BLOOD PRESSURE VARIABILITY AND CEREBRAL AUTOREGULATION IN ACUTE ISCHAEMIC STROKE.

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LIST OF ABBREVIATIONS

ABPM	ambulatory blood pressure monitor
ACEI	angiotensin converting enzyme inhibitor
ANOVA	analysis of variance
ANS	autonomic nervous system
ARI	autoregulatory index
AVM	arteriovenous malformation
BP	blood pressure
BPV	blood pressure variability
BRS	cardiac baroreceptor sensitivity
CA	cerebral autoregulation
CBF	cerebral blood flow
CEA	carotid endarterectomy
CNS	central nervous system
CO2	carbon dioxide
CPT	cold pressor test
CR	cerebral reactivity/reserve
CrCP	critical closing pressure
CT	computerised tomography
CV	coefficient of variation
CVR	cerebrovascular resistance
DBP	diastolic blood pressure
DBPV	diastolic blood pressure variability
DM	diabetes mellitus
ECG	electrocardiogram
EDCF	endothelial derived constriction factor
EDRF	endothelial derived dilating factor
EEG	electroencephalogram
FFT	fast Fourier transformation
GCS	Glasgow coma scale

GLM	general linear modelling
HDG	isometric hand grip
HR	heart rate
HRV	heart rate variability
ICP	intracranial pressure
IQR	interquartile range
LACS	lacunar stroke syndrome
LBNP	lower body negative pressure
LGT	passive leg tilt
MAP	mean arterial blood pressure
MAPV	mean arterial blood pressure variability
MCA(V)	middle cerebral artery (velocity)
MRI	magnetic resonance imaging
NIBPM	non-invasive blood pressure monitoring
NIHSS	National Institute of Health stroke scale
NO(S)	nitrous oxide (synthetase)
OCSP	Oxfordshire community stroke project
OH	orthostatic hypotension
OR	odds ratio
PACS	partial anterior stroke syndrome
PET	positron emission tomography
PI	pulse interval
PICH	primary intracerebral haemorrhage
POCS	posterior circulation stroke syndrome
PP	perfusion pressure
PPV	pulse pressure variability
PuP	pulse pressure
ROC	receiver operating characteristic
SAH	subarachnoid haemorrhage
SBP	systolic blood pressure

SBPV	systolic blood pressure variability
SD	standard deviation
SHR	spontaneously hypertensive rats
TACS	total anterior circulation stroke syndrome
TCD	transcranial Doppler ultrasonography
THC	thigh cuff
TIA	transient ischaemic attack
TPR	total peripheral resistance
VM	Valsalva manoeuvre
WKR	Wistar-Kyoto rats

STUDY DECLARATION

As required by the University this declaration outlines the persons responsible for this thesis.

Professor John F. Potter, Professor of Medicine for the Elderly, University of Leicester, and Dr Ronney B. Panerai, Senior Lecturer Department of Medical Physics, University of Leicester, conceived the idea for the study, and obtained funding from the 'Stroke Association of the United Kingdom'

I was responsible for adapting and implementing the proposed study methods under their guidance.

All patient recruitment and study was conducted by myself, but some control subjects for the autoregulation studies (Chapter 5 and 6) were jointly studied with my colleague Dr Melanie Blake (n=25). In Chapter 3 blood pressure data was also obtained from Dr T.G. Robinson, Consultant Physician, Leicester General Hospital.

Dr Ronney Panerai developed the software for recording and analysing the data needed to calculate cerebral autoregulation; he was also responsible for the adaptation of the mathematical models used to obtain autoregulation indices.

Data analysis of all the subjects used in this thesis was conducted by myself, as was data entry.

Mr Bradley Manktelow, Medical Statistician, Department of Epidemiology, University of Leicester, assisted with the analysis of the data reported in Chapter 3, otherwise I performed the statistical analysis.

ETHICAL DECLARATION

In accordance with ethical requirements for Medical research all subjects (or their next of kin, if necessary) gave written informed consent. All the techniques and studies conducted had approval from the Leicestershire Hospital Ethics Committee.

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ABSTRACT

This thesis examines the haemodynamic changes that occur following acute ischaemic stroke with reference to beat-to-beat blood pressure (BP) levels and variability as well as static and dynamic cerebral autoregulation (CA).

Elevated 24h BP levels following acute stroke are associated with a poor outcome, but whether shorter durations of recording using beat-to-beat measurements or other BP parameters such as variability have the same prognostic significance is unknown. A single 10minute non-invasive beat-to-beat BP monitoring period following acute cerebral infarction showed that increasing BP levels and beat-to-beat variability of mean arterial and diastolic BP were associated with a worse prognosis in terms of post ictal death/disability. These initial prognostic findings for BP variability might be explained if CA responses to rapid changes in systemic BP were impaired post stroke.

The second part of the thesis set out to measure dynamic and static CA using novel non-invasive techniques employing transcranial Doppler ultrasonography to measure cerebral blood flow velocity in response to non-pharmacologically induced pressor and depressor BP stimuli. The initial study found that in normal controls, the reproducibility and actual values obtained for the autoregulatory indices for both static and dynamic tests varied according to the BP stimulus used. As a result of these initial studies thigh cuff release was used as the stimulus for dynamic CA, and isometric hand grip and thigh cuff inflation as the stimuli for static CA. When the CA results for a study group of acute ischaemic stroke patients were compared to an age and sex matched control group dynamic CA was significantly reduced in the patients' affected and non-affected hemispheres, whereas static CA was unimpaired.

The prognostic significance of these changes in CA is as yet unclear, but the simple non-invasive techniques of assessing BP variability and CA in the acute stroke period described here should allow more detailed study of innovative acute therapeutic interventions.

CHAPTER 1

INTRODUCTION.

1.1. HISTORICAL BACKGROUND TO AUTOREGULATION:-

Autoregulation is the intrinsic ability of an organ to maintain a constant blood flow despite changes in arterial perfusion pressure. Changes in blood pressure (BP) and hence perfusion pressure (PP), are counteracted by changes in vascular resistance. These changes are thought to provide the organ with a constant supply of oxygen and other vital nutrients, i.e. adapt supply to demand.

Historically, autoregulation was first described by Bayliss et al in 1902 during experiments on isolated canine hindlimbs. They found that by lowering PP (either by nerve stimulation or compression of the aorta) there was a passive decrease in the volume of the limb, but on restoration of PP the volume expansion witnessed in the limb was far greater than prior to the experiment; the theory being that during the period of hypoperfusion there had been local vasodilatation. This potential change in vessel diameter was further supported in 1921 when Wachholder et al studied isolated segments of carotid artery and demonstrated contraction of the artery in response to increased PP after a delay of 8-20 seconds.

The focus of attention for studies regarding autoregulation soon switched to the renal system. Rein et al in 1931 found that blood flow to the kidney remained relatively constant during considerable ranges of systemic BP, whereas there were considerable changes in other organ systems, such as the skin. Further to these preliminary studies the concept of a lower limit of autoregulation was described by Selkurt in 1946; if PP dropped below 80mmHg blood flow became dependent on PP, with a so called pressure passive relationship. It was not until 1951 that Shipley described the upper limit of this process.

In the meantime autoregulation was described in other organs including the heart, retina, intestines, liver, skeletal muscle, and the brain; it is on this latter organ that this thesis shall concentrate.

Fog first described cerebral autoregulation (CA) in 1931, by directly measuring the diameter of cat pial arterioles during the manipulation of BP. He noted a relaxation in response to decreased PP, and a contraction to increased PP. Unfortunately the techniques available at this time often involved prolonged surgical procedures which damaged the brain and led to the finding of impaired or absent CA in many situations, increasing confusion over whether the process really existed. However, in 1948 Kety first described the nitrous oxide inert gas inhalation technique, which meant cerebral blood flow (CBF) and hence CA could be studied not only under relatively physiological conditions, but could be applied to studies in man. Using this method Harper [1965] found that lowering mean arterial BP (MAP) in normocapnic dogs to 90mmHg resulted in no significant change in CBF.

In 1959 Lassen , in a review article of cerebral blood flow and oxygen consumption in man, identified a number of small studies, conducted in the early 1950's, using Kety's inert gas method to assess CBF, which demonstrated that the process of autoregulation in response to changes in perfusion pressure was also active in man. Using patients with essential hypertension, toxaemia of pregnancy or infusion of vasopressin or noradrenaline to simulate a rise in CPP, and antihypertensive therapy, tilting, or the effect of spinal anaesthesia to simulate a fall, it appeared that CBF was kept constant at around 50ml/100gmin^{-1} whilst MAP was between 60-150mmHg, outside this MAP range there was a pressure passive relation between MAP and CBF; this is the so-called autoregulatory plateau (see Fig.1.1). It must be noted that there are a number of technical faults to some of these studies, as it is still unclear as to what effect essential hypertension, toxaemia, or certain drugs (hypertensive and anti-hypertensive) have on CBF and CA (see Chapter 1.3).

In addition, some of these studies were combined with the use of arteriovenous oxygen extraction assessment. This technique demonstrated that initially, although the CBF fell with a fall in MAP outside this autoregulatory range, the function of the brain was not adversely affected as oxygen extraction was increased; however

as CBF fell further symptoms of cerebral hypoperfusion developed, e.g. dizziness, pallor, sweating, and below 20ml/100gmin^{-1} brain ischaemia occurred; without the rapid return of CBF cerebral infarction would be inevitable. Conversely, above this upper limit of MAP, where CA was lost and a pressure passive relation between CBF and MAP also existed, disruption of the blood brain barrier occurred leading to brain oedema and malfunction.

The process of CA is more complicated than autoregulation elsewhere since PP is not just dependent on BP, but affected by the level of intracranial pressure (ICP), and possibly other factors too. An increase in ICP will affect venous distention and at higher levels arterial filling too. Therefore the equation for CBF is thought to require modification from

$CBF = \frac{PP}{CVR}$ where $PP = MAP$ to $PP = MAP - ICP$; CVR = cerebral vascular resistance.

The theories of the mechanism of CA and factors and pathophysiological states influencing the process will be discussed in the following sections.

1.2. THEORIES OF CEREBRAL AUTOREGULATION

Cerebral autoregulation is the response of the cerebral vascular resistance to changes in mean arterial blood pressure and consequently perfusion pressure, but as previously stated intracranial pressure has to also be considered in the latter. Changes in MAP can be either classified as dynamic or static [Aaslid 1989, Tiecks 1995]. Static BP changes allow the study of the whole autoregulatory action over a period of time, but they do not allow any study of the latency of this process; dynamic BP changes occurring within seconds address this concept. The distinction is important as there is a suggestion that the 'latency' of this mechanism may be affected before its 'efficiency' as different control mechanisms underlie each one [Aaslid 1994 unpublished data, Tiecks 1995]. Dynamic BP changes are followed by restoration of CBF to normal within 8-20 seconds when CA is intact, e.g. an

increase in MAP will lead to a transient increase in CBF but the autoregulatory processes will intervene within this very short time window to return the CBF to within the normal range. During a static BP stimulus small changes in CBF will occur, but there are constantly operating mechanisms to ensure that this change is not gross. It is, therefore, possible that not only these two processes, but also the responses to pressor and depressor stimuli, may be effected by different physiological mechanisms and consequently that pathological conditions affect them differently too. There are various theories of cerebral autoregulation and as yet there is not a definitive answer; however, some of them are more likely to play a significant part in the process than others. The five most considered options are the tissue perfusion, metabolic, myogenic, neurogenic, and endothelial derived factor theories, which will be discussed in this section.

1.2.1. TISSUE PERFUSION PRESSURE THEORY:-

This was one of the earliest mechanisms suggested as a possible explanation of autoregulation [Johnson 1964]. Low pressure vessels, i.e. venules, were thought to be responsible for autoregulation through their response to external tissue pressure. An increase in MAP and hence CBF was felt to lead to increased extracellular tissue fluid production, which in turn encroached on veins leading to an increase in back pressure to the arterial system reducing PP and returning CBF to baseline values. This is the only passive theory considered and as such should be immune to external influences such as drugs, which CA is not (see later sections). There are other problems with this theory too; mathematical modeling [Koch 1964] demonstrates that this would yield a pressure dependent mechanism and could not explain the autoregulatory plateau; the role of osmotic pressure on extracellular fluid formation has not been considered, and Fog's first description of CA concerned pial arterioles not venules. Consequently this is not thought to be an underlying mechanism of CA, although some of the principles could explain why ICP affects PP.

1.2.2. METABOLIC THEORY:-

CBF is certainly coupled to the metabolic demands of the brain, increasing globally e.g. during a generalised epileptic seizure, or locally in the motor cortex during exercise [Lassen 1974], to supply the necessary oxygen and nutrients, as well as remove toxic metabolites. However, these changes do not necessarily involve BP changes, and so are not truly causing changes in CA; but they do offer a possible mechanism of CA [Johnson 1964, Lassen 1974, Paulson 1990, Strandgaard 1992].

Oxygen and the metabolites produced during cellular function e.g. K+, H+, CO2, adenosine, Ca^2+, are vasoactive, mostly being vasodilators and, therefore, potentially responsible for triggering an increase in blood flow during periods of hypoperfusion. However, although adenosine levels are increased in times of hypotension and could trigger vasodilation, caffeine, an adenosine antagonist, causes no change to CBF [Kontos 1985], similarly, hypotension per se does not alter K+ and H+ concentrations [Kuchinsky 1978]. CO2 is a known potent vasodilator and does affect CA, but cerebrovascular reserve/reactivity (CR) as tested by CO2 may be impaired when CA is intact and vice-versa (see Section 3.1). Hypoxia also triggers vasodilation [Kontos 1978], but both O2 and CO2 would need to trigger the release of a mediating substance to affect CVR and hence CBF, and this would probably take longer than the 8-20 second process seen with dynamic CA. Therefore, although the metabolic theory cannot be completely rejected (especially when considering static CA) it is thought that other mechanisms must be involved as well.

1.2.3. MYOGENIC THEORY:-

In 1902 Bayliss first suggested a myogenic theory for the regulation of the *milieu intérieur*. The isolated canine hindlimbs in which he was examining the effects of altered perfusion pressure had been denervated. The postulation was that the small arteries and arterioles containing smooth muscle in their walls contract or dilate in response to increases or decreases in PP respectively. This process would be rapid

and in agreement with the time span of CA, although how the changes are made is unclear. It is possible that the cells respond directly to stretch and alter either their actin and myosin filaments, or their permeability to ions and hence their electrical activity [Paulson 1990]; certainly there is experimental evidence in arterial sections taken from rats of basal muscle tone maintained by spontaneous action potentials which increase in frequency and amplitude as MAP rises; spontaneously hypertensive rats (SHR's) having more of an increase than their normotensive counterparts, implying that SHR's have an enhanced response to increased arterial pressure, [Harder et al 1985], which might explain the differences that are thought to occur in CA with hypertension (see section 1.3.5). Symon et al [1971] have also demonstrated in baboons under general anaesthetic the restoration of CBF within seconds following dynamic changes in MAP, as have Florence et al [1992] in cats, further supporting a fast acting myogenic process.

Recently Thorin-Trescases et al [1997] examined in vitro the effects of altered perfusion pressure induced by saline infusion on human pial artery myotonic tone; (the arteries were of varying diameter and were obtained from macroscopically normal intact cerebral cortex sections removed during neurosurgical procedures). At 30mmHg intraluminal pressure the degree of myogenic tone in the arteries was kept constant and showed no relation to vessel diameter; however at pressures between 60-90mmHg there was an inverse relationship between diameter and level of tone. It was felt that this represented the increased distensibility that characterises the small pial arterioles; the high wall thickness to lumen ratio and increased stretch induced tone, leading to an increased degree of flexibility. These findings support the involvement of a myogenic process of CA at least in the extraparenchymal human arterioles.

1.2.4. NEUROGENIC THEORY:-

The effect of diseases of the Autonomic Nervous System (ANS) will be discussed in section 1.3.7. However the influence of the ANS on CBF and CA has been widely studied and its potential influence hotly debated.

There is much histological evidence for a rich neurological innervation of the extraparenchymal and intraparenchymal cerebral tissue [Rosenblum 1971, Harper 1975]. Generally the larger arteries are most densely innervated with the size of the plexuses diminishing as the vessels become smaller. Most of these are adrenergic nerves, especially around the anterior, middle cerebral, internal carotid and posterior communicating arteries. Further study of these nerves identifies contractile a receptors and dilatory $ß_1$ receptors [Heistad 1978]. There are no intracerebral arterioles with a dilatory cholinergic innervation, although extraparenchymal pial arteries do demonstrate both neuronal types on histological staining.

In vitro and in vivo studies have shown constriction of these vessels in response to direct or intravenous administration of norepinephrine, which is prevented by the adrenergic blocker phenoxybenzamine [Rosenblum 1975]. Stimulation of the sympathetic nerves at the superior cervical ganglion leads to a fall in CBF [Heistad 1978] but this is probably due to the changes mediated in the large extracranial vessels rather than those concerned with CA; but few studies have imaged the small vessels in order to witness a calibre change. Carotid baroreceptor stimulation does not cause a change in CBF [Heistad 1976], and denervation of animal cervical sympathetic input, by sectioning of the superior cervical sympathetic trunk caudal to the superior cervical ganglion, does not alter basal CBF [Heistad 1978b].

There have been many experiments in animals and humans examining the role of sympathetic denervation, stimulation, or pharmacological blockade, whilst testing CA/CR, either by pharmacological manipulation of BP, exanguination (animals

only!), CO2 inhalation [Eklöf 1971, Skinhoj 1972,1973, Heistad 1978a, Hernandez-Perez 1975, and Harper 1975], or more recently non-invasive blood pressure manipulation [Roatta 1999]. On the whole these studies have demonstrated that within the normal range of systemic BP, i.e. MAP 60-140mmHg, there is no effect of the sympathetic nervous system on CBF. However, at the extremes of the autoregulatory limits there is some evidence that stimulation of the sympathetic nervous system protects the brain from either breakthrough hyperperfusion or hypoperfusion by extending the limits of CA by altering the CVR of the extraparenchymal vessels [Harper 1975, Hernandez-Perez 1975, MacKenzie 1977, Sadoshima 1985, Talman 1994]. These findings are disputed by others who claim that pharmacological blockade of the sympathetic nervous system does not alter the upper BP level at which breakthrough is reached in hypertensives or normotensives [Skinhöf 1973]. To add even more confusion recent human studies using the cold pressor test as a non-invasive blood pressure and sympathetic stimulus have suggested that there may in fact be some effect on both large and small cerebral vessels with a moderate sympathetic stimulus leading to BP changes well below the upper limit of cerebral autoregulation [Roatta 1999].

The parasympathetic nervous system probably does not influence CA. Its stimulation in sympathetically denervated rats does not lead to increased CBF, but there is the possibility that parasympathetic denervation may reduce the lower limit of CA in rodent models [Morita 1994].

In conclusion, it would appear that the parasympathetic nervous system has little role to play in the control of CA. However, the sympathetic nervous system may be involved to a small extent during a normal range of PP, but in extreme circumstances its stimulation may extend the range of CA by its action on the extraparenchymal vessels. Consequently, it appears that there is more than one mechanism in operation to control CA, and that it varies according to vessel site and type.

1.2.5. ENDOTHELIAL DERIVED FACTORS:-

Treatment of vessels with detergents leads to the loss of endothelial integrity. In vitro experiments using this methodology to disrupt endothelial function have shown that the ability of a vessel to autoregulate its flow is lost. This led to the hypothesis of an endothelial derived relaxing factor (EDRF) which leads to vasodilatation; vasoconstriction being mediated by either a decrease in EDRF production or release of a specific endothelial derived constriction factor (EDCF) [Paulson 1990]. Possible candidates for EDRF have included acetylcholine, adenosyltriphosphate, substance P, and more recently nitric oxide (NO); and for EDCF prostanoids.

Nitric oxide (NO) is made by nitric oxide synthase (NOS) of which two classes have been identified - calcium-dependent (cNOS) and calcium-independent / inducible (iNOS). Two isoforms of calcium dependent NOS exist - endothelial (eNOS) found in endothelial cells, and neuronal (nNOS) found in the axon terminals of perivascular nerves [Hardy 1999].

In primates there is evidence that NOS is important for the maintanence of basal vascular tone [Thompson 1996], a finding supported by earlier studies demonstrating that NOS inhibitors reduce CBF in basal conditions and that NO concentration is not affected by changes in oxygen/glucose metabolism [Gardiner 1990, Prado 1992, Faraci 1991, Iadecola 1994]. In addition Thompson et al also showed in their primate models that vasodilatation in response to changes in pCO2, but not in reponse to hypotension is influenced by NO; i.e. that NO plays a role in cerebral reactivity but not cerebral autoregulation.

However, there is accumulating evidence in other animal models that NOS is important in cerebral autoregulation, and more importantly that eNOS may be protective, whereas nNOS may be harmful [Jones 1999, Martinez 1998, Hardy

1999]. Jones et al found in Sprague Dawley rats that inhibition of eNOS led to a rise in the lower limit of CA, i.e. that the rats were less able to tolerate hypotension. Martinez et al found similar results in newborn piglets, that could be reversed by providing the NOS substrate l-arginine. These results imply that eNOS allows these animal models to better tolerate low perfusion pressure states by increasing their vasodilatory capacity. Conversely, Hardy et al found that newborn piglets with high nNOS acitivity had a lower upper limit of CA, and therefore were less tolerant of hypertension as their vasoconstrictive ability was impaired. This was postulated as a reason for intraventricular haemorrhages in premature infants. In summary, these studies imply that eNOS is protective at the lower end of the cerebral autoregulatory plateau, whereas nNOS is harmful at the upper end.

More recently there have been studies examining the effect of NO/NOS in animal models of brain injury and stroke [DeWitt 1999]. L-arginine, a substrate for NOS appears to improve CBF without influencing BP/ICP/CPP, and has been shown to lead to a reduction in contusion size, and infarct volume.

Consequently, although the exact role of NO as an EDRF, and the nature of EDCF is as yet not fully understood, these factors are thought to play an important role in CA along with metabolic, myogenic and neuronal factors, and are in need of further study.

1.3. FACTORS AFFECTING CEREBRAL AUTOREGULATION:-

CBF and CA are thought to be influenced not only by pathological states, but also by an individual subject's characteristics. These parameters need to be taken into account in any study of CA, and will be outlined in this section.

1.3.1. CARBON DIOXIDE PARTIAL PRESSURE (PCO2):-

Arterial pCO2, and to a lesser degree cerebrospinal fluid pCO2, has been mentioned in the preceding section as a possible mediator for CA through a metabolic process. It is known to be a potent vasodilator and can be used to test cerebrovascular reactivity (CR), but this is not the same as CA, the response to changes in MAP, and should not be confused as the two may not be simultaneously affected, so called 'dissociated vasoparalysis' [Paulson 1972].

Studies of cerebrovascular reactivity (CR) have shown that CBF increases with increased pCO2 [Paulson 1972, Markwalder 1984, Ameriso 1994], and that there is an exponential relationship between the two allowing the mathematical calculation of 'normal CBF' at a given pCO2 [Markwalder 1984]. However, the extreme ranges of pCO2 were not studied in these experiments, and previous animal work suggests that there may be an S-shaped relationship, with blunting of the response in CBF at the extremes [Harper 1965].

There is evidence that in humans the vasodilatory response to hypercapnia is reduced in the morning compared to the afternoon and evening, and this may be a cause for the increased stroke risk in the early hours [Ameriso 1994]. Vasoconstriction to hypocapnia was not altered implying that the two mechanisms of vascular control are different; this is important as it suggests that autoregulatory responses to pressor and depressor stimuli may also differ.

But what of the effect on CA of changes to primarily arterial pCO2? It would appear that during hypercapnia dogs are unable to control their CBF in response to exanguination, and that a pressure passive response exists, i.e. CA is lost [Harper 1966]. There is further evidence using Xenon clearance techniques, and stepped BP increases induced by angiotensin, that in humans with cerebral tumours and stroke there may be dissociated vasoparalysis, with focal loss of CA and CR surrounding the pathological lesion, but only loss of CA in the contralateral hemisphere; a

situation that can be improved by inducing a state of hypocapnia [Paulson 1972]. From transcranial Doppler (TCD) studies using dynamic BP changes affected by thigh cuff release there is clear evidence that hypercapnia leads to a marked delay in restoration of CBF, i.e. CA, compared to normocapnic situations, and that during hypocapnia the CA response is augmented [Aaslid 1989]. However, baboons have been shown to have a normal vasodilatory response to CO2, i.e. CR, and a preserved vasoconstrictive response to elevations of MAP during hypercapnia [Symon 1973].

There is, therefore, some confusion over whether elevated pCO2 levels adversely affect CA, or just induce vasodilatation due to an intact CR, but some of the differences in the findings of these studies may be explained by the fact that some are testing two vasodilatory situations, others one dilatory, and one constrictive, the control of these possibly being different; and that different animal models were used, but in studies testing CBF/CA/CR it is necessary to know that the pCO2 levels are not different between subject groups, and that there are no large changes occurring during testing that could explain any intergroup differences.

1.3.2. DIABETES MELLITUS:-

Diabetes mellitus (DM) is a known risk factor for cardiovascular and cerebrovascular disease, the exact reasons are still unclear but it is known that these patients have accelerated atherosclerosis, and reduced cardiac baroreceptor sensitivity [Weston 1997].

It is, therefore, likely that DM alters CA and CR, and this has been proven clinically [Dandonna 1978, Kastrup 1986]. Diabetics have a reduced arterial vasodilatory response to increases in pCO2, and by using Xenon clearance and pharmacological induced changes in MAP it has been demonstrated that patients with known diabetic renal or retinal microangiopathy have reduced CA. These changes are thought to result from an alteration in the smooth muscle of diabetic

arterioles, and hence possibly the myogenic control of CA. More recent TCD studies have shown that in asymptomatic subjects with proliferative diabetic retinopathy there was an increased pulsatility index and a decreased CVR in response to breath-holding (i.e. increased pCO2 levels), implying reduced vasodilator reserve; it was suggested that this technique could be used as a screening test to identify subjects at particular risk of cerebrovascular disease [Ceravolo 1997].

Thus the myogenic control of CA appears abnormal in patients with diabetes mellitus, but this is not the complete story. More recent work in rats has shown that posterior cerebral arteries exposed in vitro to high glucose concentrations have a reduced vascular tone and a passive pressure response to increased transmural pressure, i.e. impaired CA; however, when the vascular endothelium was removed prior to the study the response returned to normal implying involvement of an endothelial factor in CA [Cipolla 1997]. This has been further supported by human studies that have shown healthy volunteers to have a significant rise in BP and heart rate, and a significant decrease in leg blood flow in response to hyperglycaemia, which is reversed by L-arginine, and mimicked by NO synthetase inhibitors, implying that glucose alters NO synthesis, and hence affects CA through either the endothelial mechanism or its role in the myogenic theory of CA.

1.3.3. AGE:-

Advancing age is associated with increasing levels of atherosclerosis and increased stroke risk. It is, therefore, likely that ageing influences CBF, CR, and CA.

In 1956 Kety described a decrease in CBF with advancing age using the nitrous oxide method [Kety 1956], and this has been supported by Xenon clearance techniques [Naritomi 1979, Shaw 1984,], and transcranial Doppler ultrasonography [Martin 1994]. It would also appear that there are differences between cerebral hemispheres with the left generally having higher flow rates than the right, and the

occipital and posterior superior temporal regions being subjected to much less age-related reduction than the prefrontal and parietal areas supplied by the middle cerebral artery [Shaw 1984, Naritomi 1979]. Gender also has an important influence on CBF with women generally having higher flow rates until the menopause, implying a possible role for hormones e.g. oestrogen, or the haematocrit with changes to this parameter possibly compounded by menstrual blood loss (see Section 3.4) [Kety 1956, Martin 1994, Karnik 1996].

Cerebrovascular reactivity is also influenced by age and gender; both vasodilation in response to hypercapnia, and vasoconstriction to hypocapnia are thought to decrease with advancing age, in the presence of vascular risk factors these changes are further enhanced [Yamamoto 1980, Yamaguchi 1979]. However, these findings are disputed by Davis et al [1983] who found no difference in cerebrovascular reactivity in response to CO2 inhalation, but they also claimed an unaltered CBF in cerebral white matter, contrary to others. A recent study found a significant age related decrease in CR, assessed by the breath-holding index (BHI), between pre- and postmenopausal women; the decline seen in BHI between young and old men did not reach statistical significance [Matteis 1998]. These findings were felt to reflect the greater influence of hormonal factors than age per se on changes in CR. Certainly other workers have found that pre-menopausal women have an increased vasodilatory response to acetazolamide injection compared to their male counterparts [Karnik 1996], and recently an increased vasodilatory response to CO2 inhalation in women has also been identified [Kastrup 1998]. These changes may be a reflection of either the protective hormonal make-up of pre-menopausal women, or the greater rate of sub-clinical atherosclerosis in men; certainly the more periventricular white matter change detected on MRI in asymptomatic subjects the more impairment there is in CR in response to acetazolamide administration [Isaka 1994]. Most of these studies were conducted in young subjects, consequently making a definitive distinction between the influence of age and/or gender is

difficult, but they do suggest a possible explanation for the increased incidence of migraine seen in women.

Regarding CA there is little evidence in human populations of the effects of age, but rats appear to have reduced CBF as they age, and a pressure passive response of CBF to BP, i.e. loss of CA, which is accentuated and occurs earlier in spontaneously hypertensive breeds [Hoffman 1981], implying that age-related BP changes may be as, if not more, important than age per se.

Age also confounds the changes in CBF that occur with BP (see section 1.3.5). In the frail elderly population there is an increased incidence of post-prandial hypotension; TCD studies have shown that although there is no significant change in CBFV the pulsatility index increases significantly [Krajewsli 1993] implying a change in vascular resistance. Studies of CBF and CA consequently should not be conducted in the post-prandial period in case of confounding influences.

In conclusion, in any study involving measurement of CBF and CA age and sex-matched populations are needed to make meaningful conclusions of group differences, although gender is less important in the elderly population [Shaw 1984, Martin 1994].

1.3.4. MISCELLANEOUS CHARACTERISTICS:-

Various other factors influence CBF and CR and, therefore, may influence CA.

Smoking is associated with a significant fall in CBF [Shaw 1984], and a 48% reduction in vasodilatory capacity to CO2, and a 24% reduction in vasoconstriction to 100% oxygen, compared to healthy controls [Rogers 1984]. Subjects with a heavy alcohol consumption have also been shown to have a reduced CBF on Xe inhalation studies [Shaw 1984, Rogers 1983], and hyperlipidaemia (cholesterol and triglyceride) has been found to lead to a significant reduction in CBF in patients

with transient ischaemic attacks compared to those patients with normal lipid profiles; the normal population with raised levels having a no-significant trend towards reduced CBF [Meyer 1987].

Whole blood viscoscity also probably effects CBF. It is well known that patients with polycythaemia have a reduced CBF [Nelson 1956], and a significant inverse relationship between CBF and haematocrit has also been shown [Thomas 1982]. However, plasma viscoscity is probably more likely to affect CBF than haematocrit alone, as this depends on cell rigidity, fibrinogen and immunoglobulin levels too, but assessment of this is more difficult [Thomas 1982]. It is likely anyway that under normal physiological states this has little effect on CBF in relation to e.g. oxygen requirement, but in low flow situations, e.g. carotid stenosis, it may be more important and could explain the increased stroke risk in these individuals.

1.3.5. BLOOD PRESSURE:-

It is accepted that hypertension, whether combined systolic and diastolic, or isolated systolic, is a risk factor for cardiovascular and cerebrovascular morbidity and mortality. The relative risk for stroke for combined hypertension being 2.19, and 1.42 in isolated systolic hypertension [O'Donnell 1997]. It is also known that the adequate treatment of hypertension can significantly reduce the risk of stroke, e.g. by 36% in systolic hypertension [SHEP Co-operative Research Group 1991], and in rat models prior anti-hypertensive therapy reduces infarct size [Slivka 1991].

Hypertension is not only a risk factor for stroke but it probably has important effects on CBF, CR, and CA. Similar changes may consequently persist in stroke, or arise de novo, but to date the situation is uncertain.

Cerebral blood flow:-

It is still unclear as to whether even CBF is changed in hypertension. Animal studies have shown both no change in CBF from studies comparing spontaneously

hypertensive rats (SHR) to normotensive Wistar Kyoto rats (WKR) [Hoffman 1981], and a reduced CBF in stroke prone spontaneously hypertensive rats (SPSHR) compared to WKR and stroke resistant SHR (SRSHR); this reduction was particularly evident in the frontal cortical areas. However, in this latter study the BP values were the same in SPSHR and SRSHR, consequently genetic influences, not just BP levels, may effect CBF [Yamori 1977].

Human studies have left this question equally unanswered. Kety [1947] found that both CBF and oxygen extraction fraction were unchanged in hypertensive patients, but cerebrovascular resistance increased with BP and was correlated to the degree of retinopathy; Faraci 1990, and Thulin 1993 also failed to demonstrate any change to CBF. Conversely, Strandgaard et al [1973], by assessing CBF via arteriovenous oxygen extraction, found a reduced oxygen consumption in human hypertensives implying a reduced CBF. The Xenon inhalation test has also demonstrated lower CBF values in untreated hypertensives, compared to age and sex-matched well-controlled hypertensives and normotensives [Nobili 1993], and PET and internal jugular monitoring have confirmed this, and also demonstrated regional differences, with most decreases seen in the frontal cortex and basal ganglia regions [Fujishima 1995, Lambert 1996]. These decreases are associated with age-related white matter changes and cognitive function, and this has been proposed as one of the reasons for the debate over CBF and hypertension; it may be that in neurologically normal subjects CBF is unchanged, but in the presence of cerebrovascular disease (silent or not) CBF is reduced. These studies also imply a possible beneficial effect on CBF from treatment.

Vascular structure:-

There is considerable experimental evidence demonstrating changes to vascular histology with hypertension. It would appear that with increasing blood pressure levels there is increasing smooth muscle hypertrophy and thickening of the extracellular matrix, through alterations in laminin, fibronectin, and collagen IV,

leading to an increase in the media to lumen ratio, and consequently changes in vascular resistance through reduced vascular stress (Laplace's Law) [Harper 1987, Faraci 1990, Slivka 1991, Nag 1997]. In cats moderate hypertension led to increased resistance in large and small cerebral vessels, but only small brainstem vessels; severe hypertension caused a fall in resistance in the cerebrum, i.e. impaired CA, whereas in the brainstem the resistance remained high implying intact CA [Faraci 1987]. This gives further support towards regional differences too. In SHR during baseline readings and vasodilatation induced by seizure activity, there was a marked increase in resistance in both large and small cortical pial arteries compared to WKR; with chronic sympathetic denervation this protective increase in resistance was lost [Weber 1984]. Some of these SHR developed 'sausage-string' dilatation of the arterioles, and this was felt to be an adverse structural adaptation that may increase the risk of stroke.

Cerebrovascular reactivity and cerebral autoregulation:-

Similarly whether CR is altered by hypertension is also still contended. Many studies have found no alteration to the response to inhaled CO2 or hyperventilation when pCO2 is between 20-55mmHg, but it is still unclear as to the results at higher levels or in the presence of atherosclerosis [Tominaga 1976]. However, more recent studies using transcranial Doppler have found impaired CR with hypertension [Maeda 1994].

In contrast CA is definitely reset during hypertension, but it is still unclear as to whether it is actually impaired. Studies in both animals and humans confirm a shift of both lower and upper limits of autoregulation to the right, presumably as a protective mechanism against severe hypertension [Strandgaard 1973, 1976, 1989, Hoffman 1981, Fujishima 1984], e.g. lower limits of 113, 96, and 73 mmHg for untreated hypertensives, treated hypertensives, and normotensives respectively [Strandgaard 1976]. There is evidence that this shift increases with longer durations of hypertension, and that effective treatment may allow the limits to return towards

normal [Strandgaard 1976, 1989, Harper 1987, Slivka 1991, Nag 1997]. The questions of how long after the onset of hypertension until the structural changes are permanent, or how long after treatment is instigated until improvement starts are still unanswered. In baboons after just 2 months of experimentally induced renovascular hypertension the limits of CA were reset [Strandgaard 1976]. It is likely that elderly patients and those with longer duration of hypertension will have more of the permanent structural changes such as connective tissue increase, rather than potentially reversible muscular hypertrophy The response to therapy also varies between individuals, after 18 months of antihypertensive therapy, with a combination of agents, not all subjects showed any improvement towards normal, [Strandgaard 1976], but increasing benefit in forearm blood flow has been noted up to 5 years from initiation of therapy.

Theses points are important not only regarding the need to study blood pressure matched groups if at all possible, but also regarding the question of antihypertensive therapy in acute stroke. If CA is likely to be impaired by hypertension anyway, let alone the influence of acute stroke, lowering CA below the 'higher' lower limit could be detrimental, and similarly it may be that subjects have a protective raised upper limit already to lessen the degree of cerebral oedema. These points will be further discussed in sections 1.3.6 and 1.3.7.

1.3.6 DRUG THERAPY:-

Many different classes of drug treatment may have an effect on CBF, CA, and CR, through their effect on the autonomic nervous system or blood pressure, e.g. the general anaesthetic agents isoflurane and desflurane alter dynamic and static CA (dynamic being affected sooner), whereas propofol causes no alteration in CA [Strebel 1995]. As mentioned in the previous section blood pressure has important effects on CBF, CR, and CA. It has also been alluded to that effective treatment with antihypertensive drugs may improve some of these changes by modifying vascular structural changes. In this section the effect of antihypertensives on CBF

etc. in normotensives, hypertensives, and patients with cerebrovascular disease will be discussed, although the latter will also be mentioned in section 1.4.

Normotensive and hypertensive populations:-

In normotensive and hypertensive populations the effects of various classes of anti-hypertensive have been examined (see Table 1.1).

Diuretics:- Diuretics, mainly in the form of thiazide diuretics, e.g. hydrochlorthiazide, have been shown to effectively reduce SBP in an elderly population with systolic hypertension (61-76 years) without changing cerebrovascular resistance and hence CBF, unless subjects were rendered normotensive, in which case resistance did fall [Traub 1982]. In this same group CR was impaired to 5% CO2 before the diuretic therapy was instigated, and it was unaffected by treatment. The lack of effect on CBF despite BP fall was confirmed by Venkata [1987], Semplicini [1993] and Landmark [1995], and it is therefore thought that this drug class primarily alters peripheral vascular resistance, leaving the cerebral circulation relatively untouched. Little is known about the effect of diuretics on CA in human subjects, but in SHR, WKR, and rats with renovascular induced hypertension a combination of chlorthiazide, hydralazine (a potent vasodilator), and reserpine (a sympathetic outflow blocker) not only brought the BP levels to within normal limits, but the shift in CA that had occurred to the right before treatment was nearly returned to normal through changes in vascular remodelling [Harper 1987].

Calcium antagonists:- Calcium antagonists have been considered as a therapy in acute stroke (see Section 1.4), so their effect on the non-stroke population's CBF/CA is obviously important to understand. It would appear that this class of drug is also a very effective anti-hypertensive, but again most of the vasodilatory action is on the peripheral circulation, although the effect on the coronary circulation varies according to the subgroup. CBF largely appears unchanged

[Thulin 1993, Landmark 1995, Pandita-Gunawardena 1999], however, Landmark did show a non-significant tendency towards an increase in global CBF with treatment. The very potent anti-hypertensive action may be a problem acutely whilst the autoregulatory shift induced by hypertension is still evident, reducing tolerance to hypotension, but treatment may reset this level, and if cerebral vasodilation occurs may actually improve tolerance to hypotension [Fujishima 1993].

ß blockers:- ß blockers are also effective anti-hypertensives although their mode of action is still not fully understood. It is thought that they reduce cardiac output, alter baroreceptor sensitivity, block peripheral adrenoreceptors, and depress plasma renin; the majority have no vasodilatory effect on the peripheral vasculature, instead resulting in a reflex increase in peripheral vascular resistance. In the cerebral circulation they may also cause an increase in resistance in the small vessels responsible for CA, and lower the vasodilatory capacity in times of hypotensive stress, or to CO2 challenge [Mathew 1973, Fujishima 1993]. There is some evidence though that after long-term treatment at higher dosages, there may be a vasodilatory action on the cerebral circulation increasing CBF, similar to the long term relaxation of smooth muscle that is seen in the peripheral vascular system [Globus 1983].

α adrenergic blockers:- α adrenergic blockers have been found to cause no change in CBF in the elderly despite a fall in both systolic and diastolic BP [Venkata 1987]. However, others have found a direct vasodilatory action on the cerebral circulation and an increased CBF [Mathew 1973, Fujishima 1993], again this may improve tolerance to hypotensive situations, but in the presence of dysautoregulation it may augment the problem [Mathew 1973]. There also appears to be no favourable alteration to CR by this class.

Angiotensin converting enzyme inhibitors (ACEI):- ACEI are very favourably considered at the present time because of their effect on vascular and left ventricular remodelling. In rat models administration of an ACEI led to effective treatment of hypertension, and attenuation of the smooth muscle hypertrophy and extracellular matrix formation [Nag 1997]. They also appeared to cause a resetting of the lower limit of CA towards a more normal level, i.e. improved tolerance to hypotension. CBF itself appeared unchanged and so this change was felt to represent regional differences in vasodilatory response, and there is some evidence that the microcirculation in the cortex may respond more favourably than in the thalamus [Sadoshima 1994]. A further study examining the effect of an ATP sensitive K+ channel opener on CBF found blunting of the CBF increase which was reversed by ACEI, implying that the K+ channel may be important in triggering some of the vascular changes seen during chronic hypertension [Takaba 1996]. The effect of the newer Angiotensin II receptor antagonists on the cerebral circulation is presently theoretical.

In humans it is generally agreed that there are no significant changes in CBF despite the pronounced BP reductions induced by ACEI [Waldemar 1989, 1990, Semplicini 1993, Démolis 1993]; only Rajagopalan [1984] found a change with a 20% increase in CBF after 4 days treatment with captopril, but this was not a placebo controlled study, and some subjects were also taking diuretics. The lower limit of CA may also be shifted to the left, as in the rat models, [Waldemar 1989], and the dilatory reserve may be improved, increasing the vasodilatory response to acetazolamide [Démolis 1993]. It is felt that this occurs because of regional differences in the response to Angiotensin II inhibition; the large cerebral vessels, e.g. the common carotid artery, appear to dilate and have an increased flow, whereas the middle cerebral artery flow remains unchanged because the resistance in the small arterioles controlling CA increases. The response to static CA, the BP stimulus being induced by -30mmHg of lower body negative pressure, appears unchanged [Waldemar 1990], but the magnitude of the BP stimulus is unclear. The

upper limit of CA may be lowered as well, in fact possibly more so, leading to a shortening of the autoregulatory plateau [Squire 1994]; unfortunately this may render subjects more susceptible to breakthrough hyperaemia if there was a sudden rise in BP [Fujishima 1993, Squire 1994].

Cerebrovascular disease:-

In subjects with cerebrovascular disease the effects of these drugs are important if they are to be considered as acute therapies, when the exact state of the autoregulatory capacity of the brain is still unclear (see Section 1.4).

Calcium antagonists: Preliminary work using calcium antagonists implies that in acute ischaemic stroke (<6hours post onset) they may help prevent postischaemic damage by improving CBF to the ischaemic penumbra through collaterals [Gelmers 1987, Fieschi 1988], but there is the possibility of hyperaemia and increased oedema, or further hypotensive damage if CA is impaired (see section 4). The α adrenergic blockers appear to cause no significant change in CBF in acute and subacute cerebral ischaemia/infarction, and an improvement in the metabolic byproducts of cerebral metabolism, but they may cause an increase in intracranial pressure (ICP) and a redistribution of CBF leading to the appearance of no overall change [Meyer 1974]. In rats they are felt to reduce infarct size by improving metabolism and platelet aggregation, and to have no influence on ICP [Späh 1995].

ß blockers:- This class of drugs appear to cause a detrimental decrease in CBF by increasing vascular resistance, although ICP and BP appear to alter little [Meyer 1974a,b]. This increased vasoconstriction may improve tolerance to increased perfusion pressure, but worsen it to hypotension. CR does not seem to be improved by therapy. Occasionally a paradoxical response to higher CPP was seen, i.e. a pressure dependent response, and this was felt to reflect the influence of cerebral oedema and raised ICP leading to 'false autoregulation'.

ACEI:- Rat models imply that acute treatment with ACEI reduces infarct size and improves neurological outcome [Werner 1991]. In humans it would appear that despite some reduction in BP acute ACEI introduction does not alter CBF [Waldemar 1989a,b, Dyker 1997], and only in one subject from one study was there a slight redistribution of blood to the low flow area [Waldemar 1989b].

Summary:-

In conclusion antihypertensive therapies can be divided into those with no effect on cerebral circulation, cerebral vasodilators which may maintain a normal CBF at BP levels below lower limit of CA, a blockers that may also improve tolerance to hypotension by aiding vasodilation but may cause a rise in ICP; and ACEI which shorten CA plateau, but don't alter CBF per se even in acute stroke [Strandgaard 1989]. These are important to consider in situations where treatment of blood pressure is known to be beneficial, e.g. systolic hypertension in the elderly, risk factor management and primary prevention for stroke following transient ischaemic attacks, and malignant hypertension; but because of possible impairment of CBF, CR and CA therapy needs to be introduced with caution. Drugs with no effect on CBF, nor adverse effects on cerebral metabolism or ICP, with a gradual hypotensive effect, and a positive influence on the limits of CA are to be favoured [Gifford 1983]. In the situation of acute cerebral infarction the picture is less clear; we are still unsure of the effects of acute stroke on CA, and consequently therapy could be either beneficial or cause deterioration. The role of anti-hypertensives in secondary prevention, although widely accepted as necessary, has not actually been clinically proven in a single trial, but a recently published meta-analysis shows a risk reduction of 0.72 for further fatal or non-fatal stroke [INDANA 1997]; although it is still unclear if this benefit is the same regardless of pre-treatment BP level, i.e. whether 'normotensive' patients require the same treatment as hypertensive patients, or whether it should depend on the patients overall risk profile. These matters will be further discussed in Section 1.4.

1.3.7. DISEASES OF THE AUTONOMIC NERVOUS SYSTEM:-

Although the role of the autonomic nervous system (ANS) in the mechanism of CA is still unclear, (see Section 1.2.4), autonomic dysfunction in either afferent, central, or efferent parts of the ANS causes changes in cardiovascular control, e.g. postural blood pressure regulation [Mathias 1987]. There is evidence of poorer neurobehavioural function and greater degrees of leukoaraiosis on MRI in asymptomatic subjects with orthostatic hypotension (OH) [Matsubayashi 1997]; it is, therefore, likely that patients with autonomic dysfunction will have altered CBF responses, but this could be secondary to pronounced BP changes or altered CA.

There is experimental evidence from the studies of BP and CBF responses in subjects with primary autonomic failure, e.g. Shy-Drager Syndrome, and secondary failure, e.g. due to diabetes mellitus to support both arguments. Caronna et al [1973] lowered BP with passive tilt, elevated it with norepinephrine infusion, and tested CR with CO2 inhalation. They found that Shy-Drager patients had intact CA and CR, but a patient with post-ganglionic autonomic failure had lost CA, and hyperventilation did not restore it. Similarly Wollner [1979] described BP and CBF responses to graded tilt in subjects with OH. Those who were symptomatic had a large fall in BP and CBF, and so were thought to have impaired CA, as opposed to those who were asymptomatic and had a 'stable' CBF despite a pronounced BP drop; Müller et al [1991] described similar findings, and recently a group of subjects with OH were divided into two on the basis of their CA, those with loss, and those with impaired or augmented CA, whether this was related to symptoms is unclear, but all became symptomatic with prolonged tilting [Novak 1998]. TCD studies have also added information about the underlying reasons for these changes; Schondorf et al [1997] have demonstrated in subjects with neurally mediated syncope a fall in diastolic MCA velocity alone and a consequent increase in pulsatility index and decrease in cerebrovascular resistance (CVR) as would be expected with a fall in BP, the diastolic fall thought to represent collapse of the small distal arterioles secondary to a DBP less than the critical closing pressure of

the vessels. One study has demonstrated paradoxical cerebral vasoconstriction as BP falls in subjects with unexplained syncope, and postulated abnormal baroreflex stimulation at the point of syncope leading to this change in CVR [Grubb 1991].

Others have found that the fall in CBF in response to graded tilt was much less than the BP fall, the overall regression slope relating the two not differing from that of normal controls, and consequently CA was thought to be intact in OH [Thomas 1980, Briebach 1989, Bondar 1995]. However, if the MAP fell below 60mmHg there was a sudden fall in CBF, and a pressure passive relationship [Thomas 1980]. It would, therefore, appear that these subjects probably have intact CA within the normal MAP limits and that the discrepancy between studies may occur because of falls in BP to outside this range. These results also imply that these subjects may be able to tolerate lower BP values, i.e. that the lower limit of CA is extended, similar to the right shift of the upper limit seen with sympathetic stimulation in hypertensives (see Section 1.2.4).

The above studies are examining the effects of static changes in BP. Lagi et al [1994] looked at the response in CBF to dynamic changes in MAP induced by thigh-cuff release and found that subjects with autonomic failure were unable to correct their CBF when their MAP fell, and that the two parameters moved in parallel fashion. Unfortunately static CA was not simultaneously studied in the same group so it is unclear as to whether they are affected differently.

In conclusion these results suggest that although ANS dysfunction probably does not alter static CA within the normal range of BP, at the extremes its activity may be crucial in the manipulation of the limits of CA. Dynamic CA probably is impaired, although there is a general lack of data on this matter.

1.3.8. EFFECTS OF SUBARACHNOID HAEMORRHAGE, ARTERIOVENOUS MALFORMATIONS, NEUROSURGERY, AND HEAD-INJURY:-

Subarachnoid haemorrhage is known to be associated with cerebral artery vasospasm classically within the first 3-7 days post-bleed, as this settles after about 10 days patients are at risk from re-bleeding. Nimodipine is known to help reduce this [Pickard 1989]. CA is also impaired following SAH, with both dynamic and static processes affected [Giller 1993]. However ,when CBF was measured with TCD, and cerebrovascular reactivity (CR) tested with acetazolamide, a minimum of 12months after the acute event, those subjects with definite vasospasm at the time of the bleed had no residual high flow areas, and CR has returned to normal, implying that the 'proliferative vasculopathy' that characterises the vasospasm had regressed [Szabo 1997].

Acute head injury and coma have been widely studied to examine the effects of trauma on CBF, CR, and CA. Generally following acute closed head-injury there is a fall in CBF, which recovers over the following 2-5 days, peaking at about day 5-7, then returning towards normal values. This fall in CBF tends to be related to prognosis, i.e. a larger decline is associated with a worse outcome [Obrist 1979, Miller 1985, Overgaard 1981, Cold 1989, Marion 1991]; a CBF <20ml/100g/min, especially in the frontal and parietal cortex regions, is usually fatal. Occasionally a high initial CBF is even more dangerous, this so-called 'luxury perfusion' state not improving the metabolism of the brain but leading to hyperaemia, an increase in ICP, a secondary fall in CPP, and an extension of cerebral ischaemia and oedema [Obrist 1979].

The changes following head injury have been well described [Miller 1985]. Initially there is a fall in MAP, a small rise in ICP, a period of apnoea, and flattening of the EEG recording. Within minutes the MAP, and ICP usually return to normal, respiration restarts, and the EEG recovers. Over the next few hours the degree of

brain ischaemia and the resulting neurological deficit depends on MAP, ICP, pO2, and degree of vasospasm.

Following head injury there may be 'dissociated vasoparalysis', i.e. there may be loss of CA, but CR may be intact [Enevoldsen 1978, Miller 1985, Lundar 1985, Lillywhite 1996]. This has important connotations as it used to be thought that hyperventilation to reduce ICP was a beneficial therapy in acute head injury, but it would now appear that this can lead to vasoconstriction in the area surrounding the damage if CR is intact extending the size of the ischaemic tissue, the so called 'inverse steal phenomenon' [Darby 1988]. One study [Steiger 1996] has implied that there maybe some acute impairment of CR, that may be improved by a rise in MAP, but this probably represents the pressure passive response to MAP due to loss of CA and does not imply that hyperventilation is 'safe'; in fact others have indicated that CR may actually be hypersensitive around the contusion and a further correlate to poor outcome, but this may just reflect the association between low CBF and loss of CR [Cold 1989, Marion 1991, McLaughlin 1996].

Head injury leads to an impairment of CA that tends to recover with time, although there does not appear to be a relation between this and prognosis [Cold 1978], although it is associated with degree of vasospasm [Steiger 1994]. There are some reports of improved outcome with raised CPP, but with the loss of CA this has to be performed with utmost care to prevent increasing oedema/ 'luxury perfusion' [Bouma 1990]. Occasionally studies have implied that CA was intact initially and then became impaired as the patient recovered [Enevoldsen 1978, Miller 1985], but on review of these papers it would appear that this was probably 'false autoregulation', resulting from a combination of vasospasm, increased vascular resistance, and raised ICP leading to an apparent lack of change in CBF with a rise in MAP; as the patient recovered and regained consciousness these changes disappeared and the 'true' impaired CA became evident.

Recently interest has increased on the influence of hypothermia on CBF, cerebral metabolism, and CA in head injury, with the publication of some encouraging results of total body cooling on neurological outcome following severe head injury [Marion 1997].

Arteriovenous malformations (AVMs) are associated with high rapid circulation times. They affect blood flow and CR nearby and even contralaterally, local CBF may be reduced because of 'steal' into the AVM if local CA is impaired; CR is usually intact, or even hypersensitive at their margin, with possible impairment a few centimetres away, and in the contralateral hemisphere, [Barnett 1987, Al-Rodhan 1993, Diehl 1994]. Hypersensitive CR is usually seen with high pressure AVMs, and is associated with haemorrhagic complications, whereas low pressure AVMs tend to have reduced CR and more neurological complications [Diehl 1994]. If CR was impaired it usually improves following resection [Al-Rodhan 1993]. However, there are possible problems post surgery similar to those mentioned in head injuries. Normal perfusion pressure breakthrough syndrome (PBS) is associated with hyperaemia, local haemorrhage, and oedema, and can be fatal. The mechanisms behind this are unclear, it is not solely due to impaired CA, as it occurs when this is intact [Young 1993], but it is thought to occur when there is a large rise in CPP secondary to increased perfusion pressure in the feeding artery, and reduced venous outflow [Barnett 1987, Young 1993]. It is more likely to occur if at pre-excision there was low flow surrounding the AVM, if CR was impaired, if the feeding artery was operating at low pressure pre-operatively but returned to normal suddenly post-excision, and if there was a substantial increase in local CBF post-operatively. These theories have been confirmed in rodent and feline models using surgically induced cerebral fistulae [Irikura 1996, Spetzler 1992] A similar complication post-operatively is called 'occlusive hyperaemia' [Al-Rodhan 1993]; the consequences are the same, but it is felt to be due to a passive hyperaemia due to venous occlusion, rather than an increase in inflow. The risk of this complication is increased if the AVM was large, there were only a small number of veins

draining the area, if the veins were narrowed, if high-flow was converted into low-flow post-operatively subjecting the patient to retrograde thrombosis (particularly if at a watershed area), if there was evidence of 'steal', and if there was endothelial damage.

In conclusion SAH, head injury and AVMs cause significant changes to CBF, CR, and CA. The above review of some of the evidence points out the problems with treating these situations, and many of them can be likened to the problems of therapy in acute ischaemic stroke, as it is likely that a lot of the consequences are the same.

1.4.CEREBROVASCULAR DISEASE

1.4.1 EPIDEMILOGY OF STROKE:-

Stroke is a neurological deficit lasting greater than 24 hours secondary to a vascular cause; approximately 80% are due to cerebral infarction, and 20% secondary to primary intracerebral haemorrhage. A small number of patients admitted as 'strokes' will be subsequently found to have subarachnoid/subdural/epidural haemorrhages, cerebral tumours/abscesses or infections. For the purpose of this thesis cerebral infarction will be primarily discussed.

There are essentially 4 groups of ischaemic stroke: atherothromboembolic, intracranial small vessel disease, embolic e.g. cardioembolic, and rare causes such as haemodynamic infarcts secondary to hypotensive episodes peri-operatively, arterial trauma and dissection, migraine, connective tissue diseases, and Moyomoya syndrome. These will be discussed in more detail in the next section.

Stroke was first described by Hippocrates (460-370BC) as a sudden loss of consciousness secondary to brain disease, at this stage it was referred to as apoplexy. Many years later Wepfer (1620-1695) identified an arterial lesion as the

underlying basis to the disease, and separated arterial occlusions from extravasation of blood into the surrounding parenchyma or ventricles, i.e. infarcts from haemorrhages. However, it was not until the 19th Century that the necessary preservation and staining techniques led to the histological identification of ischaemia and infarction that we now identify [Warlow et al 1996].

This disease continues to be the third most common cause of death in Western countries after ischaemic heart disease and malignancy. In England and Wales it accounted for 12% of all deaths in 1992 [Secretary of State for Health], and is one of the most important causes of long-term physical disability [Martin 1988]. It presently accounts for 6% of all hospital costs [Isard 1992], but the long-term costs of care are the real problem today, not only because 25% of those affected were working up to the time of stroke onset (i.e. are relatively young with potentially a few decades of life expectancy in this dependent state), but also because of the increased incidence that occurs with advancing age, so that with larger numbers of people reaching old age the prevalence will increase too.

Increasing age is the greatest risk factor for stroke, and the annual age specific incidence per 100,000 population in Oxfordshire has been well characterised by the Oxfordshire Community Stroke Project (OCSP) [Bamford 1986]:-

Age (years)	0-44	45-54	55-64	65-74	75-84	85+
Annual Incidence per100,000	9	57	291	690	1428	2009

Following the Kings Fund Consensus Conference [1988] the political attention paid to stroke has increased [Secretary of State for Health 1992], as has the concept of primary prevention, and the undertaking and financing of research into this area. The organisation of Stroke services is also under much review, as there is evidence that multidisciplinary teams based on specialist units, with ready access to CT scanning and vascular imaging, in conjunction with rapid outpatient assessment

facilities, and continuing care leads to better outcomes than seen in patients treated on general medical wards. Unfortunately, this is obviously more expensive, and as yet there is no widely accepted acute treatment, apart from aspirin [IST 1997] and the prevention of complications by good clinical practice, to back up the need for these services. Some of the theoretical aspects of an acute therapy, the problems complicating matters, and preliminary results of those tested to date will be discussed in the following sections.

1.4.2 PATHOPHYSIOLOGY OF STROKE:-

Atherothromboembolic disease is by far the commonest cause of cerebral ischaemia and has a number of risk factors in addition to age including, hypertension, male sex, diabetes mellitus, smoking, hyperlipidaemia, racial origin (increased incidence in Asians and Afrocarribeans, in Asians stroke occurs at an earlier age, [S. Dawson unpublished data]), alcohol, low level of physical exercise, preexisting ischaemic heart disease or peripheral vascular disease [Stroke: a practical guide to management Warlow et al 1996].

Intracranial small vessel disease is a subject under some debate; it is felt to be a separate entity from traditional atherothrombotic cortical stroke, but whether lipohyalinosis, as seen in hypertensive subjects [Bamford 1987], or a form of atheromatosis [Schmal 1998] is the underlying pathophysiological mechanism is uncertain, although risk factor profiles of affected subjects probably favours the latter. Cardioembolic stroke can be due to atrial fibrillation, prosthetic valves, acute myocardial infarction resulting in left ventricular aneurysm, and bacterial endocarditis to name but a few.

These different pathological mechanisms tend to lead to different clinical manifestations, and from a patients history, general examination, and neurological classification according to the OCSP classification (see Appendix 1) [Bamford

1991] it is possible to predict the underlying pathology and hence tailor investigations, and gain some idea of prognosis.

Ischaemic stroke is a dynamic and highly unstable process. There is an initial vascular, haematological, or cardiac event which leads to formation of a local thrombus, which halts the blood supply to the brain distal to this point. This thrombus initiates a thrombogenic and neurotoxic cascade through the release of eicosanoids, which stimulate the breakdown of the blood brain barrier, diffusion of toxins into the brain, in addition to reduced microvascular flow. These toxins lead to cellular damage by altering the cellular membrane and causing an efflux of K+, and an influx of Ca^2+ (since the mitochondria are unable to sequester this ion), this triggers a cascade of detrimental biochemical processes including the release of cell lytic proteinases, lipases etc., and possibly the release of protective protein genes such as stress proteins. The lack of oxygen in the tissue distal to this point leads to the stimulation of anaerobic glucose metabolism which produces lactic acid and free radicals as well as insufficient ATP. This cell membrane damage also causes the sequestration of water leading to oedema; this starts within hours and peaks at about 2-4 days after the start of the ischaemia. At its most severe it can lead to mass effect and uncal or transtentorial herniation and possibly prove fatal [Grotta 1994, Obrenovitch 1995, Stroke: A practical guide to management Warlow et al 1996].

The extent of damage is really dependent on the blood flow that is able to get through to the distal tissue, either through the damaged vessel because of incomplete occlusion or reperfusion, or from collaterals. Rodent models of middle cerebral artery occlusion (MCAO) have demonstrated a transcortical gradient in blood flow, with a marked decrease in the deep cortical structures, to a near normal CBF superficially. A steep change is noted in a 1-2mm rim around the infarct, and this area has been termed the ischaemic penumbra [Symon 1973, Tyson 1984]. Studies have shown that the degree of CBF and the duration of hypoperfusion will determine whether the ischaemia causes permanent damage. It would appear that in

rats a CBF of <25ml/100g/min for greater than 4 hours induces permanent damage. In humans similarly CBF determines tissue activity and viability; <8ml/100g/minute leads to infarction within minutes, 8-16ml/100g/minute causes loss of activity and can only be tolerated for 3 hours maximum, 16-23ml/100g/minute is associated with reduced function, >23ml/100g/minute can sustain normal function provided oxygen extraction is increased, and 50ml/100g/minute represents normal CBF [Olsen 1986]. TCD has yielded similar results with a velocity >30cm/sec associated with functional recovery, <30cm/sec with persistent paralysis [Halsey 1988].

The ischaemic penumbra is the area around the infarct focus where CBF has decreased so that even with increased oxygen extraction electrical activity is not possible, but the cells are in a viable condition. This is a time limited condition, and a state of 'misery perfusion' exists, i.e. there is increased oxygen extraction, acidosis, high glucose utilisation, but not enough energy. This leads to a spreading depression, i.e. an extension of this decreased electrical activity; which may be mediated by increased glutamate levels, or more likely by the continued disruption of the K+ and Ca^{2}+ transport mechanisms. This can unfortunately lead to propagation of the penumbra, and extend the size of the infarct [Obrenovitch 1995].

Theoretically the ischaemic penumbra is the optimal site for therapies to be targeted at, either to improve perfusion, or offer neuroprotection. These will be discussed in the following sections, along with other problems that make this a far from easy task, including the possibility of deranged CR and CA, and reperfusion injury.

1.4.3 CHANGES IN CBF CR AND CA WITH CEREBROVASCULAR DISEASE:-

1.4.3.1. Stenosis or occlusion of the Extracranial arteries:-

Acute common carotid artery occlusion leads to a bilateral decrease in hemispheric CBF. However, within 24 hours CBF returns to normal in normocapnic subjects

because of vasodilation in the vessels comprising the Circle of Willis and consequent increased perfusion from collaterals [De Ley 1985]; providing this is functioning CBF per se should not be affected by extracranial vascular disease. This unchanged CBF has also been described in internal carotid artery disease [Brown 1986, Powers 1991]. However, these subjects rarely have normally functioning Circles of Willis secondary to widespread atherosclerosis and changes in structure to the ipsilateral microcirculation, e.g. smooth muscle proliferation, increased permeability, and fibrinoid necrosis [Powers 1990]. Consequently there may be alterations in CBF, e.g. chronic retinal hypoperfusion leading to poor dark adaptation, which is more severely impaired ipsilateral to the carotid stenosis [Havelius 1997a]; but more importantly a state of relative vasodilatation may exist to try and optimize CBF, leading to a reduced vasodilatory capacity. Numerous studies have demonstrated a diminished or absent vasodilatory response to CO2 inhalation or acetazolamide administration in unilateral or bilateral significant carotid artery stenosis (i.e. >70%) or occlusion [De Ley 1985, Bishop 1986, Brown 1986, Keunen 1994]. This occurs in both acute and chronic situations, the severity of the impairment of the CR being positively correlated with the extent of the stenosis, the number of extracranial arteries affected, the clinical situation, e.g. post stroke and stable or continuing transient ischaemic attacks; and the ipsilateral hemisphere is more severely affected [Brown 1986, Ringelstein 1988]. This lack of vasodilatory capacity may make subjects more prone to haemodynamic infarcts as well as the thromboembolic infarcts traditionally associated with carotid disease [Bishop 1986]. There is evidence that following an occlusion there may be some improvement in CR with time, although even after 5 years there may still be impairment [De Ley 1995, Widder 1994]; similarly there may be an improvement in hemispheric CR following a stroke secondary to a significant stenosis within the first 12 months, but it is in these months that the risk of further stroke is highest [European Carotid Surgery Trialists Collaborative Group 1991, 1995], and consequently in this period that carotid endarterectomy (CEA) is most beneficial. A number of investigators have tried to assess stroke risk in subjects with

asymptomatic and symptomatic carotid stenosis using CR. It appeared that symptomatic subjects usually had the most severely impaired CR, and that these subjects when followed longitudinally over 2-5 years had the greatest stroke risk, e.g. Kleiser et al [1992] found an 8% risk of transient symptoms but no stroke risk in subjects with intact CR, compared to a 32% risk of stroke with impaired CR; findings that have been supported by Yonas et al [1993, 1994], and Gur et al [1996]. As well as improving selection in symptomatic subjects, similar future studies may help clarify the situation regarding CEA in asymptomatic significant stenoses. Endarterectomy does appear to be beneficial in terms of changes in CBF and CR, with improvements in e.g. impaired dark adaptation secondary to retinal ischaemia [Havelius 1997b], and CR especially in the previously asymptomatic group [Bornstein 1997]. This discrepancy may be because of the effects of the previous stroke on CR, but as will be discussed shortly the experimental evidence is that CR tends to be relatively spared in cerebral infarcts. In the situation of ipsilateral occlusion and contralateral significant stenosis, if the latter is surgically corrected then the CR on the side of the occlusion also improves, indicating improvement in collateral supply [Widder 1994].

There are however possible complications arising from CEA, not least the possibility of embolic or haemodynamic stroke during the procedure, but as in resection of arteriovenous malformations (AVM) a post-operative hyperaemic state may develop. The vascular changes previously mentioned are not able to withstand sudden increases in perfusion pressure, such that if CA as well as CR is impaired normal pressure breakthrough syndrome can occur [Powers 1990, Giller 1995]; cerebrovascular resistance will start to increase and CA improve post-operatively, but the damage may already have been done. There is certainly experimental evidence that a small subgroup of subjects with significant carotid stenoses also have impaired dynamic CA, in addition to impaired CR, and that this improves post-operatively [White 1997], it is probably this group that are most at risk of this post-operative complication.

In conclusion, carotid artery disease per se does not alter CBF, but it does appear to alter CR and possibly CA. The routine testing of these parameters may allow better patient selection regarding CEA.

1.4.3.2 Acute and Chronic Ischaemic Stroke:-

a. Animal Models:-

As described previously (Section 1.4.2) a cerebral infarct leads to local changes in CBF, these changes however are not necessarily isolated to the affected area/hemisphere, e.g. models of cerebral ischaemia induced by bilateral carotid artery ligation led to decreased cortical CBF during the procedure, but no effect on cerebellar flow until after the procedure was completed when both were decreased, but cortical CBF was much more severely affected [Shiokawa 1986]. These regional differences imply that there are differences in either collateral flow or CA, and these same models have shown that cortical CA is more severely impaired than cerebellar CA which recovers about 30 minutes after reperfusion. This implies that the cortical hypoperfusion has led to some permanent damage affecting CA, e.g. toxic metabolites damaging endothelial membranes. These ligation models are not the same as true infarcts, but there are experiments that have used internal carotid (ICA) or middle cerebral artery (MCA) occlusion to mimic stroke pathology. Feline models have shown loss of CR, despite preservation of EEG activity, at 6 hours post-occlusion, with some recovery of CR at 2 days, though some impairment persists up to 12 months post procedure [Schmidt-Kastner 1986]. A commonly seen phenomenon on reperfusion is hyperaemia, and it appears that this itself can cause further damage, e.g. in rodents with MCA occlusion those who had been reperfused for just 2 minutes had vasoresponsiveness comparable to control models, whereas following 24 hours of reperfusion any myogenic activity was severely impaired [Cipolla 1997], a finding supported by more extensive neurological damage following air emboli in canine models when rendered simultaneously hypertensive [Dutka 1987]. This hyperaemic reperfusion injury has been further supported by

experiments inducing hypertension following MCA occlusion to try and aid reperfusion. Those models with hypertension induced for just 15 minutes had much smaller areas with CBF <40ml/100g/minute, and consequently smaller infarcts, than those who had 90 minutes hypertension, although this group still had smaller infarcts than rats left untreated; whether functional outcome improved is unclear [Drummond 1989, Cole 1992]. It is hypothesised that reperfusion may help by 'washing' away toxic metabolites, but if prolonged can lead to hyperaemia because of the diminished vasoreactivity and hence CA caused by the ischaemia, which may lead to oedema and infarct extension. The size of infarct would also seem to determine the degree of CR/CA impairment and therefore probably prognosis [Schmidt-Kastner 1986]. Cerebral oedema not only affects regional CBF, but can alter intracranial pressure (ICP) leading to coma and death. Preliminary work in rodents with large infarcts and oedema who had a decompressive craniotomy showed a reduction in mortality and a significant reduction in infarct size compared to controls, especially if surgery was performed within 4 hours of ischaemia, although it was difficult to comment on any change in functional neurological outcome [Doerfler 1996].

As noted in previous sections there appears to be a dissociated vasoparalysis, with CA more severely affected than CR, although there have been less studies on the latter; only very early studies found the opposite and it is thought now that this was due to 'false autoregulation' secondary to oedema and raised ICP [Nemoto 1975].

Animal studies have therefore been important in the understanding of regional differences in CBF, CR, and CA, the concept of the ischaemic penumbra, the study of reperfusion injury, and of course the testing of possible neuroprotective drugs which will discussed in the next section. It is important to remember that there are significant differences between animal models and man, and comparisons must be made with caution.

b. Human Studies:-

CBF:- As previously stated various subject characteristics influence CBF, e.g. age, gender, blood pressure. There is evidence that subjects with lower CBF values, especially in the presence of vascular risk factors are more prone to periventricular white matter changes, and silent lacunar stroke, i.e. there are changes in CBF prior to an acute ischaemic event [Kobayashi 1991, Chamorro 1997]; and that CBF declines with time in longitudinal studies [Meyer 1984]. Although the measurement of temporal trends in CBF is not routinely employed as yet, this technique may allow the earlier identification of subjects at particular risk from stroke disease.

Transient ischaemic attacks (TIA) lead to further reductions in CBF especially in the striatum and thalamic regions, and this may imply a poorer vascular reserve in these territories [Fujii 1990], or a less efficient collateral supply. It is postulated that pathology in the large arteries may be better tolerated than that in smaller arteries as the vasodilatory microcirculation will be less affected [Faraci 1990]. However, it is known that infarcts do not just affect CBF locally, but can cause distant changes too, e.g. frontal infarcts lead to a significant reduction in CBF in the contralateral cerebellar hemisphere, whereas parieto-occipital infarcts cause a bilateral decrease in cerebellar flow [Martin 1983]; this implies a major cortical influence on cerebellar function. Acute infarcts could therefore lead to a global reduction in CBF, possibly through transhemispheric communication (diaschisis), which is proportional to the infarct size, and tends to recover with time. This may leave an ipsilateral decrease [Fieschi 1966, Meyer 1970] due probably to the combination of a reduced metabolic requirement in the diseased hemisphere, and the postulated development of interhemispheric shunts [Bajc 1991]. The bigger the infarct the larger this hemispheric asymmetry becomes and probably relates to functional and cognitive recovery [Mori 1994]; left hemispheric infarcts may lead to larger falls with the same asymmetry index. However, this group previously found no difference in CBF with chronic ischaemic stroke per se and related all changes to absolute BP levels, i.e. lower BP levels led to lower CBF [Mori 1993]. More recent

evidence suggests that patients with post-stroke apathy may continue to demonstrate bilateral reductions in CBF especially in the right dorsolateral frontal and left frontoparietal regions [Okada 1997], and that positional changes may improve CBF and neurological function, e.g. different gaze positions led to alterations in CBF and function in a subject with quadrantinopia, and this may have important relevance to rehabilitation [Nadeau 1997].

CA &/or CR:- Collaterals and shunts are unlikely to fully explain these differences in CBF, especially if BP is involved, and autoregulation/ cerebrovascular reactivity must play some role. Although there are reports of tests for autoregulation and vasoreactivity being comparable (admittedly in normal subjects), there are problems with the statistical comparisons used, which have not taken into account possible bias [Newell 1994].

Since there appears to be a discrepancy between the two mechanisms, with CA being affected more significantly than CR, the two process are not considered identical. If CR is impaired it appears that this is only a local phenomenon whereas CA may be disturbed at some considerable distance from the infarct [Agnoli 1968, Paulson 1972, Pistolese 1972, Olsen 1983]. There is evidence that both may improve with time, although they are probably chronically impaired [Agnoli 1968, Meyer 1973, Provinciali 1990]; the site and size of the infarct probably determine this recovery, brainstem lesions may have more residual dysautoregulation [Meyer 1973]. The problem with these studies is that they have mainly used methods of measuring CBF with very poor temporal resolution and therefore only static CA has been assessed, a situation improved with the advent of TCD. They are also limited in their ability to correlate the areas with impaired CA/CR to the infarct site, although Positron Emission Tomography, and functional Magnetic Resonance Scanning may improve this.

Hyperaemia is common in humans as it is in animal models, especially following embolic stroke as the embolus disperses [Olsen 1983]. It is primarily a problem local to the infarct and the penumbra, but there can be distant sites that demonstrate a relative hyperaemia, i.e. a blood supply in excess of metabolic requirement. This 'luxury perfusion' state was first described by Lassen in 1966, and appears to occur in areas where CA has been damaged. The question still remaining is whether this phenomenon is harmful or not, but as previously described in animal models it can lead to oedema and worsening ischaemia (in these situations 'false autoregulation' may become apparent). However, more recently studies have confirmed its occurrence at sites distant from the infarct and therefore deemed it harmless [Marchal 1996], but the imaging techniques used may not have picked up subtle ischaemic damage at these sites. There is debate over whether early reperfusion makes this hyperaemia worse, through reperfusion injury, or improves it as potentially less damage to CA may have occurred due to the shorter ischaemic time [Marchal 1996, Olsen 1983].

Because CR is often intact in ischaemic stroke hyperventilation has been postulated to reduce this hyperaemia by causing vasoconstriction, but unfortunately, as in head injuries, this may lead to inverse steal if CR is intact in the ischaemic penumbra, and worsening hyperaemia in the infarct which may also exacerbate the ischaemia in the penumbra through pressure changes [Paulson 1972, Olsen 1986, Strandgaard 1990].

Antihypertensive therapy:- The ischaemic penumbra has to take priority in any plan of therapy as it is a potentially salvageable area of tissue. If CR and CA are intact in this area then controlled hypotension may reduce the hyperaemia in the infarct and lessen the oedema surrounding the penumbra, without rendering it ischaemic. However, if CR is intact and CA lost hyperventilation will lead to ischaemia, and any change in BP will lead to a pressure passive response in blood

flow to the penumbra, any fall in supply will render the tissue non-viable, any rise possibly oedematous.

Anti-hypertensive drugs could potentially cause problems with worsening ischaemia and extension of the infarct size acutely, if there is impaired CA, as a fall in MAP would lead to a passive fall in CBF. If there is also an increase in short-term blood pressure variability with acute stroke, which may lead to a very labile perfusion pressure, this in conjunction with impaired CA may further exacerbate ischaemic damage unless the therapy itself has a beneficial effect on either of these phenomena. Despite these potential problems antihypertensive agents are still being considered as an acute therapy as well as long-term risk factor management, despite the lack of randomised controlled trials examining their use as secondary preventative measures [O'Connell 1996] (see Section 1.3.6).

In the acute setting animal models have shown encouraging results with a reduction in infarct size with calcium antagonists, but in humans their case has not been conclusively made because of reports of inverse steal [Auer 1988, Strandgaard 1990, Nuglisch 1992, Grotta 1994]. Hypertension induced with adrenaline has also been tried in acute stroke, and although a better recovery was reported the results were not convincing because of the lack of valid neurological scales, poor case mix of treatment groups, co-administration of low molecular dextrans, and poor methods for measuring CBF [Meier 1991]. It is thought that preexisting anti-hypertensive therapy could be continued as it may have altered the individuals limits of autoregulation (see Section 1.3.6). Alpha-methyldopa has been used in the subacute phase, i.e. >4 weeks post-ictus, and been shown to lower BP and cerebrovascular resistance leading to an improvement in CBF in some, but a fall in others where CA lost and a pressure passive phenomenon occurs [Meyer 1968]. At present it is thought that acute anti-hypertensive therapy should be withheld unless there is another reason for its use such as malignant hypertension, aortic dissection, acute myocardial infarction [Consensus Statement on Management of Stroke 1998],

especially since stroke patients are likely to be old, with possible haemodynamically unstable vascular lesions, e.g. stenoses, in addition to altered CA; certainly there are plenty of case reports of death and extension of neurological impairment following treatment to support this caution [Graham 1975, Britton 1980, Lavin 1986]. In the subacute stage drugs with a smooth gradual reduction in BP and little effect on the cerebral circulation, e.g. ACEI, should probably be administered, but with caution [Loyke 1983, Yatsu 1985, Strandgaard 1990].

Experimental therapeutic options:- Other therapeutic options need to be considered, and presently interest centres on either thrombolytic therapy or neuroprotective agents. The aim being that thrombolytic therapy will improve reperfusion and outcome to the same extent that it has improved the management of acute myocardial infarction [Fibrinolytic Therapy Trialists 1994], and that neuroprotective agents will salvage the potentially reversible damage in the ischaemic penumbra.

In 1995 the NINDS rtPA Stroke Trial was published leading to the licensing in the USA of rtPA as an acute therapy for ischaemic stroke in 1996. The multicentre study reported that those patients given rtPA <3hours post-stroke onset had a 11-13% absolute increase in the chance of minimal or no disability at 3months compared to those treated with placebo, along with a reduction in infarct volume. However, the treated group had a 10 fold increase in the risk of symptomatic intracerebral haemorrhage, and an increased risk of death within 36 hours, although by 3 months there was no difference in mortality between the groups.

The European trial [ECASS I 1995] failed to demonstrate the same benefit and again found a significant risk of intracerebral haemorrhage. These differences were attributed to the use of a higher dose of rtPA, a longer therapeutic window (up to 6 hours), and a number of protocol violations, in particular in terms of CT criteria. Consequently ECASS II was conducted and published in 1998, but the same

concerns remained, although there was the suggestion of a non-significant trend towards a benefit from treatment. This along with a number of other trials looking at streptokinase [MAST-E, ASK, MAST-I], which were all terminated because of increased mortality, means that as yet the American views regarding thrombolysis are still not widely accepted, and rtPA remains unlicensed in the UK.

Recent reports from the USA describing the results of rtPA in clinical practice will do little to change things for the present, since although there a few patients treated (1.8%, Katzen 2000), of these many do not fulfill the therapeutic guidelines (50%, Katzen 2000, and 33%, Albers 2000). Further studies are needed to clarify the agent and dose of choice, patient selection, and the window of opportunity.

Neuroprotective agents are designed to protect the ischaemic penumbra from further damage, mainly by modulation of the calcium influx that has been mentioned, hence the interest in calcium channel blockers, or more recently magnesium, which also alters the permeability of this channel, [the on-going IMAGES study]. Other factors exacerbate this increase, namely excitatory amino acids such as glutamate, and free radicals. Antagonists of the N-methyl-D-aspartate (NMDA) receptor and the kainate and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic (AMPA) acid receptors, all involved in amino acid transport, and glycine antagonists (glycine modulates the NMDA receptor) have been tested in animals with some encouraging results, but unfortunately their bioavailability is poor and early human studies with NMDA antagonists indicate psychomotor side effects and little improvement in neurological outcome compared to control subjects [Grotta 1997]. Adenosine may inhibit glutamate release by membrane hyperpolarisation, and serotonin may inhibit neuronal activity by altering potassium permeability, their agonists have been used in experimental models and may favourably influence infarct size [Nuglisch 1992]. It is unclear as to what effect these agents have on CA, but since they affect calcium channel receptors and their control, it is likely that they have a similar effect as calcium antagonists.

Summary:- In conclusion acute and chronic cerebrovascular disease in humans leads to changes in CBF, CR, and CA, which may improve with time. The ischaemic penumbra is affected by these changes, and this further aggravates the problems involved in the ongoing search for an acute therapy. However, there are problems with these studies; a) the techniques that have been used to measure CBF in particular have poor temporal and spatial resolution, so consequently there is very little information regarding dynamic CA, b) the subdivision into pressor and depressor responses has largely been ignored, c) the number of subjects in each study was small because of the low tolerance for the methods employed, d) many of the studies were conducted outside the acute phase, i.e.>4 days after onset, and e) there is little information regarding neurological outcome and prognosis with respect to CA. Consequently we still do not fully understand whether this process is affected detrimentally in the acute period, and if so to what extent. It is also still unclear as to the 'best' time to introduce anti-hypertensive therapy in case the penumbra is susceptible to further damage by their acute introduction. Research into neuroprotective and thrombolytic agents, however, looks promising from animal studies, but so far there are few encouraging results from human clinical trials. These differences between animal and human studies are largely because animal studies tend to have highly reproducible experimental ischaemic damage, and be 'cared for' in a very uniform situation, whereas human stroke is a very heterogeneous state. Also endpoints in animal models tend to be gross, e.g. dead or alive, or reduction in infarct size on macroscopic examination, whereas in humans an improvement in neurological outcome is the ultimate aim. In addition, animal studies tend to use different statistical methodology as they are primarily interested in minimising the chance of a Type II error, i.e. missing a positive result [Grotta 1994]. It is unlikely that any one therapeutic intervention will improve CBF, CA, CR, and possibly short-term blood pressure variability; consequently a combination of therapies will probably be identified eventually.

1.5. CARDIOVASCULAR REGULATION AND STROKE

1.5.1 BLOOD PRESSURE:-

It is known that increasing blood pressure levels are a strong risk factor for stroke; even so-called 'white coat' hypertension, i.e. patients with 24 hour levels within the normal range but clinic readings elevated above the normal range, may cause increased cardiovascular morbidity [Traub 1997]. Advancing age is also associated with an increase in both systolic (SBP) and to a lesser degree diastolic (DBP) BP levels (up to 80 years of age), and an increase in postural hypotension (OH). OH is felt to represent an increased incidence of diseases and medications leading to this rather than an age-related problem per se, high systolic BP levels are however an independent risk factor for OH [Robinson 1994, Fotherby 1994].

With the advent of 24 hour non-invasive blood pressure monitoring, which is considered valid and reproducible [British Hypertension Society 1990, O'Brien 1991], there have been many studies examining the diurnal changes and disease effects on BP. In the normal population a diurnal variation in BP has been described [Miller-Craig 1978], with readings being highest in the early morning, falling in the evening and reaching their lowest values overnight. Subsequently, subjects demonstrating this nocturnal fall have been termed 'dippers', and those who don't 'non-dippers' [O'Brien 1988]. Various criteria have been described to define the presence of dipping status, but it is usually considered as a 10mmHg or 10% fall in SBP in nighttime readings compared to daytime values, or a 5mmHg or 10% fall in DBP [Verdecchia 1990, Shimada 1992]. The percentage of the population classified as dippers depends not only on these values, but also on the definition of night and day [Wong Chung 1991]. Originally this definition was based on fixed time definitions, e.g. day 08.00-22.00 hours, night 22.01-07.59 hours, then restricted fixed time definitions, e.g. day 09.00-20.00hours, night 00.00-06.59hours. However this time defined 'night' still leads to poor reproducibility especially in hospitalised patients and shift workers where sleep patterns are often

disturbed [Miles 1980], or in subjects used to taking a siesta [Burtsztyn 1997]. The use of actigraph monitoring was postulated as a method to improve this [Youde 1996], but it was not found to do so. Various statistical models have therefore been employed to examine the diurnal change regardless of time, e.g. cumulative sums analysis (cusums) [Stanton 1992]. This has been shown to be much more reproducible with a coefficient of variation (CV) of 34%, compared to >50% for fixed time definition, and 40% for actigraph monitoring [Robinson 1995].

It is now known that nocturnal BP fall is reduced in hypertension, diseases of the autonomic nervous system, sleep apnoea, and endocrine disorders [Pickering 1982, Mann 1983, Tilkean 1976, Imai 1988]. More recently the relationship between nocturnal BP dip and mortality has been described in a large Japanese population [Ohkubo 1997]. It would appear that there is no difference in non-cardiovascular deaths with dipping status, but subjects with reverse dipping (i.e. nocturnal BP rise), and non-dippers (i.e. >0-<10% change in SBP) have a significantly increased risk of a cardiovascular related death than dippers (i.e. 10-20% fall), and extreme dippers (i.e.>20% fall).

BP changes occurring within an individual can be further described using the standard deviations and coefficients of variance (CV) of readings obtained via the ABPM at 30 minute intervals, so-called medium term BP variability [Parati 1987, Frattola 1993, Palatini 1992]. Alternatively, the standard deviations/CV of readings obtained either at 15 minute intervals from an ABPM or from beat-to-beat intra-arterial or non-invasive arterial recordings can be used; this parameter is referred to as short term BP variability (BPV) [Parati 1987, Frattola 1993, Siche 1995, Robinson 1997c]. An increase in short-term variability is thought to be related to increased end-organ damage in the hypertensive population [Parati 1987]. There is also a positive correlation between this short-term variability and both advancing age and increasing BP levels [Mancia 1995, Imai 197]. It may reflect a disturbance of baroreflex sensitivity as heart rate variability falls with age, as a result of

increasing arterial stiffness and decreased arterial compliance and consequently an increased pulse pressure.

Both an increase in BP variability and a reduced nocturnal fall have been shown to be associated with complications in the cardiovascular system. There is an inverse relationship between nocturnal dip and left ventricular (LV) mass [Verdecchia 1990]. Hypertension, and in particular increased short-term variability and high nocturnal levels, i.e. loss of nocturnal fall, are associated with an increase in common carotid intimal media thickness, and carotid artery atherosclerosis, particularly the internal carotid artery [Sander 1996, 1997]. This indicates that although hypertension is a systemic disease it has local effects, and offers some explanation as to the relation between BP and thromboembolic stroke. Cerebral imaging studies in asymptomatic hypertensive and normotensive populations have also shown a positive correlation between absolute BP levels, more so than dipping status, and vascular damage in the form of periventricular white matter lesions (PWML) or lacunes [Shimada 1992, Chamorro 1997]. PWML are associated with lacunar stroke [Hijara 1990], and may adversely affect prognosis if concurrently present [Samuelson 1996].

Following all stroke there are marked changes in absolute BP levels. These were initially described by Wallace and Levy [1981] who found that 84% of strokes were hypertensive on admission though only 50% had a history of hypertension. These levels settled over the following 10 days, so that by day 10 only 30% were still hypertensive. These findings have been confirmed in other studies, but there is still some debate as to whether this is an effect of the stroke per se or the admission to hospital. Most studies have implied that these blood pressure changes are an effect of the stroke, and demonstrated a greater decline in ambulatory BP readings in stroke patients compared to patients admitted with alternative diagnoses [Britton 1986, Harper 1994, Morfis 1997], especially in subjects with a heavy pre-morbid alcohol consumption [Harper 1994]. However Carlberg et al [1990,1991,1991b]

described the same high levels on admission whether admitted on the day of symptom onset or 3 days later. In some subjects, who were previously hypertensive, blood pressure levels may return to a normotensive value following stroke, although the mechanism behind this is unclear [Loyke 1983].

These BP changes are not thought to be related to neurological deficit or coma, but if presenting with a thromboembolic infarct they are higher in patients with a previous history of hypertension, whereas admission with a primary intracerebral haemorrhage is associated with high levels regardless of pre-morbid BP status; there are also ethnic differences in this latter case with subjects from 'black' ethnic backgrounds having particularly high levels [Britton 1986, Carlberg 1991b, Lip 1997].

What of diurnal BP change following stroke? There is evidence that following acute ischaemic or haemorrhagic stroke nocturnal fall decreases or is lost. Kario [1994] reports the conversion of a 'dipper' to a 'no-dipper' following lacunar stroke, and others have found PICH to be particularly related to a loss of fall or even a reversed dip pattern [Lip 1997]. The situation with cerebral infarction seems to be more complicated, with reports of no change or a diminution/ loss of dip depending on stroke site. Involvement of the insular cortex, multiple lacunes, or pontine regions would appear to lead to loss of a nocturnal dip, whereas involvement of the putaminal area, cortex, or single lacunes appears to have no significant effect [Sander 1994, Yamamoto 1995, Bryant 1997]. This difference with site may reflect damage to the central modulation of the autonomic nervous system, and may indicate a withdrawal of vagal tone and a subsequent sympathetic excess, which may explain the lengthening of the QT interval and the occurrence of cardiac arrhythmias and associated morbidity/mortality in acute stroke [Sander 1994]. However, others feel that this change in diurnal pattern may once again be a reflection of problems with day and night time definitions in hospitalised ill

subjects, and that if cusums analysis is employed there is no difference between patients and controls [Robinson 1996].

In an attempt to answer this question the author has studied the effect of stroke subtype on diurnal blood pressure change compared to a matched control group using both absolute and percentage differences between fixed time periods for day and night, and cusums analysis [Dawson 1998b]. Subjects with a cortical cerebral infarct (TACS/PACS according to the Oxfordshire Community Stroke Project Classification, Bamford 1991), or a PICH had both reduced diurnal systolic and diastolic blood pressure change as assessed by all methods. By contrast, subjects with subcortical cerebral infarcts (LACS), only had a reduced percentage change in systolic BP, and did not have a reduced cusums derived circadian alteration magnitude (CDCAM a measure of the magnitude of change, as opposed to the cusums plot height (CPH) which assesses both the magnitude and duration of any change). These results were thought to further support the concept that the effect of stroke on blood pressure control is related to the site of damage and resultant impairment to the central autonomic nervous system modulation.

Whether these effects have any prognostic implications is to date unclear. It may be that they are beneficial leading to an increased perfusion pressure, or they may reflect a larger volume of cerebral damage and be detrimental. However, there is evidence that there is further reduction in this diurnal BP change with subsequent events [Yamamoto 1995], but if it follows the same pathophysiological pattern as HRV it may improve in the 6 months following stroke [Korpelainen 1997].

The situation with short term blood pressure variability (BPV) is equally unclear. There are reports of an increased BPV in haemodynamic infarcts at watershed areas, which could indicate a cause or an increased risk of extension, compared to decreased medium and short term BP variability in thromboembolic infarcts that may start to recover towards normal after 7-10 days [Sander 1994, Bryant 1997]. Others, however, report an increased BPV in thromboembolic strokes [Robinson

1997], without a change in short-term pulse interval variation, implying an alteration in peripheral vascular resistance through the central control of the autonomic nervous system, rather than a change in cardiac baroreceptor function; i.e. damage to the vasomotor arm of the baroreflex. These authors found no change in their findings when the study was repeated after 14 days.

Not only is further information regarding the nature of the change to BPV in acute stroke required, but as with changes to diurnal BP it is necessary to know whether they influence prognosis, as appropriate therapies could perhaps be considered for implementation, e.g. an anti-hypertensive therapy that improves BPV. To date, advancing age, and elevated clinic and 24 hour BP levels are known to be associated with an increased mortality [Robinson 1994, Bath 1997], as is increased haematoma size in PICH [Terayama 1997]. Until further information is available regarding these and cerebral autoregulation (see Section 4) the debate over anti-hypertensive therapy in acute stroke will continue.

1.6. AIMS

This study aims to answer some of the questions raised in the preceding literature review, and to postulate on the relevance of these findings to the acute therapy of ischaemic stroke, in particular with regard to the introduction of acute anti-hypertensive therapy.

1. Continuing work previously submitted and published as an M.D. thesis from this department [Robinson T.G.:-The blood pressure and baroreceptor changes following acute stroke], the changes in short-term blood pressure and blood pressure variability in acute ischaemic stroke, and the influence of these parameters on 30 day prognosis will be studied.

2. In an attempt to understand the relevance of these changes in blood pressure and blood pressure variability, and how they may influence the pathophysiology of acute ischaemic stroke, changes in cerebral autoregulation will be examined in the acute post-ictal period. To do this initially it will be determined whether there is a valid and reproducible non-invasive method of assessing both static and dynamic cerebral autoregulation in a healthy population. This will be done by using one of the new non-invasive methods of measuring CBF that are now available, that have good patient acceptability, excellent temporal resolution, and are known to be valid and reproducible (see Methodology).

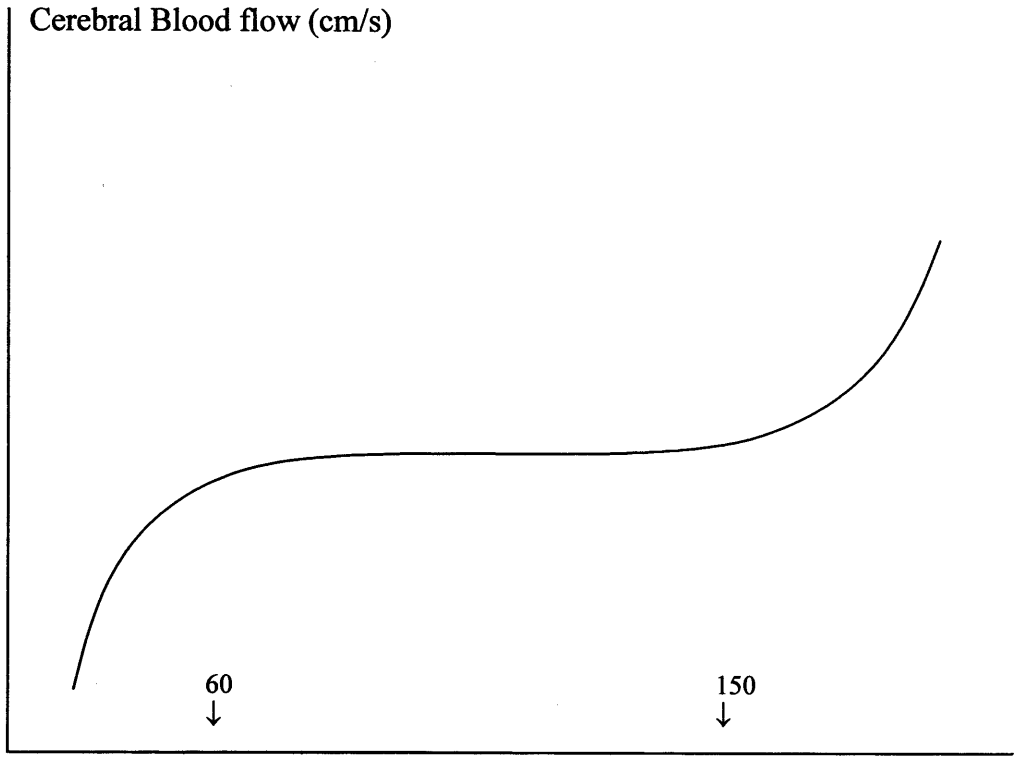
3. Using these techniques it is then hoped to be able to demonstrate whether subject characteristics affect cerebral autoregulation in this healthy control subject population. Using this population's results the author aims to determine whether there are interhemispheric differences present, and whether the response to pressor and depressor blood pressure stimuli are similar or not.

4. Finally using this methodology the effect of acute ischaemic stroke on dynamic and static cerebral autoregulation will be studied by comparing a population of acute ischaemic strokes to the control population.

Drug	Cerebral Blood Flow	Cerebral Autoregulation	Cerebral Vasoreactivity	Cerebrovascular disease
Diuretics	↔	? resets lower limit CA curve to left	? no effect	?
β blockers	acutely ↓ chronically ↑	? decreases vasodilatory capacity	? decreases vasodilatory capacity	? ↑ischaemia
Ca^{2+} antagonists	↔ or ↑	? resets lower limit CA curve to left, but danger of initial hypotension leading to hypoperfusion	?	? prevent postischaemic damage, or ? ↑ oedema
α blockers	↔ elderly ↑	?	↔	? improve metabolism, but ↑ ICP
ACEI	↔	? shortens autoregulatory plateau by moving both limits to left	? increases vasodilatory response	? ↓ infarct size in rats.

Table 1.1:- Summary of the effects of antihypertensive agents on CBF, CA, CR, and acute cerebrovascular disease

Fig. 1.1 The Autoregulatory Plateau.



CHAPTER 2

METHODOLOGY.

2.1 MEASUREMENT OF CEREBRAL BLOOD FLOW:-

Cerebral blood flow (CBF) as has been previously stated depends on perfusion pressure (PP) and cerebrovascular resistance (CVR); perfusion pressure is 'complicated' in the brain by intracranial pressure (ICP) and increasingly the concept of critical closing pressure (CrCP), which is the pressure at which the innate vasomotor tone of the cerebral vessels is exceeded by tissue/ ventricular pressure leading to collapse [Dewey 1974], is thought to be important in this regulation [Dawson 1999a].

The first studies of CBF in animals utilised invasive techniques such as bubble flow meters, but obviously the use of these methods was not possible in human subjects. The following sections will discuss the most widely used traditional techniques, namely the nitrous oxide and Xenon inhalation/ injection methods, some of the more recent radiological techniques, and the now widely employed use of transcranial Doppler ultrasonography (TCD).

2.1.1 Nitrous Oxide Method:-

This method, the first technique that could be employed in unanaethetised subjects, was first described by Kety et al in 1947 and employs the Fick principle. This states that the 'quantity of any substance taken up in a given time by an organ from the blood that supplies it is equal to the amount of the substance carried to the organ by the arterial inflow minus the amount removed by the venous drainage in the same time period', i.e.:-

$$(Q_b)_u = (Q_a)_u - (Q_v)_u$$

where $(Q_b)_u$ equals quantity of N2O taken up by whole brain

$(Q_a)_u$ equals quantity in arterial system supplying brain

$(Q_v)_u$ equals quantity in venous system draining brain within the same time period

Nitrous oxide (N2O) was the inert gas used because of its favourable solubility and diffusion characteristics; a low concentration was inhaled and CBF measurements calculated from the results of arterial and venous samples 10 minutes after inhalation began, when it was assumed that equilibrium had been established, using the following equation where 'A' = the arterial concentration of N2O, 'V' = the venous concentration, both of which are dependent on time, and TF = the total cerebral blood flow/minute:-

$$(Q_a)_u = TF\int_o^u A\,dt$$

$$(Q_v)_u = TF\int_o^u V\,dt$$

$$\therefore TF = \frac{(Q_b)_u}{\int_o^u (A-V)\,dt}$$

Problems with this technique included the possibility of unequal venous drainage by the two internal jugular bulbs, and contamination of the venous drainage by extracerebral structures. However it was this technique that first led to the concept of normal CBF being approx 50ml/100g/minute.

2.1.2. Xenon inhalation/injection Method:-

This method dated from the 1960's and involved an intracarotid bolus injection of radioactive ^{133}Xenon (Xe), but this was refined to utilise either inhaled Xe or intravenous injection [Mallett 1965, Obrist 1975, Overgaard 1981, Bouma 1990], the clearance curves of the γ radiation were measured by extracranial detectors attached to the surface of the cranium, (8 per hemisphere). The intracarotid technique was not favoured because of its invasive nature, and because it only measured CBF in one anterior hemisphere, compared to the inhalation and intravenous techniques that could examine bilateral anterior and posterior circulations. However, all were limited by the fact that the detectors only picked up changes occurring in the superficial structures of the brain, and could therefore

offer little in the way of anatomical information; and hyperventilation was often triggered by the process leading to the need for CO2 adjusted values of CBF.

2.1.3. Xenon enhanced CT Scanning

This technique was initially favoured because it combined the use of computerised tomography to increase anatomical detail, especially of deep seated structures, with the use of non-radioactive Xe [Gur 1982]. Because of the high atomic number of this element enhancement occurred on scans even at low inhaled concentrations, aided by the high permeability across the blood brain barrier. Unlike the previous studies that assessed 'wash-out' this process looked at 'build-up' in the different areas in the 4 minutes after inhalation began, when once again equilibrium was thought to exist between end tidal Xe levels and those in the arterial system. There are however problems with this method too. The slow flow areas tended to act as monocompartments whereas the fast flow areas acted as multicompartments, the calculation of CBF assumed only one compartment and although some of this mathematical error could be corrected for errors around pathological regions, e.g. between an infarct and its penumbra were substantial. In addition a high radiation dose was involved, patient movement caused considerable artefact, especially with the original CT scanners, Xenon was not without side-effects including the possibility of a raised ICP, and once again correction for alterations in end-tidal CO2 were necessary.

2.1.4. Positron Emission Scanning and other radiological techniques:-

Positron emission tomography (PET), single photon enhanced computerised tomography (SPECT) and more recently phase contrast magnetic resonance angiography (PC MRA) [Patrick 1996], are exciting tools as they give information not only on CBF, but also on cerebral metabolism in conjunction with very detailed morphological and anatomical descriptions. However, these machines are expensive and so as yet have not been widely employed in the study of CBF and autoregulation; also like the above methods they have an insufficient temporal

resolution to examine dynamic responses occurring within 10-20 seconds; the advent of TCD has revolutionised the latter situation.

2.1.5. Transcranial Doppler:-

2.1.5.1. Physics:-

In 1842 Christian Doppler first described the Doppler principle when he noted that light waves were reflected at different frequencies when a moving object disturbed them; Satomura and Karubo first used the same principle for the study of blood flow in 1960; and by 1965 Kato et al were using transcranial Doppler to study CBF during neurosurgical procedures.

Doppler study involves a piezoelectric material which is used to generate ultrasound waves that are focused into a beam by a lens. Red blood cells reflect these waves and scatter them back to the transducer which receives this information, and by detecting the frequency change calculates the Doppler shift:-

$$\Delta f = 2(v\cos\theta)f_o / c$$

where Δf = Doppler shift, v = magnitude of scatter velocity, θ = angle between ultrasound beam and direction of motion, f_o = frequency of ultrasound transmitted, and c = speed of propagation of ultrasound in blood.

Because the sample volume contains a large number of cells causing different amounts of scatter a spectrum of frequencies is achieved. The maximum Doppler shift is the highest cell velocity in the given time sample, and the mean Doppler shift the average velocity in the time sample [Gill 1985]. Accuracy is increased by the use of a Doppler beam that is uniform over the entire area of the vessel [Evans 1982], and spatial resolution by the use of pulsed wave rather than continuos wave Doppler. Initially the use of this technique for CBF was hindered by the fact that most Doppler probes were of a frequency that was absorbed or scattered so much

by the bones comprising the cranium that it was impossible to detect any blood flow. Fortunately in 1982 Aaslid et al developed a 2MHz probe that overcame this problem as it was less affected by attenuation, and they also described the non-uniformity of the cranium and the discovery of so-called acoustic windows over the temporal, and occipital bones, as well as over the orbit. By selecting a gated probe, depth could also be altered and direction of flow either towards or away from the probe could be determined [Newell 1992]. There are however some subjects that do not have an adequate acoustic window, in whom insonation is technically impossible, this is particularly so in older women and certain ethnic racial origins including the Chinese and Afro-Caribbean populations [Halsey 1990]; by increasing the power of the probe from the usual 100mW/cm^2 to 800mW/cm^2 in these subjects detection rates can be improved but scalp burns are a possibility at this higher power.

2.1.5.2. Validation as a method of measuring CBF:-

Theoretically CBF can be calculated from measurements of velocity using the following equation:

$$Flow = \sum_i v_i . \Delta A_i$$

where ΔA_i = cross sectional area of vessel, and v_i = blood velocity at the point cross section measured.

However this requires the assumption that there is no significant change in the diameter of the artery being insonated, that the angle of insonation is less than 30° to reduce error in the calculation of velocity to <15%, and that the territory supplied by the artery in question is also constant. The angle of insonation is important because it can lead to a significant underestimate of velocity:-

$\cos\theta^1 = \frac{\cos\theta}{\cos\eta}$ where θ^1 = measured angle, θ = true angle , and η = angle that the vessel crosses the plane of imaging.

and $V_t = \frac{V_{obs}}{\cos\theta}$ where V_t = true velocity, and V_{obs} = observed velocity.

It is generally considered that changes in blood pressure, CO2 concentration and O2 concentration do not significantly alter the diameter of the large basal cerebral arteries, including the middle cerebral artery, whereas as expected the small distal vessels actively concerned with CA undergo considerable variation (<4% compared with 29% respectively) [Giller 1993, Poulin 1996]. The angle of insonation is assumed to be zero in most studies using TCD since it is impossible to measure it. However, because of these assumptions calculations of CBF using this technique do not correlate well with the traditional methods in terms of absolute value of CBF, e.g. correlation between intravenous Xenon clearance studies and TCD r=0.424 [Bishop 1986b]; but if velocities are used there is a much better correlation, e.g. correlation between SPECT and TCD r=0.63 [Lindegaard 1987, Dahl 1992, Newell 1994b]. Even more encouraging are the results of changes in CBF compared to changes in TCD velocities during a manoeuvre, e.g. testing cerebrovascular reactivity, where correlation can be as good as r=0.85 for TCD and Xe [Bishop 1986b, Kontos 1989, Dahl 1992, Larsen 1994, Sugimori 1995].

In conclusion although TCD does not lend itself well to the calculation of absolute values of CBF, velocities and changes in velocity do correlate well with results from traditional techniques; consequently most studies employ TCD derived arterial velocities as a surrogate for CBF and rely on changes in velocity in one of the main basal cerebral arteries, usually the middle cerebral artery (MCA), to reflect changes in hemispheric CBF. TCD machines now display a continuous beat-to-beat velocity profile of the MCA by employing power spectral analysis using Fast Fourier transformation [Attinger 1966] to calculate the maximum and time

averaged velocity from every third beat, and the pulsatility index (PI) which is a measure of distal vasculature resistance:-

$PI = \frac{(V_s - V_d)}{V_m}$ where V_s = systolic velocity, V_d = diastolic velocity, V_m = time averaged mean velocity.

This conversion by spectral analysis also allows an analogue output similar to the BP output from a non-invasive BP monitor to be recorded, enabling beat-to-beat changes to be measured, and hence the remarkable temporal resolution that means dynamic changes can be assessed using TCD [Aaslid 1982].

2.1.5.3. Vessel Identification and Reproducibility:-

Using a 2MHz probe with a high pass filter of 100MHz and a low pass filter of 3.4-9kHz, with an emitted power of 350mW, a burst repetition of 6.8-18kHz, a pulse length of 10μsec, and an emitting area of 1.5cm^2, (i.e. 10 times the cross sectional area of the middle cerebral artery), Aaslid et al [1982] described in detail the insonation of the basal cerebral arteries constituting the Circle of Willis (see Fig 2.1) through the various acoustic windows, and techniques to aid vessel identification (see Table 2.1); however, in populations with unstable cerebral circulation carotid compression is usually excluded from the assessment in case the circulation is further compromised or atheroma dislodged.

For the purposes of this study the proximal segment of both (where possible) middle cerebral arteries (MCA) were insonated through the temporal window using a SciMed QVL120 TCD, this is a purpose built dual-channel machine as two separate machines cannot be used because of interference, and the problem of the individual machine's pulse repetition and frequency being out of sync.

The transtemporal window is a natural foramina in the temporal bone just superior to the zygomatic arch where the temporal squamosa is thinner (see Fig 2.2); there

are three main areas and the MCA lies more anterior and superior to the window the more posterior the window used. This posterior window, just in front of the external auditory meatus, is often the most successful point of insonation. Although as much as 39% of an ultrasound beam may be absorbed at this point insonation can be satisfactorily achieved in >75% of subjects. Through the temporal window it is theoretically possible to identify the terminal internal carotid artery (TICA), the anterior, middle, and posterior arteries (ACA, MCA, PCA), and the anterior and posterior communicating arteries (ACoA, PCoA). The TICA is the point just prior to the bifurcation into the MCA and ACA; the MCA is a direct continuation of the TICA and tends to lie lateral, superior, and at a shallower depth , whereas the ACA is more medial, crossing towards the mid-line of the brain, and of all the vessels appears to the be most subject to individual variation. Along with these anatomical points the vessels have different velocities to aid identification [Aaslid 1982, Arnold 1986, Martin 1994], the average MCAV being 62 ± 12 cm/sec, compared to 51 ± 12 cm/sec for the ACA.

If these points are considered it is clear that TCD not only is accurate in its vessel identification compared to cadaveric models, but if these 'rules' are followed and in particular the interhemispheric asymmetry kept to a minimal inter- and intraobserver reproducibility is very good, e.g. <8% for interobserver and intraobserver reproducibility at 2 -24 hours [Padayachee 1986, Totaro 1992, Demolis 1993, Baumgartner 1994, Bay-Hansen 1997], and 13% for intraobserver reproducibility at 2 months [Bay-Hansen 1997].

In addition TCD has been shown to be a useful alternative to cerebral angiography in subjects with acute and chronic cerebrovascular disease to assess collateral activity and determine where the lesion is situated [Mattle 1988, Zanette 1989, Seidel 1995].

In summary transcranial Doppler is a reasonably simple, and very well tolerated non-invasive technique for the assessment of CBF using MCA velocity as a surrogate for CBF, and it has been shown to not only be valid compared to more traditional techniques, but to have a high degree of reproducibility, and an excellent temporal resolution allowing dynamic and static processes to be assessed.

2.2. NON-INVASIVE BEAT-TO-BEAT BLOOD PRESSURE MONITORING:-

The assessment of cerebral autoregulation (CA) requires measurement of the beat-to-beat response in CBF/MCAV to beat-to-beat changes in mean arterial BP. The gold standard method for measuring BP is intra-arterial monitoring, but this is not only invasive and distressing to subjects, but not without considerable risk of thromboembolism, arterial dissection etc. [Mangano 1979]. There are now a number of commercially available non-invasive BP monitors including the Finapres 2300 system (Ohmeda, Colarado, USA).

The Finapres uses the concept of finger clamping, as first described by Penaz in 1973, to calculate blood pressure. An infrared finger photoplethysmograph is surrounded by a fluid filled pressure cuff. A cuff of the appropriate size is placed around the subjects finger, usually the middle finger of the right hand, and the cuff is automatically inflated until it detects the maximal plethysmographic finger pulsation; a finger volume is then calculated, and the cuff aims to keep this value constant by a negative feedback loop (servo-adjust mechanism), any adjustments reflecting a change in arterial pressure, which it duly recalculates on a beat-to-beat basis. These results can either be recorded directly onto Digital Analogue Tape, downloaded onto a computer, or printed out.

A number of studies have validated this system against intra-arterial brachial measurements in a variety of conditions. Stokes et al [1991] compared results

during general anaesthesia and found correlation coefficients of 0.82, 0.68, and 0.78 for systolic (SBP), diastolic (DBP), and mean arterial (MAP) pressures respectively. They concluded that the trends detected by the Finapres were good, but that it was not sufficiently accurate to use for assessment of absolute values. However, the use of correlation coefficients as a statistical method to compare two techniques is questionable, with the method employed by Bland-Altman considered preferable [1986].

Imholz et al [1988], Parati et al [1989], Lal et al [1995], and Rongen et al [1995], all examined the reliability of the Finapres in a variety of invasive and non-invasive physiological settings. The non-invasive tests included the Valsalva manoeuvre, cold pressor test, isometric hand grip, rest, mental arithmetic, passive leg tilt, lower body negative pressure, and passive and active standing, and were, therefore, similar to those employed in this research project. Overall they all found that the Finapres tended to underestimate readings, in particular for SBP, but that it detected the same trends of change; in particular the direction of blood pressure changes in the different phases of the Valsalva manoeuvre were accurately represented temporally, even if the magnitude of change was less.

Imholz et al found at rest that values were underestimated by 1 ± 9.6 mmHg, 9 ± 6.8 mmHg, and 4 ± 6.1 mmHg for SBP, DBP, and MAP respectively. Parati et al found that during the tests the between method differences were never greater than 4.3 mmHg and 1.9 mmHg for SBP and DBP respectively. Most of these studies were done in subjects younger than 75 years, but the study by Rongen et al was performed in people aged 71-83 years, and is therefore referable to our population, and they found comparable results.

Parati et al also looked at beat-to-beat blood pressure variability and found that over a 30 minute period variability was almost identical comparing the two methods.

The reasons for the underestimation of BP by the Finapres are thought to include inadequate positioning of the cuff, inappropriate cuff size, and the hands relation to the atrium, (the hand should be at atrial level). Finger vasospasm is also considered by some investigators, but is difficult to quantify. In our subjects an appropriate sized cuff, as suggested by the manufacturers was used, and the hand and arm were supported at atrial height using a specially built arm support. BP readings were only accepted if they were within 15/10mmHg of contralateral brachial readings. One possible criticism of our methodology would be that the paralysed limb was used in hemiplegic subjects, as a 'functioning arm' was needed for some of the tests; this raises questions regarding the concurrence between readings from the different body sides as sympathetic innervation and, therefore, vascular tone may differ, affecting BP accuracy in these circumstances, but it is trends not absolutes that are important in the assessment of CA, and therefore, it is not thought that this was a significant problem.

In conclusion, although the Finapres tends to underestimate blood pressure values in particular those for SBP, it is capable of very accurately detecting trends in BP compared to intra-arterial measurements, although the magnitude of these changes may not be as great as the true physiological changes.

2.3 MEASUREMENT OF CARBON DIOXIDE PARTIAL PRESSURE:-

As has previously been discussed CO2 can significantly alter not only CBF through its stimulation of vasodilatation, but the autoregulatory curve. In any experiment of CA it is consequently essential to monitor CO2 to determine that it remains stable during the study protocol and is therefore not the cause for any apparent differences seen between subjects.

As with BP the gold standard technique for measuring carbon dioxide partial pressure (pCO2) is arterial blood gas sampling. However this only gives results for

a single point in time, and it is again both distressing and not without complications if repeatedly performed [Downs 1973, Bedford 1977]. Previous studies of CA/CR have used end-tidal CO2 levels to detect any change in pCO2 during the course of the experimental protocol, but this requires a face mask which can be poorly tolerated; and since TCD examination requires the use of a head frame an alternative technique for assessing pCO2 was sort.

There now exists a non-invasive transcutaneous method (TINA, Radiometer, Copenhagen) [Larson 1993] which has been shown to be valid compared to arterial blood gas samples in a variety of situations [Tremper 1981, Mahutte 1984, Carter 1989, Sridhar 1993]. We have also recently demonstrated that this technique is comparable to arterialised earlobe samples for the calculation of pCO2, although it underestimates oxygen partial pressure (pO2), and cannot be recommended for assessment of this parameter [Dawson 1998a]. The results of this study are presented in Appendix 2.

Although the temporal resolution of this equipment, i.e. the time it takes to detect a change, is not clear it may well take a few minutes; however, in the experiments that will be described the recording time around static and dynamic tests was sufficient to detect this lag if it was present.

In conclusion, the TINA is an acceptable method for the non-invasive measurement of pCO2, and is a useful addition to research.

2.4 MEASUREMENT OF CEREBROVASCULAR REACTIVITY AND AUTOREGULATION:-

Although CR and CA have more traditionally been assessed using techniques for CBF measurement with poor temporal resolution, the advent of TCD has expanded

the repertoire of tests to examine both these processes. This section will discuss some of the methods that have been used in conjunction with TCD to date.

2.4.1. Cerebrovascular reactivity.

Traditionally measurement of cerebrovascular reactivity (CR), which essentially is a measure of vasodilatory reserve capacity, involved either the administration of acetazolamide (1g intravenously) or the inhalation of a fixed concentration of CO2 (usually 5%). Both stimuli trigger vasodilatation, CO2 almost instantaneously, whereas the maximum response to acetazolamide is usually within 10 minutes of the injection. A measure of CR can be obtained by calculating the maximum percentage increase in MCA velocity (MCAV), and it is therefore possible to compare hemispheres in individuals or subject groups. Both these techniques have been shown to correlate with more traditional methods such as SPECT [Dahl 1992], and to detect differences in subjects with extracranial atherosclerosis [Ringelstein 1988, Piepgras 1990]. Some investigators have tried to complicate matters by deriving indexes of reactivity through mathematical manipulation of the data, e.g. Kodaka et al [1996] derived the k index of reactivity:-

$$f_m = a \times e^{(k.pCO2)}$$

where f_m = Doppler velocity, and a = theoretical velocity at pCO2 0mmHg.

More recently there have been attempts to extend these tests to a wider population by simplifying them; one of the tests consequently established is the Breath Holding test [Ratnatunga 1990]. This involves subjects taking a normal breath and then holding it for as long as possible. The percentage change in MCAV during this breath hold, i.e. with time, yields the breath-holding index (BHI):-

$$BHI = \frac{\Delta MCAV}{BH}$$, where BH = duration of breath hold.

This method has also been found to correlate well with CO2 inhalation, and degree of stenosis [Markus 1992, Silvestrini 1996]. However, there are concerns with patient co-operation in that often subjects take a deep breath in, the breath hold mimicking a Valsalva manoeuvre with a fall in MCAV and then a larger rise as the CO2 level increases. Some studies imply that the range of results are the same in a group whether normal inspiration or deep inspiration precedes the breath holding [Stoll 1996], but if results are to be compared between studies methods need to be standardised.

2.4.2 Static Cerebral Autoregulation.

As mentioned in previous sections most studies until the advent of TCD were of static autoregulation because of the lack of temporal resolution in the measurements of CBF. Animal studies were the original tests and they usually employed either pharmacological manipulation of the blood pressure or changes induced by haemorrhage or reperfusion with autologous blood. Human studies have used mainly pressor stimuli induced by either phenylephrine or noradrenaline to effect an average 20mmHg rise in BP [Larsen 1994, Tiecks 1995a, Strebel 1995], depressor stimuli have been either passive tilt [Grubb 1991, Schondorf 1997] or lower body negative pressure [Bondar 1994].

Pressor and depressor stimuli have to be considered separately as one is testing vasodilatory responses, the other vasoconstrictive; it is still unclear whether the mechanisms behind these are the same, and whether pathological damage affects them equally.

Usually a static autoregulatory index (ARI) is calculated, and most studies have used a method similar to the following described by Tiecks et al [1995a], where the percentage change in cerebrovascular resistance (CVR) per percentage change in BP is calculated:-

$$StaticARI = \frac{\%\Delta CVR_e}{\%ABP} \times 100\%$$

$$\%\Delta CVR_e = \frac{CVR_e^{\,2} - CVR_e^{\,1}}{CVR_e^{\,1}}$$

$$\%\Delta ABP = \frac{ABP_2 - ABP_1}{ABP_1}$$

where 1 = baseline reading, 2 = higher reading, and CVR_e = estimated CVR.

100% is felt to represent full autoregulatory compensation, 0% no change in CVR and consequently a loss of CA. These principles are illustrated in Fig.2.3.

2.4.3. Dynamic Cerebral Autoregulation.

As has been mentioned dynamic CA is a relatively new concept; it has to be considered as a separate entity from static CA as it is likely that different mechanisms underlie their control.

a). The 'gold standard' to date for dynamic testing involves the inflation of bilateral thigh cuffs to 30mmHg above systolic BP for 3 minutes and then rapid deflation to stimulate a dynamic fall in BP that lasts >20seconds. This, therefore, provides an adequate stimulus for CA, but because of the delay in BP recovery CA should be completed before there is any possible contamination to the process from pressure mediated influences, or from the CO2 rich blood returning from the legs [Aaslid 1989, Newell 1994b, Tiecks 1995a]. Initially a rate of recovery (dRoR) was assessed by:-

$$dROR = \frac{\Delta CVR}{\Delta Time} \div \Delta ABP$$

$$\Delta CVR = \frac{\Delta ABP}{\Delta CBF}$$

The dROR represents the percentage recovery per second, 20% was considered to be a reasonable result. More recently mathematical modelling of this concept has

yielded autoregulatory curves, numbered 0-9 (0 = no CA, with a pressure passive recovery in MCAV; whereas 9 = best CA); subjects are assigned a number according to the best fit of their curve to one of these models [Tiecks 1995a], (Fig 2.4); the methodology behind this modelling will be further discussed with the study results.

b). This same group have more recently described the use of the Valsalva manoeuvre (VM) as a test of CA [Tiecks 1995b, 1996]. The VM involves four distinct phases of BP and consequently CBF changes, some of which are influenced by ICP. Phase I represents the start of the strain and is associated with a rise in ABP because of the increased intrathoracic pressure; BP then falls as atrial filling decreases (Phase II), a sympathetic response then results leading to an increase in heart rate and consequently an increase in cardiac output and BP (Phase IIb); at the release of strain (Phase III) the sudden fall in intrathoracic pressure leads to a sharp fall in BP, but this is rapidly followed by a large BP overshoot due to the persistent sympathetic activity and high peripheral resistance (Phase IV), finally BP levels return to baseline over the next 30-60 seconds [Hamilton 1936]. The MCAV responds to these BP changes, in particular the changes in Phase II and Phase IV are thought to stimulate CA, however the overshoot in MCAV is proportionally much larger than that seen in MAP, the reason for this is not fully understood. Nevertheless, an autoregulatory index has been calculated from the changes between Phase IV and Phase I (ARIVM):-

$$ARIVM = \frac{MCAV_{Iv} \,/\, MCAV_{I}}{ABP_{IV} \,/\, ABP_{I}}$$

This index has also been shown to correlate well with vascular pathology [Tiecks 1996].

c). Common carotid compression stimulating a transient hyperaemic response has also been used as a measure of dynamic autoregulation; however, in the elderly

stroke aged population even the 5 second compression used could lead to disastrous results. It has nevertheless been found to correlate well with neurological outcome in subjects with subarachnoid haemorrhage [Smielewski 1995, 1996]. A similar theory led to the use of light stimulation to test visually evoked responses in the visual cortex by measuring changes in posterior cerebral artery velocity [Aaslid 1987].

All of the tests mentioned so far involve an assessment of CA based on changes in MCAV, BP, or cerebrovascular resistance. Recently there has been increasing interest in the use of spectral analysis to study the changes in BP and MCAV in different spectral frequency bands and to compare the phase lead, gain , and phase shift. This has led to some encouraging results in terms of a loss of phase lead with hypercapnia, and an increase in gain, i.e. more MCAV variation, in subjects with cerebrovascular disease. A phase shift angle of 0° represents no CA, whereas an angle of 90° equals optimal CA, [Diehl 1995, Birch 1995, Blaber 1997].

In summary a number of tests have been derived that test dynamic CA using TCD and non-invasive and minimally 'invasive' methodology to stimulate pressor and depressor changes in BP. A variety of different algorithms have been devised to assign subjects an autoregulatory index; but the thigh cuff method as described by Aaslid et al is the only method that is considered to have been validated.

2.5. POTENTIAL NON-INVASIVE STATIC AND DYNAMIC PRESSOR AND DEPRESSOR TESTS:-

In this section I will discuss the tests that were used in this thesis to stimulate CA through changes in BP, and if known the effect they are thought to have on CBF. Some of them have been mentioned previously, but they may have been modified

or adapted to stimulate other processes too. The physiological consequences of these tests will be considered as they may affect the autoregulatory response.

2.5.1 Thigh Cuff Inflation and Release: a static pressor and dynamic depressor stimulus

Aaslid et al [1989] first described the use of this technique as a non-invasive means of affecting a rapid fall in mean arterial BP (MAP) for the assessment of CA. They inflated bilateral thigh-cuffs to 30mmHg above systolic BP for 3 minutes, and then rapidly released them so that a mean BP fall of 24 ± 1mmHg occurred which lasted >15secs. As mentioned in the previous section this eliminates the problem of a pressure passive relation confounding the CA process, and also the arrival of CO2 rich blood from the legs in the brain. Further studies have validated this technique in a number of different subject groups [Tiecks 1995a, Strebel 1995], and compared results to other tests, e.g. CO2 induced vasodilatory response, [Newell 1994b], although this latter study is comparing the different processes of CA and CR.

It would seem that bilateral inflation to systolic BP or levels just above for 90 seconds produces BP falls of a similar magnitude without causing so much patient discomfort. This shorter duration also theoretically reduces the build up of CO2, and the risk of an inadvertent breath holding, or Valsalva manoeuvre performance by the subject. In addition it was noted that during this period of inflation there was a static rise in MAP, with a less marked increase in heart rate (HR) presumably reflecting sympathetic stimulation due to discomfort. Consequently this procedure can be used as a static and a dynamic stimulus, but there is a possibility of the sympathetic nervous system altering CA.

2.5.2 Cold Pressor Test: a dynamic pressor stimulus

A distinction should be made between the cold face pack and the cold pressor tests. The former involves stimulation of the trigeminal nerve and brainstem vagal autonomic pathway, which primarily stimulates a bradycardia; however, it can lead

to peripheral vasoconstriction and a modest elevation in predominately systolic BP, which does not alter with age [Khuruna 1980, Heath 1990, Collins 1996]. In contrast the cold pressor test, achieved by submersion of a hand into water at <4°C for 30-120seconds, leads to an immediate increase in HR and MAP due to an increase in sympathetic activity triggered by temperature and pain afferents, which promotes tachycardia and increased peripheral resistance. The HR response reaches a peak at 60secs, whereas the MAP will continue to rise for the duration of submersion, (if <3minutes); consequently HR and MAP are thought to be under different neurological control mechanisms [Green 1965, Victor 1987, Menkest 1989, Kahn 1993]. These difference between the tests are also important as the cold pressor test is thought to isolate the central and efferent arms of the baroreceptor reflex arc, whereas the cold face pack test also involves the afferent arm; this distinction is useful for the identification of a site of damage to this control pathway. However, the situation is further complicated by the finding that β-blockers do not fully attenuate the BP or the HR response during the cold pressor test, and other experiments have shown changes in muscle sympathetic activity too, i.e. it may not be solely cardiac baroreceptors that are involved [Victor 1987].

It would appear that subjects <45 years of age who are in the quartile with the largest increase in SBP are at an increased risk of developing overt hypertension in the following 20 years [Menkest 1989]. This would imply that there is an alteration to the subjects physiology that predates the hypertension; since hypertension and ageing cause a decline in baroreceptor sensitivity this may be a possible factor involved in the pathogenesis [Dawson 1999b].

Michieli's group appear to be the only group to have looked at the influence of the cold pressor test on MCAV [Michieli 1995, Roatta 1999]. They studied healthy controls, and compared these to subjects with migraine symptomatology. They describe in migraine subjects a reduced increase in pulsatility index (i.e. resistance) despite a similar BP stimulus, possibly implying a reduced level of CA [Michieli

1995]. In more recent studies of their healthy population they report changes in the BP/CBF ratio in response to the cold pressor test with BP changes well below the upper limit of cerebral autoregulation. This suggests that the sympathetic nervous system may be involved in the control of CA in both large and small cerebral resistance vessels [Roatta 1999].

The cold pressor test is an easy to perform and reproducible test [Hines 1936, Parati 1983, 1985] that does not necessarily require patient co-operation. However, the possibility of an influence of the sympathetic stimulation on CA must be considered in analysis.

2.5.3 The Valsalva Manoeuvre: a dynamic pressor response

The concept of the Valsalva manoeuvre has been discussed in the previous section. The standard method of performing this is to blow into a syringe fitted with a constant bleed device which is attached to a transducer to record intrathoracic pressure, subjects aim to achieve 40mmHg pressure for 15 seconds after a normal inspiratory breath [Palmero 1981, Smith 1987]. The changes in CBF can be used to calculate an autoregulatory index. The much larger overshoot in CBF that is seen in comparison to the MAP in Phase IV is thought to occur because the autoregulatory mechanisms are unable to cope with changes of this magnitude; however, it is now apparent that a more physiological explanation can be made of these changes if critical closing pressure (which has been previously mentioned) is taken into account, and this measurement may be found to be important and worthy of consideration in other situations too [Dawson 1999a].

2.5.4. Isometric Hand Grip: a static pressor and dynamic depressor stimulus

Isometric hand grip performed at 10, 30, or 100% of maximum voluntary contraction (MVC), continuously or with intermittent 10sec rest periods leads to a rise in MAP, the difference is in the rate of this increase and time to fatigue as the percentage of slow to fast twitch muscle fibres in use differs [Lind 1983, Bystrom

1991, Fallentin 1992, Smith 1993]. At 30% MVC for 2minutes a 20mmHg rise in MAP usually occurs, if continued to the point of fatigue a peak pressure of 50-70mmHg above resting values may be achieved [Lind 1983]. It appears that a local vasodilation occurs to increase perfusion of the exercising muscles, and that elsewhere vasoconstriction occurs leading to the increased MAP [Pauleu 1991, Kahn 1993]. This phenomenon is caused by sympathetic activation, since there is evidence of increased circulating catecholamines post release [McDermott 1974], and of a paradoxical fall in BP secondary to local vasodilation in autonomic failure, e.g. Shy-Drager Syndrome [Khurana 1996]. Animal models have also demonstrated that the site of modulation of these changes is in the periaqueducatal grey matter and the ventrolateral medulla [Williams 1990]. Although pH is important with no change in BP occurring until pH has dropped below a threshold, usually after 30-45 seconds of exercise, the chemoreceptors are not functioning independently in causing these changes [Nishiyasu 1994].

Age per se does not appear to modify the BP response, although the factors causing it may change, e.g. there is evidence of age related changes in the adrenomedullary response to isometric handgrip with a greater fall in stroke volume in younger populations [McDermott 1974], essential hypertension does lead to an augmented rise in SBP, although isolated systolic hypertension does not [Sumimoto 1991]; finally the inadvertent performance of a Valsalva manoeuvre during the exercise must be considered as this can alter the change in MAP achieved [Williams 1987], and also the MCAV (see 2.5.3).

Isometric handgrip has not to my knowledge been used to assess CA, but it is suitable for a static pressor stimulus and the release of grip leads to a fall in sympathetic activity and a fall in MAP at least of similar rate and magnitude as seen with thigh cuff release, i.e. a dynamic depressor stimulus.

2.5.5. Passive Leg Tilt:- a static pressor and dynamic depressor stimulus

There is little information from the literature on the concept of passive leg tilt. Elevation of the legs above atrial height should lead to an increase in venous return to the right side of the heart and consequently an increased cardiac output that is sustained for the duration of the tilt. There is some evidence that it may stimulate the cardiopulmonary baroreceptors and lead to a peripheral vasodilation [Parati 1989] which would limit the magnitude of any change in BP. After 3 minutes of leg tilt a small rise was noted, but on lowering of the legs there was often a fall in BP, that could be used as a dynamic test. As with some of the other tests the problem of an inadvertent rise in intra-abdominal pressure had to be considered, so patients were asked not to assist with the elevation or lowering of their limbs.

2.5.6. Lower Body Negative Pressure:- a static depressor and a dynamic pressor stimulus

Lower body negative pressure (LBNP) is achieved by placing the subjects lower body, i.e. from the superior iliac crests downwards, in an air-tight box. Suction is then applied with a pump, in this case a domestic vacuum cleaner, to cause the formation of a vacuum around the lower limbs triggering venous pooling. The pressure can be adjusted to various limits, e.g. -30 or -50 mmHg to obtain the required stimulus via changes in MAP or the arterial baroreceptors. This stimulus can be non-hypotensive
(-10 mmHg), or hypotensive (-30 mmHg).

The application of LBNP has been used extensively in the study of the effects of the anti-gravity state on humans in space travel research [Stevens 1965]. LBNP causes an increased venous pooling in the lower limbs and pelvis, and consequently a central hypovolaemic state with a fall in cardiac output and stroke volume. This leads to activity in the arterial baroreceptors and extraarterial cardiopulmonary mechanoreceptors which lead to an increase in heart rate (HR) and total peripheral resistance (TPR) which maintains MAP, i.e. a non-hypotensive state. There are

gender and age-related differences in these responses, with men having more calf pooling, and women more thoracic impedance; with age the HR response declines as does the increase in TPR [Bassett 1988], whether this due to a change in sympathovagal balance or a change in the afferent limb of the baroreceptor reflex arc is unclear. As the degree and duration of LBNP increases this compensatory mechanism can fail, leading to a decline in MAP (a hypotensive stimulus), occasionally so suddenly that syncope is induced [Bondar 1994]. If the pressure is carefully controlled a static decline in BP can be achieved; at release of the negative pressure there is a sudden rise in circulating volume, and in conjunction with the persistent elevation of TPR a dynamic rise in BP.

There have been studies examining the effect of LBNP on CBF, primarily in young fit men [Stevens 1965, Raven 1984, Giller 1992, Ueno 1993, Bondar 1994, Levine 1994, Balldin 1996]. In general as the initial pressure is applied MAP remains constant due to an increase in TPR, during this period there is evidence of cerebral arteriolar vasodilatation [Ueno 1993]. As the pressure increases there is a decline in MCAV and evidence of vasoconstriction [Giller 1992] implying a deactivation of the sympathetic baroreceptors triggering increased efferent sympathetic activity; this relative resistance to sympathetic induced vasoconstriction is also seen in the renal circulation [Hirsch 1989]. At this point it appears that sympathetic activity overrides CA, and this may explain the shift in CA limits seen with e.g. hypertension.

Athletes have a reduced tolerance to LBNP, possibly because of their relative parasympathetic 'overactivity' , and decreased sympathoadrenal response [Raven 1984]. There is some experimental evidence that glycerol may improve tolerance to LBNP by reducing cerebral vasoconstriction [Bondar 1994]. At the point of pre-syncope the peripheral vasoconstriction suddenly drops and there is a fall in MAP, and a further decline in CBF causing syncope if not reversed [Bondar 1994].

Some studies have noted the response to the end of LBNP and the dynamic pressor BP stimulus. However, most of the subjects had been under LBNP for a considerable duration and there appeared to be a delay of >30seconds between MAP and CBF change. This may be a reflection of the excess sympathetic activity that had been induced during the application of pressure [Ueno 1993, Bondar 1994, Balldin 1996]; nevertheless we postulated the use of release of LBNP as a dynamic stimulus as well as a static depressor response, but these potential autonomic influences need to be considered.

2.5.7.Summary

In this section I have described the theory behind the tests used to stimulate static and dynamic CA. Pressor and depressor stimuli have been studied as the mechanisms of control are likely to be different, as well as for static and dynamic CA. It is clear that almost all of the tests stimulate the autonomic nervous system in some respect and that this may alter CA. The changes achieved by each test are summarised in Table 2.2.

2.6. STROKE SCALES

Research projects concerned with the pathophysiology of acute stroke, and possible therapeutic interventions need neurological scales that are easy to use, reliable (minimal measurement error) and valid (accurately describe the underlying disease), that both clinically classify stroke, and follow the changes in neurological impairment and functional disability with time, so that it is possible to determine prognostic implications in different groups of patients according to their pathophysiological findings or response to interventions. In day-to-day clinical practice these scales are also important in auditing different units and their management, including their use of appropriate investigation techniques.

Clinical subclassification has been traditionally based on division into carotid and vertebrobasilar arterial disease, or based on neuroradiological imaging results [Warlow et al Blackwell Science 1996]. However, as previously mentioned Bamford et al [1991], as part of the Oxfordshire Community Stroke Project (OCSP), devised a pathoclinical classification that aimed to determine both the site, size, and probable underlying vascular pathology and, subsequently, likely risk factors (see Appendix 1). The four clinical subgroups have also been found to correlate with the amount of infarcted tissue subsequently seen on CT scan [Lindgren 1994], and to have a high specificity and sensitivity for site as well as size of infarct, again compared to CT scanning. This subgrouping also gives immediate information on prognosis, mainly because of its reflection of tissue volume damage, with far more TACS being dead or dependent at 12 months compared to LACS [Bamford 1990, 1991].

Lindley et al [1993] have examined the interobserver reliability of this classification, and found overall a moderate agreement between two observers (kappa = 0.54; 95% confidence interval 0.39 - 0.68) with most of the difference being explained by disagreement on the presence or absence of a few of the defining neurological signs, e.g. hemianopia: kappa = 0.39, sensory loss: kappa = 0.15, compared to hemiparesis: kappa = 0.77. It was felt that agreement could have been improved somewhat if documentation of the maximum deficit had been better at the time of admission.

The OCSP Subgroup Classification is, therefore, a simple, valid, and reliable clinico- pathophysiological assessment of stroke.

There are many scales of neurological disability including the National Institute of Health Stroke Scale (NIHSS), the Canadian Neurological Scale (CNS), the European Stroke Scale, and the Unified Neurological Stroke Scale. For the purpose of this study we have used the NIHSS and the CNS because both of these have been

extensively studied for reliability and validity as a measure of neurological examination [Brott 1989, Goldstein 1989, Cote 1989, Lyden 1991, D'Olhaberriague 1996] (Appendix 2B/C). The NIHSS has also been shown to be equally reliable when used by neurologists, non-neurologists and study co-ordinators in trials of acute therapy [Goldstein 1997].

The interrater agreement for reliability of the NIHSS ranges from kappa = 0.48 - 0.69 [Brott 1989, Goldstein 1989], and for the CNS kappa = 0.76 [Cote 1989]; again certain signs scored better than others in the NIHSS and, therefore, influence the overall result, e.g. weak arm kappa = 0.85, compared to kappa = 0.58 for neglect; the CNS does not include many of these less reliable signs, hence, its greater agreement.

The validity of these two scales has also been examined [Brott 1989, Goldstein 1989, Cote 1989]. The initial NIHSS/CNS score correlates well with infarct volume (r = 0.78/0.77 respectively) and the NIHSS also with outcome at 3 months (r = 0.71); the CNS score also predicts outcome at 6 months, with a lower score indicating a higher mortality, a greater incidence of recurrent vascular events, and a lower independence. Overall, these two scores are considered the best stroke scales.

However, none of these subgroupings or scales say anything about the patients disability (capacity to perform a task) or handicap (ability to perform a role that they previously could), a patient may have little neurological deficit, but be finding it very difficult to cope with activities of daily living, and vice versa. This disability question becomes increasingly important the further from the acute event the patient is, particularly when plans for long-term placement are being considered. Similar studies of reliability on the available scales on disability and handicap have been conducted [Lyden 1991, D'Olhaberriague 1996]. From the results of these studies the Rankin Scale [Rankin 1957] as a global assessment score, and the

Barthel Index [Mahoney 1965] as a score of activities of daily living appear the best tools for measuring this concept (Appendix 1).

The Rankin Scale has a very good interrelater agreement (kappa = 0.91), as does the Barthel Index (kappa = 0.80), and the latter has also been shown to predict length of stay and discharge placement, the higher the score the more independent an existence patients are expected to have on return to the community [Granger 1989]; and it is equally reliable whether performed by telephone interview or direct examination [Shinar 1987].

In summary, the combination of the OCSP clinical subgroup classification of stroke, the NIHSS and CNS stroke scales as measures of neurological deficit, and the Rankin Scale and Barthel Index as disability/handicap scales are thought to distinguish different groups both with reliability and validity, so that any differences in study results or prognosis/outcome found in the research setting could be extrapolated to the general population.

Artery	Transducer Site	Depth of sampling (mm)	Direction of flow	Mean velocity	Response to ipsilateral carotid compression
MCA	Temporal	30-60	Toward	55 ± 12	↓ →
ACA/MCA bifurcation	Temporal	55-65	Bidirectional		↓ →
ACA	Temporal	60-80	Toward	50 ± 11	↓ →
PCA	Temporal	60-70	Toward or Away	39 ± 10	→
TICA	Temporal	55-65	Toward	39 ± 9	↓

Table 2.1:- Identification of Basal Cerebral Arteries [Transcranial Doppler. Editors D.Newell & R.Aaslid, Raven Press, New York 1992].
↓ = *decrease or loss of velocity*
→ = *no change*

	Static Pressor	Static Depressor	Dynamic Pressor	Dynamic Depressor
Isometric handgrip	+	-	-	+
Thigh Cuff	+	-	-	+
Cold Pressor	-	-	+	-
Passive leg tilt	+	-	-	+
Valsalva manoeuvre	-	-	+	-
Lower body negative pressure	-	+	+	-

Table 2.2:- Blood pressure responses affected by different tests used to assess cerebral autoregulation. See text for detailed description.

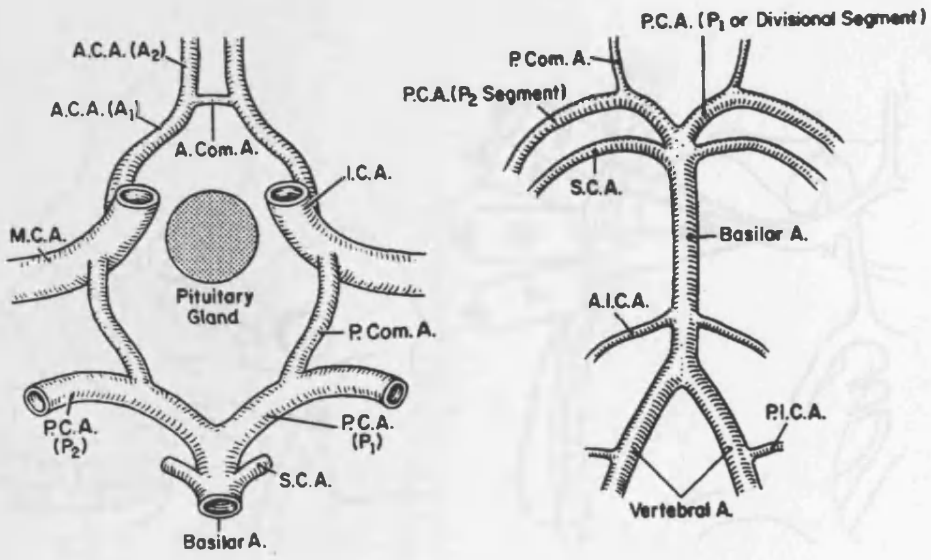


Figure 2.1. Normal Circle of Willis.

ICA = Internal carotid artery
ACA = Anterior cerebral artery
MCA = Middle cerebral artery
PCA = Posterior cerebral artery
SCA = Superior cerebellar artery

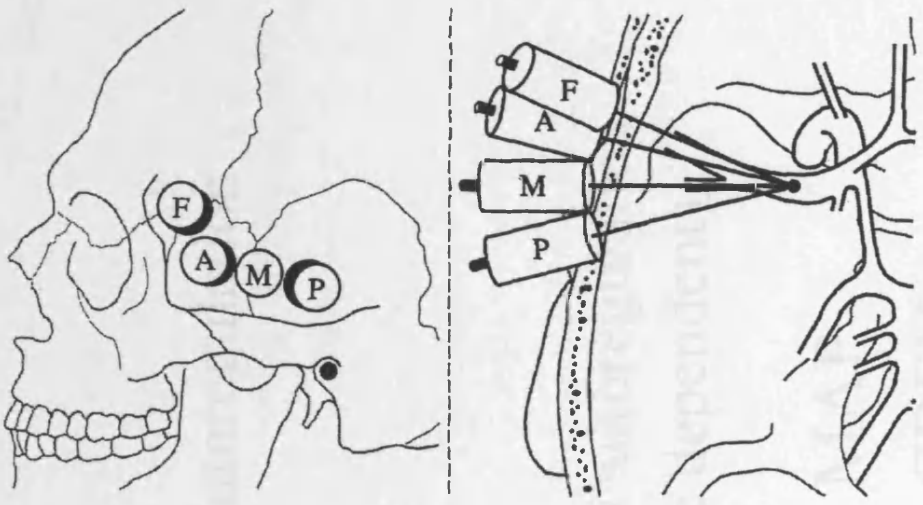
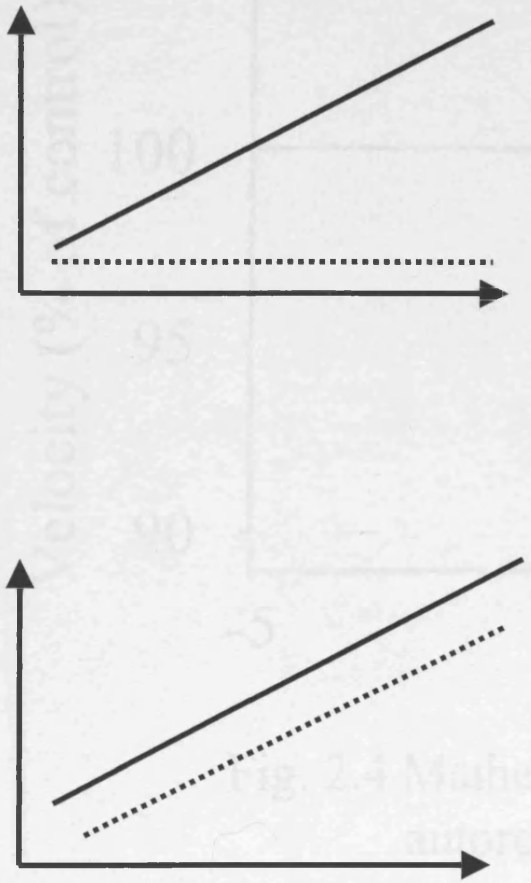


Figure 2.2. The transtemporal acoustic window.

F = frontal
A = Anterior
M = Middle
P = Posterior

Fig 2.3 Static Cerebral Autoregulatory Changes



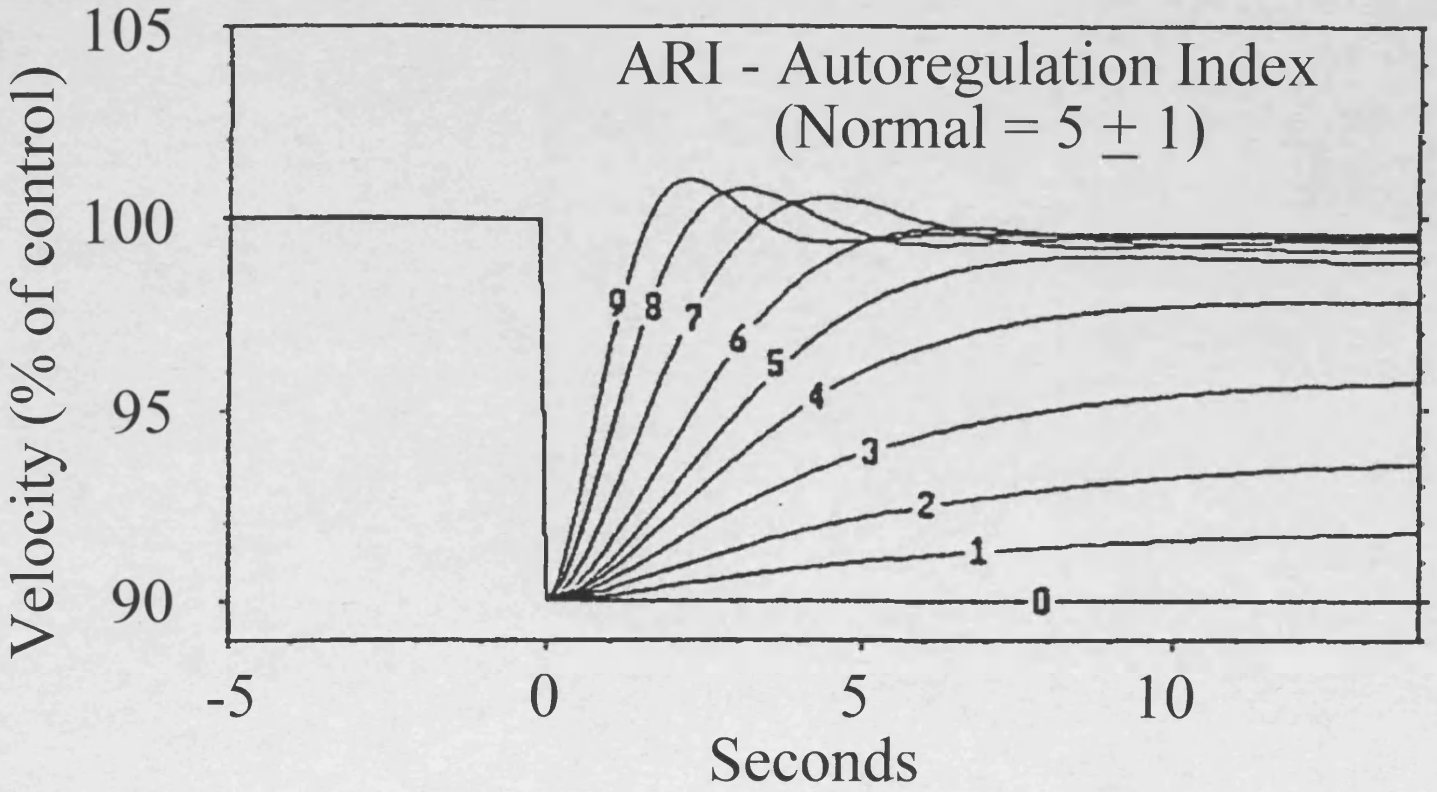


Fig. 2.4 Mathematical model curves of dynamic cerebral autoregulation in response to a step change in BP.

Tiecks, 1995

CHAPTER 3

BEAT-TO-BEAT BLOOD PRESSURE LEVELS AND VARIABILITY PREDICT EARLY OUTCOME FOLLOWING ACUTE ISCHAEMIC STROKE.

3.1. SUMMARY:-

In hypertensive populations increasing blood pressure (BP) levels and blood pressure variability (BPV) are associated with a greater incidence of target organ damage. Following stroke elevated 24 hour BP levels predict a poor outcome although it is uncertain whether shorter length BP recordings assessing mean BP levels and variability have a similar predictive role and whether these parameters are affected by stroke subtype. To investigate this further the author studied 92 consecutive admissions with a CT confirmed diagnosis of acute ischaemic stroke, of whom 54 had cortical infarction, 29 subcortical, and 9 posterior circulation infarction. Casual and two 5 minute recordings of beat-to-beat BP (Finapres, Ohmeda) were made under standardised conditions within 72 hours of ictus, with mean BP levels taken as the average of this 10 minute recording and BPV as the standard deviation (S.D.). Outcome was assessed at 30 days as dead/dependent or independent (Rankin ≤2). The effects of BP, BPV, and stroke subtype on outcome were studied using logistic regression. Stroke subjects were subsequently divided by BP quartiles and within each quartile into low and high variability groups; the influence of high BP variability on outcome was also assessed.

The odds ratio (OR) for death/dependency was significantly higher in cortical strokes, compared to subcortical and posterior circulation strokes even after controlling for differences in BP and BPV (OR 4.19, p=0.002). Beat-to-beat systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP ± SD) levels were higher in the dead/dependent group compared to the independent group (MAP 106 ± 20.4 mmHg v 97 ± 19.1 mmHg, p<0.02). DBP and MAP variability, but not SBP variability, were also higher in subjects with a poorer outcome (MAPV 6.1 [interquartile range 4.5-7.4 mmHg) vs 4.9 (3.8-6.4 mmHg, p=0.02]). The odds ratio for a poor outcome was 1.38 (p=0.014) for every 10mmHg increase in MAP, and 1.32 (p=0.02) for every 1mmHg increase in MAPV. Casual BP measurements had no prognostic significance.

For the group as a whole when separated into DBP quartiles those with a high variability within each quartile had a worse prognosis compared with those with a low BP variability.

A poor outcome at 30 days following ischaemic stroke was dependent on stroke subtype, beat-to-beat BP levels, and mean DBP and MAP variability. Important prognostic information can be readily obtained from a short period of non-invasive BP monitoring in the acute stroke patient, with DBP and MAP variability being the best predictors of outcome. These findings have important implications, particularly regarding the use of hypotensive agents in the acute stroke period, and deserve further study.

3.2 INTRODUCTION:-

The author has reviewed the information available to date regarding changes to absolute blood pressure levels and both diurnal and short-term blood pressure variability in acute stroke in section 1.5.1.. In essence 80% of stroke admissions are hypertensive on arrival [Oppenheimer 1992], but these levels often spontaneously decline over the first 10 days [Britton 1986, Harper 1994]. Increasing BP levels in acute stroke are particularly associated with black ethnic origin, primary intracerebral haemorrhage (PICH), and a prior history of hypertension [Lip 1997, Carlberg 1991]. Although there is an increasing body of evidence indicating that raised BP levels are associated with a poor prognosis [Yamamoto 1998, Terayama 1997, Robinson 1997d], some reports suggest that they are of little prognostic value [Carlberg 1993, Fiorelli 1995] or may even indicate a good prognosis [Allen 1984, Jorgensen 1994]. However, these differences may simply be related to methodological differences between the studies, e.g. the use of single casual readings compared to 24 hour BP recordings. With the recent suggestion that early anti-hypertensive therapy may improve outcome in subjects where there is co-existent cerebral oedema [Chamorro 1998], and with the implications that the

introduction of thrombolysis as an acute therapy may have on the management of blood pressure [ECASS II 1998, NINDS 1998], clarification of the situation is required.

The underlying pathophysiological mechanisms for the acute increase in BP levels following both cerebral infarction and haemorrhage are unknown but could be related to an increase in sympathetic nervous system activity as evidenced by raised plasma catecholamine and corticosteroid levels [Meyer 1973, Feibel 1981], and damage to the autonomic nervous system (ANS) in particular the baroreceptor reflex arc. The baroreceptor reflex arc is intricately concerned with the beat to beat control of BP and earlier work from this department has shown a reduction in cardiac baroreceptor sensitivity (BRS) in acute stroke [Robinson 1997b] and impairment of the vasomotor arm of the reflex arc [Robinson 1995b, 1997c], both of which imply damage to the central autonomic modulation system. The reduction in the diurnal blood pressure change following acute stroke [Dawson 1998b, Lin 1992, Fotherby 1991] is also in keeping with ANS dysfunction. It is becoming increasingly appreciated that cerebral infarction involving the insular cortex and the amygdala regions may be particularly important in the genesis of these abnormalities being associated with increased plasma norepinephrine levels and increased sympathetic and reduced parasympathetic nervous activity [Sander 1994, Butcher 1993, Cheung 1997, Korpelainen 1994].

As well as being able to assess the diurnal BP rhythm, the advent of non-invasive but accurate BP monitors has made it possible to measure beat-to-beat blood pressure variability (BPV) easily in a large number of subjects [Floras 1988, Frattola 1993, Parati 1987, Palatini 1992, Robinson 1997a, Siche 1995, Parati 1997] which would not normally be possible using previous methods which have relied on intra-arterial cannulation. Increased BPV is associated with increased evidence of target organ damage in the elderly and hypertensive populations [Frattola 1993, Parati 1992] and in cardiovascular events [Palatini 1992]. A

previous study has shown that BPV is increased following acute stroke compared to age, and sex-matched controls [Robinson 1997a] although the prognostic relevance of this finding is currently unknown.

To the author's knowledge the influence of stroke subtype on beat-to-beat BPV has not been previously studied, nor has the relation between BPV and outcome following acute stroke been reported.

3.3 AIMS

1. To assess if mean BP levels and BP variability measured by a one-off 10 minute beat-to-beat recording performed within 72 hours of ictus could predict 30 day outcome in terms of death or dependency.
2. To examine the effect of stroke subtype on these measures.

3.4 METHODS:-

3.4.1 Subjects:-

Patients with a clinical diagnosis of acute stroke were recruited from admissions to the three Leicester hospitals. Each subject was assessed by either T.G.R. or S.L.D., and examined according to the Oxfordshire Community Stroke Project classification [Bamford 1991], and the Barthel Index [Appendix 1]. All patients were haemodynamically stable, did not require intravenous or subcutaneous fluid administration and were not biochemically dehydrated. Exclusion criteria were atrial fibrillation, either past or present, diabetes mellitus, diseases known to affect the autonomic nervous system, co-existent chronic diseases limiting independent function, diminished conscious level, and drugs affecting either the cardiovascular or autonomic nervous systems. Twenty-five patients had the diagnosis of isolated systolic hypertension (SBP ≥160 mmHg, DBP <95mmHg) and 29 combined hypertension (SBP ≥160 mmHg, DBP ≥95 mmHg). Patients taking anti-hypertensive medication could be included as hospital protocol was to stop these on admission, as long as the recordings were made at least 24 hours after the last dose.

All patients had a CT confirmed diagnosis within 10 days of symptom onset. Using the CT and the OCSP classification patients were subdivided into cortical (total anterior circulation and partial anterior circulation), subcortical (lacunar stroke), and posterior circulation infarcts.

3.4.2 Protocol:-

Subjects were studied in a quiet dedicated research room kept at a constant ambient temperature (21°C), and dimly lit to minimise external stimuli. They were asked to have abstained from caffeine, nicotine, and alcohol containing products for at least 12 hours and to be a minimum of 2 hours post-prandial; they were encouraged to micturate prior to recording. All subjects were studied supine on a couch, with their head supported by two pillows, and their arm supported at atrial height within 24-72 hours of symptom onset. Casual BP was measured using a standard mercury sphygmomanometer and an appropriate sized cuff (phase V diastole), the average of three readings was taken.

Three standard surface ECG leads were attached to the subject, and a Finapres 2300 (Ohmeda Monitoring Systems, Englewood, Colorado, USA) non-invasive BP monitor (NIBPM) was fitted to the middle finger of the hemiparetic arm using an appropriately sized cuff. The Finapres has now been widely validated against intra-arterial measurements and has been shown to accurately demonstrate BP trends [Imholz 1998].

Once the Finapres readings showed <5% variability over 5 minutes, two 5 minute recordings of ECG and NIBPM were made, with at least a 2 minute interval between them, onto a dedicated PC. During the two recording periods the servo-adjust mechanism on the Finapres was disabled, and the subjects were asked to lie quietly (but not sleep), and maintain a respiratory rate ≥12 breaths per minute, in some this was facilitated by the use of a metronome and no subjects had any abnormal respiratory pattern.

3.4.3 Data analysis:-

The analogue outputs from the NIBPM and the ECG were downloaded onto the dedicated PC at a sampling rate of 200Hz/channel. Specially written software allowed the recording, calibration and editing of the digitised signal, and the subsequent derivation of the beat-to-beat systolic, diastolic, mean arterial BP and pulse pressure (PP) along with pulse interval. Systolic, diastolic, and mean arterial BPV, and pulse pressure variability were calculated using the standard deviations of the beat-to-beat recordings. The mean of the results from the two periods was used in the final analysis.

3.5 STATISTICAL ANALYSIS:-

Any association between stroke subtype and BP/BPV was assessed using analysis of variance (ANOVA). It was felt that the underlying distributions of BPV were likely to be positively skewed, therefore the logarithm transformation was used to obtain approximate normal distributions with similar variances in each group.

Stroke patients were divided into dead/dependent or independent (Rankin ≤ 2) groups depending on their functional ability at 30 days post-ictus as assessed by SLD or TGR at patient interview. The relation of BP and BPV to outcome was investigated using logistic regression. The fit of each model was checked using the Hosmer and Lemeshow goodness-of-fit test. Each BP measure ie, SBP, DBP, MAP and PP was used in a single variable logistic model and then adjusted for age and stroke type. Where there was a statistically significant association between a BP measure and outcome in the single variable model, the predictive performance of the measures was assessed by calculating the proportion of the explained variation (R^2) and the area under the receiver operating characteristic (ROC) curve (C) [Mittlbock 1996]. The calibration of the model was also investigated by dividing the subjects into quartiles according to their predicted outcome possibilities and reporting the actual dead/dependent rates.

In order to examine the effect of BPV at different BP levels, as had been similarly described in previous studies [Parati 1987, Palatini 1992] subjects were divided into 4 groups according to each BP measure to give groups of approximately equal size. Each group was then divided according to the appropriate group median BPV into low (≤median) and high (>median) variability subjects. The relationship between BPV and outcome was assessed using the chi-squared test.

Results are presented as mean ± S.D. for normally distributed data and median and interquartile ranges (IQR) for non-normally distributed data. Data summary and analysis were carried out using SAS 6.12. Statistical significance was set at the 5% level.

3.6 RESULTS:-

The 92 patients (47 male) mean age 69 ± 12 years (range 39-89 years) studied had a mean casual BP of 165 ± 32 / 90 ± 17 mmHg and mean casual pulse rate 73 ± 14 bpm with a median Barthel Index of 47.5 (IQR 30,78).

Division of subjects by stroke subtype revealed that 54 had cortical infarcts, 29 subcortical and 9 posterior circulation strokes. The odds ratio (OR) for death/dependency at 30 days was significantly increased in cortical strokes compared with subcortical and posterior circulation events with an odds ratio of 4.19 (1.73-10.12, $p<0.002$) with 69% being dead/dependent compared to 31% in the groups respectively. However, stroke subtype did not significantly influence SBP, DBP, MAP or PP levels or BP variability (see Table 3.1) and for further analysis of outcome data all stroke subtypes have been combined.

Adjusted mean beat-to-beat SBP, DBP and MAP, but not PP levels, were higher in the dead/dependent group than in the independent group (see Table 3.2), such that for a 10 mmHg increase in MAP the risk of death/dependency rose by 38% when

adjusted for by age and stroke type. DBPV and MAPV but not SBPV or PPV were also significantly greater in the dead/dependent group (p=0.001 and 0.011 respectively) such that a 1 mmHg increase in MAPV increased the risk of death and dependency at 30 days by 32% (see Table 3.3). None of the casual BP methods has a significant effect on outcome (see Table 3.3).

Dividing the patients by BP into quartiles and further splitting them into high and low BP variability (see statistical section), those in the high DBP and MAP variability were significantly at greater risk of poor outcome than those with low variability but SBP and PP variability did not influence outcome (see Table 3.3 and Figure 3.1). Of the main predictors of 30 day outcome, ie, DBP and MAP variability, mean SBP, DBP and MAP levels, no significant difference was found between these measures in their predictive value. From the logistic regression model age, stroke type, MAP and DBP levels and variability were significant independent predictors of outcome with no significant interaction between BP variability and mean BP levels. Taking the five main predictors of 30 day outcome it can be seen from Table 3.4 that the best predictors of death and dependency were DBPV and MAPV with the highest R^2 values and area under the ROC curve. These data demonstrate that for the 25% of the subjects with the best predicted outcome by DBP variability 39.1% were actually observed to have a bad outcome, whereas for the 25% of subjects with the worst predicted outcome 78.3% actually had a bad outcome.

3.7 DISCUSSION:-

This study has shown a fourfold increase in the risk of death/dependency for cortical strokes when compared to other sub-types, in keeping with previous reports of a 90% mortality rate within 12 months for large middle cerebral infarcts, in contrast to a rate of 50% for restricted cortical, lacunar, or brainstem infarcts [Bamford 1991]. The main objectives of this work were to identify any potential prognostic differences between the various measures of blood pressure, i.e. SBP vs

MAP and their variability on outcome. It has confirmed previous reports of a greater risk in terms of mortality and/or dependency following acute cerebral infarction with increasing beat-to-beat, but not casual, SBP, DBP and MAP levels, but not pulse pressure [Yamamoto 1998, Terayama 1997, Robinson 1997d, Chamorro 1998]. However, although the author found no relation between SBP variability and outcome at 30 days, increasing DBPV and MAPV did significantly relate to outcome, the greater the variability the poorer the outcome, this relation holding true even when mean BP levels were taken into account. This prognostic information was obtained just from a single 10 minute non-invasive recording of beat-to-beat BP.

For BP and outcome there was an odds ratio of 1.38 for death/dependency at 30 days with each 10mmHg increase in beat-to-beat MAP with slightly smaller odds ratios for SBP and DBP values but interestingly no relation with PP. Previous work has reported an odds ratio of 1.88 for every 10mmHg increase in 24 hour SBP levels for similar outcome measures [Robinson 1997d]. This present study's lower OR may represent differences in the study populations - the previous study had a higher percentage of cortical strokes (65% vs 58%), and fewer posterior circulation strokes (2% vs 10%), and included patients with intracerebral haemorrhage. In addition the use of different methods of BP assessment, i.e. Finapres recordings versus 24 hour BP monitor readings, and the fact that BP measurements were taken within 24 hours of ictus in the previous study compared to up to 72 hours in this study, may explain some of the differences. The Finapres device tends to underestimate MAP and DBP compared to intra-arterial measurements but SBP values are similar, as for BP variability MAP and DBP variability are similar for the two devices but SBPV is larger with the Finapres [Imholz 1998]. Finapres mean BP values are consistently lower for SBP and DBP compared to casual blood pressure measurements and therefore cannot be directly compared [Imholz 1998].

The beat-to-beat BPV results presented here are comparable to those previously

reported following stroke when longer recording periods were taken, Robinson et al reporting SBPV of 13.0 (4.6) mmHg in acute cerebral infarct patients with no significant change in BPV at follow-up 10-14 days later [Robinson 1997a]. No control group was used in this study as the main objectives of the investigation were to examine the effect of mean BP levels and BPV on outcome in stroke patients. The author did not detect any difference in BP variability between stroke subtypes though the study was too small to established whether the increased BP variability was related to any particular stroke site such as the insular cortex. The exact mechanisms underlying the beat-to-beat variability following stroke are unknown but a reduction in cardiac baroreceptor sensitivity (BRS) following acute cerebral infarction is well established [Robinson 1997a,b] and decreased BRS is well known to result in a rise in BP variability [Siche 1995, Mancia 1986]. In keeping with these findings Tokgozoelu et al [1999], have shown that heart rate variability is reduced following acute stroke, particularly where the lesion lies in the region of the insular cortex. The relation between short-term measurements of beat-to-beat BPV and target organ damage has not been previously studied in great detail. Frattola et al [1993] using intra-arterial BP measurements and a similar type analysis to the one conducted in this study have shown that BP variability is significantly related to the development of target organ damage. Again it might appear that DBPV and MAPV (both variables being strongly statistically related) may be better indicators of outcome than mean BP levels themselves.

It may also appear surprising that mean MAP and DBP levels appeared better prognostic indicators than mean SBP, with PP levels having no statistical significant effect on outcome. There is increasing evidence that the pulsatile component of BP that is pulse pressure, reflects arterial compliance and is strongly related to the development of atherosclerosis and is a potent risk factor for cardiovascular events in particular coronary artery disease [Franklin 1999]. However, mean arterial pressure which can be taken as reflecting the steady state component of BP has recently been shown to be a greater risk factor for stroke than

PP [Millar 1999], although other studies have not confirmed this [Domanski 1999]. These findings may be important when considering BP reduction following stroke and which antihypertensives may be more efficacious in terms of reducing MAP levels more than PP. These studies however have only assessed the effects of MAP and PP as predictors of primary stroke; there are virtually no data looking at these parameters on outcome following stroke, either in the acute or sub-acute phases. This study was too small to assess the effects of previous hypertension type or treatment on outcome, but this may be important.

It is unclear as to why an increase in blood pressure and blood pressure variability lead to a poorer prognosis in acute ischaemic stroke, but it may be related to the changes in cerebral blood flow and cerebral autoregulation that are thought to occur following acute stroke (see section 1.4.3). Although poorly understood these have been the main reason antihypertensive therapy has not been used routinely in the acute post ictal phase to date for fear of extending the ischaemic penumbra. An increase in BPV, i.e. sudden dynamic swings in blood pressure, could increase the size of the ischaemic penumbra if autoregulation is impaired.

There may be some concern that these results are being confounded by another factor such as stroke severity. Unfortunately, an NIH score on admission was not available on every patient, but OCSP classification and Rankin scores were. The Rankin score is not a measure of neurological function, but a measure of disability; in addition it is a non-ordinate scale. Since patients had either an MRI or a CT scan over a number of days post-infarct the use of infarct volume as a marker of severity was also felt to be unsatisfactory. However, the OCSP classification is now recognised to correlate well with infarct site and volume [Lindgren 1994, Wardlaw 1996], as well as with prognosis [Bamford 1990,1991]. It also has good interobserver reliability [Lindley 1993, see Section 2.6]. It is for these reasons that the OCSP classification was used as a surrogate marker of stroke severity, and despite the not unsuspected increase in the number of dead or dependent stroke

patients in the cortical infarct group at 30days, OCSP classification did not significantly affect any of the BP/BPV parameters.

Further large scale studies are needed to establish whether these initial findings can be confirmed, and what influence other important factors such as hypertension type, i.e. isolated systolic hypertension compared to combined hypertension have on outcome. Similarly it will be interesting to assess whether measures of arterial compliance such as pulse wave velocity or augmentation index may have a better prognostic value than measures of BP or BPV [Blacher 1999]. With increasing evidence of a poorer outcome with higher beat-to-beat and 24 hour BP levels on admission as provided by this and other studies [Yamamoto 1998, Terayama 1997, Robinson 1997d, Chamorro 1998], and the new finding that beat-to-beat BP variability may be equally as important, if not more so, than absolute BP levels a potential therapeutic opportunity has been identified. Whether these findings hold true for cerebral haemorrhage is unknown at present. Although to date there has been much debate as to whether it is safe to introduce antihypertensive agents in the acute stroke period [O'Connell 1996, Bath 1997, section 1.4.3], these results would imply that the introduction of an agent that leads to a gradual reduction in BP, improves BPV, and does not negatively effect cerebral blood flow, e.g. a centrally acting agent or an angiotensin converting enzyme inhibitor [Dyker 1997], may have a positive role to play in improving prognosis after stroke, even if confined to certain stroke subgroups. This may have particular importance with regard to BP control if thrombolysis therapy in acute stroke is to widely employed. However, until this and further work regarding cerebral autoregulation has been performed the debate surrounding blood pressure therapy in the acute stroke situation is set to continue.

3.8 CONCLUSIONS

This study has confirmed that cortical ischaemic strokes are associated with a poorer prognosis than subcortical or posterior circulation strokes (OR 4.19 for death/dependency at 30 days); and that important prognostic information can be obtained from very short non-invasive measurements of blood pressure in the acute post stoke period. For every 10mmHg increase in MAP the odds ratio for a poor outcome was 1.38 ($p=0.014$), and 1.32 ($p=0.02$) for every 1mmHg increase in MAPV.

These results have important implications for the management of acute stroke patients particularly regarding the use of antihypertensive therapy. However, before this can be routinely employed further studies are needed to confirm these findings and to further investigate changes in cerebral blood flow and cerebral autoregulation in acute stroke. The rest of this thesis is concerned with the study of both static and dynamic cerebral autoregulation in acute ischaemic stroke.

	Stroke Type			
	TAC/PAC	LAC	POC	Total
n	54	29	9	92
Blood Pressure (mmHg)	**Mean (sd)**	**Mean (sd)**	**Mean (sd)**	**Mean (sd)**
SBP	151 (32.1)	148 (30.7)	160 (38.7)	151 (32.1)
DBP	76 (16.3)	80 (21.5)	83 (14.1)	78 (17.9)
PP	76 (27.9)	69 (23.7)	78 (30.2)	74 (26.8)
MAP	100 (19.1)	102 (22.3)	109 (20.8)	102 (20.2)
Blood Pressure Variability (mmHg)	**Media (IQR)**	**Media (IQR)**	**Media (IQR)**	**Media (IQR)**
SBPV	9.6 (6.8, 11.2)	9.5 (6.8, 10.7)	5.7 (4.9, 9.9)	8.8 (6.4, 11.2)
DBPV	4.3 (3.2, 5.6)	4.7 (2.8, 5.7)	3.3 (2.6, 3.7)	4.3 (3.0, 5.6)
PPV	6.2 (4.5, 8.0)	5.6 (4.7, 7.2)	4.1 (3.7, 7.0)	5.9 (4.4, 7.4)
MAPV	5.4 (4.4, 7.1)	6.4 (4.0, 7.4)	4.0 (3.3, 5.3)	5.4 (4.1, 7.1)

Table 3.1: Finapres mean BP levels and variability (BPV taken as the standard deviation (SD) of all values from a 10 minute recording period) by stroke sub-type. SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulse pressure; MAP = mean arterial pressure; TAC/PAC = total/partial anterior circulation; LAC = lacunar; POC = posterior circulation;
n = number in each group; IQR = inter-quartile range. No significant differences were seen between stroke subtypes for any parameters.

	Status at 30 days		
	Dead / Dependent	**Independent**	**Total**
n	**50**	**42**	**92**
Blood Pressure (mmHg)	**Mean (sd)**	**Mean (sd)**	**Mean (sd)**
SBP	158 (33.5)	143 (28.7)*	151 (32.1)
DBP	81 (18.8)	75 (16.3)**	78 (17.9)
PP	78 (30.7)	69 (20.3)	74 (26.8)
MAP	106 (20.4)	97 (19.1)**	102 (20.2)
Blood Pressure Variability (mmHg)	**Media (IQR)**	**Media (IQR)**	**Media (IQR)**
SBPV	9.2 (6.79, 11.96)	8.3 (6.38, 10.39)	8.8 (6.40, 11.16)
DBPV	5.1 (3.64, 6.28)	4.1 (2.68, 5.14)*	4.3 (2.99, 5.58)
PPV	5.8 (4.25, 7.28)	6.0 (4.67, 7.79)	5.9 (4.38, 7.41)
MAPV	6.1 (4.45, 7.40)	4.9 (3.79, 6.37)*	5.4 (4.11, 7.06)

Table 3.2: Influence of mean BP levels and variability (BPV) on outcome taken as independent or dead/dependent at 30 days following acute cerebral infarction. See Table 3.1 for key to abbreviations.

* $p < 0.05$ for difference between Dead / Dependent and Independent groups adjusted for by age and stroke sub-type.
**$p<0.02$

	Odds Ratio	95% CI	P value
Finapres			
SBP (mmHg)	1.19	1.0 – 1.4	<0.03
SBPV (mmHg)	1.07	0.9 – 1.2	0.29
DBP (mmHg)	1.42	1.1 – 1.9	<0.02
DBPV (mmHg)	1.33	1.1 – 1.7	<0.03
MAP (mmHg)	1.38	1.1 – 1.8	<0.02
MAPV (mmHg)	1.32	1.1 – 1.7	<0.03
PP (mmHg)	1.09	0.9 – 1.38	0.39
PPV (mmHg)	0.91	0.8 – 1.1	0.39
Casual			
SBP	1.14	0.96 – 1.35	0.13
DBP	1.19	0.90 – 1.57	0.22
MAP	1.21	0.94 – 1.55	0.14

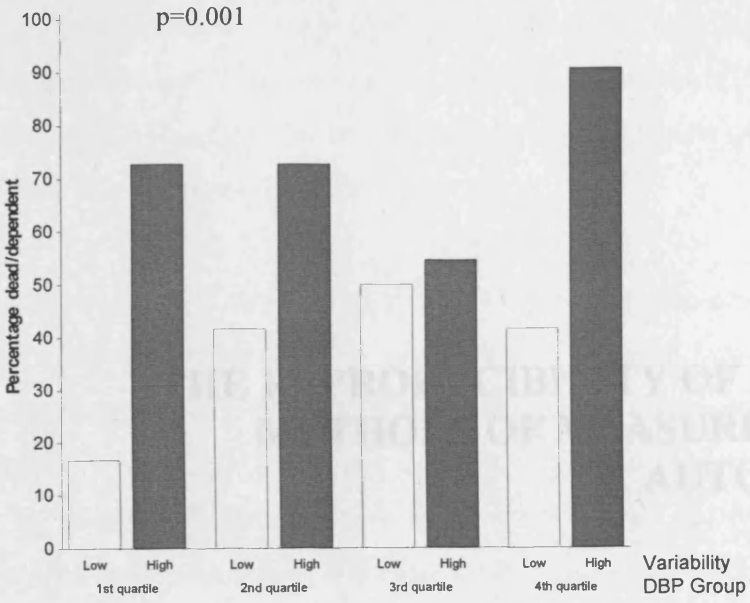
Table 3.3: Odds ratio for death/dependency at 30 days following acute cerebral infarction adjusted for by age and stroke type for every 10 mmHg increase in mean BP levels and 1 mmHg increase in BP variability for Finapres and Casual BP measurements. See Table 3.1 for key to abbreviations.

Measure	R^2	C	% observed dead or dependent by quartiles of predicted probabilities			
			1st	2nd	3rd	4th
DBP variability	0.066	0.665	39.1	39.1	60.9	78.3
MAP variability	0.066	0.654	43.5	34.8	69.6	69.6
Mean SBP	0.055	0.629	43.5	52.2	52.2	69.6
Mean MAP	0.047	0.621	43.5	69.6	69.6	60.9
Mean DBP	0.033	0.600	43.5	52.2	52.2	65.2

Table 3.4: Predictive ability for death/dependency of single variable logistic models using the five best predictors of outcome for all measures of BP and BP variability assessed in the study. R^2 = proportion of explained variation. C = Area under Receiver Operating Characteristic (ROC) curve.

Of those in the lowest quartile of the best predicted outcome for DBPV, 39.1% were dead/dependent compared to 78.3% of those in the 25% with the worst predicted outcome.

Fig. 3.1:- Percentage of patients dead/dependent at 30 days following acute cerebral infarction according to DBP quartiles split by group median DBP variability into high and low fractions. The P value for overall risk of greater death/dependency in patients with the high DBP variability irrespective of mean DBP levels.



CHAPTER 4

THE REPRODUCIBILITY OF NON-INVASIVE METHODS OF MEASURING CEREBRAL AUTOREGULATION.

4.1 SUMMARY:-

Previous studies of cerebral autoregulation (CA) have been limited by the use of invasive techniques, and equipment that had a poor temporal resolution. Transcranial Doppler has revolutionised the study of CA, and led to the concept of two distinct processes - dynamic and static CA. The aim of this study was to examine the reproducibility of methods using non-invasive blood pressure manipulations to study both dynamic and static CA on two occasions weeks apart; and to assess which of these tests would be best for detecting any temporal changes that may occur in different pathological conditions. In addition different mathematical models, and lengths of data, were compared to see if this altered the robustness of the results for dynamic CA.

Reproducibility of dynamic autoregulation indices measured using all the different blood pressure manipulations were improved by employing a correlation coefficient in the comparison of the mathematical model and the actual data. Similarly, longer data windows, i.e. 30s, yielded the best results (except in the case of spontaneous BP transients when 10s was better). The intervisit difference in dynamic and static CA varied considerably between the different tests, as did the reproducibility of the BP stimuli used (CV% 17-73%).

In conclusion, although all the tests were well tolerated and the new mathematical model improved the repeatability of dynamic CA, further work is needed to improve the reproducibility of methods for measuring CA. In the meantime these results imply that the use of thigh cuff release &/or the Valsalva manoeuvre, and thigh cuff inflation &/or isometric hand grip should be used to measure dynamic and static CA respectively. The favourable outcome for the thigh cuff test as a technique for assessing both static and dynamic CA is particularly encouraging as this test requires no active patient co-operation, and could theoretically be completed within only a few minutes.

4.2 INTRODUCTION:-

As has been discussed in Chapter 1.3 cerebral autoregulation (CA) is being increasingly used as a method of studying the pathophysiology of intracranial disease, and recently has been considered as a means of predicting prognosis, e.g. in head-injuries [Steiger 1994]. However, acutely ill patients are not the typical research population, they provide unique logistic problems, for instance in terms of co-operation with tests, and tolerance to even relatively non-invasive equipment.

Chapter 2.1 reviewed the previous research into methods of measuring cerebral blood flow and CA. These techniques have been limited by their poor temporal resolution, but the advent of transcranial Doppler (TCD) ultrasonography has revolutionised the situation [Chapter 2.1.5]. However, to date the assessment of static CA has remained a relatively invasive technique with the use of pharmacological infusions to manipulate the BP, e.g. a phenylephrine induced pressor response [Strebel 1995, Tiecks 1995a]; whereas a variety of non-invasive methods have been proposed to measure dynamic CA (see Chapter 2.4,2.5). The most widely reported of these methods is the use of bilateral thigh cuff release (THC) to induce a dynamic hypotensive stimulus [Aaslid 1989, White 1997], but others include carotid compression [Smielewski 1995] and the Valsalva manoeuvre (VM) [Tiecks 1995b, 1996].

These new methods for calculating an autoregulatory index (ARI) have been validated against both traditional techniques [Dahl 1992, Newell 1994b], and compared to one another [Markus 1992], but there are little data on their individual reproducibility. When first described by Aaslid et al [1989] the thigh cuff release test was performed on 4 successive occasions and the mean of these results used to represent the subjects dynamic ARI. White et al [1997] looked at the use of THC in the assessment of patients with carotid stenosis, using the average of 5 results performed at 3 minute intervals to calculate the dynamic ARI. Combining the ARI values from both MCA's they described a standard deviation of measurement error of 0.87 for all recordings, 0.83 in their 'patient group' and 0.92 in their 'control group'. Smielewski et al [1996] have also reported the reproducibility of both THC

and carotid compression when used to measure dynamic CA in 11 healthy volunteers aged 20-30 years. THC was much less reproducible than carotid compression with a variability of 28% (range 17-39%) and 12% (range 6-18%) respectively, under normocapnic conditions, both tests showing less repeatability under hypercapnic conditions.

However, there are inherent problems with some of these methods:- carotid compression could not be carried out in certain disease states, especially acute ischaemic stroke, and the Valsalva manoeuvre is often inadequately performed. Other possible non-invasive methods to affect either dynamic or static, pressor or depressor BP changes have been discussed in Chapter 2.5; but, it is evident that there are few reports of the use of these methods to test CA, although they have been used in the assessment of cardiac baroreceptor sensitivity.

In addition to the limited methods previously used to induce BP changes, most studies of dynamic CA have used methods of calculating an ARI based on those of Tiecks et al [1995a], where the rate of recovery of the MCAV is matched to a 'best-fit' curve. This model assumes a constant critical closing pressure (CrCP) of 12 mmHg during the period of data analysis. Critical closing pressure is the pressure at which vessels collapse, it is thought to reflect the point at which extravascular pressure exceeds perfusion pressure. The author has shown in previous work [Dawson 1999a] that during the Valsalva manoeuvre this parameter is anything but static, and actually explains to a considerable degree the changes in cerebral haemodynamics. Although the changes in CrCP during the other tests postulated to manipulate BP have not yet been examined, this finding has led to reservations regarding the assumption that CrCP is a static entity. An additional integral part of the question of 'best modelling' is the concept of data length. It is assumed that dynamic CA corrects any changes in perfusion pressure within 10-15s [Wachholder 1921], however, blood pressure spontaneously fluctuates in a normal human being, and these fluctuations may upset the calculation of an ARI based on a 'best-fit' curve.

4.3 AIMS:-

1. To see which non-invasive tests of blood pressure manipulation could be applied to study dynamic and static CA in the majority of subjects in a control population.
2. To assess the reproducibility of each test if it was performed only once on each occasion.
3. To identify reasons for variability in the autoregulation indices between the two visits, in particular whether BP stimuli variability influenced the results.
4. To compare the 'traditional' calculation of dynamic ARI to a mathematical method which incorporates the use of a correlation coefficient to compensate for the assumption of CrCP as a static entity.
5. To examine whether the use of different data window lengths affects the reproducibility of the ARI results.

4.4METHODS:-

4.4.1 Subjects

10 healthy subjects were selected from a database of subjects recruited through an advertisement in a local paper calling for healthy volunteers from the elderly population to participate in medical research. All subjects were independent in their activities of daily living and free from cerebrovascular, cardiovascular, and autonomic disease as ascertained from a clinical history and a full general physical examination, which included a 12 lead ECG, and routine blood tests (FBC, U&E, glucose). Subjects with a history of diabetes, stroke disease, significant carotid artery stenosis (>70%), recent myocardial infarction, atrial fibrillation, or taking medication known to affect cerebral blood flow or autonomic function were excluded from the study. Blood pressure readings were taken from the average of three readings using a standard mercury sphygmomanometer (Phase V diastole), and from the results of a 24 hour ambulatory blood pressure monitor (Spacelabs 90297), which was performed after their first visit. In order to test the reproducibility of the tests to measure CA subjects were asked to attend on two occasions between 1 and 6 months apart.

4.4.2 Protocol

Subjects were asked to attend wearing loose comfortable clothing having abstained from nicotine, alcohol, or caffeine containing products for at least 12 hours, and a minimum of 2 hours post-prandially. They were asked to micturate just prior to the start of the study. All recordings were made in a quiet dedicated research room which was kept at constant ambient temperature (21-24°C), and dimly lit to minimise external stimuli.

Subjects were asked to lie supine on a couch with their head supported on two pillows [Fig 4.1]. They were monitored with 3 standard surface ECG limb leads, a Finapres non-invasive BP monitor (Ohmeda, USA) [Penez 1973, Imholz 1988], using a cuff of the appropriate size attached to their right middle finger with their hand supported at atrial height on a custom made arm rest, and a transcutaneous gas monitor (TINA, Radiometer, Copenhagen) to record carbon dioxide partial pressure [Larsen 1993, Sridhar 1993, Dawson 1998a]. Both MCA's were insonated and identified as described by Aaslid et al [1982] using a bilateral TCD (SciMed QVL120); briefly the transtemporal acoustic window just superior to the zygomatic arch was used, and by altering the depth and gain of the 2MHz probe the MCA was identified from its depth (45-55 mm), direction of flow (towards the probe), relation to other basal cerebral arteries, and its velocity and waveform; we did not use carotid artery compression to verify vessel identification. Both Doppler probes were held in place using a custom made adjustable head frame. Velocity waveform spectra derived by Fast Fourier Transformation were visually displayed [Fig 4.2], and recorded along with the other parameters onto digital analogue tape (Sony Digital Instrumentation Cassette recorder PC-108M).

Once the MCA had been identified, and the subjects were accustomed to the procedure, with both the Finapres and TINA stabilised and giving physiologically acceptable results (<10% variability over 5minutes), recording was started; during the recording the servo-adjust mechanism on the Finapres was disabled, and a calibration signal was recorded prior to each test. Initially two 5 minute baseline recordings of these parameters were made with the subjects lying quietly, then in

random order the following static and dynamic tests were carried out, in each case a baseline recording of 60 seconds was made before the test, and recording continued for at least 60 seconds afterwards to allow readings to return to baseline; subjects were asked to lie still and refrain from talking throughout the tests, and also not to inadvertently raise intrathoracic or abdominal pressure by straining. Each test was only performed once. A dynamic test meant a rapid BP change >10mmHg, and a static test a prolonged steady state BP change, again >10mmHg magnitude, maintained for >45s. The criteria for the dynamic tests were based on methodology previously used by other authors [Tiecks 1995, Strebel 1995, White 1997]; whereas those for the static tests were more arbitrary since it was not felt feasible to achieve static changes >20mmHg using these techniques, but changes <10mmHg were considered to fall within the range of spontaneous variability and hence were excluded. The start and end of all tests was manually marked on the DAT tape through a pressure transducer. The tests employed have been described in more detail in Chapter 2. Although the subjects had been consented prior to the recordings, each test was explained again before it was started.

a). Spontaneous transients:- MAP varies on a beat-to-beat basis, hence the calculation of blood pressure variability from the standard deviation of readings obtained over a period of time [Chapter 1.5.1]. Data from the baseline recordings were examined for spontaneously occurring BP transients which could potentially be used as dynamic pressor or depressor stimuli. These tests were exempt from the >10mmHg requirement, and the author simply marked the largest transients occurring during the recordings.

b). Isometric hand grip: subjects were asked to grip a rolled up slightly inflated sphygmomanometer cuff at 30% maximal voluntary compression for 2 minutes, the grip pressure was visually displayed to aid compliance, and subjects were verbally encouraged to maintain the pressor stimulus. After the 2 minutes subjects were asked to release the grip suddenly leading to a dynamic BP drop, remaining still during the recording.

b) Cold pressor test: the subjects 'free' hand was placed by the author in a bowl of ice-cold water at 4°C for 45 seconds to induce a pressor response, and then removed and dried whilst the subject remained still.

c) Passive leg tilt: subjects legs were lifted by the examiner to above atrial height and supported on foam mattresses for 3 minutes to lead to an increase in BP, before being quickly lowered to stimulate a BP drop. Subjects were asked not to help in this manoeuvre as this could lead to an inadvertent Valsalva manoeuvre.
d). Thigh cuff: bilateral thigh blood pressure cuffs were attached to the subject, they were inflated gradually to the systolic BP level, and once at this level kept at a constant pressure for 45 seconds to maintain the pressor response; then the cuffs were rapidly deflated within 200 ms and subjects asked to remain motionless during this dynamic BP drop.
e). Valsalva manoeuvre: because of the head frame etc. this was performed in the supine position. Subjects were asked to blow into a syringe with an integral constant bleed device that was attached to a pressure transducer, and achieve an intrathoracic pressure of 40 mmHg for 15 seconds; the examiner could visualise the pressure achieved on the transducer and gave verbal encouragement. After 15 s the subjects released the pressure to cause a Phase IV increase in BP. This manoeuvre was repeated 3 times if possible; it was the only test performed more than once.
f). Lower body negative pressure: with all the monitoring equipment kept in place the subjects lower body, i.e. from the iliac crests down, was placed in a custom made metal box with air-tight seals achieved via a wooden end plate and foam padding. A domestic vacuum cleaner was attached to the box to create a vacuum, the suction was adjusted to achieve a gradual reduction in MAP (15-20 mmHg) for 90 seconds, the vacuum was then turned off to allow the pressure to quickly equilibrate.

In summary, *dynamic pressor tests* were achieved by spontaneous transients (+ve), the cold pressor test (CPT), Phase IV of the Valsalva manoeuvre (VM), and lower body negative pressure release (LBNPR); *dynamic depressor tests* by spontaneous transients (-ve), thigh cuff release (THCR), isometric hand grip release (HDGR), and the end of passive leg tilt (LGTR); *static pressor tests* by isometric hand grip (HDG_S), thigh cuff inflation (THC_S), and passive leg tilt (LGT_S); and the only *static depressor test* was lower body negative pressure ($LBNP_S$).

Not all subjects were able to tolerate all the tests due to tiredness, as altogether the study could take in excess of 2 hours. Consequently only 7 subjects had leg tilt and lower body negative pressure applied.

4.4.3 Data Analysis:-

The DAT recording was downloaded onto a dedicated PC in real time. A Fast-Fourier Transform method was used to convert the Doppler signals into maximum frequency velocity envelopes, with a window of 6.25 ms used to achieve temporal resolution. The Finapres, ECG, TINA, and pressure transducer output signals were converted directly at 200 Hz. Data from the individual tests were stored as separate files.

Data were subsequently visually inspected [Fig 4.3]. The BP trace was calibrated at the start of each recording. Artefactual data spikes were removed by linear interpolation. Each cardiac cycle was automatically marked to determine R-R interval from the Finapres tracing; if necessary ectopics could be manually marked and then removed by linear interpolation. Ectopics occurring in the 15 second window prior to or after the start of a dynamic test led to rejection of the data, as did >1 ectopic per 30 seconds in the static test recordings. Spline interpolation (equivalent to a 3rd order polynomial) was used to resample the data at 0.2 seconds to create a uniform time base. An estimate of systolic, diastolic and mean MCAV, systolic, diastolic and mean BP, critical closing pressure (CrCP) and resistance area product (RAP) for each cardiac cycle was calculated. The mathematical models used to calculate both static and dynamic CA are based on those described by Tiecks et al [1995a].

4.4.3.1 Determination of Dynamic Cerebral Autoregulation:-

Data were manually marked at the start of the dynamic pressor or depressor BP stimulus, including spontaneous positive or negative transients detected during the initial 5 minute recordings [Fig 4.4]. To be included in addition to the BP requirements previously stated there had to be a synchronous change in MAP and MCAV at the point of marking, with no signal noise or ectopic beats likely to upset

the subsequent modelling. From data accepted at this stage beat-to-beat MAP and MCAV readings were analysed to assess the time dependent recovery of each parameter. By applying a 2nd order linear differential equation set with variables $\chi 1$ and $\chi 2$ (which equal zero during the pre-test period) the normalised change in MAP (dP) and MCAV (mV) were calculated:-

$$dP_n = \frac{MAP_{\max} - MAP_{base}}{MAP_{base} - CrCP}$$

$$x2_n = x2_{n-1} + \frac{(x1_n - 2D.x2_{n-1})}{f.T}$$

$$x1_n = x1_{n-1} + \frac{(dP_n - x2_{n-1})}{f.T}$$

$$mV_n = MCAV_{base}.(1 + dP_n - k.x2_n)$$

where $MAP_{\max}$ equals maximum change in MAP; MAP_{base} equals MAP at start of test and $MCAV_{base}$ equals MCAV at same time point, n = sample number, n-1 = previous sample.

Tiecks et al [1995a] proposed 10 specific combinations of the parameters T (time constant), D (damping factor) and k (the autoregulatory dynamic gain) to grade the autoregulatory dynamic response by matching experimentally observed rates of recovery (dROR) to model predictions (see Table 4.1). Each of these combinations correspond to an integer value of the autoregulatory index (ARI) ranging from 0-9. A value of 0 corresponds to the absence of CA, generally a value >5 is considered normal. In addition to using the quadratic error, which requires the estimation of critical closing pressure, (in the Tiecks model estimated at 12 mmHg), we adopted the correlation coefficient (r) to obtain the value of ARI corresponding to the best match between model and data. A parabolic interpolation was performed on the r = f (ARI) curve and the optimal value of ARI was estimated with a resolution of 0.1. In both estimations different data window durations of 10, 20, and 30 s were used to investigate the influence of this parameter on the ARI, i.e. each set of data was analysed 6 times from the same starting point.

4.4.3.2 Determination of Static Cerebral Autoregulation:-

Data was again manually selected to include a baseline period and the period of static MAP change (the test period), and the previously mentioned BP requirements had to be fulfilled. Cerebrovascular resistance (CVR) was estimated and the static ARI (expressed as dROR in the following equation) calculated using:-

$$CVR = \frac{MAP}{MCAV}$$

$$dROR = \frac{\%\Delta CVR}{\%\Delta MAP}$$

$$\%\Delta CVR = \frac{CVR_{end} - CVR_{base}}{CVR_{base}}$$

$$\%\Delta MAP = \frac{MAP_{end} - MAP_{base}}{MAP_{base}}$$

where MAP_{end} / CVR_{end} represent values at the end of test period, and MAP_{base} / CVR_{base} represent values during the baseline period.

This yields a result from 0-99%, with 99% being best possible CA, a value >60% is generally thought to represent the presence of CA [Tiecks 1995a].

4.5 STATISTICAL ANALYSIS:-

Data were analysed using Minitab 10 computer software programme.

As has been previously reported [White 1997] to increase the statistical power of this type of study data from the right and left MCA's were combined, i.e. n=20, rather than n=10.

The results for the two visits are presented as mean ± s.d. (range). For each of the six methods of measuring dynamic CA, and the one static method, the differences between the ARI's on the two visits for each test were calculated and tested for normality using a Shapiro-Wilk plot. A paired Student's t-test was used to test for any significant difference. It was not thought necessary to use a Bonferroni correction for multiple comparisons as the main aim of this study was to see which method led to the smallest difference rather than whether this difference was

significant.

Intervisit BP stimuli were compared as above, but the coefficient of variation (%) as described by Bland and Altman [1986] was also calculated. This was not done for the ARI since the rating system used leads to difficulties in the interpretation of CV%, e.g. with the dynamic tests a change from 1-2 would not be of clinical significance, but would represent a CV of 100%.

Single linear regression was used to see whether any subject characteristic, or intervisit test difference, significantly influenced the reproducibility.

Significance was taken at the 5% level.

4.6 RESULTS:-

Ten Caucasian subjects (3 female) mean age 69 ± 9.6 years (46-80), and mean 24 hour BP 127 ± 15/75 ± 11 mmHg, were studied on 2 occasions an average of 6 months apart (6 weeks-8 months). There were no significant differences between BP readings obtained on the day of study, MCA velocity or depth of insonation on the two occasions, and the latter two parameters were within the range originally described by Aaslid et al [1982] for the identification of basal cerebral arteries using TCD. Subject characteristics are described in Table 4.2.

One subject's data had to be rejected in its entirety due to a problem with the Finapres recording at the second visit. Of the other 9 subjects (7 for leg tilt and lower body negative pressure) for each test a variable number of MCA readings were 'noisy', or failed to demonstrate any apparent relationship between MAP and MCAV change or contained too many ectopic beats; consequently the number of subjects used for the repeatability of each test ranged from 5 to 8 (i.e. 10-16 MCA's). For the dynamic tests CPT led to the most exclusions, all because the BP stimulus did not fulfil the selection criteria; this was the case for the transients as well. For the other dynamic tests most rejections were due to signal noise/ectopics with the thigh cuff and hand grip releases leading to the most rejected recordings,

the Valsalva manoeuvre to the least. For the static tests all rejections were due to signal noise/ectopics, not inadequate BP changes.

The ARI results for dynamic CA tests are given in Table 4.3. The values for all six methods of mathematically modelling the ARI for each of the 8 tests are shown as mean ± s.d. along with the intervisit difference. Although only 4 intervisit differences reached statistical significance, it can be seen that the smallest differences for the tests occurred if modelling was performed using the correlation coefficient and a window of 30s, except for when spontaneous transients were used as the BP stimulus, when use of the correlation coefficient with a 10s window appeared to be best. Of all the tests THCR and LGTR appear to be the most repeatable (mean intervisit difference in ARI -0.25 ± 1.52, and 0.47 ± 0.97 respectively). Although not formally tested there did not appear to be a difference in the repeatability of pressor and depressor tests. This difference was not formally tested as the aim of this study was to assess the feasibility of using these tests of CA in the future.

Four tests were used to assess static CA; all led to similar ARI's except THC_s which tended to lead to lower results, e.g. 40.6 ± 33.6% compared with 57.9 ± 32.3% for LGT_s (Table 4.4); the significance of this is unclear, and may reflect inherent differences in the tests, e.g. discomfort etc. There were no significant inter-visit differences for any of the static tests, but THC_s and HDG_s led to the smallest differences (-0.4 ± 48.4% and -13.32 ± 32.83% respectively).

Table 4.5 illustrates the results for the intervisit BP stimuli for both the dynamic (magnitude and rate of change), and static tests (magnitude only). These results, unlike those for the ARI's, were thought to be of potential importance for selecting which tests were used in the future. It can be seen that the overall BP change and rate of BP change were similar for all dynamic tests employed, both pressor and depressor, although the cold pressor test (CPT) led to a smaller and slower change, but this was not surprising in view of the number of recordings for this test that were rejected. None of the tests were significantly different between visits

($p>0.05$), although the CV(%) were large ranging from 32-73% for magnitude of BP, and 25-79% for rate of change. Overall the VALS, THCR, and LBNPR appeared to have the smallest inter-visit variation (CV 41%, 43% and 32%, respectively). For the static test BP changes there were also no significant differences in magnitude of BP change. The THC_s appeared to give the smallest inter-visit difference (CV 17% compared to 63% for HDG_s).

Using single linear regression subject characteristics, e.g. age, 24 hour BP levels, gender, BMI, and time between visits did not significantly influence the repeatability of the BP change for any of the static tests, however, for the dynamic tests it appeared that there was an inverse relation between the BP change obtained at each visit using both spontaneous transients and CPT, and 24 hour MAP (Rsq i.e. variance 45.8% and 38.8% respectively), and a positive relation between the intervisit difference in rate of BP change derived from THCR and LBNPR and 24 hour MAP (Rsq 90.1% and 76.4% respectively). These same parameters did not influence the repeatability of the static ARI, but for the dynamic ARI it appeared that there was a relation between age and the HDGR derived ARI (Rsq 33.2%), and BMI and the VALS derived ARI (Rsq 51.4%). The intervisit BP stimuli differences did not significantly influence static ARI, but for dynamic ARI the difference in the size of the BP stimulus did seem to influence the size of the difference in ARI between visits for THCR and LBNPR (Rsq 72.2% and 87.3% respectively).

4.7 DISCUSSION:-

This study reports on the reproducibility of blood pressure changes (both magnitude and rate of change) and ARI calculation for a number of non-invasive tests that could theoretically be employed to study both static and dynamic cerebral autoregulation in patient groups. These results do not demonstrate a significant intervisit difference on t-testing for either dynamic or static BP or ARI measurements. In addition, the author also examined the reproducibility of two different methods of calculating dynamic ARI using three different lengths of data, in general the use of the correlation coefficient in conjunction with longer samples of data (30s), led to better results.

The traditional method of assessing the reproducibility of medical tests, i.e. the s.d. of measurement error or coefficient of variation (CV%), as described by Bland and Altman [1986], has not been used as there are inherent problems in extrapolating this methodology to these results. For instance a change in dynamic ARI from 1 to 2 between visits represents a 100% difference, but actually still means the subject is not autoregulating, whereas the same 'change' from 8-9 would only lead to approximately a 10% variation; these changes of 1 are highly likely with the use of a 'best-fit curve' even with the use of a 0.1 resolution as here. It could be argued that subjects should have been classified into groups, e.g. dynamic autoregulation intact (6-9), impaired (3-5), or absent (0-2), similarly with static autoregulation an intact system with ARI >50%, impaired 21-49%, absent <20%, reproducibility being assessed on whether subjects remained in the same group; but the CV would still be difficult to interpret. However, for comparison with previous studies the CV for BP changes were calculated. For similar statistical reasons it was felt that the BP and ARI results between pressor and depressor tests could not be formally compared.

4.7.1 'Correlation coefficient' or 'CrCP' for assessing dynamic CA:-

Only 3 of 48 (i.e. 6 for each of the 8 tests) measures of dynamic ARI were significantly different between the two visits, and all of these were when the CrCP model was used. It would appear that the technique which employed the use of a correlation coefficient to assess agreement between the experimental data curve and the model curve led to better repeatability, especially when a period of 30s after the start of the BP stimulus were examined, except in the case of spontaneous transients when 10s appeared better. This finding is not that surprising; it is thought that the process of dynamic CA is probably completed within 15-20s, 30s would therefore incorporate information from the whole process. However, in the case of transients the BP continues to fluctuate markedly, and consequently the stimulus duration is much reduced; in addition during these 'baseline' recordings it is likely that respiratory rate and baroreceptor reflex activity are having a more significant influence on CA. Shorter segment analysis could, therefore, be expected to lead to better reproducibility in these situations.

4.7.2 Repeatability of dynamic and static blood pressure stimuli:-

For the BP changes it would appear that in general static BP changes were more reproducible than dynamic BP changes, e.g. CV 17% for THC_s compared to 77% for HDGR; and that the dynamic rates of change were more reproducible than the magnitudes of change, e.g. THCR rate of change CV 25%, compared to 43% for magnitude of change. There did not appear to be a difference between pressor and depressor tests.

Previous reports on the reproducibility of BP changes induced by the measures used here are scarce. For dynamic tests Strebel et al [1995] found a mean drop of between 16 ± 2 mmHg and 21 ± 1 mmHg using the THC, which compares well to the results found here (16.95 ± 2.9 mmHg); but reproducibility per se was not mentioned, although they did state that an average of 3 tests should be used to obtain a result. Hines et al [1936] described a variability of 10%, and Parati et al [1983,1985] 17.2% for CPT BP changes in settings other than studies of CA, both considerably less than this result of 61%. Parati et al [1983,1985] used intra-arterial measurements and reproducibility was tested only over a period of 3 hours, i.e. during the same 'sitting'; whereas Hines et al [1939] did look at long term reproducibility (3 months to 3 years) in a larger group with a wide age range (4-84 years), but used a mercury sphygmomanometer to record BP readings every 30 seconds. Possible reasons for these differences in CV are the use of a sphygmomanometer which would be less accurate than a Finapres and therefore may not detect such large differences, the use of a short intervisit time period, and the study of a younger population, as it is possible that changes in BP variability and arterial compliance with age affect the reproducibility of the Finapres. However, the Finapres has been previously validated in an elderly population [Rongen 1995], and the author did not find a relation between age and reproducibility. The use of normalised BP values rather than absolute values may have led to better reproducibility, as is graphically illustrated in Fig 4.5, which shows the average changes in BP for the study group during the thigh cuff release; it can be seen that compared to the results in Table 4.2 the reproducibility was

better than the numerical figures imply.

Regarding the reproducibility of the rate of change in the dynamic tests there are no previous reports regarding these parameters, although Aaslid et al [1989] did specify that changes had to occur within 200 ms as stipulated in this study.

For static BP changes there are reports of the reproducibility of the pressor response with isometric hand grip when used to measure cardiac baroreceptor sensitivity, with a CV of 22% (range 12.8-32.2%) compared to 63% here [Parati 1983,1985]; Khurana et al [1996] also stated that BP changes during HDG_s were reproducible, but they do not quote a CV.

No subject characteristics appeared to explain the variation in CV(%) for blood pressure stimuli, except for the negative relation between intervisit difference in transients and CPT stimulus and 24 hour BP, and the positive relation between intervisit rate of BP change and 24 hour BP for THCR and LBNPR. The former relation is not surprising as it is well known that subjects with higher BP levels have an increased blood pressure variability [Parati 1987, Frattola 1993], and an augmented response to CPT [Hines 1936], and it may be that similar reasons underlie the changes seen with THCR and LBNPR. The most reproducible dynamic BP stimuli were the ones where there was little patient control (i.e. LBNPR and THCR). Although the VALS had a reasonable CV% for the BP stimulus not all subjects could adequately perform this, and the aim of this study was to identify an alternative that required little co-operation and could be performed quickly and easily.

4.7.3 Repeatability of dynamic and static ARI:-

It would appear from these results that LGTR, THCR, and VALS are the most repeatable of the dynamic tests, and THC_s and HDG_s the best of the static tests. None of the tests yielded a significant intervisit difference. Again there did not appear to be a difference between pressor and depressor tests.

There is little previous data available for comparison of either dynamic or static

ARI results. A report of the reproducibility of dynamic thigh cuff release versus carotid compression release induced hyperaemia [Smielewski 1996] found THCR to be much less reproducible than carotid compression with a CV of 28% (range 17-39%) compared to 11.9% (5.6-18.1%) under normocapnic conditions, and 63.2% (range 31-95%) compared to 14.9% (4.1-25.7) under hypercapnic conditions. All the present subjects were normocapnic for the duration of the study according to the TINA readings, therefore CO_2 is unlikely to be a reason for the difference between these studies, although the TINA is not sensitive enough to detect changes occurring in a time interval as short as for the VM, but the CO_2 partial pressure changes in this manoeuvre are thought to be small, and in fact have been estimated at 2 mmHg for a VM of 15 seconds [Meyer 1966]. If, as with the BP changes, the group mean velocity changes are plotted against time (see Fig.4.6 using HDGR as an example) it can be seen that the normalised values are fairly similar, but there is noise in the signal; although data that was obviously noisy or contained ectopics was rejected, it is feasible that remaining undetected noise may have led to inaccuracy in the calculation of the dROR curve and hence the ARI.

Signal noise, along with the small study numbers, may also explain some of the variation seen with the static ARI, as there was no significant difference between the BP stimuli between visits. Undetected changes in pCO2 may also be important here. Imms et al [1998] have recently described changes in MCA velocity with isometric hand grip in young healthy subjects; during hyperventilation studies there was no rise in MCA flow presumably due to vasoconstriction induced by the decrease in CO2. The present subjects were more likely to hypoventilate during exercise and consequently have more pronounced changes in MCAV; these small undetected changes in pCO2 may also be subject to a learning effect as subjects knew what to expect at the second visit, consequently small alterations in CBF may have occurred between visits leading to differences in ARI. However, there did not appear to be a constant change in the 'rank' of reproducibility for BP or ARI, i.e. whether a test was consistently good or bad. Similarly the tests reported as uncomfortable by subjects, and therefore exerting possible psychological influence on CA (THCR/THC_s and $LBNP_s$/LBNPR), failed to demonstrate any pattern to

their inter-visit differences.

4.7.4 Subject characteristics and ARI reproducibility:-

For both dynamic and static ARI there was no significant relation on linear regression ($p>0.05$) between the difference in ARI and the difference in BP stimulus, except for THCR and LBNPR. These two tests had the best overall BP repeatability, therefore, this further highlights the need to improve repeatability.

Subject characteristics, e.g. age, 24 hour BP, BMI, gender, time between studies, did not have a significant influence on ARI repeatability, except for age and HDGR, and BMI and VALS, an explanation for which is not readily evident.

4.7.5 Limitations of the study:-

It is readily accepted that this study has used only a small number of subjects to assess repeatability, and that by only performing each test once at each visit even the BP stimuli were not highly repeatable, which leads naturally to problems in CA repeatability. However, the aim of this study was to identify whether non-invasive tests which could be carried out easily and without necessarily needing the patient's co-operation could be carried out.

4.8 CONCLUSIONS:-

In conclusion it has been shown that using a correlation coefficient in the mathematical modelling rather than the traditional fixed CrCP of the Tiecks model improves the repeatability of dynamic CA tests, especially when combined with longer data lengths. BP changes for all the tests employed were rarely significantly different between visits but some test were better than others, as was the case with ARI calculations on the two occasions.

Combining all these results implies that perhaps dynamic CA testing could be limited to THCR, which requires no subject co-operation, and where possible VALS, and for static testing THC_s which also requires no subject input, unlike HDG_s. Further studies employing these tests are needed to see if the reproducibility

in this patient population can be improved on, for instance using repeated measures as previously described [Aaslid 1989, White 1997]. In addition, further study of spontaneous transients to assess CA is needed as this method involves no active BP manipulation, could be completed within 10 minutes, (once satisfactory signals were obtained), and could be combined with measurement of baroreceptor sensitivity, a parameter which may have important prognostic information [Farrell 1995, Robinson 1997b]. Newer mathematical models will probably be needed to achieve this aim. In the meantime it would appear that even THCR and THC_s/HDG_s may not be sufficiently accurate or reproducible to detect small differences between subject groups, or changes during temporal studies of the same population. Hence, 'negative' results need to be interpreted with caution until these techniques have been refined and their reproducibility improved.

T (s)	D	k	ARI	dROR (%/s)
	0.00	0	0	0.0 No autoregulation
2.00	1.60	0.20	1	2.5
2.00	1.50	0.40	2	5.0
2.00	1.15	0.60	3	10.0
2.00	0.90	0.80	4	15.0
1.90	0.75	0.90	5	20.0 Normal autoregulation
1.60	0.65	0.94	6	30.0
1.20	0.55	0.96	7	40.0
0.87	0.52	0.97	8	60.0
0.65	0.5	0.98	9	80.0

Table 4.1:- Parameters used to calculate dynamic autoregulatory curve and ARI as described by Tiecks et al [1995a].

Parameter	Result [mean ± s.d. (range)]	
Age (years)	69 ± 9.6 (46-80)	
BMI (kg/m^2)	26 ± 2.5 (20-29)	
Casual SBP (mmHg)	Visit1 144 ± 16 (130-177)	Visit2 143 ± 21(119-177)
Casual DBP (mmHg)	Visit1 83 ± 13 (67-110)	Visit2 80 ± 19 (62-114)
24 hour SBP (mmHg)	127 ± 15 (108-154)	
24 hour DBP (mmHg)	75 ± 11 (63-100)	
Heart rate (bpm) (mmHg)	72 ± 9 (62-83)	
Alcohol (units/week)	15 ± 18 (0-60)	
Right MCAV (cm/s)	Visit1 42 ± 7.1 (31-52)	Visit2 38 ± 7.9 (29-49)
Left MCAV (cm/s)	Visit1 41 ± 9.5 (25-59)	Visit2 38 ± 7.6 (26-50)
Right MCA depth (cm)	Visit1 5.1 ± 0.6 (4.4-5.7)	Visit2 4.8 ± 0.3 (4.4-5.4)
Left MCA depth (cm)	Visit1 5.2 ± 0.5 (4.6-5.7)	Visit2 4.8 ± 0.5 (4.1-5.5)

Table 4.2.:- Demographic characteristics of subjects (n = 10; 3 female). Where indicated results for both visits are given.

Results presented as mean ± s.d..

No significant difference between visits in any of the variables was detected.

	THCR n=13	HDGR n=13	CPT n=7	LGTR n=10	LBNPR n=10	VALS n=16	+ve transient n=15	-ve transient n=15
30s CORR								
visit1	6.01 ± 1.2	5.29 ± 2.91	6.96 ± 0.81	7.24 ± 1.62	5.83 ± 2.64	6.50 ± 1.29	2.09 ± 1.99	2.26 ± 2.95
visit2	6.26 ± 1.87	5.11 ± 3.08	5.47 ± 0.77	6.91 ± 1.57	6.03 ± 1.39	6.04 ± 1.44	3.43 ± 2.71	1.88 ± 3.18
difference	-0.25 ± 1.52	-0.18 ± 2.87	-0.61 ± 2.37	0.47 ± 0.97	-0.36 ± 2.37	0.57 ± 1.47	-1.33 ± 2.28	0.38 ± 2.55
20s CORR								
visit1	5.49 ± 2.16	6.72 ± 1.19	6.86 ± 1.45	7.35 ± 1.48	5.85 ± 2.79	6.93 ± 1.26	3.05 ± 1.97	2.72 ± 3.02
visit2	5.79 ± 2.07	5.71 ± 2.53	5.6 ± 1.00	7.34 ± 1.72	6.45 ± 1.46	6.41 ± 1.49	4.28 ± 2.29	2.83 ± 3.27
difference	-0.29 ± 2.07	0.47 ± 2.44	1.07 ± 1.68	0.06 ± 1.77	-0.60 ± 2.93	0.62 ± 1.93	-1.23 ± 2.31	-0.11 ± 3.72
10s CORR								
visit1	5.67 ± 2.72	1 6.05 ± 2.24	4.92 ± 2.83	7.18 ± 1.34	5.86 ± 2.08	7.24 ± 0.82	4.10 ± 1.61	3.54 ± 2.78
visit2	5.82 ± 1.99	5.40 ± 2.99	6.13 ± 1.25	7.62 ± 1.52	6.16 ± 1.58	6.58 ± 1.32	4.84 ± 2.42	3.86 ± 3.03
difference	-0.15 ± 2.01	0.22 ± 3.23	-1.50 ± 3.42	0.06 ± 2.18	-0.30 ± 2.61	0.70 ± 1.81	-0.74 ± 1.83	-0.32 ± 3.87
30s CrCP								
visit1	6.15 ± 2.66	6.14 ± 3.03	4.35 ± 2.53	6.82 ± 3.35	5.01 ± 3.22	5.79 ± 2.07	3.44 ± 3.32	3.16 ± 3.41
visit2	4.87 ± 1.83	4.07 ± 3.10	3.43 ± 3.65	6.57 ± 2.69	3.55 ± 3.15	5.99 ± 1.99	3.07 ± 2.72	2.83 ± 3.35
difference	1.28 ± 3.13	1.85 ± 3.45	-3.45 ± 1.17*	0.50 ± 4.54	1.46 ± 3.26	-0.07 ± 2.53	0.37 ± 2.99	0.78 ± 1.60
20s CrCP								
visit1	7.32 ± 2.13	6.40 ± 3.15	4.36 ± 3.23	7.86 ± 1.79	4.38 ± 3.41	5.77 ± 2.19	3.83 ± 3.21	4.69 ± 3.48
visti2	4.82 ± 1.86	4.76 ± 2.68	2.57 ± 3.21	7.28 ± 1.58	4.30 ± 3.43	3.14 ± 1.42	3.19 ± 2.71	3.39 ± 3.78
difference	2.50 ± 2.45*	1.32 ± 4.01	-3.43 ± 2.67	0.48 ± 0.99	0.08 ± 3.35	-0.21 ± 2.58	0.64 ± 2.90	1.30 ± 3.27
10s CrCP								
visit1	7.19 ± 2.34	5.75 ± 3.45	4.92 ± 2.83	7.30 ± 2.01	6.65 ± 2.61	6.06 ± 2.45	3.55 ± 3.16	5.48 ± 3.02
visit2	5.02 ± 2.76	4.77 ± 2.07	6.13 ± 1.25	7.36 ± 1.79	5.11 ± 2.79	5.73 ± 1.40	3.52 ± 2.68	4.54 ± 3.28
difference	2.18 ± 3.78	0.78 ± 4.24	-0.93 ± 0.32*	0.06 ± 2.18	1.54 ± 3.81	0.57 ± 2.65	0.03 ± 2.93	0.94 ± 3.22

Table 4.3:- Results of dynamic ARI reproducibility using difference window lengths and either correlation coefficient (CORR) or Tiecks modelling with CrCP estimated at 12mmHg (CrCP).

THCR + thigh cuff release; HDGR = hand grip release; LGTR = leg tilt release; CPT= cold pressor test; LBNPR = lower body negative pressure box release; VALS = Phase IV Valsalva manoeuvre.

Results presented as mean ± s.d. for visit1 and 2 and intervisit difference. *$p < 0.05$.

n = number with suitable data for analysis (maximum possible 18, i.e. 9 subjects with R & LMCA data, except for LGTR and LBNPR where max. 14).

ARI (%)	Visit1	Visit2	Intervisit difference
HDG_s (n=16,18)	57.37 ± 30.43 (5.05-99.9)	47.95 ± 32.76 (0-89.47)	13.32 ± 32.83 (-47.49 - 84.42)
LGT_s (n=10,12)	45.7 ± 39.7 (0-99.9)	67.6 ± 35.9 (3.5-99.9)	-19.5 ± 45.1 (-50.4 - 99.3)
$LBNP_s$ (n=14,16)	43.53 ± 32.28 (0-99.9)	63.8 ± 41.9 (0-99.9)	-17.1 ± 62.3 (-99.9 - 90.2)
THC_s (n=18,14)	40.9 ± 40.2 (0-99.9)	39.89 ± 41.61 (0-99.9)	0.4 ± 48.4 (-99.9 - 64.9)

Table 4.4:- Results of static test reproducibility.

Results presented as mean ± s.d. (range).

HDG_s = isometric hand grip; LGT_s = passive leg tilt; $LBNP_s$ = lower body negative pressure;
THC_s = thigh cuff inflation.

n = number of MCA's for visit1,visit2.

* $p<0.05$ for one sample Student's t-test of differences between visits.

	Visit1	Visit2	Difference	CV (%)
Magnitude of BP change (mmHg)				
Positive Transient	13.1 ± 7.9	10.6 ± 3.1	2.6 ± 7.7	62
Negative Transient	-13.6 ± 8.5	-13.7 ± 5.5	0.1 ± 9.4	66
HDGR	-25.3 ± 10.5	-21.5 ± 10.7	-3.9 ± 17.1	73
CPT	19.7 ± 4.2	13.8 ± 2.8	5.7 ± 8.2	47
LGTR	-16.2 ± 3.7	-22.9 ± 12.6	9.7 ± 12.9	61
VALS	21.9 ± 11.0	22.1 ± 9.5	0.2 ± 9.8	41
THCR	-18.1 ± 5.4	-15.8 ± 4.2	-2.2 ± 7.6	43
LBNPR	18.0 ± 7.3	13.3 ± 2.4	4.7 ± 5.2	32
HDG_s	17.2 ± 6.9	17.8 ± 8.6	0.8 ± 11.0	63
LGT_s	16.7 ± 4.4	18.7 ± 8.0	-2.8 ± 7.1	41
$LBNP_s$	15.5 ± 3.7	14.2 ± 2.7	1.3 ± 5.0	31
THC_s	12.5 ± 2.4	16.2 ± 6.2	-0.8 ± 2.2	17
Rate of BP change (mmHg/s)				
Positive Transient	2.4 ± 1.7	1.7 ± 0.4	0.7 ± 1.7	79
Negative Transient	-2.1 ± 0.9	-1.9 ± 0.8	-0.2 ± 1.1	50
HDGR	-2.8 ± 0.7	-2.8 ± 1.5	0.1 ± 1.6	58
CPT	3.2 ± 0.5	1.1 ± 0.5	2.1 ± 1.1	49
LGTR	-3.7 ± 2.2	-4.6 ± 2.9	1.6 ± 1.9	43
VALS	3.5 ± 1.9	4.3 ± 2.0	-1.05 ± 2.1	54
THCR	-2.7 ± 0.9	-2.4 ± 0.8	-0.4 ± 0.7	25
LBNPR	2.7 ± 1.5	2.3 ± 1.2	0.5 ± 1.5	55

Table 4.5:- Results of BP stimulus for dynamic and static tests on two visits, with intervisit difference and CV(%).

Results presented as mean ± s.d.

No result was significantly different between visits ($p<0.05$).

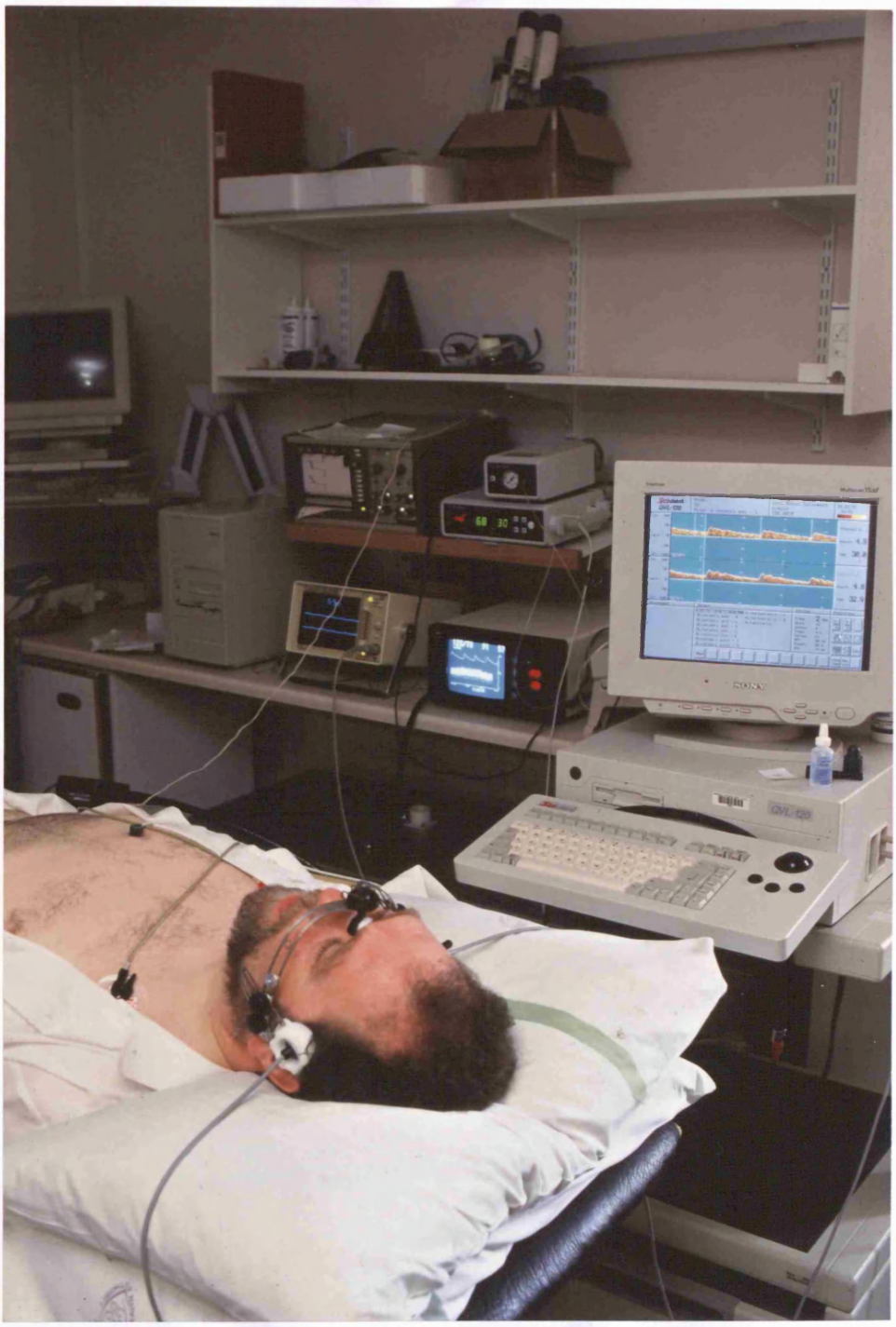


Fig. 4.1:- Volunteer Subject Undergoing Tests of Cerebral Autoregulation.

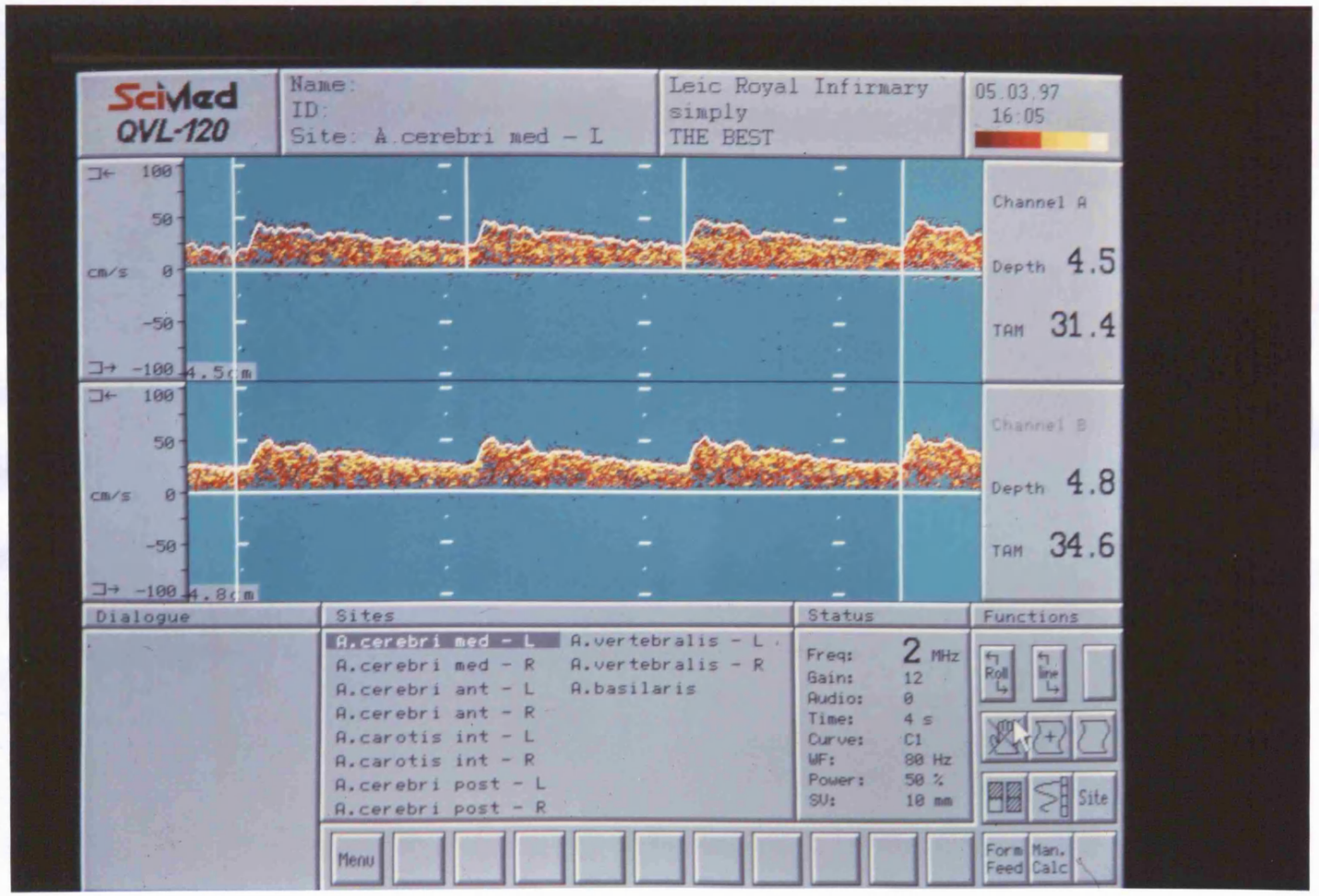


Fig. 4.2:- On-screen Representation of Middle Cerebral Artery Blood Flow.

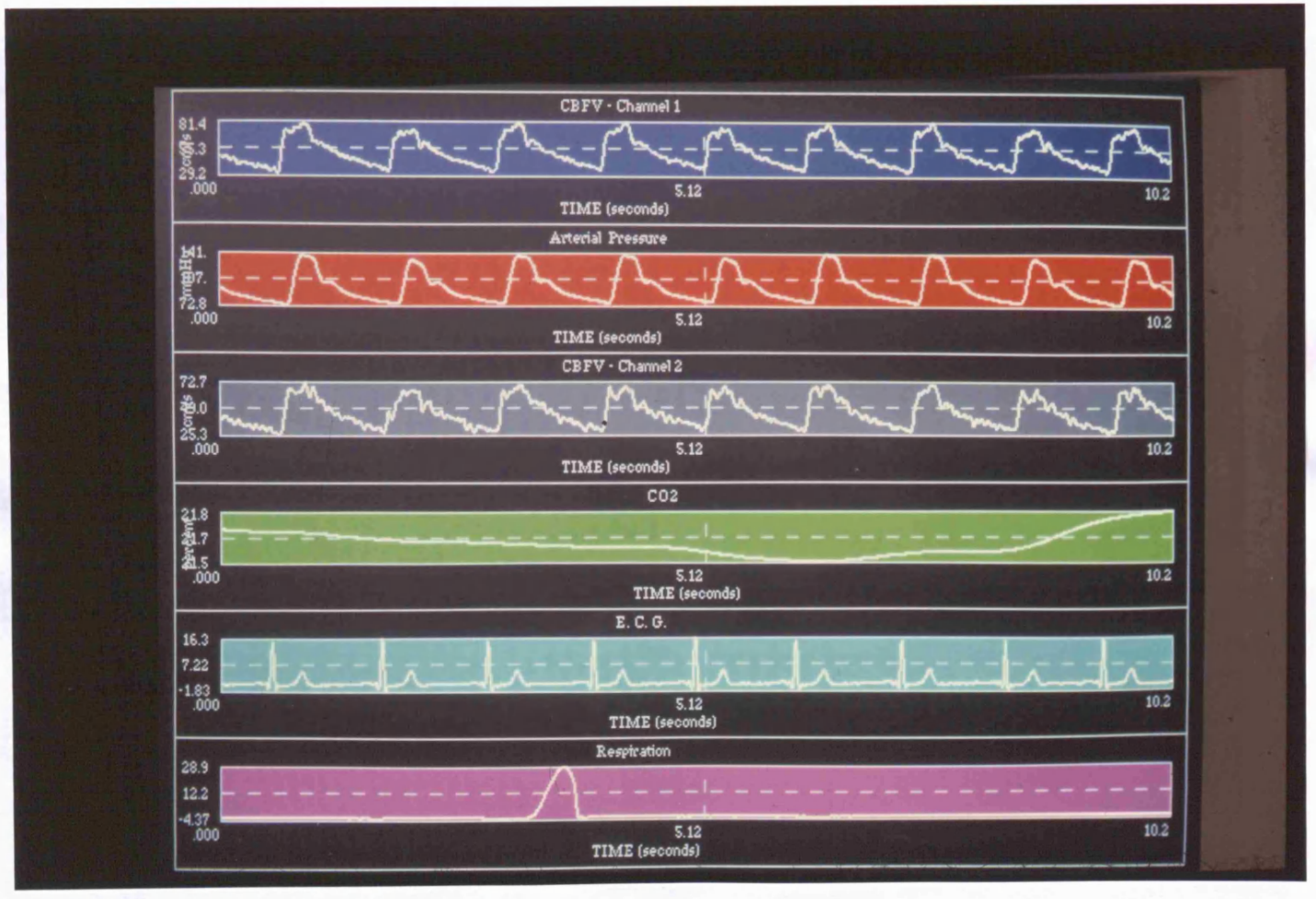


Fig. 4.3:- Visual Inspection of Data Recorded.

N.B. Respiration channel used to mark beginning and end of test.

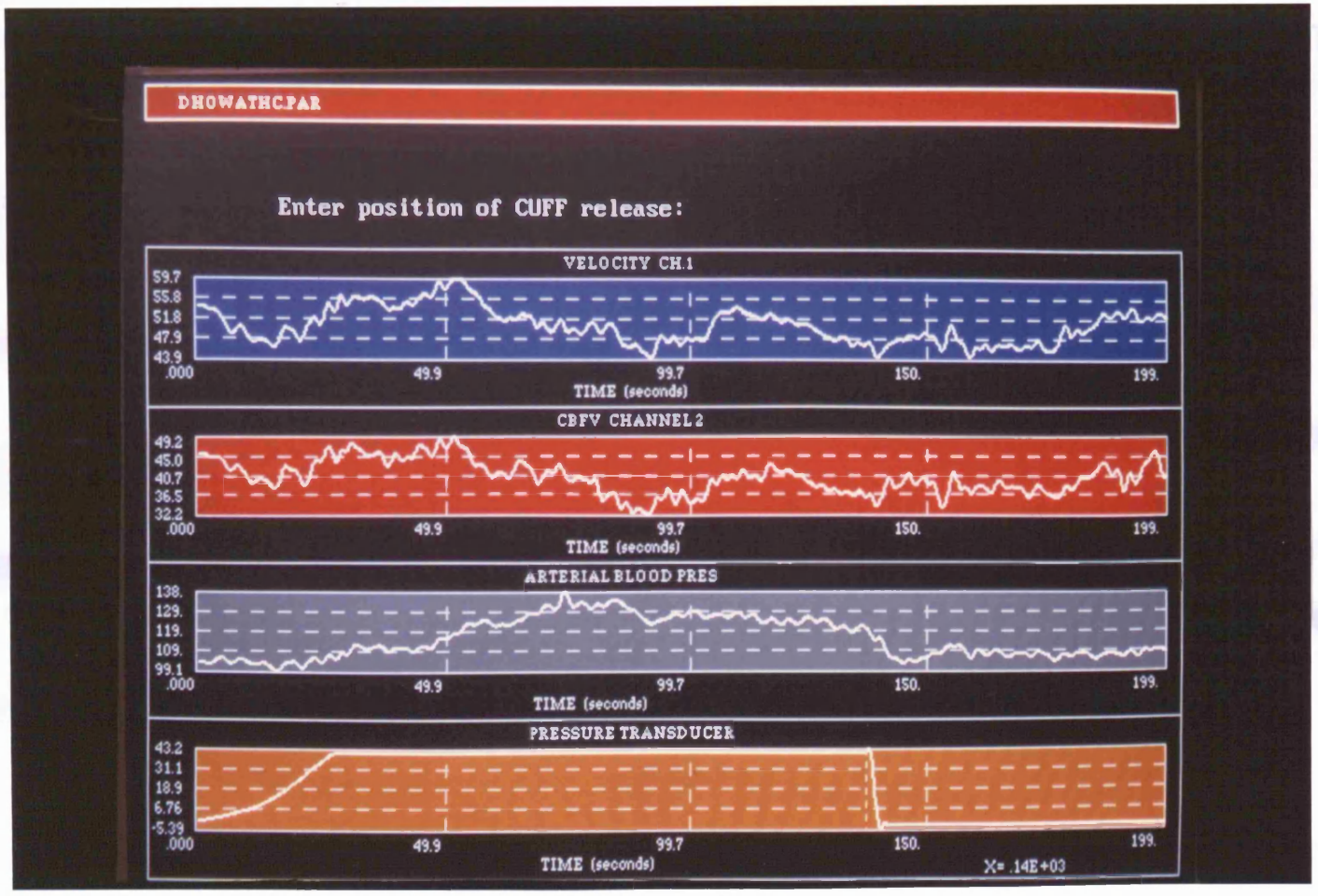
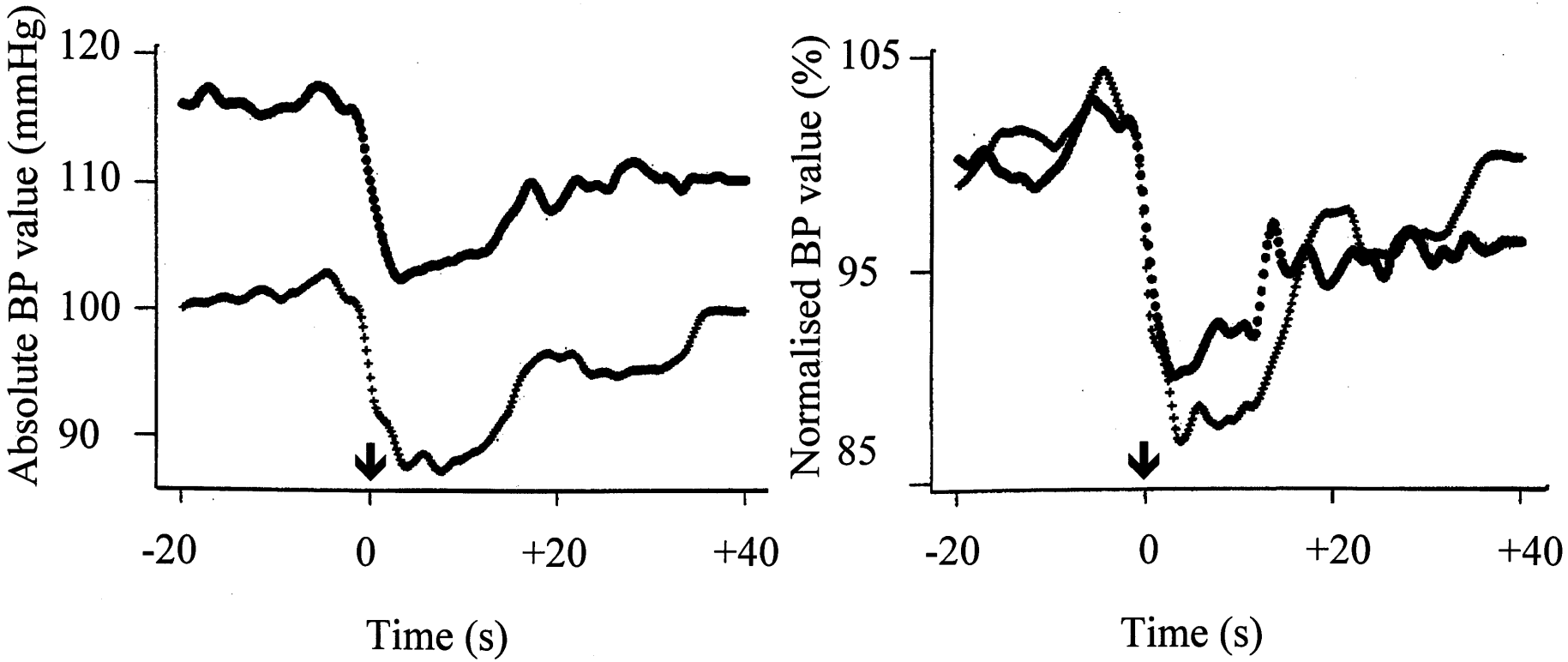


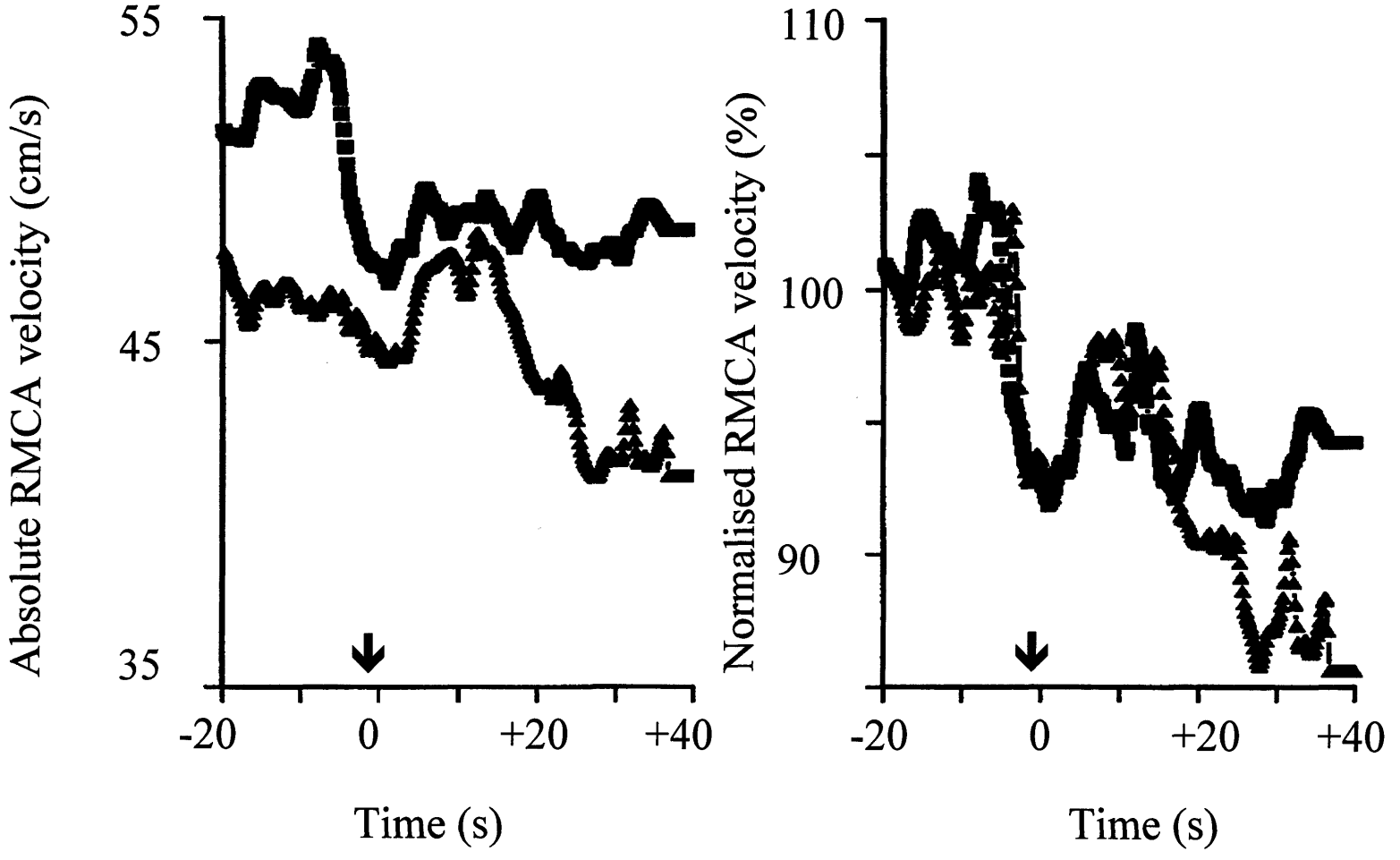
Fig. 4.4:- Marking start of dynamic depressor test – release of bilateral thigh cuff inflation.

Figure 4.5:-Reproducibility of group average BP change during THC release



• Visit 1 + Visit 2 ⬇ Point of cuff release

Figure 4.6:- Reproducibility of group average RMCAV during dynamic HDG release



CHAPTER 5

THE NON-INVASIVE ASSESSMENT OF STATIC AND DYNAMIC CEREBRAL AUTOREGULATION IN THE ELDERLY POPULATION.

5.1 SUMMARY:-

Previous studies of cerebral blood flow and CA have implied that subject characteristics such as age, gender, and blood pressure may affect the results. Obviously this has important connotations for studies comparing two different subject populations. Using the tests described in the previous chapter the aims of this study were to examine the influence of subject characteristics on dynamic and static CA in a control population; and to determine whether in this 'healthy' population there was any evidence for an interhemispheric difference in autoregulation, or the ability to respond to pressor or depressor stimuli.

There was no evidence for any interhemispheric difference in this population. The results also failed to demonstrate any consistent relation between any of the subject characteristics studied and the autoregulation indexes (ARI) derived, except for the subjects blood pressure, and the magnitude of the blood pressure stimuli used to assess CA, which both appeared to possibly influence the ARI, and will need to be taken into account in future comparison studies. Each test, however, produced markedly different ARI's; consequently, any meaningful comparison between pressor and depressor responses is difficult to make. These differences in mean ARI in a 'healthy' population also raise doubt over previous assumptions of a 'normal' autoregulation index. Further study of these processes may lead to a better understanding of the mechanisms behind cerebral autoregulation.

5.2 INTRODUCTION:-

Various factors are known to influence cerebral blood flow, and consequently may affect cerebral autoregulation and/or cerebral vasoreactivity (CR). The effects of the parameters that have been studied to date on these measurements have been reviewed in Chapter 1.3.

It is generally accepted that there is an age-related decline in CBF [Kety 1956, Shaw 1984, Martin 1994], which is influenced by gender [Martin 1994, Karnik 1996], and that this may be regional with the largest decline being seen in the

prefrontal and parietal areas [Naritomo 1978, Shaw 1984]. Cerebrovascular resistance (CVR) increases with age [Krajewsli 1993], and recently a study has shown age related changes to CR tested using the breath-holding index (BHI) [Matteis 1998].

Smoking, alcohol, raised lipid and haematocrit levels also reduce CBF, but it is unclear if they affect CA/CR [Rogers 1983, 1984, Meyer 1987, Thomas 1982]. The effect of BP on CBF is also still debated [Faraci 1990, Thulin 1993], but persistent hypertension does cause a shift of the autoregulatory plateau to the right [Strandgaard 1973, 1976, Fujishima 1984] and may impair CR [Tominaga 1976, Maeda 1994]. Carbon dioxide partial pressure (pCO2) also profoundly influences CBF through the stimulation of CR, with increasing pCO2 leading to vasodilatation [Paulson 1972, Markwalder 1984], and there is evidence that hypercapnia may impair CA, whereas hypocapnia may augment it [Aaslid 1989]. Other factors that may influence these processes include diabetes [Kastrup 1986, Ceravolo 1997], drugs [Demolis 1993, Squire 1994, Fujishima 1995, Landmark 1995], diseases of the autonomic nervous system [Caronna 1973, Bondar 1997, Novak 1998], and chronic cerebrovascular disease [Agnoli 1968, Olsen 1983, Provinciali 1990].

However, definitive answers to the effect of these parameters on CA are lacking, since until recently the methodology available to measure CBF etc. was limited, (see Chapter 2.1). In the previous chapter the author has considered the use of various non-invasive methods of measuring both static and dynamic cerebral autoregulation.

5.3 AIMS:-

1. Using the methods discussed in Chapter 3 the author aims to study a large number of healthy subjects to assess the effects of subject characteristics on both dynamic and static CA.
2. To determine whether there are interhemispheric differences in a subjects ability to autoregulate.

3. To see whether there is any difference in a subjects ability to respond to pressor or depressor BP stimuli.

5.4 METHODS:

5.4.1 Subjects & Protocol:-

Subjects were recruited from a well established database of volunteers who had responded to a local newspaper advertisement calling for healthy 'elderly' volunteers to participate in cardiovascular research projects within the University Department of Medicine for the Elderly. Subjects were all independent in their activities of daily living, and free from cardiovascular, cerebrovascular, or autonomic disease as ascertained from history, clinical examination, and routine investigations. Subjects with a history of diabetes, atrial fibrillation, or those taking medication that may affect cerebral blood flow or autonomic function were excluded. Although routine carotid doppler scanning was not performed to exclude a significant carotid stenosis, none of the subjects had a history or examination which suggested a problem, nor did they have TCD waveform changes that may indicate this.

Blood pressure monitoring, and the tests of cerebral autoregulation were conducted as described in the previous chapter (4.4.1 and 4.4.2).

5.4.2 Data analysis:-

See Chapter 4.4.3.

Since it was felt to produce the most robust results (Chapter 4) a correlation coefficient (r) corresponding to the best match between the model and data was used to obtain a dynamic ARI. Similarly, a window duration of 30s was used to calculate the dynamic ARI, except when spontaneous transients were used as the BP stimulus when a 10s window was used.

5.5 STATISTICAL ANALYSIS:-

Data were analysed using Minitab 10 statistical computer software package.

Subject characteristics, both dynamic and static ARI, and BP stimuli were described as mean ± s.d. (range). Data was assessed for normality using Shapiro-Wilk normality plots. Right and left MCA results were compared using the one-sample Student's t-test, as the differences were normally distributed.

Simple scatter plots and single linear regression analysis (including study of residual plots to check that assumptions of normality were valid) were used to see if subject characteristics significantly influenced ARI results, except for the role of gender which was examined using a two-sample Student's t-test, and smoking which was assessed using General Linear Modelling (GLM).

Pressor and depressor tests were visually compared. The author did not formally test them against each other as she felt that they could not be considered comparable (see discussion).

Significance was set at the 5% level.

5.6 RESULTS:-

Complete data were available on 61 subjects mean age 67 ± 9.7 years, mean casual SBP 150 ± 20 mmHg, mean casual DBP 87 ± 13 mmHg, mean 24 hour SBP 132 ± 14 mmHg and mean 24 hour DBP 79 ± 9.9 mmHg. Results of subject characteristics are shown in Table 5.1, which demonstrates the heterogeneity of the population studied. The values for MCAV and depth of insonation are in keeping with those originally described by Aaslid et al [1982].

5.6.1 Dynamic Tests

The results of tests of dynamic CA are presented in Tables 5.2-5.4, illustrating the

BP stimuli achieved, results of right and left MCA ARI's and interhemispheric differences, and finally the mean ARI of each test using all MCA results combined. It can be seen that the magnitude of the BP stimuli were similar for all tests, except for the spontaneous transients which as expected were smaller, and the CPT. Similarly, the rates of change were smaller for these latter 3 tests [Table 5.2]. There does not appear to be any difference between BP stimuli for pressor and depressor tests.

There was no significant interhemispheric difference in ARI for any of the dynamic tests [Table 5.3], although the size of the difference varied between tests, with the VM having the smallest difference of 0.02 ± 1.2, compared to 0.6 ± 2.7 seen with HDGR; again there did not appear to be a difference between pressor and depressor tests. Consequently for all subsequent analysis the results of all MCA results were combined, to increase the statistical power of any test. Table 5.4 shows that the mean ARI for each test. It can be seen that the results varied from 4.4 ± 2.9 for the VM, to 6.0 ± 2.3 for the THCR. There was no consistent pattern of difference between pressor and depressor tests implying that there is not an inherent difference in this groups ability to regulate CBF in response to the two different stimuli.

Table 5.5 shows the results of linear regression to assess the influence of age, gender, casual and 24 hour BP, test BP stimulus, and alcohol on ARI. Although a number of factors reached statistical significance, examination of the Rsq (%) value and a scatter plot, failed to show any large influence of any of these parameters, except for the size and rate of BP change used in the VM (Rsq 32% and 39.2% respectively), and casual SBP and LGTR (Rsq 18.9%). General Linear Modelling identified a relation between smoking status and ARI measured using CPT ($p=0.039$).

5.6.2 Static Tests

The results of the static tests are similarly displayed in Tables 5.6-5.9. Again the

four tests appear to lead to similar BP stimuli [Table 5.6], and ARI results [Table 5.7, 5.8]. There was no significant difference between hemispheres, although HDG_s demonstrated the smallest difference (-0.66 ± 19.64%) [Table 5.7]. Again there was no apparent difference between pressor and depressor tests [Table 5.7, 5.8].

Table 5.9 shows the results of linear regression as for the dynamic tests. Again a number of factors reached statistical significance, but on closer examination resulted in little influence on ARI variability . Smoking led to a significant inverse relation to ARI measured using $LBNP_s$, casual SBP contributed to 16.3% of the variability in ARI assessed by LGT_s, and 24 hour SBP 12.3% of the THC_s variability.

5.7 DISCUSSION:-

The author reports the use of a number of different methods of dynamically (i.e. within seconds), and statically (i.e. >60s) elevating or lowering blood pressure (BP), and by adapting the mathematical models of cerebral autoregulation (CA) previously described by Tiecks [1995a] has used these methods to measure CA in a heterogeneous group of 'healthy' predominately elderly volunteers. All of these methods gave similar BP stimuli, except for the spontaneous transients which were as expected smaller than those induced by formal 'tests'. The BP changes were of a similar magnitude to those previously described for dynamic CA tested by thigh cuff release [20 ± 4 mmHg] and phenylephrine induced static BP changes [24 ± 4 mmHg] [Tiecks 1995a]. However, although the static ARI's demonstrated here were similar to those previously reported, implying that an ARI >50% represents intact/preserved autoregulation [Tiecks 1995a], the dynamic ARI's in this group of subjects showed a wide variation. Previously a dynamic ARI >5 has been thought to be 'normal'; this has been calculated using THCR [Tiecks 1995a], and in this case the present set of results is comparable (mean ARI 6.0 ± 2.3), whereas most of the other dynamic tests reported here have produced a lower ARI, e.g. mean HDGR 3.7 ± 3.6. This casts some doubt over the assumption of a 'normal' ARI, and has

important implications for comparative studies. However, these differences mean that the tests cannot be directly compared; not only are they not equally reproducible (Chapter 4), but these results imply that different factors are influencing the different tests, e.g. sympathetic nervous system activity.

5.7.1 Interhemispheric differences:-

If these tests are to be used in conditions where there may be interhemispheric differences, e.g. with occlusive vascular disease, or stroke disease, it is important that there is no significant interhemispheric difference in this healthy population. It has to be noted that left and right hemispheres were grouped together regardless of handedness, but since most left handers still have a dominant left hemisphere, this should not be a criticism, and it is likely that there is no difference in ARI with dominance. Consequently in a population where it is unlikely that there is a pathological interhemispheric difference results can be amalgamated to increase statistical power.

It should be noted that TCD tends to only examine changes in MCAV, and consequently, theoretically, we have only examined changes occurring within this vascular territory. Results of ARI or interhemispheric difference cannot therefore be extrapolated at this time to other vascular areas, in particular the posterior cerebral circulation.

5.7.2 Subject characteristics and ARI results:-

This is difficult to study meaningfully even in a population of 61 subjects. A significant relation between a subject parameter and an ARI was found on a number of occasions, but if Rsq (%) was examined then the majority contributed to <10% of the ARI, and scatter plots implied little significance. The only 'real' relations seemed to be between casual SBP and LGTR, rate and magnitude of BP stimulus and VM, and smoking status and CPT; for the static tests smoking and $LBNP_s$, casual SBP and LGT_s, and 24 hour SBP and THC_s were identified as important

determinants. A valid criticism of these findings would be that with multiple testing these results may have occurred by chance, but as stated above a significant p-value was not felt to mean that two parameters were necessarily related.

This lack of any consistent influence by a subject characteristic on ARI is interesting in view of the previously reported age, gender, and BP influences on CBF &/or CA mentioned in Chapter 1. Although a statistically significant difference was found for the relation between gender and the dynamic ARI measured using HDGR and negative transients, scatter plots did not convincingly demonstrate the higher ARI in female subjects that had been suggested (see Fig 5.1).

The positive findings, however, are very important, and future studies will need to take particular care to control for these parameters when comparing different subject groups, e.g. patients versus controls.

Of particular interest is the lack of any influence of casual/24 hour BP or BP stimulus on CPT derived ARI, as it is widely thought that increasing BP levels are associated with increasing BP responses to CPT [Hines 1936]. This effect is felt to represent differences in autonomic function, particularly sympathetic activity, with elevation of BP, and adds further support to the concept of an autoregulatory plateau (see Chapter 1.1). Although we did not demonstrate any relation between ARI and BP change with this test, autonomic activation may explain the relation found between THC_s and BP, possibly mediated by patient discomfort.

The relation between BP stimulus and ARI derived from the VM, and the generally lower ARI found with this test is interesting, as it may imply the influence of other unmeasured parameters. The author has previously shown that critical closing pressure (CrCP) is crucial to the changes seen in cerebral haemodynamics during this manoeuvre [Dawson 1999a]; as yet we have not examined the role of this parameter in the other tests, but it may be that there are significant differences between the tests which are subsequently influencing the calculation of CA by distorting the mathematical model we are employing to assess the rate of restoration of blood flow.

5.7.3 Pressor versus depressor tests:-

The static tests that were performed mainly produced a pressor BP stimulus, and so any definite conclusion regarding a difference between pressor and depressor stimuli would be difficult to interpret, but it would appear that the ARI indices were similar, and therefore, as would be expected in a healthy population even if the control mechanisms to respond to these different stimuli are separate they function equally well.

For the dynamic tests it again appeared that there was no difference between the types of stimuli used, even though the Valsalva manoeuvre, a pressor test, gave a lower ARI, this was not seen with the other pressor tests. It was, however, felt inappropriate to formally statistically compare the individual tests for a number of reasons. Firstly, some of the tests were more reproducible than others [Chapter 4]; and secondly, as already mentioned the different mean ARI's imply that different factors influence the different tests in terms of both 'measured' subject characteristics (e.g. age), and 'unmeasured' parameters (e.g. CrCP, influence on the autonomic nervous system). Consequently, the tests are not thought to be necessarily measuring the same response, since the different test may have different influences on the control mechanisms of dynamic autoregulation; therefore, a statistical comparison of the tests would be difficult to interpret, (see Fig 5.2).

These inherent differences between the tests, and their reproducibility, means that care is needed when further use of these tests is considered for comparison of different populations. Combining the results from the previous chapter and those presented here the author has decided to limit the number of tests used in the subsequent chapter comparing patients with acute ischaemic stroke to this control population. Thigh cuff release will be used to assess dynamic cerebral autoregulation, and thigh cuff inflation and isometric hand grip to assess static cerebral autoregulation.

5.8 CONCLUSIONS:-

In conclusion, this study has demonstrated that there are no significant interhemispheric differences in the normal healthy population with regard to either static or dynamic CA in the MCA territory. It has also failed to demonstrate any significant influence of age, gender, smoking and alcohol on CA, despite previous reports of them influencing CBF. However, the influence of BP, and the BP stimuli used in tests is less clear, for both inter- and intra-subject comparison and should be taken into account in future studies. Although the pressor and depressor tests were not directly comparable and, therefore, could not be formally compared statistically there did not appear to be a difference in this normal population as would be expected. However, the results from the different tests are not readily comparable, and although these tests could be extrapolated to examine the influence of pathological conditions such as stroke on CA, the author feels that at present study should be limited to the use of thigh cuff inflation/release, and isometric hand grip.

Parameter	
Age (years)	67 ± 9.7 (39,80)
Gender (M:F)	35:26
BMI (kg/m^2)	26.6 ± 3.6 (20.1,35.8)
No (%) of current/ex-/non-smokers	7 (11), 23 (38), 31 (51)
Alcohol intake (units per week)	10.2 ± 13.4 (0,60)
No (%) on antiplatelet therapy	4 (7)
History of hypertension n(%)	13 (21)
History of ischaemic heart disease n(%)	1 (2)
Casual SBP (mmHg)	150 ± 20.0 (112,200)
Casual DBP (mmHg)	87 ± 13.3 (62,114)
24 hour SBP (mmHg)	132 ± 13.8 (108,164)
24 hour DBP (mmHg)	79 ± 9.9 (63,108)
24 hour HR (bpm)	72 ± 8.2 (60,88)
Resting Right MCAV (cm/s)	39.5 ± 8.5 (24,60)
Resting Left MCAV (cm/s)	39.7 ± 9.1 (24,60)
Depth of insonation of Right MCA (cm)	4.9 ± 0.45 (4.2,5.7)
Depth of insonation of Left MCA (cm)	5.1 ± 0.51 (4.1,6)

Table 5.1:-
Control subject demographic characteristics (n=61).

Results presented as mean ± s.d. (range) or number (%).

	Magnitude of Change (mmHg)	Rate of Change (mmHg/s)
Positive spontaneous transient n=109	12.5 ± 5.5 (3.3,26.5)	2.0 ± 1.0 (0.3,5.4)
Negative spontaneous transient n=106	-13.6 ± 6.1 (-30.2,-4.0)	-2.0 ± 1.0 (-4.6,-0.3)
Hand grip release n=88	-23.1 ± 10.1 (-54.2,-10.0)	-3.0 ± 1.6 (-8.0,-1.0)
Leg tilt release n=60	-21.6 ± 10.7 (-60.6,-10.0)	-4.0 ± 2.2 (-9.3,-1.8)
Cold pressor test n=83	18.3 ± 7.6 (10.0,47.3)	1.9 ± 1.0 (0.4,5.6)
Valsalva manoeuvre n=98	22.2 ± 8.4 (10.0,40.7)	3.6 ± 1.7 (0.8,7.4)
Thigh cuff release n=98	-20.6 ± 9.4 (-56.0,-10.0)	-3.0 ± 1.3 (-6.7,-1.1)
LBNP release n=66	18.8 ± 7.9 (10.0,42.0)	2.8 ± 1.3 (0.9,5.6)

Table 5.2:-
Magnitude and rate of change of blood pressure manoeuvres used to assess dynamic cerebral autoregulation in control subjects.

Results presented as mean ± s.d. (range).

	RMCA	LMCA	DIFFERENCE	p value
POSITIVE TRANSIENT (n=58,51,51)	5.6 ± 2.1 (0-9)	5.3 ± 2.5 (0-9)	0.3 ± 1.9 (-9,4.9)	0.30
NEGATIVE TRANSIENT (n=57,49,49)	4.5 ± 2.8 (0-9)	4.1 ± 2.7 (0-9)	0.2 ± 1.8 (-4.2,6.7)	0.38
HAND GRIP RELEASE (n=45,43,40)	3.6 ± 3.7 (0-9)	3.9 ± 3.5 (0-9)	-0.7 ± 2.7 (-8.3,6.3)	0.10
LEG TILT RELEASE (n=33,27,27)	5.8 ± 2.3 (0-9)	6.2 ± 2.3 (0-9)	-0.2 ± 1.1 (-3.7,2.3)	0.23
COLD PRESSOR TEST (n=43,40,38)	4.6 ± 3.1 (0-9)	4.9 ± 3.0 (0-9)	-0.4 ± 2.1 (-9,6.4)	0.26
VALSALVA MANOEUVRE (n=51,47,47)	4.4 ± 2.7 (0-8.6)	4.5 ± 2.7 (0-8.2)	-0.01 ± 1.3 (-3,3.9)	0.94
THIGH CUFF RELEASE (N=48,45,45)	6.2 ± 2.3 (0-9)	5.9 ± 2.3 (0-9)	0.2 ± 1.6 (-5.8,5.3)	0.51
LBNP RELEASE (n=35,30,30)	5.2 ± 2.7 (0-9)	4.9 ± 2.6 (0-9)	0.2 ± 1.8 (-2.7,7.2)	0.63

Table 5.3:-
Interhemispheric differences for dynamic cerebral autoregulation tests for all controls.

'n' varied with each test. Shown as number of RMCA and LMCA recordings, plus number of subjects with results for both hemispheres.

Results presented as mean ± s.d. (range).

Difference between LMCA and RMCA results shown and p-value of one-sample t-test given.

N.B. All ARI's were calculated using a 150 sample window except for spontaneous transient where a 50 sample window was employed.

	MEAN ARI
POSITIVE TRANSIENT (n=109)	5.5 ± 2.3 (0-9)
NEGATIVE TRANSIENT (n=106)	4.3 ± 2.8 (0-9)
HAND GRIP RELEASE (n=88)	3.7 ± 3.6 (0-9)
LEG TILT RELEASE (n=60)	6.0 ± 2.3 (0-9)
COLD PRESSOR TEST (n=83)	4.8 ± 3.0 (0-9)
VALSALVA MANOEUVRE (n=98)	4.4 ± 2.7 (0-8.6)
THIGH CUFF RELEASE (n=98)	6.0 ± 2.3 (0-9)
LBNP RELEASE (n=66)	5.1 ± 2.7 (0-9)

Table 5.4:-
ARI for each dynamic test using combined left & right MCA results.

Mean ± s.d. (range).

	Age	Gender	BMI	Casual SBP	Casual DBP	24 hour SBP	24 hour DBP	24 hour HR	Magnitude of BP stimulus	Rate of BP stimulus	Smoking status	Alcohol consumption
Positive spontaneous transient	-1.06 (1.1%)	0.23 (p=0.82)	-0.89 (0.8%)	-1.64 (2.5%)	-1.14 (1.2%)	-3.38*** (11.1%)	-1.3 (1.8%)	-0.97 (1.0%)	-1.02 (1.0%)	-0.44 (0.2%)	p=0.155	-2.72** (7.3%)
Negative spontaneous transient	-0.17 (0.0%)	2.11* (p=0.04)	-0.88 (0.8%)	0.77 (0.6%)	0.46 (0.2%)	-0.93 (1.0%)	-0.09 (0.0%)	-1.28 (1.8%)	-0.08 (0.0%)	-0.37 (0.1%)	p=0.205	0.62 (0.4%)
Hand grip release	-1.67 (3.0%)	2.64* (p=0.01)	-0.26 (0.1%)	-1.24 (1.6%)	-0.01 (0.0%)	-1.45 (2.5%)	0.65 (0.5%)	-0.41 (0.2%)	0.84 (0.8%)	-0.3 (0.1%)	p=0.628	-0.78 (0.7%)
Leg tilt release	-1.64 (4.2%)	-0.59 (p=0.56)	1.96 (6.2%)	-3.74*** (18.9%)	-0.7 (0.8%)	-0.85 (1.3%)	0.75 (1.0%)	-0.82 (1.2%)	-0.35 (0.2%)	1.29 (2.6%)	p=0.324	0.14 (0.0%)
Cold pressor test	-0.03 (0.0%)	0.54 (p=0.59)	-0.95 (1.2%)	-1.82 (4.0%)	-1.1 (1.5%)	-0.59 (0.5%)	-0.77 (0.8%)	-0.54 (0.4%)	0.24 (0.1%)	-0.15 (0.0%)	p=0.039*	1.59 (3.5%)
Valsalva manoeuvre	2.6** (6.6%)	-1.45 (p=0.15)	-0.31 (0.1%)	0.93 (0.9%)	1.34 (1.8%)	-0.25 (0.1%)	-0.95 (1.1%)	-2.18* (5.3%)	6.78*** (32.0%)	7.96*** (39.2%)	p=0.666	-0.48 (0.3%)
Thigh cuff release	2.97** (8.4%)	-0.49 (p=0.62)	-0.12 (0.0%)	0.83 (0.7%)	0.85 (0.8%)	1.57 (2.9%)	1.02 (1.2%)	-0.03 (0.0%)	0.91 (0.8%)	2.18* (4.7%)	p=0.339	0.46 (0.2%)
LBNP release	0.58 (0.5%)	0.49 (p=0.63)	-0.33 (0.2%)	0.06 (0.0%)	-0.49 (0.4%)	-2.15* (6.9%)	-1.82 (5.1%)	-3.74*** (18.4%)	-1.16 (1.9%)	-0.05 (0.0%)	p=0.267	-0.17 (0.0%)

Table 5.5:-

Results of linear regression (except for gender where 2-sample t-test used) of subject parameters against ARI results for different dynamic tests.

Results given as t ratio (Rsq% or for gender p value)

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.

(- = inverse relationship, or in case of gender lower value in females).

Static Test	Magnitude of BP change (mmHg)
Isometric hand grip n=86	17.8 ± 7.7 (10 - 41)
Passive leg tilt n=50	18.7 ± 7.9 (10.1 - 43.8)
Lower body negative pressure n=76	-21.2 ± 12.09 (-10.1 - -77.8)
Thigh cuff inflation n=86	20.02 ± 9.3 (10.1 - 52.1)

Table 5.6:- Mean magnitude of BP changes during static tests.

Results presented as mean ± s.d. (range).

Static Test	RMCA ARI	LMCA ARI	interhemispheric difference	p value
Isometric hand grip (n=45,41,40)	51.5 ± 36.9 (0-99)	52.8 ± 31.4 (0-99)	-0.66 ± 19.6 (-41.6-54.7)	0.66
Passive leg tilt (n=25,25,22)	62.5 ± 34.7 (0-99)	56.2 ± 38.0 (0-99)	4.84 ± 15.2 (-16.7-44.8)	0.42
Lower Body Negative Pressure (n=37,39,33)	61.4 ± 40.0 (0-99)	59.7 ± 38.7 (0-99)	-2.92 ± 18.9 (-64.7-48.9)	0.13
Thigh cuff inflation (n=45,41,39)	52.2 ± 36.9 (0-99)	58.2 ± 37.8 (0-99)	-7.26 ± 26.7 (-81-40.9)	0.06

Table 5.7:- Results of interhemispheric differences for static tests for control subjects.

Results given as mean ± s.d. (range).

n = RMCA, LMCA, subjects with results for both hemispheres.

p value given for one-sample Student's t-test of interhemispheric difference.

Static test	Mean ARI
Isometric hand grip (n=86)	52.1 ± 34.2 (0-99)
Passive leg tilt (n=50)	59.3 ± 34.2 (0-99)
Lower body negative pressure (n=76)	60.5 ± 39.1 (0-99)
Thigh cuff inflation (n=86)	55.1 ± 37.2 (0-99)

Table 5.8:- Mean ARI results from static tests, combining R & LMCA results, in control subjects.

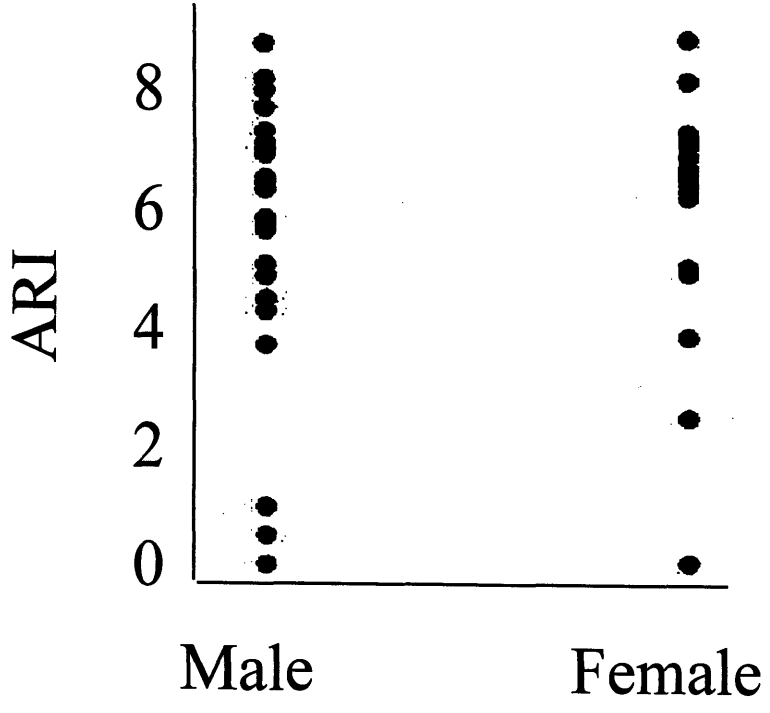
Results presented as mean ± s.d..

Static test	Age	Gender	BMI	24 hour SBP	24 hour DBP	24 hour HR	Casual SBP	Casual DBP	Smoking status	Alcohol consumption	BP stimulus
HDG_s	3.17** (11.4%)	1.74 (p=0.09)	-1.05 (1.6%)	0.44 (0.3%)	-1.18 (2%)	0.56 (0.5%)	0.43 (3.5%)	-1.62 (3.5%)	p=0.646	-0.04 (0%)	0.7 (0.6%)
LGT_s	0.37 (0.3%)	1.04 (p=0.3)	-0.5 (0.5%)	-1.77 (7.1%)	-1.69 (6.5%)	-1.72 (6.7%)	-3.03** (16.3%)	-1.09 (2.5%)	p=0.914	-1.76 (6.4%)	-0.2 (0.1%)
$LBNP_s$	-1.86 (4.8%)	2.05 (p=0.04)	1.11 (1.9%)	-1.2 (2.3%)	-0.96 (1.5%)	-2.33* (8.3%)	-1.52 (3.4%)	-0.38 (0.2%)	p=0.000*	-0.82 (1.1%)	1.1 (1.7%)
THC_s	0.07 (0%)	0.34 (p=0.73)	1.53 (3.1%)	3.13** (12.3%)	0.33 (0.2%)	-0.14 (0%)	1.27 (2.1%)	0.95 (1.2%)	p=0.683	-1.13 (1.7%)	3.21** (11.1%)

Table 5.9:- Results of linear regression of subject characteristics against static ARI (except for gender where 2 sample t-test used).
Results presented as t ratio (Rsq%, p value for gender).
* $p<0.05$, ** $p<0.01$.

Fig 5.1:- Relation between gender and dynamic ARI

a. Hand grip release



b. Negative spontaneous BP transients

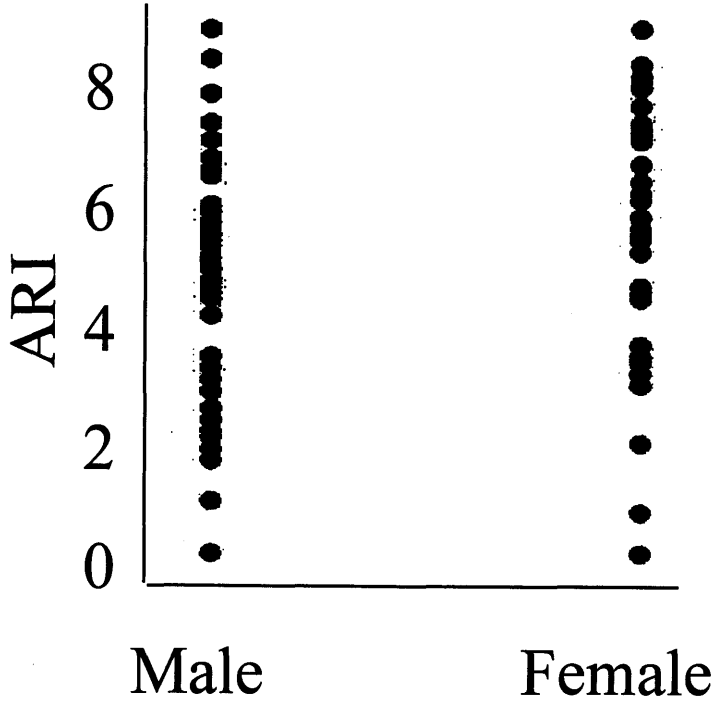
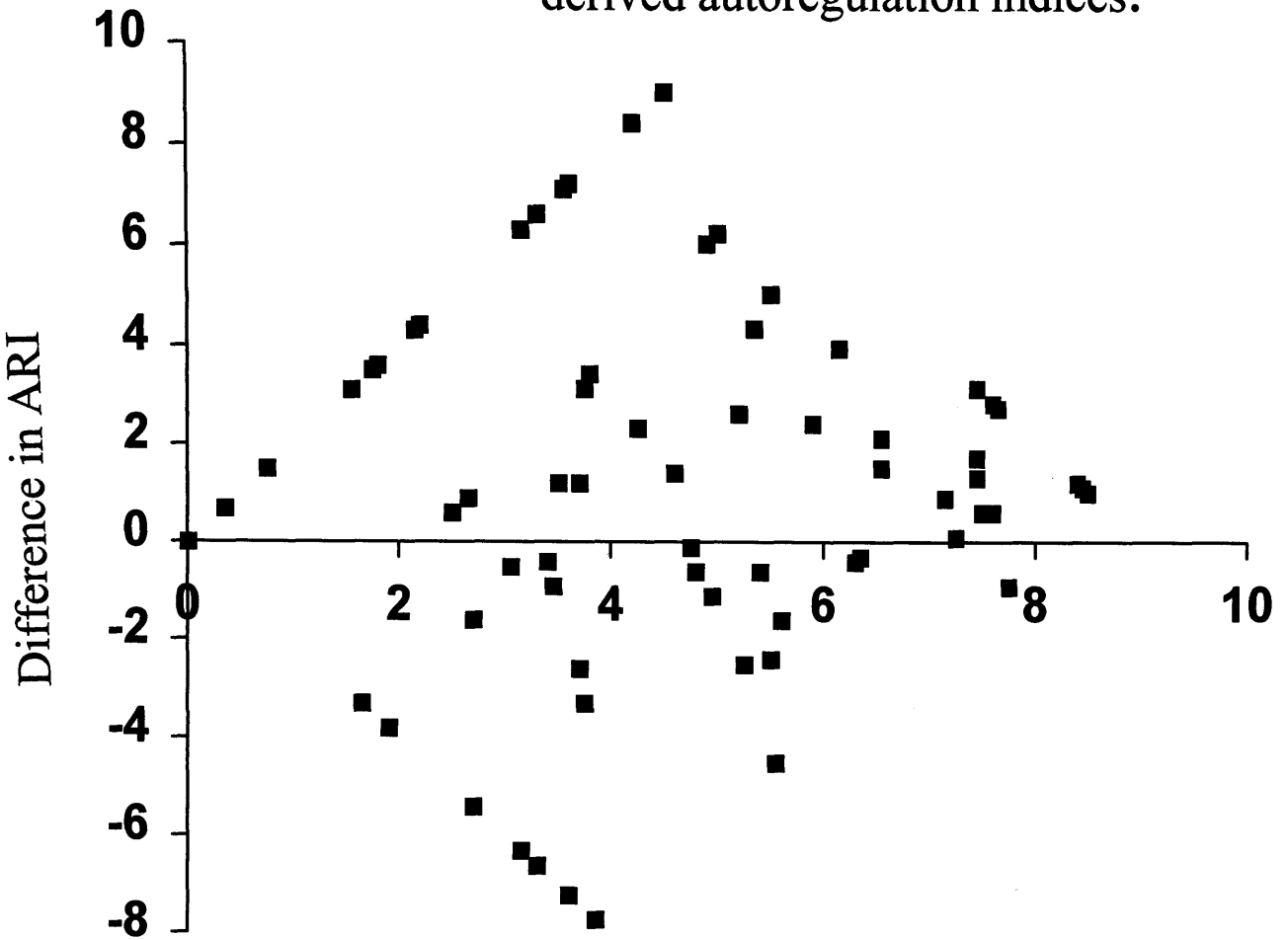


Fig 5.2:- Bland-Altman Plot comparing Cold pressor and Valsalva manoeuvre derived autoregulation indices.



CHAPTER 6

DYNAMIC BUT NOT STATIC CEREBRAL AUTOREGULATION IS IMPAIRED IN ACUTE ISCHAEMIC STROKE.

6.1 SUMMARY:-

It has been postulated that dynamic cerebral autoregulation is more susceptible to damage in pathological states than static autoregulation. Previous studies of cerebral autoregulation in ischaemic stroke have not been conducted in the acute phase, and have only measured the response to static changes in BP levels. There are in addition a number of technical problems with these previous studies. The aim of this study was to assess both dynamic and static CA in a population of acute (<96hours post-ictus) ischaemic stroke patients compared to an age and sex-matched control population. As discussed in the previous chapters dynamic CA was measured using thigh cuff release, static CA using thigh cuff inflation and isometric hand grip.

There was no difference between the two groups with regard to static CA; however, both the stroke and non-stroke hemispheres in the patient group had a reduced dynamic ARI compared to the control population. This difference persisted even after intergroup differences, e.g. in BP, were controlled for.

These results imply a global hemispheric impairment of dynamic CA following ischaemic stroke, and may reflect vasomotor damage. They have important implications for the management of BP in the acute post-stroke period and deserve further study.

6.2 INTRODUCTION:-

Cerebral autoregulation and the results and limitations of previous studies examining changes to CBF, CR, and CA in ischaemic stroke, in both animal models and human subjects, have been extensively reviewed earlier in this manuscript, particularly in chapter 1.4.3.

Animal models of acute ischaemic stroke, induced by carotid artery occlusion, have indicated that this may result in regional differences in cerebral blood flow (CBF), which are not confined to the stroke area alone [Shiokawa 1986]. CA and CR may also be impaired in these animal models, but the degree of damage appears to be

very dependent on the duration of vessel occlusion, and the extent of reperfusion hyperaemia [Schmidt-Kastner 1986, Drummond 1989, Cole 1992, Cipolla 1997, Martin 1983].

In human studies there also appears to be a global reduction in CBF following infarction, although again there are regional differences [Martin 1983, Fujii 1990]. This diaschisis is thought to be the result of transhemispheric communication either by metabolites, or interhemispheric shunts [Fieschi 1966, Meyer 1970, Bajc 1991]. At present it is unclear as to whether either CR or CA or both processes are impaired in acute ischaemic stroke in humans. If there is 'dissociated vasoparalysis', i.e. intact CR but impaired CA, hyperaemia following reperfusion may be detrimental to the ischaemic penumbra through increased oedema, but treatment with antihypertensive agents to reduce this may lead to a pressure passive fall in CBF increasing ischaemia.

It is important that we understand better how these changes in CA may be related to the pathophysiology of stroke, as this may also help settle the ongoing question of how best to manage blood pressure (BP) in the acute stages of stroke. Whilst it is generally considered that in the longer term rigorous BP control is necessary for secondary prevention, [O'Connell 1996], there is a large body of evidence that suggests that immediate reduction of BP may be detrimental [O'Connell 1996, Lavin 1986, Meier 1991, Mori 1993].

As has been mentioned in the previous chapters until the advent of TCD the study of CA was limited to static CA. Chapters 4 and 5 have shown that the measurement of both static and dynamic CA is possible using non-invasive methodology.

6.3 AIMS:-

Since it has been postulated that static and dynamic CA may have different control mechanisms, and that dynamic CA may be more susceptible to damage in pathological states [Tiecks 1995], the aim of this study was:-

1. To study the effect of acute cerebral infarction on cerebral autoregulation.

2. To examine both static and dynamic CA in a group of patients with first ever ischaemic stroke, within 96 hours of symptom onset.
3. To compare the results from this stroke population to an age-matched control group.

6.4 METHODS:-

6.4.1 Subjects:-

a) Stroke group:- Consecutive subjects with a clinical and CT diagnosis of first ever ischaemic stroke admitted within 24 hours of symptom onset to the Leicester teaching hospitals were identified. Subjects were excluded if they had a history of atrial fibrillation, diabetes mellitus, autonomic nervous system disease, recent myocardial infarction, were taking medication affecting the cardiovascular or autonomic nervous systems, or were found to have an inadequate temporal acoustic window. Subjects taking antihypertensive medication on admission were included as this was routinely stopped, as per hospital protocol; study was deferred for 24 hours in these subjects. Subjects with a reduced level of consciousness (GCS <10) or a diagnosis of pre-existing dementia were excluded. All studies were performed within 96 hours of symptom onset. Data were later rejected if subjects were found to have a significant carotid stenosis on carotid Doppler ultrasonography (i.e. >70%).

b) Control group:- See Chapter 5.3.1.

In all subjects casual blood pressure readings were taken in the ward/clinic setting using a standard mercury sphygmomanometer (diastolic Phase V), the mean of three readings was taken as the result. In addition 24 hour ambulatory BP levels were recorded (Spacelabs 90207), readings being taken at 15 minute intervals during the daytime (08.00-21.59hours) and 30 minute intervals over night (22.00-07.59hours). This ABPM was performed within 48 hours of admission in the patient group.

6.4.2 Protocol:-

See Chapter 4.4.2

Static tests:-

a) Isometric hand grip (pressor).

b) Thigh cuff inflation (pressor).

Dynamic test:-

Thigh cuff release (depressor).

6.4.3 Data analysis:- See Chapter 4.4.3

6.5 STATISTICAL ANALYSIS:-

Data were analysed using Minitab 10 software package.

Results are presented as mean ± s.d. (range). Data were assessed for normality using a Shapiro-Wilk plot; patients were then compared to control subjects using a Student's two-sample t-test. The author's previous studies have not demonstrated an interhemispheric difference in either static or dynamic CA in this control population (Chapter 5.4); consequently the results from their RMCA were used as the comparative for the patient group. General linear modelling was used to control for any inter-group differences, and statistical significance was set at $p<0.05$ level.

6.6 RESULTS:-

54 patients, mean age 69 ± 12 years and 24 hour mean arterial BP 108 ± 16 mmHg (range 78-146) with an acute ischaemic stroke, were studied within 96 hours of symptom onset (mean 2.1 ± 1.3 days). Of these stroke patients 24 had left hemisphere events, and they were moderately disabled with mean admission NIH stroke scale 8 ± 3.63, mean Barthel 57 ± 27.5, and using the Oxfordshire Community stroke project classification [Bamford 1991] there were 8 TACS, 19 PACS, 18 LACS and 9 POCS. 61 control subjects mean age 67 ± 10 years, and 24 hour mean arterial BP 98 ± 10 mmHg (range 80-123) were also studied. Subject characteristics are shown in Table 6.1. There was no significant difference between

the two groups in terms of age, gender, BMI, heart rate, alcohol intake, casual DBP, or depth of insonation of either MCA, but there were significantly less non-smokers in the patient group, and a larger proportion with a history of hypertension, ischaemic heart disease, and peripheral vascular disease ($p<0.05$, see Table 6.1). The stroke group also had significantly higher 24 hour SBP/DBP and casual SBP levels, whether the latter was assessed by sphygmomanometer readings or from the mean of two baseline 5 minute Finapres recordings; PI assessed from this Finapres recording was significantly lower in the stroke population, although 24 hour HR was similar between the two groups. The stroke population also had significantly lower MCA velocities in both the unaffected and affected hemispheres compared to control subjects.

Because of the rigorous selection criteria applied to the data for calculation of autoregulatory indices, between 13 control RMCA's and 19 affected stroke hemisphere MCA's were excluded from the final analysis. In the control group 3 RMCA's could not be insonated compared to 2 non-affected hemisphere MCA's, and 5 affected hemisphere MCA's in the stroke group. For the dynamic depressor test 1 control and 3 stroke patients did not attain a BP stimulus >10mmHg. In the static pressor tests for isometric hand grip 8 controls and 6 strokes, and for thigh cuff inflation 5 subjects in each group failed to attain a >10mmHg BP stimulus; the data from all these subjects were therefore rejected as per pre-selected criteria. Either 'signal noise' or ectopics were the reasons for any further rejection of data from the final analysis.

The magnitude and rate of BP change for the dynamic and static tests were similar in both the control and stroke groups, (Table 6.2). There was no difference between patients and controls for either static test; however for the dynamic test there was a significantly lower ARI for both the non-affected and affected hemisphere compared to the control group (4.8 vs 6.2, $p=0.022$, and 4.1 vs 6.2, $p=0.0018$ respectively), see Table 6.3.

When a General Linear Model was used to control for 24 hour blood pressure

differences between the two groups, which the author has previously found may affect the ARI results (Chapter 5), there was still no significant difference seen with either of the static tests between stroke patients and controls, whilst the difference in dynamic ARI persisted. Similarly General Linear Modelling was also used to examine the possible effect of other baseline differences between the two groups, e.g. in smoking, prevalence of ischaemic heart disease, peripheral vascular disease, previous hypertension, aspirin usage, and BP and PI variability; again none of these factors explained the finding of a significant reduction in dynamic ARI.

6.7 DISCUSSION:-

This study has compared both static and dynamic methods of assessing cerebral autoregulation in a group of CT confirmed ischaemic stroke patients within 96 hours of symptom onset with an age, sex, and BMI matched group of healthy controls. The author has shown that dynamic but not static CA is impaired in acute ischaemic stroke and that this effect appears to be global.

Thigh cuff inflation/release and isometric hand grip were chosen as the non-invasive blood pressure stimuli as previous studies of dynamic CA have used thigh cuff release [Tiecks 1995, White 1997] and the author has found these to be the most reproducible tests (Chapter 4.6). There was no significant inter-group difference in the magnitude or rate of BP change used as a stimulus to test CA, which could potentially influence measurement of ARI.

Neither static test appeared to identify any difference between the stroke group and the control subjects. However, there did appear to be a difference between the stroke and control groups in terms of their ability to regulate cerebral blood flow following a dynamic change in BP; a significantly reduced ARI was found in both the affected and non-affected hemispheres even when differences in 24 hour BP levels were statistically controlled for using General linear modelling. As none of the study subjects had mean arterial blood pressure levels >150mmHg according to previous data it was assumed that both stroke and control subjects were on the autoregulatory plateau [Lassen 1964]. However, care is needed with this

assumption since this original work was conducted in normal subjects using methods of measuring CBF with poor temporal resolution; consequently only static changes in BP were examined. Further work on the effects of hypertension on both static and dynamic autoregulation using TCD is needed to clarify the situation.

There were other differences in the baseline characteristics of the two groups, mainly in the prevalence of co-existing cardiovascular disease. These factors were also controlled for in the analysis, and did not appear to alter the findings. It is certainly known that cardiovascular disease influences the autonomic nervous system, e.g. cardiac baroreceptor sensitivity [Airaksinen 1997], and although to the authors' knowledge there are no previous studies looking at dynamic cerebral autoregulation in this population, it may be that there are differences when compared to a healthy population that need to be taken into account.

It has previously been suggested that dynamic CA may be more vulnerable to impairment than static CA in disease states, because it is a more rapid and potentially more sensitive process; consequently different control mechanisms may lie behind the two phenomenon [Tiecks 1995]. The above findings would further support this hypothesis; however, the reasons for these differences have not yet been identified. An attractive explanation lies in the theory that damage to the vasomotor control system through either central damage to the modulation of the autonomic nervous system or the efferent arms of the baroreceptor reflex arc, preferentially influences the dynamic pathway. This could lead to global impairment, and there is certainly a substantial body of evidence demonstrating damage to the autonomic nervous system in acute stroke, and a potential role in the control of cerebral blood flow [Barron 1994, Naver 1996, Robinson 1997a, Harper 1975, Sadoshima 1985, Talman 1994]. However, in this population the differences between the cerebral infarct and control groups in dynamic CA were independent of any differences in BP and PI variability, which may reflect damage to this pathway. The lack of an association between dynamic ARI and BP/PI variability is interesting in view of the results the author has presented in Chapter 3 demonstrating a worsening prognosis with increasing BP levels and BP variability.

Although, it may be that in this present study the numbers are too small to detect this relation. Certainly, one could postulate that increasing BP variability and impaired dynamic CA would be likely to extend the damage to the ischaemic penumbra and therefore worsen outcome. In addition, any difference in autonomic control between static and dynamic CA may also explain the apparent non-significant 'autoregulation paradox' seen in static CA with increased ARI's in the strokes; perhaps disturbance of the sympathetic/ parasympathetic balance places strokes in a better position on the 'static' autoregulatory curve?

Tissue carbon dioxide levels, another factor possibly affecting CA [Paulson 1972, Pistolese 1972], did not demonstrably differ between the groups, but other parameters not directly assessed here, e.g. endothelial-derived substances [Faraci 1991] may be preferentially involved in the control of dynamic autoregulation and account for the differences seen. Further study is needed to elucidate these factors; in conjunction with different techniques of measuring autoregulation, e.g. impulse response and transfer function [Panerai 1998], it may be possible to gain further insight into the mechanisms of cerebral blood flow control.

These findings have clinical relevance in terms of how stroke physicians should best manage BP in the acute phase of stroke [O'Connell 1996, Lavin 1986, Meier 1991, Mori 1993]. It is known that stroke is associated with increased BP levels [Britton 1986, Lip 1997], and that in particular large cortical strokes and primary intracerebral haemorrhages lose their diurnal BP pattern [Dawson 1998a]. In addition, as the author has previously mentioned, Chapter 3 describes changes in beat-to-beat BP variability in acute ischaemic stroke, and a link between BP levels, BPV and 30 day prognosis. Further studies may identify a link between this change in BPV, the impairment of dynamic ARI, and poor prognosis.
The results presented here and in Chapter 3 raise the possibility of a therapeutic intervention for acute ischaemic stroke. If an antihypertensive agent that gradually reduces BP levels and BPV, without impairing CBF, and which preferably improves dynamic CA could be identified it may be a means of improving prognosis and at last would give us a much needed acute treatment for stroke.

There is some evidence that certain antihypertensive agents, in particular the angiotensin converting enzyme inhibitors, may do this [Waldemar 1989, Dyker 1997].

6.7.1 Study limitations

The author has only examined a relatively small number of subjects, and some recordings were rejected because of signal noise or insufficient BP stimulus, and each test was only performed once. Obviously this reduces the statistical ability of the study to detect small changes in CA between strokes and controls, and also has meant that the author is unable to comment on the effects of lateralisation (which could be interesting with the apparent hemispheric differences in autonomic control [Barron 1994, Naver 1996, Robinson 1997a]), or stroke severity on CA, nor look at the affect of CA on prognosis. In addition, only a dynamic depressor test, and two static pressor tests have been studied, and it may be that the control of depressor and pressor changes is different; certainly regarding CR there is evidence of impaired vasodilatation to hypercapnia, but intact vasoconstriction to hypocapnia in the early hours in normal subjects [Ameriso 1994].

6.8 CONCLUSION:-

In conclusion, it would appear that acute ischaemic stroke is associated with impairment of dynamic but not static cerebral autoregulation. This has important clinical implications for the future management of blood pressure in the acute phase of ischaemic stroke, especially since the author has also shown that increasing BP levels and BPV are associated with an increased risk of death/dependency. Further study into this exciting and promising area is needed to confirm these results, and explore therapeutic interventions.

PARAMETER	STROKES (n=54)	CONTROLS (n=61)	2 SAMPLE T-TEST
Age (years)	69 ± 12	67 ± 10	NS
Gender (M:F)	31 : 23	35 : 26	NS
BMI (kg/m^2)	26.2 ± 5.8	26.6 ± 3.6	NS
24 hour SBP (mmHg)	150 ± 21	132 ± 14	0.0001
24 hour DBP (mmHg)	85 ± 14	79 ± 10	0.023
24 hour HR (bpm)	74 ± 13	72 ± 8	NS
Casual SBP	165 ± 26	150 ± 20	0.0013
Casual DBP	89 ± 16	87 ± 13	NS
Mean beat-to-beat SBP (Finapres)	159.3 ± 31.5	145.9 ± 23.1	0.023
Smoking status (% non/ex/current)	26 : 56 : 18	51 : 38 : 11	0.021
Alcohol (units/week)	9.5 ± 10	10 ± 13	NS
Affected hemisphere MCAV (cm/s)	33.94 ± 9.32	39.5 ± 8.5	0.0024
Non-affected hemisphere MCAV (cm/s)	33.89 ± 8.37	39.5 ± 8.5	0.0012
History of hypertension (%)	50	21	<0.05
History of IHD (%)	18	2	<0.05
Insonation depth (cm)	5.15 ± 0.5	4.9 ± 0.45	NS

Table 6.1:- Comparison of cerebral infarct groups and control subjects characteristics.

Results presented as mean ± s.d.

BP STIMULUS	STROKES	CONTROLS	2 SAMPLE T-TEST
Magnitude of change (mmHg)			
Thigh cuff release	-21.2 ± 11.3	-20.6 ± 9.5	NS
Isometric hand grip	17.1 ± 6.0	17.8 ± 7.8	NS
Thigh cuff inflation	22.1 ± 12.1	20.0 ± 9.4	NS
Rate of change (mmHg/s)			
Thigh cuff release	-2.7 ± 1.6	-3.0 ± 1.3	NS

Table 6.2:- Comparison of inter-group blood pressure stimuli used to test cerebral autoregulation.

Results presented as mean ± s.d.

TEST	STROKE Non-affected hemisphere (NonS)	STROKE Affected hemisphere (S)	CONTROLS	2-sample t-test NonS	2-sample t-test S	General Linear Model NonS	General Linear Model S
DYNAMIC TEST ARI							
Thigh cuff release (n=41,37,48)	4.81 ± 3.08	4.09 ± 3.32	6.18 ± 2.34	0.022	0.0018	0.011	0.000
STATIC TESTS ARI (%)							
Isometric hand grip (n=37,36,45)	57.8 ± 31.1	59.0 ± 34.0	51.5 ± 36.9	NS	NS	NS	NS
Thigh cuff inflation (n=36,35,45)	65.9 ± 37.5	54.1 ± 36.5	52.2 ± 36.9	NS	NS	NS	NS

Table 6.3:- Comparison of patients and controls dynamic and static test ARI's.

Results presented as mean ± s.d.

n=number of stroke subjects (non-affected, affected hemisphere), and control subjects with ARI results. Some subjects were excluded because of data selection criteria (see Data analysis).

Significance level $p < 0.05$ for differences between strokes and controls.

CHAPTER 7

CONCLUSIONS OF THESIS.

The aims of this thesis were two fold. Initial studies were devised to investigate the effect of acute ischaemic stroke on different parameters of blood pressure and beat-to-beat blood pressure variability as derived from a single 10 minute recording period, to see if these parameters could be used to predict outcome. The second part of the study investigated whether the initial findings of a poor prognosis associated with increased blood pressure variability could be explained by abnormalities in cerebral autoregulation. The non-invasive measurement of cerebral autoregulation was studied in both a healthy control population and in patients with acute ischaemic stroke to examine the effect of this pathological state on this intricate physiological process. This concluding chapter will summarise the author's findings, and their implications for future clinical practice and continuing research.

7.1 SUMMARY OF RESULTS:-

Chapters 1 and 2 reviewed the literature regarding the changes in cerebral blood flow, cerebral autoregulation, and blood pressure that occur following acute stroke. They examined the different methods available for measuring these parameters, and reviewed our present knowledge regarding the effect of varying subject demographic characteristics and pathological conditions on these factors. It was evident that the methodology varied widely, particularly with regard to assessment of cerebral blood flow, previously applied methods having a poor temporal resolution and consequently being only able to examine changes in cerebral blood flow occurring over a prolonged period of time, i.e. static changes. The advent of transcranial Doppler ultrasonography [Aaslid 1982], has revolutionised the study of cerebral blood flow and cerebral autoregulation allowing the response to both rapid, i.e. dynamic and more prolonged, i.e. static changes in blood pressure to be assessed. In addition, the initial tests that described the measurement of cerebral autoregulation with transcranial Doppler ultrasonography employed invasive blood pressure manipulation [Tiecks 1995a], which restricted their use in large patient groups.

The literature review also revealed that it is less than clear as to the exact nature of the changes in the various blood pressure parameters that occur in acute stroke, and whether these parameters are important in terms of prognosis. Previous work has shown that beat-to-beat blood pressure variability is increased following acute ischaemic stroke [Robinson 1997a], along with a reciprocal impairment of cardiac baroreceptor sensitivity [Robinson 1997b], and an impairment of the vasomotor arm of the baroreceptor reflex arc [Robinson 1995, 1997c]. This increased blood pressure variability post-stroke may be prognostically important by increasing the size of the ischaemic penumbra, especially if dynamic cerebral autoregulation was also impaired following stroke. Chapter 3 reported the effects of different measures of blood pressure and beat-to-beat blood pressure variability measured within 72 hours of ictus on 30 day outcome. It also examined the effect of stroke type on these results. Unlike the authors previously published work regarding diurnal blood pressure change and stroke subtype [Dawson 1998a], blood pressure and blood pressure variability were not influenced by infarct type; however, cortical infarcts had an increased risk of death/dependency at 30 days compared to subcortical and posterior circulation infarcts. An increase in death/ dependency at 30 days was also seen with an increase in blood pressure levels and blood pressure variability with an increased risk of 38% for every 10mmHg increase in mean arterial blood pressure, and of 32% for every 1mmHg increase in mean arterial blood pressure variability. Although all mean blood pressure levels were increased in those subjects with the poorer outcome, only diastolic and mean arterial blood pressure variability influenced prognosis, but overall these two parameters were the strongest predictors of outcome. Dividing the patients into blood pressure quartiles and each group into high and low variability subjects [Palatini 1992] also demonstrated that those subjects with high diastolic or mean arterial blood pressure variability were significantly more likely to be dead/dependent at 30 days post-ictus. These results add further weight to the suggestion that there is impairment of the central modulation of the autonomic nervous system following acute stroke.

This poor outcome with increasing blood pressure levels and blood pressure variability is of great interest as these parameters are open to potential therapeutic manipulation. However, it is unclear as to the mechanisms by which they are associated with a poor outcome. One attractive hypothesis is that increased blood pressure variability may compound the damage to the ischaemic penumbra if cerebral autoregulation truly is impaired in acute stroke, especially in response to rapid changes in blood pressure. The author then studied the changes in cerebral autoregulation post stroke to test this hypothesis.

The author aimed to adapt previously reported non-invasive techniques for the measurement of both static and dynamic cerebral autoregulation to a healthy control population, and a group of patients with acute cerebral infarction.

In chapter 4 the reproducibility of various methods of assessing cerebral autoregulation was undertaken. Dynamic CA was assessed using 4 pressor, and 4 depressor stimuli; static CA with 3 pressor and 1 depressor stimulus. The blood pressure responses to the various stimuli used in the tests of cerebral autoregulation varied with time and between tests, but there are few data available on the reproducibility of the blood pressure stimuli evoked by these non-invasive tests to enable a direct comparison. The magnitude of the blood pressure change for thigh cuff release was equivalent to that previously reported [Aaslid 1989], but in other studies using similar stimuli the coefficient of variance was smaller than the author found [Parati 1983,1985]. However, these differences are likely to be at least in part due to the fact that each test was only performed once in this set of studies, and that the number of subjects studied was relatively small.

Chapter 4 also explored the use of different mathematical modelling techniques (correlation coefficient and critical closing pressure), combined with different window lengths to calculate dynamic cerebral autoregulation. It was felt that reproducibility could not be assessed using the usual method of comparing two

medical tests, [Bland and Altman 1986], because of difficulties in interpreting the rating of the autoregulation index. This index is graded 0-9 [Tiecks 1995a], a change between visits from 1-2 may not be clinically relevant but would lead to a coefficient of variation of 100%! By using the size of the absolute difference in autoregulation index the results between the two visits were found to vary quite considerably depending on the test stimulus used, the length of the data window, and the mathematical model employed to calculate the autoregulation index. Overall it appeared that using a correlation coefficient combined with a 30s data window led to the smallest differences. For static autoregulation indices all the tests yielded similar intervisit differences.

As previously mentioned cerebral blood flow velocity, and consequently cerebral autoregulation measurements, may be affected by subject characteristics such as age, blood pressure, and gender. These possible effects were examined in Chapter 5, along with interhemispheric differences. Neither static or dynamic tests identified any interhemispheric differences, as would be expected in a healthy control population; therefore, to increase statistical power data from both hemispheres were combined to investigate the influence of subject characteristics on autoregulation indices.

The autoregulation indices in response to both static and dynamic stimuli appeared to be influenced by different subject characteristics, e.g. blood pressure; however, the size of this interaction varied considerably. Although the static tests yielded autoregulation indices comparable with previous studies [Tiecks 1995a], those calculated using the different dynamic tests were not readily interchangeable, even between pressor and depressor stimuli. Because of the apparently marked differences between tests it was not considered justified to formally assess whether there was a significant difference between the responses to the various depressor or pressor stimuli. Perhaps more importantly these results indicate that previous assumptions of a 'normal' dynamic autoregulation index need reconsidering as

values appear to depend on the type of stimulus used and the method of inducing that stimulus. This has important connotations when comparing results from different centres, and if a reference range for prognostic use is to be developed, e.g. for patient selection for carotid endarterectomy [White 1997].

Combining the results from chapters 4 and 5 the author concluded that it was feasible to study cerebral autoregulation non-invasively, and that these tests could be conducted in a patient group. However, in view of the variations between different tests as noted above the author decided to limit further studies to using thigh cuff release for the assessment of dynamic cerebral autoregulation, and the inflation of thigh cuffs and isometric handgrip for the assessment of static cerebral autoregulation. In addition the use of thigh cuff release and inflation meant that both dynamic and static cerebral autoregulation could be examined without the need for subject co-operation, a factor of potential importance in the patient group.

Chapter 6 presents the results of the study comparing cerebral autoregulation in an acute CT proven ischaemic stroke population within 96 hours of ictus, to an age, sex, and body mass index matched control group. Importantly the blood pressure stimuli used for the three tests were not significantly different between the two groups. Similarly there was no difference in the static autoregulation indices, derived by either technique, between the controls, and the affected or non-affected stroke hemispheres. This is contrary to previous work reporting impaired static cerebral autoregulation in chronic stroke; it may reflect the better resolution of the newer tests, but for the present must be interpreted with some caution. However, for dynamic cerebral autoregulation there was a significant reduction in the autoregulation indices for both hemispheres in the stroke group compared to the control population, even after potential intergroup differences which may have influenced the autoregulation index were statistically controlled for. This result implies that there is global impairment of dynamic cerebral autoregulation after ischaemic stroke, and further implies that static and dynamic cerebral

autoregulation are distinct entities. The mechanisms accounting for these differences were not the subject of this thesis but an attractive explanation is that dynamic cerebral autoregulation is under greater influence from the autonomic nervous system than static cerebral autoregulation.

7.2 STUDY LIMITATIONS:-

The author has attempted to highlight the limitations of these studies in each chapter, and has mentioned some of them in the above summary. It must be reiterated that the second part of the study was designed to explore the potential for studying cerebral autoregulation non-invasively in a patient group, and that due to this some of the experimental design was not ideal but was intended to test whether such a study would be possible in day-to-day clinical practice.

Consequently, one of the main criticisms regarding the techniques used for measuring cerebral autoregulation is that each test was performed only once in each subject; this meant that a considerable amount of data were rejected as unsuitable for final analysis. Combined with the limited reproducibility of the tests employed and the small number of subjects that the author was able to examine during the period of the study, the statistical power of the study was weakened. Therefore, the negative findings relating to static cerebral autoregulation in acute ischaemic stroke have to be interpreted with caution. Similarly only a depressor dynamic test and pressor static tests were studied; further work is needed before it can be assumed that the response to pressor dynamic and depressor static stimuli are equivalent.

Because of the above limitations the study was also unable to examine the influence of stroke site or severity, or the difference between acute (<96 hours post-ictus) and subacute (7-10 days post-ictus) phases of stroke on cerebral autoregulation. Nor was it possible to examine the relation between autoregulation and prognosis.

The study also employed rigorous selection criteria so that a considerable proportion of stroke admissions were excluded from study; however, this is probably not a negative feature of the study, but means caution may be needed in the extrapolation of these results to all stroke patients.

7.3 CLINICAL IMPLICATIONS:-

The results of this thesis have important potential therapeutic implications. The initial experimental chapters showed that important prognostic information could be obtained from just 10 minutes of blood pressure recording. This has great potential in routine clinical investigation. This finding of a worse prognosis with increasing blood pressure levels and blood pressure variability has implications the management of blood pressure following acute ischaemic stroke. Trials into acute blood pressure manipulation could be based on this short duration of recording that is easily obtained and very well tolerated, enabling large numbers of patients to be studied in a short period of time. The subsequent finding of impaired dynamic, but not static, cerebral autoregulation implies a possible explanation for the prognostic significance of this increased blood pressure variability. Further work into the effect of a static depressor blood pressure stimulus on cerebral autoregulation in acute stroke patients is needed, as these results imply that the gradual reduction of blood pressure by pharmacological means may not necessarily be harmful. Nevertheless, any agent employed should be introduced with caution so that subjects remain on the autoregulatory curve, and do not loose their static cerebral autoregulation. In addition, ideally an agent that doesn't affect cerebral blood flow, and improves blood pressure variability should be investigated, as these two characteristics are likely to minimise further damage to the ischaemic penumbra. There is evidence to suggest that centrally acting agents may have a more positive affect on blood pressure variability [Prattichizo 1994], and that angiotensin converting enzyme inhibitors, as well as not being detrimental to cerebral blood flow, may improve cardiac baroreceptor sensitivity and consequently reduce blood pressure variability [Egan 1993].

If an agent were identified that improved clinical outcome simply, without the need for expensive and invasive monitoring or expert intervention, then theoretically the increasing burden of acute stroke on patients, carers, the National Health Service, and the economy could be reduced. The time for a well designed randomised clinical trial of acute antihypertensive therapy is here.

7.4 FUTURE STUDIES:-

The results of these studies have identified considerable areas for further research:-

a). Future research into blood pressure manipulation needs to consider the effects of treatment not only on mean blood pressure levels but on blood pressure variability in terms of beat-to-beat changes. It may be that reducing blood pressure variability per se may be as if not more important than reducing mean blood pressure levels.

b). Further work is needed to improve the reproducibility of both the static and dynamic tests used in terms of both their methodology and the mathematical modelling used to assess autoregulation. This will allow confirmation of the above results, may lead to further information regarding the different mechanisms underlying dynamic and static cerebral autoregulation, and the response to pressor and depressor stimuli, particularly static depressor stimuli, and will lead to a clearer definition of a 'normal' autoregulation index value. In addition newer mathematical models for assessing autoregulation, e.g. impulse response, a method which involves examining the effect of blood pressure transients (spontaneous beat-to-beat blood pressure changes), on cerebral blood flow may be better in terms of reproducibility, as well as being more generally agreeable as they do not require any intervention in terms of inducing a blood pressure change, or subject co-operation. It may also be possible to use these newer methods to examine the physiological mechanisms behind cerebral autoregulation, e.g. metabolic and endothelial factors.

c). Further information is required regarding the influence of hypertension and other cardiovascular risk factors, e.g. ischaemic heart disease, on autoregulation in the non-stroke population.

d). These refined tests could then be used in a large stroke population to examine the influence of stroke site, and stroke severity on autoregulation, and subsequently the potential role of this parameter as a method of predicting prognosis.

e). These techniques could also be used to assess the influence of antihypertensive agents, preferably agents improving blood pressure variability, and other treatments on cerebral blood flow and cerebral autoregulation.

f). The logical 'conclusion' of these studies would then be to extrapolate this pathophysiological information to the study of potential therapeutic agents, e.g. angiotensin converting enzyme inhibitors or centrally acting agents, to see whether they beneficially influence outcome through an effect on either blood pressure, blood pressure variability or cerebral autoregulation. Hopefully this would identify a simple, cheap and above all effective acute stroke therapy.

7.5 CONCLUSIONS

This thesis has shown that increased blood pressure levels and blood pressure variability are associated with a poor 30 day outcome following acute ischaemic stroke. It has also been feasible to study both static and dynamic cerebral autoregulation non-invasively in a healthy stroke-aged population; and that compared to this control group acute ischaemic stroke patients appear to have impaired dynamic but not static cerebral autoregulation. This difference may be related to central damage of the autonomic nervous system. In conjunction with changes in blood pressure variability this may lead to further damage to the ischaemic penumbra, and a poor prognosis. Further studies are needed to confirm these findings, and to assess the prognostic significance of these changes in cerebral autoregulation post-stroke. These simple non-invasive techniques of assessing blood pressure variability and cerebral autoregulation in the acute stroke period should allow more detailed study of innovative acute therapeutic interventions.

APPENDICES

APPENDIX 1 :- STROKE CLASSIFICATION AND STROKE SCALES

1.1.Oxfordshire Community Stroke Project (OCSP) Clinical Classification of Stroke.

Total Anterior Circulation Stroke Syndrome (TACS).
All of:- Hemiplegia contralateral to the cerebral lesion.
Hemianopia contralateral to the cerebral lesion.
New disturbance of higher cerebral function (e.g. dysphasia, visuospatial disturbance).

Partial Anterior Circulation Stroke Syndrome (PACS).
Any of *:- Motor/Sensory deficit & hemianopia.
Motor/Sensory deficit & new higher cerebral dysfunction.
New higher cerebral dysfunction & hemianopia.
Pure motor/sensory deficit less extensive than for LACS (e.g.monoparesis)
New higher cerebral dysfunction alone.

* When more than one type of deficit is present, they must all reflect damage in the same cerebral hemisphere.

Lacunar Stroke Syndrome (LACS).
Definition:- Maximum deficit from a single vascular event.
No visual field deficit.
No new disturbance of higher cerebral function.
No signs of brainstem disturbance*.

Categories:- Pure motor stroke (PMS).
Pure sensory stroke (PSS).
Ataxic hemiparesis (including dysarthria. clumsy-hand syndrome, and homolateral ataxia and crural paresis.
Sensory-motor stroke† (SMS).

* In the future some brainstem syndromes may be reclassified as LACS.

† To be acceptable as a PMS, PSS, or SMS, the relevant deficit must involve at least two out of three areas of the face, arm and leg, and, with particular reference to the arm, should involve the whole limb and not just the hand.

Posterior Circulation Stroke Syndrome (POCS).

Any of:- Ipsilateral cranial nerve palsy (single or multiple) with contralateral motor and/or sensory deficit.

Bilateral motor and/or sensory deficit.

Disorder of conjugate eye movement (horizontal or vertical).

Cerebellar dysfunction without ipsilateral long-tract deficit (as seen in ataxic hemiparesis).

Isolated hemianopia or cortical blindness.

1.2.The National Institute of Health (NIH) Stroke Scale.

Level of consciousness:

0 = Alert, keenly responsive

1 = Drowsy, but rousable by minor stimulation to obey, answer, or respond

2 = Stuporous, require repeated stimulation to attend, lethargic or obtunded, requiring strong or painful stimulation to make movements

3 = Coma, respond only with reflex motor or autonomic effects, or unresponsive.

Level of consciousness questions:

Ask patient the month and his/her age. Score for the first answer.

0 = Answers both correctly

1 = Answers one correctly

2 = Both incorrect.

Level of consciousness commands:

Ask patient to open/close hand and eyes. Score if he/she makes unequivocal attempt.

0 = Obeys both correctly

1 = Obeys one correctly

2 = Incorrect.

Pupillary response:

0 = Both reactive

1 = One reactive

2 = Neither reactive.

Best gaze:

0 = Normal

1 = Partial gaze palsy; abnormal but not forced deviation

2 = Forced deviation/total gaze paresis.

Best visual:
Confrontation testing using finger movements, including double simultaneous stimulation. Use visual threat if consciousness or comprehension limit testing, Scoring '1' for any asymmetry demonstrated.

0 = No visual loss
1 = Partial hemianopia
2 = Complete hemianopia, to within 5 degrees of fixation.

Facial palsy:

0 = Normal
1 = Minor
2 = Partial
3 = Complete.

Best motor - arm:
Arms held for 10 seconds at 90 degrees if sitting, 45 degrees if lying. Grade weaker arm. Place arms in position if comprehension reduced.

0 = No drift after 10 seconds
1 = Drift after brief hold
2 = Cannot resist gravity, but some effort made
3 = No effort against gravity.

Best motor - leg:
While lying, patient to hold weaker leg raised at 30 degrees for 5 seconds. Place leg in position if comprehension reduced.

0 = No drift after 5 seconds
1 = Drift within 5 seconds
2 = Cannot resist gravity, falling to bed but some effort made
3 = No effort against gravity.

Plantar reflex:

0 = Normal
1 = Equivocal
2 = One extensor
3 = Bilateral extensor

Limb ataxia:
Finger-nose and heel-to-shin tests performed; ataxia is only scored if out of proportion to weakness. If total paralysis score as absent.

0 = Absent
1 = Present in leg or arm
2 = Present in leg and arm.

Sensory:
Tested with pin; only hemisensory loss scored. If comprehension or consciousness reduced, only score if obvious evidence.

0 = Normal
1 = Partial loss, subjectively different but still felt
2 = Dense loss, unaware of being touched.

Neglect:

0 = No neglect
1 = Partial neglect, visual, tactile, or auditory
2 = Complete neglect, affecting more than one modality.

Dysarthria:

0 = Normal articulation
1 = Mild to moderate dysarthria, slurring some words
2 = Near unintelligible or worse.

Best language:
Assessed from responses during evaluation.

0 = No aphasia
1 = Mild to moderate aphasia; nominal errors, paraphrasias, etc.
2 = Mute.

1.3.Canadian Neurological Scale.

Mentation:

Level of consciousness
3.0 Alert
1.5 Drowsy.
Orientation
1.0 Orientated
0.0 Disorientated, or not applicable.
Speech
1.0 Normal
0.5 Expressive deficit
0.0 Receptive deficit.

Motor function: weakness (no comprehension deficit).

Face
0.5 None
0.0 Present.

Arm, proximal
1.5 None
1.0 Mild
0.5 Significant
0.0 Total.
Arm, distal
1.5 None
1.0 Mild
0.5 Significant
0.0 Total.
Leg, proximal
1.5 None
1.0 Mild
0.5 Significant
0.0 Total.
Leg, distal
1.5 None
1.0 Mild
0.5 Significant
0.0 Total.

Motor response (comprehension deficit).
Face
0.5 Symmetrical
0.0 Asymmetrical.
Arms
1.5 Equal
0.0 Unequal.
Legs
1.5 Equal
0.0 Unequal.

1.4.Rankin Scale.

0 No symptoms at all
1 No significant disability, despite symptoms; able to carry out all usual duties and activities.
2 Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance.
3 Moderate disability; requiring some help, but able to walk without assistance.
4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention.

1.5.Barthel Index.

TASK	DESCRIPTION	SCORE
Feeding		
	Independent	10
	Food needs to be cut	5
	Dependent	0
Transfers bed to chair		
	Independent	15
	With minimal help	10
	Able to sit but maximum assistance to transfer	5
	Unable	0
Personal toilet:		
	Independent	5
	Needs help	0
Toiletting		
	Independent	10
	Needs help	5
	Unable	0
Bathing self		
	Independent	5
	Needs Help	0
Walking (or wheelchair)		
	Independent for 50 yards	15
	With help for 50 yards	10
	Wheelchair for 50 yards	5
	Unable	0
Ascend and descend stairs		
	Independent	10
	With help	5
	Unable	0
Dressing		
	Independent	10
	With help	5
	Dependent	0
Controlling bowels		
	No accidents	10
	Occasional accidents	5
	Incontinent	0
Controlling bladder		
	No accidents	10
	Occasional accidents	5
	Incontinent	0

APPENDIX 2 :- TRANSCUTANEOUS MONITORING OF BLOOD GASES: IS IT COMPARABLE TO ARTERIALISED EARLOBE SAMPLING?

Summary:

Researchers are increasingly looking for reliable non-invasive methods of assessing blood gas concentrations, and several new techniques have recently become available. Values derived using arterialised earlobe samples have been found to be comparable to conventional arterial samples, and recent studies have compared transcutaneous blood gas analysis with the traditional arterial samples and found a reasonable level of agreement in particular for the partial pressure of carbon dioxide. There are no data comparing oxygen and carbon dioxide partial pressures (pO2, pCO2) derived from arterialised samples with one of the newer transcutaneous techniques. We therefore simultaneously studied arterialised earlobe blood gas samples and values for pO2 and pCO2 obtained by a transcutaneous monitor (TINA, Radiometer, Copenhagen) in 26 subjects with varying blood gas values. There was a close agreement between the two methods for assessment of pCO2 (mean difference (95% C.I.) between transcutaneous and earlobe values 0.25kPa (-0.004, 0.5)), but not for pO2 (1.71kPa (0.35, 3.07)). Similarly, the limits of agreement were narrow for pCO2 compared to those for pO2 (-0.98, 1.47 and -6.44, 3.02 respectively). We conclude that transcutaneous measurement of pCO2 using the TINA is acceptable in the research setting, whereas, assessment of pO2 cannot reliably be made using this technique.

Introduction:

Researchers are increasingly looking for reliable non-invasive techniques to broaden the population they can reasonably study. As the role of carbon dioxide partial pressure (pCO2) on the modulation of many physiological systems is increasingly realised it is necessary to find ways to measure this easily and reliably for the duration of the study period, which may be several hours, and in a way

acceptable to the subject. We have, therefore, looked at different methods for the continuous measurement of blood gas tensions.

Traditionally blood gas analysis has involved arterial punctures either repeatedly performed or drawn from an indwelling arterial catheter. Both of these techniques can be distressing to the patient, and are not without associated complications [Bedford 1973, 1977, Machleder 1972, Downs 1973]. Arterialised earlobe blood samples are now more commonly used, and studies have found a good agreement between this technique and radial artery samples, especially for pCO2, although, there is dispute over its accuracy for measuring oxygen tension (pO2) [Pitkin 1994, Dar 1995, Sauty 1996]. Some of these differences can be explained by technical discrepancies, in particular the degree of arterialisation of the earlobe blood, and repetitive sampling can further adversely affect this.

Since the late 1950's electrodes that can assess O2 and CO2 transcutaneously have been developed [Severinghaus 1958]. More recently a combined sensor has been developed by Radiometer [Larson 1993] using both a Clark-type electrode and a Severinghaus-type electrode housed in the same casing to calculate pO2 and pCO2 respectively, the results of which are digitally displayed. A number of studies have compared the results of this and arterial samples [Sridhar 1993, Tremper 1981, Beran 1976, Carter 1989, Mahutte 1984, Brambilla 1985]. However, there are statistical criticisms with many of them, since they use correlation coefficients and regression plots to assess the agreement, therefore, making differences between the techniques (i.e. bias) difficult to interpret. Sridhar et al [1993], however, do use the statistical methods recommended by Bland and Altman [1986] for comparing two methods of clinical measurement, and found that agreement was again better for pCO2 than pO2.

To our knowledge there have been no comparisons of transcutaneous and arterialised methods. We, therefore, report a study comparing arterialised earlobe

blood samples and a transcutaneous pO2/pCO2 monitoring system (TINA, Radiometer, Copenhagen).

Methods:

26 subjects (14 female) were studied; 10 were healthy volunteers recruited from the hospital staff, the remaining were patients attending the respiratory physiology department for routine assessment of earlobe blood gases.

Subjects were asked to remove earrings if necessary, and Algipan was liberally applied to their left earlobe and massaged in to promote local vasodilatation and increased arterialisation of the blood. The transcutaneous monitor was applied using a similar method to that reported in previous studies [Sridhar 1993, Tremper 1981, Carter 1989, Mahutte 1984]. The subjects were sat upright in a chair and a small area at the top of their chest was cleaned with an alcohol wipe, and if necessary shaved, to enable a custom-made adhesive electrode holder for the TINA to be attached to their skin. A few drops of electrode fluid were then placed in the holder before the electrode was fixed in place and supported by a clip from the subjects clothing. The electrode had previously been calibrated off-line with a standard calibration gas of 5% CO2 and 20.9% O2, with adjustments for the barometric pressure being made; and its temperature was set at 45°C to promote local skin vasodilatation. The electrode was then left to equilibrate over the next 5 minutes.

A pulse oximeter was simultaneously applied to a finger on the dominant hand to measure SaO2. After 5 minutes the earlobe was cleaned and incised with a sterile scalpel blade, the arterialised blood was taken up by a heparinised capillary tube, and then analysed using a Ciba-Corning 280M blood gas analyser. Simultaneously the results of pulse oximetry and the TINA were noted.

All subjects had given informed consent to the investigation.

Statistical analysis:

Statistical analysis was performed using the Minitab 10 statistical computer package.

Results are presented as mean ± s.d.. The differences between the two methods are described as mean (95% C.I.) and also were assessed using the Student's paired t-test, along with limits of agreement as described by Bland and Altman. Regression analysis was performed to see if any independent factor, (e.g. age, arterial pO2), influenced these results.

Results:

10 healthy volunteers and 16 patients (14 female) with a mean age of 49.7 ± 14.3 years (range 27-71 years), and a variety of respiratory complaints were studied. The mean values of arterialised and transcutaneous pCO2 and pO2, along with oximetry results are given in Table 1. On earlobe blood gas values 3 subjects were hypercapnic (normal range 4.8-6.1 kPa), and 10 subjects were hypoxic (normal range 10-13.3 kPa).

The pO2 values from the two techniques were significantly different (p=0.001), with the TINA underestimating pO2 (mean difference 1.71kPa, 95% C.I. 0.35,3.07) and wide limits of agreement (-6.44,3.02kPa). The difference between the pCO2 readings was non-significant (p>0.05), although the TINA tended to overestimate the pCO2 result, (mean difference 0.25kPa, 95%C.I. -0.004,0.5); and the limits of agreement were narrow (-0.98, 1.47kPa). Oximetry results were similarly not significantly different (mean difference oximetry 0.72%, 95% C.I. -0.001,1.45), with narrow limits of agreement (-2.84, 4.28%). These results are presented graphically in Fig.1 as Bland-Altman plots.

On multiple regression analysis none of the independent variables entered, i.e. age, gender, earlobe pCO2/O2, pH, haemoglobin or bicarbonate concentration were independent predictors for the between method differences. As expected CO2, pH

and bicarbonate were significantly related, and there was a non-significant trend towards an inverse relation between pCO2 and pO2, which again was not unexpected in view of the case mix of subjects.

Discussion:

We report here a comparison between the TINA transcutaneous blood gas analyser and arterialised earlobe blood gas sampling, and demonstrate a non-significant difference and narrow limits of agreement for pCO2 measurement between the two techniques, although, there is a bias towards an overestimation with the TINA which must be considered. As in most studies comparing different methodologies we attempted to study a subject group with a wide spectrum of blood gas results, but our group did only contain a few people with pCO2 levels in the hypercapnic range (determined by earlobe sampling), so we cannot confidently say how reliable this method is for these patients, although these subjects did not appear to skew our results. However, our results do not indicate that this technique is acceptable for the measurement of pO2, with the two methods being significantly different ($p=0.001$) and the transcutaneous readings being much lower regardless of whether the earlobe values were in the normal or hypoxic range. As expected there was no significant difference between arterialised earlobe sampling oxygen saturation levels and those measured by the traditional non-invasive pulse oximeter.

Previous studies [Pitkin 1994, Dar 1995, Sauty 1996] have compared arterial and arterialised sampling and found mean differences for pCO2 from 0.07 to 0.21 kPa, which are comparable to the results we present here, although the results for pO2 are very different with mean differences of only -0.17 to 0.59 kPa. Sauty et al [1996], who found the poorer correlation for O2, felt that this was due to insufficient arterialisation of the earlobe, and with this in mind our Respiratory Physiology department proceeds to arterial sampling if there is a greater than 2% difference between the saturation of the earlobe sample and a simultaneous pulse oximetry measurement.

Sridhar et al [1993] compared arterial and transcutaneous measurements using a transcutaneous technique very similar to the one adopted in this study, and found that the mean difference for pCO2 was 0.02 kPa, and for pO2 0.08 kPa. They too showed a bias towards an underestimation of pO2 with the transcutaneous monitor. However, others have found, as we have, less good agreement for pO2 and the same bias, especially in situations of low capillary perfusion [Tremper 1981, Carter 1989, Mahutte 1984], e.g. Mahutte et al show a linear regression coefficient of only 0.57 between the two methods for pO2 assessment.

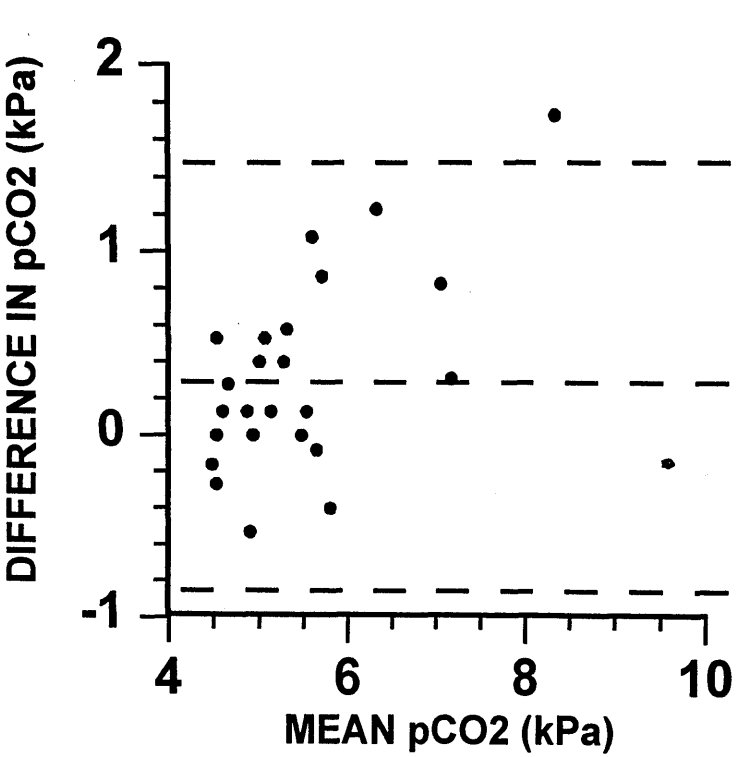
Some of the differences between our results and those of the other investigators mentioned here may have been improved by technical changes, in particular to the skin preparation. Dermatological studies [Berardesa 1993] have shown that skin thickness, stratum corneum barrier function and damage, blood vessel reactivity, arterial gas concentration, and skin and environmental temperature all influence transcutaneous gas flux. Others have shown the importance of temperature and posture especially in patients with peripheral vascular disease [Caspary 1993]. Better skin preparation with application of a vasodilator such as 'Algipan', plus more aggressive cleaning with an alcohol wipe to disrupt the stratum corneum, along with a longer run-in period to increase the local heating effect of the probe would probably improve the results for pO2.

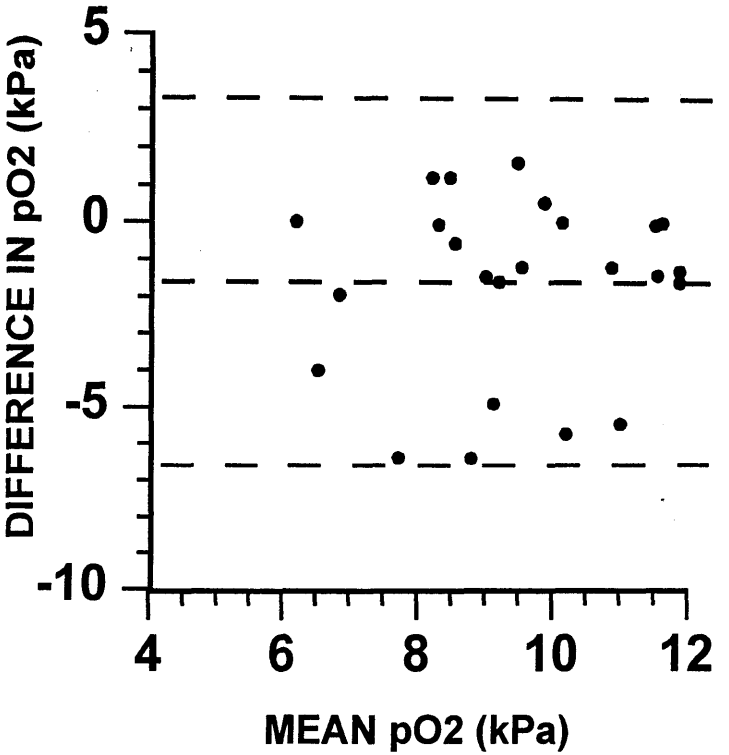
In conclusion, the TINA is a reliable non-invasive method for the assessment of pCO2. However, because its response time is at least 5 minutes (according to Radiometer), it is not suitable for studies where significant or transient changes in pCO2 are expected and need detecting. The results of this study do not support the use of this machine for assessing pO2 until technical details are improved and standardised.

Variable	mean ± s.d.
No. of subjects	26 (14F)
Age	49.7 ± 14.3 years
Earlobe pCO2	5.2 ± 0.8kPa
TINA pCO2	5.5 ± 1.2kPa
Earlobe pO2	10.6 ± 2.1kPa
TINA pO2	8.8 ± 2.3kPa
Pulse oximeter	95.8 ± 3.8%
Earlobe SaO2	95.1 ± 3.3%

Table 1: Baseline characteristics presented as mean ± standard deviation.

Fig1: Bland-Altman Plot of pO2 and pCO2 measurements.





APPENDIX 3 :- Publications arising from the Thesis

Transcutaneous monitoring of blood gases: is it comparable with arterialised earlobe sampling?
Dawson SL., Cave C., Pavord I., Potter JF..
Resp. Med. 1998;92:584-588.

Diurnal blood pressure change varies with stroke subtype in the acute phase.
Dawson SL., Evans SN., Manktelow BN., Fotherby MD., Robinson TG., Potter JF..
Stroke 1998;29:1519-1524.

Critical closing pressure explains cerebral haemodynamics during the Valsalva manoeuvre.
Dawson SL., Panerai RB., Potter JF.
J. Appl. Physiol. 1999;86:675-680.

Dynamic but not static cerebral autoregulation is impaired in acute ischaemic stroke.
Dawson SL., Blake MJ., Panerai RB., Potter JF..
Cerebrovasc Dis 2000;10:126-132.

Which parameters of beat-to-beat blood pressure and variability best predict early outcome following acute ischaemic stroke?
Dawson SL., Manktelow BN., Robinson TG., Panerai RB., Potter JF.
Stroke 2000;31:463-468.

Dynamic but not static cerebral autoregulation is impaired in acute ischaemic stroke. Dawson SL., Blake MJ., Panerai RB., Potter JF. (abstract).
Age and Ageing 1999;28(S1):44.

Does blood pressure variability affect stroke outcome?
Dawson SL., Manktelow BN., Robinson TG., Potter JF.. (abstract)
Cerebrovasc Dis 1999;9(S1):15.

Cerebral autoregulation in acute ischaemic stroke.
Dawson SL., Blake MJ., Panerai RB., Potter JF. (abstract)
Cerebrovasc Dis 1999;9(S1):95.

Dynamic cerebral autoregulation varies according to blood pressure stimulus.
Dawson SL., Blake MJ., Panerai RB., Potter JF. (abstract)
Cerebrovasc Dis 1999;9(S1):61.

Recent developments in the assessment of cerebral autoregulation.
Panerai RB., Dawson SL., Potter JF. (abstract)
Cerebrovasc Dis 1999;9(S2):12.

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