).

4.4 RESULTS

75 patients were entered into the study. There were 37 males and 38 females with an age range from 48 years to 88 years (median: 75 years). Details of patient's age, mean MCA velocity, AI, NIH score, BI, Guy's score and stroke sub-type are given in Table 5.

4.4.1 MCA VELOCITY

Absolute values

23 patients presented with occlusion of the proximal portion of the MCA and hence had a mean MCA velocity of 0 cm/s.

In the remaining 52 patients, the mean MCA velocity varied from 18.2 cm/s to 88.8 cm/s (median: 43.5 cm/s). 21 patients had a velocity below the threshold value of 40 cm/s (mean: 28.9 cm/s, range: 18.2 cm/s - 39.1 cm/s) (Figure 1).

31 patients had a mean MCA velocity above 40 cm/s (mean: 53.1 cm/s, range: 40.7 cm/s - 88.8 cm/s).

Asymmetry Index

25 patients had an AI below the normal range i.e. below -20%; range: -20.1% to -78.9% (mean: -42.1%).

24 patients had an AI within normal limits; range: -18.1% to +17.2% (mean: -3.7%).

3 patients had an AI greater than 20%: +30.9%, +47.2%, +73.5% (mean: +50.5%).

4.4.2 INITIAL CLINICAL ASSESSMENT

The NIH score on admission for all patients ranged from 3 to 31 (mean: 13.9).

The Guy's prognostic score ranged from -35.6 to +25.2 (mean: +1.8).

The number of patients according to the OCSP classification was as follows: TACI: 29, PACI: 23, LACI: 23, POCI: 0.

Figure 1a. Spectral Doppler display of middle cerebral artery velocity demonstrating markedly reduced velocity in a patient who had a large infarction in that territory.

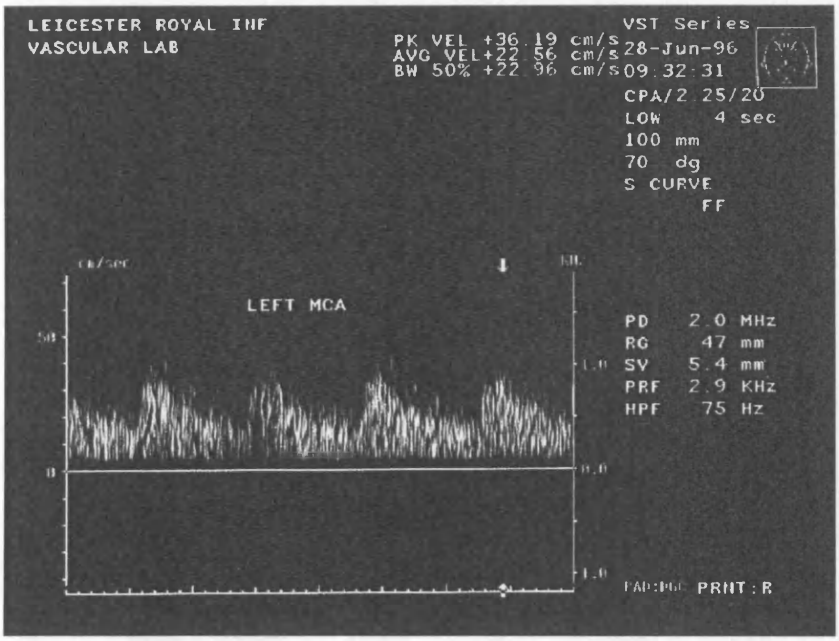


Figure 1b. A spectral display from a normal subject is shown for reference. Note the different scales used.

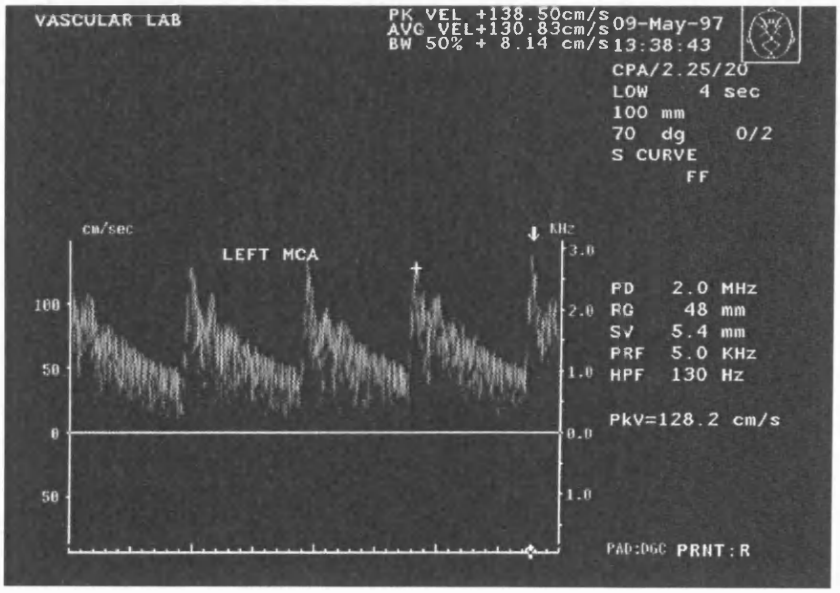


Table 5. Patient Details

no	age	Mm s	Mm as	AI	OCSP	NIH	Δ NIH	GPS	BI
1	78	0	43.8	-200	TACI	19	2	-12.2	15
2	75	0	43.8	-200	TACI	26	4	-24.0	25
3	72	0	36.7	-200	TACI	24	dead	-9.8	0
4	69	0	50.2	-200	TACI	15	dead	1.4	0
5	81	0	59.8	-200	TACI	22	4	-15.4	65
6	73	0	34.3	-200	TACI	31	dead	-12.2	0
7	75	0	66.7	-200	TACI	23	6	-11.0	45
8	79	0	43.8	-200	TACI	19	0	-12.6	0
9	82	0	47.9	-200	TACI	26	4	-25.8	10
10	80	0	55.4	-200	PACI	15	3	-3.0	10
11	77	0	47.3	-200	PACI	16	4	-2.8	75
12	74	0	38.2	-200	PACI	9	0	10.4	0
13	80	0	48.9	-200	PACI	7	-2	8.0	25
14	77	0	35.6	-200	TACI	19	-2	-1.8	0
15	72	0	40.6	-200	PACI	7	5	0.2	65
16	84	0	43.8	-200	TACI	28	-1	-35.6	0
17	75	0	44.8	-200	TACI	30	dead	-23.0	0
18	76	0	43.3	-200	TACI	26	4	-23.4	45
19	76	0	34.3	-200	TACI	28	6	-23.4	15
20	73	0	41.0	-200	TACI	17	2	-12.2	0
21	75	0	36.8	-200	TACI	22	0	-13.0	20
22	65	0	48.4	-200	TACI	21	3	-7.0	50
23	76	0	42.5	-200	TACI	21	12	-23.4	65
24	73	18.2	31.0	-52.2	PACI	13	1	10.8	20
25	75	18.5	30.1	-68.6	PACI	11	1	-2.0	15
26	69	20.5	41.9	-63.4	PACI	16	2	12.4	10
27	88	21.1	48.6	-78.9	TACI	25	-1	-18.2	0
28	73	21.3	39.6	-60.1	PACI	14	5	10.8	45
29	84	21.6	29.3	-30.3	PACI	9	3	6.4	90
30	81	21.7	30.5	-33.7	PACI	16	dead	-14.4	0
31	75	26.2	40.2	-64.8	PACI	17	1	10.0	0
32	77	28.3	44.7	-44.9	TACI	22	2	-13.8	30
33	68	29.8	41.8	-36.1	PACI	14	3	12.8	45
34	82	29.9	50.2	-50.7	TACI	24	3	-25.8	40
35	68	30.2	42.8	-35.6	LACI	8	2	20.8	60
36	61	30.4	68.5	-77.3	PACI	3	2	15.6	90
37	79	31.3	38.3	-20.1	PACI	14	nd	11.6	100
38	72	34.0	35.6	-4.6	LACI	3	0	19.2	90
39	81	34.4	46.2	-29.3	TACI	21	-1	-25.4	10
40	69	34.8	54.7	-44.5	TACI	19	2	1.4	10
41	82	37.4	43.8	-11.8	LACI	4	dis	15.2	100

42	76	38.5	48.9	-23.8	TACI	16	8	-2.4	65
43	70	38.9	54.2	-32.9	TACI	24	3	-18.0	60
44	82	39.1	48.9	-22.3	PACI	12	2	7.2	90
45	65	40.7	43.1	-10.3	LACI	3	dis	22.0	100
46	71	41.0	69.4	-51.4	TACI	18	14	-9.4	90
47	64	41.2	60.5	-32.9	PACI	6	2	2.4	95
48	79	41.5	44.8	-8.9	LACI	7	5	16.4	95
49	79	42.8	47.1	-14.0	PACI	10	dis	8.4	95
50	80	44.2	54.2	-20.3	LACI	6	-13	16.0	15
51	75	45.6	42.8	5.3	LACI	8	2	18.0	90
52	71	45.9	44.8	2.4	PACI	13	4	-0.4	100
53	78	46.3	59.4	-24.8	PACI	15	4	-3.2	95
54	80	46.7	61.5	-27.4	PACI	8	2	-1.0	100
55	62	47.9	54.2	-15.6	LACI	9	2	23.2	85
56	75	48.8	56.9	-15.3	TACI	23	4	-11.0	80
57	79	48.8	56.8	-15.1	LACI	5	3	16.4	100
58	83	51.5	60.3	-7.9	LACI	7	4	14.8	100
59	76	51.9	66.7	-25.0	PACI	13	7	-0.4	90
60	48	52.3	50.4	3.7	LACI	4	dis	24.8	100
61	81	53.2	50.1	4.9	LACI	3	0	15.6	100
62	72	53.2	51.2	1.6	LACI	9	3	19.2	100
63	76	53.6	64.9	-18.1	LACI	6	2	17.6	80
64	68	53.7	49.7	7.7	LACI	2	dis	20.8	100
65	84	54.0	49.9	17.2	LACI	7	4	14.4	90
66	78	54.1	52.3	3.4	LACI	5	5	16.8	100
67	57	55.3	56.8	-0.03	LACI	7	2	25.2	90
68	60	55.4	25.6	73.5	PACI	12	5	4.0	90
69	69	60.2	58.1	2.4	LACI	6	3	20.4	100
70	70	61.3	67.4	-11.2	LACI	5	3	20.0	95
71	75	61.3	44.9	30.9	TACI	16	0	-11.0	75
72	71	62.8	64.5	-7.0	LACI	3	dis	19.6	100
73	82	66.3	64.3	2.6	LACI	6	dis	15.2	100
74	77	76.4	47.2	47.2	TACI	19	5	11.8	75
75	57	88.8	88.6	0.2	LACI	3	dis	25.2	100

Mm s: mean symptomatic MCA velocity, Mm as: mean asymptomatic MCA velocity, AI: asymmetry index, OCSP: Oxford community stroke project classification, Δ NIH: change in NIH score from day 1 to day 7, BI: Barthel Index, GPS: Guy's prognostic score, dis: discharged, nd: not done

Change in NIH Score

49 patients had an improvement in their NIH score from day 1 to day 7 (range: 1-14, median: 3). 22 patients had a significant improvement in NIH score (i.e. >4), range: 4-14 (median: 5).

6 patients showed a worsening of their score by day 7 (range: 1-13, median: 1.5). Only 1 patient had a significant worsening (13).

In 6 patients the NIH score remained constant.

The NIH score could not be calculated on day 7 in 14 patients for the following reasons: 5 patients had died, 8 patients had been discharged home and in 1 patient the day 7 examination could not be performed due to technical reasons.

4.4.3 3 MONTH ASSESSMENT

The Barthel Index at 3 months for all patients ranged from 0 to 100 (median: 65).

12 patients died within the 3 month study period (BI: 0). Of the 63 patients alive at 3 months, the BI ranged from 10 to 100 (median: 85).

The 63 patients were divided into 2 outcome groups according to their level of dependence: good and poor. The good outcome patients consisted of those that had made a full recovery and had no symptoms and patients with some residual deficits that did not stop the patient from being self caring and living independently. The poor outcome group consisted of patients who were dependent on others for their activities of daily living and as such had a restricted lifestyle.

6 patients did not attend the 3 month appointment and were contacted by telephone.

4.4.4 CLINICAL OUTCOME AND MCA VELOCITY

The correlation between the mean MCA velocity in the symptomatic hemisphere and the 3 month BI was 0.74 (Figure 2). The significance for predicting independence for mean MCA velocity was $p<0.001$ with an odds ratio of 1.15 (95% CI: 1.08-1.23) (Figure 3).

The significance for predicting independence for mean MCA velocity category (velocity = 0 cm/s, velocity < 40 cm/s, velocity > 40 cm/s) was $p<0.001$ with an odds ratio of 33.7 (95% CI: 7.45-152) (Table 6).

Figure 2. Mean MCA velocity in the symptomatic hemisphere and 3 month Barthel Index.

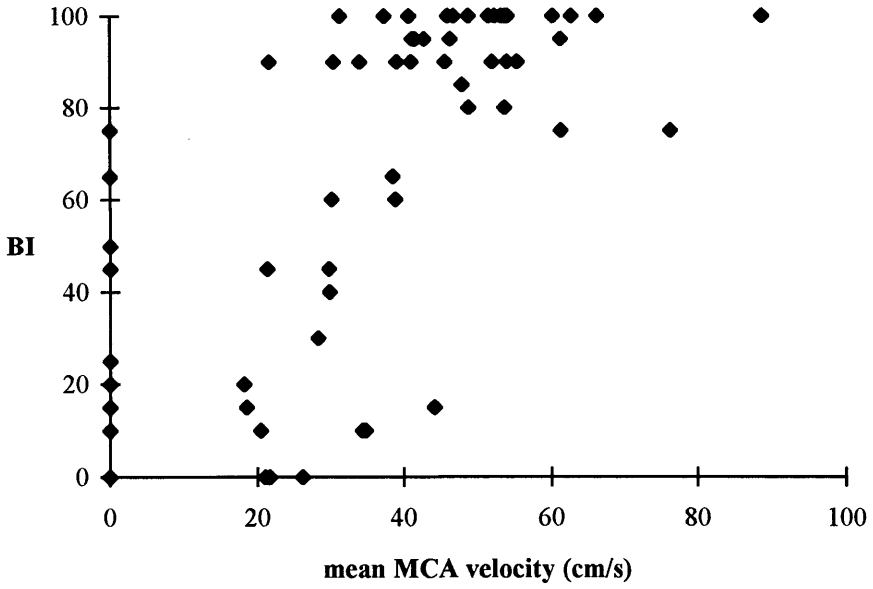


Figure 3. Mean MCA velocity in the symptomatic hemisphere and 3 month outcome. The large data point represents 22 patients with an MCA velocity of 0 cm/s.

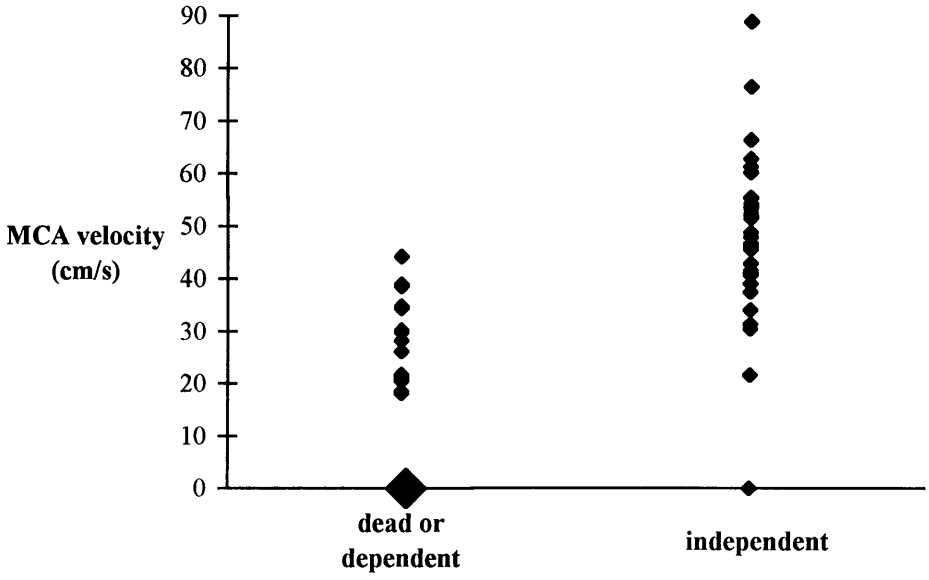


Table 6. 3 month dependency according to mean MCA velocity.

MCA velocity (cm/s)	dead or dependent n = 38	independent n = 37
0	22	1
< 40	15	6
> 40	1	30

Clinical outcome and AI

The correlation between the asymmetry index and the 3 month BI was 0.69 (Figure 4). The significance for predicting independence for the asymmetry index $p<0.002$ with an odds ratio of 1.04 (95% CI: 0.99-1.09) (Figure 5).

The significance for predicting independence for asymmetry index category (AI = -200%, AI <-20%, AI > -20%) was $p<0.001$ with an odds ratio of 24.5 (95% CI: 5.91-102) (Table 7).

Figure 4. Asymmetry index and Barthel Index at 3 months. The dotted vertical represents the lower limit of the asymmetry index.

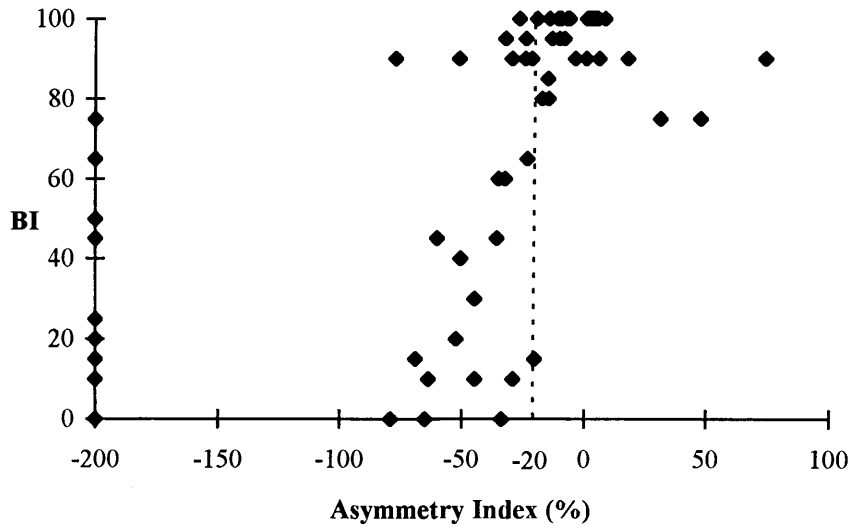
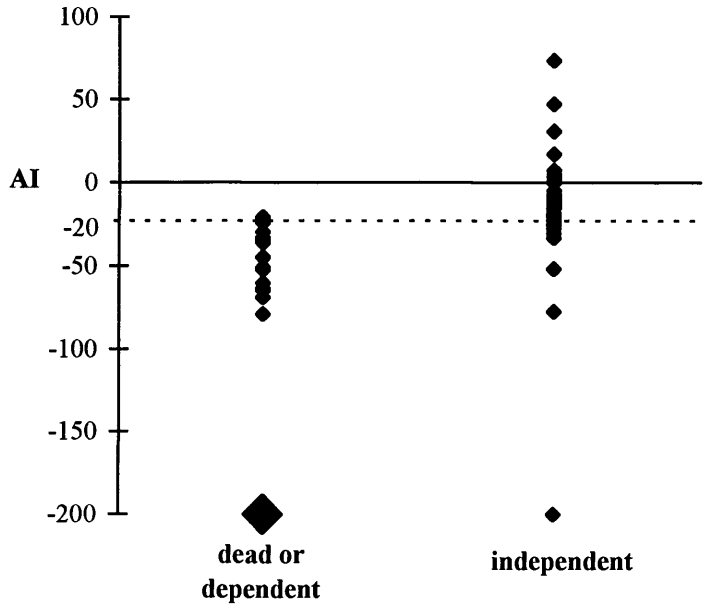


Table 7. Asymmetry index category and 3 month outcome measured as dead or dependent and independent.

AI (%)	dead or dependent n = 38	independent n = 37
- 200	22	1
< -20	16	9
> -20	0	27

Figure 5. Asymmetry index and 3 month outcome. The dotted horizontal represents the lower limit of the asymmetry index. The large data point represents 22 patients with an AI of -200%.

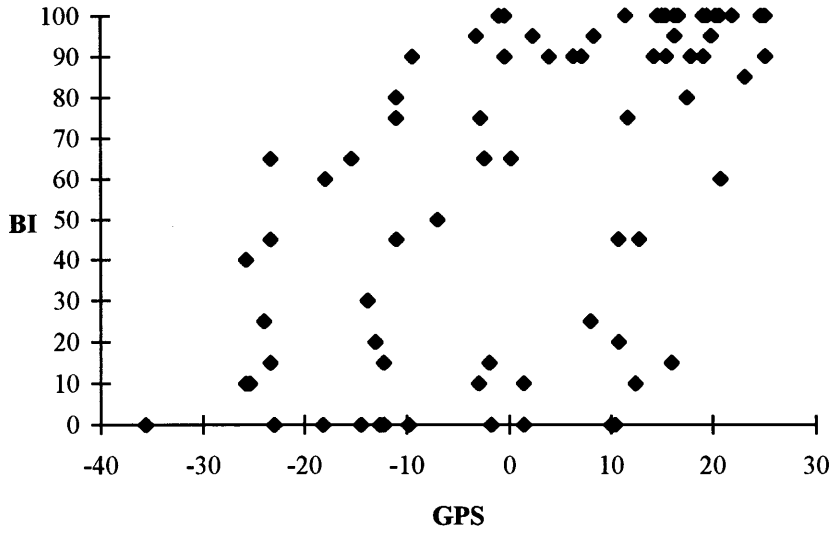


4.4.5 CLINICAL OUTCOME AND INITIAL CLINICAL ASSESSMENT

Guy's prognostic score

The correlation between the GPS and the 3 month BI was 0.60 (Figure 6). The significance for predicting independence for the GPS was $p<0.001$ with an odds ratio of 1.12 (95% CI: 1.06-1.17).

Figure 6. Guy's Prognostic score (GPS) and 3 month Barthel index.

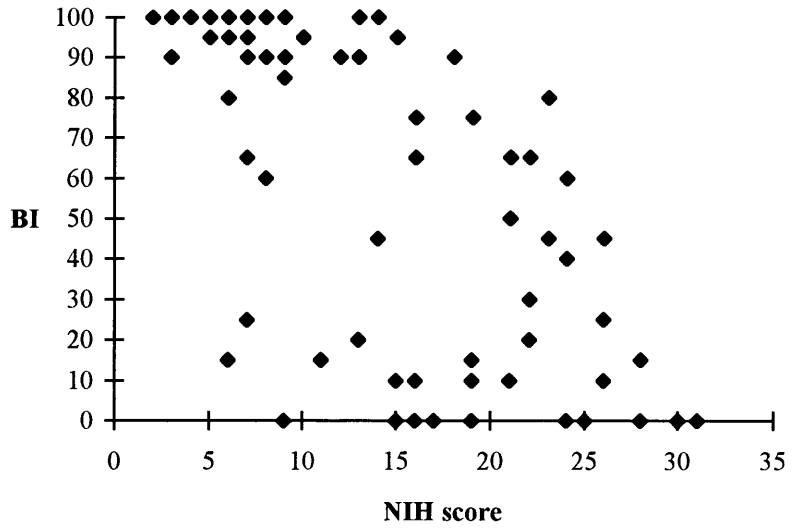


NIH Score

The correlation between the admission NIH score and the 3 month BI was 0.67 (Figure 7). The significance for predicting independence for the NIH score was $p<0.001$ with an odds ratio of 0.78 (95% CI: 0.70-0.86).

The significance for predicting independence for the change in NIH score was $p=0.14$ with an odds ratio of 1.14 (95% CI: 0.96-1.34).

Figure 7. Admission NIH stoke score and 3 month Barthel Index



Oxford community stroke project classification

The significance for predicting independence for the OCSP was $p<0.005$ (Table 8).

The OCSP and 3 month Barthel Index is plotted in Figure 8.

Figure 8. Stroke sub-type according to the OCSP and 3 month Barthel Index. The large data points represent 10 or more patients with the same BI score.

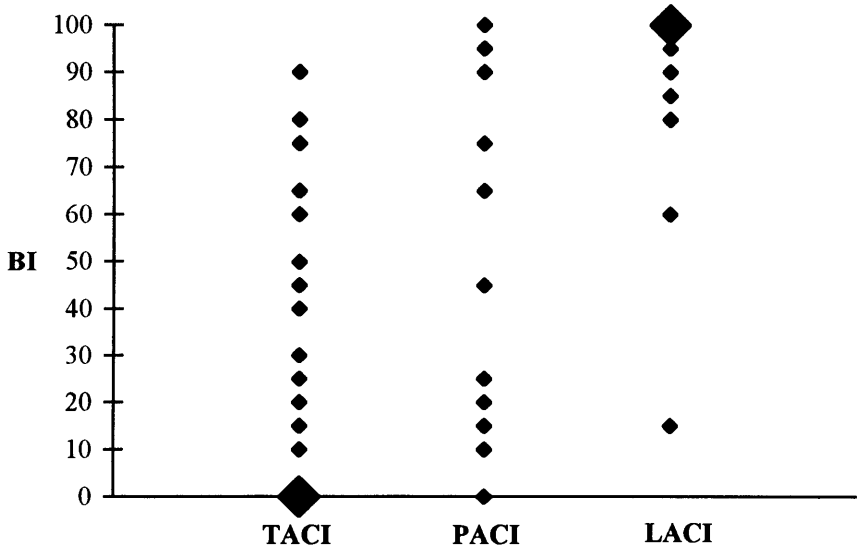


Table 8. The Oxford community stroke project classification and 3 month outcome.

OCSP sub type	dead or dependent	independent
TACI	25	4
PACI	11	12
LACI	2	21

4.4.6 COMPARISON OF MCA VELOCITY AND CLINICAL ASSESSMENT

A summary of the results of the logistic regression for each measure of MCA velocity and for each type of clinical assessment is given in Table 9.

The significance of each MCA velocity parameter *after* adjustment has been made for each type of clinical assessment is given in Table 10. It can be seen that all four measurements of MCA velocity (absolute velocity, absolute AI, velocity category and AI category) were still significant for predicting independence even after all clinical assessments had been taken into account. All velocity measurements were more significant than clinical assessments in predicting independence with the exception of the absolute asymmetry index and NIH score.

Table 9. Odds ratio, significance and 95% confidence intervals of clinical assessment and MCA velocity with 3 month outcome (independent vs. dead or dependent).

variable	p value	odds ratio	95% CI
age	0.12	0.95	0.88-1.01
NIH score	<0.001	0.78	0.70-0.86
Δ NIH	0.14	1.14	0.96-1.34
GPS	<0.001	1.12	1.06-1.17
OCSP	<0.005	15.2	2.3-68.4
mean MCA velocity	<0.001	1.15	1.08-1.23
velocity category	<0.001	33.65	7.45-151.95
AI	<0.002	1.04	0.99-1.09
AI category	<0.001	24.51	5.91-101.60

Table 10. The significance (p value and odds ratio with 95% confidence intervals) for various measurements of MCA velocity after adjusting for each clinical assessment parameter. The only MCA measurement which did not add to the predictive power of a clinical assessment was the asymmetry index versus NIH score.

	NIH score	Δ NIH	GPS	OCSP
MCA velocity	0.004 1.13 (1.06-1.21)	0.0001 1.14 (1.08-1.21)	0.002 1.14 (1.06-1.22)	0.001 1.18 (1.07-1.30)
velocity category	0.0002 21.2 (4.3-103.8)	0.0001 43.3 (6.69-280)	0.0001 22.9 (4.73-111)	0.0002 27.7 (4.83-158)
AI	0.004 1.03 (1.01-1.05)	0.0015 1.03 (1.01-1.05)	0.001 1.03 (1.01-1.05)	0.009 1.03 (1.01-1.05)
AI category	0.0004 15.5 (3.4-70.6)	0.0001 20.1 (4.61-87.5)	0.0003 14.7 (3.42-63.3)	0.0004 16.9 (3.58-79.9)

4.5 DISCUSSION

This study was performed in order to assess the ability of MCA velocity to be used to predict prognosis in acute stroke. Previous studies have investigated the relationship between MCA occlusion and outcome but very few have looked at the relationship between either the absolute MCA velocity or the side to side difference in velocities. We have shown that not only can MCA velocity be used to predict prognosis in acute stroke but also that it is a better indicator than using simple clinical assessment scales. Patients can be divided into 3 broad groups according to their MCA velocity. The first group have proximal MCA occlusion and have no flow in the MCA. The second group have an MCA velocity that is lower than the 'normal' range i.e. less than 40 cm/s. The last group have velocities above 40 cm/s. The cause for proximal MCA occlusion is thought to be due to an embolic event usually from either the carotid artery or heart. In this study, this group of patients had a very poor prognosis: only 1 patient out of 23 managed to regain full independence by 3 months, 9 were dead, 7 totally dependent on constant nursing care and 6 patients made a partial recovery but were still unable to live completely independent lives. The majority of the patients who had MCA occlusions had large infarcts on either CT or MRI and tended to have large neurological deficits. It is therefore not surprising that significant recovery in these patients was uncommon.

Patients with a low MCA velocity represented an 'intermediate' prognosis group with approximately 75% of the patients having a poor outcome. These patients tended to have milder strokes than those with MCA occlusion with lowerr NIH scores on admission. All but one of the patients with an MCA velocity above 40 cm/s had a good outcome. This reflects the fact that many of these patients had small lacunar strokes with no evidence of large vessel disease.

An important finding from this study was that all variables used to predict independence at 3 month were significant with the exception of age and change in NIH score. The fact that age was not significant is, at first, surprising especially because most previous studies have shown that it is one of the strongest predictors of outcome. The reason for this anomaly is probably due to the selection of patients

in this study. Firstly, patients had to be admitted to hospital. This immediately excludes patients with mild strokes who may well be cared for at home or sent to an urgent outpatient appointment. Older patients with severe strokes may have been cared for at home as well, if it was thought by the family and GP that hospital admission had little to offer. The age range of the patients in this study was relatively small and, in particular, there were few young patients (only 7 patients were under the age of 65 years). This may have had a large effect on the results as the young patients with a good prognosis would have been missed. In addition, the number of patients that have inaccessible acoustic windows increases with age and so this would exclude the very old.

The change in NIH score was not significant for predicting independence. This may be due to either a real effect or to statistical analysis. The parameter is a measure of change and so does not take into account the baseline NIH score. Thus, a patient who has a 6 point improvement in the score may be predicted to do very well . However, if the patient goes from a score of 30 to 24, they will probably be more disabled at 3 months than a patient who had an increase of only one point but went from 5 to 4. A confounding problem in the analysis was that not all the patients were included. This was because some of the patients had died before the 1 week assessment and, on the opposite side of the clinical spectrum, some patients were so well by 1 week that they were discharged from hospital and unable or unwilling to return for their scan.

The actual NIH score on admission was the strongest clinical predictor of outcome. This agrees with a recent study which showed it to have a high predictive validity and for it to be better than the GPS at predicting functional outcome at 3 months (Brott et al. 1989a). In this study, the NIH score also added significantly to the GPS. This is not unexpected as one of the main determinants of the GPS is age and this was not a significant predictor of outcome in this study. The other parameters used in the GPS are reflected in the OCSP. The presence of higher cognitive dysfunction plus hemianopia plus hemiparesis in the GPS is equivalent to the TACI in the OCSP. Additionally, an uncomplicated hemiparesis is equivalent to one of the lacunar syndromes. Both the GPS and the OCSP were highly significant in predicting independence at 3 months ($p<0.001$ and $p<0.005$ respectively). However,

neither OCSP or GPS were significant when the other was adjusted for. This supports the assumption that, in this study (because age was not a significant factor in outcome) they measured similar parameters.

There was a strong relationship between the AI and the absolute MCA velocity: patients with a low AI tended to have a velocity below 40 cm/s. This resulted in similar results for outcome for both AI and MCA velocity. However, using the likelihood ratio test, it can be seen that when adjusting for MCA velocity, the significance for predicting independence for AI is $p=0.54$. Therefore, it is the actual MCA velocity rather than a ratio of the ipsilateral and contralateral velocities that is more important when predicting outcome. When any measure of MCA velocity (absolute velocity, AI or dividing the parameters into the three categories of AI: -200, <-20 and >-20 and velocity: 0 cm/s, <40 cm/s and >40 cm/s) is compared to the clinical assessment, it is seen that it is a better predictor of outcome. None of the clinical assessments added significantly to the predictive ability of MCA velocity. The NIH score and AI both had a significance for predicting independence of $p<0.005$ when adjusting for each other indicating that these parameters were similar in their predictive power. In other words, the NIH score was the best clinical predictor of outcome and the AI was the least effective 'velocity' parameter.

The value of 40 cm/s was based on a previous TCCS study on healthy volunteers (Martin et al. 1994) and is therefore an arbitrary value. However, there is evidence that it may be a useful clinical value. It does agree with a TCD study in which patients with a mean MCA velocity of less than 40 cm/s had a worse outcome than those patients with higher velocities (Ni et al. 1994). However, the studies are not directly comparable not only because of the different case mix and entry criteria but also because of the difference in methods of measuring the MCA velocity. TCD does not take into account the angle between the transducer and the vessel and so the values tend to be lower than the 'true' value. TCCS allows compensation for this angle and so inevitably gives values which are at least equal to or greater than those measured by TCD. In the previous chapter it was seen that occlusion of MCA branch vessels resulted in a significant reduction in MCA velocity and that a value of less than 40 cm/s had both a high sensitivity and specificity for an abnormal MRA.

There are potential problems in using the MCA velocity as a prognostic indicator. It can, of course, only be used in patients who have MCA territory stroke and excludes any patient with vertebrobasilar ischaemia. Anterior cerebral artery strokes, although less common than MCA strokes, can result in a clinical syndrome which may be indistinguishable from an MCA stroke. Careful attention has to be paid to the ACA in the examination (as it is often difficult to see and only runs for a short length) if a correct diagnosis is to be made. The timing of the TCCS examination is of critical importance especially in cases of occlusive vessel disease. All the examinations in this study were performed within 24 hours to try to make the findings comparable and to detect vessel occlusion before recanalisation occurs. If TCCS is performed at a later stage, vessels may recanalise and so the TCCS findings may not be a true reflection of the underlying pathology. Three patients in this study had a patent MCA with increased velocity compared to the contralateral hemisphere probably reflecting early recanalisation of the artery. Two patients had a TACI and a were dependent at 3 months and the third patient, who had a PACI, was independent at 3 months. If TCCS had been performed earlier, the (presumed) MCA occlusion may have been diagnosed improving the prognostic ability.

Clinical Implications

There are several explanations of why measurements of velocity may be a better guide to functional outcome. It is known that some patients can present soon after a stroke with a lacunar syndrome who, in fact, have an occlusion of either the MCA or ICA. These patients then develop the usual clinical features of a TACI or sometimes a PACI after 24-48 hours. The reason for this may be due to an effective collateral supply keeping the MCA territory perfused for a short time. When the collateral supply begins to fall, the area of infarction increases and so the clinical signs worsen. However, TCCS will be able to detect the actual vascular pathology and so may be able to predict the eventual outcome. This may have important implications in the use of thrombolytic agents. These are generally not used in patients with lacunar infarctions because the presumed pathology is that of occlusion small deep perforating arteries and not of the major arteries. Additionally, most patients with a lacunar syndrome have a good outcome and the risk of thrombolysis

and cerebral haemorrhage outweighs any benefit that it may have. Thus, patients with major vessel occlusion, who present with a lacunar syndrome, will not be thrombolysed if the clinical findings are used to decide who receives thrombolysis. However, these patients would be identified as possible candidates for treatment if TCCS is used. Although this 'misdiagnosis' of patients is not thought to be common in clinical practice, it is probably more common in candidates for thrombolysis as these patients are usually assessed within 6 hours of stroke onset; an interval that may be too short for the full clinical syndrome to develop.

CHAPTER 5

RECANALISATION OF THE MIDDLE CEREBRAL ARTERY: INCIDENCE, TIME COURSE AND THE EFFECT ON CLINICAL OUTCOME

5.1 BACKGROUND

5.1.1 Historical Perspective

In the mid 17th century, Wepfer wrote about calcified arteries associated with 'apoplexy'. He also made the distinction between extravasation of blood into the brain substance and the obstruction to the flow of blood also seen in cases of stroke. The distinction of haemorrhage from infarction came in the early part of the 19th century with Rostan. However, he did not appreciate the different causes of infarction and haemorrhage even though he noted that some patients had 'ossification' of the cerebral arteries. Soon afterwards, Abercrombie in Scotland, put forward the theory of ossification of the arteries being the cause of infarction due to the obstruction to the flow of blood to the brain. By the mid 19th century, Virchow rediscovered the term arteriosclerosis to describe the fatty changes in the arterial wall that he proposed were the cause of arterial narrowing. He also coined the term 'embolism' and was the first person to realise the importance of this in the pathogenesis of stroke. However, it was not until many years later that the importance of carotid vessel embolism was realised; until then, it was thought that nearly all emboli were cardiac in origin. For many years, the cause of occlusion of the cerebral vessels was presumed to be due to atheroma in the vessels themselves causing a gradual decrease in the lumen diameter until the vessel eventually occluded.

The greater use of cerebral angiography in the 1950s and 1960s led to the significance of embolic rather than thrombotic stroke being fully appreciated. Serial studies employing arterial angiography in the early stages of acute ischaemic stroke showed that many patients had unequivocal evidence of either internal carotid artery or middle cerebral artery occlusion or both (Bladin, 1964; Lhermitte et al. 1970; Dalal et al. 1965; Fisher, 1951). It was also noted that if the angiograms were performed early in the course of stroke (within 24 hours) there was a large proportion of patients with occlusive disease in the major vessels (Bladin, 1964). However, if the angiograms were delayed, then they often revealed only MCA branch occlusion or, indeed, were normal. This led the authors to hypothesise that

the embolus fragmented and, as it became smaller, migrated along the ICA/MCA axis. The study by Dalal (Dalal et al. 1965) confirmed this hypothesis when serial angiography was performed in patients with occlusion of the ICA/MCA axis; the later angiograms showed refilling of the originally occluded vessels.

5.1.2 IMAGING STUDIES IN REPERFUSION

Angiography is the accepted 'gold standard' for imaging the cerebral vessels. However, it is performed less frequently due to the associated morbidity and mortality especially in the setting of acute stroke. From the studies outlined above, the frequency and possible importance of reperfusion was noted. However, it was only in the last few years that further studies have been performed looking more closely at reperfusion. This has occurred for two main reasons. Firstly, the advent of more sophisticated imaging techniques. TCD has been used to follow up patients with MCA occlusion and this has been correlated with angiographical findings. MRI has allowed areas of infarction and ischaemia to be measured in animal models of reperfusion. SPECT and PET studies have allowed cerebral blood flow to be measured and this has yielded information regarding cerebral reperfusion. Secondly, the success of thrombolysis in the treatment of acute myocardial infarction has focused attention on the potential of these agents in the treatment of acute ischaemic stroke. As the goal of thrombolysis is to recanalise occluded vessels and reperfuse ischaemic tissue, pilot studies and animal models have been set up to assess the effects of reperfusion in brain tissue.

Transcranial Doppler Studies

TCD was the first non-invasive technique for studying the cerebral vessels. It can be used as a bedside test and is thus ideally suited to follow up patients with ischaemic stroke. There have been several TCD studies examining the incidence of MCA occlusion and some have examined the role of recanalisation in relation to clinical outcome.

Fieschi (Fieschi et al. 1989) studied 80 patients with MCA territory stroke within 4 hours of stroke onset. They found that 53 patients had evidence of intracranial vessel occlusion: MCA mainstem (9), ICA (6), both (11) or MCA branch occlusion (27). The remaining patients had either normal vessels or extracranial carotid disease. They identified potential embolic sources, either cardiac or arterial, in 83% of cases. 15 patients with MCA occlusion were followed up with either TCD and/or angiography. 4 patients exhibited recanalisation within 24 hours and 7 patients had evidence of recanalisation by 1 week. However, there was no association between early, or indeed, late recanalisation and clinical outcome.

Kaps studied 23 patients with MCA occlusion diagnosed by angiography, post mortem or TCD (Kaps et al. 1990). 16 patients had evidence of recanalisation: 4 within 24 hours, 8 within 1 week and 4 within 3 weeks. 6 patients had no evidence of recanalisation by 4 weeks and 1 patient was not followed up. In this study there did not seem to be any relationship between early, late or no recanalisation and clinical outcome. In a further report by the same author (Kaps et al. 1992), recanalisation of MCA occlusion was found to be age dependent (all patients under the age of 50 years exhibited recanalisation). 60% of cases were thought to be embolic in origin as they had a potential source (e.g. mural thrombus, atheromatous ICA).

Ringelstein evaluated 31 patients with mainstem MCA occlusion and 3 patients with branch occlusion with TCD, angiography and CT within 24 hours of stroke onset (Ringelstein et al. 1992). 15 patients were treated with the thrombolytic agent tissue plasminogen activator (tPA) and unfortunately, the study does not distinguish between the 2 groups when discussing the results. Taking all patients as a whole (treated and non-treated, mainstem and branch occlusion), 65% showed recanalisation within 3 days and a further 11% recanalised by day 17. Patients with early recanalisation had a better clinical outcome than those with delayed recanalisation and also had smaller infarcts on CT. Patients with early recanalisation and a good collateral leptomeningeal blood supply had the best prognosis.

In a smaller study (Kushner et al. 1991), 14 patients with MCA occlusion (6 tandem lesions with occlusion of the ICA as well) were studied with TCD and angiography. Follow up TCD at 48 hours showed recanalisation in 7 patients. Following

recanalisation, the MCA velocity was significantly lower than that of the normal hemisphere. MCA velocity was predictive of infarct size on CT performed between 1 and 3 months post stroke. However, there was no assessment made of disability. There was no association between reperfusion and CT infarct size.

Recently, a study documented time to recanalisation in a series of patients with MCA occlusion but did not assess clinical outcome (Zanette et al. 1995). TCD and angiography were performed within 6 hours of stroke onset. In 16 patients no Doppler signal could be obtained and these patients were diagnosed as having MCA occlusion. Cumulative recanalisation rates were as follows: 5 at 24 hours, 6 at 48 hours, and 7 at 1 week. The long term follow up data was difficult to interpret due to the large drop out rate. It was noted that as the MCA recanalised, the velocities were initially low and this was thought to be due to distal migration of the embolus. Recanalisation was most common in patients with the most distal occlusions i.e. in MCA branch vessels, and was progressively rarer if the occlusion was situated more proximally e.g. in the cavernous tract. As with previous studies, there was no assessment of the patients clinical outcome and so the prognostic significance of recanalisation cannot be commented on.

Transcranial Colour-coded Sonography

There have no long term follow up studies using TCCS in acute stroke. TCCS should have advantages over conventional TCD in studying stroke, especially as one of the main limitations of TCD is the difficulty in diagnosing an occluded vessel. In essence, a 'search' has to be made for each vessel in order to obtain a Doppler shift frequency. MCA occlusion is inferred by the lack of a Doppler shift frequency at the site of where the MCA would normally be insonated (at a depth of 5-6 cm). However, the inability to detect a frequency shift may be due to other factors such as lack of a suitable acoustic window. Therefore, it is necessary to also detect signals from at least two other vessels (usually the ACA and the PCA) in order to diagnose MCA occlusion (Ringelstein et al. 1992; Mattle et al. 1988). Velocity changes have been detected in other vessels in the presence of MCA occlusion and these also help to diagnose MCA occlusion. The velocity in the ipsilateral ACA may

be increased and this is thought to be due to shunting of blood into the ACA (Zanette et al. 1989; Mattle et al. 1988; Kaps et al. 1990). TCCS allows the basal cerebral arteries to be imaged and colour-coded on a B-mode background. Thus, the diagnosis of MCA occlusion should be made with more confidence as the lack of colour signal from the MCA (but not of the ACA or PCA) will be apparent (see Figure 1). This will cut down the lengthy search for the MCA and the scan will be much quicker.

Cerebral Blood Flow Studies

Although TCD can provide information regarding the patency of cerebral vessels and the blood flow velocity within these vessels, it cannot measure tissue perfusion. Positron emission tomography (PET) is able to measure cerebral blood flow and oxygen and glucose metabolism in a quantitative fashion. Single-photon emission computed tomography (SPECT) is also able to measure tissue perfusion but only semi-quantitatively (i.e. measurements of perfusion are usually made by comparing one hemisphere with the other or with the cerebellum). PET is only available in certain centres and is logistically difficult to perform. There are, therefore, few studies employing this technique in acute stroke. SPECT is more widely available but there are still only a limited number of studies assessing the role of SPECT in the early stages of ischaemic stroke. Both techniques are time consuming and expensive and are therefore not often repeated in the same patient. Thus, sequential studies looking for reperfusion of ischaemic tissue are lacking. Instead reperfusion is often assumed if a patient presents with focal hyperaemia (SPECT) or luxury perfusion (PET) in the region of the infarct.

One study did, however, perform repeat SPECT scans on stroke patients. As part of a pilot study for a thrombolytic trial, Baird recruited 57 patients with ischaemic stroke and studied them with SPECT (Baird et al. 1994). 22 patients received streptokinase (either intravenous or intra-arterial) and the remaining 35 patients acted as controls. Mean time to SPECT was 5.4 hours in the treated group and 10.3 hours in the control group. Patients with hypoperfusion on the initial SPECT went on to have repeat imaging 24 hours later. As expected, more patients in the treated

group reperfused than those in the control group (65% vs. 52%). Patients who did exhibit reperfusion, irrespective of whether they received streptokinase or not, had a better functional outcome at 3 months (measured using the Barthel Index) than those patients who did not reperfuse. The authors concluded some reperfusion within 48 hours occurs as part of the natural history of MCA occlusion and that reperfusion within this time window is of prognostic significance.

Another SPECT study was performed on a large unselected stroke population (Jorgensen et al. 1994). 146 patients with cortical infarcts underwent scanning at a random time from stroke onset. Focal hyperaemia was interpreted as reperfusion. From this, it was estimated that the rate of reperfusion was 35% by day 3, 60% by day 7 and 80% by day 14. They found that reperfusion even as late as 1 week post stroke was associated with a better functional outcome (measured on the Scandinavian Stroke Scale) than those patients who did not reperfuse their MCA or in whom reperfusion was occurred after 1 week.

Using planar ^{133}Xe imaging and intraarterial angiography, Olsen (Olsen and Lassen, 1984) investigated 73 patients with stroke within 3 days of onset. Focal hyperaemia was seen in 21 patients, all of whom had evidence of MCA occlusion on angiography. The hyperaemic areas corresponded to both infarcted and non-infarcted areas on CT scanning. The authors proposed that the hyperaemia seen on the CBF studies was a reflection of recanalisation of the MCA due to clot fragmentation and distal migration. They also proposed that where the hyperaemia corresponded to an area of non-infarction on CT, the recanalisation had occurred early enough to salvage tissue which was critically ischaemic. Conversely, if the recanalisation occurred too late, the tissue would become infarcted and this was then visible on the CT scan. One third of the patients studied exhibited arterial recanalisation within 4 days of stroke.

A PET study performed on 18 patients within 18 hours of stroke found that 6 patients exhibited hyperperfusion with normal or slightly reduced oxygen consumption.(Marchal et al. 1993). These patients had a better prognosis and smaller areas of infarction on CT than those with both decreased cerebral blood flow and decreased oxygen consumption. The authors stated that the hyperperfusion was probably due to recanalisation of the MCA and that the limited area of infarction

was due to good collateral supply circulation. Hyperperfusion on PET has also been associated with a low risk of infarction on follow up CT (Marchal et al. 1996b).
Most other SPECT and PET studies have only performed an initial scan and then correlated the degree of hypoperfusion with clinical outcome. Additionally, very few studies have looked at the early stages of stroke (within 24 hours) so their results must be interpreted with caution. The results of these studies are variable and do not provide a consistent answer to the hypothesis that early reperfusion is beneficial.

Animal Studies of Reperfusion

There have several animal studies in which the effect of reperfusion has been examined. Generally, in experimental models, the MCA occluded for a specific period of time and then re-opened. The effects of this procedure can be measured either by imaging the animal brain using MRI or by sacrificing the animal and observing any histological changes.
MRI studies have focused mainly on diffusion-weighted imaging (DWI) as this is able to detect areas of ischaemia and infarction in their very early stages (Minematsu et al. 1992a). Müller studied 15 rats which were exposed to either 45 or 120 minutes of MCA occlusion (Muller et al. 1995). DWI was performed after 30 minutes of MCA occlusion and then repeated after 50 minutes of reperfusion. In the 45 minute occlusion group the area of abnormal signal on DWI (indicating ischaemia) fell from 24.2% to 9.9%. In the 120 minute occlusion group the area of ischaemia rose from 24.4% to 29.1%. It was concluded that early reperfusion limits the size of ischaemia but the authors remained cautious in extrapolating their findings to humans. Similar work was carried out by Minematsu in which rats underwent either 1 or 2 hours of MCA occlusion (Minematsu et al. 1992b). The rats undergoing 1 hour of MCA occlusion had smaller areas of ischaemia on DWI, no abnormalities on T2 images, less neurological deficit and smaller ischaemic lesions on histology than the rats exposed to 2 hours of MCA occlusion. These results agree with other experimental models of reversible MCA occlusion (Nagasawa and Kogure, 1989; Memezawa et al. 1992; Kucharczyk et al. 1993) that there seems to

be a window of 1-2 hours within which re-opening of an occluded vessel and reperfusion of ischaemic tissue will lead to minimal tissue necrosis.

5.1.3 SUMMARY OF PREVIOUS STUDIES

It is now generally excepted that the majority of ischaemic stroke is due to embolism rather than thrombosis of the major cerebral vessels.

The majority of cases of MCA occlusion recanalise.

If recanalisation is going to occur, it usually occurs in the first few days post stroke.

Results of TCD studies (measuring vessel patency) and SPECT and PET studies (measuring cerebral perfusion) on humans are conflicting, although they point towards a better clinical outcome in patients with early recanalisation/reperfusion.

Animal models of MCA occlusion suggest that ischaemic changes resulting from longer than 1-2 hours of MCA occlusion is permanent; occlusion of the MCA for shorter periods results in reversible ischaemia.

5.2 AIMS OF THE STUDY

At the time of writing the present study there were no published studies on the use of TCCS in the follow up of patients with MCA occlusion although there have been TCD studies. The use of TCCS should lead to quicker, more accurate assessments of the basal cerebral arteries.

This study was performed in order to assess the following:

(i) the time to recanalisation of MCA occlusion

(ii) whether recanalisation of the MCA within 48 hours was associated with a better prognosis than those patients not exhibiting recanalisation

(iii) the changes in MCA velocity following recanalisation

(iv) the changes in blood flow velocity in the other basal cerebral arteries

5.3 SUBJECTS AND METHODS

The patients in the study comprise 23 patients who were found to have MCA occlusion on TCCS and 3 patients who had significantly increased MCA velocity on the symptomatic hemisphere, which was assumed to be secondary to early recanalisation. Inclusion and exclusion were the same as for all patients in this study and were listed in chapter 2.

Patients were studied in the vascular studies unit on the Diasonics 'Spectra' scanner as described previously.

The temporal window was used to insonate the basal cerebral arteries and the vessels were then interrogated with pulsed-wave Doppler. The mean and peak velocities were recorded for each vessel insonated. MCA occlusion was diagnosed if there was no Doppler shift frequency or colour signal obtained in the presence of the ACA and PCA. Recanalisation was said to have occurred if, on subsequent examinations, the signal from the MCA returned.

Recanalisation within 48 hours was classified as 'early recanalisation'.

Patients were studied with TCCS as soon as possible following admission to hospital. They were then studied on the following day and at 1 week and lastly at 3 months. Patients who had been discharged from hospital at that stage, were sent appointment cards and telephoned prior to the appointment in order to encourage attendance.

As well as TCCS, all patients underwent carotid duplex scanning which was performed at the same time as the first TCCS scan. 11 patients underwent MRI scanning which was performed on the first day of admission. The remaining investigations were left up to the discretion of the team of doctors who were looking after the patient on a day to day basis.

Clinical assessment was made whenever a patient had a scan performed. The National Institute of Health (NIH) stroke scale was used to assess neurological dysfunction. The Barthel Index (BI) was used at 3 months as a measure of overall disability.

5.4 RESULTS

5.4.1 PATIENT DETAILS

119 patients were considered for entry into the study. 93 patients were excluded for the following reasons: 21 patients lacked an adequate acoustic window, 14 patients were shown to a have cerebral haemorrhage, 2 patients had cerebral tumours, 3 patients refused consent, 4 patients deteriorated and were too ill to undergo scanning, 49 patients did not have evidence of MCA mainstem occlusion.

The 26 patients entered in the study consisted of 13 females and 13 males, age range: 60-84 years, mean: 75.2 years (Table 1). The average time interval from stroke onset to TCCS was 12 hours (range: 4-24 hours). 16 patients were studied within 12 hours of stroke onset and 10 patients from 13 to 24 hours.

20 patients were classified as having a TACI and 6 patients had a PACI. NIH stroke score ranged from 7-16 (mean: 11) for the PACI patients and from 15-31 (mean: 22.6) for the TACI patients.

13 patients had a history of hypertension and all of these patients were on medication for this. 7 patients had a history of atrial fibrillation and were all being treated with digoxin. 2 patients were noted to be in AF which had not been previously diagnosed.

11 patients had co-existing ischaemic heart disease and 7 patients were ex-smokers. 1 patient was known to have non-insulin dependent diabetes mellitus. No patients were known to have hyperlipidaemia.

Table 1. Patient details

patient no	age (years)	sex	time to scan (hours)	stroke type	NIH score (day 1)	BI (3 months)
1	78	f	10	TACI	19	15
2	75	f	15	TACI	26	25
3	72	m	12	TACI	24	0
4	69	m	7	TACI	15	0
5	81	f	14	TACI	22	65
6	73	m	11	TACI	31	0
7	75	m	10	TACI	23	45
8	79	m	15	TACI	19	0
9	82	f	18	TACI	26	10
10	80	m	11	PACI	15	10
11	77	m	8	PACI	16	75
12	74	f	9	PACI	9	0
13	80	m	10	PACI	7	25
14	77	f	7	TACI	19	0
15	72	f	10	PACI	7	65
16	84	f	22	TACI	28	0
17	75	f	4	TACI	30	0
18	76	f	24	TACI	26	45
19	76	f	14	TACI	28	15
20	73	m	8	TACI	17	0
21	75	m	12	TACI	22	20
22	65	m	4	TACI	21	50
23	76	f	18	TACI	21	65
24	75	m	13	TACI	16	75
25	77	f	8	TACI	19	75
26	60	m	20	PACI	12	90

5.4.2 INVESTIGATIONS

All patients underwent brain imaging: 11 with MRI and 15 with CT. 12 patients had imaging performed within 24 hours of stroke onset, 3 patients within 2 days, 6 within 3 days, 3 patients within 4 days and 2 patients within 5 days.

1 patient had a large pan-hemispheric infarction, 15 patients had typical large, wedge shaped infarctions of the MCA territory, 8 patients had smaller sized infarctions of

the MCA territory and 2 patients had small scattered high signal areas in keeping with small vessel disease.

7 patients underwent echocardiography. This was within normal limits in 6 patients and in 1 patient it showed evidence of both aortic and mitral regurgitation and a dilated left ventricle. There was no evidence of thrombus seen on any of the echocardiographs.

Carotid ultrasound was normal in 16 patients, showed mild disease in 4 patients, moderate disease in 5 patients and an occlusion of the ICA in 1 patient. On the asymptomatic side, carotid ultrasound was normal in 14 patients, showed mild disease in 5 patients, moderate disease in 6 patients and severe disease in 1 patient.

5.4.3 TIME TO RECANALISATION

3 patients had patent MCAs on the symptomatic side and were considered to have recanalised before they were investigated. This was based on the fact that all 3 patients had significantly raised MCA velocities on the symptomatic vessel compared to the contralateral side suggesting early recanalisation of the MCA and subsequent hyperaemic blood flow. In addition, 1 of these patients underwent perfusion MRI and this demonstrated increased cerebral blood flow at the site of the infarction. Mean interval from stroke onset to TCCS in these 3 patients was 13.7 hours (range: 8-20 hours).

A further 5 patients recanalised by 48 hours, 4 by 1 week and 4 by 3 months. 10 patients did not show any evidence of recanalisation. 17 patients were alive at the 3 month follow up. 14 of these patients had evidence of MCA recanalisation (Table 2).

Table 2. Time to recanalisation.

Time to recanalise	number of patients	cumulative total
<24 hours	3	3 (12%)
24-48 hours	5	8 (31%)
2-7 days	4	12 (46%)
7 days-3 months	4	16 (62%)
no recanalisation	10	

5.4.4 TRANSCRANIAL COLOUR-CODED SONOGRAPHY

MCA velocity

23 patients had evidence of proximal MCA occlusion on the symptomatic hemisphere (Figure 1). Following recanalisation, the MCA velocity in 2 patients was elevated significantly (Figure 2). At the next examination, the velocity in both patients had decreased and was significantly lower than the 'normal' side. 7 patients demonstrated significantly low MCA velocities following recanalisation (Figure 3). In 4 patients, MCA velocity returned to within the normal range following recanalisation. See Table 3.

ACA velocity

Ipsilateral ACA velocity was increased in 13 patients with MCA occlusion (Table 4). The increase in ACA velocity was present throughout the length of the vessel and not confined to just one segment of the artery (Figure 4). The velocities remained elevated for a variable length of time. Of the 13 patients with a raised ipsilateral ACA velocity on day 1, 6 exhibited a normal velocity by day 2 (of these 6 patients, 4 had recanalised their MCA). 1 of the 2 patients with a raised ACA velocity on day 7 exhibited recanalisation of the MCA.

PCA velocity

There were no significant differences in side to side asymmetry of the PCA in any of the patients in the study.

Figure 1. **TCCS demonstrating occlusion of the MCA mainstem. The ipsilateral and contralateral ACA can be seen as well as the ipsilateral PCA. The ICA siphon is also seen but there is an abrupt cut off (arrow) at the point where the MCA would normally arise.**

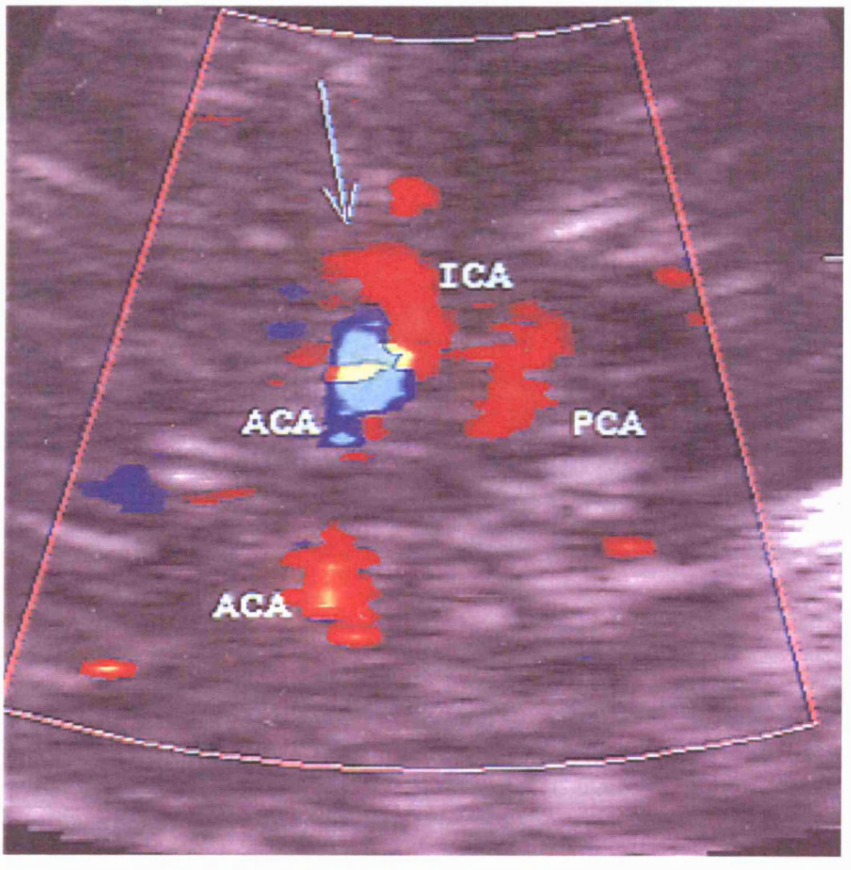


Figure 2. **Pulsed Doppler spectral display of the MCA following recanalisation of the artery. The high velocities were present throughout the course of the artery indicating hyperaemic flow.**

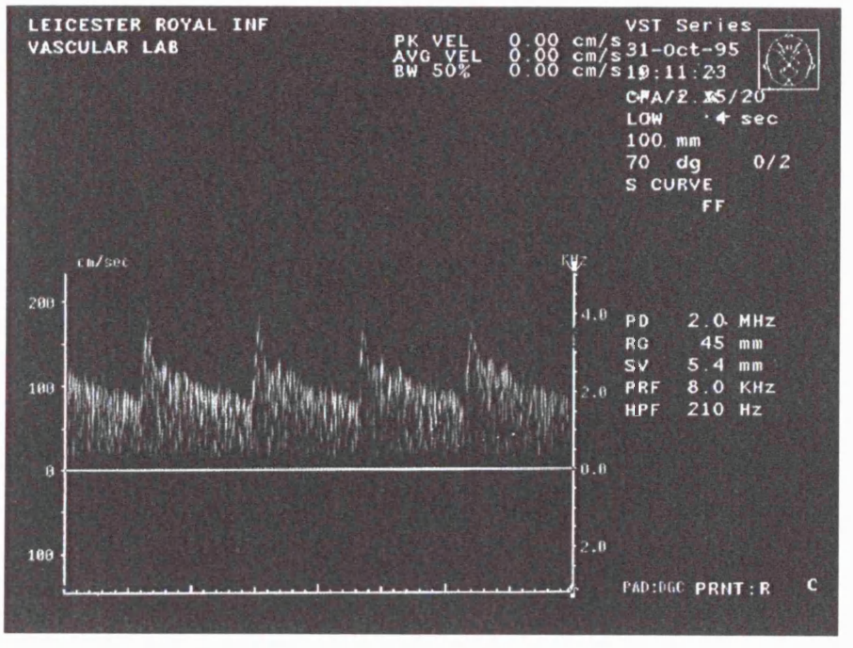


Figure 3. **The basal cerebral arteries imaged with TCCS with the pulsed Doppler spectral display of the MCA below. In this patient blood flow velocity following recanalisation was low compared to the contralateral hemisphere.**

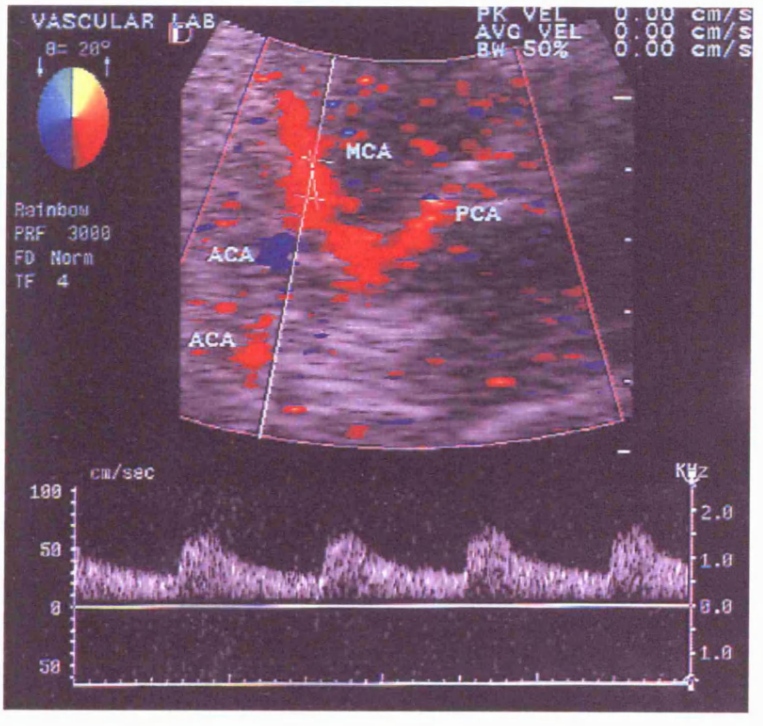


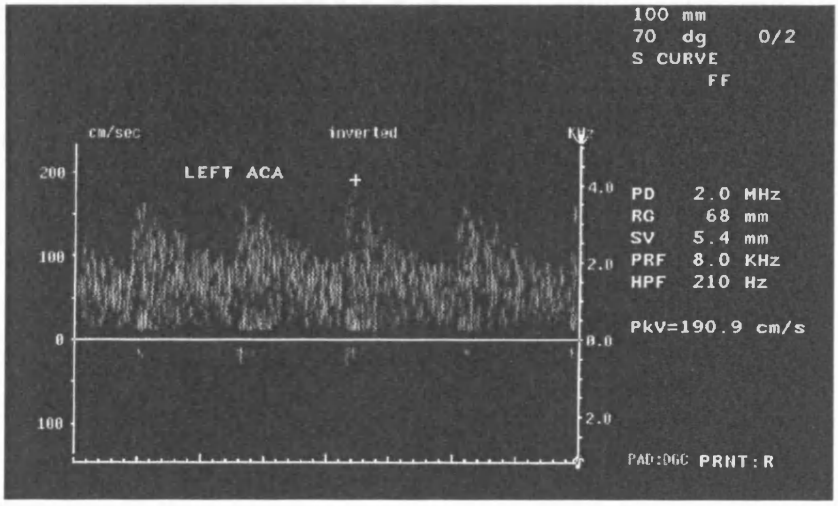
Table 3. Middle cerebral artery velocity in the asymptomatic and symptomatic hemispheres with time (mean velocity in cm/s)

patient	day 1		day 2		day 7		3 mo nths	
no	sym	asym	sym	asym	sym	asym	sym	asym
5	0	59.8	55.6	61.2	58.1	60.1	56.4	58.7
7	0	66.7	71.5	64.3	67	65.7	62.1	65.8
11	0	47.3	49.9	44.8	47.3	43.6	47	45
15	0	40.6	42.6	48.9	44.5	43.6	46.1	45.9
20	0	41	97.9	37.4	69.7	53.7	dead	
13	0	48.9	0	46.5	26.3	47.1	DNA	
14	0	35.6	0	36.3	22.4	36.2	dead	
18	0	43.3	0	42.8	21.1	45.6	24.4	60.2
22	0	48.4	0	48.9	89.3	46.3	38.4	56.9
1	0	43.8	0	45.1	0	45.7	29.8	46.2
2	0	43.8	0	43	0	40.8	40.7	41.5
10	0	55.4	0	52.9	0	50.5	32.5	53.7
21	0	36.8	0	31.9	0	34.6	23.1	32
3	0	36.7	0	39.5	dead			
4	0	50.2	dead					
6	0	34.3	0	36.8	dead			
8	0	43.8	0	40.9	0	43.4	dead	
9	0	47.9	0	45.6	0	46.2	0	45.7
12	0	38.2	0	40.1	0	39.6	dead	
16	0	43.8	0	48.3	0	44.3	dead	
17	0	44.8	0	47.2	dead			
19	0	34.3	0	39.4	0	41.6	0	50.5
23	0	42.5	0	41.8	0	44.9	0	44
24	61.3	44.9	59.6	45.4	47.6	44.1	44.2	46.1
25	76.4	47.1	60.2	49.2	50.4	46.1	49.2	46.3
26	55.4	25.6	54.8	66.6	48.8	65.4	66.1	59.6

Table 4. ACA velocity and MCA occlusion.

TCCS findings	day 1	day 2	day 7	3 months
MCA occlusion	23	17	10	3
raised ACA velocity	13	6	2	1
raised ACA velocity and MCA occlusion	13	6	1	0

Figure 4. Spectral Doppler display of the anterior cerebral artery demonstrating increased blood flow velocity as a result of occlusion of the ipsilateral middle cerebral artery. Peak velocity is approaching 200 cm/s.



5.4.5 CLINICAL OUTCOME

9 patients died during the study period: 3 within 1 week of stroke onset, 4 within 1 month and 2 within 2 months. Causes of death were: cerebral infarction (5), pulmonary embolus (2) and congestive cardiac failure (2). 1 patient did not attend the 3 month follow up assessment, and so the BI had to measured by telephone. The mean BI at 3 months for all patients was 30 (range: 0-90). For those who survived to 3 months, the mean BI was 45. Only 1 patient was discharged home having made a full recovery (BI: 90). 6 patients were discharged home (mean BI: 70) but needed a small amount of help in the house in the form of minor modifications to the house (e.g. stair rails, seat raises etc.). These 6 patients exhibited a degree of handicap that restricted their lifestyles to an extent such that they were not able to be completely self caring. 7 patients were either in hospital or a nursing home as they were fully dependent on constant nursing care (BI: 10-25). 3 patients were still in hospital at 3 months and could manage some simple tasks on their own (BI: 45-50) but were nevertheless still dependent on nursing care. Plans were being made to discharge them to their homes where they would be cared for by family members. However, it was envisaged that they would require a lot of support during the day and would not be self caring for some time.

Patient details according to time to recanalisation

Patients exhibiting recanalisation by 48 hours ('early') had a mean admission NIH score of 16.5 (range: 7-23) and those who recanalised after 48 hours or did not exhibit any recanalisation ('no recanalisation') had a mean score of 20.9 (range: 7-31). There was no significant difference between the means of these 2 groups (Student's t-Test: $p>0.05$).

The mean ages of the patients in each group were similar: early recanalisation: 73.8 years; no recanalisation: 75.9 years ($p=0.16$).

5.4.6 CLINICAL OUTCOME AND TO TIME TO RECANALISATION

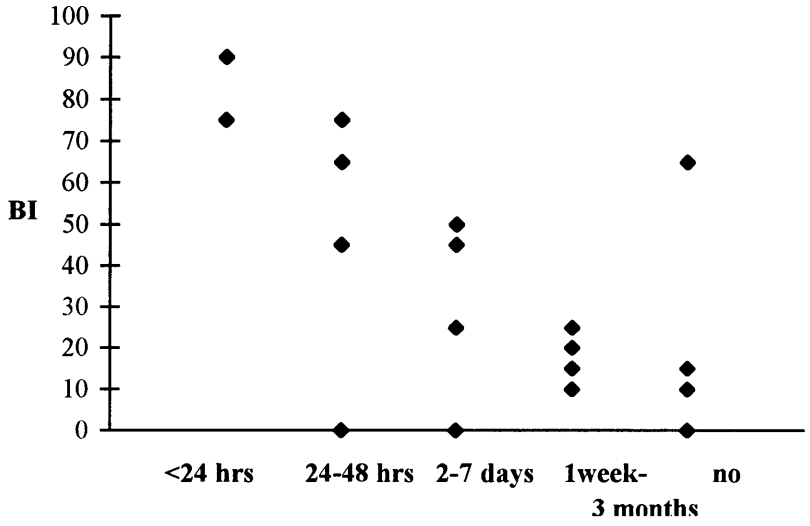
For the purposes of statistical analysis, the patients were divided into 2 outcome groups: poor and good. The first group included all patients who were dead or fully dependent at the follow up assessment at 3 months. Patients were deemed to be dependent if they needed constant nursing care. The poor outcome group consisted of 19 patients: 9 were dead (BI: 0), the remaining 10 patients had a mean BI of 26 (range: 10-50). The good outcome group consisted of patients that were able to live independently and were self caring and those patients who required a minor amount of help in performing their activities of daily living. There were 7 patients in this group (Table 5). The 3 month BI according to time to recanalisation is given in figure 5.

Table 5. Clinical outcome according to recanalisation at 48 hours.

	early recanalisation	no recanalisation
n	8	18
good outcome	6	1
poor outcome	2	17

Using logistic regression, early recanalisation was highly significant in predicting a good outcome (p=0.003) with an odds ratio of 51.0 (95% CI: 3.9-669.5).

Figure 5. Time to recanalisation and 3 month Barthel Index.



5.5 DISCUSSION

MCA occlusion is a common cause of stroke and is probably due to embolism rather than thrombosis (Bladin, 1964; Lhermitte et al. 1970). In this study, 23 patients had evidence of MCA occlusion on TCCS and a further 3 patients had MCA occlusion and subsequent recanalisation inferred from asymmetrical MCA velocities. The rate of recanalisation was 76% for those surviving at 3 months. This is in keeping with rates reported in previous studies (Kaps et al. 1990). The mechanism underlying MCA recanalisation is thought to be that of gradual fibrinolysis. It has been postulated that as the embolus is lysed, it decreases in size and then migrates distally until it lodges in the finer branches of the MCA (Bladin, 1964; Dalal et al. 1965). Eventually, the clot lyses completely and the branch vessels re-open. TCCS does not have the spatial resolution to identify the branches of the MCA with adequate accuracy to diagnose branch occlusion. However, in a previous study comparing cerebral angiography and TCD in acute stroke, it was found that blood flow velocities were significantly reduced if 3 or more MCA branch vessels were occluded (Zanette et al. 1989). 7 out of 13 patients exhibiting recanalisation in the study group went on to have significantly lower velocities in the symptomatic MCA compared to the contralateral hemisphere. This would be in keeping with the theory of distal clot migration following partial fibrinolysis. Interestingly, 2 patients exhibited raised MCA velocity following recanalisation. This may reflect transient hyperaemia following the initial ischaemic insult. When raised MCA velocities are detected, it is important to distinguish hyperaemic flow from stenotic flow. The latter usually gives rise to high velocities in only a short segment of the vessel i.e. the segment which is stenosed. This is often seen as aliasing in the colour display. If the sample volume is moved up and down the vessel, the velocity should normalise away from the stenotic area. Hyperaemic flow is characterised by an increase in blood flow velocity along the whole length of the vessel. Angiographical studies are generally unable to demonstrate hyperaemic flow, although this phenomena can be seen with TCD in acute stroke (Zanette et al. 1989; Ringelstein et al. 1992).

The ACA velocity was significantly higher in the ipsilateral hemisphere in 13 out of the 23 patients with MCA occlusion. This is thought to be due to the shunting of blood from the occluded MCA to the patent ACA and has been reported in previous TCD studies (Kaps et al. 1990; Mattle et al. 1988; Zanette et al. 1989). Indeed, the raised ACA velocity is one sign that is looked for in TCD studies to make a diagnosis of MCA occlusion. The ACA velocity normalised with time with only one patient still having a significantly raised ACA velocity at 3 months. The ACA velocity seemed to reflect the state of MCA patency: as the MCA's recanalised, the ACA velocity fell accordingly. This, again, supports the hypothesis that the cause of the elevated ACA velocity is 'mechanical' rather than physiological.

There were no side to side differences in PCA velocity in any of the patients. This is not an unexpected finding as all the infarctions were in the anterior circulation. However, abnormal PCA velocities are occasionally seen in MCA territory infarction. Mattle reported a small number of cases in which MCA peripheral branch occlusion in combination with internal carotid artery stenosis was associated with a raised ipsilateral PCA velocity although the rise did not quite reach statistical significance (Mattle et al. 1988). It was thought that the reason for the rise in velocity was again due to flow in collateral pathways. The fact that patients in this study did not exhibit raised PCA velocities may reflect the paucity of collateral vessels seen in patients with MCA disease (Sindermann et al. 1969).

The overall clinical outcome for patients with MCA occlusion was poor. In the group of 26 patients, there were 9 deaths, 6 patients were partially dependent and 10 patients were totally dependent on carers for their activities of daily living. Only 1 patient was discharged home having made a full recovery. Of the 10 patients in the 'dependent' group, 7 required constant nursing care and were either in a nursing home or still in hospital at 3 months. The other 3 patients required a slightly lower level of care but were nevertheless unable to self care and needed help with nearly all their activities of daily living.

Although the number of patients in the study is relatively small, there was a highly statistical difference in clinical outcome between the group of patients exhibiting recanalisation by 48 hours and those whose MCA remained occluded at 48 hours. There was no statistical difference between the 2 groups in admission NIH score and

so the results cannot be explained by a bias due to unmatched patients. Another major determinant of outcome, age, was also similar in the 2 groups. This finding is consistent with a number of studies regarding early and late recanalisation (Ringelstein et al. 1992; Baird and Donnan, 1993; Jorgensen et al. 1994) but differs from the results of trials of thrombolytic agents that recanalisation has to achieved within 3 hours for it to be beneficial. This may be partly explained by the large number of haemorrhages seen in the treated patients in these trials. Thrombolysis can lead to haemorrhage of the infarcted area which can result in increased intracranial pressure and a significant risk of morbidity and mortality.

von Kummer studied the effects of intra-arterial urokinase in 77 patients with acute stroke (von Kummer et al. 1995). Patients with very early recanalisation (<8 hours after onset), diagnosed with angiography or TCD, as well as late recanalisation (8-24 hours) had a more favourable prognosis than those patients without evidence of recanalisation. This study included patients with both MCA mainstem as well as branch occlusions and so is not directly comparable to the present study which only included patients with proximal MCA occlusion. However, it does highlight the fact that improvement in outcome is still possible up to 24 hours following vessel recanalisation. A recently published animal study utilising PET in experimental MCA occlusion in baboons has also challenged the view of a strict time window for the beneficial effects of recanalisation (Young et al. 1997). In this study, recanalisation, even if it was delayed, was associated with a smaller infarct volume when compared to those animals whose MCAs remained occluded. The concept of a rigid 'window of opportunity' has been the subject of recent debate (Baron et al. 1995) as some authors believe that efforts to reperfuse tissue may be successful in some patients after the standard 6 hour period has elapsed.

This study has shown that patients are less likely to be dead or dependent at 3 months if they exhibit arterial recanalisation within 48 hours of stroke onset. This time interval is greater than one might expect on the evidence of both animal studies, which suggest that brain tissue remains viable for only a few hours after MCA occlusion, and trials of thrombolytic therapy where intervention has been shown to be effective only if given within 3 hours of stroke (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. 1995). There are

many explanations for the differences between this study and the animal experiments that could explain the discrepancy in the 'time window'. Firstly, results in animal models may not be directly applicable to humans due to the species difference. Secondly, in order to occlude an MCA, the animal has to be anaesthetised and then a small nylon filament is inserted via a small neck incision into the carotid artery. The filament is then advanced until it blocks the origin of the MCA. Anaesthetic agents such as isoflurane and halothane tend to lower arterial blood pressure and this can have an adverse effect on tissue survival. The animals used in these experiments tend to have been previously healthy. In human studies, patients with stroke often have pre-existing illnesses or other risk factors such as hypertension, that may well influence the outcome of sudden arterial occlusion. Patients with chronic cerebrovascular disease often develop a network of collateral vessels that can operate if a major vessel gets occluded. This cannot be readily tested in experimental models.

Clinical Implications

It is becoming increasingly clear that stroke patients do not form a homogenous group even if patients have similar clinical findings or have similar pathology on conventional imaging such as CT. Patients being entered in large trials of thrombolytic therapy exhibit a wide range of underlying vascular pathologies. These are not readily apparent on CT imaging which is generally used to distinguish cerebral haemorrhage from infarction. TCCS is able to image the cerebral vessels and so detect the presence of vascular occlusion. This may be important in selecting patients for therapeutic trials of thrombolysis. The longer time window identified in this study may have therapeutic implications. One of the difficulties in treating patients with thrombolysis has been the paucity of patients that have been eligible for the treatment as they have to be admitted to hospital and have a CT scan within 6 hours of symptom onset. This strict time window has excluded many patients from receiving treatment as it is often very difficult to arrange not only the admission to hospital but also the CT scan within the time window. If recanalisation improves outcome up to 48 hours following stroke onset, it may be possible to treat many more patients than previously thought. TCCS may have a role in identifying patients with MCA occlusion who, if they fit the entry requirements (e.g. no evidence of

haemorrhage) would be candidates for thrombolysis. The wider use of other techniques such as perfusion and diffusion MRI, SPECT and PET may well be able to identify potentially viable ischaemic tissue that cannot be imaged using standard CT or MR techniques. The combination of tissue perfusion imaging and TCCS (which allows imaging of the basal arteries) may be invaluable in the selection and monitoring of patients following thrombolytic treatment.

CHAPTER 6

THE RELATIONSHIP BETWEEN VASCULAR PATHOLOGY AND STROKE TYPE

6.1 BACKGROUND

6.1.1 CLINICAL MANIFESTATIONS OF VESSEL DISEASE

The many different stroke syndromes that have been described are partly due to the site of the vascular lesion. The clinical syndrome is dependent upon the area of brain parenchyma that is damaged and the severity of the damage. There is variation in the cerebral vasculature from one individual to another and so occlusion of the same vessel in one person may not produce the same clinical findings as in another person. The state of the collateral circulation may play an important role in the amount of tissue that is damaged following vessel occlusion: if the collateral circulation is very effective, areas of parenchyma may be kept adequately perfused to avoid infarction and so lessen the severity of the stroke.

The OCSP divided patients into four stroke syndromes: total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS) and posterior circulation syndrome (POCS) (Bamford et al. 1991). This type of clinical classification of stroke is useful as it can be used to predict prognosis, predict the underlying pathological mechanisms and thereby direct the physician to effective use of investigations and therapy.

The middle cerebral artery (MCA) can be occluded at several places along its course: at its origin, at the level of the bi or trifurcation or at one of its 12 cortical branches. Occlusions at these different levels will give rise to different clinical manifestations and also to different sub types of stroke. The site of vessel occlusion will be discussed next along with the neurological findings and the relationship with OCSP classification.

6.1.2 Middle cerebral artery - mainstem

Atheroma rarely affects the proximal portion of the MCA although it is more common in Orientals than Caucasians. The cause of MCA occlusion in Caucasians is most likely to be due to an embolus or from extension of proximal thrombus (Olsen et al. 1985; Fieschi et al. 1989; Bozzao et al. 1989b). Occlusion of the proximal segment of the MCA will lead to ischaemia in both deep and superficial territories because of the involvement of the lenticulostriate arteries (LSA). Clinically, this will result in hemiparesis (face and arm affected more than leg), hemisensory loss and homonymous hemianopia. In the acute stages, head and eye deviation may be seen. Dominant hemisphere lesions will produce global dysphasia and non-dominant lesions will produce hemispatial neglect, aprosody constructional impairment and anosognosia or anosodiaphoria. The extent of the ischaemia will be dependent upon the collateral circulation from the ACA and PCA. If this is good, then the infarction may be limited to subcortical structures (e.g. a striatocapsular infarction) because the LSAs are end arteries (Bozzao et al. 1989c). TCD and angiographic studies have shown that the area of infarction is smaller and clinical outcome is better in patients with good collateral circulation (Ringelstein et al. 1992). If the occlusion occurs distal to the origin of the LSAs, then the leg will be relatively spared as most it will receive most of its supply from the ACA.

TACS

In the OCSP, 17% of patients with cerebral infarction had a TACS (Bamford et al. 1991). Of these, 95% had large areas of infarction in the MCA territory on CT. Only 3 patients had infarcts in areas which did not fit the clinical picture. In another population based study, 42 patients had a TACS and of these, only one patient had an 'inappropriate' infarct on CT (Ricci et al. 1991). The size of the infarct is greater than patients who have lesser degrees of neurological deficit (Lindgren et al. 1994). In the study by Wardlaw (Wardlaw et al. 1996), 91% of patients with a TACS had medium or large MCA territory infarcts or large subcortical infarcts. The vascular pathology underlying TACS is generally proximal occlusion of the MCA with infarction of both deep and superficial territories. However, occlusion of the PCA

can also produce a TACS (Wardlaw et al. 1996) but generally the dysphasia and field defect are much more marked than the hemiparesis.

6.1.3 Middle cerebral artery-main branches

The MCA runs for 1.8-2.6 cm before it divides into one of three patterns: bifurcation into superior and inferior branches (78%), trifurcation into superior, middle and inferior branches (12%) and ramification into multiple branches (10%).

The superior branch gives rise to the orbitofrontal, prefrontal, precentral and sometimes the central cortical branches. If the mainstem MCA is short, then the LSA arise from the superior branch as well. Occlusion of the superficial branch will result in a contralateral hemiparesis with a brachiofacial predominance and hemisensory loss in the same distribution. A large lesion may also cause conjugate ocular eye deviation towards the affected hemisphere. If the dominant hemisphere is affected, non-fluent dysphasia, agrammatism and impaired repetition ability may also occur (sometimes accompanied by ipsilateral limb ideomotor apraxia). Non-dominant infarctions lead to hemispatial neglect with motor predominance and abnormalities in prosody.

The inferior division of the MCA gives rise to posterior temporal artery, middle temporal artery, anterior temporal artery, temporo-polar branch and the temporo-occipital branch. Inferior branch occlusion gives rise to a very different clinical picture. Motor signs are often absent or, if present, are transitory and mild. Visual field defects are common: contralateral homonymous hemianopia or superior quadrantanopia. Hemisensory loss of the primary modalities (i.e. light touch, pain, temperature) is uncommon but agraphasthaesia and astereognosis may occur. Infarction in the dominant hemisphere results in fluent dysphasia and this may be accompanied by acute agitation and paranoia behaviour (Ross, 1993). Non-dominant hemisphere infarction results in contralateral hemineglect with sensory predominance, constructional impairment, anosodiaphoria, anosognosia and difficulty comprehending emotional prosody (Caplan et al. 1986).

6.1.4 Middle cerebral artery cortical branches

The MCA gives off 12 cortical branches (Michotey et al. 1974). These branches do not tend to anastamose with each other and although the branching patterns vary, they supply a wedge shaped area of brain parenchyma which is remarkably constant from one person to another (Saver and Biller, 1995).

Orbitofrontal

Unilateral infarction of this vessel is rare. It can present as behavioural disinhibition and contralateral grasp response (Waddington and Ring, 1968).

Prefrontal

Infarction of this territory mainly results in behavioural disturbances. Apathy, abulia, diminished mental flexibility, poor abstraction and motor perseveration can all occur. Dominant hemisphere lesions can result in poor verbal fluency while non-dominant infarctions result in motor neglect (Saver and Biller, 1995).

Precentral

Proximal upper limb weakness can be seen with this infarction. Poor speech output with paraphrasias are present with dominant lesions. Pure agraphia can be present if the infarct is confined to the posterior part of the left middle gyrus.

Central

Contralateral weakness of the face and arm along with sensory impairment is the commonest manifestation of this infarction. This can be very similar to the sensori-motor strokes seen in lacunar infarctions. A monoparesis of the arm can also occur and is specific to this territory. Mild non-fluent dysphasia (and dysarthria and dysprosody) is seen in dominant lesions while non-dominant lesions can result in a mild dysarthria.

Anterior parietal

Sensory abnormalities are the commonest feature with the arm being particularly affected. Incoordination of the hand, usually associated with a dense sensory loss, can result: the so called 'parietal hand' (Appenzeller and Hanson, 1966). Dominant lesions result in conduction aphasia with fluent speech, normal comprehension but paraphrasias and impaired repetition ability. Non-dominant lesions result in visuo-spatial impairment.

Posterior parietal

Sensory abnormalities are generally limited to 'cortical' sensations such as stereognosis and graphasthaesia (Bassetti et al. 1993). Visual field defects such as homonymous hemianopia and inferior quadrantanopia may occur. Dominant lesions can result in anomic aphasia and alexia and sometimes elements of the Gerstmann syndrome (Waddington and Ring, 1968). Non-dominant lesions produce visuospatial abnormalities.

Angular

Optikokinetic responses can be affected with angular branch infarctions. Dominant lesions can produce the Gerstmann syndrome, alexia with agraphia, anomic aphasia and constructional abnormalities. Non-dominant lesions can lead to visuospatial disturbances, neglect and asomatognosia.

Temporo-occipital/posterior temporal

Infarction of these branches are difficult to separate clinically. They cause hemianopia, fluent aphasia (dominant) and hemispatial neglect with sensory predominance (non-dominant).

Middle temporal/anterior temporal/temporopolar

Visual field defects include homonymous superior quadrantanopia. Dominant lesions result in anomic aphasia while non-dominant lesions result in mild hemi-spatial neglect.

PACS

34% of the patients in the OCSP had a PACS and 94% were due to infarction (Bamford et al. 1991). Only 3 patients out of 103 had an infarction in an 'inappropriate' territory; the rest of the patients all had lesions in the MCA or ACA territory or had a normal CT scan. In the SEPIVAC study (Ricci et al. 1991), 93% of patients had infarcts in the predicted regions. 'Inappropriate' infarcts have reported in watershed areas, the PCA territory and in territories supplied by the deep perforating arteries (Wardlaw et al. 1996). Angiographic findings in patients with a PACS range from normal to occlusion of the ICA and MCA (Olsen et al. 1985). Occlusion of the main divisions of the MCA or its smaller branches will also cause a PACS. The reason that ICA occlusion does not always result in a TACS is probably

that the symptomatic hemisphere is being supplied by the contralateral ICA via the anterior communicating artery. Similarly, in proximal occlusion of the MCA, the brain parenchyma may be perfused via leptomeningeal collaterals.

6.1.5 Lacunar Syndromes

There has been much debate over the years regarding the classification and nomenclature of lacunar strokes. It is now generally accepted that certain stroke syndromes result from the occlusion of a small deep perforating vessel. With the improvement in cross sectional imaging, many of these strokes can be correlated to a small deep infarct (often referred to as a 'lacune') in certain anatomical sites. In a report on lacunar stroke the following definition was proposed: 'a clinical situation where the mechanism of infarction involves transient or permanent occlusion of a single penetrating artery with a high degree of probability' (Donnan et al. 1993a). The classic lacunar syndromes are: pure motor stroke (PMS) (Fisher and Curry, 1965), pure sensory stroke (PSS) (Fisher, 1965), sensorimotor stroke and ataxic hemiparesis (Fisher and Cole, 1965; Fisher, 1967). The underlying vascular mechanisms involved in lacunar strokes is still not fully understood. This may reflect the paucity of good pathological data. However, cardiac sources of embolism and significant carotid stenosis are much less frequent in lacunar strokes than in TACS and PACS (Boiten and Lodder, 1995) making an embolic mechanism is unlikely. Microatheroma has been postulated as the cause of occlusive disease in lacunar strokes (Fisher, 1979).

Pure motor stroke

PMS is characterised by weakness of the face, upper and lower limb *without* the presence of sensory signs, visual field defect, dysphasia or any other disturbance of higher mental function. In order to cause a PMS, the infarct must only affect motor fibres. Anatomically, there are few places in which even a small infarct could cause just motor symptoms without disrupting other modalities. Thus, most cases of PMS are caused by small infarcts in either the internal capsule or in the pons. Other sites

such as the cerebral peduncle and medullary pyramid have been reported but are rarer (Bamford and Warlow, 1988). Although the majority of PMS result from ischaemic stroke, it can also arise from haemorrhage (Bamford et al. 1987).

Pure sensory stroke

PMS is the sensory equivalent of PMS. It is much less common than PMS and accounted for only 6% of all lacunar stroke in the Oxfordshire Community Stroke Project (Bamford et al. 1987). The lesion is invariably situated in the thalamus although it has been reported as being in the anterior limb of the internal capsule. Infarcts that give rise to PSS tend to be smaller than those producing PMS.

Ataxic hemiparesis

Ataxic hemiparesis (AH) encompasses two similar clinical syndromes both described by Fisher: homolateral ataxia and crural paresis (HACP) (Fisher and Cole, 1965) and the dysarthria-clumsy hand syndrome (DCHS) (Fisher, 1967). HACP consists of weakness of the lower limb, especially the foot and toes, with marked ipsilateral ataxia of the upper and lower limb.

DCHS was originally described as a syndrome with dysarthria and clumsiness of one hand although 2 out of the 3 patients reported also had ipsilateral pyramidal dysfunction and an ataxic gait. The lesion giving rise to AH is most often situated in the pons but there have been CT reports of lesions in the corona radiata (Bamford, 1995) and some authors have argued that AH can be caused by a partial infarct of the anterior cerebral artery (Bogousslavsky et al. 1992).

Sensorimotor stroke

SMS consists of both sensory loss and weakness in the face, upper and lower limb. The lesion causing this syndrome is thought by some authors to be in the internal capsule (posterior limb): the sensory signs arising from interruption of the thalamocortical pathways (Tuszynski et al. 1989). Other reported sites for the lesion included the corona radiata, the anterior and genu of the internal capsule and the thalamus. Infarcts causing SMS are thought to be larger than those causing PMS but are still regarded as being the result of occlusion of a deep perforating vessel. The

clinical findings of a SMS can also be caused by infarcts in other areas not due to occlusion of a perforating artery. Large subcortical striatocapsular infarcts and cortical infarcts in the rolandic fissure can cause both motor and sensory signs without any field defects or disturbance of higher function (Blecic et al. 1993).

6.1.6 TRANSCRANIAL ULTRASOUND STUDIES

There has been one reported TCD study (Naylor et al. 1993) and one TCCS study (Martin et al. 1993) investigating the vascular pathology in various stroke subtypes. In the TCD study, 26 patients were studied (TACI: 12, PACI: 11, LACI: 3). The interval from symptoms to TCD ranged from 14-34 hours, with a median time for the TACI group of 26 hours and for the PACI group of 20 hours (LACI group not specified). In the TACI group patients had either ICA or MCA occlusion or both or reduced MCA velocity and ICA occlusion. In the PACI group, the findings included normal MCA velocity, reduced velocity, increased velocity and MCA occlusion, while 2 of the 3 LACI patients had normal velocities. The authors concluded that, although the numbers in the study were small, the TCD findings were consistent with the predicted vascular pathology.

The TCCS study was also small, cranial ultrasound being possible in only 36 patients. The findings were similar to the TCD study in patients with TACI tended to have occlusive disease of either the ICA or MCA, patients with PACI formed a diverse group with MCA and ICA occlusion, low and normal MCA velocities. Only 3 patients with a lacunar syndrome were studied and all had normal MCA velocities.

6.2 AIMS OF THE STUDY

This study set about to evaluate the use of TCCS in determining the underlying vascular pathology in patients with acute cerebral infarction. The studies mentioned above had used small numbers of patients, especially in the LACS group (six in total). This study aimed to recruit a larger number of patients and to study them within 24 hours of stroke onset.

6.3 SUBJECTS AND METHODS

Patient selection was the same as described in chapter 2.

All patients were classified according to the OCSP. This was done at the same time as TCCS in order to minimise any changes either in clinical condition or in the cerebral vessels.

All patients underwent neuroimaging (either CT or MRI) in order to diagnose the underlying pathology of the stroke.

TCCS and carotid ultrasound were performed in the manner described before. The mean MCA velocity was recorded and the asymmetry index calculated.

6.4 RESULTS

119 patients were entered in the study. 30 patients were excluded for the following reasons: lack of acoustic window (21), consent not given (3), deterioration in clinical condition precluding TCCS (4) and cerebral tumour (2).
75 patients had a cerebral infarction and 14 patients had intracerebral haemorrhages. 45 patients were male and 44 were female. Age ranged from 48 to 88 years (mean: 75 years). The mean time interval from stroke onset to TCCS was 13.4 hours (range: 4-24 hours).

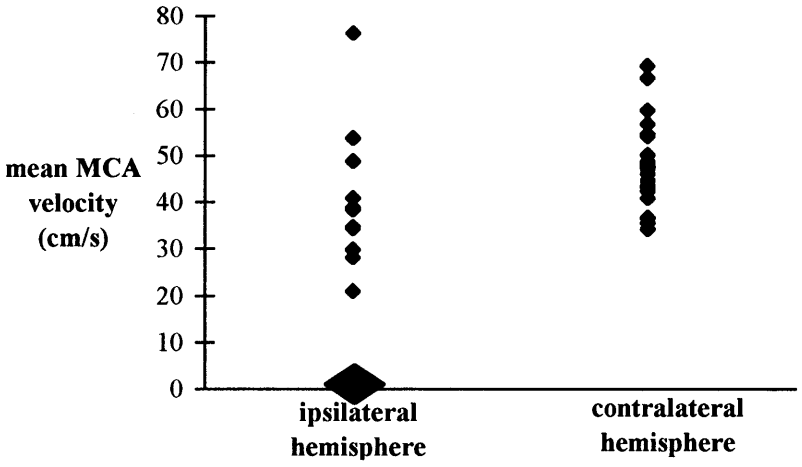
Of the 79 patients with a cerebral infarction, 29 patients had a TACS, 23 patients had a PACS and 23 patients had a LACS. In the haemorrhage group, 10 patients had a TACS, 2 had a PACS and 2 patients had a LACS. No patients in either group had a POCS.

6.4.1 TOTAL ANTERIOR CIRCULATION SYNDROME

Cerebral Infarction

4 patients had occlusion of both the ipsilateral ICA and MCA (tandem occlusion). 14 patients had occlusion of the MCA and this was accompanied by either mild ICA stenosis (11) or moderate ICA stenosis (3). Average mean MCA velocity (95% confidence intervals) was 15.6 cm/s (7.4-23.8 cm/s) and 47.0 cm/s (43.9-50.1 cm/s) for ipsilateral and contralateral hemisphere respectively ($p<0.0001$, Student's t-test) (Figure 1).

Figure 1. Mean MCA velocity in the ipsilateral and contralateral hemispheres in patients with Total Anterior Circulation Infarction (TACI). 15 patients with MCA occlusion are represented by the data point on the x-axis.



Cerebral Haemorrhage

All 10 patients had a patent MCA 2 patients had mild ICA disease and 1 patient had moderate ICA disease. Average mean MCA velocity (95% confidence intervals) was 53.6 cm/s (49.4-57.8 cm/s) and 52.8 cm/s (48.3-57.3 cm/s) for ipsilateral and contralateral hemisphere respectively (p=0.85, Student's t-test) (Figures 2 and 3).

Figure 2. Mean MCA velocity in the ipsilateral and contralateral hemispheres in patients with Total Anterior Circulation Syndrome due to cerebral haemorrhage.

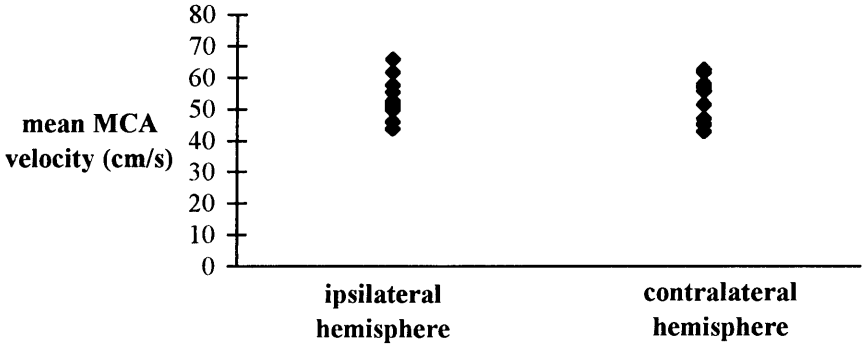
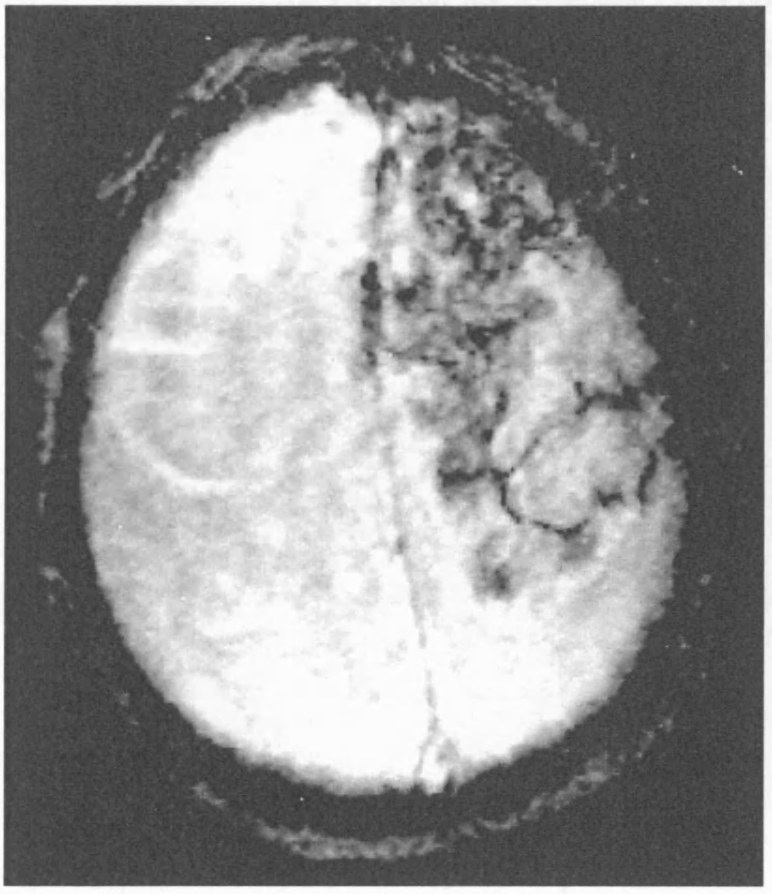


Figure 3 **T2 weighted magnetic resonance image of a patient with a large intracerebral haemorrhage. This patient presented with a total anterior circulation syndrome (right sided hemiparesis, dysphasia, and a right sided homonymous hemianopia).**

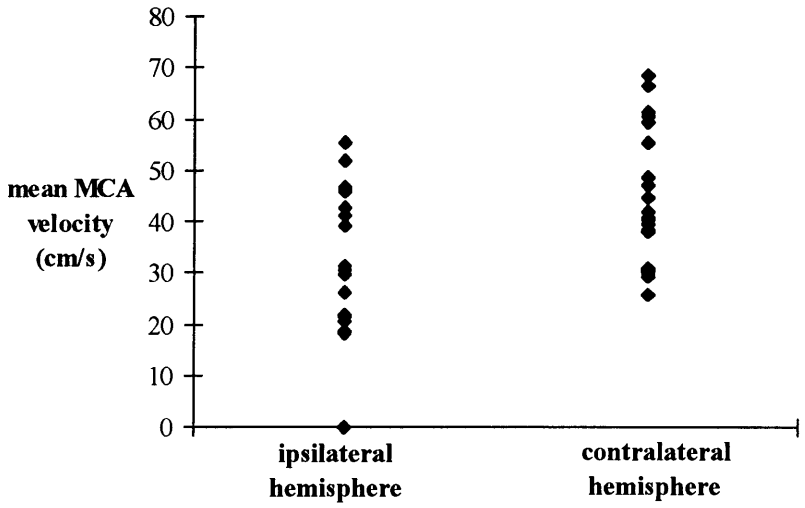


6.4.2 PARTIAL ANTERIOR CIRCULATION SYNDROME

Cerebral infarction

5 patients presented with MCA occlusion, 9 patients had mild ICA disease and 1 patient had moderate ICA disease. Average mean MCA velocity (95% confidence intervals) was 26.5 cm/s (19.2-33.8 cm/s) and 45.0 cm/s (40.0-50.0 cm/s) for ipsilateral and contralateral hemisphere respectively ($p<0.0001$, Student's t-test) (Figures 4 and 5).

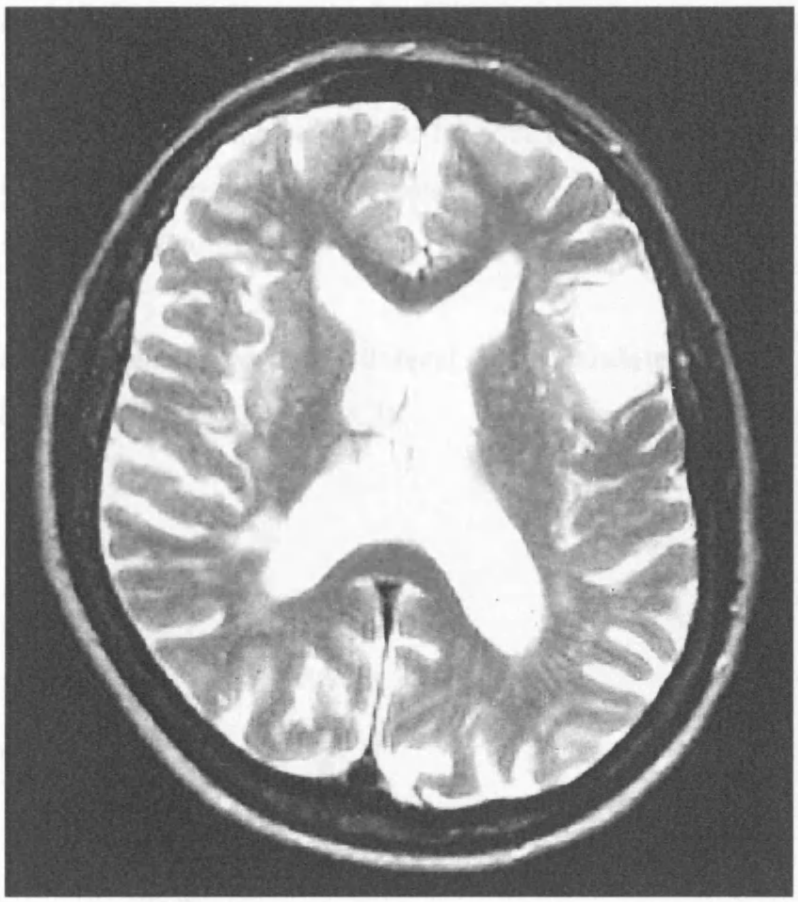
Figure 4. Mean MCA velocity in the ipsilateral and contralateral hemispheres in patients with Partial Anterior Circulation Infarction (PACI).



Cerebral haemorrhage

Mean MCA velocity was 50.4 and 58.3 cm/s (ipsilateral hemisphere) and 57.2 and 51.0 cm/s (contralateral hemisphere). 1 patient had mild ICA disease.

Figure 5. **T2 weighted magnetic resonance image of a patient with a partial anterior circulation infarct. The area of infarction is seen as the high signal in the left hemisphere.**

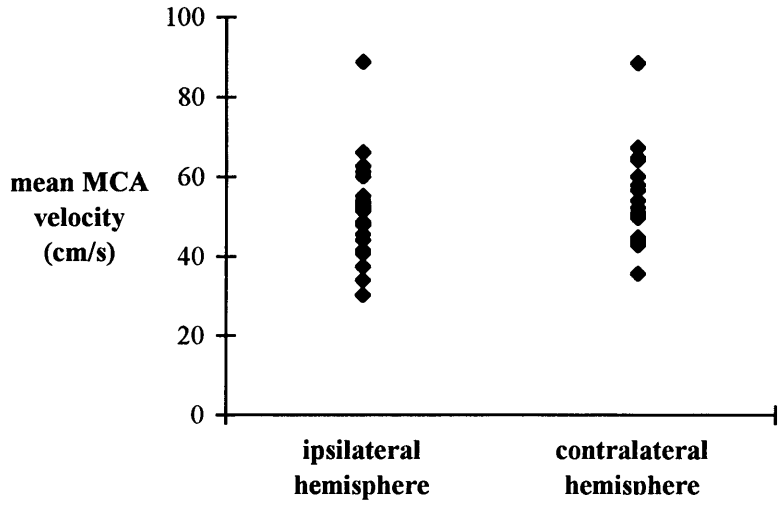


6.4.3 LACUNAR SYNDROME

Cerebral infarction

All patients with a clinical lacunar infarction had a patent MCA. 1 patient had occlusion of the ipsilateral ICA, and 6 patients had mild ICA disease. Average mean MCA velocity (95% confidence intervals) was 51.8 cm/s (46.8-56.8 cm/s) and 54.2 cm/s (49.6-58.8 cm/s) for ipsilateral and contralateral hemisphere respectively (p=0.48, Student's t-test) (Figures 6 and 7).

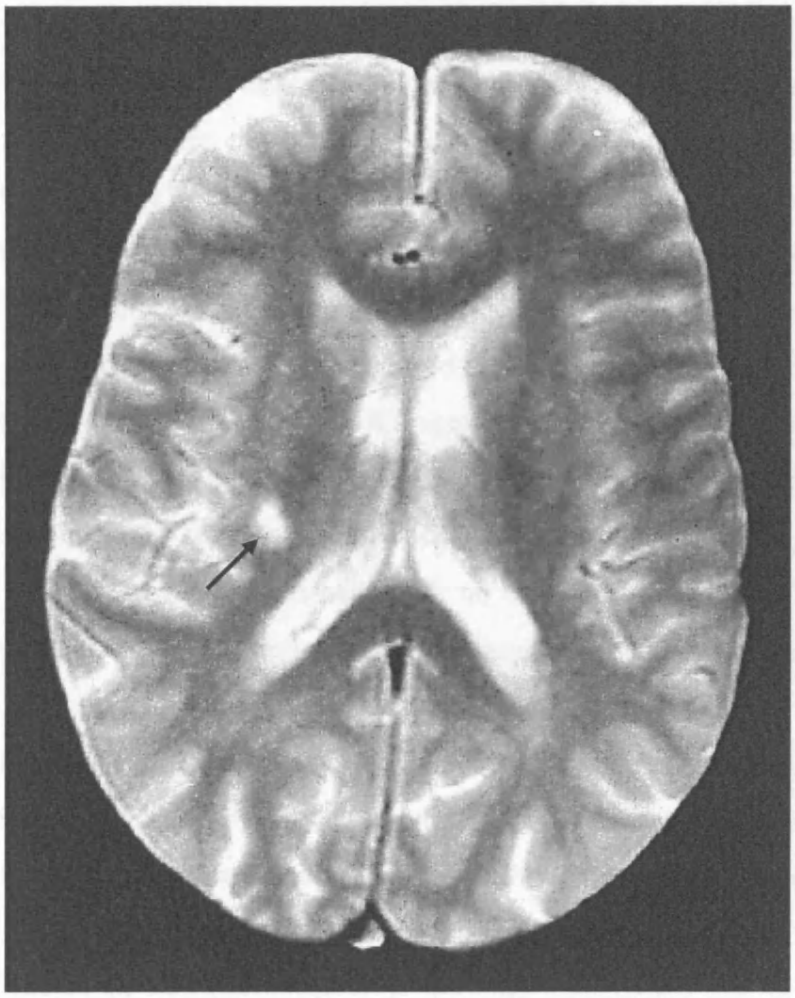
Figure 6. Mean MCA velocity in the ipsilateral and contralateral hemispheres in patients with lacunar infarctions (LACI).



Cerebral haemorrhage

Mean MCA velocity was 62.1 and 62.1 cm/s (ipsilateral hemisphere) and 60.7 and 64.9 cm/s (contralateral hemisphere). 1 patient had mild ICA disease.

Figure 7. **T2 weighted magnetic resonance image of a patient who presented with a pure motor stroke. A small deep infarct is seen in the right internal capsule (arrow).**



6.5 DISCUSSION

The classification of stroke into sub-types is an important part of the management of the stroke patient. It allows the physician to group patients together who may have similar underlying pathologies, prognoses and management requirements. For example, a TACI is generally caused by large vessel disease and so an attempt to find an embolic source would be more appropriate than in a patient with a lacunar infarct of presumed small vessel disease.

The findings in this study agree with the proposed underlying vascular pathology in the various stroke syndromes. There was no significant difference in mean MCA velocity between the ipsilateral and contralateral hemispheres in lacunar infarctions. TCCS is unable to image the smaller deep perforating vessels because of the lack of resolution. The majority of the patients had either no or mild disease of the ICA in keeping with the small vessel disease hypothesis of lacunar stroke. One patient did, however, have occlusion of the ICA. This patient presented with a sensorimotor stroke but over the next 24-48 hours developed a homonymous hemianopia, hemisensory neglect and a worsening of the hemiparesis. The patient was first assessed 18 hours after the symptoms started. Thus, although the initial presentation was that of a lacunar stroke, the final clinical syndrome was that of a TACI. The underlying mechanism of this phenomenon is not fully understood but probably reflects perfusion of the hemisphere by collateral vessels. These vessels are thought to be insufficient to maintain adequate perfusion and so larger areas of brain parenchyma become ischaemic and, in turn, necrotic. This patient had collateral flow from the contralateral ICA via the anterior communicating artery (ACoA). This can be diagnosed on TCCS by the findings of increased flow in the ACoA and reversal of flow in the ipsilateral ACA. Two out of 25 patients with lacunar syndromes had a cerebral haemorrhage. This is close to the 5% figure that was found in the OCSP (Bamford and Warlow, 1988). One reason why there were less patients in the OCSP may be that it was a community based study and so would have identified all patients with a lacunar syndrome. Hospital based studies tend to identify patients with more severe strokes that cannot be managed at home.

Five patients with a PACI had mainstem MCA occlusion. They presumably had limited areas of infarction so preventing the clinical signs of a TACI. This can occur as a result of collateral flow from leptomeningeal vessels if they arise from the proximal part of the MCA. No patients with PACI had an occlusion of the ICA which is one of the known underlying mechanisms. The mean MCA velocity on the symptomatic side was lower than the asymptomatic side and 15 patients had an asymmetry index less than -20%. A low AI has been shown to reflect occlusion of more than 3 MCA branch vessels (Zanette et al. 1989). This would be consistent with the hypothesis that PACI can be caused by MCA branch vessel occlusion. One patient had high flow velocity (hyperaemic flow) in the MCA mainstem. This may have been secondary to recanalisation of a previously occluded MCA. The 2 patients with cerebral haemorrhage did not show any MCA velocity asymmetry. This finding is not unexpected as the underlying pathology is usually rupture of small aneurysms. However, the numbers are too small to draw any firm conclusions.

Patients with a TACI showed the greatest amount of MCA flow abnormalities: MCA occlusion (14), MCA and ICA occlusion (4) and low ipsilateral MCA velocity (8). The large numbers of abnormal findings reflect the underlying vascular pathology and the fact that TCCS was performed soon after stroke onset. Two patients had hyperaemic flow in the MCA which probably reflected recanalisation of the MCA. In only one patient was the flow normal. Occlusion of the proximal segment of the MCA leads to infarction of both the superficial and deep territories of the MCA and the clinical syndrome of a TACI. Many patients also have significant ICA stenosis although this was not seen in this study. Tandem occlusion can be caused by extension of thrombus from an occluded ICA up to the origin of the MCA. Patients can have asymptomatic ICA occlusion, if it occurs gradually, as the ipsilateral MCA can be supplied by cross over flow from the contralateral ICA. However, if the thrombus extends to the ipsilateral MCA, the collateral flow will be stopped and the MCA territory will become ischaemic.

10 patients with a TACS had cerebral haemorrhage. In contrast to the patients with infarction, there were no significant MCA flow abnormalities detected in these patients. Again, as with patients with a PACS caused by haemorrhage,this is not an unexpected finding as the cause of the haemorrhage is generally aneurysmal rupture. In none of the patients could the haemorrhage be imaged although there have been

reports that echolucent areas of parenchyma corresponding to the haemorrhage can be imaged with TCCS (Becker et al. 1993). In this study, the cerebral haemorrhage was strongly suspected if the patient had a TACS clinically but had normal MCA velocity. This can be used by the clinician as a guide to the underlying vascular pathology if conventional neuroimaging is not available. This may be important if patients are being considered for treatment, especially thrombolysis. If a patient with a TACS has normal MCA velocities within the first few hours following the stroke then they may be best left untreated as they probably either have a cerebral haemorrhage or have recanalised their vessels already. TCCS may therefore be important in the early stages of stroke in stratifying patients according to their need for further neuroimaging. However, TCCS is unlikely to be of sufficient accuracy to replace CT as this test approaches 100% accuracy.

CHAPTER 7

CONCLUSIONS

7.1 TCD VERSUS TCCS

The role of transcranial ultrasound remains unclear. Conventional TCD has been used in several studies of acute stroke but the role of TCCS has not been assessed adequately. TCD has found applications in certain neurological fields: determining the timing of vasospasm following subarachnoid haemorrhage (Aaslid et al. 1984; Davis et al. 1992), assessing the collateral circulation in cases of internal carotid artery disease (Norris et al. 1990; Grolimund et al. 1987), monitoring patients undergoing carotid endarterectomy (Lindegaard et al. 1985; Halsey et al. 1989), assessing cerebral reactivity and autoregulation (Dahl et al. 1992; Aaslid et al. 1989) and investigating vertibrobasilar ischaemia (Schneider et al. 1991). The use of TCD in the acute stroke setting is less certain and early reviews regarding its role were sometimes negative, '[TCD] has no demonstrable use in managing patients with threatened or completed stroke' (Norris, 1990; Bornstein and Norris, 1994).

This study has employed the newer technique of TCCS to assess the cerebral circulation following acute stroke. The main advantage TCCS has over TCD in this context, is the imaging facility. This allows a more confident diagnosis of vessel occlusion to be made. It also cuts down scanning time as all the basal vessels tend to be imaged simultaneously if the correct imaging plane is used. The shortened examination time may have implications if TCCS is to be used in conjunction with thrombolytic agents.

Although TCCS may be superior to TCD in these respects, it does have some drawbacks. The equipment needed to perform TCCS is more expensive and more cumbersome than that required for TCD. Although the scanner used for TCCS is portable, the machine is large and heavy. The majority of the scans performed for this research took place in the vascular studies unit so that patients had to be transported to the scanning room. Ideally, if TCCS is to become more widely used in stroke, it should be based close to the stroke unit. TCCS also has a higher failure rate than TCD, mainly due to hyperostosis in the elderly preventing adequate ultrasound penetration. The use of contrast agents may improve the success rate (Otis et al. 1995).

7.2 TCCS AND MRA

This study was the first to validate TCCS against an established imaging technique in acute stroke. It is also the only study to perform MRA in stroke patients within a 24 hour time window. MRA is quickly finding many applications in neurology and has become the investigation of choice in several conditions, replacing conventional angiography. The results of this study were encouraging and showed that TCCS can be used to detect major vessel occlusion. TCCS does not have the resolution to detect abnormalities of the finer branches of the MCA but branch vessel occlusion can be inferred if the MCA velocity is significantly reduced compared to the contralateral hemisphere.

The early angiography studies in acute stroke enabled the underlying vascular pathology to be demonstrated and led to the theory that the majority of major vessel occlusions were embolic in nature. However, they did not generally alter patient management. The recent use of thrombolytic agents in stroke has resulted in more imaging procedures to be performed. Some studies have employed angiography to image the cerebral vessels to monitor the effects of thrombolysis. However, angiography carries a significant risk of morbidity and mortality especially in the acute stages of stroke. The non-invasive nature of TCCS may prove invaluable in the assessment of patients prior to thrombolysis and in their subsequent monitoring. Although MRA could provide similar information regarding the patency of the cerebral vessels, TCCS may prove to be the investigation of choice. This is because it may not be feasible to perform repeated MRA due to time availability, restless patients may produce degraded images which cannot be interpreted accurately and MRI scanners are generally available only in large city hospitals.

7.3 PROGNOSIS AND MCA VELOCITY

This study showed that not only can MCA velocity be used as a guide to predict 3 month outcome but that it also adds to the prognostic ability of clinical assessments. A criticism of many investigations that are used to predict prognosis is that they add little to a thorough clinical assessment. This is because investigations are often measuring the same as the clinical examination and it is known that stroke severity at onset is a very good predictor of outcome. Thus, occlusion of the MCA, a poor prognostic sign, is usually associated with a large area of infarction and a clinically severe stroke. Conversely, a normal MCA velocity is usually associated with a small infarction, a mild stroke and a good outcome. However, MCA velocity was still a significant predictor of outcome even after various clinical assessments had been adjusted for. This implies that the velocity measures something in addition to just the clinical state of the patient. It reflects the underlying pathological mechanism of the stroke which may be more important for outcome than the clinical state per se. For example, a patient with occlusion of the MCA may not have a clinically severe stroke at the onset but may go on to develop neurological dysfunction with time. Alternatively, a patient with a lacunar stroke and normal MCA velocity may present with severe weakness and sensory loss in the limb but may make a marked recovery with time.

If TCCS is to become incorporated into the routine clinical setting, it has to provide the clinician with practical information and not just data that is of purely academic interest. MCA velocity can be used as a guide to functional outcome and this important and relevant measure may be used in the everyday assessment of the stroke patient in the future.

7.4 MCA RECANALISATION

Recanalisation of the MCA occurs as a natural process. This study not only demonstrated when recanalisation takes place but also correlated early recanalisation with a good functional outcome. Studies on recanalisation are often difficult to perform because of the large number of stroke patients that need to be assessed in order to provide adequate numbers of patients with an occluded MCA. Early studies using sequential angiography on patients demonstrated the tendency of the MCA to recanalise following clot degradation (Dalal et al. 1965). Repeated angiography is now rarely performed due to the associated risks. TCD has been employed to follow up patients with MCA occlusion and measures of cerebral perfusion, such as SPECT, have also been used. TCCS allows a more accurate diagnosis of MCA occlusion to be made compared with TCD. Both TCD and TCCS allow the patency of the vessel to be assessed, whereas cerebral perfusion studies are only an indirect measure of recanalisation. A recanalised vessel may not always result in reperfusion of the brain parenchyma and conversely, MCA occlusion does not necessarily result in the whole territory being hypoperfused, especially if there are adequate collateral vessels. Thrombolysis is aimed primarily at recanalising vessels with the assumption that this will lead to reperfusion of the ischaemic area. The effectiveness of thrombolysis can be monitored using transcranial ultrasound while any resulting reperfusion has to be measured using SPECT, MRI or PET.

The results from this study indicate that recanalisation of the MCA results in a good outcome if it occurs within 48 hours of stroke onset. This is surprising given the fact that most experimental studies have shown that brain tissue becomes irreversibly damaged well within 48 hours. The results may have been partly due to patient selection (the patients were not consecutive) or due to the small numbers used in the trial. However, it gives support to the theory that there are patients who would benefit from recanalisation several hours after the onset of their stroke. In order to better identify these patients, other imaging studies may have to be performed. These should include measurements of the amount of tissue damage, such as diffusion-weighted imaging, as well as measurements of actual tissue perfusion, such as perfusion MRI or SPECT. These techniques are limited to only a few research

centres and so cannot be used in the routine clinical setting. However, with the increased number of stroke patients being treated with thrombolytics, there may be more opportunity to study the underlying pathophysiological changes in more detail.

7.5 VASCULAR PATHOLOGY

The underlying vascular pathology can be readily demonstrated with TCCS. It is consistent with the generally agreed hypotheses regarding the underlying vascular pathologies in various stroke types. This may be important clinically when deciding on patient management: evidence of major vessel occlusion may prompt the clinician to investigate the patient for an embolic source. TCCS may also be able to aid the clinician with patients who are difficult to examine. For example, the assessment of visual fields and some aspects of higher mental function can be difficult, especially if the patient is uncooperative, drowsy, hearing impaired or has poor visual acuity. TCCS can provide information regarding the underlying vascular pathology and so complement the clinical findings. The differentiation of infarction from haemorrhage can also be attempted using TCCS. If a definite diagnosis of MCA occlusion is made, then the underlying pathology is very unlikely to be haemorrhage. A patent MCA in combination with a large neurological deficit is more likely to be due to haemorrhage than infarction. However, caution has to be used in the latter case, as infarction due to a occluded artery which has subsequently recanalised could mimic this finding. Thus, TCCS can only be used as a guide before definitive investigations such as CT or MRI.

7.6 FUTURE ROLE OF TCCS

The work outlined in this thesis suggests that TCCS has a definite role to play in the clinical assessment of patients with acute cerebral infarction. It may be used as one of the first investigations when a patient is admitted to hospital in order to demonstrate the underlying vascular pathology. This is of importance, if thrombolysis is to be used routinely, as it may enable patients who have the most to gain from treatment to be selected. An initial guide to the overall prognosis can also be gained by measuring the MCA velocity. This will help with planning resources and future care. The cerebral circulation can be monitored in a non-invasive way which can provide important information regarding the natural history of the underlying pathology.

APPENDIX

Appendix

PATIENT INFORMATION AND CONSENT FORM

Dear Sir/Madam

Your doctors are treating you for a recent stroke. Their clinical examination and the tests you have already undergone have confirmed the diagnosis and enabled them to plan your treatment.

The Leicester Royal Infirmary has recently acquired a magnetic resonance imager (MRI). This is a very sophisticated device that allows us to obtain very detailed pictures of the brain. The magnetic resonance technique is completely safe and only requires the patient to lie still on a couch for about 30 minutes within the bore of a very large magnet. Many thousands of people have undergone this test world-wide without any harm.
When combined with an injection of a magnetic contrast medium, pictures can be obtained that show the blood supply to the brain. It may be able to show the defect arising from the recent stroke.

The Leicester Royal Infirmary has also recently acquired a special ultrasound scanner called a transcranial ultrasound. This machine allows us to image the blood supply to the brain by placing a small camera on the side of the head. The machine works on a similar principle to that used in scanning pregnant women. It is totally non-invasive and is safe. The scan takes approximately 20 minutes and is performed while you are lying on a trolley.

This hospital is one of the few centres in the world that is equipped and motivated to study the value of transcranial ultrasound and MRI. We would like to invite you to participate in this study of these techniques in order that we may better understand the effect stroke has on the brain and its blood supply. It would involve you having these two tests performed today, tomorrow and in one weeks time. We would also ask you to return to have the tests performed in three months time. This will also

allow us to examine you and to assess how much you have recovered from the stroke.

These tests may not alter the management of your condition directly and your overall care will still be under the consultant physician that you are presently attached to.

If you agree to participate in this study, please indicate your consent by signing below. Confidentiality will be respected at all times.

PLEASE DO NOT SIGN THE CONSENT FORM IF YOU FEEL THAT YOU DO NOT FULLY UNDERSTAND THE PROCEDURES INVOLVED OR THAT YOU WOULD LIKE FURTHER INFORMATION.

EVEN IF YOU DO DECIDE TO PARTICIPATE IN THIS STUDY, YOU ARE AT LIBERTY TO WITHDRAW AT ANY TIME. YOU DO NOT NEED TO GIVE AN EXPLANATION FOR YOUR WITHDRAWL AND IT WILL NOT INTERFERE WITH YOUR OVERALL CARE IN ANY WAY.

If you have any further questions about the study, please feel free to speak to myself at any time.

Thank you for discussing this research study with me. If you have agreed to participate in the study, we are very grateful.

Dr Anthony Kenton
Clinical Research Fellow
Department of Neurology
Bleep 4178

I have read and understand the nature of the study described above. I have discussed the trial with a member of the research team and consent to participate.

I have the right to withdraw from the study at any time without explanation. I understand that this will not affect my future care and treatment or my relationship with my doctors.

NAME.....

ADDRESS.....

SIGNED.....

WITNESSED.....

DATE.....

BIBLIOGRAPHY

Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg* 1982;57:769-774

Aaslid R, Huber P, Nornes H. Evaluation of cerebrovascular spasm with transcranial Doppler ultrasound. *J Neurosurg* 1984;60:37-41

Aaslid R. Visually evoked dynamic blood flow response of the human cerebral circulation. *Stroke* 1987;18:771-775

Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke* 1989;20:45-52

Aberg H. Atrial fibrillation: A study of atrial thrombosis and systemic embolism in a necroscopy material. *Acta Med Scand* 1969;185:373-379

Ackerstaff RG, Keunen RW, van Pelt W, Montauban van Swijndregt AD, Stijnen T. Influence of biological factors on changes in mean cerebral blood flow velocity in normal ageing: a transcranial Doppler study. *Neurol Res* 1990;12:187-191

Adams RJ, Meador KJ, Sethi KD, Grotta JC, Thomson DS. Graded neurologic scale for use in acute hemispheric stroke treatment protocols. *Stroke* 1987;18:665-669

Adams RJ, Nichols FT, Thompson W. Neurological assessment in acute stroke: Issues in the use of rating scales. Amery WK, Bousser M, Rose FC (eds) Clinical Trial Methodology in Stroke. Bailliere Tindall, London, 1989;54-63

Adams RJ, Nichols FT, Hess DC. Normal values and physiological variables. Newell DW, Aaslid R (eds) Transcranial Doppler. Raven Press, Ltd. New York, 1992;41-48

Allen CM. Predicting the outcome of acute stroke: a prognostic score. *J Neurol Neurosurg Psychiatry* 1984;47:475-480

American Institute of Ultrasound in Medicine BC. Bioeffects considerations for the safety of diagnostic ultrasound. *J Ultrasound Med Biol* 1988;7(Suppl):S1-S38

Ameriso SF, Paganini-Hill A, Meiselman HJ, Fisher M. Correlates of middle cerebral artery blood velocity in the elderly. *Stroke* 1990;21:1579-1583

Anderson TP, Bourestom N, Greenberg FR, Hildyard VG. Predictive factors in stroke rehabilitation. *Arch Phys Med Rehabil* 1974;55:545-553

Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. *BMJ* 1994a;308:235-246

Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994b;308:81-106

Appenzeller O, Hanson JC. Parietal ataxia. *Arch Neurol* 1966;15:264-269

Asplund K. Clinimetrics in stroke research. *Stroke* 1987;18:528-530

Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischaemia-the ischaemic penumbra. *Stroke* 1981;12:723-725

Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449-1457

Azzimondi G, Bassein L, Nonino F, Fiorani L, Vignatelli L, Re G, D'Alessandro R. Fever in acute stroke worsens prognosis. A prospective study. *Stroke* 1995;26:2040-2043

Back T, Hoehn-Berlage M, Kohno K, Hossmann KA. Diffusion nuclear magnetic resonance imaging in experimental stroke. Correlation with cerebral metabolites. *Stroke* 1994;25:494-500

Baird AE, Donnan GA, Austin MC, Fitt GJ, Davis SM, McKay WJ. Reperfusion after thrombolytic therapy in ischemic stroke measured by single-photon emission computed tomography. *Stroke* 1994;25:79-85

Baird AE, Donnan GA. Prognostic value of reperfusion during first 48 hours of ischaemic stroke. *Lancet* 1993;342:236

Baker LL, Kucharczyk J, Sevick RJ, Mintorovitch J, Moseley ME. Recent advances in MR imaging/spectroscopy of cerebral ischaemia. *Am J Roentgenol* 1991;156:1133-1143

Bamford JM, Sandercock PAG, Jones L, Warlow CP. The natural history of lacunar infarction: the Oxfordshire Community Stroke Project. *Stroke* 1987;18:545-551

Bamford JM, Sandercock PAG, Dennis MS, Warlow CP, Jones L, McPherson K, Vessey M, Fowler G, Molyneux A, Hughes T, et al. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 1. Methodology, demography and incident cases of first-ever stroke. *J Neurol Neurosurg Psychiatry* 1988;51:1373-1380

Bamford JM, Sandercock PAG, Warlow CP, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989;20:828

Bamford JM, Dennis MS, Sandercock PAG, Burn J, Warlow CP. The frequency, causes and timing of death within 30 days of a first stroke: the Oxfordshire Community Stroke Project. *J Neurol Neurosurg Psychiatry* 1990a;53:824-829

Bamford JM, Sandercock PAG, Dennis MS, Burn J, Warlow CP. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 1990b;53:16-22

Bamford JM, Sandercock PAG, Dennis MS, Burn J, Warlow CP. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;337:1521-1526

Bamford JM. Classic lacunar syndromes. Bogousslavsky J, Caplan L (eds) Stroke Syndromes. Cambridge University Press, Cambridge, 1995;366-371

Bamford JM, Warlow CP. Evolution and testing of the lacunar hypothesis. *Stroke* 1988;19:1074-1082

Baron JC, Bousser MG, Rey A, Guillard A, Comar D, Castaigne P. Reversal of focal 'misery-perfusion syndrome' by extra-intracranial arterial bypass in haemodynamic cerebral ischaemia: a case study with ^{15}O positron emission tomography. *Stroke* 1981;26:454-459

Baron JC, von Kummer R, del Zoppo GJ. Treatment of acute ischemic stroke. Challenging the concept of a rigid and universal time window. *Stroke* 1995;26:2219-2221

Bartko D, Danisova J. Pokus o kvantifikaciu stupna neurologickeho deficitu pri loziskovej cerebralnej lezii. *CS Neurol* 1977;40:331-338

Bassetti C, Bogousslavsky J, Regli F. Sensory syndromes in parietal stroke. *Neurology* 1993;43:1942-1949

Baumgartner RW, Mathis J, Sturzenegger M, Mattle HP. A validation study on the intraobserver reproducibility of transcranial color-coded duplex sonography velocity measurements. *Ultrasound Med Biol* 1994;20:233-237

Baumgartner RW, Mattle HP, Aaslid R. Transcranial color-coded duplex sonography, magnetic resonance angiography, and computed tomography angiography: methods, applications, advantages, and limitations. *J Clin Ultrasound* 1995;23:89-111

Becker G, Winkler J, Hofmann E, Bogdahn U. Differentiation between ischemic and hemorrhagic stroke by transcranial color-coded real-time sonography. *J Neuroimaging* 1993;3:41-47

Bladin PF. A radiologic and pathologic study of embolism of the internal carotid-middle cerebral aretry axis. *Radiology* 1964;82:615-624

Blecic SA, Bogousslavsky J, van Melle G, Regli F. Isolated sensorimotor stroke: a reevaluation of clinical, topographic and etiological patterns. *Cerebrovasc Dis* 1993;3:357-363

Bloomfield P, Wheatley DJ, Prescott RJ, Miller HC. Twelve year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. *N Engl J Med* 1991;324:573-579

Bluth EI, Stavros AT, Marich KW. Carotid duplex sonography: a multicenter recommendation for standardized imaging and Doppler criteria. *Radiographics* 1988;8:487-506

Bogdahn U, Becker G, Winkler J, Greiner K, Perez J, Meurers B. Transcranial color-coded real-time sonography in adults. *Stroke* 1990;21:1680-1688

Bogousslavsky J, Martin R, Moulin T. Homolateral ataxia and crural paresis; a syndrome of anterior cerebral artery territory infarction. *J Neurol Neurosurg Psychiatry* 1992;55:1146-1149

Boiten J, Lodder J. Risk factors for lacunar infarction. Donnan GA, Norrving B, Bamford JM, Bogousslavsky J (eds) Lacunar and Other Subcortical Infarctions. Oxford University Press, Oxford, 1995;56-69

Bonafe A, Manelfe B, Scotto B, Pradere MY, Rascol A. Role of computed tomography in vertibrobasilar ischaemia. *Neuroradiology* 1985;27:484-493

Bonita R, Beaglehole R. Increased treatment of hypertension does not explain the decline in stroke mortality in the United States, 1970-1980. *Hypertension* 1989;13:69-73

Bornstein NM, Norris JW. Transcranial Doppler sonography is at present of limited clinical value. *Arch Neurol* 1994;51:1057-1059

Bourestom NC. Predictors of long-term recovery in cerebrovascular disease. *Arch Phys Med Rehabil* 1967;48:415-419

Bourestom NC, Howard MT. Behavioral correlates of recovery of self-care in hemiplegic patients. *Arch Phys Med Rehabil* 1968;49:449-454

Bozzao L, Bastianello S, Fantozzi LM, Angeloni U, Argentino C, Fieschi C. Correlation of angiographic and sequential CT findings in patients with evolving cerebral infarction. *AJNR Am J Neuroradiol* 1989a;10:1215-1222

Bozzao L, Fantozzi LM, Bastianello S, Bozzao A, Argentino C, Lenzi GL, Fieschi C. Ischaemic supratentorial stroke: angiographic findings in patients examined in the very early phase. *J Neurol* 1989b;236:340-342

Bozzao L, Fantozzi LM, Bastianello S, Bozzao A, Fieschi C. Early collateral blood supply and late parenchymal brain damage in patients with middle cerebral artery occlusion. *Stroke* 1989c;20:735-740

Brass LM, Pavlakis SG, DeVivo D, Piomelli S, Mohr JP. Transcranial Doppler measurements of the middle cerebral artery. Effect of hematocrit. *Stroke* 1988;19:1466-1469

Brass LM, Duterte DL, Mohr JP. Anterior cerebral artery velocity changes in disease of the middle cerebral artery stem. *Stroke* 1989;20:1737-1740

Brass LM, Prohovmik I, Panlakis SG. Middle cerebral artery blood velocity and cerebral blood flow in sickle cell disease. *Stroke* 1991;22:27-30

Broderick JP, Phillips SJ, Whisnant JP, O'Fallon WM, Bergstralh EJ. Incidence rates of stroke in the eighties: the end of the decline in stroke? *Stroke* 1989;20:577-582

Broderick JP, Phillips SJ, O'Fallon WM, Frye RL, Whisnant JP. Relationship of cardiac disease to stroke occurrence, recurrence, and mortality. *Stroke* 1992;23:1250-1256

Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V, Rorick M, Moomaw C, Walker M. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989a;20:864-870

Brott T, Marler JR, Olinger CP, Adams HP, Jr., Tomsick T, Barsan WG, Biller J, Eberle R, Hertzberg V, Walker M. Measurements of acute cerebral infarction: Lesion size by computed tomography. *Stroke* 1989b;20:871-875

Brott TG, Haley EC, Jr., Levy DE, Barsan W, Broderick J, Sheppard GL, Spilker J, Kongable GL, Massey S, Reed R, Marler JR. Urgent therapy for stroke. Part I. Pilot study of tissue plasminogen activator administered within 90 minutes. *Stroke* 1992;23:632-640

Brown MM, Butler P, Gibbs J, Swash M, Waterson J. Feasibility or percutaneous transluminal angioplasty for carotid artery stenosis. *J Neurol Neurosurg Psychiatry* 1990;53:238-243

Burchfiel CM, Curb JD, Rodriguez BL, Abbott RD, Chiu D, Yano K. Glucose intolerance and 22-year stroke incidence. The Honolulu Heart Program. *Stroke* 1994;25:951-957

Burn J, Dennis MS, Bamford JM, Sandercock PAG, Wade D, Warlow CP. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. *Stroke* 1994;25:333-337

Busza AL, Allen KL, King MD, van Bruggen N, Williams SR, Gadian DG. Diffusion-weighted imaging studies of cerebral ischemia in gerbils. Potential relevance to energy failure. *Stroke* 1992;23:1602-1612

Camerlingo M, Casto L, Censori B, Ferraro B, Gazzaniga GC, Mamoli A. Transcranial Doppler in acute ischemic stroke of the middle cerebral artery territories. *Acta Neurol Scand* 1993;88:108-111

Caplan LR, Kelley M, Kase CS, Hier DB, White JL, Tatemichi T, Mohr JP, Price T, Wolf PA. Infarcts of the inferior division of the middle cerebral artery. *Neurology* 1986;36:1015-1020

Caplan LR. Brain embolism, revisited. *Neurology* 1993;43:1281-1287

Carriero A, Ucchino S, Magarelli N, Legnini M, Macri MA, Napolitano AM, Bonomo L. Carotid bifurcation stenosis: a comparative study between MR angiography and duplex scanning with respect to digital subtraction angiography. *J Neuroradiol* 1995;22:103-111

Censori B, Camerlingo M, Casto L, Ferraro B, Gazzaniga GC, Cesana B, Mamoli A. Prognostic factors in first-ever stroke in the carotid artery territory seen within 6 hours after onset. *Stroke* 1993;24:532-535

Cerebral Embolism Task Force. Cardiogenic brain embolism: the second report of the Cerebral Embolism Task Force. *Arch Neurol* 1989;46:727-743

Chambers BR, Norris JW, Shurvell BL, Hachinski VC. Prognosis of acute stroke. *Neurology* 1987;37:221-225

Chamorro A, Vila N, Ascaso C, Saiz A, Montalvo J, Alonso P, Tolosa E. Early prediction of stroke severity. Role of the erythrocyte sedimentation rate. *Stroke* 1995;26:573-576

Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *International Disability Studies* 1988;10:61-63

Collins R, MacMahon S. Blood pressure, antihyprtensive drug treatment and the risks of stroke and of coronary heart disease. *British Medical Bulletin* 1994;50:272-298

Cote R, Hachinski VC, Shurvell BL, Norris JW, Wolfson C. The Canadian Neurological Scale: a preliminary study in acute stroke. *Stroke* 1986;17:731-737

Cote R, Battista RN, Wolfson CM, Hachinski V. Stroke assessment scales: guidelines for development, validation, and reliability assessment. *Canadian Journal of Neurological Sciences* 1988;15:261-265

Cote R, Battista RN, Wolfson C, Boucher J, Adam J, Hachinski V. The Canadian Neurological Scale: validation and reliability assessment. *Neurology* 1989;39:638-643

Dahl A, Lindegaard KF, Russell D, Nyberg-Hansen R, Rootwelt K, Sorteberg W, Nornes H. A comparison of transcranial Doppler and cerebral blood flow studies to assess cerebral vasoreactivity. *Stroke* 1992;23:15-19

Dalal PM, Shah PM, Sheth SC, Deshpande CK. Cerebral embolism: angiographic observation on spontaneous clot lysis. *Lancet* 1965;9:61-64

Daniel WG. Should transesophageal echocardiography be used to guide cardioversion? *N Engl J Med* 1993;328:803-804

Davis SM, Andrews JT, Lichtenstein M, Rossiter SC, Kaye AH, Hopper J. Correlations between cerebral arterial velocities, blood flow, and delayed ischemia after subarachnoid hemorrhage. *Stroke* 1992;23:492-497

De Bono DP. Cardiac causes of transient neurological disturbances. Warlow CP, Morris PS (eds) Transient Ischaemic Attacks. Dekker, New York, 1982;99-124

De Witt L, Rosengart A, Teal PA. Transcranial Doppler ultrasonography: normal values. Babikian VL, Wechsler LR (eds) Transcranial Doppler Ultrasonography. Mosby Year Book, St Louis, 1993;29-38

Denes G, Semenza C, Stoppa E, Lis A. Unilateral spatial neglect and recovery from hemiplegia: a follow-up study. *Brain* 1982;105:543-552

Dennis MS, Burn JP, Sandercock PAG, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke* 1993;24:796-800

Diener HC, Hacke W, Hennerici M, Radberg J, Hantson L, De Keyser J. Lubeluzole in acute ischemic stroke. A double-blind, placebo-controlled phase II trial. Lubeluzole International Study Group. *Stroke* 1996;27:76-81

Donnan GA, Norving B, Bamford JM, Bogousslavsky J. Subcortical infarction: classification and terminology. *Cerebrovasc Dis* 1993a;3:248-251

Donnan GA, You R, Thrift A, McNeil JJ. Smoking as a risk factor for stroke. *Cerebrovasc Dis* 1993b;3:129-138

Donnan GA, Davis SM, Chambers BR, Gates PC, Hankey GJ, McNeil JJ, Rosen D, Stewart-Wynne EG, Tuck RR. Trials of streptokinase in severe acute ischaemic stroke. *Lancet* 1995;3445:578-579

Donnan GA, Davis SM, Chambers BR, Gates PC, Hankey GJ, McNeil JJ, Rosen D, Stewart-Wynne EG, Tuck RR. Streptokinase for acute ischemic stroke with relationship to time of administration Australian Streptokinase (ASK) Trial Study Group. *JAMA* 1996;276:961-966

Drake WE, Jr., Hamilton MJ, Carlsson M, Blumenkrantz J. Acute stroke management and patient outcome: the value of Neurovascular Care Units (NCU). *Stroke* 1973;4:933-945

Dumoulin C, Souza S, Walker M, Wagle W. Three-dimensional phase contrast angiography. *Magn Reson Med* 1989;9:139-149

Ebrahim S. 1990; Clinical Epidemiology of Stroke. Oxford University Press, Oxford

Edelman RR. MR angiography: present and future. *Am J Roentgenol* 1993;161:1-11

Edelman RR, Siewert B, Darby DG, Thangaraj V, Nobre AC, Mesulam MM, Warach S. Qualitative mapping of cerebral blood flow and functional localisation with echo-planar MR imaging and signal targeting with alternating radio frequency. *Radiology* 1994;192:513-520

Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. *Ann Intern Med* 1993;118:956-963

European Atrial Fibrillation Trial Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993;342:1255-1262

European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med* 1995;333:5-10

European Carotid Surgery Trialist's Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. *Lancet* 1991;337:1235-1243

European Federation of Societies for Ultrasound in Medicine and Biology. Safety considerations. *Newsletter* 1990;4:9-10

Feigenson JS, McDowell FH, Meese P, McCarthy ML, Greenberg SD. Factors influencing outcome and length of stay in a stroke rehabilitation unit. Part 1. Analysis of 248 unscreened patients--medical and functional prognostic indicators. *Stroke* 1977;8:651-656

Feinstein AR, Josephy BR, Wells CK. Scientific and clinical problems in indexes of functional disability. *Ann Intern Med* 1986;105:413-420

Fieschi C, Argentino C, Lenzi GL, Sacchetti ML, Toni D, Bozzao L. Clinical and instrumental evaluation of patients with ischemic stroke within the first six hours. *J Neurol Sci* 1989;91:311-321

Fisher CM. Occlusion of the internal carotid artery. *Arch Neurol Psychiat* 1951;65:346

Fisher CM. Occlusion of the carotid arteries. *Acta Neuropathol* 1954;12:1-15

Fisher CM. Pure sensory stroke involving face, arm and leg. *Neurology* 1965;15:49-56

Fisher CM. A lacunar stroke: the dysarthria-clumsy hand syndrome. *Neurology* 1967;17:614-617

Fisher CM. Capsular infarcts: the underlying vascular lesions. *Arch Neurol* 1979;36:65-73

Fisher CM. Lacunar infarcts-a review. *Cerebrovasc Dis* 1991;1:311-320

Fisher CM, Cole M. Homolateral ataxia and crural paralysis: a vascular syndrome. *J Neurol Neurosurg Psychiatry* 1965;28:48-55

Fisher CM, Curry HB. Pure motor hemiplegia from vascular origin. *Arch Neurol* 1965;13:30-44

Folsom AR, Eckfeldt JH, Weitzman S, Ma J, Chambless LE, Barnes RW, Cram KB, Hutchinson RG. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Stroke* 1994;25:66-73

Friedman GD, Loveland DB, Ehrlich SP. Relationship of stroke to other cardiovascular disease. *Circulation* 1968;38:533-541

Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *American Journal of Cardiology* 1981;47:525-531

Gegick CG, Danowski TS, Khurana RC. Hyperostosis frontalis interna and hyperphosphatasaemia. *Ann Intern Med* 1973;79:71-75

Gibo H, Carver C, Rhoton AL, Lenkey C, Mitchell RJ. Microsurgical anatomy of the middle cerebral artery. *J Neurosurg* 1981;54:151-169

Gillard JH, Barker PB, van Zijl PC, Bryan RN, Oppenheimer SM. Proton MR spectroscopy in acute middle cerebral artery stroke. *AJNR Am J Neuroradiol* 1996;17:873-886

Gladman JR, Harwood DM, Barer DH. Predicting the outcome of acute stroke: prospective evaluation of five multivariate models and comparison with simple methods. *J Neurol Neurosurg Psychiatry* 1992;55:347-351

Gloag D. Exercise, fitness, and health. *BMJ* 1992;305:377-378

Goldstein LB, Bertels C, Davis JN. Interrater reliability of the NIH stroke scale. *Arch Neurol* 1989;46:660-662

Gompertz P, Pound P, Ebrahim S. Predicting stroke outcome: Guy's prognostic score in practice. *J Neurol Neurosurg Psychiatry* 1994;57:932-935

Graham GD, Kalvach P, Blamire AM, Brass LM, Fayad PB, Prichard JW. Clinical correlates of proton magnetic resonance spectroscopy findings after acute cerebral infarction. *Stroke* 1995;26:225-229

Grolimund P, Seiler RW, Aaslid R, Huber P, Zurbruegg H. Evaluation of cerebrovascular disease by combined extracranial and transcranial Doppler sonography. Experience in 1,039 patients. *Stroke* 1987;18:1018-1024

Grolimund P, Seiler RW. Age dependence of the flow velocity in the basal cerebral arteries-a transcranial Doppler ultrasound study. *Ultrasound Med Biol* 1988;14:191-198

Grosset D, Lees M. Applications of transcranial Doppler sonography in acute ischemic stroke. *Stroke* 1992;23:1840-1841

Gur RC, Gur RE, Brist WD. Age and regional cerebral blood flow at rest and during cognitive activity. *Arch Gen Psychiatry* 1987;44:617-621

Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Hoxter G, Mahagne MH, Hennerici M. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995;274:1017-1025

Haley EC, Jr., Levy DE, Brott TG, Sheppard GL, Wong MC, Kongable GL, Torner JC, Marler JR. Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered 91-180 minutes from onset. *Stroke* 1992;23:641-645

Halsey JH, McDowell HA, Gelmon S, Morawetz RB. Blood velocity in the middle cerebral artery and regional cerebral blood flow during carotid endarterectomy. *Stroke* 1989;20:53-58

Halsey JH. Effect of emitted power on waveform intensity in transcranial Doppler. *Stroke* 1990;21:1573-1578

Halsey JH, Jr. Prognosis of acute hemiplegia estimated by transcranial Doppler ultrasonography. *Stroke* 1988;19:648-649

Hammermeister KE, Sethi GK, Henderson WG, Oprian C, Kim T, Rahimtoola S. A comparison of outcomes in men 11 years after heart-valve replacement with a mechanical valve or bioprosthesis. Veterans Affairs Cooperative Study on Valvular Heart Disease. *N Engl J Med* 1993;328:1289-1296

Hankey GJ, Warlow CP, Sellar RJ. Cerebral angiographic risk in mild cerebrovascular disease. *Stroke* 1990;21:209-222

Hankey GJ, Warlow CP. Lacunar transient ischaemic attacks: a clinically useful concept? *Lancet* 1991;337:335-338

Harper AM. Autoregulation of cerebral blood flow: influence of the blood pressure on the blood flow through the cerebral cortex. *J Neurol Neurosurg Psychiatry* 1966;29:398-403

Harris RJ, Symon L, Branston NM. Changes in extracellular calcium activity in cerebral ischaemia. *J Cereb Blood Flow Metab* 1981;1:203-209

Hart RG, Halperin JL. Atrial fibrillation and stroke. Revisiting the dilemmas. *Stroke* 1994;25:1337-1341

Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bulll WHO* 1976;54:541-553

Hebert RG, Gaziano JM, Hennerkens CH. An overview of trials of cholesterol lowering and risk of stroke. *Arch Intern Med* 1995;155:50-55

Hedera P, Traubner P, Bujdakova J. Short-term prognosis of stroke due to occlusion of internal carotid artery based on transcranial Doppler ultrasonography. *Stroke* 1992;23:1069-1072

Heiss WD, Hayakawa T, Waltz AG. Cortical neuronal function during ischaemia. Effects of occlusion of one middle cerebral artery on single unit activity in cats. *Arch Neurol* 1976;33:813-820

Heiss WD. Experimental evidence of ischemic thresholds and functional recovery. *Stroke* 1992;23:1668-1672

Heiss WD, Podreka I. Role of PET and SPECT in the assessment of ischemic cerebrovascular disease. *Cerebrovasc Brain Metab Rev* 1993;5:235-263

Hellstrom G, Wahlgren NG. Physical exercise increases middle cerebral artery blood flow velocity. *Neurosurg Rev* 1993;16:151-156

Hommel M, Boissel JP, Cornu C, Boutitie F, Lees KR, Besson G, Leys D, Amarenco P, Bogaert M, for the MAST Study Group. Termination of trial of streptokinase in severe acute ischaemic stroke. *Lancet* 1995;345:57

Horowitz DR, Tuhrim S, Weinberger JM, Rudolph SH. Mechanisms in lacunar infarction. *Stroke* 1992;23:325-327

Hossmann KA, Hoehn-Berlage M. Diffusion and perfusion MR imaging of cerebral ischemia. *Cerebrovasc Brain Metab Rev* 1995;7:187-217

Howard G, Walker MD, Becker C, Coull B, Feibel J, McLeroy K, Toole JF, Yatsu F. Community Hospital-based Stroke Programs: North Carolina, Oregon, and New York. III. Factors influencing survival after stroke: proportional hazards analysis of 4219 patients. *Stroke* 1986;17:294-299

Howard G, Anderson R, Sorlie P, Andrews V, Backlund E, Burke GL. Ethnic differences in stroke mortality between non-Hispanic whites, Hispanic whites, and blacks. The National Longitudinal Mortality Study. *Stroke* 1994;25:2120-2125

Hoyt WF, Newton TH, Margolis MT. The posterior cerebral artery. Newton TH, Potts DG (eds) Radiology of the Skull and Brain. Mosby, St.Louis, 1974;1540-1550

Huston J, Rufenacht DA, Ehman RL, Wiebers DO. Intracranial aneurysms and vascular malformations: comparison of time-of-flight and phase-contrast angiography. *Radiology* 1991;181:721-730

International Stroke Trial Pilot Study Collaberative Group. International Stroke Trial (IST) Pilot Study: design, baseline data and outcome in 984 randomised patients. *J Neurol Neurosurg Psychiatry* 1996;60:371-376

ISIS-3 Third International Study of Infarct Survival Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992;339:753-770

Jimenez J, Morgan PP. Predicting improvement in stroke patients referred for inpatient rehabilitation. *Canadian Medical Association Journal* 1979;121:1481-1484

Jorgensen HS, Plesner AM, Hubbe P, Larsen K. Marked increase of stroke incidence in men between 1972 and 1990 in Frederiksberg, Denmark. *Stroke* 1992;23:1701-1704

Jorgensen HS, Sperling B, Nakayama H, Raaschou HO, Olsen TS. Spontaneous reperfusion of cerebral infarcts in patients with acute stroke. Incidence, time course, and clinical outcome in the Copenhagen Stroke Study. *Arch Neurol* 1994;51:865-873

Kannel WB, Wolf PA, McGee DL, Dawber TR, McNamara P, Castelli WP. Systolic blood pressure, arterial rigidity and risk of stroke: the Framingham Study. *JAMA* 1981;245:1225-1229

Kaplan J, Hier DB. Visuospatial deficits after right hemisphere stroke. *American Journal of Occupational Therapy* 1982;36:314-321

Kaps M, Damian MS, Teschendorf U, Dorndorf W. Transcranial Doppler ultrasound findings in middle cerebral artery occlusion. *Stroke* 1990;21:532-537

Kaps M, Teschendorf U, Dorndorf W. Haemodynamic studies in early stroke. *J Neurol* 1992;239:138-142

Kaste M, Waltimo O. Prognosis of patients with middle cerebral artery occlusion. *Stroke* 1976;7:482-485

Keli S, Bloemberg B, Kromhout D. Predictive value of repeated systolic blood pressure measurements for stroke risk. The Zutphen Study. *Stroke* 1992;23:347-351

Kelley RE, Kovacs AG. Horizontal gaze paresis in hemispheric stroke. *Stroke* 1986;17:1030-1032

Kent TA, Quast MJ, Kaplan BJ, Najafi A, Amparo EG, Gevedon RM, Salinas F, Suttle AD, DiPette DJ, Eisenberg HM. Cerebral blood volume in a rat model of ischemia by MR imaging at 4.7 T. *AJNR Am J Neuroradiol* 1989;10:335-338

Kertsez A, Black SE, Nicholson L, Carr T. The sensitivity and specificity or MRI in stroke. *Neurology* 1987;37:1580-1585

Kety SS. Circulation and metabolism of the human brain in health and disease. *Am J Med* 1950;8:205-217

Kirkham FJ, Padayachee TS, Parsons S, Seargeant LS, House FR, Gosling RS. Transcranial measurement of blood velocities in the basal cerebral arteries using pulsed Doppler ultrasound: velocity as an index of flow. *Ultrasound Med Biol* 1986;12:15-21

Knopman DS, Rubens AB. The validity of computed tomographic scan findings for the localisation of cerebral functions: The relationship between computed tomography and hemiparesis. *Arch Neurol* 1986a;43:328-331

Korner-Bitensky N, Wood-Dauphinee S. Barthel Index information elicited over the telephone. Is it reliable? *Am J Phys Med Rehabil* 1995;74:9-18

Kotila M, Waltimo O, Niemi ML, Laaksonen R, Lempinen M. The profile of recovery from stroke and factors influencing outcome. *Stroke* 1984;15:1039-1044

Kucharczyk J, Vexler ZS, Roberts TP, Asgari HS, Mintorovitch J, Derugin N, Watson AD, Moseley ME. Echo-planar perfusion-sensitive MR imaging of acute cerebral ischemia. *Radiology* 1993;188:711-717

Kushner MJ, Zanette EM, Bastianello S, Mancini G, Sacchetti ML, Carolei, A, Bozzao L. Transcranial Doppler in acute hemispheric brain infarction. *Neurology* 1991;41:109-113

LeBihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: applications to diffusion and perfusion in neurologic disorders. *Radiology* 1986;161:401-407

Leenders KL, Perani D, Lammertsman AA. Cerebral blood flow, blood volume and oxygen utilisation. Normal values and effect of age. *Brain* 1990;113:27-47

Lehmann JF, DeLateur BJ, Fowler RS, Jr., Warren CG, Arnhold R, Schertzer G, Hurka R, Whitmore JJ, Masock AJ, Chambers KH. Stroke rehabilitation: Outcome and prediction. *Arch Phys Med Rehabil* 1975;56:383-389

Lenzi GL, Di Piero V, Zanette E, Argentino C. How to assess acute cerebral ischemia. *Cerebrovasc Brain Metab Rev* 1991;3:179-212

Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26 year follow up of the Framingham population. *American Heart Journal* 1986;111:383-390

Ley-Pozo J, Ringelstein EB. Noninvasive detection of occlusive disease of the carotid siphon and middle cerebral artery. *Ann Neurol* 1990;28:640-647

Lhermitte F, Gautier JC, Derouesne C. Nature of occlusions of the middle cerebral artery. *Neurology* 1970;20:82-88

Lindegaard KF, Bakke SJ, Grolimund P, Aaslid R, Huber P, Nornes H. Assessment of intracranial hemodynamics in carotid artery disease by transcranial Doppler ultrasound. *J Neurosurg* 1985;63:890-898

Lindegaard KF, Lundar T, Wiberg J, Sjoberg D, Aaslid R, Nornes H. Variations in middle cerebral artery blood flow investigated with noninvasive transcranial blood velocity measurements. *Stroke* 1987;18:1025-1030

Lindgren A, Norving B, Rudling O, Johansen BB. Comparison of clinical and neuroradiological findings in first-ever stroke: a population-based study. *Stroke* 1994;25:1371-1377

Lyden PD, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, Haley EC, Grotta J, Marler J. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke* 1994;25:2220-2226

Lyden PD, Lau GT. A critical appraisal of stroke evaluation and rating scales. *Stroke* 1991;22:1345-1352

Maeda M, Itoh S, Ide H, Matsuda T, Kobayashi H, Kubota T, Ishii Y. Acute stroke in cats: comparison of dynamic susceptibility-contrast MR imaging with T2- and diffusion-weighted MR imaging. *Radiology* 1993;189:227-232

Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Maryland State Medical Journal* 1965;14:61-65

Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of maturity onset-diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 1991;151:1141-1147

Marchal G, Serrati C, Rioux P, Petit-Taboue MC, Viader F, de la Sayette V, Le Doze F, Lochon P, Derlon JM, Orgogozo JM, Baron JC. PET imaging of cerebral perfusion and oxygen consumption in acute ischaemic stroke: relation to outcome. *Lancet* 1993;341:925-927

Marchal G, Beaudouin V, Rioux P, de la Sayette V, Le Doze F, Viader F, Derlon JM, Baron JC. Prolonged persistence of substantial volumes of potentially viable brain tissue after stroke: a correlative PET-CT study with voxel-based data analysis. *Stroke* 1996a;27:599-606

Marchal G, Furlan M, Beaudouin V, Rioux P, Hauttement JL, Serrati C, de la Sayette V, Le Doze F, Viader F, Derlon JM, Baron JC. Early spontaneous hyperperfusion after stroke. A marker of favourable tissue outcome? *Brain* 1996b;119:409-419

Marini C, Carolei A, Roberts RS, Prencipe M, Gandolfo C, Inzitari D, Landi G, De Zanche L, Scoditti U, Fieschi C. Focal cerebral ischemia in young adults: a collaborative case-control study. The National Research Council Study Group. *Neuroepidemiology* 1993;12:70-81

Marks MP, de Crespigny A, Lentz D, Enzmann DR, Albers GW, Moseley ME. Acute and chronic stroke: navigated spin-echo diffusion-weighted MR imaging. *Radiology* 1996;199:403-408

Markus HS, Boland M. "Cognitive activity" monitored by non-invasive measurement of cerebral blood flow velocity and its application to the investigation of cerebral dominance. *Cortex* 1992;28:575-581

Martin PJ, Evans DH, Naylor AR, Bell PR. Transcranial colour coded sonography as an aid to measurement of blood flow velocity in the basal cerebral arteries. *Ultrasound Med Biol* 1993;19:711-716

Martin PJ. Evaluation and Application of Transcranial Colour-Coded Sonography. MD Thesis 1994

Martin PJ, Evans DH, Naylor AR. Transcranial color-coded sonography of the basal cerebral circulation. Reference data from 115 volunteers. *Stroke* 1994;25:390-396

Mast H, Thompson JL, Voller H, Mohr JP, Marx P. Cardiac sources of embolism in patients with pial artery infarcts and lacunar lesions. *Stroke* 1994;25:776-781

Matchar DB, Divine GW, Heyman A, Feussner JR. The influence of hyperglycemia on outcome of cerebral infarction. *Ann Intern Med* 1992;117:449-456

Mattle H, Grolimund P, Huber P, Sturzenegger M, Zurbrugg HR. Transcranial Doppler sonographic findings in middle cerebral artery disease. *Arch Neurol* 1988;45:289-295

Mattle HP, Grolimund P, Huber P, Sturzenegger M, Zurbrugg HR. Transcranial Doppler sonographic findings in middle cerebral artery disease. *Ann Neurol* 1988;45:289-295

McMahon S, Rodgers A. The epidemiological association between blood pressure and stroke: implications for primary and secondary prevention. *Hypertens Res* 1994;17 (Suppl.I):S23-32

Meade TW, Ruddock V, Stirling Y, Chakrabarti R, Miller GJ. Fibrinolytic activity, clotting factors, and long-term incidence of ischaemic heart disease in the Northwick Park Heart Study. *Lancet* 1993;342:1076-1079

Memezawa H, Smith ML, Siesjo BK. Penumbral tissues salvaged by reperfusion following middle cerebral artery occlusion in rats. *Stroke* 1992;23:552-559

Michotey P, Moscow NP, Salamon G. Anatomy of the cortical branches of the middle cerebral artery. Newton TH, Potts DG (eds) Radiology of the Skull and Brain. Mosby, St.Louis, 1974;1471-1478

Minematsu K, Li L, Fisher M, Sotak CH, Davis MA, Fiandaca MS. Diffusion-weighted magnetic resonance imaging: rapid and quantitative detection of focal brain ischemia. *Neurology* 1992a;42:235-240

Minematsu K, Li L, Sotak CH, Davis MA, Fisher M. Reversible focal ischemic injury demonstrated by diffusion-weighted magnetic resonance imaging in rats. *Stroke* 1992b;23:1304-1310

Moseley ME, Cohen Y, Mintorovitch J, Chileuitt L, Shimizu H, Kucharczyk J, Wendland MF, Weinstein PR. Early detection of regional cerebral ischaemia in cats: comparison of diffusion- and T2-weighted MRI and spectroscopy. *Magn Reson Med* 1990;14:330-346

Moseley ME, de Crespigny AJ, Roberts TP, Kozniewska E, Kucharczyk J. Early detection of regional cerebral ischemia using high-speed MRI. *Stroke* 1993;24 (Suppl.I):S60-5

Muir KW, Weir CJ, Murray GD, Povey C, Lees KR. Comparison of neurological scales and scoring systems for acute stroke prognosis. *Stroke* 1996;27:1817-1820

Muller TB, Haraldseth O, Jones R, Sebastiani G, Godtliebsen F, Lindboe CF, Unsgård G. Combined perfusion and diffusion-weighted magnetic resonance imaging in a rat model of reversible middle cerebral artery occlusion. *Stroke* 1995;26:451-458

Multicentre Acute Stroke Trial-Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. Multicentre Acute Stroke Trial--Italy (MAST-I) Group. *Lancet* 1995;346:1509-1514

Nagasawa H, Kogure K. Correlation between cerebral blood flow and histological changes in a new rat model of middle cerebral artery occlusion. *Stroke* 1989;20:1037-1043

Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. The influence of age on stroke outcome. The Copenhagen Stroke Study. *Stroke* 1994;25:808-813

Naylor AR, Sandercock PAG, Sellar RJ, Warlow CP. Patterns of vascular pathology in acute, first-ever cerebral infarction. *Scott Med J* 1993;38:41-44

Ni XS, Horner S, Fazekas F, Niederkorn K. Serial transcranial Doppler sonography in ischemic strokes in middle cerebral artery territory. *J Neuroimaging* 1994;4:232-236

Norris JW. Does transcranial Doppler have any clinical value? *Neurology* 1990;40:329-331

Norris JW, Krajewski A, Bornstein NM. The clinical role of the cerebral collateral circulation in carotid occlusion. *J Vasc Surg* 1990;12:113-118

North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis. *N Engl J Med* 1991;325:445-453

Nunnally JC. Psychometric Theory. McGraw-Hill, New York, 1978

Oder W, Binder H, Baumgartner C, Zeiler K, Deecke L. Is aphasia an additional prognostic factor in ischemic stroke with regard to the severity of hemiparesis in the subacute stage? *Acta Neurol Scand* 1988;78:85-89

Olsen TS, Skriver EB, Herning M. Cause of cerebral infarction in the carotid territory: its relations to the size and the location of the infarct and to the underlying vascular lesion. *Stroke* 1985;16:459-466

Olsen TS. Arm and leg paresis as outcome predictors in stroke rehabilitation. *Stroke* 1990;21:247-251

Olsen TS, Lassen NA. A dynamic concept of middle cerebral artery occlusion and cerebral infarction in the acute state based on interpreting severe hyperaemia as a sign of embolus migration. *Stroke* 1984;15:458-468

Orencia AJ, Petty GW, Khandheria BK, Annegers JF, Ballard DJ, Sicks JD, O'Fallon WM, Whisnant JP. Risk of stroke with mitral valve prolapse in population-based cohort study. *Stroke* 1995;26:7-13

Orgogozo JM, Bogousslavsky J. Lacunar Syndromes. Vinken PJ, Bruyn GW, Klawans HL (eds) Handbook of Clinical Neurology. Elsevier Science Publishers, Amsterdam, 1989;235-269

Otis S, Rush M, Boyajian R. Contrast-enhanced transcranial imaging. Results of an American phase-two study. *Stroke* 1995;26:203-209

Ozaita G, Calandre L, Peinado E, Rodriguez-Antiguedad A, Bermejo F. Hematocrit and clinical outcome in acute cerebral infarction. *Stroke* 1987;18:1166-1168

Padayachee TS, Bingham JB, Graves MJ, Colchester ACF, Cox TCS. Dural sinus thrombosis. Diagnosis and follow up by magnetic resonance angiography and imaging. *Neuroradiology* 1991;33:165-167

Paxton R, Ambrose J. The EMI scanner: a brief review of the first 650 patients. *Br J Radiol* 1974;47:530-565

Perlmutter D, Rhoton AL. Microsurgical anatomy of the distal anterior cerebral artery. *J Neurosurg* 1978;49:204-228

Perlmutter D, Rhoton AL. Microsurgical anatomy of the anterior cerebral-anterior communicating-recurrent artery complex. *J Neurosurg* 1976;45:259-272

Powers WJ, Grabb RLJ, Raichel ME. Physiological responses to focal cerebral ischaemia in humans. *Ann Neurol* 1984;16:546-552

Powers WJ. Cerebral haemodynamics in ischaemic cerebrovascular disease. *Ann Neurol* 1991;29:231-240

Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration. *Lancet* 1995;346:1647-1653

Pulsinelli W. Pathophysiology of acute ischaemic stroke. *Lancet* 1992;339:533-536

Quast MJ, Huang NC, Hillman GR, Kent TA. The evolution of acute stroke recorded by multimodal magnetic resonance imaging. *Magnetic Resonance Imaging* 1993;11:465-471

Rankin J. Cerebrovascular accidents in patients over the age of 60, II: prognosis. *Scott Med J* 1957;2:200-215

Ricci S, Celani MG, Caputo N. SEPIVAC: a community-based study of stroke incidence in Umbria, Italy. *J Neurol Neurosurg Psychiatry* 1991;54:695-698

Ricci S. Between country variations in the use of medical treatments for acute stroke. *Cerebrovasc Dis* 1995;5:272 (abstract)

Riggs H, Rupp C. Variation in form of Circle of Willis. The relation of the variations to collateral circulation: anatomic analysis. *Arch Neurol* 1963;8:8-14

Ringelstein EB, Biniek R, Weiller C, Ammeling B, Nolte PN, Thron A. Type and extent of hemispheric brain infarctions and clinical outcome in early and delayed middle cerebral artery recanalization. *Neurology* 1992;42:289-298

Rorick MB, Nichols FT, Adams RJ. Transcranial Doppler correlation with angiography in detection of intracranial stenosis. *Stroke* 1994;25:1931-1934

Ross ED. Acute agitation and other behaviors associated with Wernicke aphasia and their possible neurological basis. *Neuropsychiatry, Neuropsychology and Behavioural Neurology* 1993;6:9-18

Rother J, Schwartz A, Wentz KU, Rautenberg W, Hennerici M. Middle cerebral artery stenosis: assessment by magnetic resonance angiography and transcranial Doppler ultrasound. *Cerebrovasc Dis* 1994;4:273-279

Rother J, de Crespigny AJ, D'Arceuil H, Iwai K, Moseley ME. Recovery of apparent diffusion coefficient after ischemia-induced spreading depression relates to cerebral perfusion gradient. *Stroke* 1996;27:980-986

Rothwell P, Slattery J, Warlow CP. A systematic review of the risk of stroke and death due to carotid endarterectomy. *Stroke* 1996;27:260-265

Sacco RL, Hauser WA, Mohr JP, Foulkes MA. One-year outcome after cerebral infarction in whites, blacks, and Hispanics. *Stroke* 1991;22:305-311

Sandercock PAG, Bamford JM, Dennis MS, Burn J, Slattery J, Jones L, Boonyakarnkul S, Warlow CP. Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire community stroke project). *BMJ* 1992;305:1460-1465

Saunders DE, Clifton AG, Brown MM. Measurement of infarct size using MRI predicts prognosis in middle cerebral artery infarction. *Stroke* 1995a;26:2272-2276

Saunders DE, Howe DE, van den Boogaart A, McLean MA, Griffiths JR, Brown MM. Continuing ischaemic damage after acute middle cerebral artery infarction in humans demonstrated by short-echo proton spectroscopy. *Stroke* 1995b;26:1007-1013

Saver JL, Biller J. Superficial middle cerebral artery. Bogousslavsky J, Caplan L (eds) Stroke Syndromes. Cambridge University Press, Cambridge, 1995;247-258

Sawada M, Yano H, Shinoda J, Funakoshi T, Kumagai M. Symptomatic middle cerebral artery stenosis and occlusion: comparison of three-dimensional time-of-flight magnetic resonance angiography with conventional angiography. *Neurol Med Chir (Tokyo)* 1994;34:682-685

Sawada M, Kazui S. Anterior cerebral artery. Bogousslavsky J, Caplan L (eds) Stroke Syndromes. Cambridge University Press, Cambridge, 1995;235-246

Scandinavian Stroke Study Group. Multicenter trial of hemodilution in acute ischemic stroke: Background and study protocol. *Stroke* 1985;16:885-890

Scandinavian Stroke Study Group. Multicenter trial of hemodilution in acute ischemic stroke: Results of subgroup analysis. *Stroke* 1988;19:464-471

Schneider PA, Rossman ME, Bernstein EF, Ringelstein EB, Torem S, Otis SM. Noninvasive evaluation of vertebrobasilar insufficiency. *Journal of Ultrasound in Medicine* 1991;10:373-379

Schoning M, Buchholz R, Walter J. Comparative study of transcranial color duplex sonography and transcranial Doppler sonography in adults. *J Neurosurg* 1993;78:776-784

Seibert JJ, Miller SF, Kirby RS, Becton DL, James CA, Glasier CM, Wilson AR, Kinder DL, Berry DH. Cerebrovascular disease in symptomatic and asymptomatic patients with sickle cell anemia: screening with duplex transcranial Doppler US-correlation with MR imaging and MR angiography. *Radiology* 1993;189:457-466

Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. *Journal of Clinical Epidemiology* 1989;42:703-709

Shaper AG, Phillips AN, Pocock SJ, Walker M, Macfarlane PW. Risk factors for stroke in middle aged British men. *BMJ* 1991;302:786-787

Shinar D, Gross CR, Bronstein KS, Licata-Gehr EE, Eden DT, Cabrera AR, Fishman IG, Roth AA, Barwick JA, Kunitz SC. Reliability of the activities of daily living scale and its use in telephone interview. *Arch Phys Med Rehabil* 1987;68:723-728

Siesjo BK. Pathophysiology and treatment of focal cerebral ischemia. Part I: Pathophysiology. *J Neurosurg* 1992;77:169-184

Sindermann F, Dichgans J, Bergleiter R. Occlusion of the middle cerebral artery and its branches: Angiographic and clinical correlates. *Brain* 1969;92:607-620

Sorensen AG, Buonanno FS, Gonzalez RG, Schwamm LH, Lev MH, Huang-Hellinger FR, Reese TG, Weisskoff RM, Davis TL, Suwanwela N, Can U, Moreira JA, Copen WA, Look RB, Finklestein SP, Rosen BR, Koroshetz WJ. Hyperacute stroke: evaluation with combined multisection diffusion-weighted and hemodynamically weighted echo-planar MR imaging. *Radiology* 1996;199:391-401

Spetzler RF, Zabramski JM, Kaufman B, Young HN. Acute NMR change during MCA occlusion: a preliminary study in primates. *Stroke* 1983;14:185-190

Stern PH, McDowell F, Miller SM, Robinson M. Factors influencing stroke rehabilitation. *Stroke* 1971;3:213-218

Stock KW, Radue EW, Jacob AL, Bao XS, Steinbrich W. Intracranial arteries: prospective blinded comparative study of MR angiography and DSA in 50 patients. *Radiology* 1995;195:451-456

Taub NA, Wolfe CD, Richardson E, Burney PG. Predicting the disability of first-time stroke sufferers at 1 year. 12-month follow-up of a population-based cohort in southeast England. *Stroke* 1994;25:352-357

Tegeler CH, Kremkau FW, Hitchings LP. Color velocity imaging: introduction to a new ultrasound technology. *J Neuroimaging* 1991a;1:85-90

Tegeler CH, Shi F, Morgan T. Carotid stenosis in lacunar stroke. *Stroke* 1991b;22:1124-1128

Terent A. Increasing incidence of stroke amongst Swedish women. *Stroke* 1988;19:598-603

The MAST group. Protocol for the Multicentre Acute Stroke Trial-Thrombolysis study. *Clin Trials Meta-Anal* 1993;28:329-344

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-1587

The Secretary of State for Health. 1992;The Health of the Nation. Her Majesty's Stationery Office, London

Tsuruda J, Saloner D, Norman D. Artifacts associated with MR neuroangiography. *AJNR Am J Neuroradiol* 1992;13:1411-1422

Turner WH, Murie JA. Intravenous digital subtraction angiography for extracranial carotid artery disease. *Br J Surg* 1989;76:1247-1250

Turski PA, Korosec FR, Graves VB, Strother CM. Vascular malformations. Potchen JE, Haacke EM, Siebert JE, Gottschalk A (eds) Magnetic resonance angiography. Concepts and applications. Mosby, St. Louis, 1993;380-404

Tuszynski MH, Petito CK, Levy DE. Risk factors and clinical manifestations of pathologically verified lacunar infarctions. *Stroke* 1989;20:990-999

Ueda K, Omae T, Hirota Y. Decreasing trend in incidence and mortality in Hisayama residents, Japan. *Stroke* 1981;12:154-160

Ueda T, Hatakeyama T, Kumon Y, Sakaki S, Uraoka T. Evaluation of risk of hemorrhagic transformation in local intra-arterial thrombolysis in acute ischemic stroke by initial SPECT. *Stroke* 1994;25:298-303

van Gijn J, Stampfer MJ, Wolfe C, Algra A. The association between alcohol and stroke. Verschuren PM (ed) Health Issues Related to Alcohol Consumption. ILSI Press, Washington, 1993;44-79

van Latum JC, Koudstaal PJ, Venables GS, van Gijn J, Kappelle LJ, Algra A. Predictors of major vascular events in patients with a transient ischemic attack or minor ischemic stroke and with nonrheumatic atrial fibrillation. European Atrial Fibrillation Trial (EAFT) Study Group. *Stroke* 1995;26:801-806

von Kummer R, Holle R, Rosin L, Forsting M, Hacke W. Does arterial recanalization improve outcome in carotid territory stroke? *Stroke* 1995;26:581-587

von Reutern GM, von Budingen HJ. Doppler examination of the basal cerebral arteries (transcranial or intracranial sonography).Ultrasound diagnosis of cerebrovascular disease. Georg Thieme Verlag, Stuggart, 1993;176-248

Vriens EM, Kraair V, Musbach M. Transcranial pulsed Doppler measurements of blood velocity in the middle cerebral artery: reference values at rest and during hyperventilation in healthy volunteers in relation to age and sex. *Ultrasound Med Biol* 1989;15:1-8

Wada T, Kodaira K, Fujishiro K, Maie KI, Tsukiyama E, Mikawa H, Shimuzu H, Fukumoto T, Okamura T. Quantitative measurement of middle cerebral artery flow velocity using transcranial Doppler sonography. *Arters et Veines* 1990;9:682-685

Waddington MM, Ring BA. Syndromes of occlusions of middle cerebral artaery branches: angiographic and clinical correlation. *Brain* 1968;91:685-696

Wade DT, Skilbeck CE, Hewer RL. Predicting Barthel ADL score at 6 months after an acute stroke. *Arch Phys Med Rehabil* 1983;64:24-28

Wade DT, Hewer RL, Wood VA. Stroke: influence of patient's sex and side of weakness on outcome. *Arch Phys Med Rehabil* 1984a;65:513-516

Wade DT, Langton-Hewer R, Wood VA. Stroke: the influence of age upon outcome. *Age & Ageing* 1984b;13:357-362

Wade DT, Skilbeck CE, Wood VA, Langton Hewer R. Long-term survival after stroke. *Age & Ageing* 1984c;13:76-82

Wade DT, Wood VA, Hewer RL. Recovery after stroke--the first 3 months. *J Neurol Neurosurg Psychiatry* 1985;48:7-13

Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? *International Disability Studies* 1988;10:64-67

Wade DT, Hewer RL. Functional abilities after stroke: measurement, natural history and prognosis. *J Neurol Neurosurg Psychiatry* 1987;50:177-182

Warach S, Chien D, Li W, Ronthal M, Edelman RR. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. *Neurology* 1992a;42:1717-1723

Warach S, Li W, Ronthal M, Edelman RR. Acute cerebral ischemia: evaluation with dynamic contrast-enhanced MR imaging and MR angiography. *Radiology* 1992b;182:41-47

Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. *Ann Neurol* 1995;37:231-241

Warach S, Dashe JF, Edelman RR. Clinical outcome in ischemic stroke predicted by early diffusion-weighted and perfusion magnetic resonance imaging: a preliminary analysis. *J Cereb Blood Flow Metab* 1996;16:53-59

Wardlaw JM, Dennis MS, Lindley RI, Sellar RJ, Warlow CP. The validity of a simple clinical classification of acute ischaemic stroke. *J Neurol* 1996;243:274-279

Warlow CP, Dennis MS, van Gijn J, Hankey GJ, Sandercock PAG, Bamford JM, Wardlaw JM. Preventing recurrent stroke and other serious vascular events. Stroke: a practical guide to management. Blackwell Science, Oxford, 1996;545-598

Welch KM, Windham J, Knight RA, Nagesh V, Hugg JW, Jacobs M, Peck D, Booker P, Dereski MO, Levine SR. A model to predict the histopathology of human stroke using diffusion and T2-weighted magnetic resonance imaging. *Stroke* 1995;26:1983-1989

Wellwood I, Dennis MS, Warlow CP. A comparison of the Barthel Index and the OPCS disability instrument used to measure outcome after acute stroke. *Age & Ageing* 1995;24:54-57

Whisnant JP. The decline of stroke. *Stroke* 1984;15:160-168

White DN, Curry GR, Stevenson RJ. The acoustic characteristics of the skull. *Ultrasound Med Biol* 1978;4:225-252

Wick M, Nagatomo Y, Prielmeier F, Frahm J. Alteration of intracellular metabolite diffusion in rat brain in vivo during ischemia and reperfusion. *Stroke* 1994;26:1930-1933

Wityk RJ, Pessin MS, Kaplan RF, Caplan LR. Serial assessment of acute stroke using the NIH Stroke Scale. *Stroke* 1994;25:362-365

Wolfe CD, Taub NA, Woodrow EJ, Burney PG. Assessment of scales of disability and handicap for stroke patients. *Stroke* 1991;22:1242-1244

Woo J, Lam CW, Kay R, Wong AH, Teoh R, Nicholls MG. The influence of hyperglycemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke. *Arch Neurol* 1990;47:1174-1177

Woo J, Kay R, Yuen YK, Nicholls MG. Factors influencing long-term survival and disability among three-month stroke survivors. *Neuroepidemiology* 1992;11:143-150

World Health Organisation. The International Classification of Impairments, Disabilities and Handicaps. *Geneva WHO,* 1980;

Young AR, Touzani O, Derlon JM, Sette G, MacKenzie ET, Baron JC. Early reperfusion in the anaesthetised baboon reduces brain damage following middle cerebral artery occlusion. *Stroke* 1997;28:632-638

Zanette EM, Fieschi C, Bozzao L, Roberti C, Toni D, Argentino C, Lenzi GL. Comparison of cerebral angiography and transcranial Doppler sonography in acute stroke. *Stroke* 1989;20:899-903

Zanette EM, Roberti C, Mancini G, Pozzilli C, Bragoni M, Toni D. Spontaneous middle cerebral artery reperfusion in ischemic stroke. A follow-up study with transcranial Doppler. *Stroke* 1995;26:430-433

Zwiebel WJ. Doppler evaluation of carotid stenosis. Zwiebel WJ (ed) Introduction to Vascular Ultrasonography. W.B. Sauders, Toronto, 1992;