

The Influence of Carotid Disease on
Cerebral Vascular Autoregulation and
Cerebral Vascular Reactivity to
Hypercapnia

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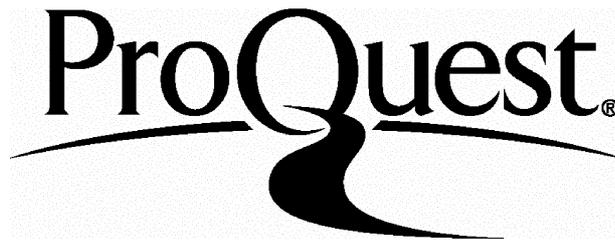
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For my parents

Abstract of thesis.

Cerebral vascular reactivity to hypercapnia, assessed using transcranial Doppler ultrasonography of middle cerebral artery blood flow velocity, is used to assess the extent of cerebral blood flow reserve. It has been assumed that in patients with carotid disease a reduced reactivity to hypercapnia can be interpreted as indicating reduced cerebral perfusion with reduced autoregulatory capacity. This relationship between reactivity to hypercapnia and autoregulation in the cerebral vasculature is tested.

A method for the non-invasive measurement of cerebral vascular autoregulation to changes in blood pressure is described and this method is used to assess autoregulation in a group of normal subjects. Hypercapnia is shown to obtund autoregulation whereas hypocapnia is shown to exaggerate cerebral vascular autoregulation to changes in blood pressure.

It is shown that volitional respiration significantly increases middle cerebral artery blood flow velocity. Cerebral vascular reactivity to hypercapnia is measured in patients with carotid disease and is shown to be reduced in the presence of internal carotid artery occlusion. It is also shown that whilst some patients with severe carotid artery disease have reduced cerebral vascular reactivity to hypercapnia, the presence of severe carotid artery disease per se does not predict a reduced reactivity index. In the presence of internal carotid artery occlusion an increased degree of contralateral internal carotid artery stenosis reduces ipsilateral cerebral vascular reactivity to hypercapnia.

The relationship between cerebral vascular autoregulation and cerebral vascular reactivity to hypercapnia is tested in a group of subjects with severe carotid disease. The methods described for the measurement of cerebral vascular autoregulation and cerebral vascular reactivity to hypercapnia are employed to measure both parameters in each individual in the group and it is shown that there is a strong correlation between the presence of reduced cerebral vascular reactivity to hypercapnia and reduced cerebral vascular autoregulation to pressure change.

Statement of originality

All work presented in this thesis was carried out by the Author as Lecturer in Surgery of the United Medical and Dental Schools of Guy's and St. Thomas', in the Surgical Unit of St. Thomas' Hospital, Lambeth Palace Road, London SE1. Technical assistance in the building of equipment was provided by Derek Rutt. Assistance in performing the two-handed task of cerebral vascular autoregulation measurement was provided by Ann Donald.

Ethical Approval

All experimental work presented in this thesis was approved by the Ethics Committee of St. Thomas' Hospital.

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Contents

	Page
Title	1
Abstract	3
Statements of originality and Ethical Approval	5
Acknowledgements	5
Description of Chapters	7
Figures and Illustrations	11
Part 1 - Introduction	15
Part 2 - Principles of transcranial Doppler ultrasonography and volume clamp plethysmography	71
Part 3 - Cerebral vascular autoregulation to pressure change	88
Part 4 - Cerebral vascular reactivity to hypercapnia	130
Part 5 - The relationship between cerebral vascular reactivity and cerebral vascular autoregulation in subjects with severe carotid disease	164
Part 6 - Conclusions	176
Part 7 - References	180
Appendix	209

Description of Chapters

<i>Page</i>	<i>Part</i>	<i>Title</i>
1		Title
3		Abstract of Thesis
5		Statements of originality and ethical approval
5		Acknowledgements
15	Part 1	Introduction
17		Synopsis
18	1.1	A history of ideas about the circulation, stroke and the cerebral vasculature
18	1.1.1	Preface
20	1.1.2	Antiquity
24	1.1.3	Renaissance
27	1.1.4	The seventeenth century
31	1.1.5	The eighteenth and nineteenth centuries
35	1.1.6	The twentieth century and the development of elective carotid surgery
39	1.2	Clinical and diagnostic features of stroke and transient ischaemic attack
43	1.3	The epidemiology of stroke and transient ischaemic attack
50	1.4	The role of surgery in the management of carotid disease
56	1.5	Cerebral vascular anatomy & physiology & the effects of carotid disease on cerebral blood flow

56	1.5.1	The anatomy of the cerebral vasculature
59	1.5.2	The physiological control of normal cerebral blood flow and the concept of flow reserve
64	1.5.3	The effects of carotid disease on cerebral blood flow
68	1.5.4	Assessment of cerebral vascular reactivity and autoregulation
71	Part 2	Principles of transcranial Doppler ultrasonography and volume clamp plethysmography
72		Synopsis
73	2.1.1	The measurement of cerebral blood flow
77	2.1.2	Transcranial Doppler ultrasonography of the middle cerebral artery
81	2.1.3	Conclusion
82	2.2	Assessment of the accuracy of the Ohmeda Finapres in the non-invasive measurement of mean arterial blood pressure
82	2.2.1	Introduction
83	2.2.2	Aims
83	2.2.3	Subjects and methods
84	2.2.4	Results
86	2.2.5	Discussion
88	Part 3	Cerebral vascular autoregulation to pressure change

89		Synopsis
90	3.1	Introduction
90	3.1.1	The measurement of cerebral vascular resistance
93	3.1.2	The generation of changes in cerebral perfusion pressure
97	3.2	Study of relative cerebral vascular resistance and rapid cerebral vascular autoregulation in normal subjects
97	3.2.1	Aims
97	3.2.2	Subjects
98	3.2.3	Methods
110	3.2.4	Calculations
111	3.2.5	Results
117	3.2.6	Discussion of results
119	3.3	Study of the effect of hypercapnia and hypocapnia on autoregulation in normal subjects
119	3.3.1	Aims
119	3.3.2	Subjects and methods
122	3.3.3	Results
125	3.3.4	Discussion of results
130	Part 4	Cerebral vascular reactivity to hypercapnia
131		Synopsis
132	4.1	Introduction
135	4.2	Study of the effect of volitional respiration on middle cerebral artery blood flow velocity

135	4.2.1	Introduction
136	4.2.2	Aims
137	4.2.3	Subjects and methods
139	4.2.4	Results
141	4.2.5	Discussion
144	4.3	Protocol for the measurement of middle cerebral artery blood flow velocity, middle cerebral artery reactivity to hypercapnia and middle cerebral artery reactivity index to hypercapnia
144	4.3.1	Method
147	4.3.2	Calculations
149	4.4	Cerebral vascular reactivity to hypercapnia in patients with carotid atherosclerosis
149	4.4.1	Introduction
150	4.4.2	Aims
151	4.4.3	Subjects and methods
151	4.4.4	Results
162	4.4.5	Discussion
164	Part 5	The relationship between cerebral vascular reactivity and cerebral vascular autoregulation in subjects with severe carotid disease.
165		Synopsis
166	5.1	Introduction

167	5.2	Study of cerebral vascular reactivity and cerebral vascular autoregulation in the presence of severe carotid disease
167	5.2.1	Aim
167	5.2.2	Subjects and Methods
169	5.2.3	Calculations
171	5.2.4	Results
174	5.2.5	Discussion
176	Part 6	Conclusions
180	Part 7	References
209	Appendix	Carotid duplex velocity criteria Manufacturers

Figures and illustrations

<i>Page</i>	<i>Figure</i>	<i>Title</i>
79	2a	The temporal bone window
85	2.1.1	Relationship between arterial line and Finapres mean arterial pressure
85	2.1.2	Histogram of the distribution of the differences between arterial line and Finapres blood pressure readings
101	3a	Transcranial Doppler ultrasound instrument
102	3b	Doppler transducer, holder and clamp
103	3c	Detail of mouthpiece and holder
104	3d	Finapres plethysmography handpiece

105	3e	Thigh plethysmography cuffs
106	3f	Chart recorder, Finapres and regulator
107	3g	Plethysmography regulator and valve
108	3h	Plethysmography valve
109	3i & 3j	The experimental setting
114	3.2.1 & table 3.2.1	Group 1 mean arterial blood pressure in the absence of a blood pressure stimulus
114	3.2.2 & table 3.2.2	Group 1 mean iCVR in the absence of a blood pressure stimulus
115	3.2.3 & table 3.2.3	Group 2 mean arterial blood pressure following blood pressure stimulus
115	3.2.4 & table 3.2.4	Group 2 mean iCVR following blood pressure stimulus
116	3.2.5 & table 3.2.5	Group 2 mean middle cerebral artery blood flow velocity following blood pressure stimulus
121	3k	Carbon dioxide mixing apparatus and analyser
123	3.3.1 & tables 3.3.1 & 3.3.1a	Variation in resting cerebral vascular resistances under eucapnic, hypercapnic and hypocapnic conditions with statistical significances of the differences
124	3.3.2 & table 3.3.2	Variation in iCVR with time in normal subjects following blood pressure stimulus under hypocapnic conditions
124	3.3.3 & table 3.3.3	Variation in iCVR with time in normal subjects following blood pressure stimulus under hypercapnic conditions
140	4.2.1 &	Change in middle cerebral artery blood flow velocity with

	table 4.2.1	voluntary control of respiration
140	4.2.2 & table 4.2.2	Ratio of MCA blood flow velocity and end-tidal CO2 concentration with voluntary control of respiration
154	4.4.1	Relationship between MCA reactivity indices calculated from peak and mean MCA blood flow velocities - non-occluded ipsilateral internal carotid artery
154	4.4.2	Relationship between MCA reactivity indices calculated from peak and mean MCA blood flow velocities - occluded ipsilateral internal carotid artery
156	4.4.3	Variation in peak reactivity index with degree of ipsilateral internal carotid artery stenosis
156	4.4.4	Variation in mean reactivity index with degree of ipsilateral internal carotid artery stenosis
159	4.4.5 a - c	Histograms of the distribution of peak reactivity index with degree of stenosis of contralateral ICA in hemispheres ipsilateral to an occluded ICA
160	4.4.5 d - f	Histograms of the distribution of mean reactivity index with degree of stenosis of contralateral ICA in hemispheres ipsilateral to an occluded ICA
161	4.4.6 & table 4.4.6	Variation in peak reactivity index with degree of stenosis of contralateral ICA in hemispheres ipsilateral to an occluded ICA
161	4.4.7 & table 4.4.7	Variation in mean reactivity index with degree of stenosis of contralateral ICA in hemispheres ipsilateral to an

occluded ICA

- 161 4.4.8 Contingency tables and statistical analysis of data from figures 4.4.6 & 4.4.7
- 172 5.2.1 Reactivity and autoregulation measurements in hemispheres ipsilateral to a severely stenosed or occluded ICA
- 172 5.2.2 Relationship between iCVR10 and peak reactivity measurements in hemispheres ipsilateral to a severely stenosed or occluded ICA
- 172 5.2.3 Relationship between iCVR10 and mean reactivity measurements in hemispheres ipsilateral to a severely stenosed or occluded ICA
- 173 5.2.4 & Variation in mean iCVR with time following blood table 5.2.4 pressure stimulus in subjects with severe ipsilateral carotid disease but normal reactivity index
- 173 5.2.5 & Variation in mean iCVR with time following blood table 5.2.5 pressure stimulus in subjects with severe ipsilateral carotid disease and reduced reactivity index

Part 1 Introduction

Synopsis

- 1.1 A history of ideas about the circulation, stroke and the cerebral vasculature
 - 1.1.1 - Preface
 - 1.1.2 - Antiquity
 - 1.1.3 - Renaissance
 - 1.1.4 - The seventeenth century
 - 1.1.5 - The eighteenth and nineteenth centuries
 - 1.1.6 - The twentieth century and the development of elective carotid surgery
- 1.2 - Clinical and diagnostic features of stroke and transient ischaemic attack
- 1.3 - The epidemiology of stroke and transient ischaemic attack
- 1.4 - The role of surgery in the management of carotid disease
- 1.5 - Cerebral vascular anatomy & physiology & the effects of carotid disease on cerebral blood flow
 - 1.5.1 - The anatomy of the cerebral vasculature
 - 1.5.2 - The physiological control of normal cerebral blood flow and the concept of flow reserve
 - 1.5.3 - The effects of carotid disease on cerebral blood flow

1.5.4 - Assessment of cerebral vascular reactivity and autoregulation

Synopsis

A historical background to the subject matter is presented. The extent of the clinical problem of stroke is explored, as are the difficulties of definition and diagnosis in stroke and transient ischaemic attack and the difficulty in predicting the probability of the occurrence of stroke in an individual. The role of carotid surgery in the management of stroke risk is discussed. A background to cerebral vascular anatomy and physiology is presented and the effects of carotid disease on cerebral vascular physiology are discussed.

1.1 A history of ideas about the circulation, stroke and the cerebral vasculature.

1.1.1 Preface

"There is little benefit in following scientists' daily grind but much in tracing the unique combinations of theoretical knowledge and manual skills, the web of personal encounters and accidental observations, the experience, temperament, moods and clashes that go into the making of discoveries, even though the crucial leap of mind is often impenetrable. There is also something to be said for finding out why others, seemingly just as able, were too blind to grasp what Nature tried to tell them". (Perutz, 1991)

In charting the development of a branch of science or medicine one's aim is to describe how things arrived at a predetermined point; the state of the art today. In such a history, picking out figures associated with particular advances can give the impression that the course of events described was an inexorable progression from ignorance into understanding, from "darkness into light", brought about by the activities of individuals of particular genius; the 'Great Man' theory of history. While this account may look like that it should not be read as such. Although it is full of names of people and descriptions of the discoveries which they made, it should be stressed at the beginning that no discoveries or advances, in science or in medicine, are made in isolation from the received opinion of the day or from the society in which the individual lived. An

account like this one is therefore artificially limited to those people and subjects who are obviously connected with the matter in question. Little time can be spent discussing the social, economic, political and religious forces which put those people where they were or led them to think the way they did, even though such a discussion may be as enlightening as a description of the personalities and their achievements.

Similarly, since the transactions of modern western medicine have become so complex that specialisation is the norm, it is easy to forget that such specialisation was unheard of before the twentieth century, especially in the field of surgery. Since it is possible to deal with only a small part of each individual's work and only briefly describe the intellectual environment into which it was projected, the incorrect impression that there was some kind of concerted effort towards the present-day state of affairs is invariably given. It can therefore be deceptive to look for the influences which may have led to the development of a surgical speciality or a specific intervention (such as the use of carotid surgery in the treatment or prevention of stroke) because, whilst attempting to be informative the account will always be incomplete.

As for how the changes described were received at the time, the regular use of the word controversy is a catch-all which fails to do justice to the complexities of the process of assimilation of scientific change. Suffice to say that it is unclear how those changes (which are described as, and which with hindsight appear as historical events) were incorporated into the science or medicine of the day, and the reader is referred to other texts for treatment of this subject (Kuhn, 1970; Suppe, 1977). I would also

suggest that whilst the processes of change in the pure sciences such as physics (which perhaps one would have expected would be relatively straightforward) continue to be the subject of vigorous debate, so changes in medicine with their profound social, political and ethical implications are even harder to pin down.

1.1.2 Antiquity

The clinical entity which is now known as stroke - the cluster of symptoms and signs which result from an acute cerebrovascular accident - was widely known until the early part of the twentieth century as apoplexy. A typical definition of apoplexy can be found in Harris' dictionary of 1855, which states: 'Apoplexy; ...to strike or knock down; because when a person is attacked by this disease, he suddenly falls down. A disease characterised by a sudden loss of sense, motion and stertorous breathing. The term is used by some to denote a sudden effusion of blood into the substance of organs or tissues, but it is usually restricted to the brain, and the above are among phenomena which characterise cerebral apoplexy' (Harris, 1885). Descriptions of the condition can be traced back in historical medical writings as far back as the fourth and fifth centuries BC, to the Hippocratic texts of Ancient Greece (Willius & Dry, 1948).

The Greek word apoplexia means being struck with violence, being struck by lightning or by a thunderbolt, and in the Hippocratic writings the term apoplexy is used to describe any condition whereupon a patient suffers rapid loss of consciousness, with a fatal outcome in a high proportion of cases (Clarke, 1963). This condition can be

interpreted in the light of modern diagnostic terminology as encompassing many causes of sudden and rapidly fatal loss of consciousness such as myocardial infarction and massive pulmonary embolism. However, the term apoplexy was also used to describe the symptoms of both minor attacks and the residual afflictions should an attack prove non-fatal, including paralysis of an arm or leg or the loss of a function such as speech, which indicates that many of the cases which described as apoplexy in the Hippocratic writings were caused by acute cerebrovascular disease (Clarke, 1963).

It is clear that there was a distinction drawn, even at that early stage in the process of formal classification of disease, between apoplexy and epilepsy (Clarke, 1963).

Epilepsy was known to the ancients as 'the sacred disease' but renamed in the Hippocratic texts 'the falling sickness' in an attempt to remove the stigma of superstition of possession by evil spirits from this condition. In the Hippocratic opus there are whole texts exclusively describing epilepsy, its symptoms, signs and critically for the time, prognosis. Apoplexy is not dealt with in nearly such a defined manner. Since the word apoplexy was in common non-medical usage in early Greek literature to mean both paralysis and loss of senses with the connotation of being thunderstruck (Homer in the Iliad book XIV uses 'apoplexia' in the sense of 'to strike a blow'), it has been proposed that the word was originally a lay term which was taken into the medical sphere by contemporary physicians. The appropriation of lay terms and the limitation of their meaning by application of technical knowledge (in the case of medicine, that knowledge would comprise theory of aetiology and treatment and knowledge of prognosis) is a theme found in Ancient Greek medicine but perhaps lost to modern medicine. In Hippocratic times the ability to communicate with the educated laity was

prized, and the skills of logic and rhetoric were highly valued. This is in contrast to the complexity of modern medicine which lends itself to the use of technical jargon which tends to exclude even the most educated of non-medical people.

The aetiology of apoplexy is discussed in the Hippocratic writings in terms appropriate to the theory of disease used at the time. It was thought that it was an affliction of the brain, and arose as a result of an excess of black bile or phlegm in the veins in the head, cooling the brain. This led to the appearance of the symptoms of headache and visual disturbance. Treatment could be by warming the head or by venesection, though it was recognised that a severe attack was impossible to cure. The importance of prognosis to Hippocratic medicine is profound and the characteristics of apoplexy which enabled the doctor to assess the patient's prognosis are described in detail. Generally, a severe attack would be fatal on the third or fifth day, but if the patient survived until the seventh day he would recover. Recovery of consciousness was recognised as a good sign, whereas a prolonged pyrexia, a sweat or respiratory difficulties were seen as implying a poor prognosis (Clarke, 1963).

Whilst the Hippocratic texts described mild and severe apoplexy, Galen in the First century AD differentiated between four degrees of severity depending upon the respiratory difficulty experienced by the patient, and death was usually attributed to failure of respiration. He described the apoplectic as "one who became suddenly senseless as if struck by lightning, with loss of all motion except that of respiration. The worst are those in whom stertor and foaming at the mouth occur" (McHenry, 1969). He also placed at greatest risk elderly men, those who experienced high

emotion, those who were plethoric and who indulged in sloth, drunkenness and gluttony. (Plus ca change, plus c'est la meme chose). Galen's description of the anatomy of the brain and cerebral vasculature is not extensive and contains an interesting anomaly; it is asserted that the rete mirabile exists in humans, whereas modern comparative anatomists recognise this structure anastomosing internal and external carotid circulations as existing only in species such as dogs and cats ((McHenry, 1969), & see discussion of the anatomy of the cerebral vasculature in section 1.5.1). The implication is that at least some of Galen's dissection was of animal subjects, and that he either performed this dissection only in animals and assumed that there was no difference between species, or that he did examine human anatomy but failed to recognise from his dissections that there were differences in such structures from species to species.

After the fall of the Roman Empire practically nothing of merit was contributed to medicine for the next eight hundred years. The traditions of Galen were carried on by Arabian physicians such as Avicenna in the great civilisations of Islam and Byzantium, and to a lesser extent by the European Monastic orders. It was not until the Twelfth and Thirteenth centuries AD that Arabic copies of ancient Greek texts began to leak back into the universities of Southern Europe. The recovery of many of Aristotle's works from Arabic sources created an intellectual ferment which has been interpreted subsequently as heralding the dawn of the Renaissance in Europe.

1.1.3 Renaissance

When the new thought of the Renaissance was applied to medicine, the facts of anatomy as laid down by Galen, and his teleological approach to physiology were called into question by many figures such as Leonardo da Vinci and Vesalius of Padua.

Galen, led by the philosophical reasoning of his time, never asked in his anatomical or medical studies 'what is the function of this organ?' but rather 'why should it subserve the function assumed for it a priori?'. While some of Galen's anatomical drawings were done from dissection of human subjects (acquired as a result of his position as physician to the Emperor in Rome; he had access to the bodies of the 'losers' from the games at the Coliseum), many of them are obviously from animal studies (c.f. the above example of the rete mirabile). The root of the contribution of the Renaissance thinkers to the study of anatomy was in the realisation that the 'truth' was to be found not in the re-examination of ancient texts but in the investigation of the world as it existed around them. Leonardo's anatomical drawings are documented to have been done from human dissection (Keele, 1977). While Leonardo had no interest in medicine in the sense of curing people, his anatomical studies from observation are typical of the age in which received wisdom, even that of the ancients, was placed next to that which could be demonstrated, and found to be wanting.

Leonardo was not part of any philosophical 'Establishment'. These existed in the great European Universities. Particularly in Padua an extraordinary thread of continuity can be traced in the advances made in the study of human anatomy during the sixteenth

century, a continuity which nevertheless leads backwards and forwards through the deep controversies which surrounded the reassessment of Galenic anatomy and eventually Galen's physiology. Andreas Vesalius of Brussels was Professor of Anatomy at Padua. In his beautiful and revolutionary work *De Humani Corporis Fabrica* he established the basis of modern anatomy (Saunders & O'Malley, 1982; Graubaud, 1964). It was published in 1543, the same year that Copernicus' *De Revolutionibus Orbium Caelestium* inaugurated a similar upheaval in astronomical and cosmological thought (Kuhn, 1957). Criticism of both works was acrimonious. Vesalius' teacher in Paris, Jacques Dubois (Sylvius) was a passionate Galenist and violently disagreed with much of Vesalius' teachings but even so performed human dissection and in his *'Isagoge'* published in Venice in 1556 he named the jugular, subclavian, renal and popliteal vessels as well as the Sylvian aqueduct and the Sylvian fissure (Willius & Dry, 1948) (through which runs the middle cerebral artery). The next accurate description of the anatomy of the cerebral vasculature was made by Gabriel Fallopius, who was a student of Vesalius at Padua, and went on to teach anatomy there. He confirmed much of Vesalius' findings regarding the heart and great vessels, he was the first to describe the existence of an arterial circle at the base of the brain, and demonstrated the coronary vessels by dissection (Willius & Dry, 1948).

The *'Fabrica'* is recognised as a milestone in medical history, in the same way as *'De Revolutionibus'* was the core event in the Copernican revolution. (The content of the *'Fabrica'* was popularised by the most famous surgeon of the renaissance, the Frenchman Ambrose Pare who wrote an epitome of the *Fabrica* in the vernacular which made it available to contemporary surgeons, who tended not to be University educated

and therefore were unable to read Latin. He made practical application of it in his work as surgeon to Henry II, Francis II and Charles IX, and in his extensive writings on surgery). It was not just the theoretical content of the 'Fabrica' which was remarkable, but its presentation also. The nature of Italian society during the Renaissance was such that activities in philosophy, medicine and art were irretrievably entwined, and this is amply demonstrated by the fact that the 'Fabrica' was illustrated by artists from the Venetian studio of Titian. Although Titian himself is unlikely to have undertaken any of the work directly, the use of dramatic pose for the larger figures, especially the magnificent 'musclemen', and the extraordinary skill in the execution of the landscapes in which the figures are set, are said to reveal the hand of Jan Van Kalkar and Domenico Campagnola under the supervision of Titian (Saunders & O'Malley, 1982). However, the illustrations in the Fourth Book (of the vasculature) were probably drawn by Vesalius himself, who whilst no mean artist was not up to the extraordinary standards seen in the other books. While this fourth book corrects much of the erroneous vascular anatomy of Galen the treatment of the cerebral vasculature is not extensive, possibly since to the sixteenth-century physician the arrangement of the peripheral venous system was of paramount importance as it formed the basis for phlebotomy, which was the main therapeutic intervention of the day.

1.1.4 The seventeenth century

The association between Renaissance Italian advances in medicine and intellectual activity in England had been established early in the sixteenth century by Thomas Linacre who studied at both Oxford and Padua in the early part of the sixteenth century and who went on to become Physician to Henry VII and Henry VIII (Willius & Dry, 1948). His footsteps were later followed by William Harvey, who at the turn of the Seventeenth century went from Oxford to Padua to study under Vesalius' successor, the celebrated surgeon and anatomist Hieronymus Fabricius (Willius & Dry, 1948; Graubaud, 1964). Fabricius had rediscovered the valves of the veins, first described by Sylvius. His concept of their function was to prevent overdistension of the veins in the constant ebb and flow of blood through the venous system; this ebb and flow was the essence of the Galenic view of the movement of blood about the body, with the action of the heart being a passive response to a fermentation or effervescence of the blood. Harvey's great contribution to the understanding of the physiology of the circulation was to postulate its existence, with the movement being caused by the action of the heart rather than vice versa. As described initially in his Lumleian lectures in 1616; "It is plain from the structure of the heart that the blood is passed continuously through the lungs to the aorta as by the two clacks of a water bellows to raise water. It is shown by the application of a ligature that the passage of the blood is from the arteries into the veins. Whence it follows that the movement of the blood is constantly in a circle, and is brought about by the beating of the heart. It is a question, therefore, whether this is for the sake of nourishment or rather for the preservation of the blood

and the limbs by the communication of the heat, the blood cooled by warming the limbs being in turn warmed by the heart." (Davis, 1973)

The exposition of this idea that blood flowed around in a circle from arteries to veins and through the right heart to the lungs and back to the body via the left heart, fully described in Harvey's monumental "*Exercitatio anatomica de motu cordis et sanguinis in animalibus*" of 1628, was no less revolutionary than the work of Vesalius or Copernicus (Harvey & Leake, 1970). Harvey's concept of the motion of the blood required that a large volume of blood pass through the heart, which he was able to prove by experiment, but in dispensing with the Galenic idea of fermentation within the heart there was no explanation for the motive force which kept the heart itself moving and thus kept the blood coursing about the body. Furthermore, no mechanism to account for transport of the blood from arteries to veins could be described; the existence of a tissue communication between arteries and veins had been postulated before Harvey, but such a communication could not be demonstrated with the simple microscopes available in the early seventeenth century. The issue of motive force was to prove to be a constant source of controversy during the seventeenth century (Davis, 1973). The development of the microscope advanced considerably however, and in 1660 Marcello Malpighi described the existence of capillaries and postulated correctly that these were the predicted connections between arteries and veins (Willius & Dry, 1948; Graubaud, 1964).

In the light of Harvey's model of the circulation, the later seventeenth century saw many changes in the description of the vasculature and in describing the role of the vasculature in disease. There was also an increasing interest in the correlation between

clinical symptoms found in patients and the results of post-mortem examination. Two figures of the middle of the seventeenth century were to make major advances in the understanding of cerebral blood flow and the relationship between that and apoplexy. The German physician Johann Jacob Wepfer established the causative relationship between cerebral haemorrhage and apoplexy in his "Observationes anatomicae ex cadaveribus eorum quos sustulit apoplexia" in 1658. He discussed the existence of an arterial circle at the base of the brain and its possible anastomotic function. This contribution was acknowledged by Thomas Willis who reiterated Wepfer's findings and illustrated the arterial circle in his "Cerebri Anatome" in 1664. Willis also recorded the clinical significance of the anastomotic function of the arterial circle by describing in his *London Practice of Physick* the case history of a patient with an occlusion of the carotid arteries who did not succumb to apoplexy during life:

"when his skull was opened, we beheld those things belonging to the head, and found the right carotid, rising within the skull plainly bony or rather stony, its cavity being almost wholly shut up; so that the influx of the blood being denied by this passage, it seemed wonderful, wherefore this sick person had not died before of an apoplexy" (Davis, 1973)

Willis reasoned that the remaining large vessels flowing towards the arterial circle were able, by way of their "mutual conjoinings", to "supply or fill the channels or passages of all the rest". Thus, "if by chance one or two be stopt, there might easily be found another passage instead of them: as for example, if the carotid of one side should be obstructed, then the vessels of the other side might provide for either province...further, if both the carotids should be stopt, the offices of each might be supplied through the vertebrales" (Davis, 1973).

The practice described by Willis of performing a post mortem examination on a patient whilst considering the premortem clinical symptoms and signs displayed by the patient was to become more common during the later seventeenth and early eighteenth centuries. The correlation between symptoms, signs and postmortem findings led to advances in the understanding of the relationship between disease and structural changes in the body, and reached its pinnacle in the "De Sedibus et causis morborum per anatomen indagatis libri quinque", of 1761, the collection of the work of John Baptist Morgagni, professor of anatomy at Padua since 1715.

Willis' description of the structure which now is named for him is further notable for the extraordinary clarity of the illustrations in *Cerebri Anatomi*, which were engraved by Willis's contemporary, the noted artist and architect Sir Christopher Wren. Willis's position as both an eminent society physician and a leading member of the 'Oxford Club', the informal intellectual circle which was to become institutionalised as the Royal Society, enabled him to enlist the aid of Wren and others such as Richard Lower (who demonstrated that blood is changed in the lungs as it passes through the pulmonary circulation, which he postulated occurred by the acquisition of some quality from the air) in his dissection of the brain and nerves and in his theoretical consideration of disease (Davis, 1973). The completeness of the anatomical investigation recorded in "Cerebri Anatomi" along with Willis's extensive recording of case notes and his contributions to the theory of medicine establish him as an important figure in the history of ideas about the cerebral vasculature.

By the end of the seventeenth century therefore the anatomy of the cerebral arteries was known, the concept of the circulation of the blood (by whatever mechanism, and for whatever function) was established and the anastomotic role of the arterial circle at the base of the brain had been postulated. As a result of post-mortem examination of the brains of patients who had died, apoplexy was regarded as occurring as a result of haemorrhage into the substance of the brain.

1.1.5 The eighteenth and nineteenth centuries

During the eighteenth century experimentation was applied to life sciences as it was to the physical sciences. The ability of the circulatory system to overcome obstruction was demonstrated by direct experiment. John Hunter ligated the carotid artery of a deer and observed that the growth of its antler on that side was only transiently inhibited; as collateral circulation developed, the antler regained its warmth and growth recommenced. Hunter's statement that blood "goes where it is needed", is a statement of the teleological physiology of his day (Owen, 1879). The lesson of this experiment, that surgical carotid ligation was possible and would not inevitably lead to the death of the patient, was learned by contemporary surgeons. Surgery to ligate the carotid in cases of trauma to the neck had been reported during the eighteenth century, but it was not until the early nineteenth century that elective surgery to the carotid was reported. Notable in this respect was Sir Astley Cooper of Guy's Hospital, who reported in 1806

a case of aneurysm of the carotid artery treated by ligation. This patient died some three weeks post-operatively; at post-mortem "the aneurysmal sac was found inflamed, and around the clot of blood which it contained, there was a considerable quantity of pus...the cause of her death then was the inflammation of the aneurysmal sac and the parts adjacent, by which the size of the tumour became increased so as to press on the pharynx...and ultimately to impede respiration. A similar event, however, may be in future prevented, by performing the operation when the tumour is small, and pressure has not been made by it upon important parts, or if it is of considerable size, as in this case, by opening the tumour and discharging the coagulum, as soon as inflammation appears" (Cooper, 1809). Thus the initial success of the procedure encouraged belief that the technique had merit, and in 1808 Cooper saw a similar patient with a left carotid aneurysm which he successfully ligated, and the patient survived (Cooper, 1809). In 1821 that patient died, and Cooper performed the post-mortem examination himself. He describes the cerebral vessels:

"The [left] middle cerebral artery [was] larger than that on the right side...accounted for by the increased size of the communicating branch, which, receiving its blood from the basillary, had become as large as an ordinary radial artery. The basillary...was evidently the channel which supplied the middle cerebral artery." Further, "From an inspection of the base of the brain after the vessels had been injected, it immediately struck the observer that the left side of the arterial circle of Willis was much more developed than the right, and that the left side of the brain received its full share of arterial blood" (Cooper, 1836).

Although surgery involving the carotid arteries became more widespread during the nineteenth century, ligation was the only procedure performed, and indications were limited to ligation for aneurysm and to arrest haemorrhage following trauma. The difficulty of such surgery for trauma is attested to by the account in 1845 by John Ellis of Grand Rapids, Michigan, of the case of a man who sustained a gunshot wound to his neck, tongue and jaw whilst out hunting, having been mistaken for a bear by his companion (Ellis, 1845). Seven days after the injury haemorrhage from the tongue wound could only be arrested by left carotid compression, and the left carotid was ligated. Four days later further haemorrhage required the ligation of the right carotid artery:

"an operation attended with a good deal of difficulty, owing to the swollen state of the parts, the necessity of keeping up pressure [on the artery], the bad position of the parts owing to the necessity of keeping the mouth in a certain position to prevent his being strangled by the blood, and the necessity of operating by candle light...The young man now enjoys comfortable health, and is attending to business" (Ellis, 1845).

The second half of the nineteenth century saw two major advances in medical technology which led to the explosion of surgery as a speciality and transformed the reputation of the profession. In 1846 an operation was performed under general anaesthesia for the first time (Jackson, 1992). Prior to this the technique of surgery had to take second place to speed, strength and courage in the surgeon, who was operating on a conscious patient with perhaps alcohol or an opiate as an analgaesic. Thus open surgery was undertaken rarely and then usually for life-threatening conditions. General anaesthesia allowed the development of surgical technique in which speed was not the

key attribute. The development of anaesthetics as a speciality in its own right paralleled the advances in physiology, pharmacology and technology which continue to this day. Listerian antisepsis was to have an equally profound effect on surgical practice (Fisher, 1977; Jackson, 1992). Influenced by the work of Louis Pasteur on germ theory in which Pasteur had shown that particles in the air were necessary for fermentation and putrefaction, Lister had learnt of the use of carbolic acid at a sewage plant in Carlisle to control the smell, and of the simultaneous fall in the number of cases of typhus in the city. He reasoned that carbolic acid was toxic to the infecting particles and that if these particles were responsible for surgical sepsis then perhaps carbolic acid would control it. The theoretical discussion over whether the infecting particles were themselves alive was of great concern to the scientists but Lister makes little comment about it; he was interested in results, and his results with a series of compound fractures treated with antiseptic dressing instead of amputation were excellent (Lister, 1867; Lister, 1867). However, his technique was not adopted universally; surgeons such as Spencer Wells claimed equally good results in terms of avoiding sepsis by scrupulous cleanliness and the washing of hands, instruments and patient with copious amounts of clean water (Fisher, 1977). The end result of the controversy was that the pragmatism of the surgical community won the day; whilst the antiseptic technique was eventually widely accepted as having a sound theoretical basis, its complicated and unpleasant application meant that it was not widely used, and the practice of aseptic technique - scrupulous cleanliness and sterility of instruments and dressings - became the accepted norm by the turn of the century.

1.1.6 The twentieth century and the development of elective carotid surgery

Carotid surgery at the beginning of the twentieth century was still essentially only performed for the indications described above, that is, ligation for aneurysm and operation following trauma. Stroke was widely thought to be an expression of cerebral haemorrhage, occurring as a result of pathology in the intracerebral vessels and thus not amenable to therapeutic intervention. In 1914 the American neurologist J. Ramsay Hunt called for a re-evaluation of the role of the carotid vessels in the aetiology of vascular lesions of the brain (Ramsay Hunt, 1914). He pointed out that in the examination of the peripheral vasculature the examination of the peripheral pulses was integral to the process of making a diagnosis. He extrapolated this to his experience of cerebrovascular disease, describing his observation that in examining a series of subjects the carotid pulses were usually equal on both sides, whereas "the only exceptions noted were in a small series of hemiplegic cases of vascular origin, in which a definite and distinct weakness of the carotid pulsation was noted on the side corresponding to the cerebral lesion". This turned attention from the intracranial vasculature to the extracranial cerebral vasculature, but progress in the investigation of this site as a possible origin of cerebral disease was hampered by the limited amount of information that could be gleaned by clinical examination.

Two further advances were to occur before the extracranial carotid arteries could be implicated in the aetiology of cerebral vascular disease. A method of imaging the cerebral vasculature was developed by Egaz Moniz of Lisbon and described in 1927

(Moniz *et al.* 1937). Cerebral angiography was initially used as a method of localising cerebral tumours, but he found that it revealed details of the extracranial carotid circulation as well. Following the use of plates to record the state of the neck vessels he reported that of 537 cerebral angiograms, four had occluded internal carotid arteries.

Meanwhile, the findings of Ramsay Hunt were reassessed by Miller Fisher, a neurologist at the Massachusetts General Hospital (Fisher & Adams, 1951). He examined at post-mortem the brains of 373 patients who had died with a diagnosis of cerebral vascular disease. He reported that haemorrhagic infarcts were present in only 20% of cases and concluded that the remainder were probably embolic in origin, citing atherosclerosis at the carotid bifurcation as a likely source of such emboli.

The early 1950's saw several almost simultaneous surgical assaults on the problem of cerebral ischaemic symptoms arising as a result of atheroma at the carotid bifurcation. In 1951 in Buenos Aires Carrea, Molins and Murphy operated on a man who had recently suffered from a right sided hemiparesis associated with aphasia (Carrea *et al.* 1955). He had been shown by angiography to have a stenosis of his left internal carotid artery, and they partially resected the diseased internal carotid and anastomosed the external carotid to the distal internal carotid artery, with a successful outcome. In 1953 De Bakey in Texas operated on a man who was complaining of intermittent attacks of right sided weakness with difficulty speaking. A clinical diagnosis of atherosclerosis at the carotid bifurcation was made and at operation internal carotid occlusion was confirmed. Endarterectomy of the common, internal and external carotids was performed. The patient did well and lived for a further nineteen years without cerebral symptoms. De Bakey subsequently reported the case with follow-up

(but unlike Cooper or Willis was unable to report his observations at post-mortem) (DeBakey, 1975). The following year Eastcott, Pickering and Rob described a similar case to that which De Bakey had seen, in a woman who was having repeated attacks of right sided weakness and loss of vision in the left eye (Eastcott *et al.* 1954). Pickering had pointed out in 1948 that these intermittent attacks of cerebral paralysis were found in patients with mitral stenosis and atrial fibrillation, when they could only be embolic (Pickering, 1948). When the diagnosis of carotid stenosis was confirmed pre-operatively by angiography they felt that the patient's symptoms were probably due to showers of emboli from the carotid plaque. Eastcott therefore performed a resection of the carotid bifurcation with reconstruction by end-to-end anastomosis of the common and internal carotid arteries, again with a successful outcome and resolution of the patient's symptoms.

This case report, of a patient with transient symptoms of cerebral ischaemia, diagnosed as having carotid bifurcation atherosclerosis and internal carotid artery stenosis with the diagnosis confirmed by angiography, and treated by reconstructive surgery to the internal carotid artery, is regarded as a landmark in the history of vascular surgery. Following this such surgery performed to relieve symptoms of transient cerebral ischaemia and prevent stroke became widespread, with endarterectomy to the internal carotid artery replacing carotid reconstruction as the commonly performed procedure. The controversies which ensued over the following decades centred mainly on the indications for its application; in symptomatic patients with severe internal carotid artery stenosis these controversies have to a certain extent been resolved by the findings of large randomised trials comparing surgery to medical treatment, but for large groups

of symptomless patients the indications for surgery remain unclear (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; European Carotid Surgery Trialists' Collaborative Group, 1991).

1.2 The clinical and diagnostic features of Stroke and Transient Ischaemic Attack

The generic term 'stroke' encompasses a heterogeneous group of disorders with a number of different aetiologies and different pathological and clinical manifestations. However, clinical diagnosis of stroke can be confidently made provided the following definition is adhered to:

A neurological deficit of sudden onset; with focal rather than the global neurological dysfunction; with symptoms lasting more than 24 hours or resulting in death before 24 hours; and in which, after adequate investigation, symptoms are presumed to be of a non-traumatic vascular origin (Bamford, 1992).

Whilst this definition includes subarachnoid haemorrhage it excludes subdural and extradural haematoma and transient ischaemic attacks. A transient ischaemic attack (TIA) is defined by Bamford as an acute episode of focal loss of cerebral or visual function lasting less than 24 hours (Bamford, 1992). Hankey goes further in his definition; 'an acute loss of focal cerebral or monocular function with symptoms lasting less than 24 hours and which after adequate investigation was presumed to be due to embolic or thrombotic vascular disease' (Hankey *et al.* 1991). Amaurosis fugax was 'acute total or partial loss of vision in one eye with symptomatic recovery within 24 hours [which] after adequate investigation was presumed to be due to embolic or thrombotic vascular disease. Emboli may have been seen and there should not be any retinal or ocular pathology to account for the symptoms'. Minor stroke is diagnosed by Hankey in 'patients with the clinical criteria of a stroke [see above] in whom symptoms lasted more than 24 hours and less than one week. Neurological signs of no functional significance (see above) were acceptable thereafter'. Major stroke is diagnosed in

'patients with the clinical criteria of a stroke in whom symptoms lasted more than one week or lead to an earlier death'.

The symptoms of a transient ischaemic attack are attributed to inadequacy of blood supply to the cerebral region supporting the area in which the patient exhibits the symptoms (Landi, 1992). It has been disputed whether the 24 hour time limit allowed for in the diagnosis of TIA should apply only to symptoms or to signs as well (Landi, 1992). It is now felt that the persistence of functionally unimportant signs such as an extensor plantar response is not sufficient to allow the diagnosis of a minor stroke rather than a TIA, and therefore that assessment of duration of symptoms after the event is sufficient to make the diagnosis of transient ischaemic attack. Hankey stresses that the persistence of neurological signs of no functional significance such as reflex asymmetry or plantar extensor response may be disregarded in the diagnosis of TIA, and that non-focal neurological symptoms such as faintness should be taken into account only if accompanied by focal signs (Hankey *et al.* 1991). The use of computerised tomography (CT) in the assessment of patients with TIA to identify areas of cerebral infarction has led to the suggestion that an anatomically compatible low density area on CT should lead to the reclassification of such a patient as having had a cerebral infarction with transient signs. The practical difficulties introduced by this policy include the fact that diagnosis of TIA would then depend on the availability of CT scans, and that brainstem events would be proportionately overdiagnosed compared to hemispheric events since brainstem infarcts are more difficult to detect on CT. Furthermore, since there seems to be little difference in prognosis of patients with

TIA and cerebral infarct with transient signs, reclassification is felt to be unnecessary (Dennis *et al.* 1990).

Diagnosis of TIA can thus be much more difficult than the diagnosis of stroke; whereas with stroke the application of the above clinical criteria can lead to a false positive rate of diagnosis of less than 5% in a co-operative patient (Bamford, 1992), the variability in diagnosis of TIA can be very high. One study reports a kappa index (of agreement between two observers) of only 0.65, indicating that up to 35% of agreement between two clinicians in the diagnosis of TIA may be due to chance (Kraaijeveld *et al.* 1984); another reports that of 1307 patients referred to a department of neurology with suspected TIA the final diagnosis in 31% was 'possible TIA' (Calanchini *et al.* 1977). This diagnostic conundrum is worth exploring because numerous studies cite TIA as a risk factor for stroke (Dennis *et al.* 1990; Hankey *et al.* 1991), and in patients with carotid stenosis the only firm indicators for carotid surgery in order to reduce the risk of stroke come from studies which used TIA as a diagnostic criterion (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; European Carotid Surgery Trialists' Collaborative Group, 1991).

The criteria for the diagnosis of TIA are therefore based mainly on the symptoms described by the patient. Since the attacks are rarely witnessed and there are no objective tests which can confirm the diagnosis, the patient's history is critical. The differentiation between focal and non-focal symptoms is of first importance. Non-focal symptoms are not accepted as evidence of TIA; thus loss of consciousness, dizziness,

generalised weakness or incontinence should not be interpreted as TIA since they more often result from diffuse cerebral ischaemia or from non-vascular causes. Similarly, isolated symptoms such as vertigo, diplopia, tinnitus and sensory symptoms confined to one part of the face are unlikely to indicate TIA. However, the patient with transient monocular blindness carries the same stroke risk as those with a clearly defined cerebral TIA and therefore should be included under the same diagnostic heading.

The main differential diagnoses of TIA are migraine and focal epilepsy, but may include many other conditions; structural brain lesions such as tumours, chronic subdural haematoma and vascular malformations may be considered, as well as non-vascular causes such as hypoglycaemia, Meniere's disease and disseminated sclerosis. In patients with transient monocular symptoms the differential diagnosis includes giant cell arteritis, malignant hypertension, glaucoma and papilloedema. The differentiation between focal epilepsy and TIA is usually easily made. Whereas TIA usually manifests symptoms of decreased or absent function, focal seizures usually cause 'positive' symptoms such as paraesthesia or jerking movements which show a characteristic progression, beginning distally and spreading up the limb or half of the body. However, focal motor seizures may occasionally be inhibitory and associated with aphasia (Landi, 1992) which can lead to confusion with TIA. Migraine similarly usually exhibits 'positive' symptoms, often with visual involvement (for example scintillating scotoma). Onset of symptoms in migraine is usually of slower onset than in TIA, with a more pronounced progression. However, the symptom of headache is not invariably associated with either condition and is not therefore diagnostic of either.

1.3 The epidemiology of stroke and transient ischaemic attack

The burden of stroke in western industrialised populations is huge. Stroke is the third leading cause of death, causing one in ten of all deaths, and for each fatal stroke there will be one further non-fatal but severely disabling event and two or three less disabling ones (Bonita, 1992; Bamford *et al.* 1988; Malmgren *et al.* 1989). The costs of this both to the individual and to society lie in several areas; in expensive hospital care in the acute phase, in the rehabilitation costs in those patients who go on to become independent again and in the chronic care costs in those patients who continue to be disabled. Less well documented but no less important is the loss to society of wealth creators, when men and women of working age are affected either directly by a stroke or when their working lives are curtailed in order to care for another affected individual. Reduction in the morbidity and mortality associated with stroke is of prime importance in the planning of health care provision and in medical research.

Community based studies of stroke and transient ischaemic attack have given an impression of the incidence and prevalence of these conditions, as well as giving an indication of their natural history. In the assessment of the incidence of stroke most studies use first-ever stroke (that is, the incidence of stroke in those people with no previous history of stroke) as a measure. Age standardised rates are often calculated as they offer a means of comparing results between studies and between countries (Bonita, 1992). The Oxfordshire Community Stroke Project and the Auckland Stroke Study give similar crude (non age-adjusted) incidence rates of about 2 strokes per 1000

population per year, with a 26-28% higher risk in males than in females. Total rates of incidence of first-ever stroke were shown in both studies to rise steeply with age, from less than 0.1 per 1000 population at age 25 - 34 years to 6 per 1000 in the 65 - 74 year old age group and 20 - 30 per 1000 in the over 85 year olds (Bonita *et al.* 1984; Bamford *et al.* 1988). These figures are similar to those found in the Rochester (Matsumoto *et al.* 1973), Tilburg (Herman *et al.* 1982), and Shibata (Tanaka *et al.* 1981) studies.

The latter figures (of stroke rate in the elderly) are important since it is this age group in which the highest incidence of stroke morbidity and mortality occurs. It is thought that it is this group which should be considered when making projections about the way that future demographic changes in the age structure of the population will affect the overall stroke rate. It is projected that the proportion of elderly people in the population will rise in the next forty years (Office of Population Censuses and Surveys, 1985). It has been assumed that this increase in the number of the elderly will inevitably lead to a parallel increase in the number of long-term disabled people who are survivors of a stroke; this assumption has been tested by Malmgren by projection of the incidence of first-ever stroke according to age strata for the expected population demographics until 2023 (Malmgren *et al.* 1989). The number of first-time strokes is projected to rise by about 30% and the number of deaths within six months of a first-time stroke is projected to rise by about 40%; however, the number of people who are severely handicapped by stroke is expected to rise by only 8% [1064]. This apparent inequality arises because of the nature of the population which the condition affects and because of the commonly fatal outcome of stroke. A proportion of those affected by

first-time stroke are already disabled or dependent, and some of those will die rather than continue to be handicapped and thus the overall numbers of stroke-affected individuals may not increase by the expected amount. Furthermore, despite an expected 99% increase in the proportion of over 85 year-olds in the population, the fact that these numbers are still relatively small reduces the anticipated absolute increase in numbers of individuals experiencing a first-time stroke.

Unfortunately however, information about incidence rates does not give direct information about the prevalence of stroke, meaning the number of people in the population who have already had a stroke; neither does it give information about the numbers of people with recurrent strokes and their outcome. Prevalence of stroke - the number of stroke-affected individuals in a population at any one time - is the best measure of the total burden which the condition imposes on society. Whilst figures can be calculated from combining incidence rates and case fatality rates (case fatality being a variable dependent upon the type of pathology present; the 30 day case fatality rate varies from 10% for cerebral infarction to 45% for subarachnoid haemorrhage and 52% for primary intracerebral haemorrhage (Bamford *et al.* 1990), and the overall case fatality rate is 41% at one year (Bonita *et al.* 1984)), figures for prevalence of stroke disability from population studies are rare. One study estimates crude prevalence rates of approximately 4 per 1000 of the population over the age of 25 for people who have had a stroke within the last two years and 8 per 1000 for people who have ever had a stroke (Christie, 1981).

The epidemiology of transient ischaemic attack and the relationship between stroke and transient ischaemic attack has been established by a number of studies (Dennis *et al.*1989; Hankey *et al.*1991; Dennis *et al.*1990). Transient ischaemic attack occurs with an overall crude incidence rate of 0.3 - 0.4 per 1000, and shows a marked increase with age (Dennis *et al.*1989). Whilst the occurrence of a transient ischaemic attack confers only a slightly increased overall risk of death, in those examined in a community-based project there was a thirteen-fold excess risk of stroke in the first year after a transient ischaemic attack (an actuarial risk of 11.6%) and a seven-fold excess risk of stroke over the first seven years after the event (Dennis *et al.*1990). In this study the actuarial risk of stroke in the first five years after the event was 5.9%, and the risk of stroke, death or myocardial infarction over five years was 8.4%. In a population examined as a result of referral to hospital (Hankey *et al.*1991) these risks were found to be slightly reduced and the improved prognosis has been ascribed to the impact of referral bias; the hospital-referred patients were younger and assessed later after their transient ischaemic attack than the community based patients. However, two things are clear; firstly, the occurrence of a transient ischaemic attack confers a high risk of stroke which is at its greatest in the first year after the event, but secondly even if all those who had a transient ischaemic attack were to go on to have a stroke (and they do not) there are still a large number of people who experience a first-time stroke without having had a preceding transient ischaemic event. This variability in the presentation of the stroke patient or the 'at risk' patient leads to a number of different strategies to prevent stroke.

Separate approaches to the primary prevention and secondary prevention of stroke have been adopted (Marmot & Poulter, 1992; Warlow, 1992).

Primary prevention of stroke can be divided into two main types, that of 'mass strategy' and that of 'high-risk strategy'. The 'high-risk strategy' in primary prevention aims to identify risk factors in individuals which predispose to increased risk of stroke in that individual, and to perform appropriate intervention in that person to modify their risk. This is in contrast to the 'mass strategy' which seeks to identify risk factors in the population as a whole which increase the overall incidence of stroke in the population, and by mass health education to reduce population risk. The two strategies tend to merge into one as mass health screening and education singles out individuals who smoke or have hypertension or hyperlipidaemia for special attention or treatment (Marmot & Poulter, 1992). Secondary prevention - that is, reducing the continuing risk in a individual after a stroke or a transient ischaemic attack - can be seen as an extension of the 'high-risk strategy' of primary prevention. While these individuals are known to be at a markedly increased risk of stroke, the interventions available for the treatment of the post-stroke patient which are different to those available for pre-stroke risk modification are limited, and furthermore it is merely a matter of semantics whether to view the occurrence of a transient ischaemic attack as a neurological event per se or as merely a marker for stroke risk (Dennis *et al.* 1989).

The relationship between carotid disease and stroke is not a simple one. 55% of patients with carotid territory stroke and 64% of patients with transient ischaemic attack have no carotid artery disease and in the majority of these cases the aetiology of their neurological symptoms remains unexplained (Zhu & Norris, 1990). In the presence of an asymptomatic carotid bruit the incidence of severe carotid stenosis detectable by ultrasound is 17%; however, the overall incidence of stenosing carotid

artery disease in the asymptomatic elderly population is lower at 5% and that of severe carotid stenosis is about 1% (Zhu & Norris, 1990; Colgan *et al.*1988; Hennerici *et al.*1981). (It should be noted that these studies used ultrasound techniques to assess carotid stenosis in their patients and therefore will not have accurately detected atheroma producing less than 35% stenosis of the carotid vessels, and will classify these lesions as non-stenosing. This degree of stenosis has however been shown to carry a low risk of stroke (Chambers & Norris, 1986; Norris *et al.*1991), and the loss of this group from the analysis is unlikely to alter the conclusion that the overall incidence of carotid disease which may be responsible for stroke is low). The neurological prognosis of patients with carotid atherosclerosis depends on the degree of stenosis caused by the carotid disease and on whether there are any neurological symptoms referable to the carotid disease. There is however a significant contribution to the overall prognosis of this group of patients made by the risk of cardiac disease; Norris (Norris, 1993; Norris *et al.*1991) prospectively assessed the vascular risks of asymptomatic carotid stenosis and found that with asymptomatic carotid stenosis of <75% the stroke rate was 1.3% annually whilst the combined risk of cardiac event (new onset angina, myocardial infarction or sudden death from proven or presumed cardiac causes) was 9.9%. In patients with carotid stenosis of >75%, the annual rate of ipsilateral stroke was 2.5% with a further 7% experiencing transient ischaemic attack, with a similarly high risk of cardiac event. However, in patients with severe carotid stenosis (>70%) which is producing symptoms the risk of major or fatal ipsilateral stroke is high; estimates vary from a two-year risk of 13% (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991) to a three-year risk of 11% (European Carotid Surgery Trialists' Collaborative Group, 1991), risks which can

be substantially reduced by carotid endarterectomy (as described in the following section).

On the basis of the above figures, the role of carotid surgery in the prevention of stroke thus falls into the category of 'high-risk strategy' for reducing stroke rate, since it is applied to individuals who have been found to be at personally increased risk of stroke and death as a result of their carotid artery disease. Since carotid endarterectomy is at present recommended for people who have symptomatic carotid disease it is strictly speaking a manifestation of secondary prevention; however, the proviso mentioned above about the classification of transient ischaemic attack remains.



1.4 The role of surgery in the management of carotid disease.

Carotid endarterectomy is performed to remove atheroma from the carotid sinus, the carotid bifurcation and the first part of the internal carotid artery to reduce stenosis and remove intimal irregularity at these sites. The rationale for the procedure is that it is believed that the atheroma has a detrimental effect on the cerebral circulation in two ways; the atheroma is thought to be an actual or potential source of emboli to the cerebral circulation in the carotid territory, and the haemodynamic effect of stenosis of the carotid vessels caused by atherosclerosis may reduce the circulation of blood to the brain. Furthermore, following progression of the atheroma or haemorrhage into the substance of the plaque a resultant occlusion of the internal carotid artery may similarly reduce blood supply to the brain. Each of these detrimental actions may result in transient ischaemic attacks, stroke or death of the patient, and to remove their source reduces the likelihood of these events occurring. However, carotid endarterectomy itself is not without risk; a small proportion of patients who undergo the procedure will have a stroke or die; that is, they will suffer the very complications which the procedure is performed to prevent (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; European Carotid Surgery Trialists' Collaborative Group, 1991). Furthermore, there is a risk associated with the diagnostic procedure of angiography, used to delineate the existence and extent of the carotid disease (Burnand, 1992).

Following the introduction of carotid endarterectomy in the early 1950's, its use as prophylaxis against stroke became widespread, especially in the United States, without strong evidence of the efficacy of the procedure. As a consequence, concern was raised that carotid endarterectomy, with its attendant risks, was being applied indiscriminately to patients in whom it had not been shown to confer a benefit, and small trials of the effectiveness of the procedure compared to best medical treatment had failed to indicate whether patients with carotid disease did better or worse with surgery. It was seen that the procedure had to be shown to confer benefit; it had to be shown that a patient with carotid disease undergoing surgery would have a lower risk of stroke or death than the patient could already expect from the disease itself.

Two major trials (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; European Carotid Surgery Trialists' Collaborative Group, 1991) have now reported their findings in respect of the effectiveness of surgery in the prevention of stroke and death in patients with extracranial carotid disease. The first to report was the MRC European Carotid Surgery Trial, which reported interim results for symptomatic patients with both severe (70 - 99%) and mild (0 - 29%) carotid stenosis, and the second was the North American Symptomatic Carotid Endarterectomy Trial, which reported results based on a stratification of symptomatic patients into moderate (30 - 69%) and severe (70 - 99%) stenosis. Both unequivocally show the benefit of surgery in patients who have had symptoms of TIA or minor stroke referable to a carotid stenosis of greater than 70%.

The European Carotid Surgery Trial was a multicentre randomised trial of carotid endarterectomy for patients who, after a carotid territory non-disabling ischaemic stroke, transient ischaemic attack or retinal infarct, were found to have a stenotic lesion in the ipsilateral carotid artery. Control groups and surgically treated groups both received appropriate medical treatment, comprising aspirin, treatment of hypertension and advice to give up smoking. For the patients with moderate lesions (30 - 69% stenosis) the balance of surgical risk and eventual benefit was not resolved, and for this group the trial continues to recruit. However, the trial reported its results for groups of patients with mild (0 - 29%) stenosis and severe (70 - 99%) stenosis. In the former group the three-year risk of stroke, even in the absence of surgery, is low and therefore any benefit of surgery is outweighed by its early risks. Surgery can therefore not be recommended as a reliable prophylaxis against stroke in this group of patients. In the latter group, with severe symptomatic stenosis, the early risks of surgery were significantly outweighed by the later benefits; although the rate of disabling stroke or death within 30 days of surgery was 3.7% in the operated group, by three years the overall rate of disabling stroke or death was 6% in the operated group and 11% in the control group. The total risk of surgical death, surgical stroke, ipsilateral ischaemic stroke or any other stroke at three years was 12.3% in the operated group and 21.9% in the control group, a highly significant difference.

The North American Symptomatic Carotid Endarterectomy Trial reported shortly after the MRC Trial, and its findings were remarkably similar. It too was a randomised multicentre trial of carotid surgery in patients with carotid stenosis of either moderate (30 - 69%) or severe (70 - 99%) degree, and who had had a hemispheric or retinal

transient ischaemic attack or non-disabling stroke within the 120 days before entry to the trial. Both control and surgically treated groups again received optimum medical care. Whilst study of patients with moderate stenosis continues, the randomisation of patients with severe stenosis was stopped after interim analysis revealed that had surgery conferred significant benefit to this group of patients. After two years of follow up this study showed a cumulative risk of any ipsilateral stroke which was 9% in the surgically treated group and 26% in the control group, whilst the risk of a major or fatal ipsilateral stroke was 2.5% in the surgical group and 13.1% in the control group. Thus in this study surgery resulted in an absolute reduction of 17% in the risk of stroke in patients with severe symptomatic carotid stenosis. The qualitative conclusions which can be drawn from both of these trials are twofold. Firstly, surgery carries definite risk; in both trials the serious morbidity and mortality of carotid endarterectomy was around 3%. Secondly however these trials show that the consequence of successful surgery in patients with severe symptomatic stenosis is that the majority of the excess risk of ipsilateral ischaemic stroke and death is avoided. The further conclusion to be drawn is that the lower the institutional surgical risk the greater the potential benefit to the set of patients operated on in that institution.

The strict stratification criteria applied to the patients entered into these trials do not allow the findings to be generalised to groups of patients not included in the trials. Thus the case for offering carotid surgery to patients with moderate disease, even if symptomatic, or to patients with severe disease which is symptomless, is not made. The role of symptomless carotid disease in the aetiology of stroke and the possible application of carotid surgery in the prophylaxis of stroke in these patients has been

addressed by a number of trials (The Asymptomatic Carotid Atherosclerosis Study Group, 1989; Hobson *et al.* 1993), the largest of which has yet to report (The Asymptomatic Carotid Atherosclerosis Study Group, 1989). The findings of the Veterans Affairs Study of the efficacy of carotid endarterectomy for asymptomatic carotid stenosis are interesting. In this study a group of 444 men with symptomless carotid stenosis of greater than 50% shown on angiography were randomised to carotid surgery plus best medical treatment or to best medical treatment alone. The rate of ipsilateral neurological event was 20.6% in the medical group and was reduced to 8.0% in the surgically treated group. However, the breakdown of these figures is important. Whilst the incidence of transient ischaemic attack and amaurosis fugax was reduced in the surgical group, there was found to be no difference in the incidence of stroke or death between the two groups. This differentiation is important; the inference is that in patients with carotid disease but without symptoms referable to that carotid circulation, surgery will not reduce the incidence of stroke or the overall death rate, but will reduce the incidence of transient neurological events. However, the aim of carotid surgery in these patients is to reduce the incidence of fatal or disabling strokes; once a patient experiences a transient neurological event they are no longer symptomless and may therefore fall under the indications for surgery to symptomatic disease. The implication of the findings of this trial is that to operate on symptomless carotid disease is to perform a procedure in order to reduce the incidence of an indication for surgery occurring.

It is clear then that if further groups of patients are to benefit from carotid endarterectomy it will be necessary to identify those who have a higher risk of stroke

and death from their carotid disease than that which is associated with the procedure of carotid endarterectomy. Symptomless disease per se does not appear to confer such a risk, but large clinical trials continue to address that issue (The Asymptomatic Carotid Atherosclerosis Study Group, 1989). However, there may be symptomless patients with severe bilateral carotid disease, or with a carotid occlusion contralateral to a severe stenosis, in whom a higher risk of stroke referable to their carotid disease exists.

If it were possible to identify such a group who were at higher risk of stroke from asymptomatic carotid disease, their risk may be greater than that associated with the procedure of carotid endarterectomy, and this group may then expect to benefit from surgery. In the absence of clinical or anatomical information to stratify patients physiological parameters have been sought, and studies (Kleiser & Widder, 1992; Kleiser *et al.* 1991) have shown that the presence of a reduced cerebral vascular reserve in patients with carotid disease is an indicator of poor prognosis.

1.5 Cerebral vascular anatomy & physiology & the effects of carotid disease on cerebral blood flow.

1.5.1 The anatomy of the cerebral vasculature

In most mammals, including humans, the brain is supplied with blood from the two carotid arterial systems and from the basilar arterial system (Harper, 1990). The basilar artery is formed on the clivus from the junction of the two vertebral arteries which ascend alongside the cervical vertebrae (Romanes, 1986). In primates, including man, the internal carotid arteries and the basilar artery supply blood almost exclusively to the brain and surrounding tissues; the extracranial tissues of the scalp and face are supplied by the external carotid arteries. Uniting the carotid and basilar vessels at the base of the brain through a series of communicating vessels is the arterial circle of Willis. In the normal circulation however, there is little cross-flow either from side to side between carotid circulations or from anterior to posterior between the basilar and carotid circulations (Ringelstein EB *et al.* 1990). In species with this anatomical arrangement measurement of the blood flow in the internal carotid artery corresponds closely to hemispheric blood flow. In some other animals there is a different anatomical arrangement; for example in the cat the internal carotid artery is rarely patent beyond the carotid sinus and the carotid region blood supply to the brain is derived from an extensive arterial anastomosis with the external carotid artery known as the rete mirabile (Harper, 1990). This arrangement is also found in the dog and the rabbit (hence the assertion in modern times that early anatomical texts such as those of Galen

which showed the human cerebral vasculature as containing a rete mirabile were probably done from animal dissection - see section 1.5.1). This becomes important when considering the experimental preparation of animal models of cerebral blood flow; if the experiment requires the measurement of blood which flows exclusively through brain tissue, this may not be possible by examining large vessel flow in animals with a rete mirabile (Harper, 1990).

In humans then cerebral blood flow is almost exclusively from the internal carotid and basilar arteries. The basilar artery supplies blood to the brainstem, cerebellum and the occipital lobes and inferior parts of the temporal lobes of the cerebrum, whilst the carotid supply is to the bulk of the cerebrum, from the frontal lobes to the upper parts of the temporal lobes of the cerebral hemispheres. The middle cerebral artery is the larger of the two terminal branches of the internal carotid artery, the other being the anterior cerebral artery. The bifurcation occurs in a shallow pit, the valleculla, immediately inferior to the anterior perforated substance, lateral to the optic chiasma and tract and close to the medial end of the lateral sulcus. At this point the internal carotid artery gives off two other branches: The posterior communicating artery passes posteriorly, joining the posterior cerebral artery and forming part of the arterial Circle of Willis. It is normally a small vessel carrying little blood flow, but may enlarge to form a major conduit between the anterior and posterior cerebral circulations. The other branch of the internal carotid artery is the anterior choroidal artery which passes posterolaterally to supply the choroid plexus of the inferior horn of the lateral ventricle in the temporal lobe. The anterior cerebral artery runs anteromedially towards the longitudinal fissure and anterosuperiorly to the optic chiasm it is joined by the anterior

communicating artery which provides anastomosis between left and right carotid circulations and completes the arterial Circle of Willis. The middle cerebral artery itself runs from medial to lateral in the lateral sulcus between the temporal lobe and the frontal and parietal lobes, giving branches supplying much of these regions (Romanes, 1986). It is in this region that it is possible to insonate the middle cerebral artery using a transcranial Doppler ultrasound technique (see section 3.3).

1.5.2 The physiological control of normal cerebral blood flow, and the concept of flow reserve

Until the 1950s it was widely thought that the blood flow through the brain was dependent entirely upon the perfusion pressure, and that changes in blood flow would passively follow changes in mean arterial pressure (Roy & Sherrington, 1890; Sagawa & Guyton, 1961), although the existence of a regulatory mechanism had been considered as early as 1938 (Fog, 1938). Harper showed in 1966 that in experimental preparations examining cerebral blood flow it was critical to control for carbon dioxide concentration, and that if this was done a marked vascular response to changes in perfusion pressure could be demonstrated which tended to stabilise cerebral blood flow (Harper, 1966). This vascular response was known as 'autoregulation', and was shown to be mediated by the changing diameter of cerebral resistance vessels (Kontos *et al.* 1978).

It is now recognised that under normal circumstances the blood flow through the brain is controlled by homeostatic mechanisms within very fine tolerances (Harper, 1990; Heistad & Kontos, 1983). Since there are effectively no stores of nutrition in the brain itself and the neurones in the central nervous system are exquisitely sensitive to hypoxia, the survival of the brain depends on the continuous adequate delivery of oxygen and nutrients. Failure of the cerebral circulation will result in irreversible damage to nerve cells within five minutes (Harper, 1990). It appears therefore that the homeostatic mechanisms involved in the control of cerebral blood flow have evolved in

part to protect the brain from the potentially deleterious effects of changes in its blood supply. Furthermore, blood flow is finely adjusted locally to the fluctuating metabolic needs of the tissues (Tyrrell, 1990). Thus the physiological control of the cerebral circulation appears to have two components; autoregulation, or the response to changes in perfusion pressure, and chemical regulation, the response to alterations in the metabolic environment (Harper, 1990; Heistad & Kontos, 1983).

Heistad & Kontos have defined autoregulation as 'the occurrence of vasodilatation as cerebral perfusion pressure decreases and the occurrence of vasoconstriction as cerebral perfusion pressure increases' (Heistad & Kontos, 1983). The overall effect of this phenomenon is that within fairly wide limits of mean systemic arterial blood pressure cerebral blood flow remains relatively constant. This is achieved by the alteration of the cerebral vascular resistance to blood flow, by dilatation and constriction of the resistance arterioles. Thus when perfusion pressure drops, arterioles dilate reducing vascular resistance and maintaining blood flow, and conversely when perfusion pressure increases the arterioles constrict, increasing vascular resistance and again maintaining relatively constant cerebral blood flow.

Two hypotheses have been proposed to explain the process of cerebral vascular autoregulation; a myogenic mechanism and a metabolic mechanism (Harper, 1966; Harper, 1990; Heistad & Kontos, 1983). A third hypothesis, that of a neurogenic mechanism (that is, that autoregulation may be under sympathetic or parasympathetic control), has generally been discounted since it has been shown that autoregulation is preserved (in a modified fashion, but not abolished) following chemical blockade or

anatomical division of the autonomic nervous system (Harper, 1990; Edvinsson, 1990; Faraci *et al.* 1989).

The myogenic hypothesis states that autoregulation of blood flow through cerebral vessels results from an intrinsic property of vascular smooth muscle to contract in response to a rise in transmural pressure (known as the Bayliss effect (Bayliss, 1902)) and to relax in response to a fall in transmural pressure. Thus an increase in perfusion pressure results in an increase in vascular transmural pressure and a constriction of vascular smooth muscle, with an increase in vascular resistance and a reduction in blood flow (Harper, 1990; Heistad & Kontos, 1983).

The metabolic hypothesis suggests that vasoconstriction and vasodilatation are mediated by changes in the local concentration of vasoactive metabolites. Thus a reduction in perfusion pressure causes a transient reduction in flow. This causes a build-up of metabolites which results in vasodilatation and increased flow. Similarly, an increase in perfusion pressure causes a transient increase in flow, washing out metabolites and causing vasoconstriction, again restoring flow (Harper, 1990; Heistad & Kontos, 1983).

More recently the role of possible chemical mediators and the role of the vascular endothelium in autoregulation have been examined (Florence & Seylaz, 1992; Faraci *et al.* 1989). Whilst there does not yet appear to be a consensus on the importance of an intact endothelium to autoregulation (Faraci *et al.* 1989; Katusic *et al.* 1987; Harder, 1987), proposed mediators of the vasodilatory response to a drop in perfusion pressure

include adenosine and the hydrogen ion (Harper, 1990). In an experimental setting it has been shown that vasoconstriction may be mediated by an intrinsic myogenic response which may be dependent on extracellular calcium concentration (Harper, 1990; Halpern & Osol, 1985; Faraci *et al.* 1989).

In the normal resting cerebral circulation therefore, blood flow is not perfusion dependent. Flow is controlled by the resistance of the cerebral vasculature which is above its minimum possible value; the resting tone in the resistance vessels maintains blood flow at a lower level per unit of perfusion pressure than it would be if no resting tone existed. The difference between the normal resting resistance and the lowest possible resistance in the cerebral circulation is known as the autoregulatory reserve. Alternatively, this concept can be described in terms of the difference between the normal flow and the greatest possible flow for a given perfusion pressure, which is known as the cerebral flow reserve.

The concept of reserve as a measure of autoregulatory capacity is one which has been applied to both cerebral and coronary circulations (Collins, 1993; Holdright *et al.* 1993).

Whereas in the cerebral circulation (where autoregulation mainly acts to maintain constant flow in the face of changes in perfusion pressure) the use of autoregulation reserve is intuitively more appropriate, in describing the coronary circulation (where autoregulation acts to increase or decrease flow given a constant perfusion pressure) the use of flow reserve seems more useful. Both however are describing a similar phenomenon, which is the change in resistance of a vascular bed to alter the relationship between the perfusion pressure across it and the flow through it. In both

cases again, the rationale behind the desire to investigate the effectiveness of autoregulation is the same. It is thought that the presence of a normal autoregulatory reserve (or flow reserve) implies that there is a normal resting tone in the resistance vessels, and that this exists as a consequence of the presence of an adequate blood supply (perfusion pressure) to the region. By the same token, abnormal autoregulatory reserve indicates that resting tone may be absent, either because of a locally reduced perfusion pressure or because there is an abnormality in the underlying mechanism. For example, in the case of the coronary circulation, abnormalities in autoregulation have been demonstrated in the absence of significant coronary stenosis (in patients with 'syndrome X', who have chest pain and a positive exercise test but angiographically normal coronary arteries (Holdright *et al.* 1993)). Direct investigation of autoregulation in the cerebral circulation would allow assessment of the accuracy of other indirect techniques and may reveal the presence of similar abnormalities in the mechanisms of local autoregulation.

1.5.3 The effects of carotid disease on cerebral blood flow

In the normal cerebral vasculature, blood supply to each hemisphere is mainly from the ipsilateral internal carotid artery (Kelley *et al.* 1990). Should one of these arteries become narrowed or occluded by atherosclerosis then the blood flow to the ipsilateral hemisphere has to be supplied via the arterial circle of Willis from the vertebrobasilar system or from the contralateral carotid system, or via other collateral vessels from the external carotid system such as the ophthalmic artery or leptomeningeal vessels (Powers, 1991; Powers *et al.* 1987). The effect of carotid disease on the cerebral circulation therefore depends not only upon the extent of the carotid disease but also upon the extent of collateralisation of blood flow. Thus a severe unilateral internal carotid artery stenosis in the absence of adequate collateral vessels may severely limit the blood flow into the ipsilateral cerebral hemisphere, whereas even severe bilateral disease in the presence of good collateral flow may not have an important effect on the cerebral blood flow. It is clearly of interest to discover if any carotid disease present in a subject affects the haemodynamic status of the brain (that is, whether or not blood flow to the brain is compromised by the presence of carotid disease). Because of the possible existence of collateral blood flow however, the occlusion or degree of stenosis of a carotid artery may not necessarily be the limiting factor in the delivery of blood to its ipsilateral hemisphere. It therefore becomes necessary to find a measure of the haemodynamic status of the brain (i.e. the adequacy or otherwise of blood flow to the brain) other than the simple assessment of the extent of the carotid disease present. It is now felt that measuring the amount of cerebral vascular reserve (that is, the amount of

potential vasodilatation left in the cerebral vessels) is a good measure of the adequacy of overall cerebral perfusion (Powers, 1991; Frackowiak, 1985). The reasoning behind this is clearer when positron emission tomography is used to look at the cerebral circulation both under normal conditions and under conditions of reduced perfusion (Tyrrell, 1990; Frackowiak, 1985).

Using positron emission tomography, measurements can be made of regional cerebral blood flow, cerebral blood volume and the amount of oxygen extracted from the blood passing through the brain (known as the oxygen extraction fraction) using ^{15}O isotopes. These measurements show that under normal conditions there is a close match maintained between the local metabolic rate of the brain tissues and regional blood flow. When autoregulation functions under normal perfusion pressure there is a correlation between regional cerebral blood flow and regional cerebral blood volume, and the ratio of volume to flow remains constant (Powers, 1991; Frackowiak, 1985). Furthermore, under these conditions of normal circulation the amount of oxygen extracted from the blood passing through the brain (the oxygen extraction fraction) remains relatively constant. When there is a fall in cerebral perfusion pressure, the cerebral arterioles dilate, reducing the vascular resistance of the cerebral circulation and thus maintaining flow. Under these circumstances the cerebral blood volume and the cerebral volume-flow ratio increase. The regional cerebral oxygen extraction fraction however remains unchanged, and cerebral metabolism is not affected. Should cerebral perfusion pressure continue to fall the capacity of the cerebral resistance vessels to dilate and reduce the cerebral vascular resistance reaches its limit. Any further falls in perfusion pressure once this limit of vasodilatation has been reached will result in a

drop in cerebral blood flow. The increase in cerebral blood volume-flow ratio at this point levels out and the supply of oxygen to the brain tissues is maintained by an increase in the oxygen extraction fraction (that is, more oxygen is extracted from the same amount of blood passing through the brain). Should brain perfusion pressure fall from this point then cerebral oxygen supply will be compromised. Cerebral metabolic rate of oxygen begins to fall and brain function deteriorates.

Measurement by positron emission tomography of the parameters described above can therefore give an accurate guide to the adequacy of brain perfusion. However, positron emission tomography is a technique requiring the use of extremely expensive equipment which is not widely available, and the injection of radioactive isotopes (albeit in minute quantities) which in the case of the oxygen isotopes have a short half-life and so need to be manufactured on site; furthermore, blood flow and volume measurements demand repeated arterial blood sampling which is usually performed through an indwelling arterial catheter. This technique is therefore not appropriate for use as a tool for the routine assessment or screening of large numbers of people. In order to use the haemodynamic status of the cerebral vasculature as a parameter which can be widely applied in a clinical setting it has been necessary to find another, more easily applied method of measuring it. It has been shown that measurement of cerebral vascular reactivity, that is the measurement of the capacity of the cerebral vasculature to vasodilate in response to a pharmacological stimulus such as acetazolamide or hypercapnia, gives results which correlate well with measurement of cerebral blood flow in the assessment of the adequacy of cerebral perfusion (Herold *et al.*1988; Brooks *et al.*1986; Newell *et al.*1994; Dahl *et al.*1994). Cerebral vascular reactivity

can be measured relatively easily in a number of ways (Markus & Harrison, 1992; Ringelstein EB *et al.* 1992; Pickard *et al.* 1990; Bishop *et al.* 1986), the least invasive of which uses transcranial Doppler ultrasound to assess changes in blood flow in the basal cerebral arteries. This standard technique is considered in more detail in section 3.3. However, both cerebral vascular reactivity to a pharmacological stimulus and positron emission tomography essentially make static observations of cerebral blood flow. Both techniques make assumptions about the relationship between the static experimental condition and the dynamic condition of the intact subject which have not been explored. These assumptions are discussed below.

It is of course necessary to consider the clinical situation as well as the purely physiological effects of carotid disease. In patients with carotid atherosclerosis there are two clinically important effects which carotid disease can have on the cerebral circulation. The first is as a real or potential source of emboli, and the second is as a source of haemodynamic disturbance. This haemodynamic disturbance has both local and distant effects. The local effect is one of disturbing the normal flow of blood around the carotid bifurcation, upsetting the flow separation which normally allows blood to enter the internal and external carotid arteries with minimal interference to laminar flow. As well as producing an occlusion or a stenosis which may reduce the amount of blood flowing into the distal circulation, turbulence and eddy flows are set up which alter the shear forces at the endothelium, potentiating platelet deposition and thrombus formation, which may in turn act as a source of emboli to the distal circulation. Thus the local haemodynamic effects of carotid disease are intimately associated with the embolic effects. The distant haemodynamic effect of carotid

disease depends not only upon the degree of internal carotid artery stenosis but also to a large extent on the patency of the arterial anastomoses of the circle of Willis. If the arterial circle is complete and contralateral perfusion is adequate then blood flow distal to a severe carotid stenosis or occlusion can be compensated for by flow across the communicating vessels. If however the arterial circle is incomplete, the vessels are inadequate in calibre or contralateral perfusion is poor (perhaps due to the presence of contralateral disease) then cerebral circulation ipsilateral to carotid disease can be substantially limited.

1.5.4 Assessment of cerebral vascular autoregulation and the effects of carotid disease on the cerebral circulation

As has been described above, the cerebral circulation compensates for reduced perfusion by dilatation of resistance vessels, until the autoregulatory reserve is reduced or exhausted. However, the presence of severe carotid disease alone is insufficient to produce such flow limitation to the cerebral circulation because of the compensating effect of flow across the circle of Willis. In order to assess the haemodynamic effect of carotid disease upon the cerebral circulation it is necessary either to image the circle of Willis to assess its patency or to measure the autoregulatory reserve of the cerebral vasculature. Imaging of the intracerebral vessels is at present only achievable with any degree of accuracy by performing a cerebral angiogram, a procedure which is invasive and not without risk (Burnand, 1992). Assessment of the extent of the vasodilatory reserve can however be non-invasively tested indirectly by measuring the cerebral vascular reactivity to vasodilator agents. This has been done by stressing the cerebral

circulation with a pharmacological vasodilator such as carbon dioxide and measuring the extent to which this non-physiological stimulus increases cerebral blood flow (Bishop *et al.*1986; Ringelstein EB *et al.*1992). However, the cerebral vascular reactivity to a pharmacological stimulus such as hypercapnia has not been shown to be the same phenomenon as cerebral vascular autoregulation. Autoregulation is essentially a fast-acting homeostatic response to perfusion pressure change, and animal and human studies have shown that the main autoregulatory response occurs within seconds (Aaslid, 1987; Aaslid *et al.*1989; Newell *et al.*1994). Cerebral vascular reactivity to pharmacological stimuli occurs over a period of minutes; it is not clear whether this slow response is because the stimulus is applied slowly or if there is a genuinely slow reaction time because of the actions of a mechanism different to that of autoregulation. Since it is difficult to apply the pharmacological stimulus step-wise over a shorter period, this is difficult to test.

In order to justify the continued use of cerebrovascular reactivity as an indirect measure of cerebral vascular autoregulation it is necessary to determine whether there is a relationship between cerebrovascular reactivity to pharmacological stimuli and cerebrovascular autoregulation to pressure change. This could be done by microvascular techniques to examine the mechanisms involved, or by measuring both phenomena in the intact subject and then comparing the effects of carotid disease on both measurements. Since the ultimate aim of the exercise in the assessment of cerebral vascular reserve is to uncover the effects of carotid disease in the intact subject, it is the measurement of cerebral vascular autoregulation in the intact subject, and the

relationship between cerebral vascular autoregulation and reactivity which is explored in the following experiments.

Part 2 Principles of transcranial Doppler ultrasonography and volume clamp plethysmography

Synopsis

2.1.1 - The measurement of cerebral blood flow

2.1.2 - Transcranial Doppler ultrasonography of blood flow in the middle cerebral artery

2.1.3 - Conclusion

2.2 - Volume clamp plethysmography in the non-invasive measurement of mean arterial blood pressure

2.2.1 - Introduction

2.2.2 - Aims

2.2.3 - Subjects and methods

2.2.4 - Results

2.2.5 - Discussion

Synopsis

The problems associated with the measurement of cerebral blood flow in man are discussed. The principles, advantages and limitations of transcranial Doppler ultrasonography are described. The principles of the volume clamp plethysmography method of non-invasive blood pressure measurement are described as is an experiment to determine the accuracy of the method.

2.1.1 The measurement of cerebral blood flow

The measurement of cerebral blood flow is a particularly difficult endeavour. Wiggers in 1905 wrote that "perhaps no other organ of the body is less adapted to an experimental study of its circulation than the brain" (Wiggers, 1905), and there are several factors which contribute to this difficulty. There is not a single inflow/outflow to the organ, so the use of arterial flowmeters or timed venous outflow is prone to error (Harper, 1990). In many experimental animals (see section 1.5.1 above) there is an extensive anastomosis between the extracranial and intracranial vasculature which makes it difficult to separate the blood flows to the two beds. This is important since it is known that the intracerebral and the extracerebral vasculature exhibit different responses to some vasoactive stimuli (Harper, 1990). The experiments described in this thesis are concerned with the measurement of changes in human cerebral blood flow which occur as a result of changes in local cerebral vascular resistance (see section 1.5).

There are a number of experimental methods available for the assessment of resting and changing cerebral blood flow and resistance. Direct measurement of the absolute diameter and change in diameter of cerebral vessels can obviously give a great deal of information about changes in the resistance properties of any one particular vascular bed. Direct observation of the surface vessels of the brain is possible in experimental preparations; these usually involve craniotomy and perfusion of the surface of the brain with vasoactive substances. However, control of absolute local tissue pressure and of the partial pressure of diffusible gases such as carbon dioxide is difficult in such

preparations, problems which can be overcome by the placement of a cranial window, bringing back to normal the tissue pressure and gas tension by re-establishing the integrity of the skull (Bevan & Hwa, 1985). It is clear however that while the use of craniotomy and cranial window techniques are useful in animal preparations they are generally inappropriate for use in the study of human cerebral vascular physiology.

Other techniques which have been employed to examine the mechanisms of autoregulation include the *in vitro* investigation of the responses of isolated cerebral vessels in an organ bath environment, and the use of radiolabelled microspheres. In the first of these, the effects on the isolated cerebral vessel of variables such as pH and carbon dioxide concentration, and the responses to vasoactive substances such as adenosine, calcium and potassium can be closely examined (Halpern & Osol, 1985). In the second, the amount of radioactivity in a part of the brain which has been perfused with radiolabelled microspheres is found to be proportional to the total blood flow through that locality. However, accurate data is only acquired with the use of autoradiography after physically sectioning the region of interest (McPherson *et al.* 1988). Again, whilst these invasive types of technique are useful in the examination of the properties of brain tissue of animal origin, it is inappropriate to consider their use in investigating the human subject, since normal human cerebral tissues (including human cerebral blood vessels) are essentially unavailable for *in vitro* examination.

There are however several methods for measuring cerebral blood flow which are non-invasive and can be used in the intact subject. Whilst the commonest techniques are those which use radioisotopes such as xenon-133 (Vorstrup, 1988; Keyeux *et al.* 1988;

Bishop *et al.* 1987; Hojer Pedersen, 1987), also described is the use of radiolabelled microspheres similar to the technique described above, but assessing local radioactivity with single photon emission computed tomography or scintillation counters (DeWitt *et al.* 1989) rather than autoradiography. The xenon-133 methods using either single photon emission computed tomography or stable Xe\computed tomography gives an accurate assessment of cerebral blood flow, but the limitation of all these methods is that they are relatively slow. A single measurement takes several minutes to perform (Gur *et al.* 1982), and thus can only give a value which represents the average cerebral blood flow during the course of the measurement. A further limitation which should be noted is that the use of radioisotopes adds to the complexity, invasiveness and expense of the techniques.

Positron emission tomography is another non-invasive technique which can be used to measure not only cerebral blood flow but cerebral blood volume as well (Tyrrell, 1990; Frackowiak, 1985; Powers, 1991; Schroeder, 1986). It has been used in several studies to investigate cerebral vascular physiology in carotid disease (Frackowiak, 1985; Levine RL *et al.* 1991) as well as in many other conditions (Costa & Ell, 1991), and has added considerably to the understanding of cerebral pathology. Although requiring the use of radioactive isotopes, the amount of radioactive material used in such studies is vanishingly small. However, positron emission tomography does have its drawbacks, when used to study such blood flow\volume relationships as are of interest in patients with carotid disease, it is slow (a full examination may take up to two hours), invasive (requiring the use of indwelling arterial lines) and fiendishly expensive (Tyrrell, 1990).

It is thus not useful for the investigation of rapid cerebral vascular autoregulation as defined in the first part of this section.

It is clear then that if the processes of normal human cerebral vascular autoregulation are to be studied then the experimental models regularly used in animals cannot be used except in very restricted and invasive circumstances such as during neurosurgery. The experimental model employed has to be one which studies the responses of the cerebral vasculature in the intact subject, and the techniques used have to be non-invasive. It is not possible to directly observe cerebral vessels to measure changes in the diameter of the resistance arterioles, and so the processes and effects of autoregulation have to be measured indirectly; that is, the required information has to be inferred from the measurement of other, more easily observed and less invasive physiological parameters.

Having made these concessions however, there is a further constraint which has to be placed on the methodology employed in the indirect observation of autoregulation.

Because it is known from animal experiments that the processes of autoregulation occur relatively rapidly, the methods employed have to be sufficiently sensitive in the time domain to detect changes occurring within seconds. It was with these constraints in mind that the method described in the following sections for the measurement of cerebral vascular autoregulation in the intact human subject was developed.

2.1.2 - Transcranial Doppler ultrasonography of blood flow in the middle cerebral artery

The principles of the measurement of blood flow velocity using Doppler-shifted reflected ultrasound are well established (Burnand, 1992; Arts & Roevros, 1972; Shung *et al.* 1992). The velocity of the insonated blood stream (or rather the velocity of the sound scattering particles, which in the case of blood are thought to be the erythrocytes (Shung *et al.* 1992)) is related to the frequency of the reflected Doppler-shifted sound waves according to the relationship shown in equation 1:

$$\Delta\omega = \omega - \omega_0 = \frac{\omega_0}{c} v \cdot \cos\theta \quad 1$$

Where delta-omega is the Doppler shifted frequency, omega is the frequency of the received signal, and omega-0 is the frequency of the transmitted signal. V is the velocity of the sound-scattering particles, c represents the velocity of sound in the medium and theta is the angle of insonation (that is, the angle subtended between the axis of the transmitted ultrasound beam and the axis of flow of the insonated blood stream) (Arts & Roevros, 1972).

In 1982 the Doppler ultrasound technique was adapted by Aaslid and his co-workers, with the use of a relatively low frequency (2MHz) transducer and a pulse-gating

technique to enable the transtemporal insonation of blood flow in the basal cerebral arteries, particularly the middle cerebral artery (Aaslid *et al.* 1982).

The anatomical position of the middle cerebral artery allows the insonation of the vessel through the thin part of the squamous temporal bone (see illustration 2a). The M1 segment of the middle cerebral artery is the region between the bifurcation of the internal carotid artery and the trifurcation of the middle cerebral artery, and is a portion of the vessel with an angle of insonation from the temporal window which is low (theta approaches 0 and therefore cosine theta approaches 1) and an insonation depth of between 40 and 60mm, both values being fixed in any one individual (although side-to-side variation exists) (Ringelstein EB *et al.* 1990). It is the M1 portion of the middle cerebral artery which is interrogated in all experiments described here (see section 4.3).

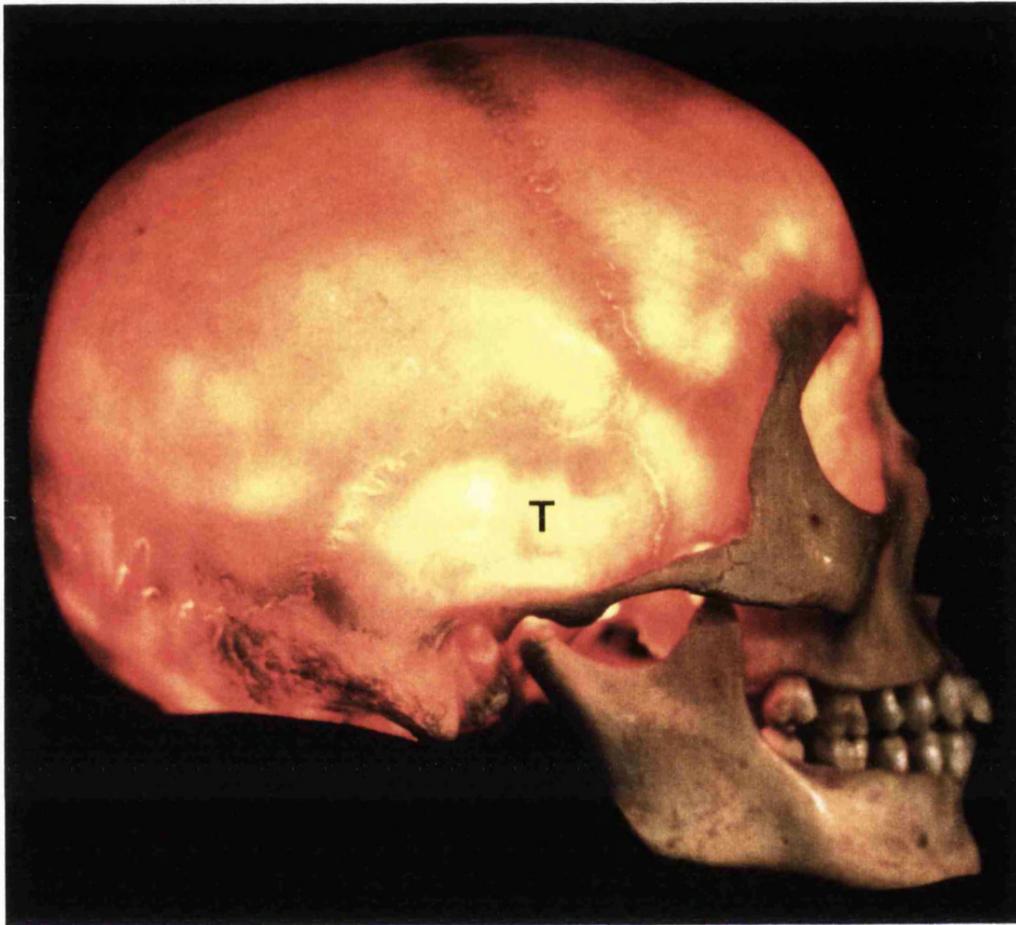


Illustration 2a

A skull illuminated from within demonstrating the temporal bone window (T), the thin part of the squamous temporal bone (superior and slightly anterior to the external auditory meatus) through which transcranial insonation of the middle cerebral artery is possible

The relationship between middle cerebral artery blood flow velocity and cerebral blood flow as measured by isotope techniques has been explored in a number of studies and whilst there has been shown to be little correlation between resting middle cerebral artery blood flow velocity and resting cerebral blood flow, there is a strong correlation between relative change in middle cerebral artery blood flow velocity and relative change in cerebral blood flow following the application of a cerebral vasoactive stimulus such as hypercapnia or intravenous acetazolamide (Bishop *et al.*1986; Piepgras *et al.*1990; Dahl *et al.*1992; Dahl *et al.*1994). The anatomical landmarks, normal velocity values and reproducibility of the transcranial Doppler ultrasound method have been demonstrated by several groups (Maeda *et al.*1990; Lindegaard *et al.*1987; Vriens *et al.*1989; Brouwers *et al.*1990; Ringelstein EB *et al.*1990; Demolis *et al.*1993).

2.1.3 Conclusion

Isotope techniques as described in section 2.1.1 do not have the time resolution to distinguish rapid changes in cerebral blood flow. Transcranial Doppler ultrasound of blood flow in the middle cerebral artery gives adequate time resolution to assess cerebrovascular autoregulation (Aaslid *et al.*1982; Maeda *et al.*1990; Sorteberg *et al.*1989), and while the relationship between velocity of blood flow and absolute volume flow is inconsistent, there is a good correlation between change in velocity in middle cerebral artery blood flow and change in cerebral blood flow. Transcranial Doppler ultrasonography of blood flow velocity in the middle cerebral artery is therefore used in the following experiments as a measure of relative change in cerebral blood flow. The fact that relative changes in flow velocity (reported in units of frequency rather than velocity (Phillips DJ *et al.*1989)) are used in subsequent calculations rather than absolute flow measurements means that it is not possible to calculate absolute vascular resistance to blood flow, only resistances relative to a resting state. This is taken into account in the reporting of results. All resistance results are reported in arbitrary units or as resistance relative to a resting state in that subject. Pooled results are the result of pooling numbers in arbitrary units or pooling ratios of resistances rather than absolute values.

2.2 - Volume clamp plethysmography in the non-invasive measurement of mean arterial blood pressure.

2.2.1 Introduction

The Ohmeda Finapres has been used in experiments described in this thesis to non-invasively measure rapid changes in mean systemic arterial blood pressure. The instrument measures blood pressure by using the volume clamp method of Penaz (Penaz, 1973). The blood volume flow through finger skin blood vessels is monitored with an infra-red photoplethysmograph mounted inside a finger cuff. The finger cuff pressure is controlled by a pneumatic servosystem which is capable of pulsing at high frequency (up to 1000Hz). The pressure applied by the finger cuff is that which maintains arterial transmural pressure at zero, at which pressure the arteries under the cuff are not occluded but remain open at about half their normal diameter as shown by the photoplethysmograph. Since the pressure in the cuff is capable of being varied at high frequency to follow changes in pressure in the vessels being monitored, the variation in pressure of the finger cuff corresponds to the variation in the arterial pressure wave in the finger skin blood vessels. The validity of this form of non-invasive arterial blood pressure monitoring has been assessed in several studies (Kinsella *et al.* 1989; Imholz *et al.* 1988; Molhoek *et al.* 1984) and shown to be reliable in the recording of both static blood pressures and changing blood pressures as a result of subjects performing the Valsalva manoeuvre (Imholz *et al.* 1988). The accuracy of the

instrument used in the experiments described in this thesis is assessed in the following study comparing blood pressure measurements made using the Ohmeda Finapres and direct pressure measurements from indwelling arterial lines.

2.2.2 Aims

The aim of this study was to test the hypothesis 'the Ohmeda Finapres provides an accurate non-invasive measurement of systemic mean arterial blood pressure'.

2.2.3 Subjects and methods

Eleven subjects who had had indwelling arterial lines placed as a routine part of monitoring perioperative and postoperative arterial blood pressure were studied. All were studied between 24 and 48 hours following cardiac or vascular surgery. All were in sinus rhythm, all were self ventilating and none were receiving intravenous inotropes.

The arterial blood pressure was monitored via an indwelling radial artery cannula. The Finapres servo plethysmography cuff was applied to the middle finger of the opposite hand.

Once a stable blood pressure had been recorded on the arterial line and a clear and stable trace was recorded by the Finapres instrument the mean arterial blood pressures from the transducer attached to the arterial cannula and from the Finapres display were recorded simultaneously and separately by two observers blinded to the other's measurement. Five readings were taken from each subject at fifteen second intervals.

2.2.4 Results

The results of the comparison between blood pressure measurements made using an arterial line pressure transducer and an Ohmeda Finapres are presented in figure 2.2.1. The histogram of the distribution of the differences between the two measurement methods is shown in figure 2.2.2. The correlation coefficient between the two measurements $r = 0.97$. The mean difference between the arterial cannula values and the Finapres values is 0.75 mmHg; the Finapres tends to give the lower reading. The standard deviation of the differences is 1.95 mmHg, thus the limits of agreement between the two measurement methods are that 95% of the Finapres readings should be between 4.7mmHg below and 3.2mmHG above the transduced arterial line pressures.

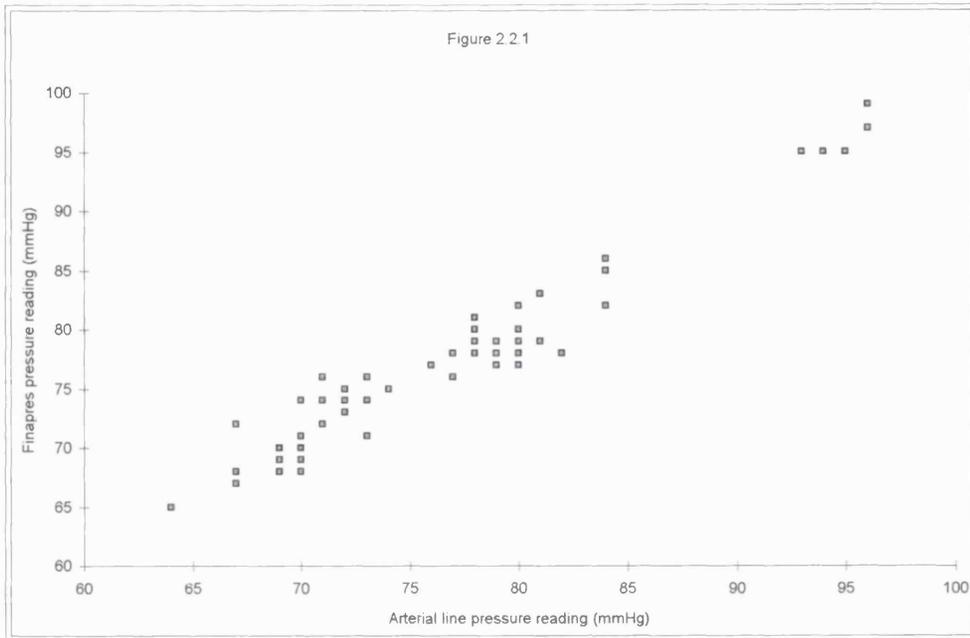


Figure 2.2.1 (above)
 Relationship between arterial line mean arterial blood pressure and Finapres mean arterial blood pressure. $n=11$ (total of 55 observations, 7 points overlying). $r=0.97$.

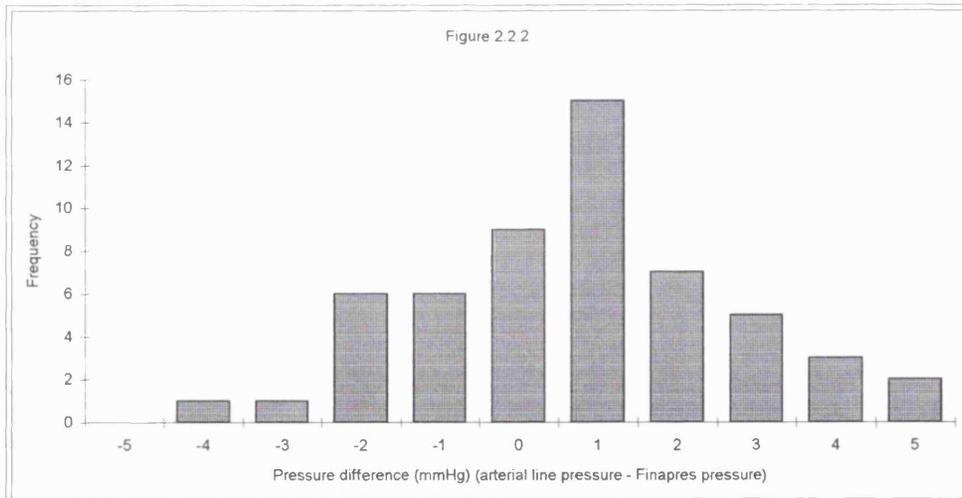


Figure 2.2.2 (above)
 Histogram of the distribution of the differences between arterial line mean arterial blood pressure and Finapres mean arterial blood pressure. $n=11$ (total of 55 observations).

2.2.5 Discussion

The above results show an extremely strong correlation between mean arterial blood pressure measurements made using pressure transduction from indwelling arterial lines and those made using the Ohmeda Finapres ($r = 0.97$).

The method of 'limits of agreement' (Bland & Altman, 1986) assesses the distribution of the differences between two methods of measurement as they are applied to measuring the same clinical entity. The mean difference between the two methods (d) and the standard deviation of the differences found in each case between the two methods (s) are calculated and the limits of agreement are bounded by $d+2s$ and $d-2s$, limits within which 95% of the differences between the two measurement methods will lie if the differences are normally distributed. If the limits $d+2s$ and $d-2s$ describe a difference between the two methods of measurement which is not clinically important then the two measurement methods can be used interchangeably.

Calculation of the limits of agreement shows that 95% of the Finapres readings of mean arterial blood pressure should lie between about 5mmHg below and about 4mmHg above the arterial line readings. Other studies have shown the tendency of the Finapres to underread blood pressure when compared to arterial pressure measurements (Imholz *et al.* 1988). These limits of agreement are within clinically acceptable limits. The variation between the measurement methods may represent an inaccuracy in the Finapres method or may represent a true variation between monitoring sites; although

an ideal experimental environment would allow the measurement of blood pressure by the two methods in the same limb, at the same point in the arterial system, it was found that the presence of a radial arterial line produced a damped arterial pressure trace when the Finapres was used on the ipsilateral hand. Some of the observed variation may therefore have been caused by true between-limb variation in the arterial blood pressure within individuals or by true variation in the arterial blood pressure between radial and finger arterial pressures.

The results of this study and others demonstrate the presence of a strong correlation between the two measurement methods (Finapres and direct arterial pressure transduction) and suggest that whilst absolute mean arterial pressure readings given by the Finapres will only give the accuracy described above, changes in mean arterial blood pressure are accurately reflected by changes in mean arterial blood pressure as measured by the Ohmeda Finapres. Furthermore, the fact that the method is non-invasive allows continuous blood pressure monitoring to be performed under circumstances where the placement of an indwelling arterial pressure line cannot be justified.

Part 3 Cerebral vascular autoregulation to pressure change

Synopsis

3.1 - Introduction

3.1.1 - The measurement of cerebral vascular resistance

3.1.2 - The generation of changes in cerebral perfusion pressure

3.2 - Study of relative cerebral vascular resistance and rapid cerebral vascular autoregulation in normal subjects

3.2.1 - Aims

3.2.2 - Subjects

3.2.3 - Methods

3.2.4 - Calculations

3.2.5 - Results

3.2.6 - Discussion of results

3.3 - Study of the effect of hypercapnia and hypocapnia on autoregulation in normal subjects

3.3.1 - Aims

3.3.2 - Subjects and methods

3.3.3 - Results

3.3.4 - Discussion of results

Synopsis

The physiology of cerebral vascular autoregulation to pressure change is discussed and the requirements for the experimental measurement of autoregulation are laid out. A method for the non-invasive measurement of cerebral vascular autoregulation to changes in blood pressure is described and this method is used to assess autoregulation in a group of normal subjects. The effect of hypercapnia and hypocapnia on cerebral vascular autoregulation in normal subjects is tested. Hypercapnia is shown to obtund autoregulation whereas hypocapnia is shown to exaggerate cerebral vascular autoregulation to changes in blood pressure.

3.1 Introduction

As discussed in section 1.5 above, the phenomenon of maintenance of cerebral blood flow in the face of changes in cerebral perfusion pressure is known as autoregulation. It is mediated by a change in arteriolar diameter in response to a change in perfusion pressure, such that the resistance to blood flow in the cerebral vasculature falls when perfusion pressure falls, and resistance increases when perfusion pressure climbs. Since blood flow through the brain depends upon both the cerebral vascular resistance and the cerebral perfusion pressure, cerebral blood flow can be kept relatively constant by this mechanism in the face of fluctuations in perfusion pressure. It is known from animal experiments that autoregulation is a process which can occur rapidly, over a period of seconds, in response to rapid changes in perfusion pressure (Heistad & Kontos, 1983). Few studies have examined cerebral blood flow in normal human subjects under conditions of rapidly changing perfusion pressure, and these demonstrated regulation of cerebral blood flow but did not calculate or demonstrate changes in cerebral vascular resistance (Newell *et al.* 1994; Aaslid *et al.* 1989).

3.1.1 The measurement of cerebral vascular resistance

The resistance to blood flow through a vascular system can be defined in terms of the relationship between the volume flow through the system and the perfusion pressure difference between the inflow and the outflow points of the system (Guyton, 1977). In

order to quantify this relationship, an analogy can be drawn between the haemodynamic and the electrical environments (Guyton, 1977; Ganong, 1987). In an electrical circuit, Ohm's Law describes the relationship between resistance of, current through and potential difference across an element of the circuit as given in equation 2;

$$V = I.R(2)$$

or as in equation 3;

$$R = \frac{V}{I} (3)$$

where R represents resistance. I represents current and V represents potential difference (Godman & Payne, 1979).

The haemodynamic terms this represents can be described by equation 4;

$$\Delta P = Q.R (4)$$

or equation 5;

$$R = \frac{\Delta P}{Q} (5)$$

where delta P represents perfusion pressure, Q represents flow and R represents resistance (Guyton, 1977). In this situation, perfusion pressure is analogous to electrical potential difference and volume of blood flow is analogous to electrical current.

It is of course the case that in the normal intact circulation blood flow is pulsatile, and therefore a more complete analogy may be with pulsatile electrical flow, for example alternating current (although of course whilst alternating current flows backwards and forwards in a smoothly sinusoidal fashion, blood flow is unidirectional with a complex waveform). The concept of resistance only incompletely describes the impediment to flow of an alternating electrical current; impedance is the entity applying to alternating current flow which corresponds to resistance in direct current flow (Godman & Payne, 1979). Analogy with impedance has been used in the mathematical treatment of pulsatile blood flow (Zuckerman *et al.* 1989; Wright *et al.* 1988; Latham *et al.* 1987), but only under circumstances of constant overall flow. There is no satisfactory treatment of the way in which the mathematics of impedance may be adapted to the modelling of rapidly changing blood flows and indeed, since blood has a unidirectional flow of complex waveform it may be inappropriate to use the concept of impedance to solve problems of estimating impediment to normal blood flow.

Resistance is both the simpler of the two mathematical entities and has been used previously in the modelling of rapid changes in coronary artery blood flow in response to changes in perfusion pressure (that is, coronary autoregulation) (Holdright *et al.* 1993). For the purposes of the studies described below therefore, resistance as defined in equation (5) above is the simplest way of describing the changing impediment to blood flow offered by the cerebral vasculature. In view of this fact and of the fact that resistance has been used to model coronary autoregulation, it is resistance rather than impedance which is used in the calculations described below.

From equation (5) then, it can be seen that if it were possible to measure both blood flow through a vascular system and at the same time measure the perfusion pressure to the system, then the resistance to blood flow offered by the system could be estimated. Applying this to the determination of cerebral vascular resistance, the necessary values which would need to be determined are cerebral blood flow and cerebral perfusion pressure. This would give the relationship given in equation 6:

$$CVR = \frac{CPP}{CBF} \quad (6)$$

where CVR is cerebral vascular resistance, CPP is cerebral perfusion pressure and CBF is cerebral blood flow. In order to use this relationship to explore the nature of cerebral vascular autoregulation in the intact subject, the constraints described above (that is, non-invasive techniques which are sufficiently sensitive in the time domain to give information about changes occurring over seconds) have to be applied to the measurement of cerebral blood flow and cerebral perfusion pressure.

3.1.2 The generation of changes in cerebral perfusion pressure

In order to measure cerebral vascular autoregulation it is necessary to observe blood flow during a change in cerebral perfusion pressure. In general terms cerebral perfusion pressure can be described by the relationship given in equation 7 (Marks & Redfern, 1992):

$$CPP = MAP - ICP \quad (7)$$

which can be modified to that in equation 8:

$$CPP = MAP - (ICP + VP) \quad (8)$$

Where CPP is cerebral perfusion pressure, MAP is mean arterial blood pressure, ICP is intracranial pressure and VP is cerebral venous pressure. In the technique described below it has been necessary to assume that intracranial pressure and cerebral venous pressure are unchanged in each individual during the course of each measurement, and that changes in cerebral perfusion pressure are therefore proportional to changes in systemic blood pressure. These assumptions are difficult to test, but the positioning of subjects (as described below) at 15 degrees of head-up tilt reduces cerebral venous pressure to around zero or sub-atmospheric levels (Marks & Redfern, 1992), and reduces the potentially confounding contribution of this factor.

Having made the assumptions described above, the problem of producing a change in cerebral perfusion pressure can be somewhat simplified to the production of a change in systemic blood pressure. As with the measurement of cerebral blood flow, there are a number of constraints which have to be applied to the method of inducing such a change if it is to be a useful component in an experiment to measure autoregulation. Whilst in animal experiments invasive techniques such as aortic clamping or controlled haemorrhage are useful (Aadahl *et al.* 1991; Bickell *et al.* 1989; Shackford *et al.* 1990), these are inappropriate for use in man (except perhaps during aortic surgery). The use of pharmacological agents to produce hypotension or hypertension is effective but has

drawbacks. It is difficult to time the onset of the effect of a pharmacological agent unless it is given as an intravenous bolus, which adds to the invasiveness of the technique and indeed invariably adds to the potential hazard associated with the investigation. Furthermore, any systemically administered agent may have a direct effect on the vascular system under investigation, an effect which may confound the results of the experiment. For these reasons the use of pharmacological agents has been eschewed in these experiments in favour of a physical method of producing a hypotensive state. This is a modification of a method described by Aaslid (Aaslid *et al.* 1989) using the sudden deflation from suprasystolic pressure of large plethysmography cuffs placed around the thighs of the subject. The method has the multiple advantages of being relatively non-invasive and of producing a sudden and easily timed change in systemic blood pressure.

With the subject supine, large plethysmography cuffs (see illustration 3e) are placed around the subject's upper thighs and inflated to 10mmHg above systolic blood pressure, resulting in ischaemia of the subject's legs and a reflex vasodilatation in the ischaemic vascular beds. The subject's position is changed from supine to supine with 15 degrees of head-up tilt. After two minutes the pressurised air in the plethysmography cuff is allowed to expel suddenly via a large-bore release valve (see illustration 3h) and the cuff pressure rapidly falls to zero (atmospheric) pressure. The ischaemic (low resistance) leg circulation is thus suddenly opened to the systemic circulation, resulting in a step decrease in systemic vascular resistance. This results effectively in a physiological step decrease in systemic blood pressure. Blood rich in metabolites and carbon dioxide is released from the legs upon release of the cuff

pressure and the circulation of this to the brain may produce vasoreactivity, and so this technique is only useful to study changes which occur within the leg-brain circulation time (assumed to be greater than the known 15 seconds of arm-brain circulation time (Ganong, 1987)).

3.2 Study of relative cerebral vascular resistance and rapid cerebral vascular autoregulation in normal subjects

3.2.1 Aims

The aim of this study was to test the following hypothesis:

'it is possible to measure relative cerebral vascular resistance and rapid cerebral vascular autoregulation using non-invasive techniques in man.'

3.2.2 Subjects

Twenty subjects (four female and sixteen male, age range 19 to 41 years) who had no clinical evidence of vascular disease and who were taking no medicines were recruited.

Informed consent to participate was obtained from each subject.

The subjects were randomly allocated to one of two groups. The first group (n = 10) underwent investigation as described below but no blood pressure stimulus was applied (that is, no plethysmography cuff inflation\deflation took place). The second group (n = 10) underwent investigation with application of a blood pressure stimulus as described.

3.2.3 Methods

Measurements were performed in a quiet, temperature controlled environment at 20 degrees centigrade. Subjects rested supine for ten minutes prior to examination. Duplex Doppler examination of the carotid and vertebral vessels was performed and measurements were made to determine the middle cerebral artery reactivity and reactivity index to hypercapnia according to the protocol described in section 3.3 below. However, the results were not calculated until the measurements to determine autoregulation had been made. This ensured that investigators were blind to the results of the reactivity to hypercapnia measurements whilst making measurements of autoregulation on each subject.

The right middle cerebral artery of the hemisphere under investigation was insonated through the ipsilateral temporal bone window (Ringelstein EB *et al.*1990) using a SciMed PCDOP 842 Transcranial Doppler ultrasound instrument (illustration 3a). This had been modified by the manufacturers with a digital-to-analogue convertor board to provide an analogue output of peak and mean middle cerebral artery blood flow velocity, and the output from this board was directed to the main data chart recorder described below. The subject's head was fixed comfortably in position using evacuated sand-bags and the Doppler transducer was held in position using a specially designed fully adjustable spring-loaded probe-holder fixed to the table with a magnetic clamp (illustration 3b). The subject was required to breathe through a mouthpiece with an occluding noseclip (illustration 3c) which continuously sampled the inspired and

expired air and allowed end-tidal carbon dioxide concentration to be monitored and recorded on a separate chart recorder to the main data recorder. The systemic blood pressure was monitored using an Ohmeda 2300 Finapres attached to the subject's right middle finger (illustration 3d). The subject's right arm was placed outstretched with the fingers at heart level. Large size wide plethysmography cuffs (Hokansen 77C) were wrapped around the subject's upper thighs (illustration 3e). A further two minutes rest were allowed.

Data was recorded in two ways. Middle cerebral artery blood flow velocity information was stored digitally in twenty-five seconds long segments on the computer hard disc of the transcranial Doppler instrument. (The timing of this data acquisition can be adjusted by the investigator.) Information stored included patient data, peak and mean velocity waveform, total reflected signal power waveform, transducer power and gain and insonation depth. Analogue data was also stored on a paper chart recorder. On four channels of a W&W six channel paper chart recorder were recorded the continuous analogue tracings of peak middle cerebral artery blood flow velocity, systemic blood pressure, pulse rate and a step signal which represented the timing of release of pressure from the plethysmography cuffs (illustration 3f).

The plethysmography cuffs were inflated to 10mmHg above systolic blood pressure using a custom built two stage pressure regulator and valve (illustration 3g). The subject's position was then changed from supine to supine with 15 degrees of head-up tilt, and the position of the transcranial Doppler transducer was adjusted to maintain the optimum signal power. After two minutes of cuff inflation, baseline middle cerebral

artery blood flow velocity and systemic blood pressure readings were recorded on the computer hard disc and on the chart recorder. The plethysmography cuff air pressure was allowed to suddenly expel via a large-bore release valve (illustration 3h). The leg circulation was suddenly opened to the systemic circulation, resulting in a step decrease in systemic vascular resistance, and effectively causing a physiological step decrease in systemic blood pressure. The middle cerebral artery blood flow velocity, systemic blood pressure, pulse rate and timing signals were recorded as above for a period of five seconds before cuff pressure release and for fifteen seconds after cuff pressure release. The experimental setting is demonstrated in illustrations 3i and 3j.



Illustration 3a

The SciMed PC Dop 842 Transcranial Doppler ultrasound instrument.

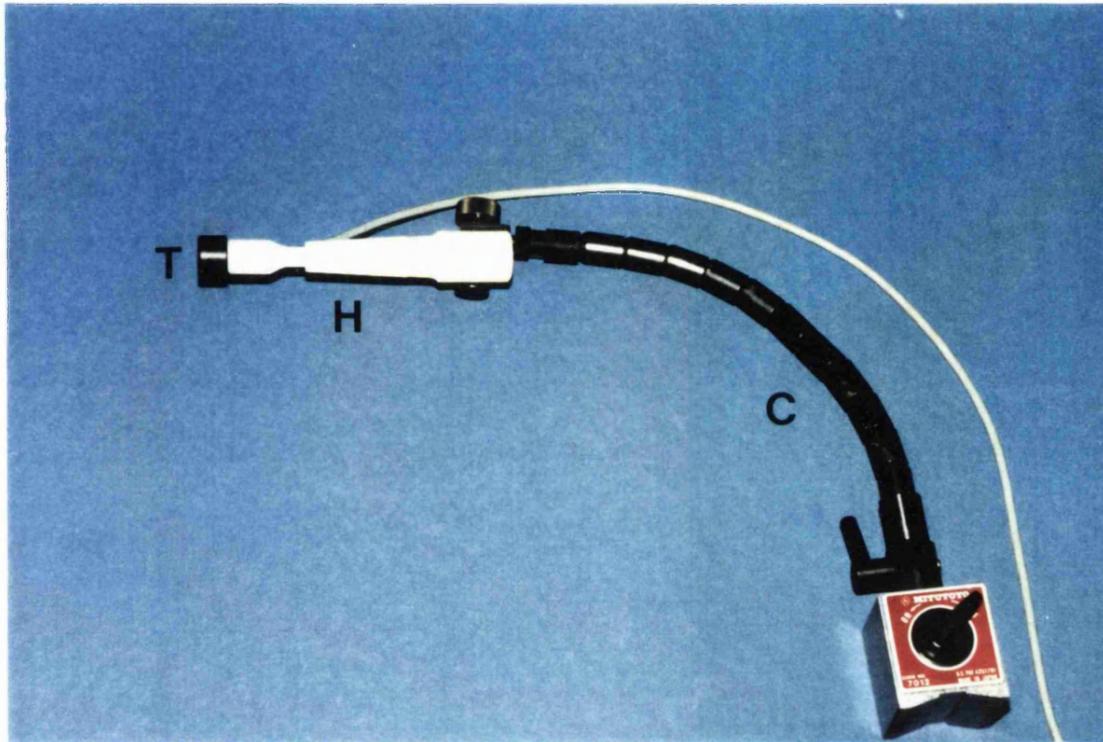


Illustration 3b

The transcranial Doppler ultrasound transducer (T) with spring-loaded holder (H) and locking adjustable magnetic table clamp (C).

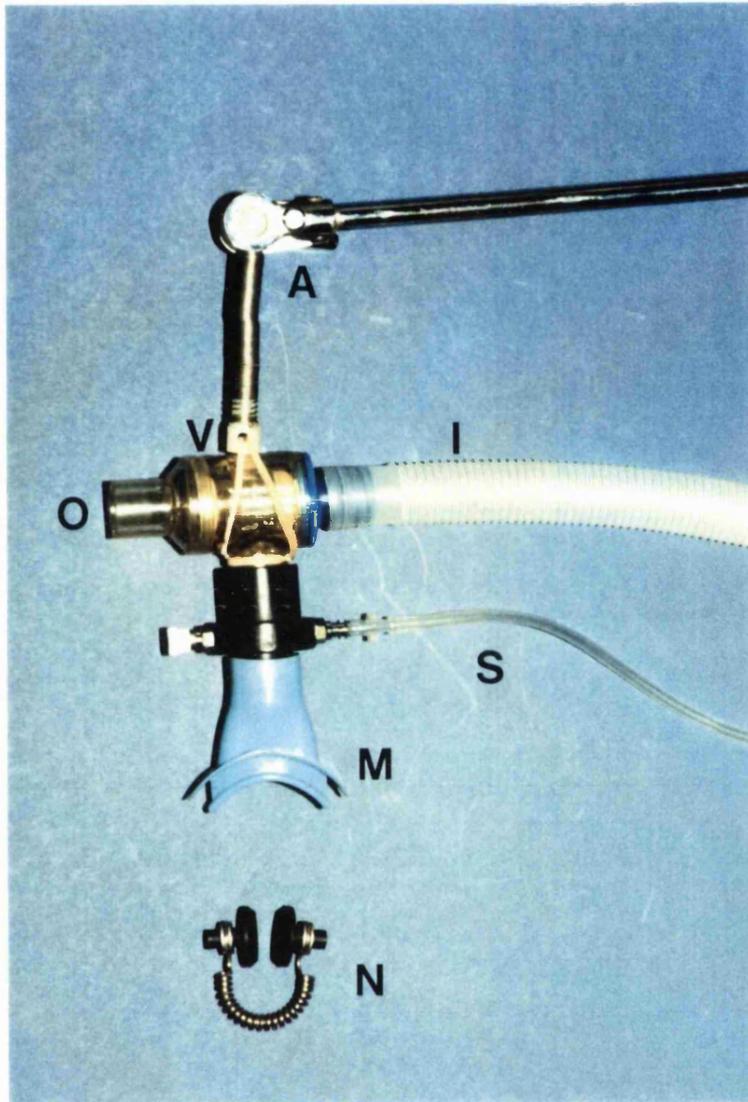


Illustration 3c

Mouthpiece (M) with adjustable holder (A), gas inflow pipe (I), gas outflow (O) and non-return valve (V), carbon dioxide sampling line (S) and occluding noseclip (N).

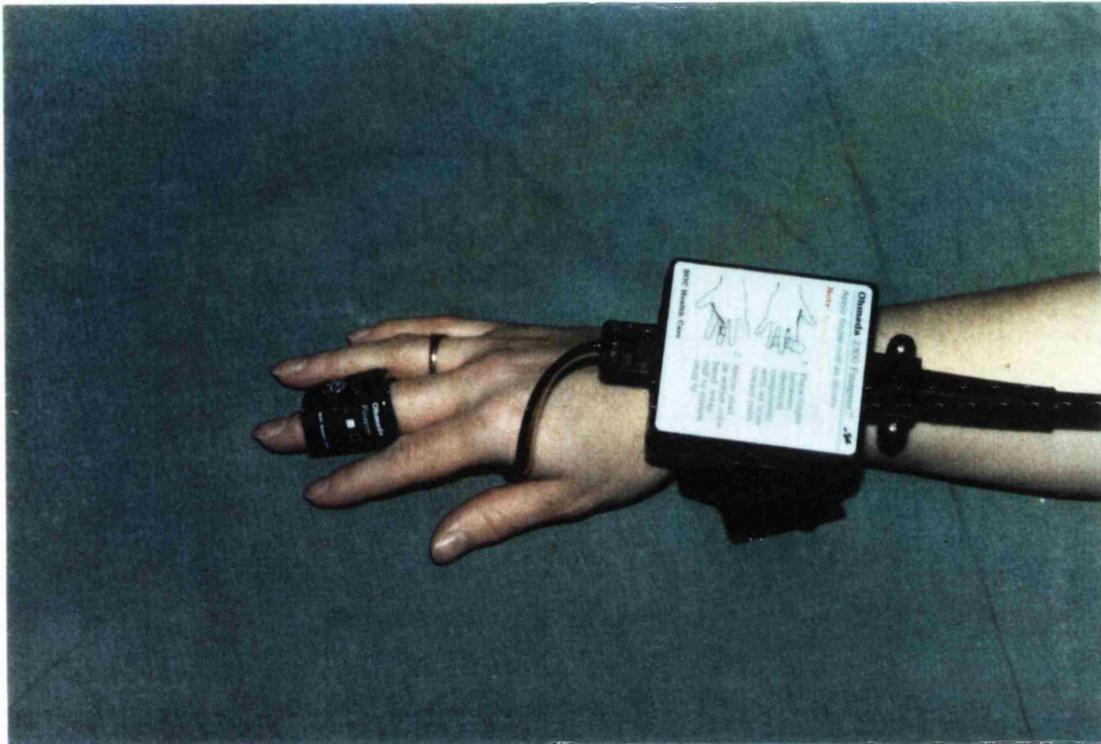


Illustration 3d

The Ohmeda Finapres volume clamp plethysmography hand piece



Illustration 3e

Large plethysmography cuffs (70 cm by 20 cm) with wide bore inflation-deflation tubes

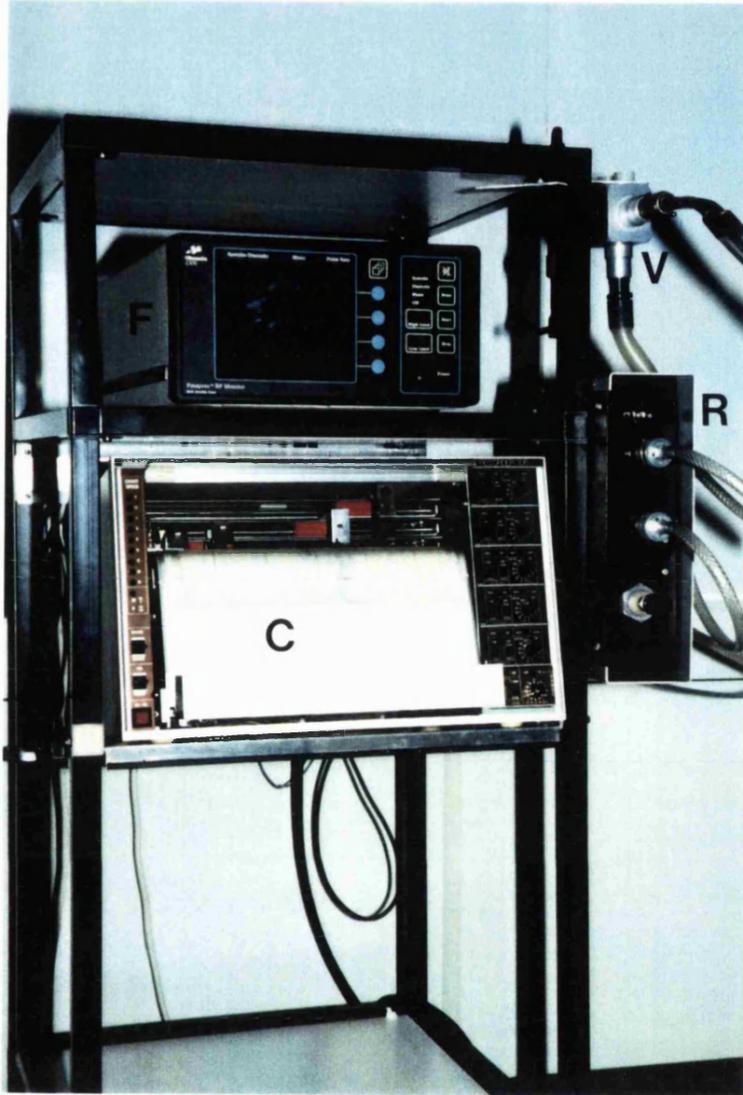


Illustration 3f

W & W six channel paper chart recorder (C) on trolley with the Ohmeda Finapres (F) and plethysmography cuff pressure regulator (R), and valve (V).

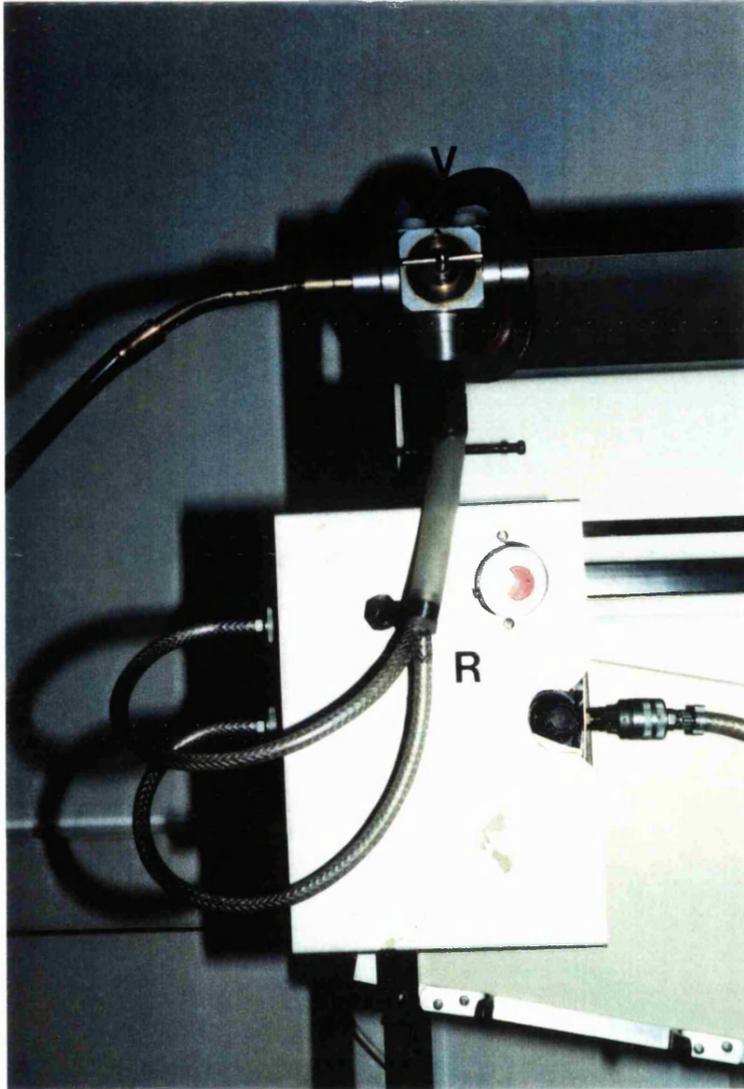


Illustration 3g

Plethysmography cuff air inflation pressure regulator (R), and deflation valve (V).

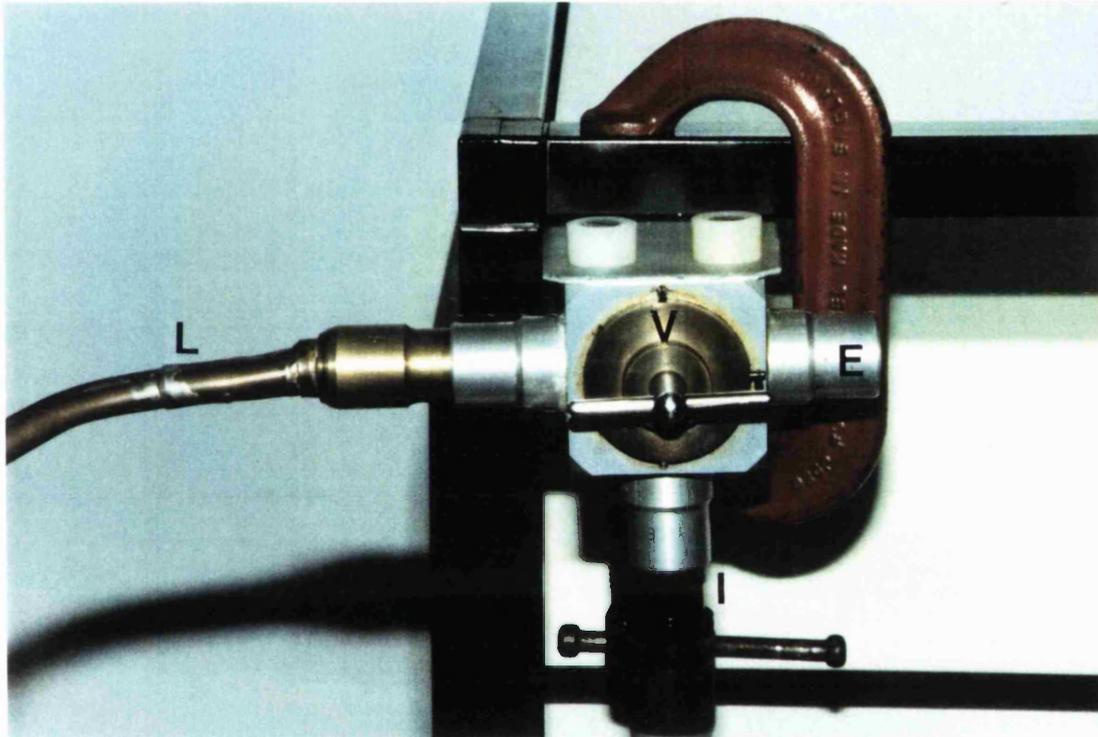
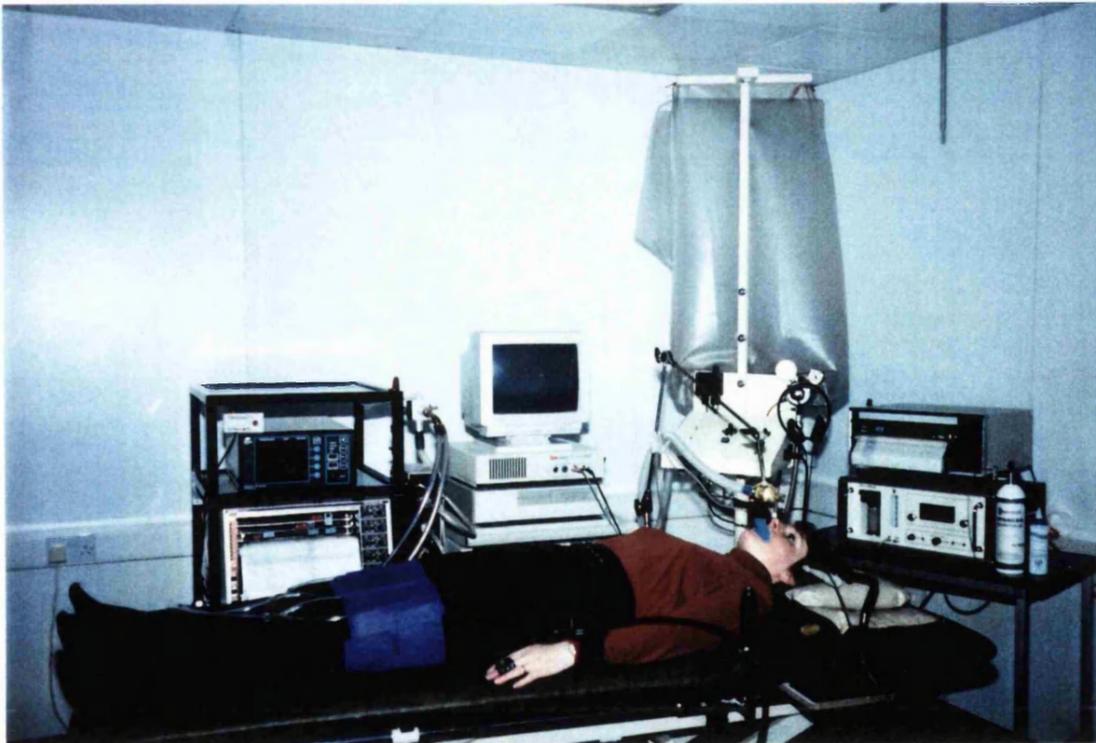
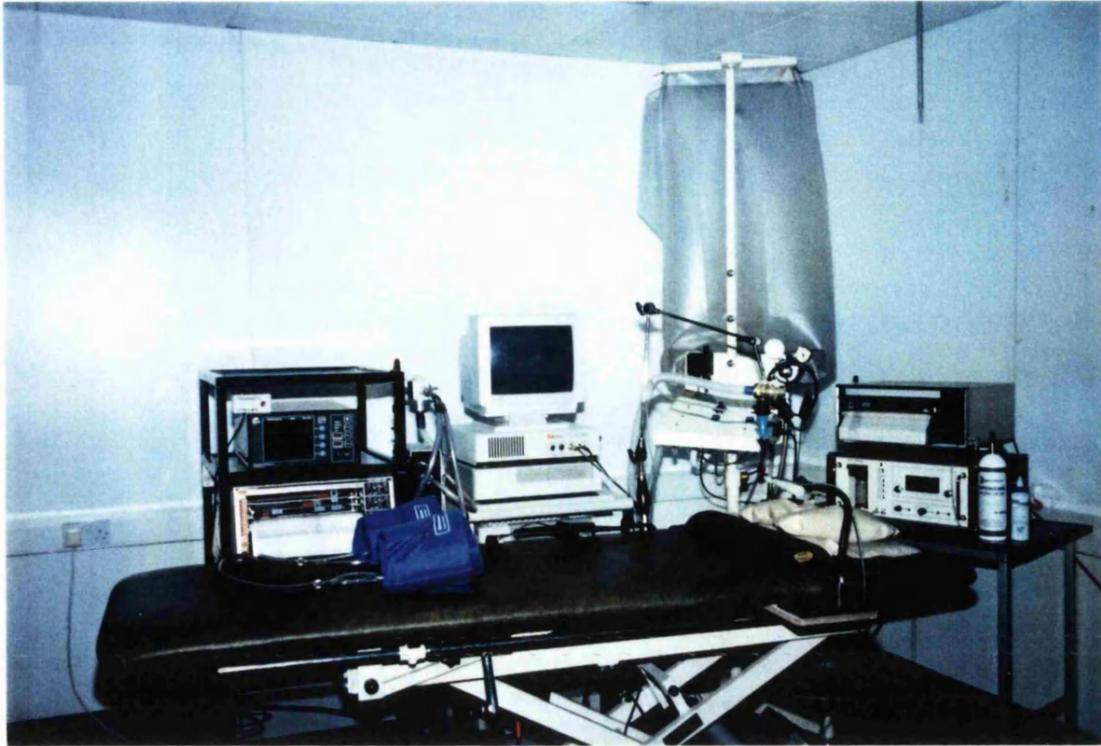


Illustration 3h

Plethysmography cuff deflation valve (V) with inflow line from regulator (I), inflow-outflow line to plethysmography cuffs (L) and exhaust port (E).



Illustrations 3i (top) and 3j (bottom)

The experimental setting.

3.2.4 Calculations

Mean arterial blood pressure was calculated using the relationship given in equation 9:

$$MAP = DBP + 1/3(SBP - DBP) \quad (9)$$

where MAP is mean arterial pressure, DBP is diastolic blood pressure and SBP is systolic blood pressure (Ganong, 1987).

Mean middle cerebral artery blood flow velocity over a given time period is calculated by the transcranial Doppler instrument as the integral of the stored mean velocity waveform between time points set by the investigator. Peak systolic blood flow velocity information is extracted from the stored waveform by the manual adjustment of a screen cursor placed by the investigator.

Cerebral vascular resistance can then be calculated, either for each cardiac cycle or over a period of time, by the relationship given in equation (6) above.

Resting cerebral vascular resistance in each subject is determined from measurements made in the five seconds before plethysmography cuff release. Following cuff release a value for resistance is calculated for each cardiac cycle for the fifteen seconds after the timing signal marked on the chart recorder. In order to facilitate comparisons between subjects the timing of each cardiac cycle is determined relative to the cuff deflation, and those beats occurring from 0 to 1 seconds after the event are deemed to have occurred

at time 1, those beats between 1 and 2 seconds are deemed to have occurred at time 2 and so on to time 15. These time segments then correspond to the 15 seconds of recorded data after the pressure stimulus. Direct comparison between individuals or groups can then be made by comparing the results found in specific time segments.

The cerebral vascular resistance for each cardiac cycle or for each time segment following the pressure stimulus can be calculated relative to the resting resistance in that individual. When the resistance value for a time segment is expressed as a percentage of the resting resistance, this value is named the instantaneous index of cerebral vascular resistance (iCVR).

3.2.5 Results

No subject had abnormal internal carotid artery blood flow velocity, and the cerebrovascular reactivity to hypercapnia was in the normal range in all subjects.

There was no significant difference in the resting cerebral vascular resistances of groups one and two.

Group 1:

Mean resistance 10.25 units (95% confidence interval 9.54 to 10.97).

Group 2:

Mean resistance 9.59 units (95% confidence interval 8.07 to 11.10).

P = 0.47 by ANOVA.

In group 1 the mean arterial blood pressure and mean middle cerebral artery blood flow velocity did not vary significantly from their resting values during the investigation. For this group the mean arterial blood pressure for the 15 seconds following the timing event is shown in figure 3.2.1, and the mean iCVR for the 15 seconds following the timing event is shown in figure 3.2.2. Mean and 95% Confidence Interval of the mean are shown. In this group, who did not experience a perfusion pressure stimulus, the iCVR did not vary significantly from the resting value during the duration of the investigation.

For group 2, figure 3.2.3 shows the mean arterial blood pressure for the 15 seconds following the timing event (the deflation of the plethysmography cuffs). Mean and 95% Confidence Interval of the mean are shown. In this group, there was a significant fall in mean arterial blood pressure following deflation of the plethysmography cuffs, which was sustained to the end of the measurement period. The change in middle cerebral artery blood flow velocity in this group is shown in figure 3.2.4. This shows a significant fall in the mean middle cerebral artery blood flow velocity during the first four seconds of the measurement period followed by a return towards the baseline value. By five seconds after the blood pressure stimulus there was no significant difference between the middle cerebral artery blood flow velocity under conditions of hypotension and the resting middle cerebral artery blood flow velocity. The calculated iCVR in this group is given in figure 3.2.5. A significant drop in the iCVR after 4 seconds is noted, which is sustained almost to the end of the measurement period. The

timing of the onset of this drop in relative cerebral vascular resistance corresponds with the return of middle cerebral artery blood flow velocity to its baseline value.

Table 3.2.1

Time (s)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
95% CL	100	102.59	101.47	102.33	102.06	102.47	102.27	101.41	100.78	100.82	100.75	100.47	100.96	101.37	102.38	102.78
Mean blood pressure	100	99.81	98.95	99.47	99.30	98.49	98.53	98.27	98.12	98.32	98.45	98.25	98.45	98.71	99.37	98.89
95% CL	100	97.04	96.42	96.60	96.53	94.52	94.78	95.13	95.46	95.82	96.15	96.02	95.93	96.05	96.37	95.01

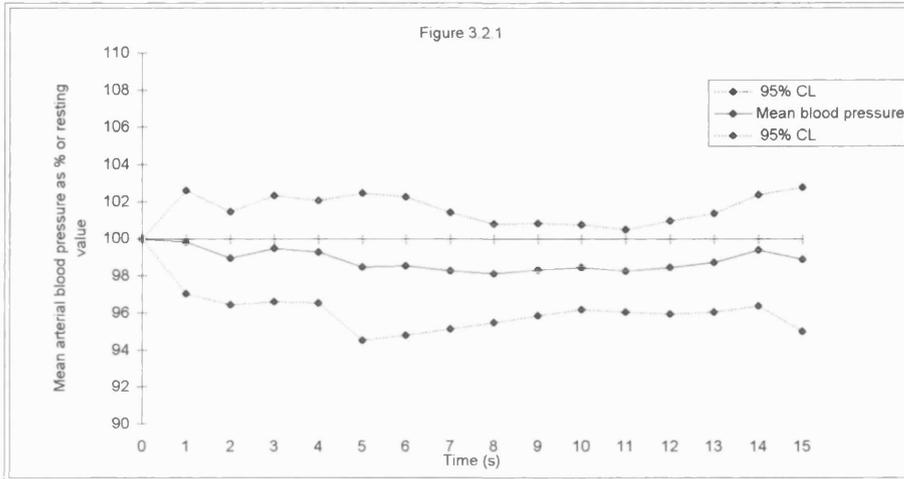


Figure 3.2.1 (above)
 Group 1 mean arterial blood pressure in the absence of blood pressure stimulus. Mean and 95% confidence intervals (CI) of the mean shown. n=10. Values given in table above chart. Curve shows no significant variation from the resting value.

Table 3.2.2

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
95% CL	100	101.61	101.66	101.89	101.58	101.58	102.77	103.82	101.05	100.82	101.22	100.93	101.98	101.57	102.87	102.57
Mean iCVR	100	100.23	100.09	100.76	100.05	98.19	99.74	100.19	98.34	98.49	98.96	98.96	98.67	98.22	100.56	99.40
95% CL	100	98.89	98.57	99.66	98.57	95.02	96.88	98.80	95.78	96.26	96.79	97.07	97.47	96.97	98.35	96.43

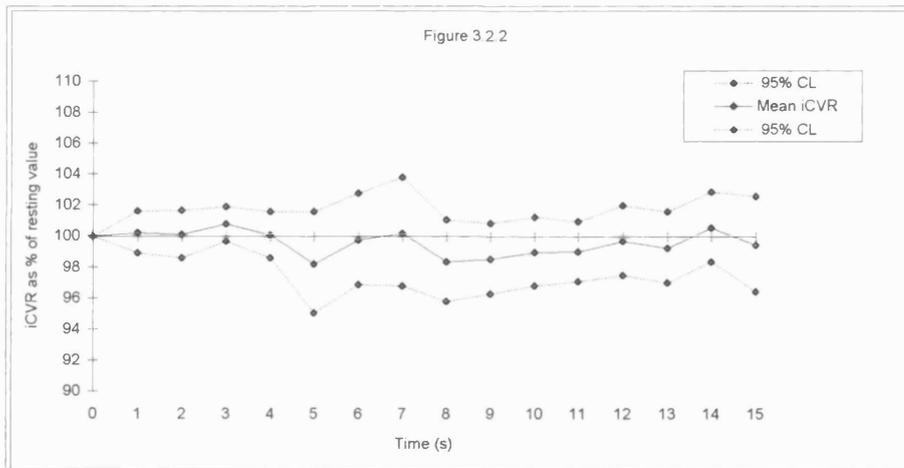


Figure 3.2.2 (above)
 Group 1 mean iCVR in the absence of blood pressure stimulus. Mean and 95% CI of the mean shown. n=10. Values given in table above chart. Curve shows no significant variation from the resting value.

Table 3.2.3

Time (s)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
95% CL	100	97.83	95.84	93.44	93.67	94.65	94.63	95.96	96.43	96.16	96.63	95.84	95.54	97.08	97.98	99.00
Mean blo	100	96.08	93.64	91.44	90.79	91.55	91.26	92.75	92.83	92.53	93.47	92.80	93.45	94.68	95.97	96.95
95% CL	100	94.33	91.45	89.43	87.90	88.44	87.90	89.53	89.22	88.90	90.30	89.77	91.35	92.28	93.95	94.91

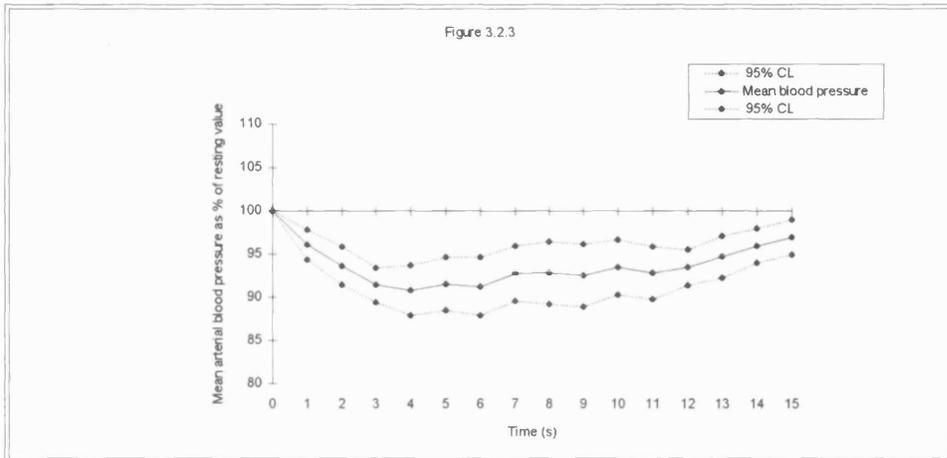


Figure 3.2.3 (above)

Group 2 mean arterial blood pressure following blood pressure stimulus (deflation of thigh plethysmography cuffs). Mean and 95% CI of the mean shown. n=10. Values given in table above chart. Curve shows a significant fall in mean arterial blood pressure immediately following cuff deflation.

Table 3.2.4

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
95% CL	100	109.72	105.78	104.47	100.22	99.19	98.06	96.51	96.51	97.36	97.86	96.01	95.61	98.07	100.48	99.74
Mean iCVF	100	104.81	102.38	100.30	96.52	95.75	95.02	93.40	94.68	94.05	94.72	93.19	92.74	93.49	95.63	96.31
95% CL	100	99.90	98.97	96.13	92.82	92.31	91.97	90.30	90.85	90.73	91.58	90.37	89.87	88.90	90.78	92.87

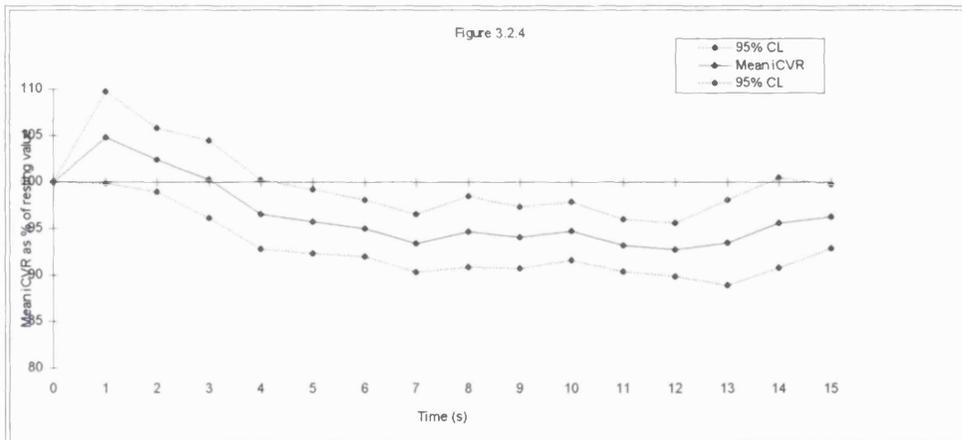


Figure 3.2.4 (above)

Group 2 mean iCVR following blood pressure stimulus. Mean and 95% CI of the mean shown. n=10. Values given in table above chart. Curve shows a significant fall in cerebral vascular resistance from 4 seconds after the stimulus.

Table 3.2.5

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
95% CL	100	97.19	96.80	97.22	100.15	101.15	101.06	104.46	103.24	103.30	102.75	103.40	103.97	106.26	105.46	104.63
Mean MCA velocity	100	92.24	91.85	91.89	94.56	96.03	96.38	99.62	98.37	98.69	98.88	99.73	100.99	101.76	100.89	101.07
95% CL	100	87.30	87.10	86.56	88.98	90.90	91.70	94.78	93.50	94.09	95.01	96.06	98.00	97.26	96.32	97.50

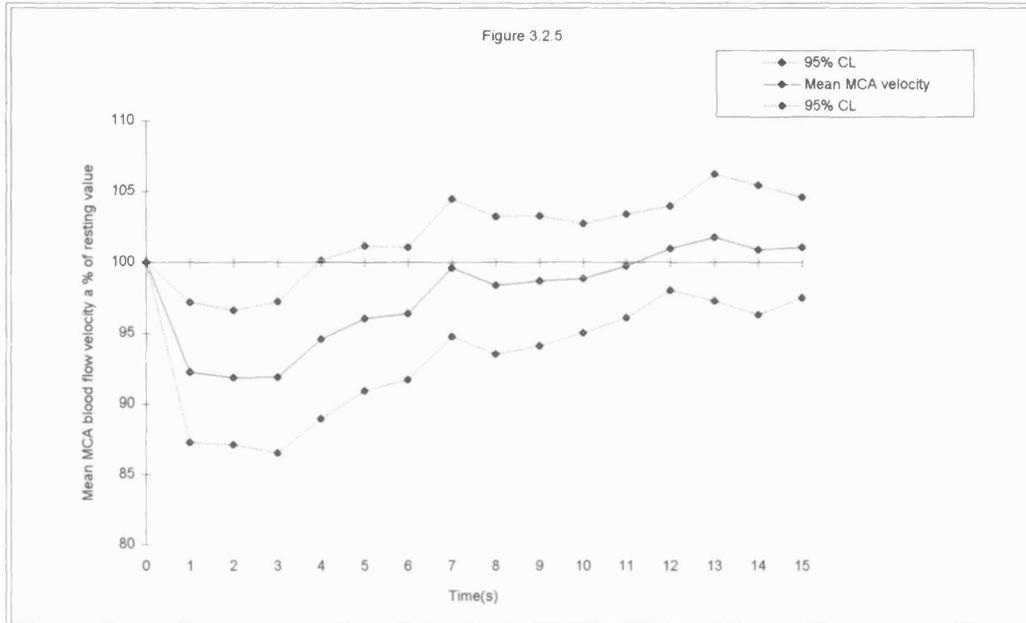


Figure 3.2.5 (above)

Group 2 mean middle cerebral artery blood flow velocity following blood pressure stimulus. Mean and 95% CI of the mean shown. n=10. Values given in table above chart. Curve shows an early fall in MCA blood flow velocity which returns towards the resting value by 4 seconds after the stimulus.

3.2.6 Discussion of results

The results from group 1 in whom no blood pressure stimulus was applied are important. This group demonstrates that under these experimental conditions without any blood pressure stimulus the relative cerebral vascular resistance during the fifteen second test period does not vary in a statistically significant way from that in the preceding five second resting state. The resting value for iCVR can therefore be regarded as a stable entity under these circumstances, showing no statistically significant variation in the absence of a blood pressure stimulus. This lack of variation has bearing when assessing the results from group 2 in whom a blood pressure stimulus was applied. In this group a physiological drop in systemic blood pressure was induced, which was sustained until the end of the measurement period. This has been assumed to approximate to a drop in cerebral perfusion pressure. Whilst this fall in cerebral perfusion pressure resulted in an initial drop in middle cerebral artery blood flow velocity, within five seconds of the blood pressure stimulus the middle cerebral artery blood flow velocity had returned to a value which was not significantly different from that found in the resting state. The calculated iCVR in this group showed a statistically significant fall occurring between three and five seconds following the blood pressure stimulus.

This is interpreted as being a demonstration of cerebral vascular autoregulation. The results of this experiment demonstrate that with a drop in cerebral perfusion pressure the middle cerebral artery blood flow velocity falls, and that before the perfusion

pressure is restored there is a return of blood flow velocity to its resting value.

Comparison of the results found in the two groups is revealing. Calculation of the relative cerebral vascular resistance in group 2 shows that a value which is found to be stable in group 1 in the absence of a blood pressure stimulus falls following a drop in perfusion pressure with the result that middle cerebral artery blood flow velocity is restored to its resting value.

3.3 Study of the effect of hypercapnia and hypocapnia on autoregulation in normal subjects.

3.3.1 Aims

The aim of this study was to test the hypothesis:

'Relative cerebral vascular resistance and rapid cerebral vascular autoregulation in normal subjects are dependent upon end-tidal carbon dioxide concentration.'

3.3.2 Subjects and methods

The ten normal subjects who formed group 2 in section 3.2.2 above were studied.

Subjects were positioned and monitored as described in section 3.2.3 above; measurements of carotid artery blood flow velocity and middle cerebral artery reactivity to hypercapnia were not repeated.

Two investigations were carried out on each subject.

1. The subject was required to breathe air with 5% carbon dioxide provided via the mouthpiece from a custom-built air-carbon dioxide mixing device (PK Morgan & Co., see illustration 3k), and the end-tidal carbon dioxide was monitored and recorded until a stable hypercapnic state was reached. Using the method described in section 3.2.3 above the subjects then underwent measurement of rapid cerebral vascular autoregulation to a drop in systemic blood pressure.

2. Following a five minute washout period the subject was required to breathe air normally and then to hyperventilate by increasing their rate and depth of respiration. End tidal carbon dioxide was monitored until a stable hypocapnic state was reached and a further measurement of rapid cerebral vascular autoregulation was made.

Calculation of cerebral vascular resistance and relative change in cerebral vascular resistance was performed as described in section 3.2.4 above.

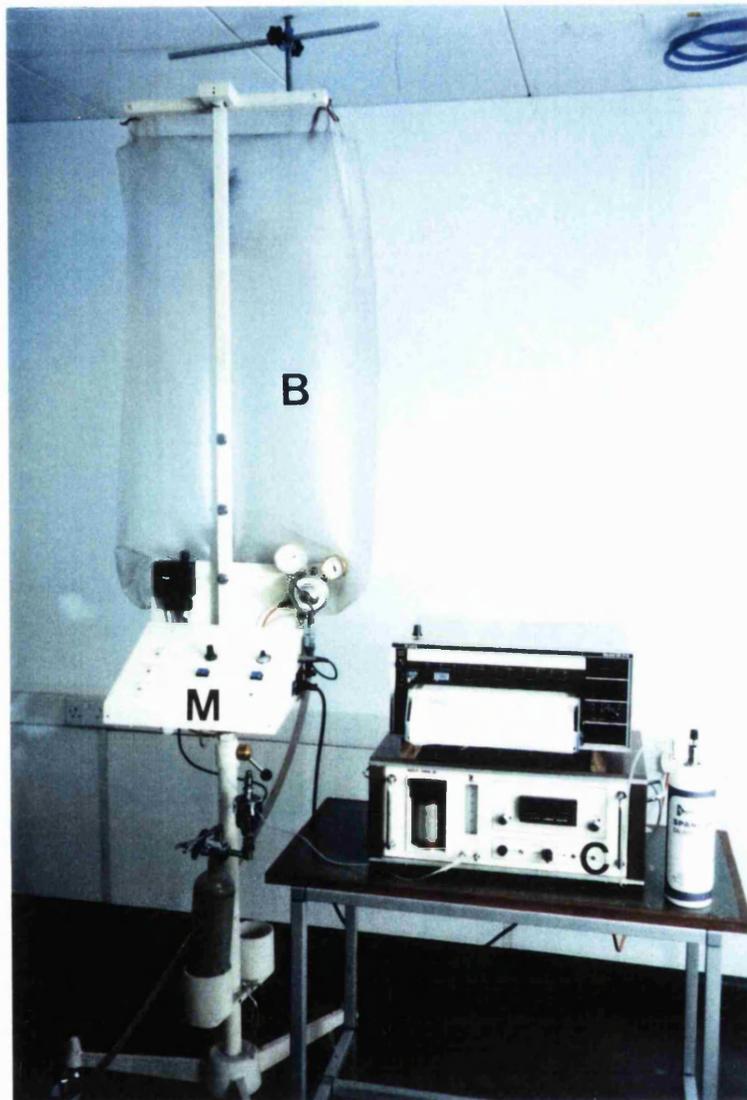


Illustration 3k

The carbon dioxide/air mixing apparatus (M) with mixed gas storage bag (B), infra-red carbon dioxide analyser and canister of calibration gas (C).

3.3.3 Results

The mean values for resting relative cerebral vascular resistance at hypercapnia, eucapnia and hypocapnia are given in figure 3.3.1 (eucapnia data from section 3.2 above). The mean resting cerebral vascular resistance is significantly raised under hypocapnic conditions and is significantly reduced under hypercapnic conditions, as would be predicted a priori.

The results of the measurement of autoregulation in this group under hypocapnic conditions are given in figure 3.3.2 and those under hypercapnic conditions are given in figure 3.3.3. It can be seen that under hypercapnic conditions there is a loss of the response of relative cerebral vascular resistance to a drop in systemic blood pressure, since there was no significant difference between the calculated resistance and that found during the resting hypercapnic condition during any of the time segments measured. This is in contrast to the results found under hypocapnic conditions. Under hypocapnic conditions the response of the cerebral vasculature to a fall in cerebral perfusion pressure appears to occur in two phases. There is an initial short-lived but highly statistically significant rise in relative cerebral vascular resistance lasting some two seconds. This is followed by a rapid fall in relative cerebral vascular resistance to a level significantly lower than that found in the resting state. The proportionate fall in resistance in the second phase of the hypocapnic response relative to the hypocapnic resting phase is also larger than the proportionate fall in resistance under eucapnic conditions.

Table 3.3.1

	<i>Hypocapnia</i>	<i>Eucapnia</i>	<i>Hypercapnia</i>
95% CL	22.60	13.72	9.38
Mean resting iCVR	19.33	11.34	8.15
95% CL	16.05	8.95	6.93
End-tidal CO ₂	2.60%	3.90%	5.10%

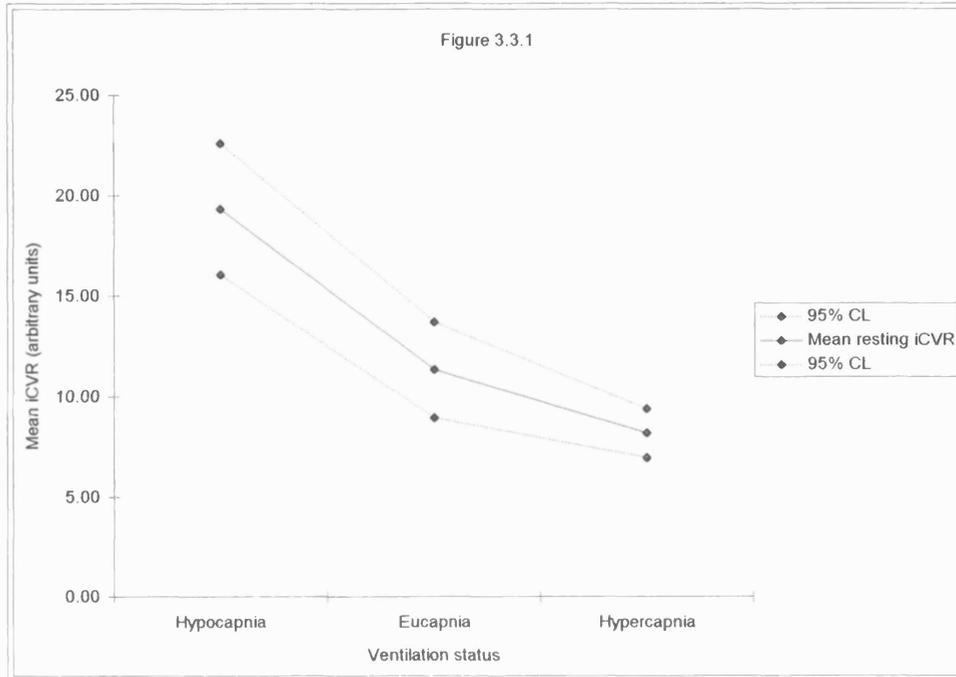


Table 3.3.1.a

	<i>hypocapnia vs eucapnia</i>	<i>hypercapnia vs eucapnia</i>
p value (ANOVA)	<0.001	<0.02

Figure 3.3.1

Resting cerebral vascular resistance under hypocapnic, eucapnic and hypercapnic conditions. Mean and 95% CI of the mean are shown. n=10 in each group. Values are given in the table above the chart. Significance of the differences between the groups (by analysis of variance) is given in table 3.3.1.a below the chart. There is a significant difference in resting cerebral vascular resistance between eucapnia and hypocapnia, and between eucapnia and hypercapnia

Table 3.3.2

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
95% CL	100	127.24	120.97	103.27	95.39	90.22	90.49	96.03	94.97	95.41	101.64	100.48	98.43	106.54	104.43	100.02
Mean iCVR	100	115.56	111.29	97.77	90.50	85.74	87.43	88.60	88.81	90.93	95.93	94.64	94.25	99.34	96.69	96.24
95% CL	100	103.88	101.60	92.26	85.61	81.26	84.37	81.16	82.65	86.45	90.23	88.80	90.07	92.13	88.94	92.47

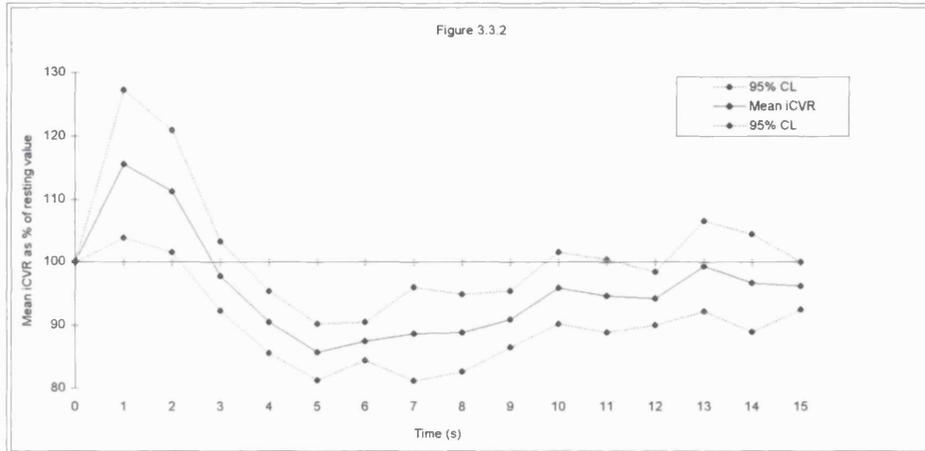


Figure 3.3.2 (above)

Variation in instantaneous cerebral vascular resistance (iCVR) with time following blood pressure stimulus under hypocapnic conditions. Mean and 95% CI of the mean shown. n=10. Values given in table above chart. Curve shows significant increase in iCVR from 1 to 2 seconds following stimulus (first phase) followed by more prolonged fall in iCVR (second phase).

Table 3.3.3

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
95% CL	100	110.97	108.92	103.83	104.65	105.70	109.78	106.06	104.38	104.02	105.96	108.27	104.06	102.23	103.48	104.73
Mean iCVR	100	106.20	103.80	101.66	101.61	102.57	104.62	102.14	100.15	100.10	100.92	101.06	99.82	98.71	99.25	101.29
95% CL	100	101.44	98.69	99.49	98.58	99.43	99.45	98.22	95.93	96.19	95.88	93.84	95.57	95.19	95.02	97.84

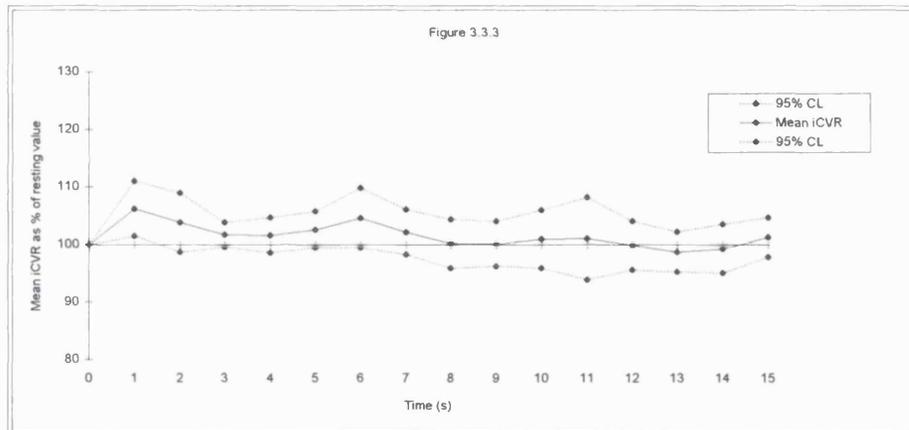


Figure 3.3.3 (above)

Variation in instantaneous cerebral vascular resistance (iCVR) with time following blood pressure stimulus under hypercapnic conditions. Mean and 95% CI of the mean shown. n=10. Values given in table above chart. Curve shows no significant change in iCVR following stimulus apart from a short-lived response in the first second.

3.3.4 Discussion of results

These results demonstrate that both the resting relative resistance of the cerebral vasculature and the response of the cerebral vasculature to a fall in systemic blood pressure are dependent upon arterial carbon dioxide concentration. The effects of carbon dioxide concentration on resting cerebral vascular resistance are shown to be as expected, with hypercapnia reducing relative resistance and hypocapnia increasing relative resistance. The mechanism of this change in relative cerebral vascular resistance with local carbon dioxide concentration is effected via a change in the resting tone of the vascular smooth muscle in the resistance arterioles, with hypercapnia reducing tone and hypocapnia increasing tone. This change in resting tone provides a starting point for the discussion of the differing responses to change in blood pressure which are found at the different carbon dioxide concentrations.

Under hypercapnic conditions resting tone in the cerebral vasculature resistance vessels is low, and middle cerebral artery blood flow velocity is high. A reduction in cerebral perfusion pressure similar to that under eucapnic conditions fails to elicit a similar response in terms of changes in relative cerebral vascular resistance to that found under eucapnic conditions: there is no further increase in middle cerebral artery blood flow velocity and no further reduction in relative cerebral vascular resistance with the blood pressure stimulus.

Under hypocapnic conditions resting tone in the cerebral resistance vessels is high. A sudden reduction in cerebral perfusion pressure elicits a complex response in cerebral

vascular resistance which appears to be in two phases, and the appearance of this biphasic response under hypocapnic conditions prompts a reassessment of the response under eucapnic conditions. It can be seen from figure 3.2.5 that there is indeed a biphasic response under eucapnic conditions, the first phase of which just fails to reach statistical significance. However, the results of a similar experiment described below in section 5.2 shows a statistically significant first phase response at eucapnia in a different, larger, group. This suggests that the failure to reach statistical significance in the first phase response in the group described here may represent a type 1 error. Under hypocapnic conditions the speed of the change in cerebral vascular resistance and its magnitude in response to the blood pressure stimulus applied are increased.

This biphasic response of relative cerebral vascular resistance to a fall in perfusion pressure has not been described before. The second part of the response, that of a fall in relative resistance which is seen at eucapnia, comprises the expected phenomenon of autoregulation. Its augmentation under conditions of hypocapnia and loss under hypercapnic conditions suggest that it is dependent upon resting cerebral vascular tone and may be effected by rapid local changes in that tone. The early change in relative cerebral vascular resistance, which is seen at eucapnia and is augmented at hypocapnia, appears to be paradoxical in that it shows an early apparent rise in resistance in response to a fall in perfusion pressure. A full explanation of this paradoxical first phase cannot be made using the data presented here, but a possible aetiology can be suggested.

The phenomenon may of course be an artefact of the calculations, equipment or experimental method, and thus spurious. This could be tested by designing an experiment to test rapid cerebral vascular autoregulation using different equipment and/or methods, to see if the phenomenon is preserved.

Assuming that the phenomenon is not artefactual, some insight may be gained from recognising that its magnitude is augmented by hypocapnia, which increases vascular tone. Consider the way in which autoregulation is stimulated and relative cerebral vascular resistance is calculated in these experiments; following a resting measurement the systemic blood pressure is suddenly lowered and the effect of this change is assessed by observing the changes in middle cerebral artery blood flow, and resistance is calculated from the continuous changes in the relationship between blood pressure and flow. The observed initial increase in relative cerebral vascular resistance implies that blood flow falls proportionately more than blood pressure during this first phase of the response. The magnitude of the difference between pressure fall and reduction in flow is increased when the vascular tone is increased, which again suggests that the first phase of the response is dependent on vascular tone.

Whilst vascular resistance is dependent upon vascular tone, it is not the tone per se which affects flow but the diameter of the vessels, and the function of smooth muscle tone is to maintain vascular diameter in the face of a distending pressure. In the example of the experiments described here, it can be postulated that during the paradoxical first phase there is a fall in pressure without change in vascular tone, and that constant vascular tone in the presence of reduced pressure will cause a transient

reduction in diameter of the vessels, until the autoregulatory response causes vasodilatation (by whatever mechanism).

Blood flow through a vessel is affected by the radius of the blood vessel according to Poiseuille's law, described in equation 10:

$$Q = \frac{\pi \Delta P r^4}{8 \eta l} \quad (10)$$

in which Q is blood flow, delta P is the pressure difference across the ends of the vessel, r is the radius of the vessel, eta is the blood viscosity and l is the vessel length (Guyton, 1977). It can be seen that flow is therefore proportional to the fourth power of the radius of the vessel, and so even a small change in the radius of a vessel can produce a large change in blood flow.

It is postulated that the paradoxical apparent increase in relative cerebral vascular resistance seen in the early part of these experiments is caused by a transient reduction in the diameter of cerebral resistance vessels as described above, and that since flow is proportional to the fourth power of the radius there is a greater reduction in flow than would be expected from the pressure change alone. The increased effect found under conditions of hypocapnia tends to corroborate this explanation; the increased vascular tone would tend to produce a more marked transient reduction in vessel size for the same pressure change with a correspondingly larger proportionate fall in flow and a larger apparent increase in relative vascular resistance.

From the above argument it can be seen that the paradoxical first phase response found in autoregulation in these experiments is a transient event which occurs, it is proposed, as a result of the suddenness of the blood pressure stimulus and the lag in the response of the cerebral vasculature. It may well be that the blood pressure stimuli which occur normally in an individual to stimulate autoregulation are not so sudden, and thus such a lag phase response does not occur in the normal physiological setting. Should this be proved to be the case, in this respect the first phase response may be described as an artefact of the experimental method, but one which nevertheless represents a real event in the cerebral circulation under these experimental conditions. Again, should the above arguments describe accurately the nature of the early part of the autoregulatory response generated by this experimental method, then the magnitude of the first phase response gives an indication of the resting vascular tone in the cerebral circulation (or rather, changes in the magnitude between experimental conditions can give an indication of changes in resting vascular tone), and its duration gives an indication of the speed of response of the autoregulatory mechanism. This raises the possibility in future experiments of using changes in the first phase response, as well as examining the magnitude of the second phase of autoregulation, to non-invasively investigate the mechanism of autoregulation.

Part 4 Cerebral vascular reactivity to hypercapnia

Synopsis

4.1 - Introduction

4.2 - Study of the effect of volitional respiration on middle cerebral artery blood flow velocity

4.2.1 - Introduction

4.2.2 - Aims

4.2.3 - Subjects and methods

4.2.4 - Results

4.2.5 - Discussion

4.3 - Protocol for measuring Cerebral vascular reactivity to hypercapnia

4.3.1 - Method

4.3.2 - Calculations

4.4 - Cerebral vascular reactivity to hypercapnia in patients with carotid atherosclerosis

4.4.1 - Introduction

4.4.2 - Aims

4.4.3 - Subjects and methods

4.4.4 - Results

4.4.5 - Discussion

Synopsis

A study of the effect of volitional control of respiration on middle cerebral artery blood flow velocity in normal subjects is described and it is shown that volitional respiration has a significant effect on middle cerebral artery blood flow velocity. These results are taken into consideration in the described protocol for the measurement of cerebral vascular reactivity to hypercapnia and calculation of reactivity index, which does not require the subjects to volitionally control their respiratory pattern. Cerebral vascular reactivity to hypercapnia is measured in a series of patients with carotid disease and is shown to be reduced in the presence of internal carotid artery occlusion. It is also shown that whilst some patients with severe carotid artery disease have reduced cerebral vascular reactivity to hypercapnia, the presence of severe carotid artery disease per se does not predict a reduced reactivity index. In the presence of internal carotid artery occlusion it is shown that an increased degree of contralateral internal carotid artery stenosis reduces ipsilateral cerebral vascular reactivity to hypercapnia.

4.1 Introduction

Transcranial Doppler ultrasound (TCD) can be used to measure changes in the velocity of blood flow through the basal cerebral arteries(Aaslid *et al.* 1982). Such changes have been shown to correlate well with changes in cerebral perfusion in response to vasoactive stimuli such as hypercapnia(Bishop *et al.* 1986) and acetazolamide(Hurn *et al.* 1991). However, the response to such vasodilating agents is obtunded in a proportion of patients with extracranial carotid stenosis or occlusion. It is thought that the lack of a normal vasodilatory response in a cerebral hemisphere ipsilateral to severe carotid disease indicates that there is pre-existing vasodilatation in the cerebral vasculature as a response to the chronic reduction in blood flow to that hemisphere, and the autoregulatory reserve which normally exists in the cerebral vasculature is exhausted. This phenomenon has been used as a non-invasive method to assess whether carotid disease has a haemodynamically significant effect on the cerebral blood flow in an individual (Kleiser & Widder, 1992; Norris *et al.* 1990).

Several different stimuli have been employed clinically to induce cerebral vascular reactivity in patients with carotid disease in an attempt to assess the effect of the carotid disease of the cerebral circulation, and similarly several different characteristics of middle cerebral artery blood flow have been used to describe the changes in cerebral blood flow. The use of hypercapnia(Bishop *et al.* 1986), a combination of hypercapnia and hypocapnia(Ringelstein EB *et al.* 1986; Maeda H *et al.* 1993), intravenous acetazolamide(Vorstrup *et al.* 1986) and a breath-holding technique(Markus & Harrison, 1992) have all been described to produce cerebral reactivity; which of these

is the most clinically appropriate vasoactive stimulus for such tests has not yet been established.

Acetazolamide is an inhibitor of the enzyme carbonic anhydrase which catalyses the dissociation/formation of carbonic acid(Heuser *et al.*1975). The use of acetazolamide in adequate doses (1g intravenous bolus injection) causes a marked cerebral acidosis producing maximal vasodilatation, and has been used in several studies of cerebral vascular reactivity(Vorstrup *et al.*1986; Karnik *et al.*1992; Ringelstein EB *et al.*1992) but its use is invasive and once administered the effects cannot be reversed. Should side effects such as severe headache or dizziness be caused treatment has to be symptomatic. The techniques for measuring reactivity using a combination of hypercapnia and hypocapnia (where hypocapnia is induced by requiring the subject to voluntarily hyperventilate) and that using voluntary breath-holding both require the subject to cognitively control their breathing pattern(Ringelstein EB *et al.*1986; Markus & Harrison, 1992). However, cognitive control of respiration has been shown using positron emission tomography to alter cerebral blood flow(Colebatch *et al.*1991; Ramsay *et al.*1993) and therefore measurements of cerebral vascular reactivity made using techniques which require the subject to voluntarily control their breathing pattern, such as hyperventilation or breath-holding, may be confounded by this effect. The study described in section 4.2 was designed to assess whether this possible confounding effect is detectable by transcranial Doppler ultrasound of the middle cerebral artery.

Section 4.3 describes the protocol used to measure the cerebral vascular reactivity of patients with carotid disease which is employed in all subsequent studies reported here.

Some studies of cerebral blood flow which use transcranial Doppler ultrasound of the middle cerebral artery describe the use of the peak systolic blood flow velocity as the measurement upon which calculations of reactivity are made (Bishop *et al.* 1986; Bishop *et al.* 1986), whilst others use the mean velocity of blood flow in the middle cerebral artery (Ringelstein EB *et al.* 1992; Ringelstein EB *et al.* 1988; Dahl *et al.* 1992; Maeda H *et al.* 1993; Karnik *et al.* 1992). Others studies still describe the measurement of middle cerebral artery blood flow velocity but do not specify whether peak systolic velocity or mean velocity is the measured entity. Section 4.4 describes a study comparing cerebral reactivity calculations made using both peak blood flow velocity and mean blood flow velocity measurements in each subject. In this study population the effect on cerebral vascular reactivity of both ipsilateral and contralateral carotid disease is assessed to investigate the role of the cerebral collateral circulation in determining reactivity to hypercapnia.

4.2 Study of the effect of volitional respiration on middle cerebral artery blood flow velocity.

4.2.1 Introduction

It has been shown using both positron emission tomography and transcranial Doppler ultrasonography of the brain that regional cerebral blood flow can be increased by cerebral activity(Ginsberg *et al.*1988). This has been shown to be the case for somatosensory tasks(Ginsberg *et al.*1988), for visual stimulation(Aaslid, 1987) and for cognitive tasks(Kelley *et al.*1992). Positron emission tomography has been used to show an increase in regional cerebral blood flow during volitional respiration in man(Colebatch *et al.*1991; Ramsay *et al.*1993). The effects of volitional control of respiration on middle cerebral artery blood flow have not been investigated using transcranial Doppler ultrasound. However, it is clear that if the increase in cerebral blood flow which occurs as a result of the cognitive task of voluntarily controlling respiration is detectable using transcranial Doppler ultrasound of the middle cerebral artery, then the effect of volitional control of respiration on middle cerebral artery blood flow may confound the results of experiments under circumstances which measure middle cerebral artery blood flow velocity while a cognitive task such as voluntary control of respiration is undertaken by the subject. Whilst such circumstances are rare, they do occur when cerebral vascular reactivity is tested using transcranial Doppler ultrasound of middle cerebral artery blood flow, and the method of application of the

vasoactive stimulus to the brain requires the subject to hyperventilate(Ringelstein EB *et al.*1988) or to breath-hold(Markus & Harrison, 1992). Both hyperventilation and breath-holding in this context are designed to change the local carbon dioxide concentration in the brain to induce vasoreactivity, but both techniques also require the subject to voluntarily control their respiratory pattern. Other techniques of testing cerebral vascular reactivity such as the use of hypercapnia induced by the inhalation of 5% carbon dioxide(Bishop *et al.* 1986) do not require such cognitive activity on the part of the experimental subject. If the cognitive act of controlling respiration changes middle cerebral artery blood flow then cerebral reactivity tests which require such activity on part of the of the subject may be prone to error, and therefore tests which do not require cognitive activity on the part of the subject are to be preferred. This study was designed to determine if in normal individuals the volitional control of respiration, independently of changes in end-tidal carbon dioxide concentration, caused a change in cerebral blood flow which could be detected by transcranial Doppler ultrasound examination of the blood flow in the middle cerebral artery.

4.2.2 Aims

The aim of this study was to investigate the hypothesis 'there is an increase in middle cerebral artery blood flow caused by volitional respiration which is a) independent of end-tidal carbon dioxide concentration and b) detectable by transcranial Doppler ultrasound of the middle cerebral artery blood flow velocity'.

4.2.3 Subjects and Methods

14 normal volunteers were studied. None had any history suggestive of cardiovascular disease or were taking vasoactive medication. Studies took place in a quiet, temperature controlled room.

Right middle cerebral artery blood flow velocity was monitored continuously using Transcranial Doppler ultrasound (SciMed PCDOP 842, see illustration 3a), with the ultrasound transducer fixed in place over the subject's squamous temporal bone window using an adjustable headband. Arterial blood pressure was continuously monitored non-invasively using a servo cuff plethysmography device (Ohmeda 2300 Finapres). The carbon dioxide concentration of the air breathed by the subject was controlled by requiring the subject to breath through a non-return mouthpiece from a purpose-built air/carbon dioxide mixing device (P.K. Morgan & Co.). End-tidal carbon dioxide concentration was monitored continuously via the non-return mouthpiece using a Morgan 901-MK2 infra-red carbon-dioxide analyser. The respiratory flow patterns exhibited by the subjects were monitored using a Fleisch pneumotachograph and recorded on a Racal Thermionic four channel high fidelity FM analogue tape recorder, and these recordings were played back to the subject via a Gould two channel digital storage oscilloscope.

In each subject the right middle cerebral artery was insonated and the Doppler ultrasound transducer fixed in position. The subject was allowed to rest breathing air

with their eyes open until both a steady respiratory pattern and a steady end-tidal carbon dioxide concentration were achieved, and then a two minute recording of the subject's respiratory pattern was made. During the second minute of this period the subject's middle cerebral artery mean blood flow velocity was measured (averaged over 60 seconds). The recording of the subject's respiratory flow pattern was then played back over the second channel of the oscilloscope whilst their real-time respiratory flow pattern was displayed on the first channel. The subject was then required, without changing position, to visually follow both the playback of their earlier resting respiratory pattern and their real-time respiratory pattern on the oscilloscope and to attempt to match the two traces. Thus the subject was required during this phase of the experiment to voluntarily control their respiration whilst maintaining a normal resting respiratory flow pattern, in an attempt to control for the effects of changing end-tidal carbon dioxide concentration. End-tidal carbon dioxide was again recorded during this period for later assessment of accuracy of ventilatory matching, and during the second minute of ventilatory matching the middle cerebral artery mean blood flow velocity measurements (averaged over 60 seconds) were again made. Following this the cerebrovascular reactivity index for the subject was measured using a standard technique (see section 4.3 below) with 5% carbon dioxide as the vasodilatory stimulus.

Hospital Ethical Committee approval was obtained, and each subject gave informed consent to participate in the study. Statistical analysis was performed using the Wilcoxon test for paired non-parametric data.

4.2.4 Results

The standard reactivity index was normal (see section 4.4 below) for all subjects (median 31.3, range 17.7 to 91.9 units). For each subject the change in middle cerebral artery blood flow velocity between the resting and test conditions is given in figure 4.2.1. The ratio of middle cerebral artery velocity between resting and test conditions is compared with changes in end-tidal carbon dioxide concentration in figure 4.2.2. There was a mean increase in middle cerebral artery mean velocity with voluntary control of breathing of 8.8% (95% Confidence Limits 1.8% to 15.8%, $0.05 > p < 0.01$) compared to quiet resting breathing, despite a mean change in end-tidal carbon dioxide of -0.16% ($p = 0.05$). Three subjects (a, e and l in figure 4.2.2) were unable to match their previous respiratory pattern to achieve an end-tidal carbon dioxide concentration similar to their resting value. Thus 11 of the 14 subjects achieved an end-tidal carbon dioxide concentration during controlled respiration which was within 0.2% of their resting value, and in this group there was a mean change of less than -0.05% ($p = 0.36$). In these 11 subjects, during voluntary control of respiration there was an increase in middle cerebral artery mean velocity of 12.2% (95% Confidence Limits 5.0% to 19.3%, $p < 0.005$). There was no significant difference in blood pressures between the resting and the test conditions.

Table 4.2.1

Subject	(Hz) rest	(Hz) volitional	difference in end-tidal CO ₂ (%)
a	856	830	-0.4
b	1430	1520	-0.2
c	824	1048	0.2
d	1480	1820	0
e	1600	1730	-0.5
f	670	690	0
g	1670	1950	0
h	2040	2250	0
i	1577	1472	0
l	1820	1930	-0.2
k	1848	2032	0
l	1253	1050	-1
m	1470	1490	0
n	780	1070	-0.2

Figure 4.2.1 (below)
 Change in middle cerebral artery blood flow velocity between resting and voluntary respiratory matching conditions. n=14. Values given in table (left). There is a mean increase in MCA blood flow velocity of 8.8% (95% CI 1.8% to 15.8%, 0.05 > p < 0.01). In subjects with well-matched end-tidal CO₂ (all except subjects a, e & l) the mean increase in MCA blood flow velocity was 12.2% (95% CI 5.0% to 19.3%, p < 0.005).

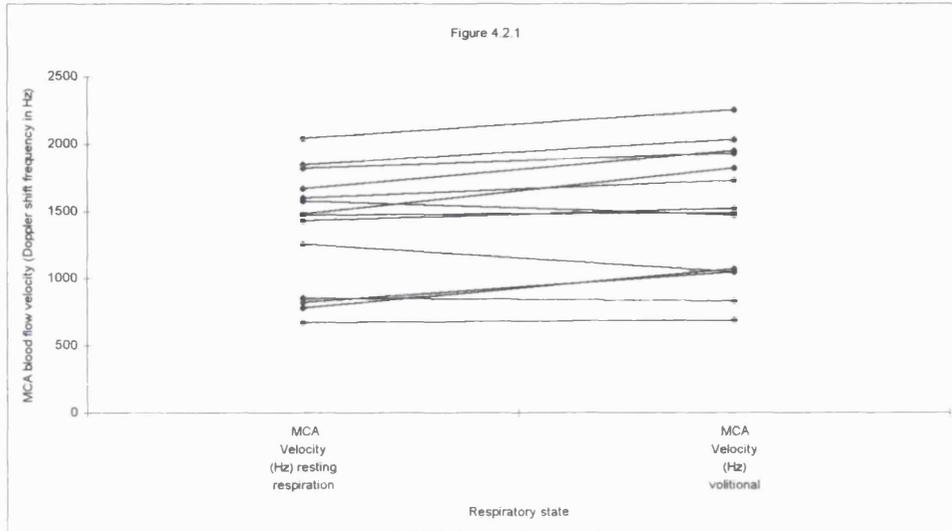
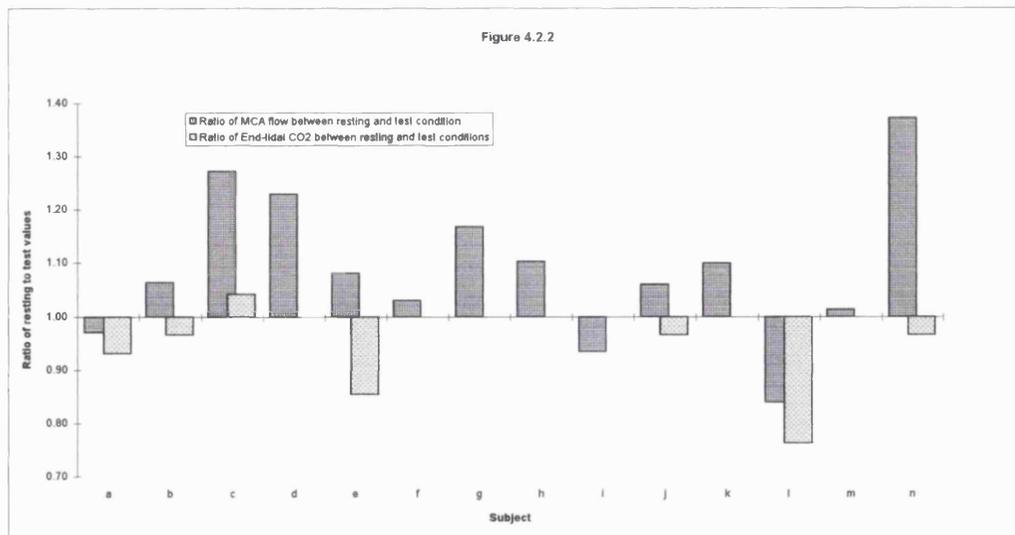


Table 4.2.2

Subject	Ratio of MCA flow between resting and test condition	Ratio of End-tidal CO ₂ between resting and test conditions
a	0.97	0.93
b	1.06	0.96
c	1.27	1.04
d	1.23	1.00
e	1.08	0.85
f	1.03	1.00
g	1.17	1.00
h	1.10	1.00
i	0.93	1.00
l	1.06	0.96
k	1.10	1.00
l	0.84	0.76
m	1.01	1.00
n	1.37	0.96

Figure 4.2.2 (below)
 Chart showing the ratios of the values for middle cerebral artery blood flow velocity and end tidal carbon dioxide concentration between the resting and the ventilatory matching conditions by individual subject. Values given in table (right). Dark bars represent MCA blood flow velocity ratios and light bars represent end-tidal carbon dioxide ratios.



4.2.5 Discussion

The results of this study demonstrate that right middle cerebral artery blood flow velocity is increased when respiration is controlled voluntarily compared to the resting condition, and that the change is independent of end-tidal carbon dioxide concentration.

The mechanism of the flow change observed in the middle cerebral artery with voluntary respiratory activity would appear to be similar to that proposed in other studies of cerebral blood flow involving cerebral activation; increased local metabolism associated with mental activity and voluntary breathing has been described using positron emission tomography(Colebatch *et al.* 1991; Ramsay *et al.* 1993; Ginsberg *et al.* 1988), and this is thought to result in a local increase in metabolites with dilatation of resistance arterioles and locally increased flow to the region.

The nature of the cerebral activation in the subjects in this study is complex, involving both visual feedback and motor co-ordination in the act of matching respiration. The motor task of controlling respiration is mediated both via the basal ganglia and somatic motor cortex to the intercostal nerves, and via the brain stem to the phrenic nerves.

There is also known to be an area in the primary motor cortex whose stimulation causes contraction of the contralateral diaphragm(Colebatch *et al.* 1991). Whilst the region of supply of the cerebral arteries is variable(van der Zwan & Hillen, 1991), the middle cerebral artery is likely to supply blood to most of the lateral cerebral cortical regions. The changes in middle cerebral artery flow measured in this study are therefore likely to represent changes in motor activity.

It could be suggested that a proportion of the flow changes found could have been induced by visual stimulation; this is however unlikely since such changes have been found to occur mainly in the posterior cerebral arteries, and those changes in middle cerebral artery blood flow caused by visual stimulation have been found to be of small magnitude (around 3%) and relatively short lived, lasting only 10-15 seconds(Aaslid, 1987).

These results should be taken into account when interpreting cerebral reactivity measurements made using hyperventilation or breath holding as a vasoactive stimulus. Hyperventilation tends to reduce arterial carbon dioxide concentration and cause vasoconstriction in the cerebral vasculature. The cognitive act of controlling respiration which is necessary to produce hyperventilation will however tend to locally increase blood flow in the middle cerebral artery. This local increase may confound calculation of cerebral reactivity index using hyperventilation as the stimulus, and indeed Ringelstein has reported in one study that using an additional hypocapnic phase in carbon dioxide reactivity measurements adds little to the power of the technique(Ringelstein EB *et al.*1992). Similarly, when breath-holding is used for cerebral reactivity measurements the stimulus to the cerebral vasculature may be partly an increase in systemic arterial carbon dioxide concentration and partly a local metabolic effect of cerebral activation.

Some techniques for measuring cerebral vascular reactivity may therefore be confounded if the subject is required to perform cognitive control of respiration. In the

experiments described in the following chapters, cerebral vascular reactivity is measured using a standard technique comparing resting middle cerebral artery blood flow velocity to that under hypercapnic conditions induced by the inhalation of 5% carbon dioxide. No cognitive control of respiration by the subject is required and thus this potential source of error is avoided.

4.3 Protocol for the measurement of middle cerebral artery blood flow velocity, middle cerebral artery reactivity to hypercapnia and middle cerebral artery reactivity index to hypercapnia.

4.3.1 Method

The following protocol describes the technique, standardised after Bishop(Bishop *et al.*1986), used for the measurement of cerebral vascular reactivity and reactivity index. In view of the results of the study described in section 4.2 above, in which it has been shown that voluntary control of respiration can increase middle cerebral artery blood flow velocity, a hypocapnic phase of reactivity measurement induced by voluntary hyperventilation by the subject is not employed.

Measurements are taken with subjects supine and relaxed.

1. Prior to middle cerebral artery blood flow velocity measurements, subjects undergo duplex Doppler ultrasound scanning of their carotid and vertebral vessels to assess the presence and extent of extracranial cerebrovascular disease. On each side, the common carotid artery, the internal & external carotid arteries & the vertebral arteries are visualised. The presence of atherosclerosis is assessed using B-mode ultrasound &

stenosis of the internal carotid artery is assessed by measuring the maximum velocity of systolic blood flow, the velocity of diastolic blood flow & the CC\IC velocity ratio.

2. The subject's head and neck are placed comfortably in position using a 'bean-bag' support from which air can be evacuated using standard wall suction to fix the position.

The ultrasound transducer is positioned over the ipsilateral squamous temporal bone window using an adjustable headband, and the ultrasound signal from the middle cerebral artery is identified using the criteria defined by Ringelstein(Ringelstein EB *et al.*1990). Briefly, a Doppler signal reflected by a blood stream passing predominantly towards the transducer at a depth of forty to sixty millimetres from the surface of the transducer is identified. The depth of insonation is incrementally increased by five millimetre steps until the Doppler signal zone of insonation encompasses a flow towards the transducer and a flow away from the transducer, corresponding to the point of bifurcation of the internal carotid artery into anterior and middle cerebral artery. The depth of insonation is then incrementally decreased until the insonated flow is solely towards the transducer, a point which corresponds to the M1 segment of the middle cerebral artery. The transducer is then fixed into position using a locking holder on the headband.

3. The subject breathes normally through a mouthpiece connected to a non-return valve. A low volume sampling line is connected to the mouthpiece and through this the carbon dioxide concentration of the inspired and expired gas is continuously monitored using an infra-red carbon dioxide analyzer (Morgan 901-MK2). The inspired gas inflow to the mouthpiece is from a purpose built air/carbon dioxide mixing device (P.K.

Morgan & Co.) which can be set to deliver air or a pre-mixed air-carbon dioxide mixture of a concentration determined by the experimenter. Arterial blood pressure is continuously monitored non-invasively using a servo-cuff plethysmography device (Ohmeda 2300 Finapres) attached to the subject' left or right middle finger.

4. The subject's mouthpiece is opened to air and when a stable end-tidal carbon dioxide concentration is recorded middle cerebral artery blood flow velocity characteristics (see below) are recorded for one minute.

5. The subject's mouthpiece is opened to a 5% carbon dioxide/95% air mixture, and when a stable end-tidal carbon dioxide is recorded middle cerebral artery blood flow velocity characteristics are recorded for one minute.

6. The subject's mouthpiece is again opened to air and when a stable end-tidal carbon dioxide is recorded middle cerebral artery blood flow velocity characteristics are recorded to confirm return to baseline values.

7. Steps 4 - 6 are repeated for the contralateral middle cerebral artery.

The characteristics of the middle cerebral artery blood flow which are recorded are the average peak systolic blood flow velocity, identified both by the experimenter and automatically by the transcranial Doppler ultrasound machine, and the average mean blood flow velocity. The mean blood flow velocity is the time-averaged mean of the

maximum blood flow velocity over the whole cardiac cycle, and is calculated by an algorithm internal to the transcranial Doppler ultrasound machine.

4.3.2 Calculations

The reactivity to hypercapnia of blood flow velocity in the middle cerebral artery has been defined by Bishop as the proportional increase in blood flow velocity during the test condition (hypercapnia) compared to the resting condition (eucapnia). However, the use of an inhaled 5% carbon dioxide in air mixture does not produce maximal cerebral vasodilatation in man. Maximal cerebral vasodilatation can be produced by the use of an inhaled 8% carbon dioxide in air mixture, but this is unpleasant for the subject and indeed is not tolerated by many subjects. The extent of cerebral vasodilatation in these experiments is therefore submaximal. Since the extent of cerebral vasodilatation is known to be dependent upon the intensity of the applied stimulus, that is, dependent upon the extent of hypercapnia achieved in each subject, a further value known as the reactivity index is calculated to take into account the extent of hypercapnia in each subject (Bishop *et al.* 1986). The reactivity index describes the percentage change in middle cerebral artery blood flow velocity per unit change in end-tidal carbon dioxide concentration.

Middle cerebral artery reactivity to hypercapnia is calculated using the formula given in equation 11:

$$Reactivity = \frac{100 * (MCA_2 - MCA_1)}{MCA_1} \quad (11)$$

where

MCA_1 = average MCA velocity at eucapnia

MCA_2 = average MCA velocity at hypercapnia

From this value, reactivity index is calculated using the formula given in equation 12:

$$ReactivityIndex = \frac{Reactivity}{etCO_{2_2} - etCO_{2_1}} \quad (12)$$

where

et1CO_1 = average end tidal carbon dioxide concentration at eucapnia

et2CO_2 = average end tidal carbon dioxide concentration at hypercapnia.

4.4 Cerebral vascular reactivity to hypercapnia in patients with carotid atherosclerosis

4.4.1 Introduction

Several studies have addressed the issue of assessing the relationship between the presence of carotid disease and changes in cerebral vascular reactivity. Results of reactivity studies are usually reported in terms of the reactivity index as defined above but some calculations are reported using as their data source the peak middle cerebral artery blood flow velocity whilst others use the mean middle cerebral artery blood flow velocity. An investigation into both the relationship between reactivity measurements made using these two characteristics of middle cerebral artery blood flow and the relationship between cerebral vascular reactivity and ipsilateral carotid disease is described below.

Whilst cerebral reactivity measurements have shown there to be a population of patients with severe carotid disease or internal carotid artery occlusion who have reduced cerebral vascular reactivity, there is also a population of patients with similar carotid disease who have normal cerebral vascular reactivity. The existence of this second group has been attributed to the phenomenon of cross-flow of blood from one carotid system to the other across a patent Circle of Willis (that is, through a patent anterior communicating artery) in those patients with severe carotid disease but normal reactivity. If this is the case then it can be postulated that cerebral vascular reactivity

ipsilateral to severe carotid disease may be affected by the presence of severe contralateral carotid disease. An investigation into the effect of the presence of contralateral severe carotid disease on cerebral vascular reactivity in hemispheres ipsilateral to severe carotid disease is also described below.

4.4.2 Aims

The aims of this study were to investigate the following hypotheses:

- a) Cerebral vascular reactivity calculations made using peak middle cerebral artery blood flow velocity measurements and those made using mean middle cerebral artery blood flow velocity measurements are equivalent and therefore interchangeable.
- b) There is a predictable relationship between the degree of vascular reactivity to hypercapnia in a cerebral hemisphere and the severity of ipsilateral carotid artery disease.
- c) In the presence of severe carotid artery disease, the degree of cerebral vascular reactivity in the ipsilateral hemisphere is affected by the presence of severe contralateral carotid artery disease.

4.4.3 Subjects and methods

The subjects of this study were patients referred to the Vascular surgical unit at St. Thomas' Hospital, London for investigation of suspected carotid artery disease.

All subjects underwent assessment of bilateral carotid and vertebral artery blood flow by duplex Doppler ultrasound and assessment of bilateral middle cerebral artery reactivity to hypercapnia was carried out according to the protocol described in section 4.3 above by an investigator who was unaware of the results of the scan of the neck vessels.

4.4.4 Results

97 patients were examined. All had satisfactory visualisation of the neck vessels by Duplex Doppler ultrasound. In 11 cerebral hemispheres there was unsuccessful insonation of the middle cerebral artery (unilaterally in 3 subjects and bilaterally in 4 subjects). 2 patients were unable to tolerate inspiration of 5% carbon dioxide for long enough to allow reactivity measurements to be performed. This gave rise to a rate of successful measurement of cerebral reactivity of 90% (92% if individual hemispheres are considered), which is similar to other published reports (Ringelstein EB *et al.* 1992; Markus & Harrison, 1992; Dahl *et al.* 1992).

a) Comparison of reactivity indices calculated using peak blood flow velocity and mean blood flow velocity values.

In 144 hemispheres ipsilateral to non-occluded internal carotid arteries the reactivity index was calculated separately using the peak middle cerebral artery blood flow velocities at eucapnia and at hypercapnia (RI_{Peak}) and the mean middle cerebral artery blood flow velocities at eucapnia and at hypercapnia (RI_{Mean}). The scattergram in figure 3.4.1 shows the relationship between RI_{Peak} and RI_{Mean} . The mean value for RI_{Peak} in hemispheres ipsilateral to non-occluded internal carotid arteries is 21.8 (95% confidence limits 19.4 to 24.3, 99% confidence limits 18.6 to 25.1), and the mean value for RI_{Mean} in hemispheres ipsilateral to non-occluded internal carotid arteries is 28.2 (95% confidence limits 25.3 to 31.1, 99% Confidence limits 24.5 to 32.1). By paired t-test $p < 0.0001$.

Initial examination of these data appears to show a good correlation between the two calculated indices; the correlation coefficient is 0.855 with a slope to the best-fit line of 0.723 and an intercept of 1.23. This would suggest that the two indices are interchangeable, allowing for the slope of the best-fit line which gives the relationship shown in equation 13:

$$RI_{Peak} = 1.23 + 0.723 * RI_{Mean} \quad (13)$$

In 35 hemispheres ipsilateral to occluded internal carotid arteries the RI_Peak and RI_Mean were assessed. The scattergram in figure 3.4.2 shows the relationship between RI_Peak and RI_Mean for this group. The mean value for RI_Peak in hemispheres ipsilateral to occluded internal carotid arteries is 9.1 (95% confidence limits 6.1 to 12.1, 99% Confidence limits 5.2 to 13.0), and the mean value for RI_Mean ipsilateral to occluded internal carotid arteries is 13.4 (95% confidence limits 9.3 to 17.6, 99% Confidence limits 8.0 to 18.9). The correlation coefficient in this group is 0.78, the slope to the best-fit line is 0.56 and the intercept is 1.55. By paired t-test $p=0.003$.

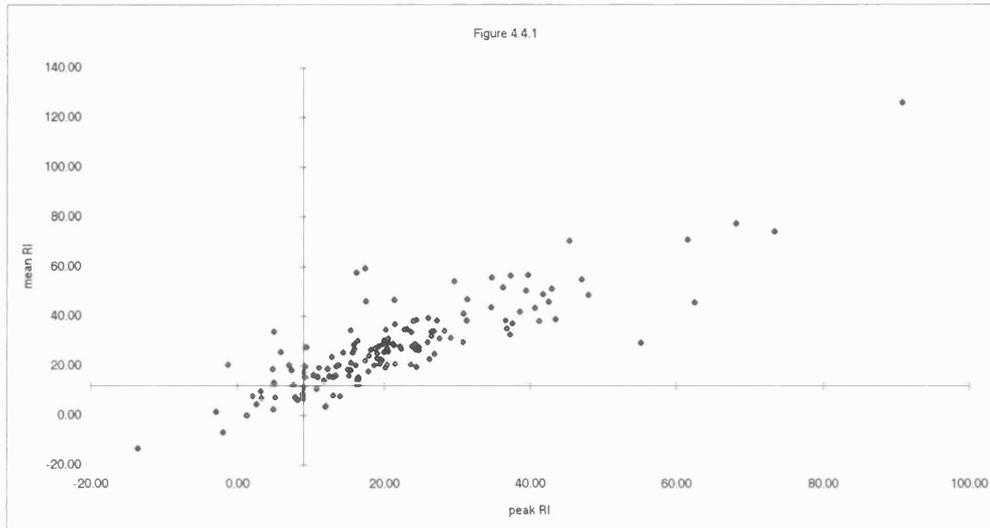


Figure 4.4.1 (above)
 Scattergram showing the relationship between middle cerebral artery reactivity indices to hypercapnia in cerebral hemispheres calculated using peak MCA blood flow velocity (peak RI) and mean MCA blood flow velocity mean RI), in hemispheres ipsilateral to non-occluded internal carotid arteries. n=144 hemispheres. There is a highly significant relationship between the two values ($p < 0.0001$ by paired t-test).

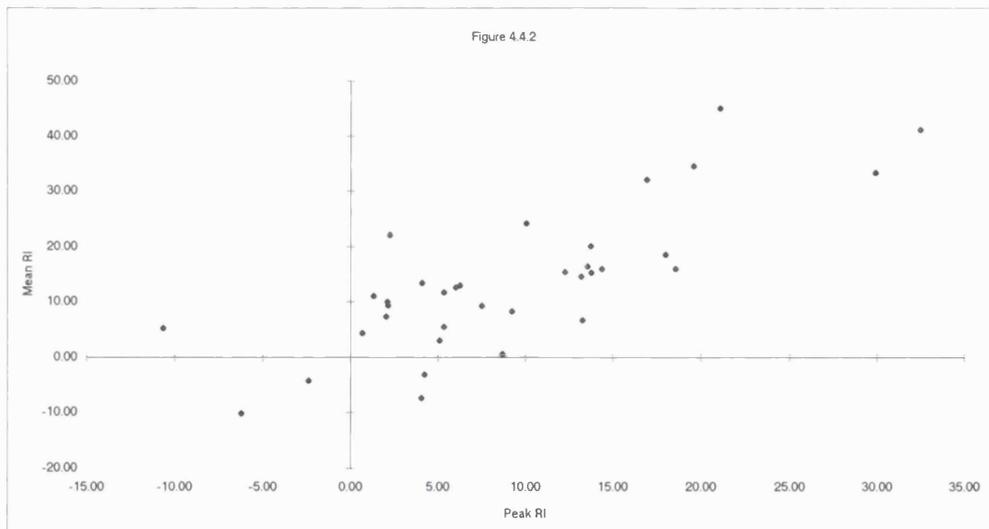


Figure 4.4.2 (above)
 Scattergram showing the relationship between middle cerebral artery reactivity indices to hypercapnia in cerebral hemispheres calculated using peak MCA blood flow velocity (peak RI) and mean MCA blood flow velocity mean RI), in hemispheres ipsilateral to occluded internal carotid arteries. n=35 hemispheres. There is a significant relationship between the two values ($p = 0.003$ by paired t-test).

b) The relationship between reactivity index to hypercapnia and the severity of ipsilateral carotid artery disease.

Reactivity indices to hypercapnia were calculated using both peak and mean middle cerebral artery blood flow velocity values in 179 hemispheres in which the ipsilateral internal carotid artery was assessed for stenosis or occlusion using duplex Doppler ultrasound according to velocity criteria (Baker *et al.* 1986). The results found using peak middle cerebral artery blood flow velocity values and those found using mean middle cerebral artery blood flow velocity values were assessed independently. The relationship between reactivity values and degree of ipsilateral internal carotid artery stenosis is shown in figures 4.4.3 and 4.4.4. The mean and 95% Confidence limits for the reactivity indices for each of the stenosis groups are shown. There was no significant difference between the values found for any of the groups ipsilateral to a non-occluded internal carotid artery. However, the value found for the reactivity indices ipsilateral to an occluded internal carotid artery was significantly lower, for both RI_Peak and RI_Mean measurements, than that found ipsilateral to non-occluded internal carotid arteries ($p < 0.001$ for each relationship by unpaired t-test).

Table 4.4.3

Category of stenosis	0 0%-60%	1 60%-80%	2 80%-99%	3 Occlusion
95% CL	25.44	29.47	22.00	12.07
Mean of Peak RI	21.80	24.65	18.16	9.10
95% CL	18.16	19.83	14.31	6.12
p		ns	ns	<0.001

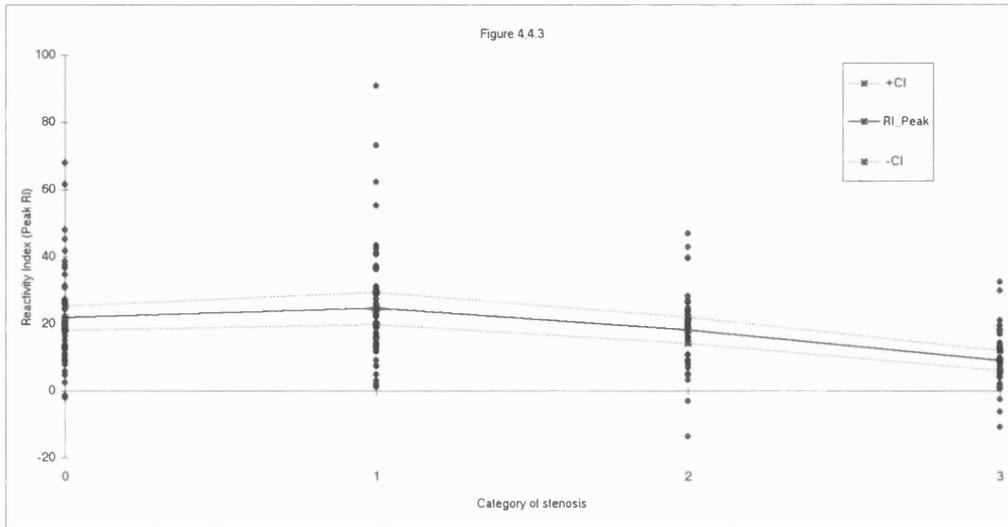


Figure 4.4.3 (above)

Variation in Peak RI with degree of ipsilateral internal carotid artery stenosis or occlusion. Category 0, 0-60% stenosis; category 1, 60-80% stenosis; category 2, 80-99% stenosis; category 3, occlusion of ipsilateral internal carotid artery. Means and 95% CI of means shown. Values and statistical significance given in table above chart. There is a significant fall in peak RI with occlusion of the ipsilateral ICA.

Table 4.4.4

Category of stenosis	0 0%-60%	1 60%-80%	2 80%-99%	3 Occlusion
95% CL	32.87	35.49	30.76	17.59
Mean of Mean RI	28.52	30.00	25.63	13.45
95% CL	24.17	24.52	20.50	9.31
p		ns	ns	<0.001

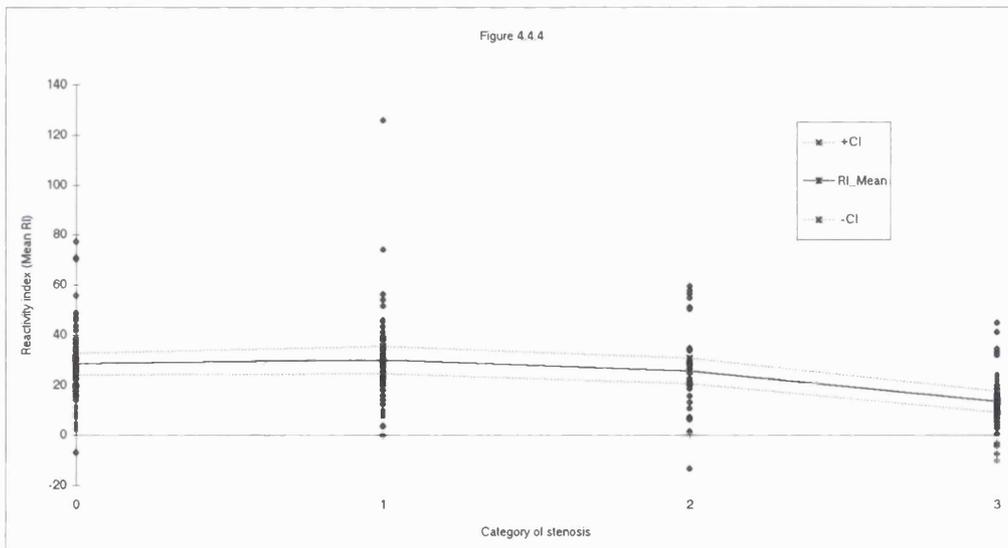


Figure 4.4.4 (above)

Variation in Mean RI with degree of ipsilateral internal carotid artery stenosis or occlusion. Category 0, 0-60% stenosis; category 1, 60-80% stenosis; category 2, 80-99% stenosis; category 3, occlusion of ipsilateral internal carotid artery. Means and 95% CI of means shown. Values and statistical significance given in table above chart. There is a significant fall in mean RI with occlusion of the ipsilateral ICA.

c) The relationship between reactivity index to hypercapnia ipsilateral to an occluded internal carotid artery and the degree of contralateral internal carotid artery stenosis.

Of the 35 hemispheres ipsilateral to an internal carotid artery occlusion, two were opposite a hemisphere in which it was not possible to insonate the middle cerebral artery. Reactivity indices to hypercapnia were therefore calculated using both peak and mean middle cerebral artery blood flow velocity values in 33 hemispheres which were ipsilateral to an occluded internal carotid artery, diagnosed using duplex Doppler ultrasound. The degree of stenosis of the contralateral internal carotid artery was assessed using duplex Doppler ultrasound according to velocity criteria (Baker *et al.* 1986). The results found using peak middle cerebral artery blood flow velocity values (RI_Peak) and those found using mean middle cerebral artery blood flow velocity values (RI_Mean) were assessed independently. The distribution of reactivity indices in these groups are demonstrated in figures 4.4.5a to 4.4.5f. The relationship between the value for reactivity index to hypercapnia in the hemisphere ipsilateral to the occluded internal carotid artery and the degree of contralateral internal carotid artery stenosis is shown in figures 4.4.6 and 4.4.7. The mean and 95% Confidence limits and the variances for the reactivity indices for each of the groups are shown. The statistical relationship between the two groups can be assessed either by comparing the means using an unpaired t-test without assuming equal variances for the groups, or by compiling a contingency table using the relationship of each value to the mean of the whole group. The contingency tables thus compiled are shown in figure 4.4.8 as are the probability values given by each of the statistical tests. Such two-by-two

contingency tables are amenable to analysis by the chi-squared test if all expected frequencies are greater than 5 (page 245 in (Bland, 1987)); these groups are therefore just large enough but have been further analyzed using Fisher's Exact test for small groups as a comparison (page 255 in (Bland, 1987)). The results for RI_Peak show good concordance between the various statistical methods; the probability of there being no difference between the groups varied between $p=0.024$ and $p=0.026$, thus it is probable that an increased degree of contralateral internal carotid artery stenosis is associated with a reduced RI_Peak ipsilateral to an occluded internal carotid artery. However, there was poor concordance between the results of statistical analysis of RI_Mean values, the probability of there being no difference between the groups varied between $p=0.027$ and $p=0.123$. This may represent a genuine lack of relationship between the two variables or it may represent an error of the second kind, as a result of the small numbers in the test population.

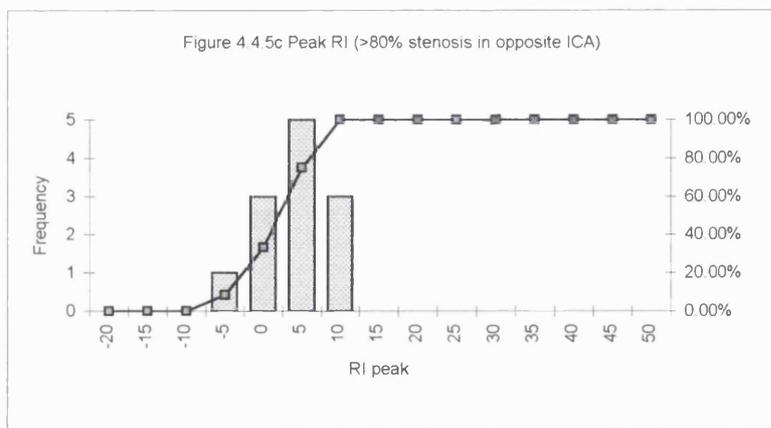
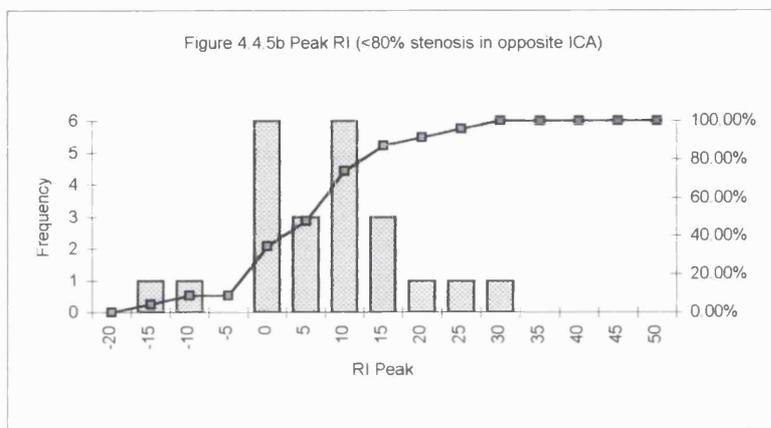
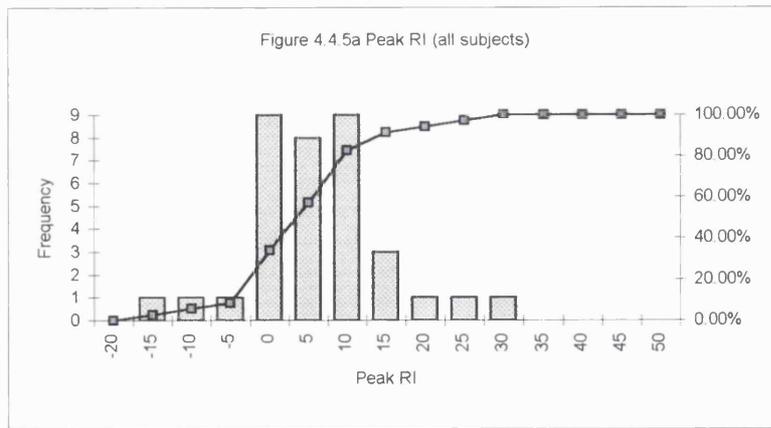


Figure 4.4.5 a-c (above)
 Histograms of the distribution of peak RI ipsilateral to an occluded internal carotid artery according to the degree of stenosis of the contralateral internal carotid artery.

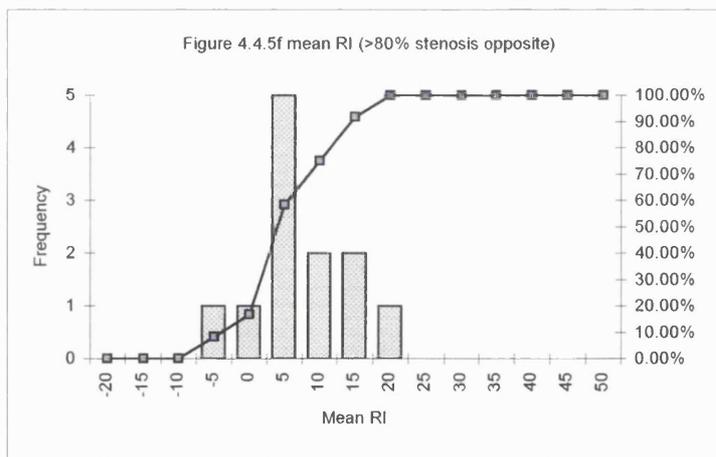
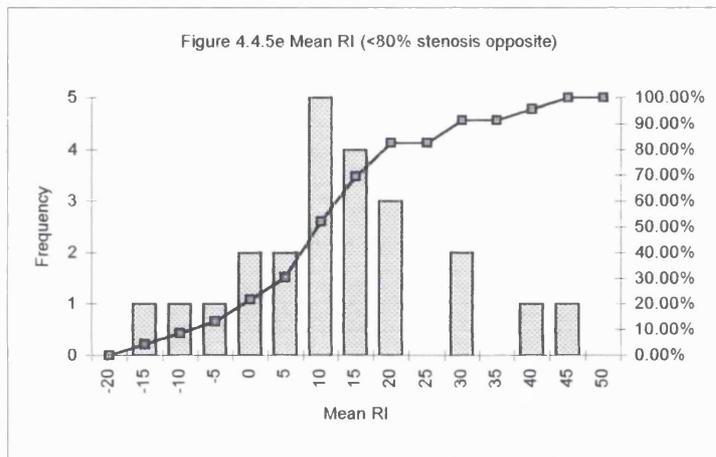
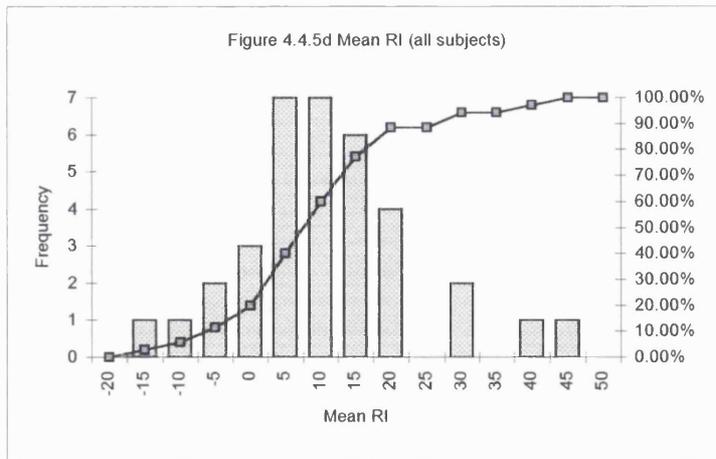


Figure 4.4.5 d-f (above)
 Histograms of the distribution of mean RI ipsilateral to an occluded internal carotid artery according to the degree of stenosis of the contralateral internal carotid artery.

Table 4.4.6

Category of stenosis	Occlusion +stenosis	Occlusion -stenosis
95% CI	9.16	14.51
Peak RI	6.45	10.33
95% CL	3.74	6.15

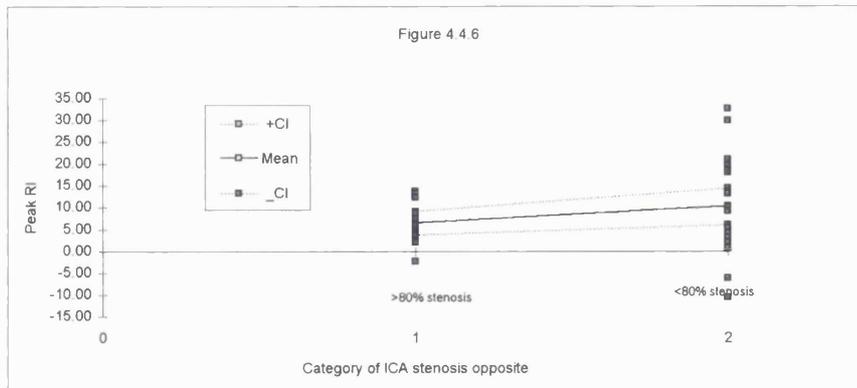


Figure 4.4.6 (above)
Variation in peak RI ipsilateral to an occluded ICA with degree of stenosis of contralateral ICA. Mean and 95% CI of the mean shown. Values given in table above chart. Statistical analysis in figure 4.4.8.

Table 4.4.7

Category of stenosis	Occlusion +stenosis	Occlusion -stenosis
95% CI	13.21	20.63
Mean RI	9.39	14.98
95% CL	5.58	9.34

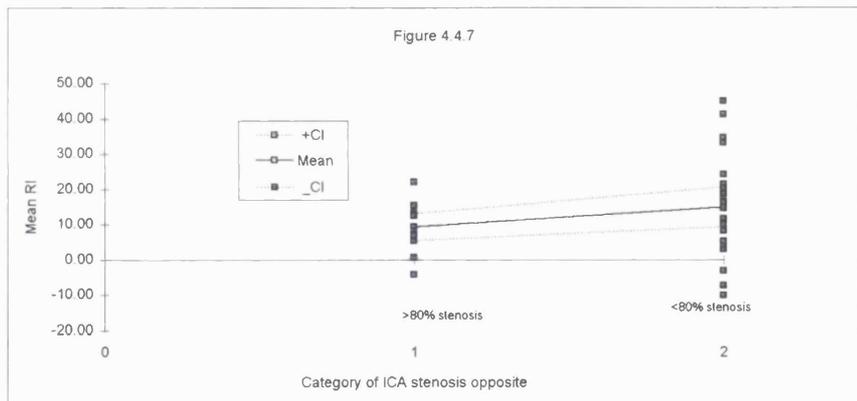


Figure 4.4.7 (above)
Variation in mean RI ipsilateral to an occluded ICA with degree of stenosis of contralateral ICA. Mean and 95% CI of the mean shown. Values given in table above chart. Statistical analysis in figure 4.4.8.

Figure 4.4.8		Contingency tables	
Peak Reactivity index		Mean Reactivity index	
Occlusion +stenosis	Occlusion -stenosis	Occlusion +stenosis	Occlusion -stenosis
>9	2 13	>13	3 12
<9	10 10	<13	9 11
Statistical analysis			
unpaired t test p =	0.026	unpaired t test p =	0.027
chi-square p =	0.0237	chi-square p =	0.1231
fisher exact p =	0.0264	fisher exact p =	0.0916

Figure 4.4.8 (above)
Contingency tables of distribution of reactivity indices ipsilateral to occluded ICA according to degree of stenosis of contralateral ICA. There is a fall in reactivity index associated with increasing contralateral ICA stenosis. This is consistently statistically significant for peak RI but not for mean RI.

4.4.5 Discussion

This study investigated several problems related to the measurement of cerebral reactivity to hypercapnia in a population of patients with carotid artery disease.

Reactivity index was calculated from peak middle cerebral artery blood flow velocity (RI_Peak) and from mean middle cerebral artery blood flow velocity (RI_Mean) and the relationship between the two values assessed. A strong correlation between the two measurements was found. In the presence of a non-occluded ipsilateral internal carotid artery, neither RI_Peak nor RI_Mean was found to vary significantly with the degree of ipsilateral internal carotid artery stenosis. There was however a significantly lower mean value for both RI_Peak and RI_Mean in the presence of an occluded ipsilateral internal carotid artery. These two results suggest that the whilst the two methods of calculating reactivity index may not be strictly interchangeable, providing that one or the other is used in any set of experiments they will tend to give the same information about the reactivity of the cerebral vasculature.

The effect on ipsilateral reactivity index of contralateral internal carotid artery stenosis in the presence of an ipsilateral internal carotid artery occlusion was less clear-cut. Both the mean RI_Peak and the mean RI_Mean values were reduced by an increased severity of contralateral internal carotid artery stenosis; this reduction reached statistical significance in the case of the RI_Peak value but in the case of the RI_Mean value the significance was unclear. Consideration of the distribution of reactivity

indices in these groups with occluded ipsilateral internal carotid arteries is of interest, particularly the histogram of distribution of RI_Peak in the group with a low degree of contralateral internal stenosis. There appears to be a bimodal distribution in this group.

It could be conjectured that such a bimodal distribution may occur as a result of there being two populations here, one in which there is adequate cross-flow from the contralateral carotid system (the group with the higher reactivity index) and one in which there is inadequate cross-flow from the contralateral carotid system (the group with the lower reactivity index). However, since such subgroup analysis was not a stated aim of the study no statement about the significance of these findings can be made; this group would be suitable for analysis in a further study.

Thus, the measurement methods of RI_Peak and RI_Mean appear to be affected in a similar way as a result of variations in the degree of ipsilateral internal carotid artery stenosis. This suggests that in reporting the results of reactivity measurements or in the assessment of such reports it is not important which value of middle cerebral artery blood flow velocity (peak or mean velocity) is used to calculate reactivity index, as long as it is made clear which is used and the same value is used consistently in any series of investigations. Furthermore, the finding that contralateral internal carotid artery disease can be important in determining reactivity index ipsilateral to an occluded internal carotid artery supports the idea that flow between carotid systems can occur across the anterior circle of Willis, and consideration of the distribution of reactivity indices suggests that such cross-flow may be important in the maintenance of normal cerebral reactivity in the presence of severe carotid disease.

Part 5 The relationship between cerebral vascular reactivity and cerebral vascular autoregulation in subjects with severe carotid disease.

Synopsis

5.1 - Introduction

5.2 - Study of cerebral vascular reactivity and cerebral vascular autoregulation in the presence of severe carotid disease

5.2.1 - Aim

5.2.2 - Subjects and methods

5.2.3 - Calculations

5.2.4 - Results

5.2.5 - Discussion

Synopsis

The relationship between cerebral vascular autoregulation and cerebral vascular reactivity to hypercapnia is tested in a group of subjects with severe carotid disease.

The methods described in previous sections for the measurement of cerebral vascular autoregulation and cerebral vascular reactivity to hypercapnia are employed to measure both parameters in each individual and it is shown that there is a strong correlation between the presence of reduced cerebral vascular reactivity to hypercapnia and reduced cerebral vascular autoregulation to pressure change.

5.1 Introduction

The studies described in the preceding chapters have demonstrated the phenomena of cerebral vascular autoregulation to perfusion pressure change and of cerebral vascular reactivity to hypercapnia. It has been shown that it is possible to measure rapid cerebral vascular autoregulation non-invasively in man and that its expression in normal individuals is dependent upon end-tidal carbon dioxide concentration. Cerebral vascular reactivity to hypercapnia has been demonstrated, and a range of values for reactivity in normal subjects and those with carotid disease has been described. A variation from this range has been shown in some patients with severe carotid disease.

As is described in section 1.5 of the Introduction, it has been assumed that the presence in a subject of reduced reactivity to hypercapnia in the cerebral hemisphere ipsilateral to severe carotid disease indicates that this hemisphere is similarly unable to achieve autoregulation of its blood flow in response to a drop in cerebral perfusion pressure. It is the existence of this assumed relationship between reduced reactivity and reduced autoregulation which underlies the use of measurements of reactivity in the clinical setting to assess the adequacy of blood supply to a cerebral hemisphere. However, this relationship between loss of reactivity to hypercapnia and reduction in capacity for autoregulation has not been demonstrated. In the study described below a selected group of patients with severe carotid disease had both their cerebral vascular reactivity and cerebral vascular autoregulation measured in order to investigate whether or not such a relationship exists.

5.2 - Study of cerebral vascular reactivity and cerebral vascular autoregulation in the presence of severe carotid disease

5.2.1 Aim

The aim of this study was to test the hypothesis 'In patients with severe carotid artery disease there is a correlation between the presence in a cerebral hemisphere of reduced vascular reactivity to hypercapnia and the presence in that hemisphere of reduced vascular autoregulation to a fall in cerebral perfusion pressure'.

5.2.2 Subjects and methods

Twenty six cerebral hemispheres in fifteen patients with severe internal carotid artery disease or internal carotid artery occlusion were investigated. Eleven patients had bilateral disease and four patients had unilateral disease.

The patients were selected primarily on the basis of the severity of their carotid disease and secondarily on the basis of their suitability to undergo autoregulation measurement; it was felt that there was a theoretical possibility that the technique used to measure autoregulation (as described in section 3.2.3 above) may have deleterious effects on the

leg circulation of patients with severe lower limb atherosclerosis, in view of the need to compress the femoral artery to suprasystolic pressures. Patients with symptoms of calf claudication or absent popliteal pulses were therefore excluded from the study. Following the experiments described below there was no incidence of compromised lower limb blood flow after release of the thigh compression cuffs, and indeed experience in another centre with over one hundred examinations using a similar technique of thigh compression to induce a fall in blood pressure has produced no complications related to lower limb blood flow without selecting out patients with lower limb blood vessel atherosclerosis (Personal communication; D Newell, Dept of Neurology, Institute of Applied Physiology and Medicine, Seattle Washington, USA). This technique of measuring autoregulation may therefore be suitable for use in patients with femoral artery disease; it remains to be seen however if would be possible to achieve the same degree of hypotension using this technique in subjects with femoral artery occlusion as it is in those with patent lower limb vessels.

Experiments were performed in a quiet, temperature controlled environment at 22 degrees Centigrade. Patients underwent duplex Doppler examination of their carotid and vertebral circulations and measurement of the cerebral vascular reactivity to hypercapnia in the hemisphere ipsilateral to the carotid disease was performed (according to the protocol described in section 4.3). A five minute rest period was allowed following which, in the same hemisphere, the cerebral vascular autoregulation to a fall in cerebral perfusion pressure was measured (as described in section 3.2). In patients with bilateral carotid disease a ten minute rest period was allowed before cerebral vascular reactivity and autoregulation were similarly measured on the second

side. Calculation of both reactivity to hypercapnia and autoregulation to fall in perfusion pressure were carried out after the conclusion of the experiment.

This study was approved by the Ethics Committee of St. Thomas' Hospital.

5.2.3 Calculations

Cerebral vascular reactivity to hypercapnia and reactivity index were calculated as described in section 4.3.2. Cerebral vascular autoregulation was calculated as described in section 3.2.4.

It can be seen that calculation of both the reactivity to hypercapnia and the reactivity index for a particular cerebral hemisphere produce single values for each measurement, values which can be formally described as being interval data (Bland, 1987). The measurement of autoregulation however produces a set of results which describe a variation in relative resistance of the cerebral vasculature over time, and this data can not therefore formally be described as interval data. In order to compare the reactivity index and the autoregulation of a cerebral hemisphere it becomes necessary to identify a single value to represent autoregulation in each hemisphere, which ideally should also be an interval datum (Bland, 1987).

Consideration of the results of autoregulation studies in normal subjects at eucapnia reveals that the applied fall in cerebral perfusion pressure induces a fall in relative cerebral vascular resistance which effectively lasts from five to fifteen seconds after the application of the blood pressure stimulus. It was therefore decided to use the single value of relative resistance in the middle of this period (that is, at ten seconds after application of the blood pressure stimulus) as being representative of the autoregulatory response in each hemisphere. The value used (denoted by the shorthand iCVR10) is the amount by which cerebral vascular resistance is calculated to have fallen by 10 seconds after onset of the blood pressure stimulus, expressed as a percentage of the resting cerebral vascular resistance. This value for each individual cerebral hemisphere is an interval datum and can therefore be compared to the reactivity index for that hemisphere. The decision to use the value of amount of fall in relative cerebral vascular resistance at ten seconds after application of the blood pressure stimulus ('iCVR10') is essentially an arbitrary one, though it was made as a result of the consideration of the results of a separate set of experimental data. However, since such autoregulation data have not been generated before there is no convention to follow and no guidelines exist to indicate a more appropriate method of conversion of the data to an interval scale. Comparison is therefore made between reactivity index and iCVR10, by rank correlation using Spearman's rho (for interval data without the assumption of normal distributions or uniform variances for the variables) (Bland, 1987).

5.2.4 Results

The results of cerebral vascular autoregulation measurements (relative resistance at 10 seconds after application of blood pressure stimulus - iCVR10) and for cerebral vascular reactivity index calculated using both peak and mean middle cerebral artery blood flow velocity measurements for the twenty six cerebral hemispheres examined are given in figure 5.2.1. The relationship between the iCVR10 and peak reactivity index is displayed in figure 5.2.2 and that between iCVR10 and mean reactivity index is displayed in figure 5.2.3. There is a highly statistically significant relationship between the iCVR10 and both reactivity indices; the calculated correlations are -0.65 (peak) and -0.68 (mean), and $p < 0.001$ for both relationships.

Using the values for reactivity indices defined in section 4.4 the above results were further analysed by separating the hemispheres examined into those with normal reactivity index (RI peak > 9) and those with reduced reactivity index (RI peak < 9). From figure 5.2.1 it can be seen that there were 17 hemispheres with normal reactivity and 9 hemispheres with reduced reactivity. The full autoregulation data for these two groups are displayed in figures 5.2.4 (normal reactivity) and 5.2.5 (reduced reactivity).

Figure 5.2.1

Number	Subject	RI Peak	RI mean	% Relative cerebral vascular resistance at 10 seconds	iCVR10
1	84R	1	11	99	-1
2	85L	3	7	93	-7
3	88L	1	4	99	-1
4	88R	2	7	99	-1
5	93L	24	27	77	-23
6	93R	6	12	97	-3
7	94L	20	27	89	-11
8	94R	5	11	97	-3
9	102R	-5	3	105	5
10	104L	14	21	92	-8
11	104R	12	19	70	-30
12	105L	18	23	90	-10
13	105R	10	15	91	-9
14	106L	13	19	76	-24
15	106R	14	20	83	-17
16	108L	25	34	74	-26
17	108R	13	24	61	-39
18	109L	11	16	93	-7
19	109R	10	15	89	-11
20	110L	18	30	86	-14
21	110R	24	36	84	-16
22	111L	26	31	86	-14
23	111R	22	31	77	-23
24	112R	27	32	80	-20
25	120L	6	18	91	-9
26	120R	6	11	99	-1

Figure 5.2.1 (left)
Peak and mean reactivity indices and cerebral vascular autoregulation measurements in 26 cerebral hemispheres ipsilateral to severely stenosed or occluded internal carotid arteries.

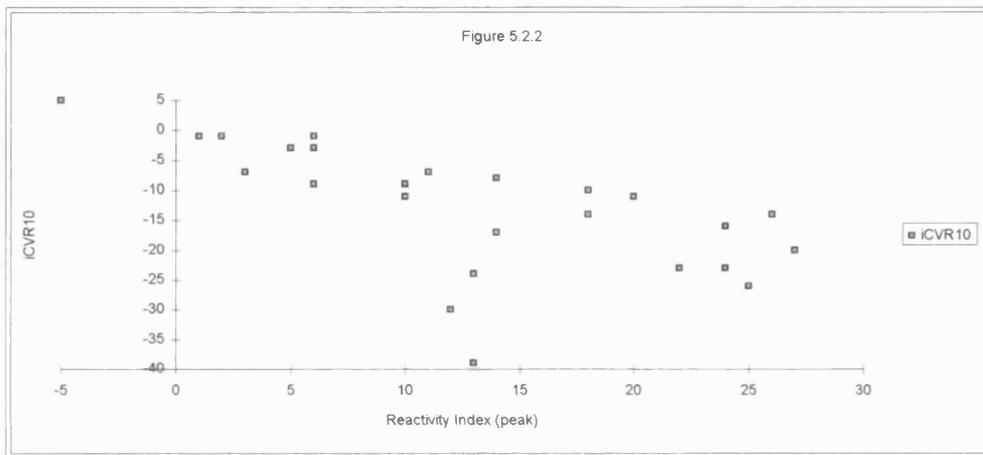


Figure 5.2.2 (above)
Relationship between iCVR10 and peak reactivity index in 26 cerebral hemispheres ipsilateral to severely stenosed or occluded internal carotid arteries. $r=-0.65$. $p < 0.001$. There is a fall in the amount cerebral vascular autoregulation to a fall in cerebral perfusion pressure in cerebral hemispheres with reduced peak reactivity index to hypercapnia.

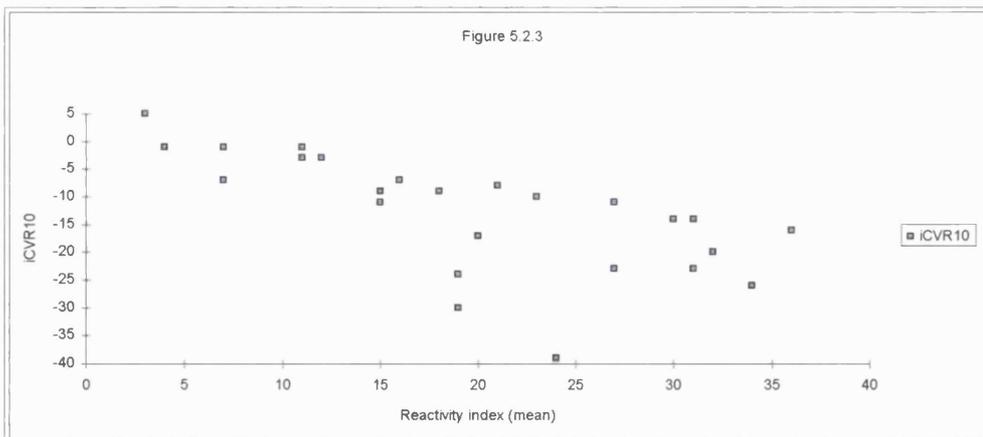


Figure 5.2.3 (above)
Relationship between iCVR10 and mean reactivity index in 26 cerebral hemispheres ipsilateral to severely stenosed or occluded internal carotid arteries. $r=-0.68$. $p < 0.001$. There is a fall in the amount cerebral vascular autoregulation to a fall in cerebral perfusion pressure in cerebral hemispheres with reduced mean reactivity index to hypercapnia.

Table 5.2.4

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
95% CI	100	103.12	99.90	94.37	89.29	87.32	86.25	85.39	83.22	83.52	81.58	81.03	82.37	79.58	78.67	81.91
Mean iCVR	100	109.01	105.23	97.03	92.94	90.89	89.02	88.24	87.08	86.87	85.28	85.06	85.40	83.52	83.25	87.54
95% CI	100	115.60	111.17	99.83	96.91	94.77	91.97	91.28	91.32	90.50	89.32	89.53	88.66	87.68	88.41	90.01

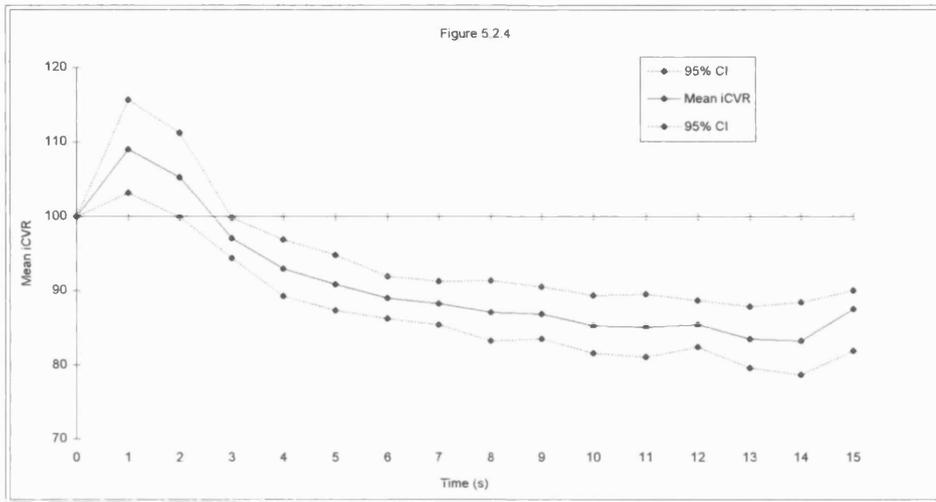


Figure 5.2.4 (above)
 Variation in mean iCVR with time following blood pressure stimulus, in 17 cerebral hemispheres ipsilateral to severely stenosed or occluded internal carotid arteries but with normal reactivity indices. Mean and 95% CI of the mean shown. Values given in table above chart. Curve shows an autoregulation response similar to that found in normal subjects under eucapnic conditions (see part 3).

Table 5.2.5

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
95% CI	100	97.40	99.80	100.65	99.86	97.41	97.56	92.60	90.67	94.24	95.48	92.58	96.52	91.63	94.30	92.20
Mean iCVR	100	104.64	105.54	105.30	106.04	101.59	103.00	99.49	97.94	101.10	103.97	98.74	102.42	97.51	99.91	95.87
95% CI	100	113.05	111.98	110.39	113.03	106.14	109.09	107.50	106.48	109.05	114.11	105.79	109.08	104.18	106.25	99.85

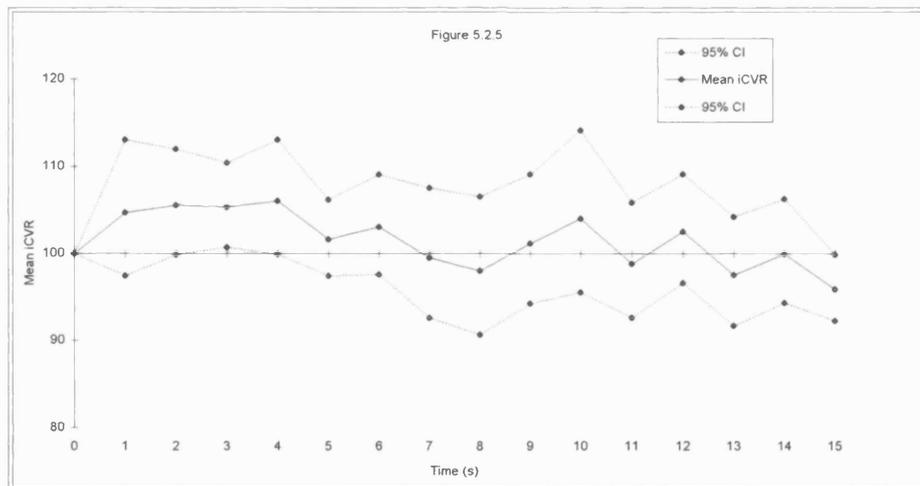


Figure 5.2.5 (above)
 Variation in mean iCVR with time following blood pressure stimulus, in 9 cerebral hemispheres ipsilateral to severely stenosed or occluded internal carotid arteries and with reduced reactivity indices. Mean and 95% CI of the mean shown. Values given in table above chart. Curve shows an obtunded autoregulation response similar to that found in normal subjects under hypercapnic conditions (see part 3).

5.2.5 Discussion

These results show the existence of a strong correlation between the degree of cerebral vascular reactivity to hypercapnia in a cerebral hemisphere and the degree of cerebral vascular autoregulation to a fall in cerebral perfusion pressure in that hemisphere, in this group of patients with severe carotid disease. Loss of cerebral vascular reactivity to hypercapnia is strongly associated with a reduction in the capacity of the cerebral vasculature to autoregulate blood flow in response to a fall in cerebral perfusion pressure. Furthermore, separation of the population into subgroups shows a marked difference in behaviour between those hemispheres with normal reactivity to hypercapnia and those with abnormal (reduced) reactivity to hypercapnia. It can be seen in those hemispheres which displayed normal reactivity to hypercapnia that despite the presence of severe internal carotid artery disease there was an autoregulatory response similar to that found in normal subjects. However in those hemispheres with a reduced reactivity to hypercapnia the autoregulatory response to a fall in perfusion pressure was lost. The inference which may be drawn from this is that the autoregulatory response of the cerebral vasculature to a fall in perfusion pressure is affected by severe carotid disease in the same instances as those in which there is a loss of the vasodilatory response which is normally elicited from the cerebral vasculature by the application of hypercapnia. Whilst these results do not give any indication as to whether or not a similar mechanism may be responsible for the two responses, the closeness of the correlation suggests that there may indeed be at least a partial common

pathway involved in the mechanisms of the response of the cerebral vasculature to the two different stimuli.

Examination of the data displayed in figures 5.2.2 and 5.2.3 shows that there are a number of outliers in the data set. The presence of an outlier to a data set can indicate a technically unsatisfactory examination (or a genuine outlying result), and if it is an erroneous result it can produce a confounding influence on the degree of correlation calculated between the variables considered (Bland & Altman, 1986). Outliers existing as a result of technically unsatisfactory examinations can produce an apparently significant result where none in fact exists. Exclusion of the three outliers in this data set (the results with autoregulation below 70% and normal reactivity, and the result with negative reactivity) actually tends to increase rather than decrease the calculated correlation coefficient ($\rho = -0.84$), and the statistical significance of the relationship between reactivity and autoregulation remains high ($p < 0.001$). These outlying values, although they tend to reduce the statistical significance of the relationship demonstrated, are therefore included in the analysis described in the results section above from which there are no exclusions.

Part 6 Conclusions and suggestions for further work

Stroke has been affecting mankind for centuries, and remains a major cause of death and disability. Despite being widely prevalent, the probability of the incidence of a stroke occurring in an individual is difficult to predict. There are some factors which are known to substantially increase the risk of stroke in an individual and which can be definitively treated; the presence of symptomatic severe carotid stenosis and its treatment by endarterectomy is an example of one such risk factor.

However, the precise role of carotid disease in the aetiology of transient ischaemic attack and stroke is not yet established, and it is difficult to non-invasively assess the effects of carotid disease on the cerebral vasculature; the anatomy of the cerebral blood vessels mitigates against the sole means of investigation being that of looking at the carotid disease itself. Testing cerebral reactivity to hypercapnia has been thought to provide a means of assessing cerebral vascular physiology and the way in which it may be affected by carotid disease. Thus far however it has not been possible using non-invasive techniques to look at the response of the cerebral vasculature to physiological pressure changes, that is, autoregulation.

Cerebral vascular autoregulation is the process whereby cerebral blood flow is maintained at a relatively constant level in the face of fluctuations in cerebral perfusion pressure. It occurs as a result of changes in cerebral vascular resistance. Described in section 3 are experiments which measure cerebral vascular autoregulation in normal individuals and in patients with carotid disease. In section 3.1 the mathematical basis of

the calculation of cerebral vascular resistance is discussed as are the assumptions which it has been necessary to make in order to allow the non-invasive measurement of autoregulation. In section 3.2 studies of cerebral vascular resistance show it to be stable in the absence of a blood pressure stimulus, and in normal subjects cerebral vascular resistance is shown to fall rapidly in response to a sudden fall in systemic blood pressure. This autoregulatory response is further shown to be modified by changes in end-tidal carbon dioxide concentration; studies described in section 3.3 show that the autoregulatory response of the cerebral vasculature to a fall in systemic blood pressure is lost in the hypercapnic subject and exaggerated in the hypocapnic subject. An a posteriori examination of these results suggests that there is a lag in the response of the cerebral vasculature to the sudden blood pressure stimulus employed producing a biphasic autoregulation curve under these experimental conditions. It is postulated therefore that the first of these phases occurs as a passive response to the fall in pressure whilst the second represents the active mechanism of autoregulation. The description of this biphasic autoregulatory response under these experimental conditions suggests the possibility in future experiments of observing changes in the timing and magnitude of this response to investigate the mechanism of the cerebral vascular autoregulatory response, and the way it may be modified by disease or by pharmacological agents.

The experimental studies described in part 4 consider firstly the method of measurement of cerebral vascular reactivity to hypercapnia and secondly the application of that method to the measurement of cerebral reactivity in a population of patients with carotid disease.

The results of the study described in section 4.2 demonstrate that there is a significant effect on middle cerebral artery blood flow velocity of the cognitive act of voluntarily controlling respiration, an effect which may confound the results of measurements of cerebral reactivity to hypercapnia made using techniques which require the subject of the study to perform hyperventilation or breath holding. Therefore a technique for measuring reactivity to hypercapnia which uses neither hyperventilation nor breath holding is described in section 4.3 and this technique is used in the study described in section 4.4 to assess cerebral reactivity to hypercapnia in a group of patients with carotid disease. This study shows that reactivity index to hypercapnia can be measured using either peak middle cerebral artery blood flow velocity measurements or mean middle cerebral artery blood flow velocity measurements with similar results, but that it is necessary to use one or the other of these consistently in any series of investigations as they are not interchangeable. A reduced reactivity index to hypercapnia is found in association with ipsilateral occlusion of the internal carotid artery; the reactivity index ipsilateral to an internal carotid artery occlusion is further reduced in the presence of severe contralateral internal carotid artery disease.

The techniques described in sections 3 and 4 to measure both cerebral vascular reactivity to hypercapnia and autoregulation to pressure change have been employed in the study described in section 5 to assess the cerebral vasculature of subjects with severe carotid disease. The measurements in this group have shown that in the presence of severe carotid disease there is a strong correlation between the presence of reduced cerebral vascular reactivity to hypercapnia in a cerebral hemisphere and the

existence in that hemisphere of reduced capacity to autoregulate blood flow in response to a drop in cerebral perfusion pressure. Furthermore, the relationship between autoregulation and reactivity to hypercapnia is similar whether reactivity index is calculated using the middle cerebral artery peak blood flow velocity or the mean blood flow velocity.

These results indicate that cerebral vascular reactivity to hypercapnia is a useful investigation modality in the assessment of cerebral perfusion, since the presence of reduced reactivity to hypercapnia in a hemisphere correlates strongly with reduced autoregulation in that hemisphere.

This correlation between reduced reactivity to hypercapnia in a cerebral hemisphere and reduced autoregulation to a fall in cerebral perfusion pressure can be applied to a number of clinical circumstances. Studies have shown that the presence of reduced cerebral vascular reactivity to hypercapnia implies a poor prognosis in patients with carotid disease (see section 1.4); the results of studies described here provide a physiological rationale for this finding.

The measurement of cerebral vascular reactivity to hypercapnia is a simple, non-invasive and widely available investigation the results of which have been shown to represent real changes in cerebral vascular physiology. It should be a part of the routine investigation of patients in whom the management of carotid disease is unclear, and incorporated into larger studies of the role of surgery in the management of asymptomatic carotid disease.

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Appendix

Manufacturers

<u>SciMed</u>	<u>P.K. Morgan</u>
Stoke View Buisness Park	4 Bloors Lane
Stoke View Road	Rainham
Fishponds	Gillingham
Bristol BS16 3AE	Kent ME8 7ED
Tel. 0272 583754	Tel. 0634 373865

Carotid Duplex Velocity Criteria

<i>Degree of internal carotid artery stenosis</i>	<i>Duplex Criteria</i>
<60%	peak systolic velocity < 130 cm/s
60 - 79%	peak systolic velocity < 240 cm/s
80 - 99%	peak systolic velocity > 240 cm/s with or without spectral broadening
Occlusion	no ICA flow detected

