

The Cardiovascular and Cerebrovascular Changes following Acute Stroke and the Effects of Thiazide Diuretics

Doctor of Medicine Thesis.

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List of Abbreviations.

95% CI	95% confidence interval
ABPM	ambulatory blood pressure monitor
ACE	angiotensin converting enzyme
Ang	angiotensin
ARI	autoregulatory index
A-VDO ₂	arteriovenous oxygen difference
BP	blood pressure
BRS	baroreceptor sensitivity
CA	cerebral autoregulation
CBF	cerebral blood flow
CBFV	cerebral blood flow velocity
CCB	calcium channel blocker
CO ₂	carbon dioxide
CPP	cerebral perfusion pressure
CR	cerebrovascular reactivity
CT	computerised tomography
CVR	cerebrovascular resistance
DBP	diastolic blood pressure
ECG	electrocardiogram
FFT	fast Fourier transform
H ⁺	hydrogen ion
HF	high frequency (0.15-0.4 Hz)
ICP	intracranial pressure
IQR	interquartile range
K ⁺	potassium ion
LACS	lacunar stroke syndrome
L-NMMA	N ^G -monomethyl-L-arginine
LF	low frequency (0.05-0.15 Hz)
MAP	mean arterial pressure
MCA	middle cerebral artery
MRI	magnetic resonance imaging
mRS	modified Rankin scale
NHS	National Health Service
NIHSS	National Institute of Health stroke scale
NO(S)	nitric oxide (synthetase)
O ₂	oxygen
OCSP	Oxfordshire community stroke project
PACS	partial anterior stroke syndrome
pCO ₂	arterial carbon dioxide tension
PET	positron emission tomography
PI	pulse interval
POCS	posterior circulation stroke syndrome
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SHR	spontaneously hypertensive rat

SPECT	single photon emission tomography
TACS	total anterior circulation stroke syndrome
TCD	transcranial Doppler ultrasound
THC	thigh cuff
TIA	transient ischaemic attack
VLF	very low frequency (0.01-0.05 Hz)

Study Declaration

In accordance with University of Leicester requirements I detail here the contributions of the persons responsible for this thesis.

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

I was responsible for implementing the study proposal under their guidance.

For the work presented in Chapter 3: in addition to patients recruited and studied by the author (PE) (n=29 patients), cardiac baroreceptor sensitivity and outcome data was also obtained from Dr. Thompson Robinson (TGR), Senior Lecturer, Department of Medicine for the Elderly, University of Leicester and Dr. Suzanne Dawson (SLD), Consultant Physician, Leicester General Hospital (combined n=95 patients and n=62 controls).

For the work presented in Chapter 4: in addition to patients recruited and studied by myself (n=23 patients), Dr. Dawson also provided raw data on cerebral blood flow velocity, beat to beat blood pressure, ECG and transcutaneous carbon dioxide measurement (n=33 patients and n=56 controls) for inclusion in the analysis. The raw data were all reanalysed by the author to avoid bias in the manual selection of blood pressure stimuli.

For the work presented in Chapters 5 and 6: all patients and controls studied were recruited and studied solely by myself.

Professor David Evans and Dr. Ling Ke Fan developed the cerebral blood flow Doppler analyser used in processing the transcranial Doppler signals and Professor Ronney Panerai developed the software used in all of the analyses of indices of cerebral autoregulation, cardiac baroreceptor sensitivity and blood pressure and pulse interval variability.

Mr. Thomas Hotz provided statistical advice.

Ethical Declaration.

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

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Publications arising from this thesis

Eames P, Blake MJ, Dawson SL, Panerai RB and Potter JF (2002) Dynamic cerebral autoregulation and beat-to-beat blood pressure control are impaired in acute ischaemic stroke. *Journal of Neurology, Neurosurgery and Psychiatry* **72**, 467-472.

Robinson TG, Dawson SL, Eames PJV, Panerai RB and Potter JF (2003) Cardiac baroreceptor sensitivity predicts long-term outcome after acute ischaemic stroke. *Stroke* **34**:10.1161/01.STR.0000058493.94875.9F.

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1. **Introduction.**

Stroke, with its attendant high morbidity and mortality, is a major global healthcare problem. In most developed countries stroke is the third commonest cause of death after coronary heart disease and cancer with a prevalence of 5 per 1000 population and an annual incidence 2 per 1000 population, of which a fifth are recurrent events [17]. Closer to home, there are about 125,000 strokes per year in the UK [268]. Mortality rates from stroke have been falling over 20 to 30 years, possibly due to reduced incidence and severity of strokes and increased survival after the event [27]. Twenty five percent of strokes occur in those under 65 years of age and 50% in the over 75 year olds. Stroke is the commonest cause of neurological disability and is a huge clinical and financial burden on the health service in the UK, representing more than 15% of hospital bed occupancy and more than 5% of total NHS healthcare expenditure. The serious consequences and the high incidence of stroke mean that even small improvements in primary or secondary prevention, or in outcome will have dramatic benefits.

Following acute stroke systemic haemodynamics are abnormal with raised blood pressure (BP) levels, increased BP variability and reduced cardiac baroreceptor sensitivity (BRS). Cerebral haemodynamics, including cerebral blood flow (CBF), cerebrovascular reactivity (CR) and cerebral autoregulation (CA), are also abnormal following acute stroke. The impact of these abnormalities on outcome following stroke is unclear. Impaired cardiac BRS is already well established as an independent predictor of worse outcome in myocardial infarction [159] and its prognostic implications in acute ischaemic stroke are investigated in Chapter 3. In theory the impaired CA seen following acute stroke may allow large fluctuations in CBF driven

by changes in systemic BP and this might affect the viability of neurones in the critically underperfused ischaemic penumbra, increasing infarct size and worsening prognosis. In order to investigate this possible interaction a widely applicable, reliable method to measure CA is needed for both research and clinical purposes and the measurement of dynamic CA under resting conditions in acute ischaemic stroke patients is investigated in Chapter 4. Pharmacological lowering of BP in acute stroke has so far been the focus of only a few small studies mainly involving β -blockers and calcium channel blockers (CCB) [302]. In this work I present the results of 2 pilot studies investigating the efficacy of the antihypertensive bendrofluazide in the acute and subacute post-stroke periods, while making careful measurement of its effects on short term outcome and on some of the systemic and cerebral haemodynamic parameters mentioned above namely, BP and BP variability, CA and cardiac BRS. Thiazide diuretics have not been tested in acute stroke before and bendrofluazide was chosen in the present work because it is a widely used, well-tolerated, cheap and effective antihypertensive agent with a proven track record in primary and secondary prevention of stroke (see sections 1.6.7 and 1.6.8). In addition thiazide diuretics are not known to have any direct effect on cerebral haemodynamics (section 1.5.1). On admission to hospital, of the 40 % of acute ischaemic stroke patients already receiving antihypertensive medication, 69% are already taking thiazide diuretics (data from the Stroke Register for the University Hospitals of Leicester NHS Trust).

This thesis is concerned with the following questions:

- Do abnormalities in cardiac BRS in the early phase of ischaemic stroke predict short-term outcome (in terms of death or disability at <30 days) and/or long-term outcome (mortality)?

- Can abnormalities in dynamic CA in acute stroke patients be detected from spontaneous transient changes in BP?
- Does bendrofluazide, introduced early (26-118 hours) or later, (7 to 13 days) following ischaemic stroke have a significant hypotensive effect after one and four weeks respectively?
- What are the effects of such a treatment regime on CA (both static and dynamic), BP levels, BP variability and cardiac BRS?

In this introductory chapter I will outline the current understanding of CA processes followed by detailed discussion on stroke and its relation to BP, CA, and cardiac BRS.

1.1 Cerebral autoregulation (CA).

In order that CBF does not fluctuate excessively with changes in cerebral perfusion pressure (CPP), CA maintains CBF at a relatively constant level even when there are marked changes in CPP. Mean arterial pressure (MAP) levels can be taken as equivalent to CPP providing intracranial pressure (ICP) is not raised.

Cerebral autoregulation is effected through continual adjustment of cerebrovascular resistance (CVR), mainly at arteriolar level (vessel diameter <200µm) but is modulated by the larger cerebral arteries (vessel diameter >200 µm) [88] especially at higher BP levels [23]. A measure of CVR can be taken as:

$$\text{CVR} = \text{CPP}/\text{CBF} \text{ where } \text{CPP} = \text{MAP}-\text{ICP}$$

In man, large cerebral arteries contribute 20-30% of total CVR [88]. Under normal circumstances CA is effective between MAP limits 60-150 mmHg (figure 1.1a) [164],

but the pressure range and the relation between CBF and CPP depend on the state of

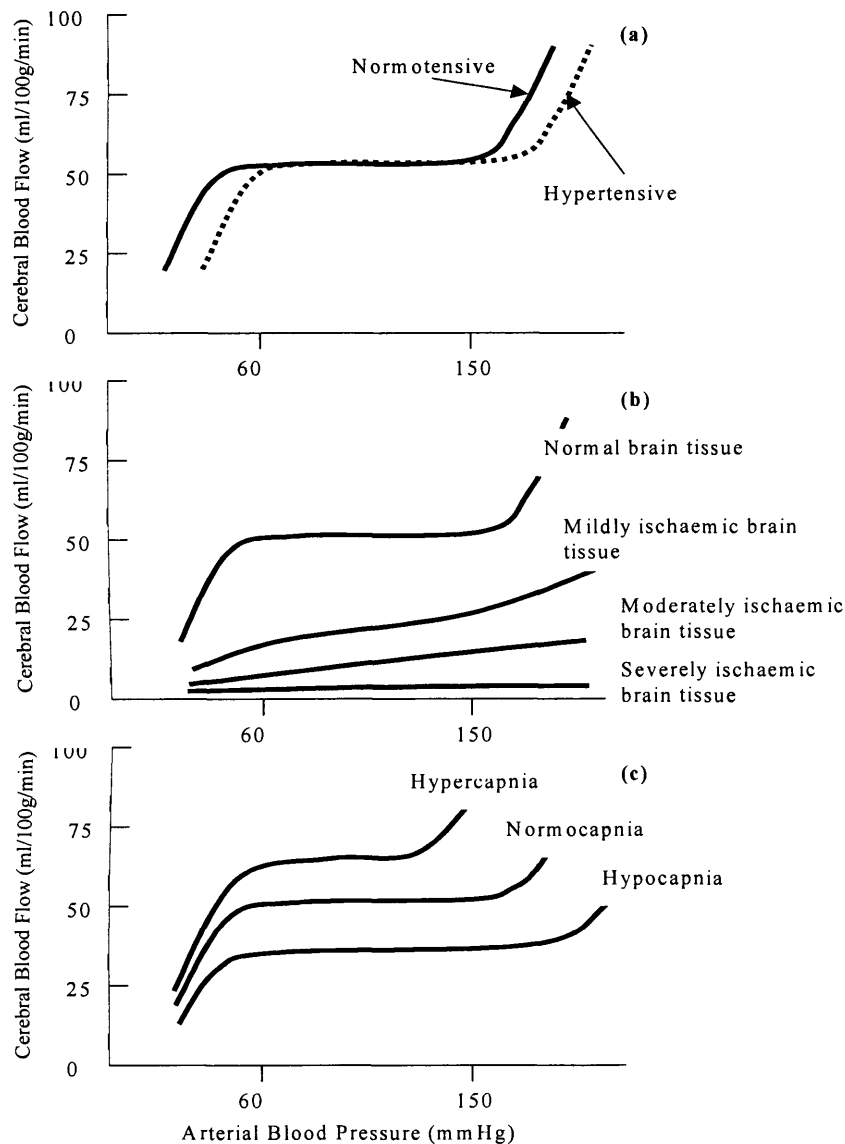


Figure 1.1 (a) Static autoregulatory curve, dotted line indicating shift with longstanding hypertension; (b) Effect of ischaemia on static autoregulatory curve; (c) Effect of CO₂ level on static autoregulatory curve.

the vascular bed [146]. The relationship between CPP and CBF becomes steeper and the range of CA narrower under conditions where the vascular bed is dilated e.g. hypercapnia, and the cerebral pressure-flow relationship becomes shallower and the range of CA wider when the cerebral vascular bed is constricted e.g. during hypocapnia (figure 1.1c) [146]. There is some evidence of regional heterogeneity in CA with more effective CA in the brainstem compared to the cerebellum or cerebrum

[23]. Cerebral autoregulation is likely to be controlled by several physiological responses working together and 2 ways to represent different aspects of CA have evolved. Static CA characterises the relationship between CBF and MAP in the steady state but, with normal CA, CBF is restored within a few seconds of a BP change [241] and dynamic CA includes measurement of the rate of recovery of the CBF immediately after the change in MAP. It is likely that the physiological mechanisms underlying the fast-acting phase of CA differ from those governing the steady state and that the measurement of static and dynamic CA will be reflecting these different processes. These physiological mechanisms are poorly understood but are discussed in section 1.12. Measurement of static and dynamic CA is discussed in detail in chapter 2 – Methodology.

1.1.1 History.

In 1902 Bayliss noticed local vasodilatation in response to lowering of perfusion pressure when a passive reduction in volume of denervated canine hind limb was followed by an increase in volume above baseline on restoration of normal perfusion, indicating vasodilatation had occurred. In 1931 the first evidence of pressure-regulation of CBF was found in pial vessels in cats by Fog [93] and in 1946 Selkurt proposed the concept of a lower limit of autoregulation below which flow was passively dependent on perfusion pressure. In 1959 Lassen drew together the results of over 200 studies of CBF and controlled hypotension in man and constructed the first version of the now classical graph representing CA in man (Fig 1.1a) [164], concluding that CBF remained relatively constant on an autoregulatory plateau with a lower limit at about 60 mmHg MAP and in the 1970s, the upper limit of 150 mmHg

was finally demonstrated in man. Below the lower limit of CA vasodilatation becomes inadequate and CBF becomes pressure passive although there is still a certain amount of vasodilatory reserve in the vessels until BP falls much lower. Pressure passive flow above the upper limit of autoregulation, when the resistance vessels are maximally constricted, forcibly dilates the vessels, damaging the arteriolar walls and breaching the blood brain barrier causing cerebral oedema.

Until the development, in the 1980s, of techniques with the ability to measure CBF or cerebral blood flow velocity (CBFV) with good time resolution only static CA could be measured. Transcranial Doppler ultrasound (TCD) enabled the time course of the CBFV (an accurate surrogate measure for CBF) response to rapid changes in BP to be included in the calculation of a dynamic autoregulatory index (ARI) [3]. Dynamic CA starts within 2 seconds of the pressure change and is completed in 10-15 seconds. It is likely the underlying physiology of static and dynamic CA is not identical and there is some evidence that the 2 are affected differently in disease states [60] and by some drugs [295].

1.1.2 Mechanisms.

The physiology underlying CA is poorly understood, but a combination of myogenic, metabolic, neurogenic and endothelial (particularly nitric oxide (NO)) mechanisms are likely [30;35;146;241].

1.1.2.1 Myogenic.

The myogenic contribution to CA refers to the reflex change in the tone of cerebral arteriolar smooth muscle in response to changes in transmural pressure. The vessels constrict and dilate with increasing and decreasing perfusion pressures respectively and the speed of action is consistent with that of CA, starting within seconds and complete within 15 to 30 seconds [241].

Bayliss first developed the myogenic hypothesis following an experiment on an isolated segment of carotid artery and it has subsequently been demonstrated, mainly in animal preparations, in the cerebral circulation [110]. In vivo, the relative contribution of the myogenic reflex to CA is difficult to define [146] but in feline preparations it was found to be a relatively small effect in comparison to the metabolic influence [323]. In vitro, where other mechanisms can be controlled for, the size of the myogenic effect seen in rats posterior cerebral artery preparations was thought to be less than 20% of that required for perfect flow regulation [110].

In humans isolated segments of human resistance arteries were seen to develop spontaneous intrinsic tone when intravascular pressure was artificially altered between 20-90 mmHg and the observation that this property was lost in the absence of extracellular calcium and retained in the absence of functional endothelium is highly suggestive that this is an inherent property of vascular smooth muscle [320].

1.1.2.2 Metabolic.

Global CBF is normally relatively stable at about 50ml/100g/min with regional variations corresponding to fluctuating metabolic requirements although, during seizures global CBF is very high [88] and in comatose states it is low [167;190;294] [2]. The metabolic theory of CA suggests that chemical vasodilators are released in

response to a change in CBF [241]. Various vasodilator metabolites have been suggested to explain this flow-metabolism coupling including the production, by neural cells, of hydrogen ion (H^+), potassium (K^+) or adenosine, their fluctuating concentrations in the extracellular fluid surrounding the brain arterioles resulting in changes in the arteriolar diameter and local CBF [35;146].

Systemic changes in CO_2 and hypoxia also increase CBF globally [35;148;241]. In severe hypoxia CBF is increased to all areas of the brain [164], although favouring grey matter over white matter [35;146] and this effect overrides the effects of hypocapnia [164]. Potassium ion concentration is raised immediately following electrical and physiological neuronal stimulation and adenosine levels also rise within seconds of brain activity such as seizures [35].

On a local level vasoneuronal coupling tightly regulates local CBF relating to neuronal activation via changes in the local concentration of vasodilator metabolites. Metabolism increases with neuronal activation, and oxygen (O_2) consumption and carbon dioxide (CO_2) production are in turn increased causing vasodilatation, increased flow and restoration of the metabolic balance [35]. Metabolism-flow coupling was originally assumed to be relatively slow, occurring over many seconds to minutes and so less likely to be involved in dynamic CA, but visually evoked dynamic blood flow responses in the human cerebral circulation were demonstrated to act within 5 seconds [2], and CBF changes within seconds in response to seizure activity [241]. Metabolic mechanisms may still play a significant role in both static and dynamic CA.

1.1.2.3 Neurogenic.

Perivascular innervation of cerebral vessels was first noted by Willis in 1664. It has subsequently been found that all cerebral arteries and arterioles, both intraparenchymal and extraparenchymal, are innervated by a network of nerve fibres arising in the periphery [114;241;267] with the larger vessels being most densely innervated. Most of the nerves are adrenergic but the α receptors (contractile) in the cerebral vasculature are much less sensitive to agonists and transmural nerve stimulation, compared to those found elsewhere in the body [119] and large arteries respond to sympathetic stimulation much more than the smaller arterioles [146] although responses are species dependent [120;146].

There is no evidence of resting tonic sympathetic control of CBF in a variety of animal species [120;146]. However, in severe hypertension in animals, all species studied showed sympathetic activation causing vasoconstriction of large cerebral arteries, extending the autoregulatory plateau towards higher levels and protecting the cerebral microcirculation from large increases in BP [146], but accompanied by small vessel constriction resulting in important effects on CBF [88]. In vivo in animals, total chemical denervation using tetrodotoxin had no apparent effect on CA [241] and in vitro cerebral vessels treated with tetrodotoxin retained a pressure-flow relationship after denervation. Vasomotor nerves may have a second order effect on CA by changing the tone of the cerebral vascular bed but were not thought to be required for CA [146].

Although extraparenchymal cerebral vessels have cholinergic innervation, intraparenchymal vessels do not, making a role in regulation of cerebrovascular tone unlikely [119].

Very little work in human volunteers regarding neural control of the cerebral circulation has been performed, but CBFV has been noted to decrease significantly in the absence of systemic hypotension during physiological manoeuvres known to increase sympathetic activity e.g. head-up tilt [26;170;339]. Also, dynamic CA was altered after ganglion blockade with trimethaphan, known to block both sympathetic and parasympathetic nerve activity, suggesting that there is a significant autonomic influence in dynamic CA [338].

Sympathetic stimulation via the superior cervical ganglion does, however, affect other parameters that influence cerebral haemodynamics causing a marked increase in cerebral blood volume, an increase in ICP and cerebrospinal fluid formation [241], resetting both upper and lower limits of CA to higher levels [29;241] and may attenuate CR [241] and increase metabolic demands.

In summary, there is little evidence of tonic nervous control of CBF in animal experiments and sympathetic stimulation, and denervation of the cerebral circulation has little effect on CBF and CA within normal autoregulatory limits. Certainly sympathetic stimulation can modulate microvascular pressure and increase both the upper and lower limits of CA, which is beneficial in acute hypertensive states but detrimental in haemorrhagic hypotension. In man, although there have been only a few small studies so far, there is some evidence to suggest some autonomic control of the cerebral circulation and a role in dynamic CA, although further work is needed to clarify this. There is little evidence for a significant role for the parasympathetic nervous system.

1.1.2.4 Nitric Oxide.

The vasodilator, NO, is produced locally when L-arginine is converted to NO by the one of the 3 isoforms of the nitric oxide synthetase (NOS) enzyme and the response of cerebral arteries to NO has been shown to be reduced in arteriosclerosis in primates [76].

Neuronal NOS (found in parenchymal neurones including perivascular nerves) and endothelial NOS (found in vascular endothelium) produce NO phasically and are activated by calcium ion transients, whereas immunological NOS (inducible) is expressed if cells, including neural cells such as astrocytes or microglia, are exposed to endotoxin or cytokines [127]. Nitric oxide has a role in the maintenance of basal cerebrovascular tone [127;324;326] and may play a part in CR, a role supported by most animal [127] but not human studies [326].

The role for NO in the cerebral vasodilatation associated with neuronal activation is also uncertain, with approximately half the animal studies finding attenuation of the response if production of NO is inhibited [127]. The little work so far in man has shown no change in the CBF response to neuronal activation provoked by learning a novel sequence of finger movements [324].

A small study involving human volunteers strongly suggests a role for NO in dynamic CA [327] where the recovery of the CBFV following a sudden fall in arterial BP was significantly slowed after inhibition of NO production compared to baseline. The few animal studies assessing the influence of NO on static CA have not convincingly shown any change in the lower limit of CA and have not assessed the upper limit of CA [127], but a small study involving cats did find static CA was impaired when L-NMMA was administered [145].

It has been suggested from rat experiments that regions of the brain with greater NOS activity have increased vulnerability to ischaemia [12]. Nitric oxide appears to have both protective and detrimental effects in ischaemic brain tissue with eNOS in the protective role causing cerebral vasodilatation, inhibiting platelet aggregation and inhibiting expression of redox sensitive genes, and nNOS contributing to cytotoxic injury through the formation of potent oxidants that damage both proteins and DNA. In summary, there is good evidence that NO is involved in basal cerebrovascular tone, and animal studies suggest a role in the vasodilatory response to hypercapnia and possibly also to neuronal activation, although human studies are very sparse to date and so far negative on both counts. NO has a complex role in ischaemic cell damage that may be protective or harmful. It is probable that atheroma inhibits the vascular responsiveness to NO and, although little work has been done so far on the place of NO in CA, early results suggest a possible role.

1.2 Cerebrovascular Reactivity.

Cerebrovascular reactivity is the CBF response to vasodilators e.g. arterial carbon dioxide tension ($p\text{CO}_2$) or acetazolamide and can be used to determine the vasodilatory reserve capacity of the cerebral vessels as an index of the integrity of intracranial haemodynamics. Cerebrovascular reactivity is moderated by instantaneous arterial BP [115] and, although CA and CR may both be impaired in disease states, they are not measuring exactly the same responses and in some circumstances e.g. in the ischaemic penumbra CR can remain intact even when CA is impaired, dissociated vasoparalysis.

1.3 Carbon Dioxide and Cerebral Autoregulation.

Hypercapnia causes vasodilatation and hypocapnia vasoconstriction, both profoundly affecting CVR and CBF, but prolonged exposure to high or low $p\text{CO}_2$ levels results in chronic adaptation with a return of CBF to baseline values [166]. By altering the tone of the vascular bed, changes in $p\text{CO}_2$ alter the characteristics of CA: hypocapnia tends to restore CA and widen the autoregulatory plateau [240], whereas hypercapnia weakens the autoregulatory responses, both static and dynamic, shifts autoregulation to higher BP levels, and narrows the autoregulatory plateau until at high $p\text{CO}_2$ it is lost [228] (section 1.1c).

1.4 Age, Gender and Blood Pressure and Cerebral

Haemodynamics.

Ageing is associated with stiffening of arterial walls [139;189] even in the absence of atherosclerosis [16] and the diameter of the large cerebral arteries increases but CBF is reduced [136;153;184], possibly in response to reduced metabolic demand [187]. Women appear to have higher CBF than men up to 60 years of age [184] and this may be hormone related. Some studies have demonstrated a reduction of CR with age [173] although other work only reported a reduced CR in post-menopausal compared to pre-menopausal women and no age related change in CR in men, also suggesting a hormonal influence [137;188]. An increase in the lower limit of the static CA curve with age was seen in animal studies [123] and dynamic CA has been shown to be unaffected by ageing in the age range 20-79 years [39].

The effects of sustained hypertension on cerebrovascular histological structure and haemodynamics have been extensively studied in both man and animals. Sustained hypertension causes remodelling of the small cerebral arterioles with a reduction in internal and external diameter and thickening of the vessel wall. Initially there are reversible changes with muscular hypertrophy and medial hyperplasia together with increased water and electrolytes in the vessel wall, but with longstanding hypertension irreversible changes occur, and connective tissue, elastin and fibrous proteins replace the degenerating muscular and elastic layers [20;75]. There may be regional heterogeneity in susceptibility to hypertensive damage within the brain with sparing of the brainstem as demonstrated in spontaneously hypertensive rats (SHR) [23].

The morphological changes increase CVR [141;210] and improve tolerance of the brain to hypertension by reducing vessel wall stress, hence protecting the resistance vessels. Long standing hypertension may also cause an element of reversible, functional cerebral vasoconstriction contributing to the marked increase in CVR [332].

Although early studies in man showed that the increase in CVR maintained CBF in sustained hypertension [141], more recent studies show a reduction in CBF in man [96;210] and SHR [96]. In a study including both treated and untreated hypertensive patients CBF was higher in the treated group suggesting that good BP control may preserve CVR and CBF [210], and CBF was maintained at the normal levels with good BP control in stroke-prone SHR [332]. No study so far has shown an improvement in the same individuals with antihypertensive treatment.

A meta-analysis of studies in man measuring the respiratory quotient for brain metabolism showed a smaller CO₂ yield for O₂ consumed in sustained hypertension that could indicate that cerebral metabolism had partly switched to other metabolic

pathways in addition to glucose e.g. ketones in response borderline ischaemia in parts of the circulation [74].

Sustained hypertension appears to reduce CR in both animal and human studies [91;177;197;332]. It is now well established that hypertension raises the lower limit of static CA [97;123;292;293] and there is some evidence to show that this may also be partly reversible in the early stages of hypertension if good BP control is achieved [123;289]. There is little information on the effect of sustained hypertension on the upper limit of static CA in man but in baboons this has been shown to increase in hypertension [291].

Few data have been collected on the effect of chronic hypertension on the efficiency of static CA within the autoregulatory limits, or on dynamic CA, but Lipsitz et al [173] reported that in young and elderly normotensives, and elderly treated hypertensives, CA was retained in response to an immediate postural fall in BP. However, the change in CBFV for a given change in MAP was smaller in the older groups with an apparently exaggerated CBFV response in the young group possibly due to greater cardioacceleration or higher critical closing pressure in the young group on standing.

Recently a small study comparing treated hypertensives with normotensive controls demonstrated no effect of treatment on dynamic CA [309] and data from this department also found intact dynamic CA in never treated hypertensive volunteers compared with age, sex and BP matched controls [83].

Systemic BP levels can usually be lowered by about 25% before the lower limit of CA is reached, below which increased O₂ extraction allows BP to be lowered by another 20-30% before any symptoms occur. Overzealous reduction of BP can occasionally cause cerebral ischaemia, especially in certain clinical situations such as: tight intra-

or extracranial arterial stenosis where there is already borderline ischaemia, following acute stroke, during the initial treatment in patients with accelerated hypertension and in the elderly [237].

1.5 Antihypertensive therapy and Cerebral Haemodynamics.

A large number of studies have been performed on both animal and human subjects to investigate the effect of the various commonly used antihypertensive drugs on cerebral haemodynamics.

1.5.1 Thiazide Diuretics.

Thiazide diuretics have been used as antihypertensives since 1957 and they inhibit of active reabsorption of sodium and chloride in the distal nephron increasing excretion of sodium and water and cause peripheral vasodilatation via a poorly understood direct action on the blood vessels [256]. They have several dose dependent side effects, notably hypokalaemia, hyperuricaemia, impairment of glucose tolerance and adverse effects on lipid profiles but the dose-response curve for BP is relatively flat [41;255] and the dose used in this study, 2.5mg daily, gives effective BP control with minimal side effects [41;255].

The onset of antihypertensive action of bendrofluazide occurs 3 to 4 days after the initial dose and, after 4 weeks treatment with bendrofluazide 2.5mg daily, a fall in BP was 11.3/8.7 mmHg was seen in a group of hypertensive volunteers aged 25-70 years (compared to a fall of 0.9/2.9 mmHg for a similar group receiving placebo) [41], and BP continued to fall over 12 weeks [41], a pattern also reported using bendrofluazide

1.25 or 5mg daily [118]. In patients with mild hypertension given bendrofluazide 10mg daily, the fall in BP was steepest in the first 2 weeks of treatment continuing more gradually for about 3 months, although the BP values recorded in the first fortnight were not published [201]. Thiazide diuretics have also been shown to restore night time fall in BP in hypertensive patients who have lost their circadian rhythm of BP and become so called 'non-dippers', a condition thought to be associated with end organ damage [243;313].

Thiazide diuretics were one of the most widely used agents, along with β -blockers, in early trials of antihypertensive treatment in the primary prevention of stroke and coronary heart disease and have been convincingly demonstrated to reduce the risk of both in hypertensive patients (see 1.6.7). They, and related diuretics, have also been shown to be effective in the secondary prevention of stroke in both normotensive and hypertensive patients (see 1.6.8).

Thiazide diuretics are not thought to have any direct effect on cerebral vessels and of the small studies of hypertensive patients taking hydrochlorothiazide most have not shown any significant change in CBF with up to 15 weeks of treatment [310] although one study reported slight changes in regional CBF [254;276]. The effects of thiazide diuretics on CA have not been studied before to the authors' knowledge.

1.5.2 Dihydropyridine Calcium Channel Blockers.

The dihydropyridine CCBs have vasodilator properties, both systemically and also affecting large cerebral vessels.

Studies showed acute intravenous administration of felodipine or nicardipine did not alter CBF in awake patients [249;305], but in patients under propofol anaesthesia,

nicardipine was found to impair both static and dynamic CA [85;85] possibly attributable to its potent vasodilating effect on the cerebral arterioles.

Chronic oral administration of dihydropyridine CCBs up to 12 weeks duration also did not have any significant effect on CBF in hypertensive [162;224;305] or normotensive [138] patients but in a study of 15 hypertensive patients randomised to 3 months treatment with lacidipine 4-6mg daily or hydrochlorothiazide 25-50mg daily, slight regional changes in CBF were seen with both treatments [275].

1.5.3 Beta Adrenoreceptor Blockers.

The effect of β -blockers on cerebral haemodynamics has been intensively studied and in patients with acute stroke and intracarotid propranolol significantly reduced CBF [186;191;192], and cerebral metabolism [192], but did not alter CR when CO₂ increased [186;191] although it did reduce CR to hyperventilation in those with acute hypertensive haemorrhage [186]. In dogs with primary intracerebral haemorrhage intravenous labetalol did not significantly affect the penumbral or distal CBF [252]. Chronic oral administration of propranolol may have a dose dependent effect as demonstrated in 31 hypertensive patients where CBF was unchanged in those taking <120mg daily but increased CBF at doses >120mg daily [99].

1.5.4 Angiotensin Converting Enzyme Inhibitors.

Angiotensin converting enzyme (ACE) inhibitors prevent the conversion in the lungs and in the vascular endothelium of angiotensin I to angiotensin II (AII), a potent vasoconstrictor with mineralocorticoid properties, which is also thought to have other

direct actions on the vasculature such as a role in remodelling and distensibility. In studies on SHR, CBF was unaffected but the lower limit of static CA was significantly lowered by administration of imidapril [37] and captopril [270], possibly mediated by the accumulation of bradykinins resulting from the inactivation of kinase degrading enzymes by the ACE inhibitors [299] in addition to the attenuation of large artery constriction by AII. In very small studies in man single doses of captopril, ramipril and enalapril did not alter CBF in normotensive volunteers [274], hypertensive patients with carotid artery stenosis [232] or in patients within 5 days of acute stroke [318], but lisinopril increased CBF in one group of normotensive, healthy young men [69]. A single dose of captopril 50mg also increased CR [274] whereas lisinopril did not [69]. Chronic administration of enalapril [94] or fosinopril [317] did not reduce CBF in hypertensive patients but, in hypertensive patients with a history of stroke more than 3 months before, alacepril increased CBF significantly in both hemispheres but more markedly in the diseased hemisphere although no control subjects were studied [203].

In acute ischaemic stroke patients (within 4 days of ictus) without severe carotid artery disease Dyker et al [81] showed there was no reduction of CBF with 2 weeks of perindopril treatment compared to placebo and work from the same group later showed no changes in CBF, either between stroke and non-stroke hemispheres or local to the lesion, or in CBFV in the middle cerebral artery (MCA) or internal carotid artery (ICA), with 2 weeks of perindopril treatment compared to placebo (14-62 days post-ictus) in patients with severe ICA disease [321]. Several very small studies of the effects of captopril in patients with severe congestive cardiac failure have shown initial CBF to be lower than normal at baseline and to improve with the ACE inhibitor therapy [238;239;253].

1.5.5 Cerebral Vasodilators.

Drugs such as sodium nitroprusside, hydralazine, dihydralazine and some CCBs cause cerebral vasodilatation such that CBF is maintained below the lower limit of CA in a patchy and uneven fashion. This is accompanied by a rise in intracranial pressure and loss of CA [294] and, therefore, these agents are best avoided in situations where there is raised ICP e.g. hypertensive encephalopathy and in acute stroke where they may cause 'steal' syndromes.

In summary, thiazide diuretics and CCBs seem to have little effect on CBF but the effect of β -blockers may depend on dose and route of administration. Calcium channel blockers may impair static CA and dynamic CA when give intravenously.

ACE inhibitors do not reduce CBF and may increase it in normal subjects, chronic stroke and severe congestive cardiac failure. They may improve CR, but do not impair CA in normal man, and in rats and a reduction in both the upper and lower limits of static CA.

1.6 Stroke.

1.6.1 Definition.

The WHO definition of stroke is a rapidly developing episode of focal (or global if referring to coma or subarachnoid haemorrhage) loss of cerebral function, with

symptoms lasting more than 24 hours or leading to death, with no apparent cause other than a vascular one.

It is a clinical definition and one relying on investigation to exclude other pathologies.

The main types of stroke in western societies are cerebral infarction (80%), primary intracerebral haemorrhage (10%) and subarachnoid haemorrhage (10%) but in China and Japan there is a higher proportion of primary intracerebral haemorrhage [322].

1.6.2 Cerebral Metabolism.

The brain has a high metabolic rate, heavily dependent on aerobic metabolism with tight metabolism–blood flow coupling. Other than under conditions of starvation, brain tissue relies solely on the oxidation of glucose to provide energy, in the form of adenosine triphosphate (ATP), for maintenance of the structural and functional integrity of neural cells. However, the brain has virtually no fuel stores and requires a continuous supply of glucose and O₂ to be delivered at an appropriate level. Providing that blood levels of O₂ and glucose are normal then regulation of delivery occurs by maintaining CBF in tune with metabolic needs with normal CBF of 50 ml/100g/min.

1.6.3 Pathophysiology of Ischaemic Stroke.

An ischaemic stroke occurs if the blood supply to an area of brain is obstructed long enough for irreversible cell damage to occur. It is usually the result of thrombus, thromboembolism, or severe prolonged hypotension or hypoxia, or hypotension in the setting of a critical arterial stenosis [269].

If the metabolic demands of the tissue are not met because of reduced CBF the consequences depend on the degree and duration of ischaemia that, in turn, is influenced by the collateral blood supply to that area. If CBF drops to 20-50 ml/100g/min increased O₂ extraction delays the onset of brain tissue hypoxia. Below 20 ml/100g/min consciousness and neurologic function persist but with reduced alertness, reaction time, accuracy and appropriateness, and the electroencephalogram and evoked potentials are abnormal. Between CBF of 10-15 ml/100g/min consciousness is lost and all cerebral electrical activity ceases and below 6 ml/100g/min there is massive release intracellular potassium and irreversible cell damage and the cascade of changes that eventually result in cell death are represented in figure 1.2.

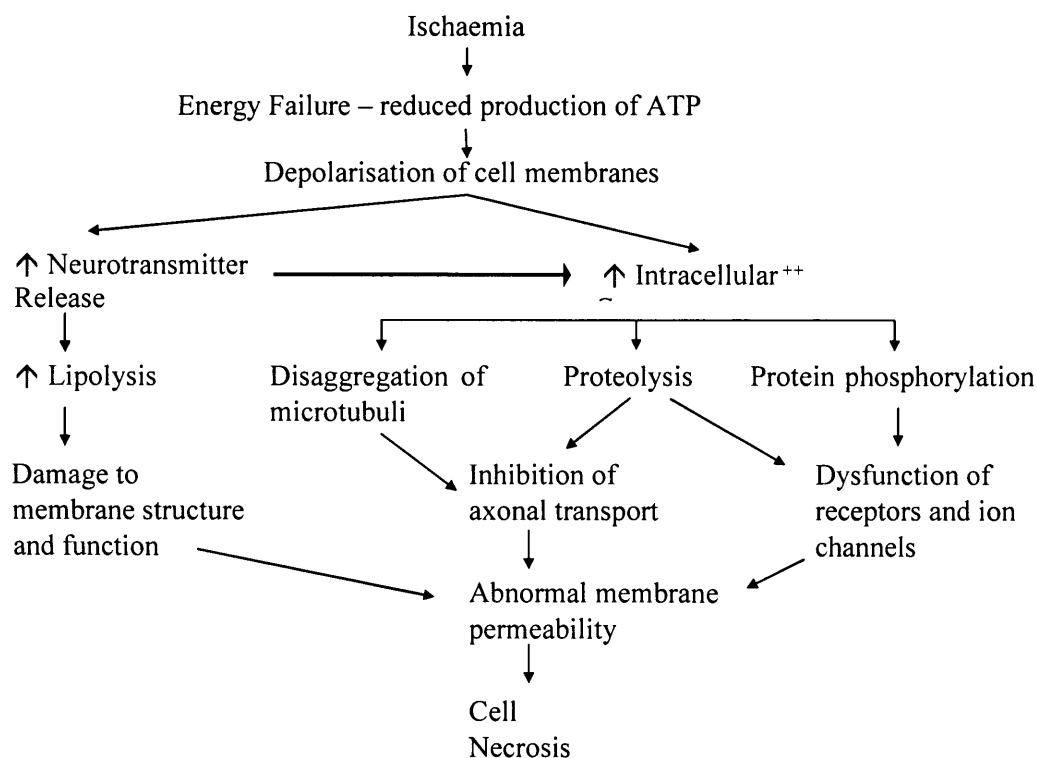


Figure 1.2 Diagrammatic representation of pathophysiological changes in ischaemic neuronal cell necrosis.

When cell wall integrity is breached, cytotoxic oedema forms and, as the cells break down, there is a massive release of intracellular K^+ (a potent vasodilator) and an acute local metabolic acidosis. Vasogenic oedema accumulates and in severe cases can cause brain shift and tentorial herniation. Stroke is a dynamic event in the early stages and begins with an immediate reduction in CBF in the occluded territory. If there are functional collateral vessels available they open up almost immediately and supply blood to part or, occasionally, all of the territory involved. Cerebral blood flow is highly abnormal in collaterally perfused brain tissue [218], which typically constitutes an area or rim of non-functioning but viable tissue, known as “the ischaemic penumbra” [14] where O_2 extraction is increased, CBF is low and CA is abolished although CR is usually retained to some degree. The period of viability of the ischaemic penumbra is under debate and, although presumably dependent on the prevailing conditions, it is generally thought to be of the order of a few hours [14] providing only a narrow therapeutic window for treatment such as thrombolysis. There is some evidence of a “chronic ischaemic penumbra” in a small minority of cases [15] and there are several case reports of improvement in long lasting neurological deficit immediately following surgical revascularisation suggesting suppression of function in viable neurones by chronic hypoperfusion [217;285]. If the occlusion improves within about 30 minutes there may be no permanent tissue damage [165] and normal CBF within 6 hours of ischaemic stroke is associated with a good prognosis [308].

It is thought that the majority of thromboembolic occlusions do clear or fragment and move downstream hours to days post-ictus following which, there is hyperaemia in about a third of infarcts with CBF increasing by 2 or 3 times the normal level for up to 2-3 weeks [8;183;206;217;219]. Excess flow beyond metabolic requirements, or

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‘luxury perfusion’, is probably due to an acute localised metabolic acidosis and there is total vasoparalysis in this region [166]. Subsequently CBF falls below the premorbid levels, possibly because of reduced metabolic demand in the damaged tissue [294] and low CBF and reduced static CA has been noted in baboons several years after infarction [298]. Ischaemic infarcts can undergo haemorrhagic transformation where there is bleeding into the infarcted zone, usually occurring after restoration of flow, and correlated to the severity and duration of ischaemia before reperfusion [217]. Clearly, the cerebral haemodynamics status in acute stroke is unpredictable.

1.6.4 Large Artery Disease.

The blood supply of the brain is shown in figure 1.3.

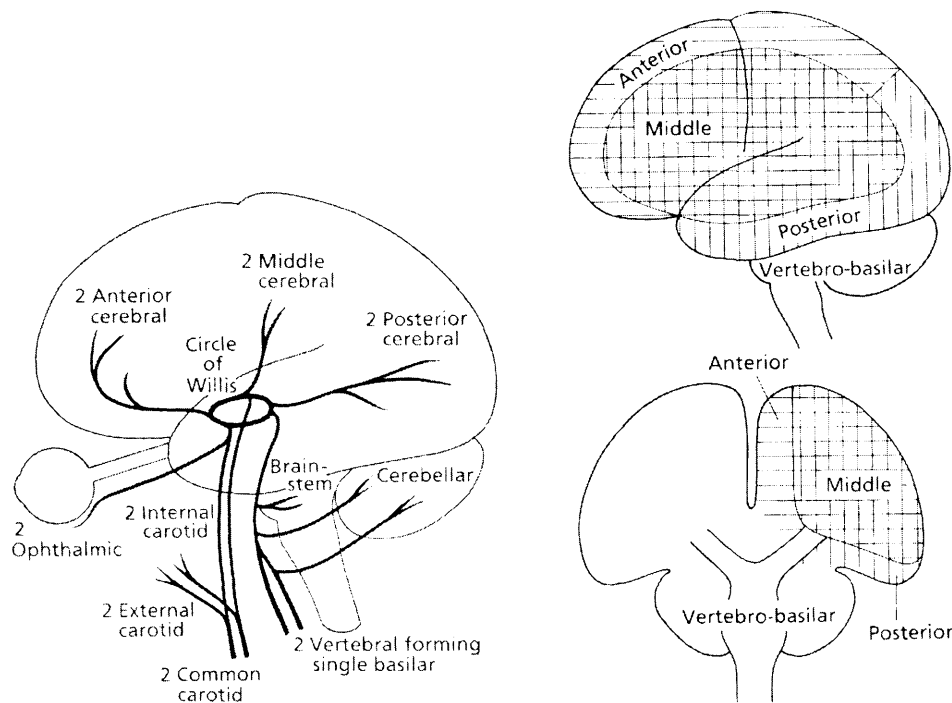


Figure 1.3 Arteries supplying blood to the brain (left panel). Regions of brain supplied by each of: middle cerebral artery (cross-hatched); anterior cerebral artery (horizontal lines); posterior cerebral artery (vertical lines); vertebro-basilar system (unlined) (right panel). Figure from Wilkinson [129].

Human atherosclerosis commonly affects the bifurcation of the common carotid artery, carotid siphon, Circle of Willis, proximal ICA, origin of the major arteries with the aorta, arch of the aorta, the origin and termination of the vertebral arteries and the proximal basilar artery. It is strongly influenced by hypertension [6;296], male gender, age, smoking [296], diet and genetics, and the earliest manifestation, the fatty streaks, are detectable even in teenagers in Western societies, although atherosclerosis is rare in China and Japan even in middle aged individuals.

The Circle of Willis is the basis for collateral blood supply between different areas of the brain and up to 60% of patients with complete ICA occlusion have no evidence of haemodynamic compromise because of flow through the Circle of Willis [71].

Atherosclerotic plaques impinge on the vessel lumen impeding blood flow and can reduce distal CPP and, depending on the quality of the collateral circulation, may cause reflex cerebral vasodilatation, increased O₂ extraction and impairment of CA [234;316] and CR [105;258;315;328] in the compromised tissue [71], which may [335] or may not [334] be more susceptible to stroke. Rupture of atherosclerotic plaque releases emboli, which are associated with an increased risk of stroke in both asymptomatic and symptomatic carotid artery stenosis [312]. In contact with blood, the thrombogenic plaque contents cause thrombosis in situ resulting in sudden occlusion of the vessel, and propagation of thrombus along the artery.

1.6.5 Small Vessel Disease.

Hypertensive disease of the small arteries and arterioles including microatheroma and lipohyalinosis predispose to small deep white matter infarcts known as lacunar infarcts that are caused by occlusion of single small deep perforating end-arteries

[272]. It is not yet clear whether hypertension is more predictive of lacunar infarction than other types but also appears to be particularly associated with age, diabetes and smoking [58].

1.6.6 Hypertension and Stroke.

Hypertension is the commonest and most powerful treatable risk factor for stroke [134] through its association with the development of vascular disease but also by producing a hypercoagulable state. In practice, untreated or undertreated hypertension means that there remains a large potential for the reduction of stroke risk. [140;144;200].

The relationship between hypertension and stroke, both ischaemic and haemorrhagic was first convincingly demonstrated by the Framingham data [236]. Atherothrombotic stroke was 7 times more frequent in those with hypertension than in normotensives, in both sexes, and the risk of stroke was proportional to the level of arterial BP throughout its range [134]. Both systolic and diastolic BP levels have been found to be predictive of stroke [134;135;176;181;251;278] but in older people, isolated systolic hypertension (ISH) is a more powerful risk factor than combined hypertension, whereas, in younger age groups combined hypertension carries more than twice the relative risk of stroke than ISH [246]. The risk of stroke attributable to hypertension falls with age suggesting other factors associated with ageing, such as cerebral vessel wall integrity, CA, increasing glucose intolerance, coagulation factors or physical inactivity become increasingly important [51]. A meta-analysis of 45 prospective observational cohorts involving 450,000 volunteers with 5-30 years of follow up reported that the risk of stroke attributable to diastolic hypertension was 5 times

higher in the age group <45 years compared with those >65 years old, although the absolute risk of stroke was actually 4 times higher in the older age group with more strokes occurring in those with a 'normal' BP [251].

Although most studies report a continuous relationship between BP and risk of stroke some have reported a 'J' shaped relationship between diastolic BP (DBP) and the incidence of stroke in treated but not untreated elderly hypertensive subjects [316].

The Systolic Hypertension in the Elderly Program (SHEP) also found an increased the risk of stroke, coronary heart disease and cardiovascular disease in the active treatment group when DBP was lower than 70 mmHg [284]. However, in a very large population (<10,000) of elderly volunteers an association between systolic BP (SBP) below 129 mmHg and increased risk of stroke was reduced if subjects with serious comorbidity were excluded [50]. The question of the 'J' shaped curve is still hotly debated because of the implications for the choice of target BP levels in treating elderly hypertensive patients.

Pulse pressure in elderly patients, which increases with arterial stiffness, has been found by some to be an independent risk factor for stroke [78] although a less good predictor than MAP although others found no association with stroke but a strong association with cardiovascular disease [314].

The relationship between BP and stroke in the very elderly is not so clear and the Hypertension in the Very Elderly Trial is currently in progress to address this question in the over 80's.

1.6.7 Blood Pressure Control and Primary Prevention.

Research has confirmed the benefit of BP reduction in the primary prevention of stroke related to the control achieved. A reduction in BP of 15/6 mmHg will decrease stroke incidence by nearly 50% in younger and about 34% in older people with similar benefit in those with combined or systolic hypertension [245]. A meta-analysis of the results of the 4 largest, and combined results of 13 smaller unconfounded, randomised trials, including all ages and using mostly thiazide diuretics and β -blockers are shown in figure 1.4 [49] indicating a highly significant reduction in stroke with antihypertensive treatment of $38 \pm 4\%$ (95%CI 31-45%).

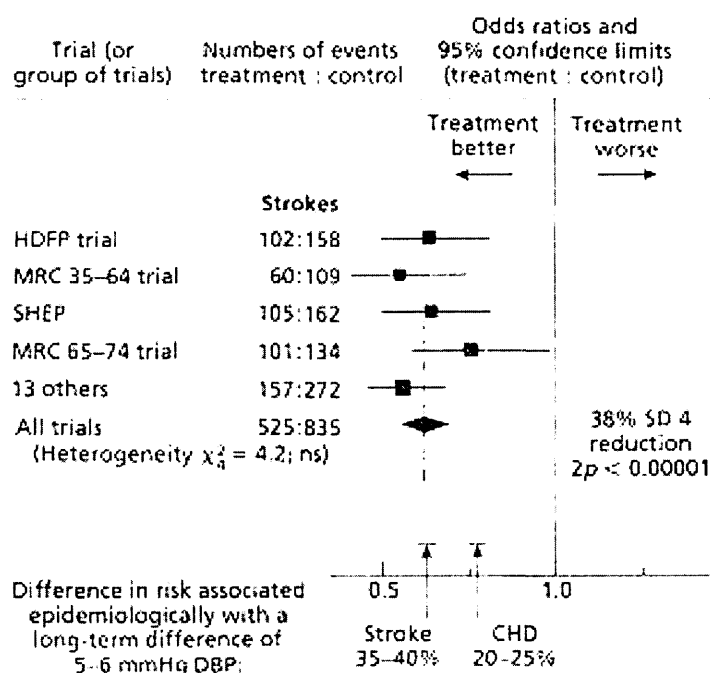


Figure 1.4 Results of meta-analysis of the 4 largest, and combined results of 13 smaller unconfounded, randomised trials including: the Hypertension Detection and Follow-up Program (HDFP) [125] (chlorthalidone), MRC 35-64 trial [201](bendrofluazide or propranolol), Systolic Hypertension in the Elderly trial [279] (chlorthalidone+atenolol (or reserpine)), MRC 65-74 trial [202] (atenolol or hydrochlorothiazide), 13 combined trials [49](diuretic, β blocker). Collins [49].

The relative efficacy of diuretics versus β -blockers is unresolved and the large Medical Research Council trials [143] found diuretics to be more effective in reducing

stroke risk than β -blockers in middle aged subjects (RR, 2.28; 95% CI, 1.31-3.96) with a similar non-significant trend in elderly subjects, although other smaller studies found no significant difference between diuretics and β -blockers [304;329].

In a population based case-control study where detailed information on antihypertensive use prior to first ischaemic stroke was available in 611 previously treated hypertensive patients and age and sex matched treated hypertensive controls, thiazides appeared to confer additional protection from stroke above other agents [143]. In patients without previously known cerebrovascular disease those on antihypertensive drug regimes without a diuretic had an 85% (RR 1.85; 95% CI, 1.26-2.71) increased risk of stroke above those including a diuretic [143].

The most recent studies also demonstrated benefits in the primary prevention of stroke for some of the newer antihypertensives and provide some comparison of the newer and older agents. The Captopril Prevention Project trial [113] found both diuretics and β -blockers more effective than captopril but, in contrast, the Swedish Trial in Old Patients with Hypertension-2 study (STOP-2) [112] found no difference in incidence of stroke in treated elderly hypertensive patients whether allocated to receive ACE inhibitors and CCBs or diuretics and β -blockers. The recent large Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) found chlorthalidone was superior to lisinopril in preventing cardiovascular disease including stroke to the ACE inhibitor lisinopril [9]. The Syst-Eur Trial [287] found that a treatment regime starting with nitrendipine but with the possible additions of enalapril and hydrochlorothiazide, reduced the incidence of stroke in elderly patients with isolated systolic hypertension.

Benefits additional to BP reduction have also been suggested regarding losartan, a selective AII receptor antagonist, when data from the Losartan Intervention For

Endpoint reduction in hypertension study (LIIFE) [56] showed it to be superior to atenolol in reducing stroke risk when a similar BP reduction was achieved with both agents in hypertensive volunteers with ECG criteria for left ventricular hypertrophy. A recent press release from Takeda ® detailing preliminary data from the Study on Cognition and Prognosis in the Elderly (SCOPE) reported a 28% reduction in non-fatal stroke in elderly people with mild hypertension treated with Candesartan, an AT1 receptor blocker.

Other ongoing comparative trials of different drug regimes including the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) may shed more light on the question of the best antihypertensive therapy in primary prevention of stroke.

1.6.8 Blood Pressure Control and Secondary Prevention.

Data from the Oxford Community Stroke Project has shown that, by 5 years after first ever stroke the actuarial risk of recurrence was 9 times higher than for the general population, with the highest risk in the first year following the initial event [34]. It is therefore crucial to identify effective strategies of secondary prevention. Fifty percent of stroke survivors remain hypertensive after 3 months [42;212] and, although some studies did not find any relationship between recurrent stroke and BP [34], most showed highly significant relationships between SBP and/or DBP and stroke risk throughout the range of BP (i.e. including both normotensives and hypertensives) comparable to that in first stroke, and with no lower level below which the risk of stroke did not continue to fall [10;265]. A meta-analysis of the available studies showed that there was an increased relative risk of stroke recurrence, 1.7 (95% CI 1.3-2.4), with raised post-stroke BP levels [246]. Irie et al [131] found a linear relation

between stroke recurrence rate and SBP but a 'J' shaped relationship with DBP, with the diastolic nadir between 80-84 mmHg, possibly influenced by the independent association of severe stroke with hypotension and increased recurrence, or artefactual in that those with very low BP are "ill". If, however, the hypotension itself caused a worse outcome then the 'J' shaped curve raises the question of the optimum BP target levels for treatment in the secondary prevention of stroke.

A recent meta-analysis of trials involving antihypertensive treatment in secondary stroke prevention showed a risk reduction for non-fatal stroke of 0.74 (95% CI 0.65-0.83) with similar results for total stroke reduction (figure 1.5a) but fatal strokes were not significantly reduced (RR 0.80, 95% CI 0.64-1.01) (Professor J. F. Potter- private communication). Clarification that both normotensive and hypertensive stroke patients benefit from BP reduction came from the recent perindopril PROtection aGainst Recurrent Stroke Study (PROGRESS) [250]. In this international trial 6105 patients with stroke or TIA, irrespective of BP, were randomised to antihypertensive treatment (perindopril 4mg \pm indapamide 2.5mg daily) or placebo within 5 years of stroke (median interval from qualifying event to inclusion 8 months) with a mean follow up of almost 4 years. There was a 28% (95% CI 17-38%) reduction in risk of further stroke among patients on single or combination therapy but the result was mainly driven by those on combined treatment (risk reduction 43% [95% CI 30-54%]) in whom BP was lowered by a mean of 12/5 mmHg [250] (figure 1.5b). Notably, stroke risk was reduced among those conventionally classified as normotensive as well as hypertensive, as was the risk of major vascular events. The data suggest that 1 fatal or major non-fatal stroke could be avoided for every 11 patients with a history of stroke or TIA treated with the combination of perindopril 4mg and indapamide 2.5mg for 5 years [250]. Data from the Heart Outcomes Prevention Evaluation study (HOPE) [28]

indicate that monotherapy with the ACE inhibitor ramipril can reduce stroke risk by 32% in normotensive subjects at high cardiovascular risk with only a modest BP reduction 3.8/2.8 mmHg, possibly indicating benefits of ramipril beyond its effect on BP level although this is much debated.

It is now clear that secondary prevention of recurrent stroke with antihypertensive treatment is effective to a similar degree as seen in primary prevention but large numbers of hypertensive post-stroke patients are undertreated [140].

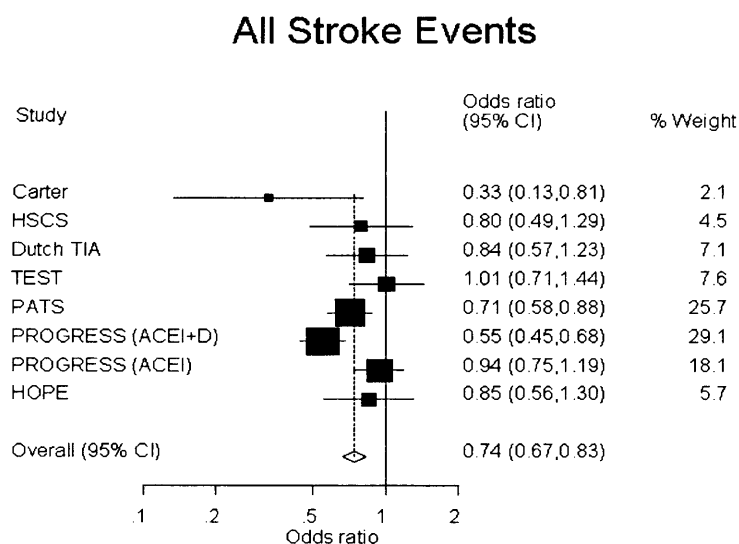


Figure 1.5a

Trials of Blood Pressure Reduction Post-Stroke

	Yr	N	Entry BP (mmHg)	Time From Stroke	BP Difference during trial (mmHg)	Active Treatment	F/U (yrs)
Carter	1970	97	>160/110	>2/52	?	D/MD/GB	4
HSCS	1974	452	167/100	>4/52	25/12	Des + D	3
Dutch TIA	1993	1473	158/91	>1/52	6/3	BB	2.6
TEST	1995	720	161/89	>1/52	4/3	BB	2.3
PATS	1995	5665	154/93	>4/52	6/3	D	2
HOPE	2000	1013	139/79	>4/52	3/2	ACEI	4.5
PROGRESS	2001	6105	147/86	>4/52	12/5 (A+D) 5/3 (A)	ACEI ± D	3.9

Figure 1.5b

Figure 1.5a Meta-analysis and **1.5b** summary of trials involving antihypertensive treatment in secondary stroke prevention.

Carter [43]; HSCS [126]; Dutch TIA [303]; TEST [86]; PATS [234]; HOPE [28]; PROGRESS [250].

ACEI: angiotensin converting enzyme inhibitor; BB: beta-blocker; D: diuretic; Des: deserpidine; GB: ganglion blockers; MD: methyldopa.

Figure courtesy of Professor J. F. Potter.

1.6.9 Acute Stroke, Blood Pressure and Outcome.

Systemic haemodynamics are abnormal in acute stroke, systemic BP levels are raised (>160/90 mmHg) in about 80% of patients [319], half of whom have a history of hypertension [32]. The BP tends to fall over the next 7-10 days [116;117;319] but remains in the hypertensive range in a third of cases. Cardiac BRS is reduced in acute stroke patients compared to normal controls [260] and BP variability is increased [263] and is associated with a worse outcome in terms of death and disability at 30 days [63].

The rise in BP may be a physiological compensatory mechanism to maintain CBF to the ischaemic brain tissue. Animal experiments have shown that the rise in BP in

response to temporary bilateral carotid artery occlusion was related to the degree of reduction in cerebral perfusion and may be influenced by a combination of factors including pre-existing hypertension, psychological stress, impairment of BRS, increased sympathetic nervous system (SNS) activity, ACTH-cortisol and renin-angiotensin-aldosterone systems and the Cushing reflex.

Loss of nocturnal 'dipping' on 24-hour ABPM assessment [172] is related to stroke subtype although it is not clear whether this precedes or results from the ischaemic event [62].

Most studies have found an association between high initial BP in the acute post-ictal phase and poor outcome [31;169;262] although one study found this only in patients with impaired consciousness [40] and another reported that higher BP was related to a reduction in progression of stroke [133]. Robinson et al showed that for every 10 mmHg increase in 24-hour SBP level on admission there was a 2-fold increase in death or dependency at 30 days [262]. A recent meta-analysis of 8 studies found a significant association between raised BP levels in the acute stroke period and mortality ($p=0.012$), with estimated hazards ratio of 1.48 (95% CI; 1.32-1.66) [246]. However, analysis of data from the International Stroke Trial suggests a 'U' shaped association between immediate post-stroke SBP and outcome [169] with the SBP nadir at 150 mmHg above which there was a 3.8% increased risk of early death (within 14 days) for every 10 mmHg increase presumably resulting from cerebral oedema. Low SBP was associated with early fatal coronary heart disease events and for every 10 mmHg fall in SBP below 150 mmHg there was a rise of 17.9% and 3.6% in risk of early death and death or dependency at 6 months respectively [169].

The associations of high and low initial BP with worse outcome after stroke do not provide any evidence that pharmacological manipulation of BP in the acute post-stroke period would be beneficial.

1.6.10 Treatment of Blood Pressure in Acute Stroke.

Dynamic and static CA are impaired acutely following stroke [60;82;194] (figure 1.1b) and may have higher than 'normal' limits of static CA through longstanding hypertension (figure 1.1a) [241].

In principle it might appear to be a good idea to increase blood flow to the ischaemic penumbra by increasing BP but, theoretically, this may also increase the risk of haemorrhage or oedema, raising ICP, possibly reducing flow to the ischaemic area. Animal studies, where the haemodynamics of induced strokes are very predictable, have demonstrated that raising BP following reperfusion after an experimentally induced MCA occlusion was beneficial if limited to 15 mins but produced a larger infarct if sustained for 90 mins [80]. Pharmacological elevation of BP in acute stroke in man has been investigated only in very small studies. A small single blind, controlled study using an intravenous haemoglobin analogue (diaspirin cross-linked haemoglobin) reported a significantly increased case fatality and end of trial disability at end of trial compared with control [271]. Two further small trials, one uncontrolled (265) and one retrospective [264], found increased CBF with elevation of BP and symptomatic improvement with increased BP in some patients respectively although these results cannot be generalised.

There are several anecdotal reports of neurological deficits worsening with rapid BP reduction in the acute stroke period, sometimes with recovery on quickly restoring the

BP to its original levels [168;248;264]. In theory lowering BP may lead to a reduction in CBF if CA is impaired, but there are currently very few randomised controlled trials and no large trials assessing the effect of deliberately lowering or elevating BP during the first few weeks following stroke. The Cochrane Database of Systematic Reviews, Blood Pressure and Acute Stroke II [302] is a review of randomised controlled trials to date where vasoactive drugs were used in the treatment of acute ischaemic or haemorrhagic stroke within 2 weeks of symptom onset. Intravenous CCBs, oral CCBs, β -blockers and probably ACE inhibitors lower BP in acute stroke. Beta-blockers appeared to worsen outcome including early case fatality (figure 1.6a) and intravenous CCBs appeared to increase early death and deterioration but reduce case fatality and disability at the end of trial, whereas oral CCBs appeared to increase case fatality and disability at the end of trial compared to controls (figure 1.6b). However, it should be noted that in some of the trials included in this Cochrane meta-analysis, BP manipulation was not the main aim of the work, but a consequence of using certain vasoactive drugs to test, for example, the neuroprotective properties of these agent. Additionally, BP measurement was variable between studies and in some only a single baseline measurement was available having implications for accuracy.

Figure 1.6 (a) The effect of β blockers calcium channel blockers on early case fatality when administered within 2 weeks of acute ischaemic stroke.
IV: intravenous
O: oral

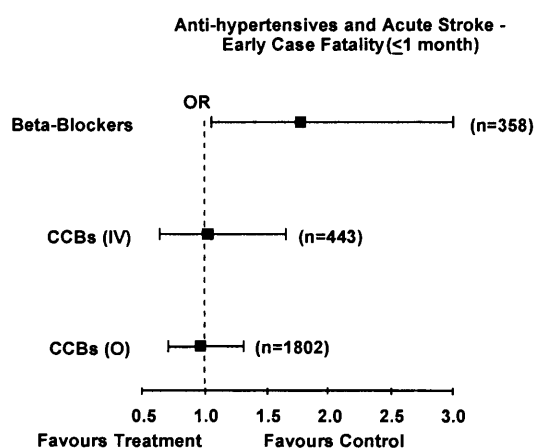


Figure 1.6 (b) The effect of β blockers and calcium channel blockers on case fatality at end of trial when administered within 2 weeks of acute ischaemic stroke.
IV: intravenous
O: oral

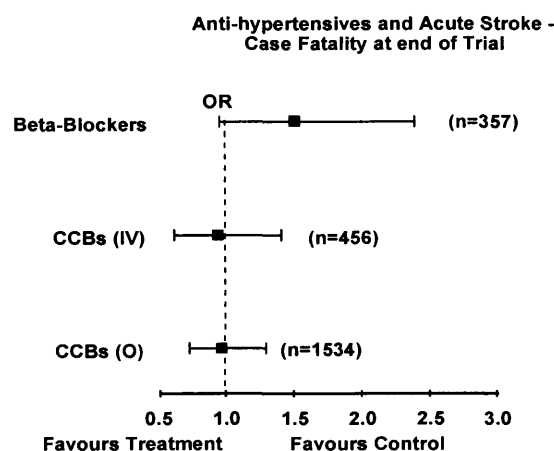


Figure 1.6 (c) The effect of β blockers and calcium channel blockers on early case fatality and deterioration (< 1 month) when administered within 2 weeks of acute ischaemic stroke.
IV: intravenous
O: oral

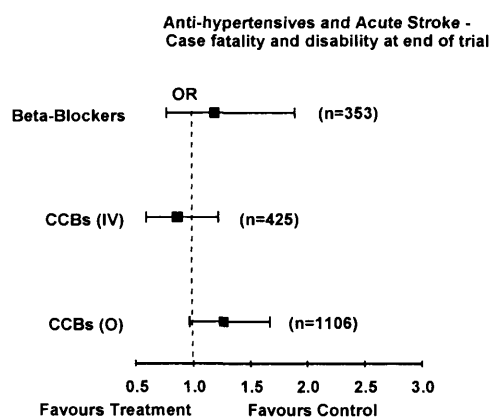
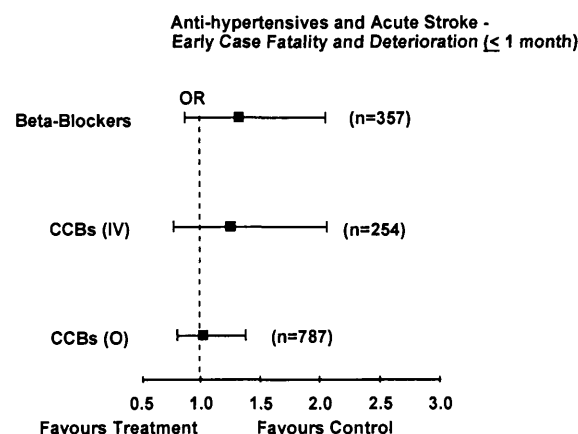


Figure 1.6 (d) The effect of β blockers and calcium channel blockers on case fatality and disability at end of trial when administered within 2 weeks of acute ischaemic stroke.
IV: intravenous
O: oral

Bath P, 2002

Figures taken from The Cochrane Database of Systematic Reviews, Blood Pressure and Acute Stroke II [302]

However, limitations of the data did not allow the effect of changing BP on outcome to be assessed.

It is currently recommended that following stroke antihypertensive treatment should be delayed for a few days, if not weeks, unless severe hypertension (systolic pressure exceeding 220 mmHg), cardiac failure, cardiac ischaemia, hypertensive encephalopathy, aortic dissection or continued intracerebral bleeding are present.

1.7 Cerebral Autoregulation, Cerebral Reactivity, Cerebral Haemodynamics and Cerebrovascular Disease.

Independent of the nature of the insult, acute brain injury generally leads to complete vasoparalysis in the infarcted area and dissociated vasoparalysis in the ischaemic penumbra and sometimes, remotely [72;194;218;241]. There are also local and remote changes in CBF and metabolism [193] and the duration of impairment of all of the above parameters is variable depending on the individual case.

Animal Studies. Abnormalities in the function of the cerebral circulation persist even after energy metabolism has recovered [215] although the duration of impairment is not known. In cats CR was abolished after 1-hour of complete cerebral ischaemia and, although some recovery of CR was evident at 2 days, complete restitution was not seen after 1 year [273]. After unilateral common carotid artery occlusion in Wistar rats a similar reduction in CBF in both hemispheres was observed as well as marked ipsilateral impairment of CR that improved with time but was still present at 1 month [67]. The transtentorial remote effects of acutely induced cerebral ischaemia have been demonstrated in rat brains where absent static CA and CBF in the ischaemic cortex and impaired static CA and CBF in the cerebellar hemispheres were recorded following bilateral carotid occlusion [280]. Apparently preserved static CA following

15 minutes of global cerebral ischaemia has been demonstrated in a canine model where CR to CO₂ was abolished but is likely to be a case of ‘false’ autoregulation. This is when local oedema increases with increasing BP, exerting external pressure on the cerebral vessels and reducing CBF giving the appearance of autoregulation but by a passive method [206]. Stroke-prone SHR lose their ability to autoregulate prior to stroke, raising the question of whether abnormalities in CA are a consequence of stroke rather than a causal factor [283].

The finding that in a rat model chronic cerebral hypoperfusion reduced the upper limit of CA is interesting as, following stroke, parts of the brain can remain underperfused for long periods of time [298].

Human Studies. Degree and duration of impairment of static CA following stroke seem to be related to the severity [7;282] and position of the infarct with severe hemispheric infarction and brainstem lesions (including TIAs) or lesions near the diencephalons causing more severe and longer lasting dysautoregulation than small or hemispheric infarcts [186;194].

Several studies have demonstrated impaired dynamic CA compared to normal controls within 96 hours of acute stroke [60;82] with no improvement in dynamic CA 10-14 days later.

As with other focal neurological pathology, stroke can have remote effects on CBF, cerebral metabolism, CR and CA [60;82;92;175;185;195] and large and medium infarcts can cause a reduction in contralateral hemisphere CBF and to a greater extent in the contralateral cerebellum, called “crossed cerebellar diaschisis” [90]. These flow reductions are never sufficient to cause ischaemia and the O₂ extraction fraction is always normal. The underlying mechanisms are uncertain but theories include raised ICP arising from a focal site but with global consequences, minor cerebral oedema

spreading along white fibre tracts or loss, in the focal event, of facilitatory neurones whose axons extend to remote sites [90].

In summary, although there is little information available, impairment of CA and CR are probably related to stroke type, severity and duration of the occlusion, but the prognostic implications are unknown. Many animal models of stroke have been studied but the haemodynamics of such infarcts are much more predictable than the dynamic situation in real stroke events in man. There is no information on the interaction between hypertension and CA following stroke nor any data on the effect of antihypertensive treatment on cerebral haemodynamics and some of these questions are addressed in this thesis.

1.8 Cardiovascular Homeostasis-Baroreceptor Sensitivity.

1.8.1 The Baroreflex Arc.

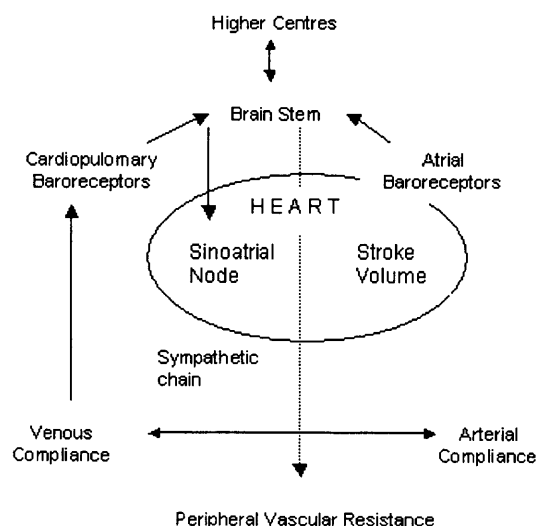


Figure 1.7 Schematic diagram illustrating the main components of the baroreceptor reflex arc.

Short term BP stability is primarily under the control of the baroreflex arc modulated by the hypothalamus, cortex and other higher brain centres (figure 1.7). Systemic BP is sensed through baroreceptors (stretch receptors) in the adventitial layer of certain parts of the large arteries including carotid sinus, enlarged parts of the ICAs, the aortic arch and its proximal branches. Afferent information from baroreceptors reaches the brainstem nuclei via the glossopharyngeal and vagus nerves. The baroreceptors have a basal tonic discharge but also respond to BP changes and the gain of the baroreceptor is decreased by inspiration and exercise, but increased by venous congestion and raised $p\text{CO}_2$. Efferent discharges via parasympathetic and sympathetic outflow tracts modulate BP via the sinoatrial node, myocardium, peripheral arterioles and capacitance vessels.

The main rhythmic components affecting the BP and pulse interval (PI) in addition to the cardiac cycle include respiration, vasomotion and Mayer waves (slow arterial pressure oscillations with a period 10s) [182]. Rhythmic sympathetic and vagal discharges in phase with respiration and vasomotor waves have also been described, the neural regulation of the circulation being mainly effected through the interplay of sympathetic and vagal outflows [182]. There appears to be a 'sympathovagal balance' where excitation of one component is accompanied by inhibition of the other, modulated by peripheral reflex mechanisms and central neural integration [182].

A measure of cardiac BRS can be calculated based on this natural variability of BP and PI using spectral analysis techniques as described in section 2.7. The fast Fourier transform (FFT) [13], describes the underlying oscillatory components in the SBP and PI tachograms in terms of their frequency and amplitude spectra, which may contain 3 spectral peaks in different frequency ranges (figure 1.8): very low frequency 0.01-0.05 Hz (VLF), low frequency 0.05-1.5 Hz (LF) and high frequency 0.15-0.4 Hz (HF). The

power in a frequency band represents the square of the variability of the parameter at that frequency, equivalent to the standard deviation.

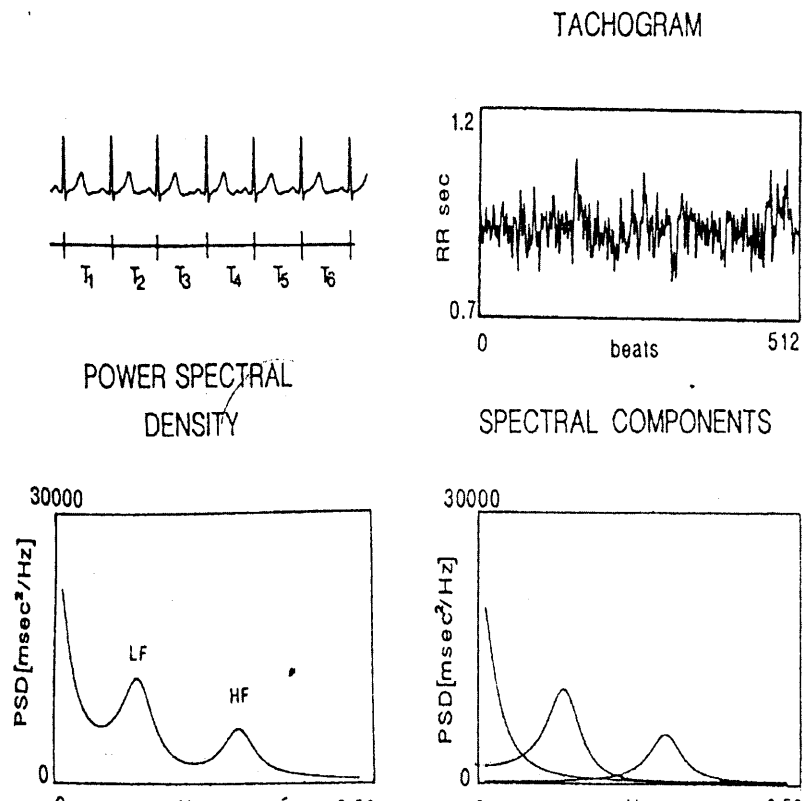


Figure 1.8 Example of ECG, Pulse Interval Tachogram, Power Spectrum and Spectral Components. [182]

In the SBP spectrum the HF variability is largely independent of vagal tone and is influenced by the mechanical effects of respiration on the heart and great vessels [68]. The LF variability depends on sympathetic activity, vagal tone, the cardiac BRS and vasomotor reactivity [231]. In the PI spectrum the HF variability is a reliable marker of vagal cardiovascular control [182;223;231] and the LF variability gives some measure of sympathetic nervous system activity [223;231].

1.8.2 Baroreceptor Sensitivity and Stroke.

Reduced cardiac BRS has been demonstrated in both animal models of stroke [47;77] and patients with chronic cerebrovascular disease [11;104] associated with central autonomic cardiovascular dysautoregulation [104]. In acute ischaemic and haemorrhagic stroke patients the autonomic consequences of cerebral hemisphere infarction have been demonstrated in terms of abnormal cardiac BRS and heart rate variability [19;151;205;222;260] and increased beat-to-beat BP variability, perhaps reflecting impaired cardiac BRS, is associated with poor outcome at 30 days [63]. Cardiac complications of acute stroke, including arrhythmias and ischaemic heart disease, are common [221;300] and impaired cardiac BRS may be important in the development of such complications.

There are contradictory reports of hemispheric laterality in the effects of stroke on autonomic control, with some authors suggesting there is reduced parasympathetic nervous activity following right hemispheric stroke, and others finding indications of reduced sympathetic activity in left hemisphere [259] and right hemisphere stroke [307].

Evidence demonstrating the relationship of BRS and outcome after myocardial infarction convincingly shows that reduced BRS is not a benign phenomenon [154;159;333] but, the prognostic significance of impaired cardiac BRS following acute stroke has not previously been studied.

In the following chapters I first explain the instruments and methods used in the studies in this thesis. I then present the 4 experimental chapters concerning the acute post ictal period of ischaemic stroke where I investigate; the prognostic value of

cardiac BRS, a method of measurement of dynamic CA using spontaneous BP transients and the effects of bendrofluzide on systemic and cerebral haemodynamic parameters. The final chapter discusses the conclusions of the thesis and the implications for future studies.

2 Methodology.

In this chapter the equipment for measurement of CBFV, non-invasive beat-to-beat finger BP and CO₂ estimation used in the studies presented in this thesis are described. Details of the protocols used in the studies along with the recording and editing of the data and the physiological manoeuvre, thigh cuff (THC), are then discussed. Finally the different analyses used for static and dynamic CA, BP variability and cardiac BRS are described.

2.1 Measurement of Cerebral Blood Flow.

2.1.1 Background.

The measurement of CBF has undergone a revolution over the last 100 years. Initially measurements were only made in animals because of the invasive nature of the procedures involving bubble meters, microspheres and highly traumatic surgical procedures that, themselves often caused radical changes in CBF and CA. In the 1930s and 1940s techniques that could be used in man based on the Fick principle were developed including the arteriovenous oxygen difference (A-VDO₂) technique [290] and the inert gas inhalation methods [142] giving relative assessments of CBF as the total weight of the brain could not be measured. In the 1960s the intra-arterial xenon injection method was first used allowing crude regional variations in CBF to be measured but other than A-VDO₂, no technique could be easily or quickly repeated. Due to the nature of these methods few individual measurements were possible in each subject, commonly 2, sometimes with a large delay (up to 12 hours) between

them, and occasionally only one baseline CBF reading followed up by A-VDO₂ readings. If the delay between readings is more than a few minutes then there is a risk of inaccuracy resulting from changes in pCO₂, cerebral metabolism, temperature and haematocrit.

The late 1970s and early 1980s saw the development of methods that allowed measurement of flow and metabolism in deep structures of the brain but with poor spatial resolution including radionuclide-scanning, Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT). Stable xenon enhanced computerised tomography (CT) [109] had much improved spatial resolution, whereas TCD was able to measure CBFV with poor spatial but excellent temporal resolution. More recently magnetic resonance phase contrast angiography has also been used to measure CBF in the estimation of CR [233].

Transcranial Doppler ultrasound, used in this thesis is discussed in detail in the following pages.

2.1.2 Transcranial Doppler Ultrasound.

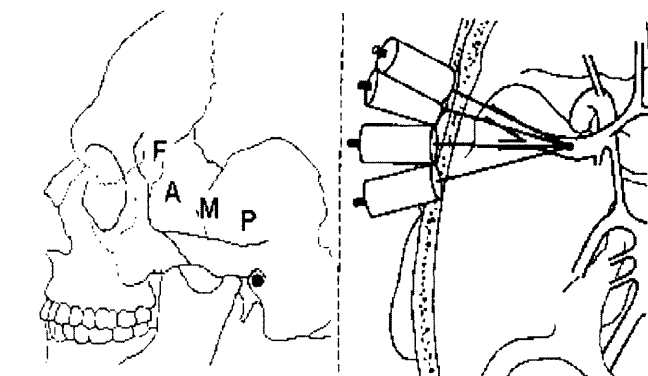
2.1.2.1 Principles.

In 1842, Doppler stated the hypothesis that a change in frequency of wave-motion should be observed when a source of sound or light is moving and this is known as the *Doppler effect*. The change in frequency observed in the Doppler effect can be used, not only to calculate the velocity of the sound or light source, but also to calculate the velocity of an object simply reflecting a wave of known frequency and this is the principle used in TCD.

Once it was realised that low frequency ultrasound could penetrate the skull, the first TCD recordings were made by Aaslid in 1981 [4]. Transcranial Doppler ultrasound was quickly included in research and eventually clinical applications, and has the advantages of being relatively simple to use, cheap, non-invasive, with excellent temporal resolution and ideal for repeated measurement or continuous monitoring. Applications range from detection of structural vascular abnormalities such as intracranial stenosis, identification of occlusion and subsequent recannalisation of cerebral arteries in stroke patients and perioperative monitoring of microemboli during carotid endarterectomy, to functional measurements of CR or CA.

A piezoelectric crystal is used to generate a 2MHz ultrasound beam, which is used to insonate a cranial blood vessel through the skull (Figure 2.1).

Figure 2.1: Transtemporal Acoustic Windows. Figure from Newell [207].



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

Blood cells flowing through the vessel reflect the ultrasound with a frequency change, known as the Doppler shift, that depends on their velocity and is calculated according to the formula:

$$\Delta f = 2(v \cos\theta) \frac{f_0}{c}$$

Where Δf is Doppler shift; v is the magnitude of the scatter velocity; θ is the angle between the ultrasound beam and direction of motion of the blood; f_0 is frequency of transmitted ultrasound; c is propagation velocity of ultrasound in soft tissues.

In practice the angle of insonation is adjusted until the maximum velocity possible is achieved.

In this work the equipment is used in pulsed mode, the same crystal switching constantly between transmit and receive modes, picking up the reflected signal. Bursts of ultrasound sent out from the transducer in a periodic fashion are reflected from structures within the beam, arriving back at the transducer in a time given by their depth. The time after transmission that the probe is switched to receive the reflected signal can be adjusted, effectively varying the depth from the transducer, from which the Doppler signals are received. Receive mode is maintained for a time interval defining a range of depth that can be observed with the pulsed ultrasound and signals are averaged over this time interval, known as 'range gating'. The lateral focussing of the probe, the length of the transmitted burst and duration of opening of the range gating define the spatial region, from which the Doppler shifts are detected, known as the 'sample volume'.

The relatively large sample volume used means that, in practice, the entire cross-section of the artery, branches and curving sections maybe insonated together necessarily including blood flowing at different velocities. Even within a vessel the blood in the centre of a vessel will have a greater velocity from that flowing near to the walls and each different velocity within the ultrasound beam will contribute to a mixture of Doppler shifts consisting of many frequencies. Using spectral analysis, the signal power of each velocity component can be computed. From this, the spectral

outline velocity, defined by the maximal Doppler shift and, therefore, the maximal velocity component of the velocity profile can be displayed and, usually, corresponds to velocity in the lumen centre.

2.1.2.2 Cranial Windows.

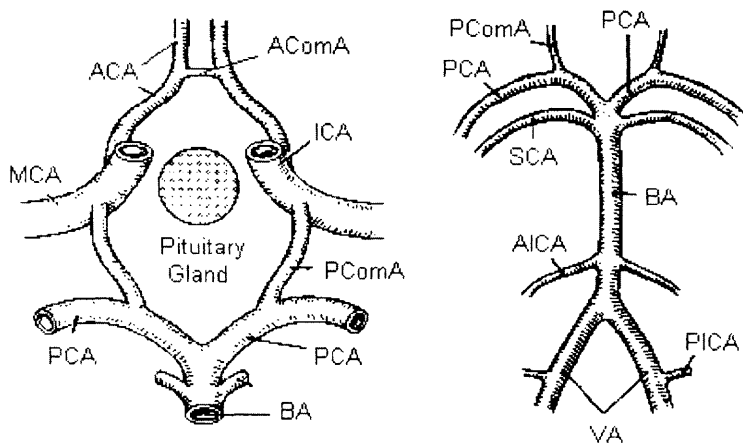
Three areas in the cranium offer natural acoustical windows for insonation, either where the bone is thin, in the transtemporal (Figure 2.1) and transorbital windows, or taking advantage of a natural opening between the cranium and atlas, the transforaminal window. Each different window allows access to a specific and limited range of intracranial arteries and this helps in identification.

The transtemporal window is used in this work (Figures 2.1 and 2.2) and is the most consistently thin area of bone in the cranium. Satisfactory insonation can usually be achieved in over 75% of subjects even though there is a minimum of 65% loss of original ultrasound signal intensity in the temporal bone [95] and window failure is common, increasing with age, female gender and in Chinese and Afro-Caribbean populations [111]. The transtemporal window can be subdivided into 3 regions, posterior, middle and anterior (figure 2.1) and the posterior window provides the best access in most people, although all windows should be explored for the best signal in each individual.

2.1.2.3 Vessel Identification and Reproducibility.

Identification of an insonated vessel requires knowledge of the anatomy of the cerebral circulation (Figure 2.2) and a systematic approach is to consider the six criteria shown in Table 2.1.

Figure 2.2: **Circle of Willis** Figure from Newell [207].



ACA	=	Anterior cerebral artery
PCA	=	Posterior cerebral artery
BA	=	Basilar artery
VA	=	Vertebral artery
ICA	=	Internal carotid artery
PComA	=	Posterior communicating artery
AComA	=	Anterior communicating artery
MCA	=	Middle cerebral artery
PICA	=	Posterior inferior cerebellar artery
AICA	=	Anterior inferior cerebellar artery

For the studies presented in this thesis the proximal segment of the MCA was insonated, bilaterally if possible, through the transtemporal acoustic window using a Scimed QVL 842 dual channel TCD machine with 2 MHz probes (Figure 2.3) and continuous MCA CBFV profiles are shown in Figure 2.4.

Figure 2.3. A subject undergoing transcranial Doppler ultrasound via the temporal window with the SciMed 120 QVL apparatus.

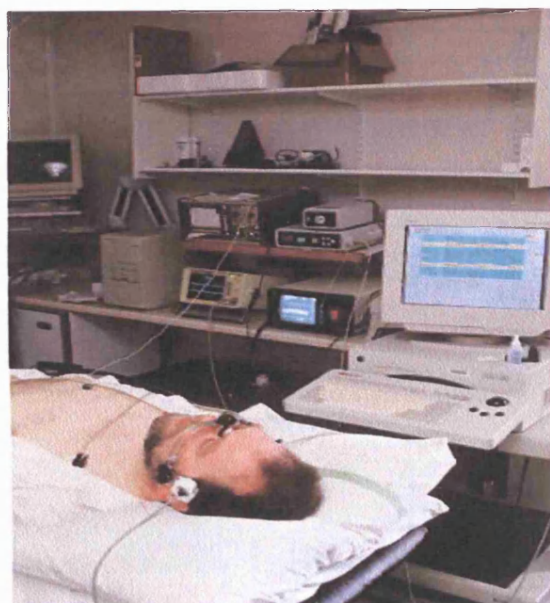
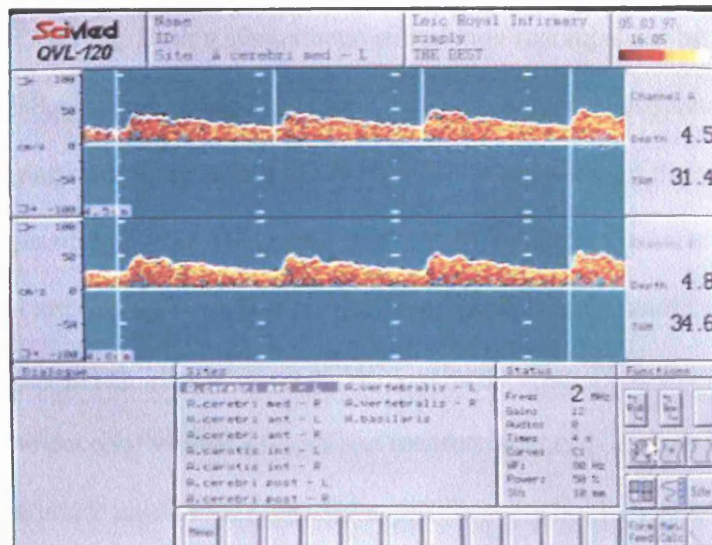


Table 2.1. Identification of basal cerebral arteries

Artery	Transducer position	Depth of sampling (mm)	Direction of flow	Spatial Relationship ACA/MCA Bifurcation	Mean Velocity (cm/sec)
MCA	Transtemporal	30 – 60	Toward	Same	55 ± 12
ACA / MCA Bifurcation	Transtemporal	55 – 65	Bi-directional	-	-
ACA	Transtemporal	60 – 80	Away	Anterior & Superior	50 ± 11
Proximal PCA	Transtemporal	60 – 70	Toward	Posterior & Inferior	39 ± 10
Distal PCA	Transtemporal	60 – 70	Away	Posterior & Inferior	40 ± 10
TICA	Transtemporal	55 – 65	Toward	Inferior	39 ± 9
OA	Transorbital	40 – 60	Toward	-	21 ± 5
VA	Transforaminal	60 – 90	Away	-	38 ± 10
BA	Transforaminal	80 - 120	Away	-	41 ± 10

ACA: Anterior cerebral artery; MCA: Middle cerebral artery; PCA: Posterior cerebral artery; TICA: Terminal internal carotid artery; OA: Ophthalmic artery; VA: Vertebral artery; BA: Basilar artery. Table from Tiecks [306].

Figure 2.4. Continuous middle cerebral artery blood flow velocity profiles as displayed using the Scimed QVL 842 transcranial Doppler ultrasound apparatus.



2.1.2.4 Validation.

Transcranial Doppler ultrasound only gives an indirect measurement of the CBFV and absolute volume CBF cannot be deduced without knowing the arterial diameter, a quantity that it is impractical to accurately measure in most cases. However, CBFV can be used as a surrogate for CBF and will accurately mirror changes in CBF providing the diameter of the insonated vessel remains constant and several studies under differing conditions have been done to investigate this.

2.1.2.5 Middle Cerebral Artery Diameter.

In the 1970s and early 1980s it was demonstrated, in man and animals, that the change in calibre of the large cerebral arteries in the steady state during reductions of BP were less than 5% [147]. No changes in MCA diameter were detected on magnetic

resonance imaging (MRI) with BP changes during lower body negative pressure, or during changes in end-tidal CO₂ levels [277] and direct observation of the MCA during surgery detected only minor changes in diameter with relatively large changes in BP and pCO₂ [98]. During sympathetic stimulation accompanied by sudden changes in BP, good agreement was found between changes in absolute flow, measured using microspheres and simultaneous measurements of blood flow velocity in pial arteries of dogs [36]. No change has been found in the diameter of large intracerebral arteries following the pressor response to an intracarotid infusion of norepinephrine [216]. Measurement of MCA velocity using TCD was seen to accurately reflect relative changes in direct measurement of ICA flow in response to THC release under anaesthetic [208] and at rest there are unlikely to be any significant changes in MCA diameter.

The power of the Doppler signal is theoretically proportional to the volume of blood within the sample volume of the ultrasound beam and was considered as a means of measuring volume flow using TCD and estimating vessel diameter [247]. However, in vivo, unpredictable attenuation and distortion of the ultrasound beam by passage through the temporal bone [73] means that the uniformity of insonation across a vessel cannot be guaranteed and results in poor reproducibility [87].

2.1.2.6 TCD Velocities compared with Volumetric Flows.

Multiple studies have been undertaken to evaluate the agreement between TCD and various different volumetric flow measurements, including Xenon clearance measurements with [54;70] and without [24] tomography, electromagnetic flowmetry [171], thermodilution, A-VDO₂ difference, PET [297] and M-mode colour duplex

systems [84]. Baseline CBFV was correlated to volumetric flow in various conditions including hypertension, diabetes mellitus, minor cerebrovascular disease and carotid artery stenosis or occlusion [24;70;171;297] although the results were more controversial when regional CBF was measured [70;297]. Most authors reported good correlation between relative changes in CBFV and CBF with acetazolamide [70;244] or hypercapnia [24;297] although one group found no relationship between CBFV increase and increase in regional CBF (measured using SPECT) in healthy volunteers [55] but did find qualitative agreement in evaluation of CR with acetazolamide, as well as in patients with cerebrovascular disease and carotid artery stenosis [53;54]. Demolis et al [70] suggested that, in subjects with cerebrovascular disease, where anastomotic blood flow may be significant i.e. tissue in the normal distribution of an MCA might receive collateral supply bypassing the MCA, TCD may not accurately mirror changes in volumetric flow.

In summary, TCD is a useful technique for the measurement of CBFV with excellent temporal resolution. Volumetric blood flow cannot be inferred from CBFV measurements but, in many circumstances, changes in CBFV will accurately mirror changes in CBF as the MCA diameter has been shown to change little under various conditions.

2.2 Non-invasive Beat-to-Beat Blood Pressure Monitoring.

In order to assess dynamic CA beat-to-beat BP recording is required to accurately characterise the dynamic BP change. Beat-to-beat BP recordings can be averaged over any time period and used in the calculation of static CA. Beat-to-beat BP can also be

used to calculate cardiac BRS from short-term variations in BP by spectral analysis or sequence analysis.

Intra-arterial monitoring is the 'gold standard' in beat-to-beat BP measurement but is an invasive, unpleasant procedure associated with a small risk of thromboembolism and arterial dissection. In 1982 the Dutch Biomedical Instrumentation Group TNO developed the first prototype non-invasive FINGER Arterial PRESSure monitor based on the volume clamp method of Penaz [242]– the Finapres® (Figure 2.5).

Figure 2.5. The Ohmeda 2300 Finapres device with cuff applied to the middle finger.



2.2.1 Description of Finapres.

The Finapres inflatable finger cuff containing an infrared transmission plethysmograph is positioned around the middle phalanx of the finger such that the blood volume pulsations in the digital arteries are recorded. The air pressure in the cuff is adjusted using a compressed air source according to information from the plethysmogram via a fast acting servo system. This minimises plethysmographic excursions, volume clamping the finger and maintaining transmural pressure in the

artery constant. Thus, cuff pressure follows the contours of the arterial pressure waveform instantaneously and can be recorded. Regular, automatic calibration is incorporated into the system where cuff pressure is briefly brought stepwise to the level where the arteries are about to collapse so that cuff pressure equals MAP. This servo calibration interrupts beat-to-beat BP measurement but can be safely disabled for short periods of time without affecting the recording, although over longer periods the readings drift and become inaccurate.

The servo was disabled for the duration of each of the recordings in the present work, a maximum of 10 minutes, and was re-enabled between recordings. If there was any suspicion of the readings drifting then the Finapres was allowed to recalibrate and the recording repeated or only part of the recording was used in the analysis.

2.2.2 Validation.

Recently the results 20 studies investigating the performance of the Finapres compared to intra-arterial BP measurements were reassessed using a novel resampling statistical method [281]. The studies involved patients over a variety of ages and included normotensive and hypertensive patients, some with known cardiovascular disease and some under anaesthetic. The overall findings suggested little systematic bias in the Finapres readings but substantial variability and much less accuracy in the systolic compared to diastolic and mean pressure values. The average systolic bias was 2.2 ± 12.4 (-22.6 to 26.9) mmHg, with average precision 12.2 ± 8.4 mmHg and the average diastolic bias was -0.3 ± 7.9 (-16.1 to 15.5) mmHg, with average precision 7.6 ± 5.3 mmHg.

Individual studies have generally found the Finapres to give highly variable results, with a systematic overestimation of BP, particularly SBP when compared with intra-arterial measurements in some study groups including healthy elderly [266], normotensive and hypertensive subjects under 65 years old [230], or an underestimation of BP in arteriopathies under anaesthetic [288]. This may be partly due to the sensitivity of the device to finger-tip temperature [301] and even small degrees of misapplication of the finger cuff with underestimation of BP if the cuff is too tight and overestimated if the cuff is too loose [132] although Dorlas et al [79] found that the Finapres functioned well, even during peripheral vasoconstriction.

Most authors found the Finapres to be accurate in monitoring beat-to-beat arterial pressure trends during anaesthesia [288]; during a variety of physiological manoeuvres causing both pressor and depressor BP changes including the Valsalva manoeuvre [128;230], head up tilt, standing, and mental arithmetic [266] and during vasomotor tests with no BP change e.g. lower body negative pressure and passive leg raise [230].

Blood pressure variability and cardiac BRS calculated from concurrent Finapres and intra-arterial measurements gave very similar results [230] but with a tendency to overestimate SBP variability [220], similar to findings with other finger BP monitors such as the Portapres [46].

Discrepancy between radial or brachial intra-arterial measurements and finger BP readings does not necessarily indicate inaccuracy in the Finapres itself. They may be a function of sampling the arterial tree at different points, a possibility that gains credibility if principles governing the shape of the arterial pulse are considered along with the observation that the diastolic readings are much closer to the intra-arterial readings than the systolic. As the pulse wave travels to the periphery it is influenced

by factors that tend to affect mainly the systolic BP and vary with age, hypertension and vascular disease [213] such as heart rate, arterial compliance, pressure gradient along the arterial tree, augmentation by the reflected pulse wave, pulse wave amplification and dispersion (higher pressure points travelling faster than lower pressure points).

In conclusion, although on average there is little bias in the Finapres BP readings, the low precision means that there may be a large, unpredictable discrepancy, particularly in SBP for any given patients. However, the Finapres does track beat-to-beat changes in BP at rest and during physiological manoeuvres with only a small loss of accuracy and considering this with its other advantages makes it ideal for the present application.

2.3 Measurement of Carbon Dioxide Partial Pressure.

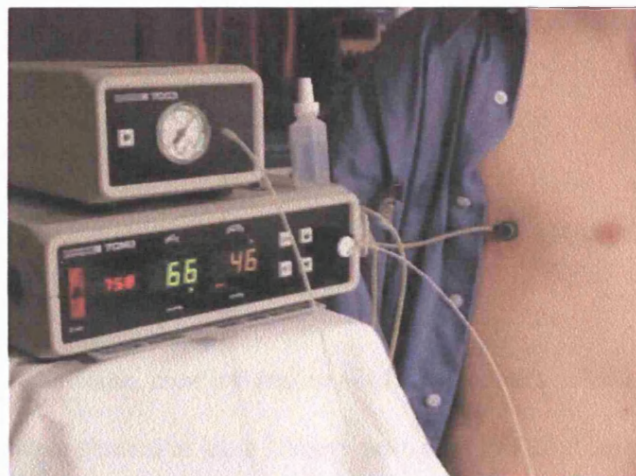
Carbon dioxide is a potent cerebral vasodilator and alters the gain of the cerebral autoregulatory curve and it is therefore important to monitor $p\text{CO}_2$ throughout studies of CA. The gold standard for measuring arterial gas tensions is arterial blood gas sampling but multiple measurements are neither practical nor ethical and non-invasive alternatives include transcutaneous monitoring, if good temporal resolution is not required, or end tidal monitoring if a breath-by-breath assessment of CO_2 is required. Transcutaneous CO_2 monitoring was used in the studies presented in this thesis and was adequate for monitoring during the steady state recordings but, in retrospect, it would be better to measure CO_2 with greater temporal resolution during dynamic physiological testing such as the application and removal of THC. During THC it is possible that breathing patterns, and hence CO_2 , may change in anticipation of the

manoeuvre being performed, or the manoeuvre itself may influence CO₂, perhaps by the release of CO₂-rich blood from the legs on cuff release.

2.3.1 Transcutaneous Carbon Dioxide Monitoring.

The TINA (Radiometer, Copenhagen) transcutaneous gas monitor functions via a probe that sits in electrolyte solution applied directly to the skin (Figure 2.6). The warm probe causes local vasodilatation and CO₂ in the surface blood readily dissolves into the electrolyte solution causing a pH change allowing the monitor to deduce the CO₂ level.

Figure 2.6. TINA transcutaneous gas monitor with probe attached to the skin at heart level in the anterior axillary line.



The TINA has a delay of 50 s to 90% maximum value and cannot track rapid changes in CO₂ but is adequate to monitor trends. The TINA has been validated against arterial blood gas samples in a variety of situations [44;180;286;311] and against arterialised earlobe samples [61].

In this work the TINA probe was applied with an operating temperature of 43° to minimise the possibility of thermal injury to the skin and allowed to stabilise over several minutes. To ensure accuracy, care was taken to exclude air bubbles in the electrolyte solution and the membranes on the probe were regularly renewed. With careful application of the equipment transcutaneous CO₂ monitoring provides an acceptable alternative to arterial pCO₂ measurements.

2.4 Study Protocols and Recording and Processing of the TCD, Finapres, ECG and TINA Signals Before Analysis.

2.4.1 Informed Consent.

All subjects gave written informed consent unless they were confused or dysphasic when consent was sought from a close relative. The Leicestershire Local Research Ethics Committee gave approval for all the work presented in this thesis. Copies of the Local Ethical Committee approval letters relating to studies reported in this thesis are found in Appendix II.

2.4.2 Protocol for Chapters 4,5 and 6 where Cerebral Autoregulation was measured.

Subjects avoided caffeine, nicotine and alcohol for 12 hours prior to the CA recordings and were studied at least 2 hours post-prandial. Studies were conducted in a dedicated research room kept at a constant temperature (20-24°C) with external stimuli minimized. After 10 mins supine rest 3 brachial BP readings were taken (Omron 711, Ohmeda) and the mean of the last 2 readings, providing pressures differed by less than 10 mmHg, were taken as the baseline casual BP level. The equipment set up for a recording is shown in Figure 2.2. The MCAs were insonated

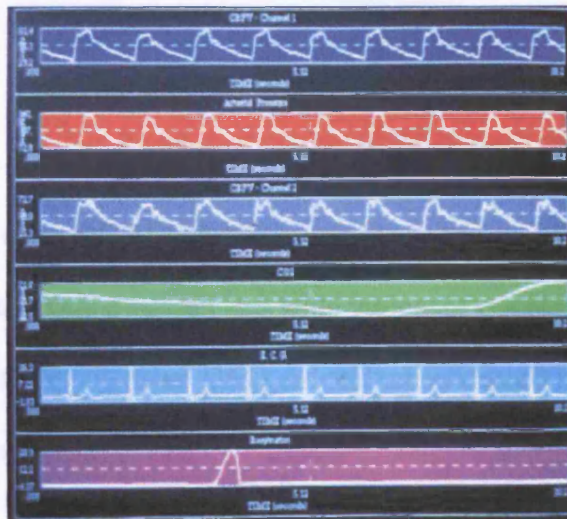
bilaterally and CBFV measured using TCD (SciMed QVL 842X, Bristol, UK)(section 2.1.2). A three lead surface ECG was fitted and beat-to-beat BP was measured using the Finapres (section 2.2.1) on the middle finger of the non paretic hand in stroke patients or left hand in all other subjects, supported at atrial level throughout the studies. Transcutaneous CO₂ levels were measured using the TINA.

The TCD, Finapres BP, ECG and TINA output signals were continuously recorded on digital tape (DAT, Sony PC-108M).F

2.4.3 Data Handling.

The digital audiotape recording was downloaded onto a microcomputer and FFT was used to extract the maximum frequency velocity envelope with the use of a time window of 5 ms. The BP, ECG, and TINA recordings were also sampled at a rate of 200 samples/s. The BP signal was calibrated at the start of each recording, all signals being visually inspected for artefacts or noise. Narrow spikes on the CBFV signals were removed by linear interpolation and the four signals were low pass filtered with a zero-phase eighth-order Butterworth digital filter with a cut-off frequency of 20 Hz. An example of the raw data can be seen in Figure 2.7. The beginning and end of each cardiac cycle was detected from the ECG and beat-to-beat estimates of mean CBFV and mean BP were obtained by integration. Beat-to-beat values of mean CBFV, SBP, DBP, MAP and PI were interpolated with a third-order polynomial and resampled at 0.2 Hz to produce signals with a uniform time-base. The CBFV, BP, PI and CO₂ series were then available for analysis.

Figure 2.7 Raw data as down loaded onto microcomputer for editing and extraction of parameters.



2.5 Non-Invasive Pressor and Depressor Tests.

Throughout the literature on CA a wide variety of drugs and physiological manoeuvres have been employed to produce pressor and depressor BP changes to stimulate CA for study [225]. For the study of dynamic CA rapid BP changes are required that cannot be produced pharmacologically but physiological manoeuvres that can be used in studying both static CA and dynamic CA include THC inflation and release, lower body negative pressure application and release, isometric hand grip, cold pressor test, the Valsalva manoeuvre, passive leg tilt, head up tilt, postural changes and periodic breathing [225]. Many of these manoeuvres have disadvantages particularly when a patient may not be able to co-operate in performing the manoeuvre because of confusion, weakness or dyspraxia or when the manoeuvre itself may induce a sympathetic response or a change in $p\text{CO}_2$. To avoid these potential

problems the use of spontaneous transient BP changes found in continuous recordings are studied in this thesis as well as the THC technique.

2.5.1 Thigh Cuff Inflation and Release.

The THC technique (Figure 2.8) was introduced by Aaslid et al in 1989 [3] and has since been used to stimulate a BP fall in a wide variety of clinical conditions including stroke [60], orthostatic hypotension [161], carotid artery disease [325], head injury [209] and during anaesthesia [295].

Figure 2.8. A volunteer undergoing thigh-cuff inflation



The THC technique, as originally described, involved inflation of large pneumatic cuffs around both thighs to above SBP for 2 minutes to produce leg hyperaemia, during which period the MAP was seen to rise. Very rapid THC deflation, such that THC pressure fell below diastolic BP within 200ms, was then associated with a sharp drop in arterial BP (because of reduced peripheral resistance) of 10-20 mmHg, lasting about 10 seconds before returning to its resting level under baroreflex control. The

sharp fall in MAP is accompanied by a simultaneous fall in CBF that can be monitored simultaneously with TCD. Ten seconds allows enough time for almost complete restoration of CBF [225], and dynamic CA can be calculated from the recovery of the CBF during this period. Static CA can also be calculated from the same recording by using a period before the THC inflation and the duration of THC inflation where the MAP is increased.

In this study Duracuff Johnson&Johnson THC were used and the Velcro fastenings were ripped open in one brisk movement to deflate the cuffs. The THC were applied twice with a minute baseline recording before inflating the cuffs to 140 mmHg for 90s rather than above SBP. All of the stroke patients studied were hypertensive and would not tolerate further cuff inflation. In most cases this level of cuff inflation elicited the required BP changes (≥ 10 mmHg) for analysis of dynamic CA. The quality of the BP fall can be a problem with THC also noted by other researchers [179;325].

The technique is uncomfortable and may result in sympathetic stimulation or may induce the patient to perform an involuntary Valsalva manoeuvre and so alter their $p\text{CO}_2$. Despite of this the technique has been used successfully in many studies and a validation study has demonstrated that in normal human subjects measurement of dynamic CA using a unilateral THC stimulus yields similar results to static testing in normal CA as well as in pharmacologically impaired CA [306].

The great advantages of the technique are that it is non-invasive, easy to perform and does not require the subject to take any active part.

The THC technique was not used in patients with severe peripheral vascular disease or a history of deep vein thrombosis.

In summary, this non-invasive technique for producing a BP stimulus for CA is, not only one of the most studied and best validated manoeuvres for this purpose, but

would be expected to be ideal for use in stroke patients who may not be able to take an active part in a procedure. However, my experience of its use in stroke patients in this thesis was that it is not well tolerated because of discomfort.

2.6 Measurement of Cerebral Autoregulation.

2.6.1 Static Cerebral Autoregulation.

Prior to the 1980s it was possible to study only static CA because techniques for measuring CBF with good temporal resolution had not been developed. Static CA characterises the relationship between CBF and MAP in the steady state before and after a change in arterial BP has been induced through pharmacological or other manoeuvres [225]. Several ways of classifying static CA, often simply as present or absent, have been published [225] including the change in CVR or CBF, linear regression, graphical representation and depend, to some extent, on the number of measurements made but, more usually, calculation of an ARI similar to that suggested by Tiecks et al [306] is now used.

In this work a static ARI is calculated as the percentage change in CVR per percentage change in BP [306]. Data were selected from the THC recordings (see 2.5.1) to include a baseline period and the period of static BP change during THC inflation and then divided into contiguous 8s intervals and the mean values of MCA velocity and BP were calculated for each interval. Cerebrovascular resistance was estimated for each segment and a static ARI was calculated:

$$\text{Static ARI} = \frac{\% \Delta \text{CVR}_e}{\% \Delta \text{ABP}} \times 100$$

$$\% \Delta \text{CVR}_e = \frac{(\text{CVR}_e 2 - \text{CVR}_e 1)}{\text{CVR}_e 1}$$

$$\% \Delta \text{ABP} = \frac{(\text{ABP} 2 - \text{ABP} 1)}{\text{ABP} 1}$$

where 1 = baseline reading; 2 = reading after BP change; CVR_e = estimated CVR.

A change in CVR that would fully compensate for the MAP change gives a static ARI of 100% and no change in CVR, i.e. absent autoregulation, would give a result of 0%.

A value of > 50% being considered normal [306].

2.6.2 Dynamic Cerebral Autoregulation.

The time delay required to effect a change in CVR in response to a change in BP is characterised by dynamic CA. Initially the THC technique (see 2.5.1) was used to produce a rapid depressor BP change [3] and this remains the closest to a ‘gold standard’ in terms of induced BP changes. However, many other manoeuvres mentioned in 2.5 have subsequently been used, providing both pressor and depressor stimuli and it is still not certain whether pressor and depressor stimuli evoke exactly the same physiological responses, although studies so far have not identified any difference in ARI between them [227].

Different approaches to evaluate dynamic CA have been taken including subjective evaluation by visual inspection [161], coherent averaging [229], ‘area under the curve’ [226], calculation of indices of dynamic autoregulation [306] and frequency domain analysis [229].

The present work is concerned with Aaslid's method applied to spontaneous pressor and depressor transient BP changes and THC manoeuvre [227].

2.6.2.1 Time Domain Analysis: Aaslid's Method.

In its most common form and used in the present work, calculation of an index of dynamic autoregulation is based on the rate of change of CVR with time per mmHg change in BP [3;209], although several different algorithms have been used.

Aaslid proposed a second order differential equation to model the CBFV response to the dynamic BP change [306]. The measured BP signal is used to generate a series of 10 curves (figure 2.9) representing different model responses by altering the time constant, T, damping factor, D and autoregulatory gain, K in the equation (Table 2.2).

Aaslid's Model

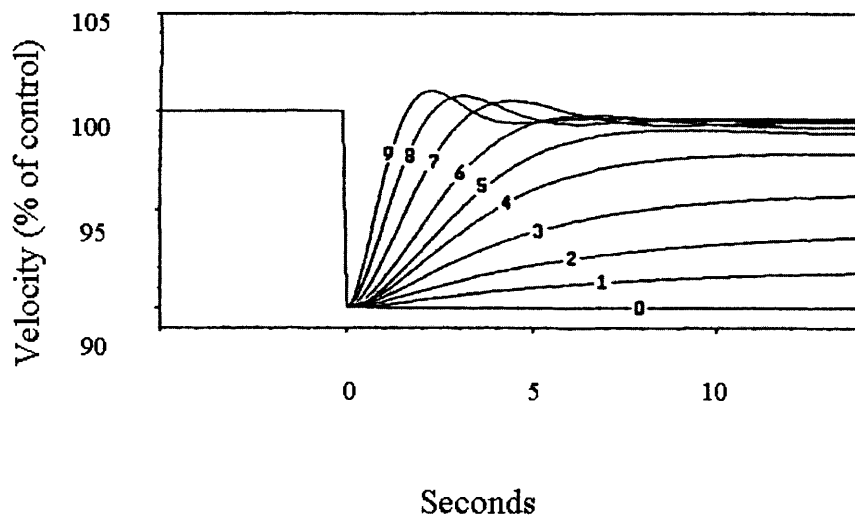


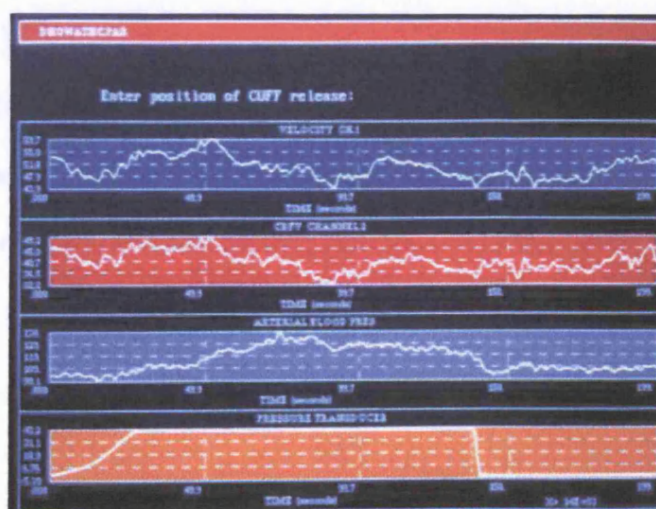
Figure 2.9. 10 theoretical curves generated from a step change in BP using Aaslid's model. Curve 0 represents absent autoregulation; curve 9 represents perfect autoregulation. Figure taken from Tiecks [306].

Table 2.2. Parameters used to calculate dynamic autoregulatory curve and ARI.

T(s)	D	K	dynamic ARI	dROR (%/s)
	0.00	0.00	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	0.50	0.98	9	80.0

Each curve represents a different level of dynamic CA from 0 to 9 where 0=absent autoregulation, 9= best autoregulation and >5='normal' autoregulation [306]. The measured actual CBFV response is compared to the curves (in this work using the correlation coefficient (r) although Aaslid originally used the minimum quadratic error) and is given a dynamic ARI value corresponding to the best match between model and data, using a window duration of 30s. Essentially the experimental rate of recovery of CBFV is matched to the mathematical model predictions.

Figure 2.10 CBFV and MAP displayed with pressure trace (bottom) from THC for manual marking of position of BP fall due to THC release for Aaslid's analysis.



In practice CBFV and MAP were displayed on the computer (Figure 2.10) so the data could be manually selected at the start of the dynamic BP stimulus i.e. where the THC was released. Only MAP changes > 10 mmHg for THC and 5 mmHg for spontaneous transient BP changes occurring within 200ms were accepted as an adequate stimulus and subjects had to have a synchronous and physiological change in MAP and CBFV. Beat-to-beat MAP and CBFV readings were analysed to assess the time dependent recovery of each parameter. By applying the 2nd order differential equation set with state variables x1 and x2 (which were assumed to equal zero during the pretest period) the normalised change in MAP (dP) and CBFV (mV) were calculated: -

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

$$x2_n = x2_{n-1} + \frac{(x1_n - 2Dx2_{n-1})}{fT}$$

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

$$mV_n = CBFV_{base} \times (1 + dP_n - Kx2_n)$$

Where dP_n = normalised change in MAP; MAP_{max} = MAP at point of maximum change; MAP_{base} = MAP at start of test and CBFV_{base} = CBFV at same time point; n=sample number; T= time constant; D=damping factor; K =autoregulatory gain; CrCP = critical closing pressure; f = sampling frequency (5 HZ).

Although Aaslid originally developed this analysis for use with THC induced changes in BP it can be used with any suitably rapid pressor or depressor BP stimulus including spontaneous transient changes selected from baseline recordings.

The reproducibility of the dynamic ARI derived using spontaneous transient BP changes and THC, has been reported in normal volunteers. No significant difference was found in measurements made on 2 occasions 6 weeks apart with a standard deviation of the difference for dynamic ARI of 2.3, 2.6 and 1.5 based on pressor and depressor BP stimuli, and THC respectively [59]. The immediate reproducibility of dynamic ARI from THC has been investigated using a series of 6 THC manoeuvres in healthy volunteers and gave a normal distribution of ARI values 4.98 ± 1.06 [179]. It was concluded that there was little improvement in precision in ARI beyond the use of 3 good THC tests although, in this work the average of 2 manoeuvres was used as the patients tolerated THC badly. A similar analysis has not been carried out with regard to the immediate reproducibility of ARI calculated from spontaneous BP transient stimuli but the average of 2 ARI were used for both pressor and depressor stimuli to enhance precision. One ARI was calculated from each of the 2 rest recordings done for Chapters 4, 5 and 6.

2.7 Baroreceptor Sensitivity.

Cardiac BRS, or the heart rate response to BP changes, has been assessed from pressor and depressor changes invoked pharmacologically, during phase 4 of the Valsalva manoeuvre, passive tilt, standing and by directly unloading the carotid sinus baroreceptors using neck suction. The regression coefficient for the relationship between evoked SBP change and PI being taken as an index of cardiac BRS. Since the development of reliable non-invasive finger BP monitors allowing continuous beat-to-beat BP recording with, or without, concurrent ECG it has subsequently become more usual to assess cardiac BRS under more physiological conditions at rest, avoiding

interference of other reflexes invoked by large BP changes, direct action of drugs on the baroreceptor and allowing assessment in patients who might not tolerate other methods e.g. the very ill.

One approach to assess cardiac BRS from baseline rest recordings has been to pick out pressor and depressor sequences where SBP and PI change in the same direction and use regression as above. An alternative, used in the thesis, is frequency domain analysis based on FFT algorithms.

2.7.1 Frequency Domain Analysis of Cardiac BRS based on FFT.

Spectral analysis techniques, in this case FFT [13], decomposes the SBP and PI tachograms into their oscillatory components in terms of their frequency and amplitude spectra (Figure 1.8) and requires stationary conditions (i.e. no slow trends or step changes in the parameter), strict periodicity of the data and is frequently used with an a priori selection of the number and frequency range of oscillatory components. In this work data segments of 512 points were used. The power spectra were smoothed with a 13-point triangular window and estimates of power spectra of PI and SBP, coherence function, and frequency response between PI and SBP with 58 df were produced. Coherence between BP and PI variability reflects the amount of linear coupling between the two spectra comparable to the correlation coefficient in regression analysis and a coherence value >0.40 was considered significant. Recordings with an ectopy rate $>2\%$ were rejected. Spikes on the resampled tracings of the PI and SBP recordings were manually removed, and a straight line was interpolated by the computer, although resampled tracings with >4 spikes were excluded from subsequent analysis to avoid bias. The frequency and amplitude

spectra may contain 3 spectral peaks in different frequency ranges (figure 1.8): very low frequency 0.01-0.05 Hz (VLF), low frequency 0.05-0.15 Hz (LF) and high frequency 0.15-0.4 Hz (HF). The power in a frequency band represents the square of the variability of the parameter at that frequency, equivalent to the standard deviation. Power spectral analysis estimates of PI and SBP variability were obtained by taking the square root of the powers of PI and SBP respectively for the VLF, LF and HF bands. Simultaneous spectral analysis of SBP and PI allow the gain of the baroreceptors to be represented by an 'α' index:

$$\alpha \text{ index} = \sqrt{\frac{(\text{Power of spectral components PI (HF, LF or combined HF+LF)})}{(\text{Power of spectral components SBP (HF, LF or combined HF+LF)})}}$$

Cardiac BRS assessed in this way compares well with estimation of gain of the baroreceptor using the phenylephrine method [182].

In this thesis the LF or combined α index is used as a measure of cardiac BRS.

2.8 Stroke Classification and Stroke Scales.

2.8.1 The Oxford Community Stroke Project Classification.

The Oxford Community Stroke Project Classification (OCSP) was devised as a way of clinically subdividing patients into 4 categories that may relate to the underlying aetiology and natural history of stroke type based entirely on examination findings [18] (see Appendix 1). However, the OCSP Classification does not give very accurate pathophysiological information about the stroke aetiology and an alternative system has been developed for categorization of subtypes of ischemic stroke mainly based on aetiology known as TOAST (Trial of Org 10172 in Acute Stroke Treatment) [5].

Future studies may consider using this new approach although a greater amount of clinical data (including results of investigations) would need to be recorded to allow classification using TOAST.

In order to quantify neurological impairment and functional disability in patients after stroke and to have some measure of the changes over time 3 stroke scales were chosen: the National Institute of Health Stroke Scale (NIHSS), the Barthel Index and the modified Rankin Scale (mRS) (see Appendix 1).

2.8.2 National Institute of Health Stroke Scale (NIHSS).

The NIHSS stroke scale (Appendix 1) is a simple, short neurological examination scale taking 5-8 minutes to complete [33] and is one of the most accurate clinical stroke scales available [52]. It has high interrater reliability [101], is relatively independent of the expertise of the examiner [33] and has been shown to correlate highly with infarction volume on the day 7 CT scan ($r=0.68$) and with the 3 month outcome ($r=0.71$) [33].

The NIHSS stroke scale is ideal for the purposes of this work in stroke patients to quantify neurological outcome over the period of this study.

2.8.3 Barthel Index.

The Barthel index [178] (Appendix 1) is a disability scale that gives an index of the patient's performance in 10 activities of daily living. Interrater agreement is very good [33] and the Barthel index is the most reliable disability scale [52] and is, not only,

highly correlated with the immediate post-stroke condition [331] but also, valid in long term follow-up [330].

2.8.4 Modified Rankin Scale.

The Rankin scale [257] assesses handicap and the modified Rankin score (mRS) was used in this work (Appendix 1). It measures independence rather than performance in specific tasks and so incorporates mental as well as physical adaptations to the neurological deficits and is slightly more subjective than the Barthel index [331]. Interrater agreement for mRS is good, although slightly less so than with the Barthel index, kappa 0.75 vs. 0.88 [331].

The three clinical and functional stroke scales chosen for use in this thesis are the most reliable available and are widely used by other workers facilitating comparison between studies.

3 Predictive value of cardiac baroreflex sensitivity in the early phase of acute ischaemic stroke.

3.1 Summary.

Cardiac BRS is impaired following acute stroke (see section 1.8) and this work explores the short and long term prognostic implications of this finding. In this study cardiac BRS was measured within 24 hours of stroke symptom onset by spectral analysis techniques in 124 acute ischaemic stroke patients and 62 age, sex and BP matched controls. Cardiac BRS was significantly lower in patients than controls. Over a median follow-up period of 1508 days, stroke patients with significantly impaired cardiac BRS ($<5\text{ms/mmHg}$) had a significantly poorer prognosis with a mortality rate of 28% compared to 8% in patients without significantly impaired cardiac BRS ($>5\text{ms/mmHg}$) independent of other well-recognised variables, including age, BP, stroke severity and stroke subtype. Cardiac BRS did not, however, influence short-term outcome (30 days post-ictus).

3.2 Introduction

The baroreceptor reflex arc is important in the short-term regulation of the cardiovascular system (section 1.8.1) and, considering its central connections, it is not surprising that the reflex arc may be damaged following stroke (see 1.8.2). Abnormal BRS has been demonstrated in both animal models of stroke [47;77] and patients with chronic cerebrovascular disease [11;104]. In acute ischaemic and haemorrhagic stroke patients the autonomic consequences of cerebral hemisphere infarction have been

demonstrated in terms of abnormal cardiac BRS and heart rate variability [19;151;205;222;260].

Such abnormalities of cardiovascular autonomic control following acute myocardial infarction have been demonstrated to be of prognostic significance [333]. Impaired cardiac BRS is associated with increased cardiac death and life-threatening ventricular arrhythmias [159]. The Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) study assessed cardiac BRS within a mean of 16 days in 1284 post-acute myocardial infarction patients, and reported that significantly reduced cardiac BRS (<3.0 ms/mmHg) was significantly associated with increased mortality over a mean follow-up period of 21 months. This effect was independent of other poor prognostic indicators, including impaired left ventricular function and frequent ventricular premature complexes [154].

Cardiac complications of acute stroke, including arrhythmias and ischaemic heart disease, are common [221;300] and impaired cardiac BRS may be important in the development of such complications. Increased beat-to-beat BP variability, perhaps reflecting impaired cardiac BRS, is associated with 30-day outcome; the odds ratio for a poor outcome was 1.32 (1.1 to 1.7) for every 1 mmHg increase in mean arterial BP variability [63]. However, to my knowledge, the prognostic significance of impaired cardiac BRS following acute stroke has not been studied and the aim of this study was to investigate the effects of acute ischaemic stroke on cardiac BRS, and to assess the short- and long-term prognostic significance of any observed changes.

3.3 Subjects and Methods

3.3.1 Subjects

One hundred and twenty-four patients with neuroradiologically confirmed ischaemic stroke and admitted to the Medical Wards and Stroke Units of the teaching hospitals within the University Hospitals of Leicester NHS Trust within 24 hours of acute ictus were studied. Stroke patients were identified by liaison with a central Bed Bureau, the Accident and Emergency Department, the Medical Admissions Wards and Stroke Units TGR and SLD (n=95 patients). The Stroke Unit and the Acute Admissions Unit at Glenfield Hospital were visited daily during the week and the Stroke Unit and Acute Admission Unit at Leicester General Hospital were visited between one and three times weekly to recruit patients PE (n=29 patients). Stroke type (OCSF classification - section 2.8.1) and the NIHSS score (section 2.8.2) were recorded. Those patients requiring the continuation of antihypertensive therapy or any treatment with effects on cardiovascular or autonomic function were excluded. Unconscious patients and those with atrial fibrillation or neurological signs lasting <24 hours were excluded, as were patients with a past medical history or evidence at the time of study of diabetes mellitus, impaired renal function (creatinine >200 μ mol/ l), acute myocardial infarction, unstable angina, or other conditions with autonomic dysfunction.

A control group of 62 healthy subjects chosen to have a similar age, sex and BP distribution were recruited (TGR & SLD) from among respondents to a local newspaper advertisement, from among outpatient attendees at the University Hospitals of Leicester NHS Trust Hypertension Clinic and through a liaison with several large local general practices. Control subjects with known diagnoses of atrial fibrillation, ischaemic heart disease, diabetes mellitus, or other conditions associated with autonomic dysfunction were excluded.

3.3.2 Protocol

All patients were assessed within 24 hours and studied within 72 hours of symptom onset. If symptoms were first noticed by the patient on waking, then the time of stroke onset was taken as the time of onset of sleep. Casual BP was measured in the hemiparetic arm according to recent British Hypertension Society guidelines (i.e. three consecutive readings in the supine position with the arm at heart level, using a standard mercury sphygmomanometer and cuff of appropriate size), to the nearest 2mmHg. Control subjects were also assessed with casual BP recorded in the non-dominant arm. The mean value was taken in subsequent analysis.

Twenty-four-hour BP monitoring was performed immediately after casual BP measurements but within 24 hours of ictus, using a Spacelabs 90207 recorder (Spacelabs, USA), programmed to record BP at 15-minute intervals during the day (0700 to 2200 hours) and at 30-minute intervals at night (2201 to 0659 hours). The mean 24-hour, day and night SBP and DBP, and the difference between mean day and night SBP and DBP, were recorded.

Subjects avoided caffeine, nicotine and alcohol for 12 hours prior to the BRS recordings and were studied at least 2 hours post-prandial. Studies were conducted in a dedicated research room kept at a constant temperature (20-24°C) with external stimuli minimized. After 15 min supine rest surface ECG (three lead) and Finapres BP (section 2.2) output signals (sampled at 200Hz) were continuously recorded on digital tape (DAT, Sony PC-108M) for 3 consecutive 5 min periods during which subjects were asked to maintain a respiratory rate >15 breaths per minute, although respiratory rate and tidal volume were not formally measured. The DAT recording was downloaded onto a microcomputer the derived PI and SBP series were analysed by means of power spectral analysis with fast Fourier transform (FFT) and cardiac BRS

(combined α) calculated as described in 2.7.1. Pulse interval variability was assessed from the standard deviation (SD) of the beat-to-beat recordings.

Patients were further reviewed at one month after ictus, and the mRS (section 2.8.4) recorded. Patients were then classed as dependent if exhibiting a moderate to severe handicap (mRS ≥ 3) or independent with no to mild handicap (mRS ≤ 2) [48]. Finally, mortality was recorded over a median follow-up period of 1508 days (range 9 to 2656 days) following acute ictus and was assessed from a number of sources including hospital medical records, hospital information systems, General Practitioner records, and Health Authority returns from General Practitioners and from the Registrar for Births, Marriages and Deaths.

3.3.3 Statistical Methods

For normally distributed data the results are presented as mean (SD), and statistical comparisons between acute stroke and control groups were made with the Student's unpaired t-test. For non-normally distributed data, results are presented as median (interquartile range (IQR)), and statistical comparisons between groups were made with the Mann-Whitney U test. Using multiple logistic regression analysis, all clinically important variables were included in the model to predict death or dependency. Thereafter, the differences between groups for cardiac BRS measurement were inspected by plots of Kaplan-Meier survival functions. Statistical significance was taken at the 5% level.

3.4 Results

Demographics, BP data and cardiac BRS for acute stroke patients and control subjects are shown in Table 3.1.

Table 3.1 Demographic and Blood Pressure Variables in Acute Stroke Patients and Control Subjects

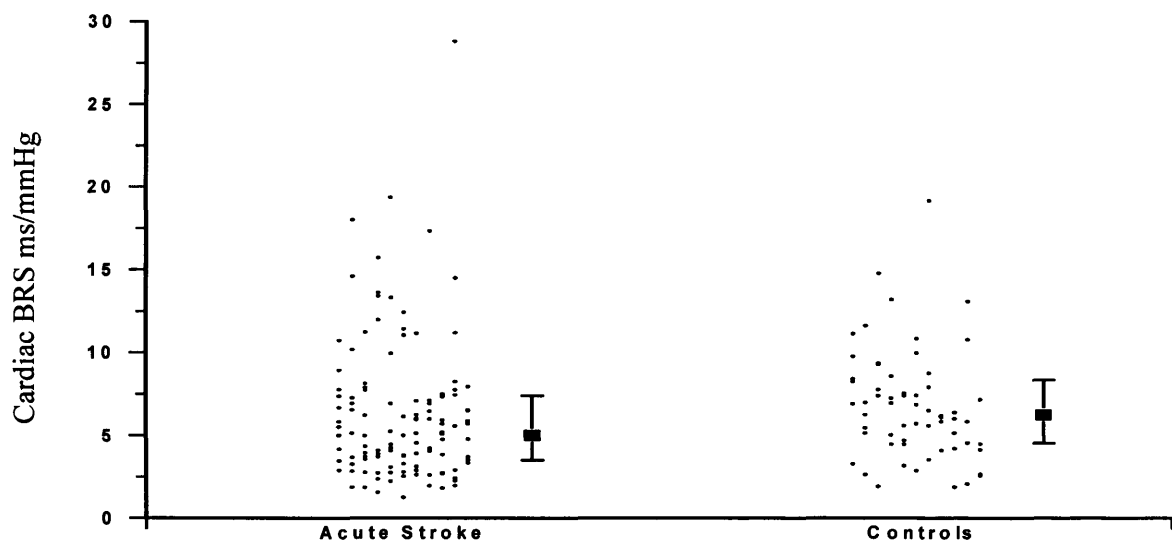
Variable	Acute Strokes (n=124)	Control Subjects (n=62)	P value
Age (years)	70.4 (11.1)	68.2 (8.6)	0.14
Age range (years)	39-89	39-82	N/A
Sex (M: F)	68: 56	36: 26	>0.2
Casual BP (mmHg)			
Systolic	163 (27)	161 (20)	0.68
Diastolic	88 (15)	90 (14)	0.42
Mean Arterial	113 (17)	113 (14)	0.76
Pulse Pressure	75 (21)	71 (15)	0.22
24-hr BP (mmHg)			
Systolic	155 (21)	143 (17)	<0.001
Diastolic	86 (12)	82 (12)	0.02
Mean Arterial	112 (15)	104 (13)	<0.001
Pulse Pressure	68 (15)	61 (12)	<0.001
Diurnal BP fall			
Systolic	5 (-2, 13)	15 (12, 21)	<0.001
Diastolic	5 (-1, 10)	13 (8, 16)	<0.001
Cardiac BRS (ms/mmHg)	5.0 (3.5, 7.4)	6.2 (4.5, 8.3)	0.04

Values presented as mean (standard deviation) for normally distributed data and median (IQR) for non-normally distributed data.

Clinical diagnosis using the OCSF classification (Appendix 1) identified 43 total anterior circulation strokes (TACS), 35 partial anterior circulation strokes (PACS), 34 lacunar strokes (LACS) and 12 posterior circulation strokes (POCS). Median NIHSS

score on admission was 6 (IQR: 3 to 10). No significant differences were seen in casual BP between the groups (Table 3.1). 24-hour BP monitoring was successful in 101 acute stroke patients and all control subjects. 24-hour BP was significantly higher in the acute stroke group (Table 3.1). There was also a significant reduction in diurnal BP fall in acute stroke patients compared to control subjects (Table 3.1). Cardiac BRS, assessed by the combined α -index, was significantly lower in acute stroke patients compared to control subjects (Table 3.1 & Figure 3.1).

Figure 3.1 Median, Interquartile Range and All Values of Cardiac Baroreceptor Sensitivity (ms/ mmHg) Assessed by the Combined α -index in Control Subjects and Acute Stroke Patients.



Sixty-three of the acute ischaemic stroke patients were dead or dependent ($mRS \geq 3$) at one month following ictus. Compared to the 61 independent patients ($mRS \leq 2$), these

patients were significantly older, more likely to be female, more likely to have had a higher admission NIHSS score, and more likely to have sustained a TACS (Table 3.2).

Table 3.2 Admission Parameters in Acute Ischaemic Stroke Patients Classed as Dead/Dependent or Independent at One Month Following Ictus

Variable	Dead/ Dependent (n=63)	Independent (n=61)	P value
Age (years)	74.3 (10.0)	66.4 (10.8)	<0.001
Sex (M: F)	27: 36	41: 20	<0.01
NIHSS Score	9 (7, 14)	3 (2, 5)	<0.001
OCSF (TACS:PACS:LACS:POCS)	29: 12: 17: 5	14: 23: 17: 7	<0.01
<u>Casual BP (mmHg)</u>			
Systolic	166 (29)	159 (19)	0.17
Diastolic	87 (16)	89 (15)	0.65
Mean Arterial	113 (18)	112 (16)	0.68
Pulse Pressure	78 (22)	72 (20)	0.09
<u>24-hour BP (mmHg)</u>			
Systolic	158 (23)	152 (19)	0.11
Diastolic	87 (13)	86 (11)	0.34
Mean Arterial	113 (16)	110 (13)	0.26
Pulse Pressure	71 (16)	65 (14)	0.06
<u>Diurnal BP Fall (mmHg)</u>			
Systolic	1 (-4, 10)	9 (1, 14)	0.02
Diastolic	1 (-3, 7)	7 (1, 12)	0.004

Values presented as mean (standard deviation) for normally distributed data and median (IQR) for non-normally distributed data.

Dead or dependent patients had non-significantly higher casual BP compared to independent patients (Table 3.2). Similarly, no significant differences were observed in BP parameters between the 50 dead or dependent and 51 independent patients with complete 24-hour BP recordings, though a significantly reduced diurnal BP change

was recorded in the dead or dependent patients (Table 3.2). However, no differences were found in cardiac BRS measured by the combined α -index within 72 hours of acute ischaemic stroke between dead or dependent and independent patients at 30 days following acute ictus (5.5 ms/ mmHg (IQR: 3.7 to 7.1) vs. 5.0 (3.3. to 7.7), $p=0.62$). On multiple regression analysis, only age and TACS were predictive of short-term (30-day) outcome (Table 3.3).

Table 3.3 Predictor Variables at Admission of Death/ Dependence versus Independence at Day 30 Following Acute Ischaemic Stroke: Results of a Multiple Regression Analysis.

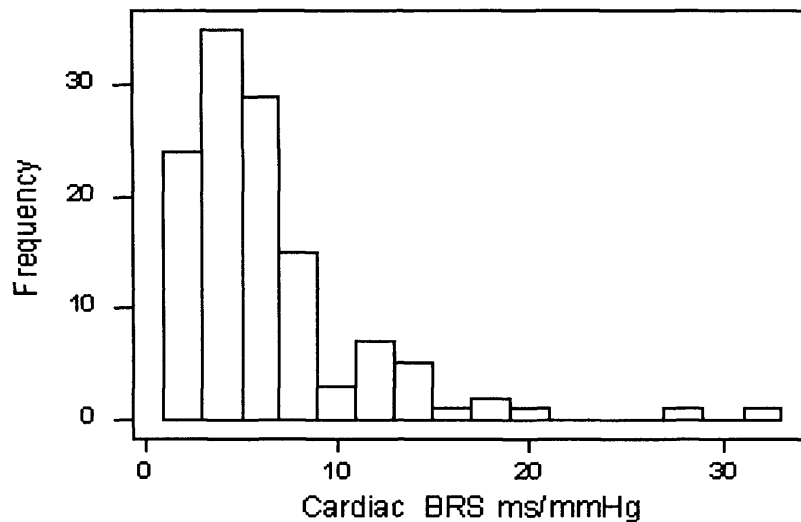
Predictor	Coefficient	P value
NIHSS score >8	0.59	<0.001
Age (years)	-0.01	0.004
Total Anterior Circulation Stroke	-0.30	0.05
Cardiac Baroreceptor Sensitivity (ms/ mmHg)	0.01	0.21
Admission Diurnal SBP Fall (mmHg)	0.00	0.24
Admission Casual SBP (mmHg)	0.00	0.68
Admission 24-hour SBP (mmHg)	0.00	0.93

$S = 0.37$, $R\text{-Sq} = 54\%$, $R\text{-Sq (adj)} = 45.6\%$.

The overall mortality rate at the end of follow-up was 17.7% ($n=22$), over a median period of 1508 days (range 9 to 2656 days). Outcome was compared between the sixty-three patients with cardiac BRS values greater than the median (5.0 ms/ mmHg) for the whole group and sixty-one patients with cardiac BRS values equal to or below the median for the whole group. In the 63 patients with lower than median BRS the median (IQR) BRS for this group was 3.4 ms/mmHg (2.7-4.1). In the 61 patients with

higher than median BRS the median (IQR) BRS for this group was 7.4 ms/mmHg (6.0-11.2) and the BRS distribution curve can be seen in figure 3.2.

Figure 3.2. Cardiac BRS distribution Curve.



There were also significant differences in PI variability, assessed from SD of beat-to-beat recordings, with reduced variability seen in the impaired cardiac BRS group (26.4 ms [IQR: 18.6 to 49.8] versus 51.0 [34.4 to 63.7], $p < 0.001$). There were no significant differences in age, sex, admission NIHSS score, stroke type using the OCSP classification, or BP parameters between the two groups (Table 3.4).

Table 3.4 Admission Parameters in Acute Ischaemic Stroke Patients with Impaired (<median) and Normal (>median) Cardiac Baroreceptor Sensitivity.

Variable	Cardiac BRS (≤ 5.0 msec/ mmHg)	Cardiac BRS (> 5.0 msec/ mmHg)	P value
Age (years)	70.2 (10.5)	70.6 (11.7)	0.83
Sex (M: F)	33: 28	35: 28	>0.2
NIHSS score	5 (3, 9)	8 (4, 11)	0.13
OCSF Classification (TACS:PACS:LACS: POCS)	22: 15: 18: 6	21: 20: 16: 6	>0.2
Casual BP (mmHg)			
Systolic	164 (25)	161 (28)	0.59
Diastolic	91 (15)	85 (16)	0.05
Mean Arterial	115 (16)	111 (18)	0.15
Pulse Pressure	73 (21)	76 (20)	0.48
24-hour BP (mmHg)			
Systolic	157 (22)	153 (21)	0.35
Diastolic	89 (11)	84 (13)	0.06
Mean Arterial	113 (14)	110 (15)	0.24
Pulse Pressure	68 (16)	68 (15)	0.88
Diurnal BP Fall			
Systolic	4 (-6, 11)	6 (-1, 15)	0.18
Diastolic	3 (-1, 9)	6 (0, 11)	0.55

Values presented as mean (standard deviation) for normally distributed data and median (IQR) for non-normally distributed data.

However, those patients with impaired cardiac BRS (\leq median) had a significantly higher mortality rate during the follow-up period (28 vs. 8%, $p<0.006$, Figure 3.3). Furthermore, those patients with impaired cardiac BRS had a significantly higher mortality rate even when admission stroke severity (using the NIHSS score) was considered (Figure 3.4) and in the multiple regression analysis BRS was highly significant in influencing survival ($p=0.007$) with a positive regression coefficient.

Figure 3.3 Kaplan-Meier Survival Curve by Subgroups of Cardiac Baroreceptor Sensitivity in Ischaemic Stroke Patients.

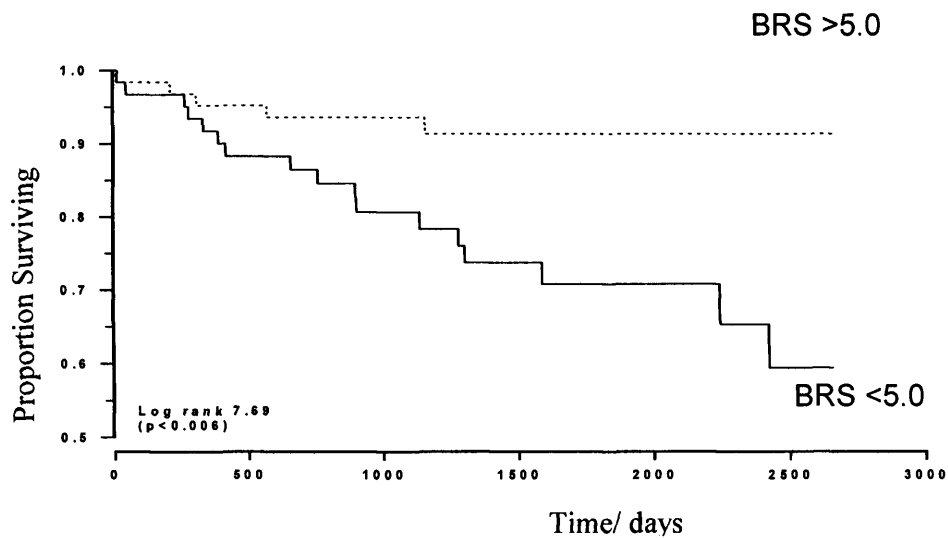
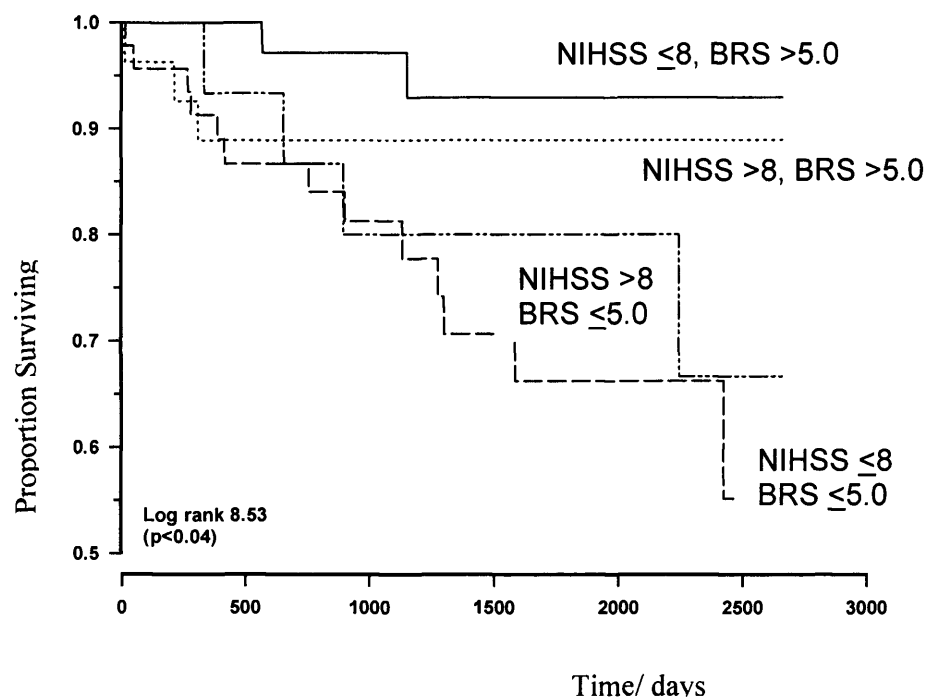


Figure 3.4 Kaplan-Meier Survival Curve by Subgroups of Cardiac Baroreceptor Sensitivity and National Institutes of Health Stroke Scale score in Ischaemic Stroke



3.5 Discussion

To my knowledge, this is the first study to report the long-term prognostic significance of impaired cardiac BRS following acute ischaemic stroke. Over a median follow-up period of 1508 days, stroke patients with significantly impaired cardiac BRS (\leq median) had a significantly poorer prognosis with a mortality rate of 28% compared to 8% in patients without significantly impaired cardiac BRS ($>$ median). The long-term prognostic significance of cardiac BRS was independent of other well-recognised variables, including age, BP, stroke severity and stroke subtype. Cardiac BRS, assessed by the combined α -index, was significantly lower in 124 stroke patients studied within 72 hours of neuroradiologically-confirmed acute ischaemic stroke compared to control subjects matched with respect to age, sex, and casual BP confirming previously reported findings in a smaller study of 37 separate acute ischaemic and haemorrhagic stroke patients [260] and also the results of Chapter 4.

Impairment of cardiac BRS as an indicator of poor prognosis has also been demonstrated in patients following acute myocardial infarction. La Rovere et al [160] assessed cardiac BRS within 30 days of acute myocardial infarction, and reported a mortality rate of 50% during a follow-up period of 2 years in patients with a cardiac BRS <3.0 ms/mmHg compared to 3% in patients with a cardiac BRS >3.0 ms/mmHg. In the much larger multi-centre ATRAMI study [154], cardiac BRS was found to be independent of other significant prognostic indicators including left ventricular ejection fraction.

Possible mechanisms to explain the prognostic significance of impaired cardiac BRS have been extensively studied in post-myocardial infarction patients. Impaired vagal

reflexes may be associated with the development of life-threatening arrhythmias and/or sudden death [66;89;124;160] in post-myocardial infarction patients with reduced cardiac BRS during a follow-up period of up to 2 years. Reduced cardiac BRS is associated with a shift in autonomic balance towards sympathetic dominance, not only as a result of impaired parasympathetic function, but also as a result of increased sympathetic activity that, in addition to arrhythmogenesis, also leads to an increase in coronary vasoconstriction. Post-myocardial infarction patients with more depressed cardiac BRS are at greater risk of having significant 3-vessel coronary artery disease and an occluded infarct-related coronary artery [199], whereas increased cardiac BRS is associated with increased coronary artery patency following thrombolysis treatment [214]. Sympathetic hyperactivity following myocardial infarction has other important effects, including increased platelet aggregability and impaired ventricular remodelling [57;157].

Impaired cardiac BRS following acute stroke may also be associated with central autonomic cardiovascular dysautoregulation, involving both the parasympathetic [149;150;152;222] and sympathetic nervous systems [204;211;221;300] and the poor prognosis associated with impaired cardiac BRS may be manifest through cardiac arrhythmias, which are a common complication of acute stroke [163;196;211;221;300]. In a small study of 10 patients, Guibilei et al [108] reported that the 4 patients with cardiac arrhythmias had significantly lower high frequency power of heart rate variability than those without arrhythmias. It is a limitation of this study that causes of death were not recorded, neither was 24-hour electrocardiography undertaken making it impossible to confirm or refute arrhythmia as a possible pathological mechanism to explain the poor prognosis in impaired cardiac BRS in stroke patients. Furthermore, any treatment, including antithrombotic, statin and ACE

inhibitor therapy, instituted during follow-up was not recorded. Such agents may be of prognostic benefit and influence disease mechanisms, although there is no reason to suppose that the impaired cardiac BRS group were less or more likely to receive these therapies. Furthermore, this study has reported other evidence of autonomic disturbance, including reduced PI variability in the impaired cardiac BRS group, again reflecting sympathetic predominance, and associated with poor prognosis in acute myocardial infarction patients secondary to arrhythmias [333]. The reduced diurnal BP fall in acute stroke patients compared to control subjects seen in this study is in keeping with previous findings, and again likely to reflect central autonomic dysfunction [62].

There is some evidence for hemispheric laterality in autonomic cardiovascular and baroreceptor control and Hilz et al [121] studied cardiac BRS in 15 patients with epilepsy refractory to drug therapy during ipsilateral hemispheric inactivation by intra carotid artery amobarbital sodium injection. They found that increased sympathetic nervous system activity and impaired cardiac BRS was only seen in left hemispheric inactivation [121], a finding that was repeated in other epilepsy studies [336;337]. Contradictory evidence of hemispheric laterality has also been reported in acute stroke patients. A reduction in the high frequency power and an associated increase in the low-to-high frequency ratio of PI variability following right hemisphere stroke have been reported [260]. Barron et al [19] found reduced parasympathetic cardiac innervation following right hemisphere stroke, again confirming sympathetic predominance in association with right hemisphere stroke. However, Korpelainen et al [151] found autonomic cardiovascular disturbances in both right and left hemisphere and medullary, but not pontine, infarcts. It is therefore possible that impaired cardiac

BRS may be related to stroke site and type, though this information is not provided from the present study.

3.6 Conclusion.

1. Cardiac BRS is significantly lower in stroke patients compared to control subjects matched for age, sex and casual BP.
2. Impaired cardiac BRS is of long-term prognostic significance following acute stroke.
3. The mechanisms may include the arrhythmogenic potential of alterations in cardiovascular autonomic balance or other manifestations of sympathetic predominance, including increased platelet aggregability.
4. Further work is needed to elucidate the pathophysiological mechanisms, and in particular the importance of stroke type and site so therapeutic strategies, including prophylactic arrhythmic agents to high-risk groups or ACE inhibitors to increase cardiac BRS activity, could then be tested.

4 Dynamic cerebral autoregulation in acute ischaemic stroke patients detected from spontaneous transient changes in blood pressure.

4.1 Summary.

To allow the degree and duration of impairment of dynamic CA following acute stroke to be assessed and the relationship between dynamic CA, BP and prognosis to be investigated there remains a need for a clinically practical, widely applicable technique for the measurement of dynamic CA. Dynamic CA is usually calculated from the CBFV response to BP changes produced by physiological manoeuvres especially THC release (section 2.5.1). Some of these manoeuvres are poorly tolerated or may introduce confounding factors such as CO₂ changes or sympathetic nervous system stimulation. A more physiological approach would be to use data collected with minimal disturbance to the patient, avoiding confounding of the results.

In this chapter the use of Aaslid's analysis (section 2.6.2.1) applied to spontaneously occurring pressor and depressor BP changes to estimate dynamic CA in acute ischaemic stroke patients was investigated.

Using this analysis I was able to demonstrate the significant impairment in dynamic CA from both pressor and depressor BP changes expected in acute ischaemic stroke patients compared to age and BP matched controls that has previously been shown in studies using THC [59]. In addition, an increase in BP variability and a reduction in cardiac BRS was also demonstrated in keeping with earlier work [253;256].

4.2 Introduction.

Cardiovascular homeostasis is abnormal following acute stroke and is discussed in some detail in section 1.6.9. Initially there is an increased BP, which tends to fall over the next week, and an increase is also seen in beat-to-beat BPV, both of which are associated with a worse prognosis in terms of death and disability [263], independent of MAP levels and stroke severity. Most studies have shown hypertension in the acute phase of stroke to be associated with a worse outcome but the mechanisms are unclear. One possibility is that impaired dynamic CA in acute stroke allows CBF flow to be passively dependent on systemic BP so that the brain is not protected from fluctuations in systemic BP and when transmitted to the cerebral circulation these may affect viability of the ischaemic penumbra and infarct size, although this remains to be proven. It is therefore important to find a widely applicable method of measuring dynamic CA in acute stroke patients, to allow detailed investigation of the relationship between dynamic CA, altered cardiovascular homeostasis and outcome, and to allow study of the relative merits of treatment of BP in the acute stroke period.

Non-pharmacological manoeuvres to induce rapid perturbations in BP, e.g. the sudden release of THC or the Valsalva manoeuvre have commonly been used to assess dynamic CA but may be problematic (section 2.5). They may be unacceptable or impractical for some patients and can induce changes in sympathetic nervous system activity, respiration, cardiac output and $p\text{CO}_2$, all of which may affect dynamic CA directly or indirectly. These potential problems could be avoided by using spontaneous BP fluctuations in recordings made at rest.

The aims of this study were to assess if impaired dynamic CA following acute cerebral infarction could be demonstrated using spontaneous transient BP changes as

the BP stimulus, and to study the relation between the changes in dynamic CA post-stroke with cardiac BRS and beat-to-beat BPV.

4.3 Methods.

4.3.1 Subjects.

Fifty-six CT or MRI diagnosed ischaemic stroke patients were recruited (PE (23), SLD (33)) within 72 hours of ictus from 2 of the 3 the Stroke Units of the University Hospitals of Leicester NHS Trust. The Stroke Unit and the Acute Admissions Unit at Glenfield Hospital were visited daily during the week and the Stroke Unit and Acute Admission Unit at Leicester General Hospital were visited between one and three times weekly to recruit patients (PE). Stroke types were classified using the OSCP classification and functional severity was graded using the Barthel index (section 2.8). Patients were excluded if they had a history of previous stroke. They were pair-matched for age (to within 10 years), sex and MAP (to within 10mmHg) with 56 controls who were recruited from a volunteer register and from departmental staff SLD (n=56). Some controls were hypertensive (systolic BP \geq 160/90mmHg) but were otherwise free from significant cardiovascular or cerebrovascular disease based on history, clinical examination and baseline investigations including a 12 lead ECG. None of the patients or controls was in atrial fibrillation or diabetic, had autonomic disturbance, or was taking any medication known to affect the cardiovascular or autonomic nervous system at the time of the study.

4.3.2 Protocol.

Cerebral autoregulatory studies were conducted as described in 2.4.2.

Once a stable baseline had been achieved (<10% variation in BP and CBFV) two recordings of 5 minutes duration, taken 5 minutes apart, were then made with the subject remaining supine and awake and the mean values from these two recordings were used for statistical analysis.

The TCD, Finapres, ECG and TINA signals were then processed and edited as described in section 2.4.3 producing the parameters for analysis.

4.3.3 Dynamic Cerebral Autoregulation.

The MAP trace was inspected and spontaneous transient pressor and depressor changes were manually selected. Using the method of Aaslid [306], the calculated dynamic ARI was derived from the response of the CBFV to spontaneous transient pressor and depressor changes in MAP (transient BP changes defined as ≥ 5 mmHg) (section 2.6.2.1).

4.3.4 Cardiac baroreceptor sensitivity and SBP and pulse interval variability.

Power spectral analysis estimates of PI variability, SBP variability and cardiac BRS (combined α) were obtained as described in section 2.7.1.

SBP, MAP and DBP beat-to-beat variability were separately calculated as the standard deviation of the beat-to-beat changes derived from the 10 minute baseline recordings.

Analysis of CA indices from CBFV involves manual selection of the point of BP stimuli on the recordings and all of the raw data (i.e. data recorded by PE and SLD) was therefore fully reanalysed from scratch by the author to avoid bias.

4.3.5 Statistical Methods.

Student's paired t-tests were used for comparison between the individual pairs for stroke patients and controls and to test for differences within non-stroke and stroke hemispheres in the same subject. These data are presented as mean (SD) along with 95% confidence intervals (CI).

Data not normally distributed were compared using the Mann-Whitney U test, which was used for comparison of variables between right hemisphere and left hemisphere strokes, and these data are presented as median (IQR).

To compare variables between three categories of stroke types a Kruskal-Wallis test was used.

Linear regression was used to assess the relationship between ARI and age, sex, MAP, stroke severity, BRS and BP variability.

Spearman's rank correlation was used to assess the relationship between ARI and stroke severity.

Statistical significance was taken at the 5% level using the statistical package, Minitab for Windows, release 12.21, Minitab Inc.

4.4 Results.

56 age, sex and MAP matched stroke patients and controls were studied, baseline demographic and BP details are given in Table 4.1. Clinical diagnosis using the OCSF classification identified 25 TACS and PACS, 21 LACS and 10 POCS.

Transcutaneous CO₂ levels remained constant in all subjects throughout the study with no difference between stroke patients and controls.

Table 4.1. Baseline demographic data for stroke and control groups.

	Control n=56	Stroke n=56	Difference (95% CI)
Age (years)	69±7 (51-81)	70±9 (45-87)	↑2±5 (0, 3) †
Gender m:f	43:13	43:13	N/A
BMI* (kg/m ²)	28±4 (20-35)	25±4 (17-35)	↓3±6 (1, 4) †
Systolic BP (mmHg)	150±22 (103-208)	156±29 (104-215)	↑6±31 (-2, 14)
Diastolic BP (mmHg)	76±13 (53-112)	80±17 (47-129)	↑4±15 (0, 15) †
Mean BP (mmHg)	101±15 (68-146)	106±18 (71-146)	↑4±17 (0, 9)
Mean PI (ms)	960±154 (652-1325)	866±114 (584-1195)	↓90±177 (41, 140) †
CBFV (cm/s)	44±9	41±11	↓2±12 (-1, 6)
Barthel Index	N/A	60 (35, 89)	N/A

*BMI=body mass index; PI=pulse interval

† p≤0.05 for differences between stroke and control groups.

BP taken as mean of two 10-minute Finapres recordings.

Data presented as mean±SD. Range in parentheses.

Barthel Index presented as median and IQR.

Of the 56 stroke patients, a spontaneous transient BP rise or fall ≥5 mmHg could not be found in 4 and 3 subjects respectively, and for the 56 controls, a spontaneous transient BP rise or fall ≥5 mmHg could not be found in 4 and 7 subjects respectively. Mean CBFV was similar for both hemispheres in the stroke and control groups and also between controls and the non-affected side in stroke patients (43.5±8.7 cm/s and 42.1±10.6 cm/s respectively). No difference was found in the magnitude or rate of change of spontaneous pressor and depressor BP transients between stroke patients and controls (see Table 4.2).

Table 4.2. Dynamic cerebral autoregulation index, along with magnitude and rate of blood pressure change for spontaneous transient pressor and depressor stimuli in the stroke and control groups.

	Stroke	Control	Difference	P value
<u>Pressor Stimulus</u> n=48				
BP rise (mmHg)	9.2±2.8	8.7±2.8	0.5±4.8 (95% CI -0.9, 1.9)	(p=0.47)
Rate of BP change (mmHg/s)	3.4±1.9	3.1±1.1	0.3±2.3 (95% CI -0.4, 0.9)	(p=0.42)
DARI	3.2±2.0	4.5±2.0	1.3±2.9 (95% CI 0.5, 2.1)	(p=0.003)
<u>Depressor Stimulus</u> n=47				
BP fall (mmHg)	10.3±4.2	9.5±3.2	0.8±3.2 (95% CI -0.9, 2.5)	(p=0.33)
Rate of BP change (mmHg/s)	2.9±1.7	2.7±1.2	0.2±2.2 (95% CI -0.4, 0.9)	(p=0.46)
DARI	3.8±2.2	4.7±2.2	1.0±2.9 (95% CI 0.1, 1.8)	(p=0.03)

Mean of data for right and left hemispheres used in each case. Data presented as mean±SD.

n=number of stroke and control matched pairs used for comparison.

Not all subjects had a pressor or depressor stimulus ≥5mmHg during the two 5 minute recordings (see results section).

p value for differences between stroke and control groups.

dARI= dynamic ARI

There was no significant difference in dynamic ARI between the affected and unaffected hemispheres in the stroke group (see Table 4.3) or between the right and left hemispheres in the controls so the mean value for the two hemispheres was used in further comparisons. Dynamic CA, whether assessed using pressor or depressor BP transients, was significantly reduced in stroke patients compared to controls (see Table 4.2). Linear regression showed that dynamic ARI in both stroke patients and controls was independent of baseline BP levels, age and gender. Stroke type, defined using OCSF classification, did not significantly influence dynamic ARI (see Table 4.4). No significant correlation was found between stroke severity, as reflected by the Barthel

Index, and dynamic ARI derived using pressor BP stimuli ($p=0.09$) or depressor stimuli ($p=0.052$) when tested using Spearman's rank correlation test.

Table 4.3. Differences in dynamic ARI in stroke subjects between stroke hemispheres and with pressor and depressor stimuli.

		Pressor Stimulus		Depressor Stimulus	
	n	dARI (IQR)	n	dARI (IQR)	Difference in dARI †
<u>Right hemisphere stroke</u>					
Affected side	20	3.2 (1.4, 5.0)	22	3.7 (1.7, 6.6)	0.4 ± 2.4 (95% CI -1.6, 0.7) $p=0.4$
Non-affected side	19	3.0 (1.8, 4.8)	20	4.0 (2.2, 5.3)	0.3 ± 1.4 (95% CI -1.0, 0.4) $p=0.35$
<u>Left hemisphere stroke</u>					
Affected side	28	3.0 (2.1, 4.5)	29	2.8 (1.8, 4.8)	0.4 ± 2.7 (95% CI -0.7, 1.5) $p=0.47$
Non-affected side	30	3.3 (0.6, 4.8)	29	3.3 (1.0, 5.6)	0.0 ± 3.0 (95% CI -1.2, 1.1) $p=0.94$
Difference between right and left hemisphere stroke. *		0.1 (95% CI -1.5, 1.1) $p=0.93$		0.7 (95% CI -0.8, 2.1) $p=0.37$	

Data presented as medians (IQR).

* Comparison between right and left hemisphere strokes (using Mann Whitney U test).

† Comparison of dynamic ARI (dARI) derived from pressor and depressor stimuli (using Student's paired t-test)

A spontaneous transient BP rise or fall ≥ 5 mmHg could not be found in 4 and 3 stroke patients respectively

Table 4.4. Dynamic ARI, pulse interval and SBP variability and cardiac baroreceptor sensitivity for stroke patients in different OCSF classification groups.

		PACI /TACI n=25	LACI n=21	POCI n=10
dARI pressor	Affected hemisphere	3.0 (2.0, 4.0)	3.4 (1.4, 5.0)	4.3 (2.9, 5.2)
	Unaffected hemisphere	2.3 (0.4, 5.4)	3.5 (1.9, 4.1)	3.0 (1.8, 4.5)
dARI depressor	Affected hemisphere	2.9 (2.0, 5.7)	3.4 (1.7, 6.0)	2.8 (1.4, 4.2)
	Unaffected hemisphere	4.8 (1.0, 6.0)	3.2 (1.5, 4.9)	4.3 (1.5, 5.2)
Pulse Interval variability (ms)		25 (20,35)	20 (18,27)	22 (15, 30)
SBP variability (mmHg)		6.0 (4.9,8.0)	7.3 (5.5,9.3)	4.7 (4.1, 8.4)
BRS (ms/mmHg)		4.3 (3.5, 6.7)	4.2 (2.5, 5.9)	5.2 (2.4, 7.8)
Barthel index		43 (20, 65)	80 (54, 100)	65 (44, 93)

Data presented as median (IQR). dARI= dynamic ARI

BRS taken as the square root of the ratio of the powers of PI to SBP from spectral analysis.

SBP variability taken as the square root of the total power of SBP from spectral analysis.

PI variability taken as the square root of the total power of PI from spectral analysis.

No significant differences were seen between stroke types for the above parameter

Systolic BP variability, assessed using power spectral analysis, was significantly greater in the stroke group compared to the controls in the VLF band ($p=0.008$) but was similar in the LF and HF bands (see Table 4.5). SBP, DBP and MAP variability were also all significantly higher in the stroke group compared to the controls when taken as the standard deviation of all measurements during the recording period, being 8.2 ± 3.1 mmHg, 3.9 ± 1.5 mmHg and 5.2 ± 1.8 mmHg respectively in the patient group, and 6.7 ± 2.1 mmHg, 3.2 ± 1.3 mmHg and 4.3 ± 1.5 mmHg respectively in the control group ($p<0.05$ for all BP groups). Pulse interval variability was similar in the stroke patients and controls, and between right and left hemisphere strokes (see Tables 4.5 & 4.6).

Table 4.5. Pulse Interval and SBP variability assessed by spectral analysis.

	n	Pulse interval variability (ms)				SBP variability (mmHg)			
Frequency		All	VLF	LF	HF	All	VLF	LF	HF
ranges *		Frequencies				Frequencies			
Stroke	51	28.8±19.7	16.4±12.7	13.0±10.7	10.4±7.4	6.6±2.2	4.2±1.8	2.6±1.1	1.9±0.9
Control	51	31.2±13.4	16.0±7.6	14.6±6.9	13.1±7.7	5.7±1.7	3.4±1.2	2.5±0.8	1.8±0.9
Difference		2.4±23.9	0.4±14.3	1.6±13.4	2.7±11.5	1.0±2.9	0.8±2.1	0.1±1.4	0.2±1.3
95% CI		(-4.3,9.1)	(-4.0,3.6)	(-2.1,5.4)	(-0.6,5.9)	(0.2,1.8)	(-0.2,-1.4)	(-0.5,0.3)	(-0.5,0.2)
p-value		p=0.476	p=0.849	p=0.388	p=0.107	p=0.018	p=0.008	p=0.49	p=0.337

* VLF=0.02-0.05Hz; LF=0.05-0.15Hz; HF=0.15-0.4Hz.

Data presented as mean±SD with 95% confidence interval.

p values are for the differences between stroke and control groups.

2 stroke patients and 3 controls had too many ectopic beats on their ECG to be included in spectral analysis, therefore 51 pairs used in analysis.

Table 4.6. Pulse Interval Variability and SBP variability for right and left hemisphere stroke patients.

Hemisphere affected by stroke	n	Pulse interval variability (ms)				SBP variability (mmHg)			
		All Frequencies	VLF	LF	HF	All Frequencies	VLF	LF	HF
Right	24	24.7 (19.3, 31.0)	13.2 (9.8, 18.7)	9.9 (8.9, 13.7)	8.1 (6.6, 12.2)	6.1 (4.8, 8.2)	3.7 (3.0, 5.0)	2.4 (1.7, 3.1)	1.9 (1.2, 2.7)
Left	30	21.2 (18.0, 30.6)	12.4 (10.1, 15.9)	8.9 (6.3, 13.0)	6.8 (4.7, 12.2)	6.4 (4.5, 8.5)	3.7 (2.8, 5.3)	2.5 (1.6, 3.4)	1.7 (1.2, 2.3)
95% CI		(-2.8, 7.7)	(-2.0, 4.9)	(-0.4, 4.1)	(-0.9, 3.4)	(-1.0, 1.6)	(-0.7, 1.2)	(-0.4, 0.9)	(-0.3, 0.7)
p-value		p=0.38	p=0.40	p=0.11	p=0.21	p=0.83	p=0.86	p=0.46	p=0.4

Data presented as median (IQR).

2 patients had too many ectopic beats on their ECG to be included in spectral analysis.

Cardiac BRS was significantly reduced in the stroke patients, being 4.9 ± 2.6 msec/mmHg compared to 6.2 ± 3.2 msec/mmHg in the control group ($p=0.026$). Stroke type, as defined by the OSCP classification or stroke severity (based on Barthel index) did not influence PI or SBP variability or BRS (see Table 4.4).

4.5 Discussion.

In the present study dynamic CA in stroke patients, assessed using spontaneous transient pressor and depressor changes in MAP recorded over a 10 minute period, was globally impaired, systolic BP variability was increased and cardiac BRS reduced when compared to an age, sex and MAP pair matched control group.

This is consistent with a smaller study that used only THC release to stimulate a depressor change, where a dynamic ARI value of 4.1 ± 3.3 and 6.2 ± 2.3 was found for the stroke and the control groups respectively [60]. As the THC technique is often painful it was unclear whether the previously reported difference was related to the possible increase in sympathetic nervous system activity provoked by the stimulus itself or was a true phenomenon related to cerebral ischaemia. That significant differences in dynamic CA were also found using spontaneous transient BP stimuli suggests that this is a true phenomenon but as the mechanisms underlying CA are poorly understood it cannot be assumed that pressor and depressor stimuli necessarily invoke the same pathophysiological mechanisms.

As far as I know this is the first use of spontaneous transient BP changes in the analysis of dynamic CA in stroke patients. The use of spontaneous transient changes in BP avoids stimulation of the sympathetic nervous system, eliminates the need for subject participation and does not affect respiratory rate or depth and, hence, $p\text{CO}_2$

levels and cardiac output, which may occur to varying degrees in interactive tests such as THC release or the Valsalva manoeuvre. In normal subjects dynamic ARI was found to be independent of the type of manoeuvre used to induce the BP change when positive and negative spontaneous transients, THC release, the cold pressor test, isometric hand grip, lower body negative pressure release and the Valsalva manoeuvre were tested in spite of the different magnitudes of the BP stimuli produced by the different manoeuvres [227].

The reduction in dynamic CA in stroke patients compared to controls could not be accounted for by differences in systemic MAP levels or age as matching eliminated these as factors and, additionally, linear regression showed dynamic ARI to be independent of these variables. This is in keeping with recently published data from our group showing no effect of age [38], or BP [25;38] on dynamic CA, and with work by Lipsitz et al showing cerebral autoregulatory capacity is retained in elderly normotensive and elderly hypertensive subjects in response to orthostatic hypotension [173]. In the present study the stimuli used to test dynamic CA were similar in the stroke and control groups in both the magnitude of the BP rise and fall and in its rate of change and so stimulus characteristics could also not account for the differences found.

The impairment in dynamic CA was not confined to the stroke hemisphere and the lack of a significant difference in dynamic CA between the affected and unaffected sides indicates a global impairment of dynamic CA with stroke. It has previously been shown that cerebral haemodynamics, including static and dynamic CA can be depressed both locally and distant from the site of infarction and the mechanism of this transhemispheric communication are discussed in section 1.7.

Overall BP variability was increased, mainly in the VLF band in stroke patients compared to controls but no significant difference was found in PI variability in any spectral band. In the BP spectra the HF band is largely independent of cardiac vagal tone and is mostly influenced by the mechanical effects of respiration on the heart and great vessels. The LF power is determined by a combination of factors including sympathetic activity and vagal tone, the cardiac baroreflex arc (which was impaired in the stroke group) and vasomotor reactivity. The VLF band is thought to be influenced by certain factors that contribute to vasomotor tone, such as the renin-angiotensin system, endothelial factors and local thermoregulatory mechanisms. The increase in BP variability in the absence of a change in PI variability might be explained by changes in the baroreflex control of vasomotor tone which has been demonstrated in acute stroke patients [261] and by the reduction in cardiac BRS although the exact underlying mechanisms are uncertain.

Increased beat-to-beat BP variability has been shown to be associated with a worse prognosis in terms of death and disability in acute stroke patients [63] and although the exact mechanism of these findings is unknown it could hypothetically be related to the impairment in dynamic CA. As CBF becomes more passive to changes in BP, even a small fall in BP may reduce CBF enough to make the difference between viability and cell death in the ischaemic penumbra.

No relation was seen between stroke severity, OCSF classification or affected hemisphere and dynamic CA, BRS or BP variability but this may be just due to the size of the study.

Changes in CBF can only be reliably deduced from CBFV providing changes do not occur in the diameter of the insonated vessel and this is discussed in detail in 2.1.2.5. We do not know whether the impairment of dynamic CA is a permanent or transient

change following stroke and, as yet, there is no long-term follow up data available. Data obtained using THC release in the acute post ictal phase and again 14 days later showed no recovery of dynamic CA over that period [60]. We also do not know whether abnormalities in dynamic CA occur as a consequence of the stroke, as is commonly supposed, or whether the reduction in dynamic CA actually predates the stroke and therefore defines a population more at risk of cerebrovascular disease. More work is needed to explore the relation between impaired dynamic CA and acute stroke.

4.6 Conclusion.

1. Acute ischaemic stroke is associated with a global impairment of dynamic CA.
2. Spontaneous pressor and depressor BP transients can be used to successfully detect the difference in dynamic ARI with minimal disturbance of the patient.

5 The effects of bendrofluazide on static and dynamic cerebral autoregulation, blood pressure variability and cardiac baroreceptor sensitivity in the immediate post-stroke period.

5.1 Summary.

The optimal management of elevated BP levels following acute ischaemic stroke is unknown. There are many factors that may affect outcome in relation to interventions to lower raised BP levels including the characteristics of the particular stroke i.e. whether it is ischaemic or haemorrhagic, the site and size of the infarct and also the state of CA at that time (demonstrated to be impaired in Chapter 4) and its ability to protect the brain tissue during abnormal BP activity.

In this double blind, randomised, placebo controlled pilot study the effect of oral bendrofluazide 2.5mg daily administered for 1 week on both static and dynamic CA and other haemodynamic parameters, starting within about 4 days of ischaemic stroke onset in patients with mild to moderate hypertension was studied.

No significant change in BP or any other haemodynamic parameter was found over the study period and neither static nor dynamic CA in the active treatment or the placebo groups differed significantly after 7 days of treatment. It is likely that onset of antihypertensive activity of bendrofluazide is too slow to be useful in this setting and bendrofluazide was not found to have any significant effect on CA independent of its antihypertensive effects. It is concluded from this that if BP reduction is required in the acute post-ictal phase of ischaemic stroke, bendrofluazide is ineffective and the

use of other antihypertensive agents, possibly ACE inhibitors should be considered (section 1.5.4).

5.2 Introduction.

Optimal BP management in terms of starting, continuing or stopping antihypertensive treatment in the acute and sub-acute post-stroke phases is unclear. The paucity of studies assessing the effects of deliberately elevating and lowering BP immediately following stroke have been discussed in section 1.6.10. The interaction of abnormal systemic haemodynamics (section 1.6.9) and impaired CA (Chapter 4 and section 1.7) may theoretically influence prognosis after stroke by allowing large fluctuations in CBF in response to changes in systemic BP rather than maintaining CBF within the stable, narrow limits required for optimal cerebral metabolism. This may be most critical for neurones in the ischaemic penumbra and may influence infarct size and could be relevant to the question of how to manage hypertension in the acute stages of stroke.

No previous studies have addressed the effect of any antihypertensive drug on static or dynamic CA in the acute or subacute post ictal phase of stroke. The choice of different antihypertensives is wide and their effects on cerebral haemodynamics, as far as they are known, are discussed in 1.5. Bendrofluazide (section 1.5.1) fulfils many of the characteristics of an ideal antihypertensive for this situation in that it is known to be effective in lowering BP with few side effects, has a gradual onset of antihypertensive effect avoiding a precipitous fall in BP, important in view of the likely impairment of dynamic CA, and is effective in the primary (see 1.6.7) and secondary (see 1.6.8) prevention of stroke. Also, bendrofluazide is already in common use in 69% of patients admitted to hospital with an acute ischaemic stroke

who are already receiving antihypertensive medication (data from the Stroke Register for the University Hospitals of Leicester NHS Trust).

This pilot study was designed to test the hypothesis that oral bendrofluazide 2.5mg daily would reduce systemic BP over 7 days of treatment without causing further impairment of static and dynamic CA in patients who were hypertensive within the first few days of an ischaemic stroke. To the authors knowledge thiazide diuretics have not been tested in acute stroke before, and their effect on CA has not previously been studied although they are not thought to significantly affect on cerebral vessels or CBF [254;276;310].

5.3 Methods.

5.3.1 Subjects.

Sixty-eight CT or MRI diagnosed hypertensive ischaemic stroke patients were recruited within 96 hours of ictus from 2 of the 3 Stroke Units of the University Hospitals of Leicester NHS Trust. The Stroke Unit and the Acute Admissions Unit at Glenfield Hospital were visited daily during the week and the Stroke Unit and Acute Admission Unit at Leicester General Hospital were visited between one and three times weekly to recruit patients. Stroke types were classified using the OSCP classification and graded using the Barthel index, mRS and NIHSS scales (section 2.8). Within 96 hours of stroke onset subjects underwent 24-hour ABPM (Spacelabs 90207) recording at 20-minute intervals during the day (0700hrs-2200hrs) and 30-minute intervals at night (22.01hrs-06.59hrs) and were only included in the study if their 24-hour mean BP >130/80 mmHg or their daytime mean BP >135/85 mmHg. The

4 patients who refused 24-hour ABPM were included if the mean of 3 casual BP readings were >140/85 mmHg on 2 consecutive days.

5.3.2 Exclusion Criteria.

Patients were excluded if they had a functional deficit from a previous stroke, atrial fibrillation, diabetes, autonomic disturbance, recent myocardial infarction, significant electrolyte disturbance, were taking any medication known to affect the cardiovascular or autonomic nervous system at the time of the study or if they were unable to swallow safely.

5.3.3 Protocol.

The subjects were block randomised (4 per block) to receive a capsule containing either bendrofluazide 2.5mg daily for one week or matching placebo. The volunteers underwent cerebral autoregulatory studies prior to taking the first study capsule and again after one week when trial medication was stopped.

Cerebral autoregulatory studies were conducted as described in 2.4.2.

Once a stable baseline had been achieved (<10% variation in BP and CBFV) two recordings of 10 minutes duration were made with the subject remaining supine and awake and the Finapres was allowed to servo between the recordings. Following this 2 THC manoeuvres were performed, as described in 2.5.1.

The TCD, Finapres, ECG and TINA signals were then processed and edited as described in 2.4.3 producing the parameters for analysis as follows.

Static and dynamic ARI were calculated as described in section 2.6.

BP stimuli were only accepted for analysis if they were accompanied by a corresponding change in CBFV and were ≥ 5 mmHg for spontaneous BP transients and ≥ 10 mmHg for THC responses.

5.3.4 Cardiac baroreceptor sensitivity (BRS) and SBP and pulse interval variability.

Power spectral analysis estimates of PI variability and SBP variability cardiac BRS were obtained as described in section 2.7.1.

SBP, MAP and DBP beat-to-beat variability were separately calculated as the standard deviation of the beat-to-beat changes derived from the 10 minute baseline recordings.

5.3.5 Statistical Methods.

Student's paired t-tests were used for comparisons of normally distributed data. These data are presented as mean (SD).

Non parametric data (ARI) are presented as median (IQR) and were compared using the Wilcoxon signed rank test for paired cases and Mann-Whitney U test for unpaired cases e.g. differences between right hemisphere and left hemisphere strokes.

Spearman's correlation was used to assess the relationship between ARI and age, BP and stroke severity.

Statistical significance was taken at the 5% level using the statistical packages, Minitab for Windows, release 12.21, Minitab Inc and SPSS version 10.1 for windows and R version 1.6.0.

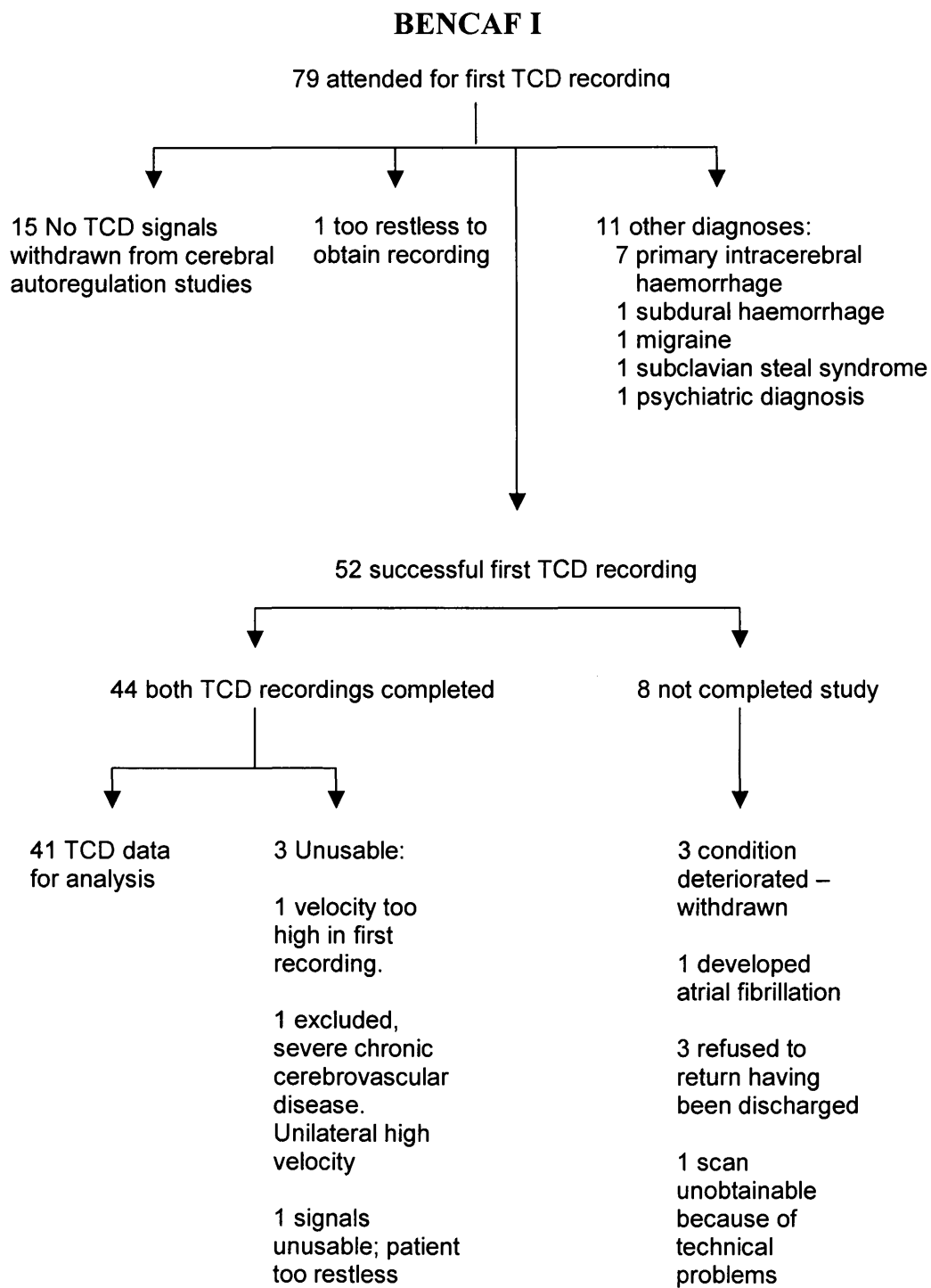


Figure 5.1: Flow Chart of Recruitment

5.4 Results.

Enrolment of patients is shown in a flow chart (figure 5.1). Sixty-eight hypertensive ischaemic stroke patients were enrolled in the study and a further 11 initially enrolled for a first scan were subsequently found to have other diagnoses: 7 had primary intracerebral haemorrhage, 1 subdural haemorrhage, 1 migraine, 1 psychiatric diagnosis with functional symptoms and 1 subclavian steal syndrome. Of the initial 79 recordings no TCD signals could be obtained in 15 (19%) and one patient was too restless to obtain a continual recording. The volunteers without TCD signals were withdrawn from the CA study. Two subjects had very high velocity signals (>100 cm/s) unilaterally suggesting post-stenotic flow or spasm, but a recordable second signal, one in the group that refused to return for a second recording and one who was excluded because of severe chronic cerebrovascular disease after attending for both recordings. Of the 52 volunteers who had a first TCD scan (including those with high velocity signals), 44 completed the full study and attended for both scans. Reasons for failure to attend for the final recording included 3 whose condition deteriorated (one on placebo study treatment sustained an early extension of his stroke and he was no longer able to swallow, one patient on active study treatment experienced angina requiring treatment with nitrates and one was too restless at the second scan to use the recording); one patient went into atrial fibrillation during the study week; 3 patients refused to return for a second recording having been discharged home; one second recording was lost through technical problems.

Table 5.1. Baseline demographic data for all subjects and after randomisation to active and placebo therapy.

	All n = 41	Bendrofluazide n=18	Placebo n=23
Age (years)	69±9 (47-86)	69±8 (52-82)	69±9 (47-86)
Gender m:f	35:7	15:3	19:4
BMI (kg/m ²)	26.4±4.5 (17.6-36)	26.9±4.7 (17.6-34)	26.0±4.4 (19.6-36)
Mean time to Randomisation/ hours	73±22 (26-118)	65±21 (26-98)	79±21 (30-118)
Casual SBP (mmHg)	169±16 (140-199)	172±16 (147-199)	167±16 (140-196)
Casual DBP (mmHg)	93±14 (68-128)	91±14 (68-128)	95±13 (75-127)
Casual MAP (mmHg)	118±12 (101-150)	118±12 (102-148)	119±13 (101-150)
24-hour ABPM: SBP (mmHg)	160±13 (140-186)	160±15 (140-184)	162±11 (142-186)
DBP (mmHg) †	93±10 (65-111)	90±10 (65-104)	97±8 (81-111)
Mean BP (mmHg)	118±10 (97-136)	114±10 (97-132)	120±8 (102-136)
CBFV-affected side (cm/s)	43.3±13.0 (23.2-73.0)	44.1±14.0 (23.2-71.9)	42.6±11.6 (27.3-73.0)
CBFV- unaffected side (cm/s)	44.5±10.0 (25.6-68.1)	45.3±10.5 (25.6-63.5)	43.6±10.3 (27.9-68.1)
Cardiac BRS (lf α) (ms/mmHg)	5.1±2.5	5.1±1.7	5.1±3.0
Barthel Index	85 (45, 100)	95 (40, 100)	75 (45, 100)
National Institute of Health Score	4 (2, 6)	3 (2, 7)	5 (3, 6)
Modified Rankin	3 (2, 4)	2 (2, 4)	3 (2, 4)

BMI=body mass index; † $p \leq 0.05$ for differences between active and placebo groups. Parametric Data presented as mean±SD. Range in parentheses. Barthel Index, National Institute of Health Score, Modified Rankin: median (IQR). Time to Randomisation: time from when last symptom free to time receiving treatment.

5.4.1 Demographics of patients who completed the study.

Baseline demographic details are given in Table 5.1. Of the 44 patients who completed the study, 41 had TCD signals that could be used in the analysis. After randomisation there were 18 patients in the active treatment group and 23 in the placebo group. Using the OCSF classification, the whole group comprised 25 TACS and PACS, 21 LACS and 10 POCS and there were 19 right hemisphere and 22 left hemisphere strokes.

Only the BP data for the 41 patients who had usable TCD signals is presented in this report for clarity, although BP data for the 3 remaining patients did not affect the main results and conclusions of the study.

There was no significant difference in age or BMI between the active and placebo groups (Table 5.1). Mean CBFV was similar in both hemispheres i.e. in the affected and the non-affected sides in the stroke patients and between the first and second recordings in both the active treatment and placebo groups. Cerebral blood flow was 44 ± 14 cm/s and 43 ± 13 cm/s in the group on active treatment in the first and second recordings respectively and 43 ± 12 cm/s and 43 ± 11 cm/s in the placebo group. No patients reported any adverse effects with either active or placebo treatment. All but one patient took all of the study medication and 1 patient missed 3 capsules of active treatment. Exclusion of this subject made no difference to the analysis and the data were included on the grounds that more than half of a long acting drug that is effective at half the dose [41;118] was taken.

The mean time to randomisation to active or placebo treatment was 73 ± 22 hours including one subject who's TCD scan was delayed to 118 hours.

Barthel and NIHSS scores improved in both active and placebo groups over the week of the study but improvement in the mRS score was only significant in the placebo group (Table 5.2).

Table 5.2. Comparison of Stroke Scales for First and Second Recordings.

	First Recording	Second Recording	*Difference (95% CI)	P value
Active				
Barthel Index	95 (40, 100)	95 (80, 100)	15 (0, 30)	0.057
NIHSS	2 (2, 7)	2 (1, 4)	2 (1, 3)	0.002
Modified Rankin	2 (2, 4)	2 (1, 4)	†	0.339
Placebo				
Barthel Index	75 (45, 100)	90 (65, 100)	20 (10, 30)	0.003
NIHSS	5 (3, 6)	3 (1, 5)	2 (1, 3)	0.001
Modified Rankin	3 (2, 4)	2 (2, 4)	†	0.014

Data presented as median (IQR).

*Comparison between first and second recordings i.e. before and after the week of study treatment (Wilcoxon signed rank test).

† Unable to compute 95% CI as values too similar.

5.4.2 Blood Pressure.

There was no significant difference in casual BP between the active treatment and placebo groups but the baseline 24-hour daytime DBP was slightly lower in the active group compared to the placebo group ($p=0.019$) (Table 5.1).

There was no significant difference in casual SBP, DBP or MAP between the first and second recordings in either the active treatment or placebo groups (Table 5.3).

Table 5.3. Blood Pressure at First and Second Recordings.

	First Recording	Second Recording	*BP difference	P value
Active n=18				
Casual SBP (mmHg)	172±16	167±26	-5±14	0.164
Casual DBP (mmHg)	91±14	90±14	0±9	0.937
Casual MAP (mmHg)	118±12	116±15	-2±9	0.460
Finapres SBP (mmHg)	156±26	158±24	2±23	0.668
Finapres DBP (mmHg)	76±21	78±15	2±13	0.459
Finapres MAP (mmHg)	103±22	104±17	1±16	0.764
Finapres Heart Rate (beats/s)	68±11	70±10	2±8	0.379
Placebo n=23				
Casual SBP (mmHg)	167±16	164±19	-3±19	0.397
Casual DBP (mmHg)	95±13	92±14	-3±15	0.392
Casual MAP (mmHg)	119±13	116±15	-3±15	0.372
Finapres SBP (mmHg)	174±32	170±33	-4±23	0.454
Finapres DBP (mmHg)	89±23	80±18	-8±17	0.026
Finapres MAP (mmHg)	117±25	110±22	-7±19	0.078
Finapres Heart Rate (beats/s)	72±10	70±9	-3±10	0.218

Data presented as mean±SD.

* Comparisons between first and second recording (Student's paired t-test)

5.4.3 Static Cerebral Autoregulation.

There was no significant difference in static ARI between the affected and unaffected hemispheres in the right or left hemisphere strokes and the affected side was used in further comparisons. Using THC no difference was found in the magnitude of pressor stimulus or static ARI between first and second recordings in either the active treatment or placebo groups (see Table 5.4).

Table 5.4. Static cerebral autoregulation index and BP change for THC at first and second recordings in active treatment and placebo groups.

	First Recording	Second Recording	*Difference (95% CI)	p value
THC – active treatment n=9				
static CA % (affected side)	57 (24, 78)	64 (40, 79)	9 (-31, 42)	0.652
BP change (mmHg)	19±5	18 ±4	-1 (-3, 3)	0.951
THC – placebo n=13				
static CA % (affected side)	62 (31, 88)	79 (53, 98)	8 (-11, 30)	0.262
BP change (mmHg)	21±6	24±12	3 (-4, 10)	0.354

Static ARI data presented as median (IQR).

BP change presented as mean±SD

*Comparison between first and second recordings i.e. before and after the week of study treatment: static ARI (Wilcoxon signed rank test), BP change (Student's paired t-test).

No correlation was found between the static ARI on the affected side at the first recording and baseline BP levels ($p=0.974$, $r=-0.007$; 0.463 , $r=-0.154$; 0.524 , $r=-0.134$ for casual SBP; DBP and MAP respectively and $p=0.544$ $r=0.130$; 0.619 , $r=-0.107$; 0.829 , $r=0.047$ for 24 ABPM SBP; DBP and MAP respectively) and age ($p=0.119$, $r=0.314$). No correlation was found between stroke severity, as reflected by the Barthel Index, and static ARI derived using THC BP stimulus ($p=0.258$, $r=0.23$).

5.4.4 Dynamic Cerebral Autoregulation.

Of the 41 stroke patients, a spontaneous transient BP rise or fall ≥ 5 mmHg could not be found in 7 and 10 subjects respectively. Twenty-nine patients had the THC manoeuvres at both recordings and of these only 15 recordings were suitable for analysis because of either ectopic beats occurring within 30s of the BP stimulus, an

inadequate BP fall on cuff release or the absence of a concurrent CBFV fall. Ten patients who did not have THC data on both occasions simply refused because of discomfort and 6 were not performed because of a history of deep vein thrombosis or severe peripheral vascular disease.

Table 5.5. Differences in dynamic ARI in stroke subjects between stroke hemispheres and with pressor and depressor stimuli.

	Spontaneous Transient Pressor Stimulus		Spontaneous Transient Depressor Stimulus		Thigh Cuff Release	
	n	dARI	n	dARI	n	dARI
<u>Right hemisphere stroke</u>						
Affected side	14	(1.5, 4.6)	14	4.1 (0.0, 4.9)	5	5.7 (5.3, 7.7)
Non-affected side	15	4.9 (2.6, 6.6)	15	4.0 (0.0, 5.4)	6	6.7 (5.0, 8.4)
<u>Left hemisphere stroke</u>						
Affected side	20	5.4 (2.0, 7.6)	20	4.0 (2.4, 6.4)	16	6.7 (5.5, 8.2)
Non-affected side	15	5.9 (1.8, 7.1)	19	4.1 (1.8, 6.9)	14	6.9 (5.7, 7.8)
Difference		1.9 (-0.7, 3.6)		0.4 (-1.1, 2.7)		0.4 (-1.9, 2.5)
P value*		p=0.189		p=0.481		p=0.741

Data presented as median (IQR).

* Comparison between dynamic ARI for right and left hemisphere strokes (Mann-Whitney U test).

A spontaneous transient BP rise or fall ≥ 5 mmHg could not be found in 7 and 10 patients respectively.

dARI= dynamic ARI

There was no significant difference in dynamic ARI between the affected and unaffected hemispheres in the right or left hemisphere strokes (see Table 5.5) and the affected side was used in further comparisons. No difference was found in the magnitude of spontaneous pressor and depressor BP transients or BP fall on THC release between first and second recordings although the THC stimulus was

Table 5.6. Dynamic cerebral autoregulation index of side affected by stroke, along with magnitude and rate of blood pressure change for spontaneous transient pressor and depressor stimuli in the active treatment and placebo groups.

		First Recording	Second Recording	*Difference (95% CI)	P value
Active					
<u>Pressor Stimulus</u>	Spontaneous Transient BP rise (mmHg)	8.1±2.0	7.7± 2.4	-0.4 (-1.2, 0.4)	0.333
	dARI (affected side) n=14	4.4 (0.7, 6.1)	3.2 (2.5, 5.3)	0.13 (-2.2, 3.1)	0.839
<u>Depressor Stimuli</u>	Spontaneous Transient BP fall (mmHg)	7.3±1.2	6.9±1.0	-0.4 (-1.2, 0.2)	0.220
	dARI (affected side) n=14	3.1 (0.0, 4.3)	3.7 (2.6, 5.7)	1.5 (-0.6, 3.8)	0.191
<u>Thigh Cuff Release</u>	BP fall (mmHg)	15.0±3.7	18.1±8.8	3.1 (-1.0, 5.0)	0.256
	dARI (affected side) n=7	6.2 (5.7, 7.6)	7.8 (5.5, 8.3)	0.7 (-2.1, 5.5)	0.528
Placebo					
<u>Pressor Stimulus</u>	Spontaneous Transient BP rise (mmHg)	8.9±2.5	9.1±4.2	0.2 (-1.4, 1.8)	0.767
	dARI (affected side) n=20	4.5 (2.0, 7.2)	4.0 (2.4, 6.2)	-0.4 (-2.0, 1.4)	0.548
<u>Depressor Stimuli</u>	Spontaneous Transient BP fall (mmHg)	9.0±2.3	8.7±2.8	-0.3 (-2.3, 1.9)	0.776
	dARI (affected side) n=17	4.5 (2.7, 6.0)	4.7 (2.5, 6.4)	1.0 (-0.4, 2.8)	0.159
<u>Thigh Cuff Release</u>	BP fall (mmHg)	16.8±5.2	19.3±10.8	2.5 (-2.5, 7.5)	0.353
	dARI (affected side) n=8	7.1 (5.3, 8.4)	6.6 (3.9, 7.4)	0.7 (-4.8, 1.0)	0.383

Mean of data for right and left hemispheres used in each case.

Not all subjects had a pressor or depressor stimulus ≥ 5 mmHg during the two 5 minute recordings (see results section).

Dynamic ARI (dARI) data presented as median (IQR). BP change presented as mean±SD. *Comparison between first and second recordings i.e. before and after the week of study treatment: static ARI (Wilcoxon signed rank test), BP change (Student's paired t-test).

significantly greater than the spontaneous transient stimuli (see Table 5.6). Dynamic CA, whether assessed using pressor or depressor BP transients or the THC technique, was not significantly different between the first and second recordings in either the active treatment and placebo groups (see Table 5.6).

No correlation was found between the dynamic ARI and baseline casual SBP levels ($p=0.773$, $r=-.053$; 0.701 , $r=-0.071$; 0.810 , $r=0.056$ for dynamic ARI from pressor BP transients, depressor BP transients and THC respectively), casual DBP levels ($p=0.884$, $r=0.027$; 0.655 , $r=0.082$; 0.147 , $r=0.328$), casual MAP levels ($p=0.993$, $r=-0.002$; 0.951 , $r=-0.011$; 0.553 , $r=0.137$), 24 ABPM SBP levels ($p=0.808$, $r=0.045$; 0.380 , $r=0.16$; 0.662 , $r=-0.107$), 24 ABPM DBP levels ($p=0.29$, $r=0.193$; 0.161 , $r=0.254$; 0.974 , $r=0.008$), 24 ABPM MAP levels ($p=0.544$, $r=0.111$; 0.163 , $r=0.252$; 0.947 , $r=-0.016$), and age ($p=0.731$, $r=-0.061$; 0.256 , $r=-0.2$; 0.742 , $r=-0.077$). No significant correlation was found between stroke severity, as reflected by the Barthel Index, and dynamic ARI derived using spontaneous transient pressor BP stimuli ($p=0.610$, $r=0.091$), spontaneous transient depressor BP stimuli ($p=0.361$, $r=0.162$) or THC ($p=0.935$, $r=-0.019$).

5.4.5 Blood Pressure Variability, Pulse Interval Variability and Cardiac Baroreceptor Sensitivity.

Systolic BP variability and PI variability, from spectral analysis, were not significantly different between the first and second recordings in either the active treatment or placebo group in any frequency band (see Table 5.7). SBP, DBP and MAP variability, taken as the standard deviation of all measurements during the

Table 5.7. Pulse Interval and SBP variability assessed by spectral analysis in the active treatment and placebo groups.

	n	Pulse interval variability (ms)			SBP variability (mmHg)		
Frequency ranges *		All Frequencies	LF	HF	All Frequencies	LF	HF
Active							
First Recording	15	30.2±16.2	13.1±6.3	12.8±11.9	6.7±2.4	2.7±1.0	2.0±0.7
Second Recording	15	31.3±14.1	14.0±7.0	13.9±10.3	7.3±2.2	2.8±0.9	2.2±0.9
Difference		0.7±14.8	0.6±8.5	0.8±11.0	0.7±2.7	0.1±0.9	0.2±0.8
p-value		0.845	0.777	0.770	0.325	0.562	0.354
Placebo							
First Recording	20	30.0±14.5	14.8±8.9	9.8±5.2	7.6±2.5	3.1±1.3	1.9±0.6
Second Recording	20	29.0±17.5	14.2±10.5	10.8±10.0	8.0±2.7	3.2±1.4	2.2±1.1
Difference		0.7±19.3	0.2±11.1	1.6±9.5	0.4±3.0	0.1±1.2	0.2±0.9
p-value		0.875	0.937	0.454	0.514	0.657	0.254

* VLF=0.02-0.05Hz; LF=0.05-0.15Hz; HF=0.15-0.4Hz.

Data presented as mean±SD.

p values are for the differences between first and second recordings.

3 patients had too many ectopic beats on their ECG to be included in spectral analysis, therefore 16 pairs used in analysis.

recording period, were also not significantly different between the first and second recordings in either the active treatment or placebo group (see Table 5.8).

Table 5.8. Systolic, Diastolic and Means BP Variability – Standard Deviation of Finapres Values.

Active	First Recording	Second Recording	BP difference	P value
Systolic BP Variability (mmHg)	9.3±4.0	8.7±2.6	0.6±4.8	0.627
Diastolic BP Variability (mmHg)	3.8±1.1	3.8±0.9	0.0±1.5	0.989
MAP Variability (mmHg)	5.4±1.5	5.3±1.4	0.1±2.2	0.857
Placebo				
Systolic BP Variability (mmHg)	10.0±4.3	11.0±6.1	1.0±4.7	0.362
Diastolic BP Variability (mmHg)	4.8±1.9	5.1±3.1	0.3±2.7	0.628
MAP Variability (mmHg)	6.6±2.7	7.1±4.1	0.4±3.4	0.574

Data presented as mean±SD.

Systolic BP variability and PI variability were not significantly different between right and left hemisphere strokes in any frequency band at the first recording (see Table 5.9).

Cardiac BRS (If α) was not significantly different between the first and second recordings in either the active treatment or placebo group, being 5.1±1.7 and 5.2±2.1 ms/mmHg in the first and second recordings respectively in the active treatment group (p=0.950) and 5.1±3.0 and 4.5±2.4ms/mmHg respectively in the in the placebo group (p=0.319).

Table 5.9. Pulse Interval Variability and SBP variability for right and left hemisphere stroke patients at first recording.

Stroke Hemisphere	n	Pulse interval variability (ms)			SBP variability (mmHg)		
		All Frequencies	LF	HF	All Frequencies	LF	HF
Right	17	32.7±15.6	15.4±8.3	12.9±11.5	7.0±2.5	2.9±1.4	2.1±0.8
Left	21	27.3± 14.7	12.5±7.3	10.5±7.0	7.1±2.4	2.9±1.0	1.8±0.5
p-value		p=0.281	p=0.253	p=0.436	p=0.928	p=0.978	p=0.147

Data presented as median ±SD.

3 patients had too many ectopic beats on their ECG to be included in spectral analysis.

5.5 Discussion.

This is the first study to my knowledge to measure the effect of antihypertensive treatment on CA in patients with high BP within a few days of acute ischaemic stroke. No significant difference in casual BP was found in either the active treatment (oral bendrofluazide 2.5mg daily) or placebo group after 7 days of treatment and there was no trend in static or dynamic ARI with age or BP. No change in static or dynamic CA was seen in either the active treatment or placebo group over the study period nor was there any significant difference in BP or PI variability or cardiac BRS.

The question of how to best manage hypertension in the early days after a stroke arises commonly but has not yet been adequately answered in clinical trials. There are several anecdotal reports of neurological deficits worsening with rapid reduction of

BP in the immediate acute stroke period [168;248;264] and for ethical reasons a rapid fall in BP immediately post-stroke i.e. within 24 hours, was avoided here. The impairment of CA in acute stroke [60;82] (section 1.7 and Chapter 3) could mean that even a small change in systemic BP, accompanied by a passive change in CBF could make the difference between cell death and viability in the ischaemic penumbra. On admission to hospital with an acute ischaemic stroke 40 % of patients are already receiving antihypertensive medication and admission SBP levels are raised in over half of all patients [45;130]. There are no large randomised, placebo controlled trials clarifying the effects of any class of antihypertensive within the first hours, days or weeks following acute ischaemic stroke (section 1.6.10). The Blood pressure Acute Stroke Collaboration (BASC) reviewed the limited information available where vasoactive agents were administered within 2 weeks of symptom onset for the Cochrane Database of Systematic Reviews, Blood Pressure and Acute Stroke II [302]. Most information was available on the use of CCBs and β -blockers, both of which effectively lowered BP although they were being used mainly for their potential neuroprotective effects. The reduction in circulating catecholamine levels associated with β blockade would theoretically reduce myocardial and neurological damage and reduce metabolic demands of ischaemic brain. In spite of this, β -blockers were associated with a trend towards early deterioration, death and worse end of trial disability (figure 1.6). The expected benefits of CCBs included cerebral vasodilatation, increasing CBF to the ischaemic brain and a limiting effect on the massive intracellular calcium influx associated with neuronal cell death, but intravenous CCBs appeared to increase early death and deterioration although reducing case fatality and disability at the end of trial, whereas oral CCBs appeared to increase case fatality and disability at the end of trial compared to controls (figure

1.6). ACE inhibitors appeared to lower BP in acute stroke without a detrimental effect on CBF or any drug-related adverse effects but the 2 studies involving ACE inhibitors [81;174] in acute stroke were too small to be conclusive in terms of outcome.

Transdermal glyceryl trinitrate, a cerebral vasodilator with antiplatelet and antileucocyte activity [21] was used in a small study on ischaemic stroke patients and caused an initial BP reduction that was not sustained but the study was too small to clarify the effect on clinical outcome [22].

Data from the Stroke Register for the University Hospitals of Leicester NHS Trust shows that 69% of patients with acute stroke admitted on antihypertensive treatment were already taking bendrofluazide. Bendrofluazide has not previously been tested in the acute stroke period and this drug was an obvious choice for this study in view already wide use, its favourable characteristics already discussed in the introduction to this chapter and the expectation that it is unlikely to worsen CA (section 1.5.1). The absence of antihypertensive effect over the week of treatment could have several explanations including the slow onset and build-up of action of the drug.

Bendrofluazide is known to be effective in lowering BP but the onset of antihypertensive action occurs only 3 to 4 days after the initial dose [1], after which BP falls steadily over the next 2 weeks [201] and then continues to fall more slowly until the full effect is reached at about 3 months [41;118] (see 1.6.1). In this study compliance was good and was checked by reviewing drug charts, questioning the patients and nursing staff and by counting returned capsules and the one patient who missed 3 out of 7 active study capsules incidentally had a small fall in BP over the study period. As the effect of BP reduction was being tested rather than suggesting that bendrofluazide has any other action on cerebral haemodynamics, on balance, the data were included in the analysis presented here. It is probable that the effect

achieved after 7 days is too small to be useful in the first 7 to 10 days after a stroke.

Other agents such as ACE inhibitors or angiotensin II receptor antagonists may be a suitable choice for future studies in BP lowering in acute stroke. A small spontaneous fall, in systemic BP might have been expected during the present study independent of the study treatment but probably much less than 10/5 mmHg because the mean time to randomisation in the present study was 73 ± 22 hours and therefore outside the time window for a large part of the expected spontaneous BP fall. Haper et al [116] showed that at least half of the spontaneous BP fall after stroke occurs in the first 24 hours with a BP fall of 12/7 mmHg in the first 24 hours following admission and then a total fall of 22/12 mmHg by the end of the first week with about a third of the subjects studied continuing on antihypertensive medication.

No change in static or dynamic CA was seen in either the active treatment or placebo group over the study period in keeping with previous work using similar techniques that showed that dynamic but not static CA was impaired within 96 hours of acute stroke [59] and that there was no significant change in either parameter after a further 14 days later [64]. However, it should be noted that the study was probably underpowered as the original recruitment target was not met. Recruitment of 60 patients would have given the study an 85% power to detect a 5/4 mmHg BP difference, 3 ms/mmHg cardiac BRS difference and a 2 unit difference in dynamic ARI between the thiazide and placebo groups. Initially patients previously on antihypertensives and over the age of 80 years old were excluded from the study but this was changed by protocol amendment after the first 4 months of recruitment. In addition to details included in the flowchart of recruitment (figure 5.1) the requirement for a safe swallow markedly reduced the number of patients eligible for the study. Also it was not always practical in terms of equipment and personnel

available to perform scans at both hospitals. The small number of suitable patients who refused consent was not recorded.

Thiazide diuretics are thought to have some peripheral vasodilator activity but are not known to have any direct effect on cerebral vessels [254;276;310] and an effect on cerebral haemodynamics was therefore not expected in the absence of any changes in systemic BP.

The yield of data from the THC release was disappointing and the 25% who simply refused partly reflects a reduced tolerance to procedures in acutely ill people. It is possible that higher and longer inflation of the cuffs may have yielded more usable data from THC recordings that were made but may have also yielded more refusals. Even in cases where significantly greater cuff pressures have been used (above systolic BP) the quality of the BP fall has still been a problem with failure to achieve an adequate BP fall in 2 out of 27 patients with carotid artery disease [325]. In the case of stroke and other acute illness THC is not the ideal method for measurement of CA and the use of spontaneous transient BP changes is more suitable as demonstrated in chapter 4.

5.6 Conclusions.

1. Bendrofluazide 2.5mg daily is not an effective antihypertensive agent when used in the acute stroke period, probably because of its slow onset of action.
2. No change in static or dynamic CA was seen in stroke patients over the course of a week in either the active treatment or placebo groups in keeping with previous findings on a different group of untreated stroke patients.

3. No change in BP or PI variability or cardiac BRS was seen in either the active treatment or placebo groups over the course of a week.
4. The THC manoeuvre gave a poor yield of results when used in the acute stroke setting and other methods such as the use of transient BP fluctuations in rest recordings should continue to be refined.

6 The effects of bendrofluazide on blood pressure levels and variability, cardiac baroreceptor sensitivity and cerebral autoregulation pressure in the subacute post-stroke period.

6.1 Summary.

The use of thiazide or related diuretics, alone or in combination with ACE inhibitors, has been shown to be beneficial in secondary prevention following ischaemic stroke. Although recent intervention studies suggest that pharmacological BP reduction started 4 weeks or more post-ictus prevents stroke recurrence and other cardiovascular events, the optimal time for introduction of antihypertensive secondary prevention is unclear and may be influenced by the ongoing impairment of CA after stroke. It is unknown whether lowering BP earlier after stroke is of benefit or whether thiazide diuretics are effective in the early post-stroke phase. In this chapter oral bendrofluazide 2.5 mg or matching placebo was prescribed 10 days after acute ischaemic stroke and continued for 4 weeks in hypertensive patients. The effects on systemic BP levels and variability, static and dynamic CA were assessed and compared to a never treated hypertensive control group.

Bendrofluazide did not reduce BP levels in stroke patients during the 4 week treatment period but in the placebo treated stroke patients casual BP rose by 13/5 mmHg and in the control group there was a significant reduction in SBP levels with active treatment. No change in static or dynamic CA, BP variability or cardiac BRS was seen with either active or placebo treatment in strokes or controls during the study period and the effects of BP reduction on static and dynamic CA remain to be tested.

6.2 Introduction.

The benefits of lowering BP in the secondary prevention of stroke recurrence and cardiovascular events by antihypertensive treatment, including ACE inhibitors and thiazide or related diuretics in stroke patients are now well established [107;246], even when those previously deemed to have ‘normal’ BP levels are included [250].

However, the optimum time to introduce antihypertensive treatment post-stroke is uncertain and currently the introduction of such therapy is based on local policies. It is not clear whether impaired dynamic CA affects prognosis after acute ischaemic stroke as seems likely or how it is affected in stroke patients by pharmacological lowering of BP. What little is known about the effects of different pharmacological agents on cerebral haemodynamics is discussed in section 1.5. The time course of improvement of static [194;237] and dynamic CA is uncertain following impairment caused by stroke [60;82]. Serial assessments indicated that in many cases the impairment in dynamic CA is likely to persist at least until at least 14 days post ictus and impairment of static CA has been found even later than this, but these data are from cross-sectional and not longitudinal studies [194]. Lowering BP levels in the presence of impaired CA requires consideration because of the implications for CBF and the possibility of reducing flow further to the already critically underperfused ischaemic penumbra. At 7-14 days post-ictus cerebral haemodynamics may still be abnormal (section 1.7) and so bendrofluazide was chosen for the same reasons detailed in Chapter 5 to test the hypothesis that oral bendrofluazide 2.5mg daily would safely and effectively lower BP in the subacute post-stroke period without further impairment of static or dynamic CA.

6.3 Methods.

6.3.1 Subjects.

Seventy-two CT or MRI diagnosed hypertensive ischaemic stroke patients were recruited 10 days after the onset of their symptoms from 2 of the 3 the Stroke Units of the University Hospitals of Leicester NHS Trust. The Stroke Unit and the Acute Admissions Unit at Glenfield Hospital were visited daily during the week and the Stroke Unit and Acute Admission Unit at Leicester General Hospital were visited between one and three times weekly to recruit patients. Exclusion criteria are described in section 5.3.2. Stroke types were classified using OCSF classification and severity was graded using the Barthel index, mRS and NIHSS scales (section 2.8). Twelve, never-treated hypertensive controls were also recruited from the Outpatient Hypertension Clinic and a volunteer register and were otherwise free from significant cardiovascular or cerebrovascular disease based on history, clinical examination, 12 lead ECG and baseline biochemical, haematological and radiological investigations. None of the controls was in atrial fibrillation or diabetic, had autonomic disturbance, or were taking any medication known to affect the cardiovascular or autonomic nervous system at the time of the study. Both stroke patients and controls underwent 24-hour ABPM (Spacelabs 90207), recording at 20-minute intervals during the day (0700hrs-2200hrs) and 30-minute intervals at night (22.01hrs-06.59hrs) and were only included in the study if their 24-hour mean BP > 130/80 mmHg or their daytime mean BP > 135/85 mmHg. The 4 patients who refused the 24-hour ABPM were included if their mean casual BP (mean of 3 readings) > 140/85 mmHg on 2 consecutive days.

6.3.2 Protocol.

All stroke patients and controls were block randomised (4 per block) to receive a capsule containing either bendrofluazide 2.5mg daily for 4 weeks or matching placebo. Controls continued in a crossover fashion to receive a further 4 weeks of treatment with the alternative option. All volunteers underwent cerebral autoregulatory studies prior to taking the first study capsule and again after 4 weeks when the capsules were withdrawn. The controls underwent a third recording at the end of their second 4 weeklong arm of the crossover.

Cerebral autoregulatory studies were conducted as described in 2.4.2.

Once a stable baseline had been achieved (<10% variation in BP and CBFV) two recordings of 10 minutes duration were made with the subject remaining supine and awake and the Finapres was allowed to servo between the recordings. Following this 2 THC manoeuvres were performed, as described in 2.5.1.

The TCD, Finapres, ECG and TINA signals were then processed and edited as described in 2.4.3 producing the parameters for analysis as follows.

Static and dynamic ARI were calculated as described in section 2.6.

BP changes were only accepted for analysis if they were accompanied by a corresponding change in CBFV and were ≥ 5 mmHg for spontaneous transients and ≥ 10 mmHg for THC responses.

6.3.3 Cardiac baroreceptor sensitivity (BRS) and SBP and PI variability.

Power spectral analysis estimates of PI variability and SBP variability cardiac BRS (If α) were obtained as described in section 2.7.1.

SBP, MAP and DBP beat-to-beat variability were separately calculated as the standard deviation of the beat-to-beat changes derived from the 10 minute baseline recordings.

6.3.4 Statistical Methods.

Student's paired t-tests were used for comparisons of normally distributed data. These data are presented as mean (SD).

Non parametric data (e.g. ARI values) are presented as median (IQR) and were compared using the Wilcoxon signed rank test for paired cases and Mann-Whitney U test for unpaired cases e.g. differences between right hemisphere and left hemisphere strokes.

Spearman's correlation was used to assess the relationship between ARI and age, BP and stroke severity.

Statistical significance was taken at the 5% level using the statistical packages, Minitab for Windows, release 12.21, Minitab Inc, SPSS version 10.1 for windows and R version 1.6.0.

6.4 Results.

73 hypertensive ischaemic stroke patients were enrolled in the study and a further patient was initially enrolled for a first scan but it was subsequently thought that the symptoms were due to peripheral vascular disease. Figure 6.1 illustrates recruitment and reasons for non-completion of the study. Of the 56 hypertensive ischaemic stroke patients who had a first TCD scan 41 completed the full study and 36 were included in the analysis.

BENCAF II

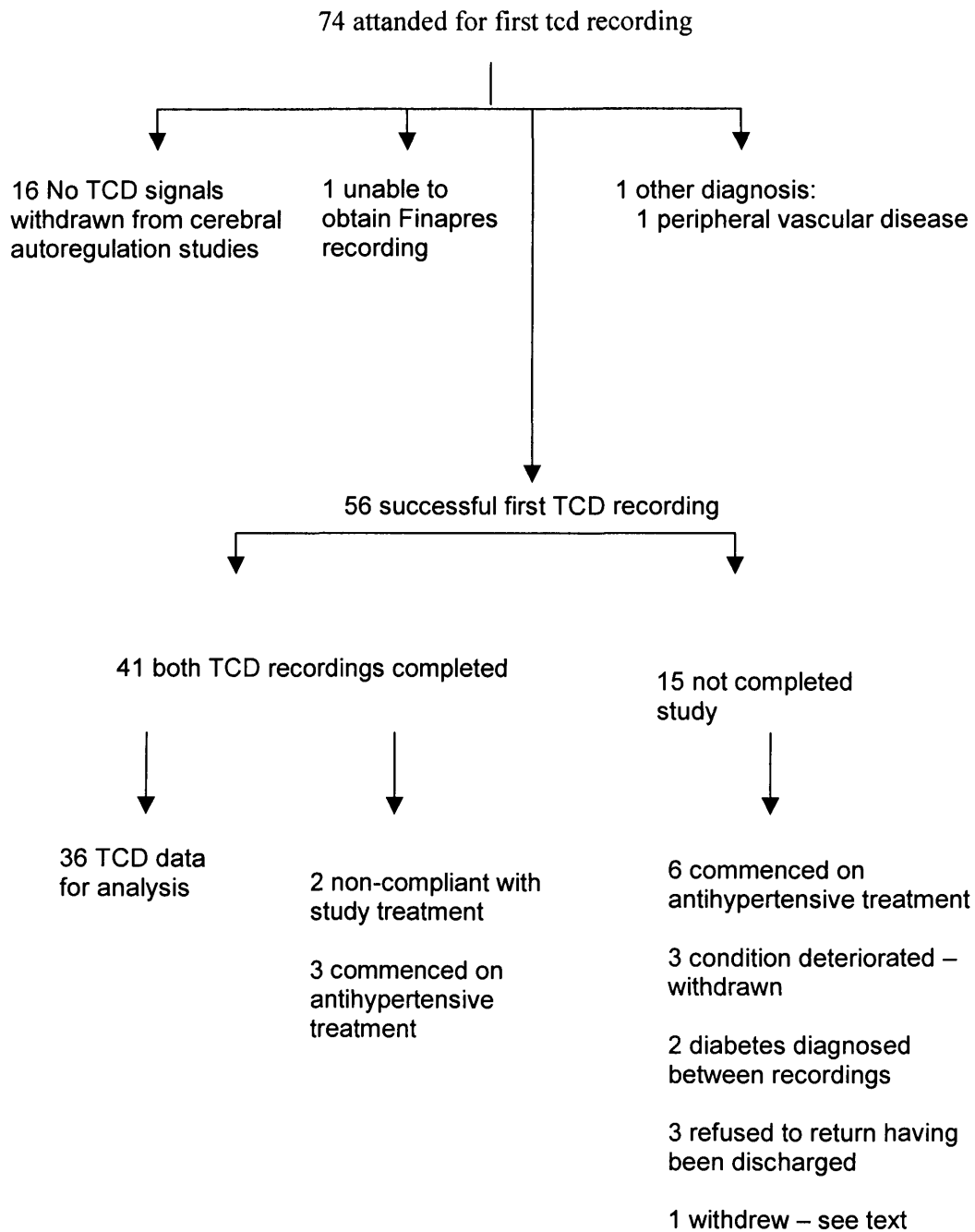


Figure 6.1 Flow Chart of Recruitment

Of the 3 patients who were too unwell to return, 2 had chest infections after discharge, one on placebo and one on active study treatment and 1 patient on placebo treatment developed pseudo-obstruction. One patient with a POCS, on active study treatment, withdrew consent. Three patients refused to return for a second recording having been discharged home. The two non-compliant patients took the study medication for the first 16 days (placebo treatment) and 3 days (active treatment) of the study period but still returned for the final recording. Compliance was otherwise greater than 90% amongst stroke patients and controls.

6.4.1 Demographic Data.

Baseline demographic details for stroke patients and controls are given in Table 6.1. Of the 36 stroke patients who completed the study, 18 of these were in the active treatment group and 18 in the placebo group. There was no significant difference in age or BMI between the active and placebo stroke groups but there were significantly more male than female participants (Table 6.1). The control group was younger than the stroke group by 19 ± 4 years, $p=0.003$ (Table 6.1).

6.4.2 Stroke Scales.

The Barthel Index, mRS and NIHSS scores were similar between the active and placebo groups at the beginning and end of the study and there was significant improvement in all the stroke scales during the 4 weeks of the study in both the active treatment and placebo groups ($p<0.007$) (Table 6.1).

6.4.3 Cerebral Blood Flow Velocity.

In stroke patients there was no significant difference in CBFV between the affected and non-affected hemispheres in the first recording in either the active treatment or placebo groups, or in CBFV in either the affected or non-affected hemisphere between the active treatment or placebo groups (Table 6.1). There was no significant difference between the CBFV in the affected hemisphere in the first and second recordings in the active (43.0 ± 11.4 cm/s, 42.4 ± 10.7 cm/s respectively) or placebo groups (45.5 ± 12.1 cm/s, 45.8 ± 12.5 cm/s) or in the non-affected hemispheres in the active (46.6 ± 14.8 cm/s, 42.5 ± 14.3 cm/s) and placebo groups (41.4 ± 9.9 cm/s, 44.5 ± 12.6 cm/s).

In the control group right and left CBFV were not significantly different and the mean of the two, used in further comparisons, was significantly higher compared to the CBFV for the affected side in the first recording in the stroke patients ($p=0.002$) (Table 6.1). Cerebral blood flow velocity was not significantly different between first and second recordings after a month of active (55.4 ± 13.0 cm/s, 55.1 ± 10.1 cm/s respectively) or placebo treatment (54.0 ± 12.7 cm/s, 55.1 ± 10.6 cm/s).

6.4.4 Blood Pressure Data.

There was no significant difference in casual or 24-hour ABPM daytime BP in stroke patients between the active and placebo groups (Table 6.1). Casual DBP was slightly lower in the stroke patients compared to the controls ($p=0.025$), but otherwise casual and 24 ABMP BPs were similar between the stroke patients and controls at the first recording (Table 6.1).

Table 6.1. Baseline demographic data for stroke patients (whole group and after randomisation) and controls.

	All CVA n=36	Active n=18	Placebo n=18	Controls n=12
Age (years) ††	74±9 (46-90)	76±8 (63-90)	72±9 (46-89)	55±18 (27-79)
Gender m:f	23:13	10:8	13:5	5:7
Time to randomisation (days)	10±2 (7-13)	10±2 (8-13)	10±2 (7-13)	N/A
Duration of treatment (days)	28±1 (25-33)	28±2 (25-33)	28±1 (27-32)	N/A
BMI* (kg/m ²)	26.4±5.4 (14.0-47.5)	27.4±6.3 (20.9-47.5)	25.3±4.2 (14.0-32.3)	29±6 (22-39)
OCSF classification	18: 15: 3	9: 8: 1	9: 7: 2	N/A
Hemisphere (right/ left)	19: 17	8: 10	11: 7	N/A
Casual SBP (mmHg)	161±19 (127-206)	168±18 (132-206)	155±19 (127-192)	155±12 (141-186)
Casual DBP (mmHg) ††	83±14 (50-109)	83±13 (50-105)	83±15 (63-109)	93±9 (75-111)
Casual MAP (mmHg)	109±14 (88-137)	111±13 (88-137)	107±15 (88-137)	113±7 (101-127)
24-hour ABPM Daytime:				
SBP (mmHg)	157±16 (132-192)	155±16 (132-184)	159±17 (137-192)	150±10 (138-172)
DBP (mmHg)	85±13 (59-113)	82±12 (59-102)	90±13 (70-113)	92±13 (68-109)
Mean BP (mmHg)	111±13 (88-139)	108±11 (88-126)	114±14 (93-139)	129±11 (93-129)
CBFV-affected side††	44±12 (27-74)	43±11 (31-74)	46±12 (27-70)	Mean CBFV 57±12 (35-82)
CBFV- unaffected side	45±13 (23-87)	46±15 (28-87)	42±10 (23-57)	N/A
Cardiac BRS (lf α) ††	5.1±2.7 (1.2-12.3)	4.7±2.6 (2.3-12.3)	5.5±2.8 (1.2-10.9)	7.1±3.9 (2.7-14.9)
Barthel Index (median (IQR))	90 (40, 100)	85 (25, 100)	90 (75, 100)	N/A
Modified Rankin	3 (1, 4)	3 (1, 5)	90 (80, 100)	
National Institute of Health Scale	3 (1, 6)	4 (2, 8)	2 (1, 4)	

*BMI=body mass index. † p≤0.05 for differences between active and placebo groups for stroke patients. †† p≤0.05 for differences between strokes and controls. Data presented as mean±SD. Range in parentheses. Stroke scales presented as median and IQR.

Table 6.2. Blood pressure for active and placebo groups for stroke patients and controls at first and second recordings.

			First Recording	Second Recording	BP difference	P value
Strokes Active n=18	Casual	SBP (mmHg)	168±18	162±26	-6±22	0.291
		DBP (mmHg)	83±13	85±16	2±11	0.377
		MAP (mmHg)	111±13	111±18	0±14	0.932
	Finapres	SBP (mmHg)	169±24	163±25	-6±22	0.280
		DBP (mmHg)	74±17	72±16	-2±14	0.649
		MAP (mmHg)	105±18	101±17	-4±14	0.243
Strokes Placebo n=18	Casual	SBP (mmHg)	155±19	168±22	13±13	0.000
		DBP (mmHg)	83±15	89±15	6±7	0.003
		MAP (mmHg)	107±15	115±16	8±8	0.001
	Finapres	SBP (mmHg)	152±32	157±25	5±40	0.598
		DBP (mmHg)	75±18	77±15	2±20	0.732
		MAP (mmHg)	101±22	104±15	3±27	0.636
Control Active n=12	Casual	SBP (mmHg)	156±15	144±14	-12±16	0.029
		DBP (mmHg)	94±11	92±7	-2±9	0.386
		MAP (mmHg)	115±10	109±7	-6±11	0.115
	Finapres	SBP (mmHg)	160±24	140±24	-20±24	0.015
		DBP (mmHg)	81±14	73±17	-8±14	0.081
		MAP (mmHg)	107±16	96±19	-11±15	0.030
Control Placebo n=12	Casual	SBP (mmHg)	152±9	152±14	0±20	0.999
		DBP (mmHg)	93±9	94±12	1±8	0.686
		MAP (mmHg)	113±7	113±11	0±12	0.849
	Finapres	SBP (mmHg)	148±18	148±17	0±16	0.973
		DBP (mmHg)	78±17	78±15	0±11	0.931
		MAP (mmHg)	103±17	103±17	0±12	0.873

Data presented as mean±SD. Minus sign indicates a fall in BP between first and second recordings.

In stroke patients casual SBP and all parameters of Finapres BP fell during the active treatment period but the differences did not reach statistical significance (Table 6.2).

In the placebo group of stroke patients there was a significant increase in casual systolic, diastolic and mean BP of 13 ± 13 , 5 ± 7 and 7 ± 9 mmHg respectively ($p<0.003$) over the 4 weeks of the study and, although the same pattern of BP increase was seen, the difference in Finapres BP recordings did not reach statistical significance (Table 6.2). The change in casual SBP between the first and second recordings was significantly different between the active and placebo groups by 19 ± 32 mmHg, $p=0.004$ (95%CI 7, 31).

Thirty-one patients (14 on active treatment) were discharged home before the second assessment. In stroke patients on active treatment who were discharged home before the second assessment their BP fell by $3\pm 24/3\pm 12$ mmHg compared to a fall of $14\pm 16/1\pm 6$ in the 4 stroke patients on active treatment who remained inpatients and the difference between the two is non significant (95% CI -9, 31). In stroke patients on placebo who were discharged home before the second assessment their BP rose by $12\pm 11/5\pm 7$ mmHg compared to a rise of $14\pm 20/6\pm 7$ in the 3 stroke patients on placebo who remained inpatients and the difference between the two is non significant (95% CI -25, 21).

In the control group casual and Finapres SBP and Finapres MAP fell significantly with active treatment, whereas in the placebo group both casual and Finapres BP remained unchanged (Table 6.2).

6.4.5 Static Cerebral Autoregulation.

On 36 stroke patients, 26 had THC manoeuvres at both recordings: 8 refused to tolerate the THC, 1 had a recent varicose vein operation and 1 had severe peripheral vascular disease. Of these, in 20 patients both recordings were suitable to measure static ARI, the remaining 6 containing too many ectopic beats or not achieving a BP rise of 10 mmHg or more.

In 1 control subject the cuffs were too small to use, a further 3 refused a repeat of THC on 1 or more occasions, 1 volunteer had too many ectopics and 1 no suitable BP rise to use in this analysis, leaving 9 paired recordings suitable to measure static ARI during the active treatment arm and 6 during the placebo arm of the study.

Using the THC static pressor stimulus there was no significant difference in static ARI between the affected and unaffected hemispheres in the right or left hemisphere strokes and the affected side was used in further comparisons. In stroke patients there was no significant difference in static ARI or magnitude of BP stimulus between the active or placebo groups in the first or second recordings 4 weeks apart (Table 6.3). In stroke patients no difference was found in the magnitude of pressor stimulus or static ARI between first and second recordings in either the active treatment or placebo groups (Table 6.3).

Spearman's correlation showed that the static ARI for stroke patients on the affected side at the first recording was related to baseline casual DBP but not SBP or MAP ($r=-0.2$, $p=0.298$; $r=-0.5$, $p=0.024$; $r=-0.3$, $p=0.131$; for SBP, DBP, MAP respectively) and daytime ABPM BP ($r=-0.5$, $p=0.038$; $r=-0.5$, $p=0.040$; $r=-0.5$, $p=0.032$) though the correlation was weak. No significant correlation was found with age ($r=0.2$, $p=0.363$) or stroke severity, as reflected by the Barthel Index, mRS or NIHSS scores ($r=0.3$, $p=0.213$; $r=-0.3$, $p=0.127$; $r=-0.1$, $p=0.525$; respectively).

Table 6.3. Static cerebral autoregulation index (THC) and BP change for stroke patients and controls at first and second recordings in active treatment and placebo groups.

	First Recording	Second Recording	Difference (95% CI)	p value*
Strokes THC –active n=13				
static ARI % (affected side)	63 (38, 77)	54 (23, 73)	0.3 (-22, 17))	1.000
BP change (mmHg)	22±5	23±8	1(-6, 7)	0.856
Strokes THC – placebo n=7				
static ARI % (affected side)	42 (11, 69)	56 (21, 76)	-8 (-59, 39)	0.578
BP change (mmHg)	22±9	19±3	-3 (-11,6)	0.501
Control THC –active n=9				
static ARI % (affected side)	67 (14, 90)	59 (55, 95)	14 (-19, 52)	0.426
BP change (mmHg)	20±6	19±7	-1 (-4, 2)	0.502
Control THC –placebo n=6				
static ARI % (affected side)	65 (51, 94)	47 (5, 78)	-7 (-79, 30)	0.843
BP change (mmHg)	21±6	22±4	1(-5, 7)	0.692

ARI presented as median (IQR), difference in pseudomedians (95%CI) (Mann Whitney U)

BP change presented as mean (SD), difference (95%CI) (Student's paired t-test)

* p value for difference between first and second recordings.

A spontaneous transient rise or fall ≥ 5 mmHg could not be found in 6 and 7 patients respectively.

Static ARI was higher in the control group compared to stroke patients in the first recording (median (IQR) 82 (65, 91), 53 (17, 76) respectively, $p=0.048$). In the control group static ARI did not change significantly with active or placebo treatment (Table 6.3). Spearman's correlation showed that the static ARI for the first recording in the control group was unrelated to baseline casual or daytime ABPM BP or age ($p=0.939$).

6.4.6 Dynamic Cerebral Autoregulation.

Of the 36 stroke patients, a spontaneous transient BP rise or fall ≥ 5 mmHg could not be found in both recordings in 8 and 10 subjects respectively. Data suitable for dynamic THC analysis was available on both occasions in 14 of the 26 patients with paired THC recordings. In the other cases either a suitable BP fall was not obtained, the CBFV did not initially fall along with the BP or was spoiled by ectopic beats. In controls no spontaneous fall in BP was found in both recordings in 1 subject whilst on placebo treatment and recordings suitable for dynamic THC analysis were available in 8 and 7 patients during the active and placebo arms of the study respectively.

In stroke patients there was no significant difference in dynamic ARI between the affected and unaffected hemispheres and the affected side was used in further comparisons. There was no significant difference in dynamic ARI between the right and left hemisphere strokes (Table 6.4).

Table 6.4. Differences in dynamic ARI in stroke subjects between stroke hemispheres with pressor and depressor stimuli at the first recording.

	Spontaneous Transient Pressor Stimulus		Spontaneous Transient Depressor Stimulus		Thigh Cuff Release	
	n	Dynamic ARI	n	Dynamic ARI	n	Dynamic ARI
<u>Right hemisphere stroke</u>						
Affected side	17	3.1 (0.7, 4.2)	17	3.8 (1.4, 5.5)	9	5.0 (0.0,
Non-affected side	16	2.4 (0.7, 3.5)	15	3.4 (0.0, 5.2)	9	7.0)
						5.9 (3.0,
						7.1)
<u>Left hemisphere stroke</u>						
Affected side	13	3.2 (0.8, 5.6)	13	4.1 (1.8, 6.5)	9	6.9 (4.9,
Non-affected side	13	2.1 (0.2, 3.8)	13	4.5 (2.8, 5.6)	9	7.6)
						6.7 (5.0,
						7.7)
*Difference (95%CI) (affected side).		0.4 (-1.7,2.8)		0.4 (-1.8, 2.9)		1.6 (-0.8,
		p=0.614		p=0.760		6.1)
p value.						p=0.120

ARI presented as median (IQR).

* Comparison between right and left hemisphere strokes difference in pseudomedians (95%CI) (Mann Whitney U).

A spontaneous transient BP rise or fall ≥ 5 mmHg could not be found in 7 and 10 patients respectively

In stroke patients no significant difference was found in the magnitude of spontaneous pressor and depressor BP transients or BP fall on THC release, or dynamic ARI for these stimuli, between first and second recordings although the THC stimulus was significantly larger greater than the spontaneous transient stimuli (Table 6.5 and figure 6.2).

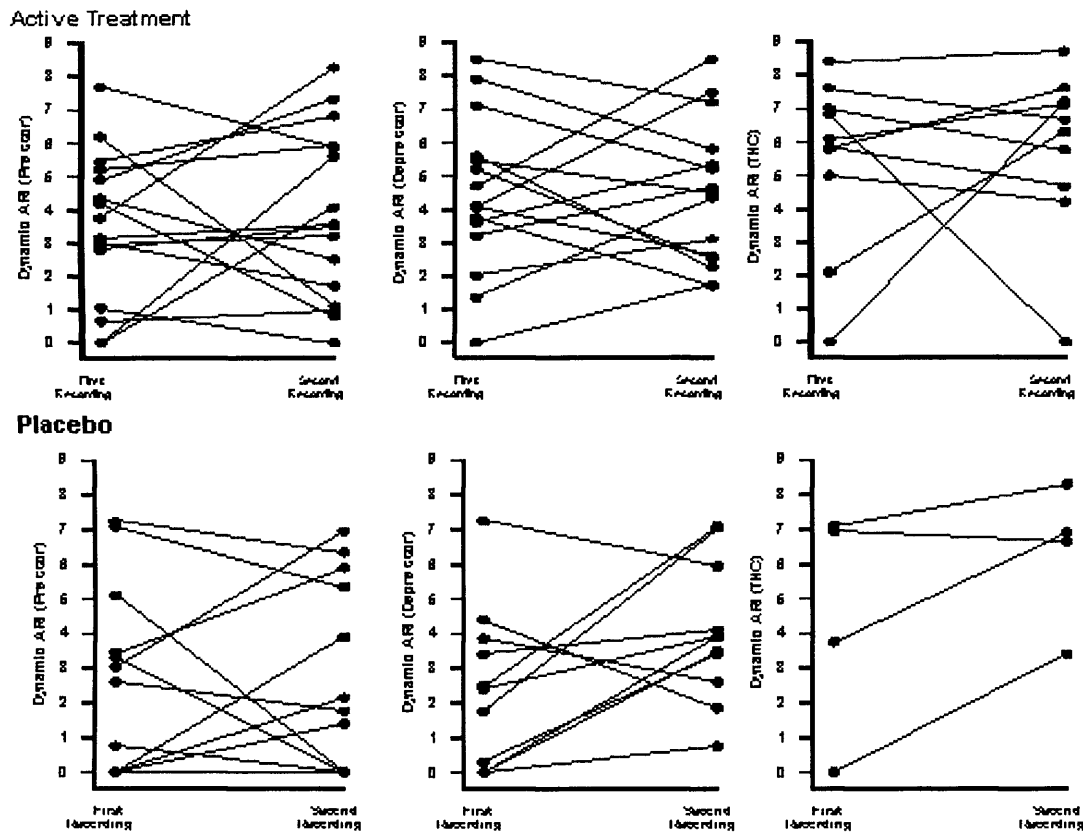
Table 6.5. Dynamic cerebral autoregulation index of stroke affected side, along with magnitude and rate of blood pressure change for spontaneous transient pressor and depressor stimuli in the active and placebo groups for stroke patients and controls.

			First Recording	Second Recording	Difference	*P value
Stroke Active	<u>Pressor Stimulus Spontaneous Transient</u>	BP rise (mmHg)	8.7±2.6	8.2±2.8	-0.5 (-2.0, 1.0)	0.522
		dARI (affected side) n=16	3.4 (1.3, 5.1)	3.6 (1.6, 6.0)	0.4 (-1.3, 1.9)	0.660
	<u>Depressor Stimuli Spontaneous Transient</u>	BP fall (mmHg)	-10.7±4.7	-9.8±2.9	-0.9 (-2.6, 4.4)	0.587
		dARI (affected side) n=15	4.4 (3.3, 6.5)	4.6 (2.5, 6.9)	0.0 (-1.7, 1.4)	0.978
	<u>Thigh Cuff Release</u>	BP fall (mmHg)	-14.6±3.0	-18.1±7.4	3.5 (-1.9, 8.8)	0.180
Stroke Placebo	<u>Pressor Stimulus Spontaneous Transient</u>	dARI (affected side) n=10	6.0 (2.8, 7.5)	6.7 (4.5, 7.3)	0.2 (-1.3, 3.0)	0.856
		BP rise (mmHg)	7.9±2.7	8.4±1.6	0.5 (-1.4, 2.3)	0.618
	<u>Depressor Stimuli Spontaneous Transient</u>	dARI (affected side) n=12	2.8 (0.0, 5.1)	3.0 (0.0, 5.9)	0.3 (-2.0, 2.2)	0.824
		BP fall (mmHg)	-10.1±3.4	-10.9±4.2	0.8 (-3.7, 2.2)	0.592
	<u>Thigh Cuff Release</u>	dARI (affected side) n=11	2.5 (0.0, 4.4)	3.2 (2.6, 6.2)	1.7 (-0.3, 3.7)	0.083
Control Active	<u>Pressor Stimulus Spontaneous Transient</u>	BP fall (mmHg)	-15.0±5.3	-18.0±7.7	2.9 (-11.2, 17.1)	0.594
		dARI (affected side) n=4	5.4 (0.0, 7.1)	6.0 (4.5, 6.9)	1.9 (-0.3, 3.4)	0.250
	<u>Depressor Stimuli Spontaneous Transient</u>	BP rise (mmHg)	10.1±2.5	8.6±2.4	-1.5 (-3.2, 0.2)	0.080
		dARI (affected side) n=12	4.5 (3.2, 5.8)	4.8 (2.7, 5.9)	0.2 (-2.0, 1.8)	0.677
	<u>Thigh Cuff Release</u>	BP fall (mmHg)	-9.4±2.4	-10.3±2.5	0.9 (-0.7, 2.7)	0.235
Control Placebo	<u>Pressor Stimulus Spontaneous Transient</u>	dARI (affected side) n=12	5.5 (2.4, 6.5)	5.7 (3.0, 6.7)	0.5 (-0.6, 1.5)	0.519
		BP fall (mmHg)	-18.4±6.7	-15.0±3.9	-3.4 (-10.4, 3.5)	0.281
	<u>Depressor Stimuli Spontaneous Transient</u>	dARI (affected side) n=8	6.6 (5.3, 7.3)	5.9 (4.4, 6.4)	-0.9 (-1.7, 0.3)	0.109
		BP rise (mmHg)	8.1±2.1	9.7±2.4	1.6 (-0.4, 3.5)	0.103
	<u>Thigh Cuff Release</u>	dARI (affected side) n=12	5.3 (3.0, 5.9)	4.5 (3.2, 5.6)	-0.7 (-2.3, 0.9)	0.424
	<u>Depressor Stimuli Spontaneous Transient</u>	BP fall (mmHg)	-11.7±6.2	-9.0±3.2	-2.7 (-7.8, 2.5)	0.282
		dARI (affected side) n=11	5.4 (2.9, 6.8)	3.5 (2.5, 6.2)	-0.3 (-2.1, 2.0)	0.638
	<u>Thigh Cuff Release</u>	BP fall (mmHg)	-18.0±4.6	-16.8±4.1	-1.2 (-3.9, 1.5)	0.313
		dARI (affected side) n=7	6.4 (6.2, 7.1)	7.2 (6.1, 7.3)	0.2 (-0.8, 1.1)	0.688

Dynamic ARI (dARI) presented as median (IQR), difference in pseudomedians (95%CI) (Mann Whitney U). BP change presented as mean (SD), difference (95%CI) (Student's paired t-test). * value for difference between first and second recordings.

Not all subjects had a pressor or depressor stimulus ≥5mmHg during the two 5 minute recordings (see results section).

Figure 6.2. Illustration of individual dynamic ARI changes between first and second recordings in stroke patients in the active treatment (top row) and placebo (bottom row) groups.



In the stroke patients dynamic ARI was independent of baseline BP levels and there was no significant correlation between stroke severity (as reflected by the Barthel Index, mRS or NIHSS scores) and dynamic ARI derived using from any of the BP stimuli used. There was a weak correlation between age and dynamic ARI for spontaneous pressor transient ($r=0.5$, $p=0.009$).

Comparing initial dynamic ARI for the whole stroke group with the controls, the values from pressor and depressor transient BP changes and TNC were lower in the stroke group. In the stroke patients dynamic ARI was 3.1 (0.8, 5.1), 3.8 (1.8, 5.6), 6.0

(2.1, 7.1) for pressor transient BP changes, depressor transient BP changes and THC respectively and in the controls 4.9 (3.2, 6.7), 5.4 (2.9, 5.9), 6.6 (6.2, 7.7), significant at the 5% level for pressor transients only ($p=0.045, 0.653, 0.220$). In controls no significant difference was found in the magnitude of BP change or dynamic ARI for spontaneous pressor and depressor BP transients or THC release between first and second recordings (Table 6.5).

In the control group dynamic ARI was independent of baseline BP levels and age.

6.4.7 Blood Pressure Variability and Cardiac Baroreceptor Sensitivity.

Systolic BP variability and PI variability from spectral analysis were not significantly different between the right and left hemisphere strokes in any frequency band (Table 6.6) or between the first and second recordings in either the active treatment or placebo group in any frequency band in stroke patients or controls (Table 6.7). SBP, DBP and MAP variability (standard deviation of all Finapres measurements during the recording period) were also not significantly between the first and second recordings in the active treatment or placebo group in stroke patients or controls (Table 6.8).

Systolic BP variability from spectral analysis for the whole frequency range was significantly greater in stroke patients compared to controls, 7.6 ± 2.3 mmHg, 5.4 ± 1.5 mmHg respectively ($p=0.004$) and SBP, DBP and MAP variability (standard deviation of all Finapres readings in baseline recordings) also tended to be higher in the stroke group (10.9 ± 5.2 mmHg, 5.1 ± 2.1 mmHg, 7.0 ± 3.0 mmHg respectively) compared to controls (7.8 ± 3.5 mmHg, 4.4 ± 2.1 mmHg, 5.5 ± 3.0 mmHg) ($p=0.067, 0.310, 0.156$).

In stroke patients cardiac BRS (lf α) was not significantly different between the first and second recordings in either the active treatment or placebo group, being 4.7 ± 2.6 and 4.5 ± 2.0 ms/mmHg in the first and second recordings respectively in the active treatment group ($p=0.792$) and 5.6 ± 2.8 and 4.6 ± 2.1 ms/mmHg in the in the placebo group ($p=0.249$).

Table 6.6. Pulse Interval Variability and SBP variability for right and left hemisphere stroke patients at first recording.

	n	Pulse interval variability (ms)			SBP variability (mmHg)		
Hemisphere affected by stroke		All Frequencies	LF	HF	All Frequencies	LF	HF
Right	18	26.3 ± 6.9	11.2 ± 3.0	10.8 ± 5.5	8.0 ± 2.5	2.8 ± 1.1	2.2 ± 1.1
Left	15	31.9 ± 18.4	15.5 ± 3.0	11.0 ± 6.4	7.2 ± 2.0	2.7 ± 0.8	2.0 ± 0.9
p-value		0.310	0.138	0.924	0.349	0.942	0.529

Data presented as mean and standard deviation.

3 patients had too many ectopic beats on their ECG to be included in spectral analysis.

Table 6.7. Pulse Interval and SBP variability in active treatment group assessed by spectral analysis.

Stroke Active	n	Pulse interval variability (ms)			SBP variability (mmHg)		
Frequency ranges *		All Frequencies	LF	HF	All Frequencies	LF	HF
First Recording	16	27.9±14.6	13.8±10.2	11.1±6.7	7.8±2.1	2.9±0.8	2.2±1.0
Sec. Recording	16	27.7±13.3	12.5±7.0	11.4±8.8	7.1±2.3	2.9±1.3	2.4±1.2
Difference		0.2±20.3	1.3±11.9	0.3±8.9	0.7±3.1	0.0±1.2	0.2±0.9
p-value	n	0.968	0.659	0.896	0.363	0.911	0.585
Stroke Placebo		Pulse interval variability (ms)			SBP variability (mmHg)		
Frequency ranges *	17	All Frequencies	LF	HF	All Frequencies	LF	HF
First Recording	17	29.4±12.0	12.2±5.6	10.2±5.0	7.3±2.4	2.6±1.1	2.0±1.0
Sec. Recording		27.7±13.6	11.3±5.7	10.6±6.7	7.9±3.0	2.7±0.9	1.9±0.7
Difference		1.7±12.0	0.9±5.5	0.4±6.9	0.6±3.8	0.1±1.4	0.1±0.7
p-value	n	0.540	0.514	0.794	0.531	0.841	0.836
Control Active	n	Pulse interval variability (ms)			SBP variability (mmHg)		
Frequency ranges *		All Frequencies	LF	HF	All Frequencies	LF	HF
First Recording	†11	30.0±14.2	15.7±9.2	14.3±11.1	6.2±1.6	2.8±0.8	1.6±0.6
Sec. Recording	11	28.3±19.6	14.8±12.0	15.1±14.6	6.4±2.9	2.8±1.0	1.7±0.8
Difference		1.7±8.7	0.9±5.0	0.8±5.7	0.2±3.2	0.0±1.0	0.1±0.4
p-value		0.533	0.551	0.667	0.882	0.892	0.510
Control Placebo		Pulse interval variability (ms)			SBP variability (mmHg)		
Frequency ranges *		All Frequencies	LF	HF	All Frequencies	LF	HF
First Recording	11	30.5±17.2	16.4±10.6	16.2±12.4	5.8±3.1	2.6±1.1	1.7±0.8
Sec. Recording	11	30.1±14.5	15.9±10.1	14.0±10.8	6.5±2.9	2.8±0.8	1.6±0.6
Difference		0.4±7.3	0.5±5.7	2.1±5.8	0.7±1.6	0.2±0.7	0.1±0.4
p-value		0.855	0.767	0.251	0.174	0.429	0.345

* VLF=0.02-0.05Hz; LF=0.05-0.15Hz; HF=0.15-0.4Hz. Data presented as mean and SD. p values are for the differences between first and second recordings. 3 patients and 1 control had too many ectopic beats on their ECG to be included in spectral analysis.

Table 6.8. Systolic, Diastolic and Means BP Variability – Standard Deviation of Finapres Values.

	First Recording	Second Recording	BP difference	P value
Stroke Active				
Systolic BP Variability	12.1±6.0	9.8±4.8	2.3±7.3	0.182
Diastolic BP Variability	5.6±2.5	4.7±2.5	0.9±2.5	0.141
MAP Variability	7.8±3.7	6.2±3.1	1.5±3.9	0.106
Stroke Placebo				
Systolic BP Variability	9.5±3.7	9.7±3.7	0.2±5.0	0.860
Diastolic BP Variability	4.7±1.4	4.9±2.0	0.2±2.1	0.634
MAP Variability	6.2±1.8	6.3±2.3	0.2±2.8	0.807
Control Active				
Systolic BP Variability	8.1±3.4	7.8±4.6	0.3±6.0	0.859
Diastolic BP Variability	4.1±1.9	3.7±1.7	0.4±2.8	0.653
MAP Variability	5.3±2.9	4.8±2.4	0.5±4.0	0.674
Control Placebo				
Systolic BP Variability	7.6±4.8	8.2±4.4	-0.6±2.8	0.514
Diastolic BP Variability	4.1±1.8	3.5±0.8	0.7±1.8	0.317
MAP Variability	5.0±2.5	4.7±1.7	0.3±2.1	0.608

Data presented as mean±SD.

p values are for the differences between first and second recordings.

In the controls cardiac BRS (lf α) was not significantly between the first and second recordings in either the active treatment or placebo group, being 5.9±3.6 ms/mmHg and 5.7±4.5 ms/mmHg respectively in the active treatment group (p=0.745) and 7.5±4.6 ms/mmHg and 6.4±4.6 ms/mmHg in the in the placebo group (p=0.306). Cardiac BRS (lf α) was lower in the stroke patients compared to the control group but this did not quite reach statistical significance, possibly because of the small number of control subjects (5.1±2.7 ms/mmHg, 7.1±3.9 ms/mmHg respectively, p=0.059).

6.5 Discussion.

This is the first study to my knowledge to measure the effect of bendrofluazide on CA in patients with hypertension in the subacute phase of ischaemic stroke. In the stroke patients no significant change over 28 days in casual BP levels was found in the active treatment group, but BP did increase in the placebo group by $13 \pm 13 / 5 \pm 7$ mmHg over the study period suggesting that bendrofluazide may have prevented a rise in BP in the stroke patients on active treatment. However, BP levels at baseline were lower in the placebo group and so possibly their increase in BP could, in part, be explained by regression to the mean. In the control group SBP fell significantly with active treatment compared to the placebo phase.

No difference in static or dynamic ARI was seen between affected and non-affected hemispheres in the stroke patients suggesting a global effect on CA that has been previously noted and discussed in Chapter 4 and section 1.7. No change in static or dynamic CA was seen in either the active treatment or placebo group in stroke patients or controls over the study period suggesting that static and dynamic CA did not improve spontaneously between day 10 and day 38 post ictus, nor were they significantly affected by bendrofluazide. Static CA was lower in the stroke patients compared with the control group and dynamic CA tended to be lower in the stroke group but was only statistically significant for the pressor transients, possibly because of the small number of controls used. Using similar techniques but larger numbers of subjects dynamic, but not static, CA has previously been demonstrated to be reduced in ischaemic stroke patients [60]. In general, there is increasing awareness of the benefits in reducing BP levels and difficulty in recruiting never treated hypertensive volunteers as controls meant that the control group was younger than the stroke group

and had higher DBP, although, theoretically, this should not have influenced dynamic CA [38;83;173;309].

There was no significant difference in BP variability, PI variability or cardiac BRS over the treatment period in either the active or placebo stroke or control groups. In keeping with other work, SBP variability was higher [63;82] and cardiac BRS tended to be lower (non significant) in stroke patients compared to controls. From other studies, cardiac BRS would be expected to be lower in ischaemic stroke patients and the statistical power may have been too low to show this here because of the small control group. The discrepancy in age between the stroke and control groups would not be expected to affect comparisons of cardiac BRS where the main age related decrease in cardiac BRS occurs in the age range 20 to 50 years [65].

Hypertensive stroke patients were chosen in this study and it is likely that a large proportion of such patients were hypertensive before their stroke, even if undiagnosed [212]. They would therefore be expected to exhibit some of the well-known effects of longstanding hypertension on cerebral haemodynamics that are discussed in section 1.4. It is well established in human [289;292] and animal [122] studies that the lower limits of static CA are increased in sustained hypertension and it is possible that the upper limit of static CA may also be increased [291]. Recent small studies suggest there is no significant effect on dynamic CA from hypertension alone [83;173;309] so the impairment in CA following stroke is unlikely to be related to BP levels and was not found to correlate with BP in this work.

The highest risk of stroke recurrence occurs in the first year after the event [34] and is strongly associated with post-stroke BP levels [10;246;265] (section 1.6.8). Meta-analyses, involving trials mainly using thiazide diuretics and β blockers have found a reduction in stroke recurrence with treatment in normotensive and hypertensive

patients [107;246] and more recently the PROGRESS trial [250] confirmed that the benefits held also for normotensive stroke survivors treated with Perindopril±Indapamide. None of these studies have clarified what is the optimal time to treatment after stroke. As a rule of thumb 7-10 days [212] is often quoted based on the time for the initial acute BP rise with stroke to settle in most patients, or 4 weeks based on the earliest time, post-stroke, for admission to the PROGRESS trial [250]. One of the arguments for caution in lowering BP early is that the impairment of CA [60] may allow CBF to fall if BP falls endangering potentially viable neurones in the ischaemic penumbra. The time course and quality of recovery of CA is uncertain and, in static CA at least, appears to depend on the size and position of the infarct lasting up to several months in severe lesions [7;194;282] (section 1.7.11). Using similar techniques to this work Dawson et al [63] found no improvement in serial measurements of dynamic CA 10-14 days after ischaemic stroke. However, it was notable that overall difference in dynamic ARI between the first and second recordings in this work was positive in stroke patients, both those on active and placebo treatment, although it was very variable on an individual basis (figure 6.2), and one therefore wonders whether there may have been a slight overall improvement in dynamic ARI with time that this study was underpowered to show. Bendrofluazide, introduced 10 days post ictus, appeared to be a good choice of anti-hypertensive treatment because of its gradual onset of action, avoiding large or sudden BP changes, but in practice it failed to improve hypertension and patients remained in need of treatment. Carlsson et al [42] found that BP rose in two thirds of patients after discharge compared to their inpatient readings and in this study group 31 out of 36 patients were discharged home before the final recording and the rise in casual BP found in the placebo treated group might be partly explained by this effect in addition

to regression to the mean for the placebo group who started with lower baseline SBP and a similar trend, although non-significant, was evident from the Finapres BP readings. The Finapres has been shown to have little bias in comparison to intra-arterial measurements (section 2.2.2) and, in a larger group (92 vs. 18) of younger stroke patients than presented here, has been successfully used to predict outcome after stroke in terms of absolute BP levels and BP variability [63]. It can however show an unpredictable degree of variability in a few subjects (section 2.2.2) that could affect the results in small groups such as presented here.

In stratifying the data according to discharge before or after the final assessment there were only 3 patients in the placebo group who remained inpatients throughout the study, and 4 who received active treatment and therefore a meaningful analysis of the effect of being discharged versus remaining an inpatient could not be made.

Bendrofluazide may thus have partly prevented the increase in BP after discharge without an adverse effect on CA, but its failure to reduce BP may perhaps be related to its mechanism of action. The increased sympathetic nervous system activity following acute stroke [204;300] is likely to explain some of the BP increase seen and bendrofluazide has no effect on autonomic balance. Beta-blockers, that reduce circulating catecholamine levels, appear to be associated with worse outcome if given within 2 weeks of acute stroke [302], but ACE inhibitors, that reduce sympathetic activity and apparently lower BP in acute stroke without a detrimental effect on CBF [174] may be a more effective agent in the acute post-stroke period although their effect on CA and outcome in this setting remain to be clarified.

The absence of a BP fall with active treatment means that the effect of BP reduction on dynamic and static CA in the subacute post-stroke period remains to be tested and

bendrofluazide was not expected to have any significant effect on cerebral haemodynamics independent of its effect on BP [254;276;310].

Limitations of the study, in common with Chapter 5 include the poor tolerance of the THC technique. The small numbers of patients studied precluded stratification of the data by stroke subtype, which would have been desirable bearing in mind the diverse aetiologies of the different OCSF subtypes. The study lacked power for exactly the same reasons cited at the discussion for Chapter 5 and the aim was originally to recruit 60 patients and 30 controls. The failure of bendrofluazide to produce a fall in BP levels in stroke patients during the study period means that the effect of lowering BP in the subacute post-stroke period on static and dynamic CA remains to be tested. Methodological limitations are discussed in detail in Chapter 2.

6.6 Conclusions.

Oral bendrofluazide 2.5mg daily for 4 weeks did not reduce casual and Finapres measured BP levels in the subacute post-stroke period.

Bendrofluazide did not influence static or dynamic CA, which did not improve in the follow-up period 28 days post-ischaemic stroke.

Bendrofluazide did not influence outcome as measured by the Barthel Index, mRS or NIHSS over the short time course of 4 weeks treatment but there are no data on long-term outcome.

The effect of lowering BP in the subacute post-stroke period on static and dynamic CA remains to be tested.

Further studies involving serial measurements of static and dynamic CA are needed to clarify the time course and influences on recovery of CA following acute ischaemic stroke.

7 Conclusions.

The initial section of this thesis is concerned with the measurement and prognostic implications of some of the systemic and cerebral haemodynamic abnormalities seen in the acute post-ictal phase of stroke. The second section is concerned with the effects of trying to alter some of these parameters acutely by pharmacological intervention. It is hoped that these studies will advance areas of research that will eventually lead to therapeutic strategies for the management of acute stroke patients.

The first experimental chapter deals with the short and long-term prognostic significance of reduced cardiac BRS (a parameter open to pharmacological manipulation) assessed in the acute post-stroke period. The next chapter considers a non-invasive method to measure dynamic CA in acute stroke patients that is more widely applicable than previously used techniques, overcomes some of the problems of induced BP changes and could be carried out in 10 mins while concurrently measuring cardiac BRS. The final section of the thesis deals with pharmacological interventions to lower elevated BP levels in the acute and subacute phases of ischaemic stroke using the commonly prescribed antihypertensive agent bendrofluazide. The effects of such treatment on short-term outcome and some of the haemodynamic parameters previously noted to be abnormal in the acute post-ictal phase of stroke including systemic BP, cardiac BRS and dynamic as well as static CA were studied.

7.1 Summary of results of experimental chapters.

Cardiac BRS is known to be impaired following acute ischaemic stroke and in other pathological situations e.g. myocardial infarction its reduction is recognised as a predictor of poor prognosis [155;158;333]. In the first experimental chapter I investigate the short and long-term prognostic implications of impaired cardiac BRS following acute ischaemic stroke. In chapter 3 cardiac BRS was measured within 24 hours of stroke symptom onset by non-invasive spectral analysis techniques in 124 acute ischaemic stroke patients and 62 age, sex and BP matched controls and was found to be significantly lower in patients compared to controls. Over a median follow-up period of 1508 (range 9 to 2656 days) days, stroke patients with impaired cardiac BRS ($<5\text{ms/mmHg}$) had a significantly poorer prognosis with a mortality rate of 28% compared to 8% in patients without impaired cardiac BRS ($>5\text{ms/mmHg}$). These findings were independent of other well-recognised prognostic variables, including age, BP, stroke severity and stroke subtype. Cardiac BRS levels did not, however, influence short-term outcome (30 days post-ictus). Similar findings have not been demonstrated before in stroke patients but are in keeping with results from work undertaken in patients with acute myocardial infarction. The increase in mortality in both coronary heart disease and myocardial infarction may be related to the arrhythmogenic potential resulting from abnormalities in cardiovascular autonomic balance towards sympathetic predominance, as indicated by reduced cardiac BRS and PI variability, but this needs confirmation as the study was relatively small [105]. The mechanisms of impairment of cardiac BRS following acute stroke were not within the remit of this work but damage to the central autonomic connections is an obvious theoretical possibility. Also, in some circumstances such as congestive cardiac failure, impaired cardiac BRS can be improved pharmacologically [198]. These 2 points need to be investigated in further studies in the context of acute stroke.

The abnormality in cardiac BRS may well explain the increased BP variability seen following stroke in this thesis and other studies [62]. As elevated BP levels and BP variability have been shown to have be associated with an adverse prognosis following acute stroke it has been suggested that these parameters should be reduced immediately post-ictus. However, it is important to know that systemic BP reduction is not going to reduce CBF and compromise the ischaemic penumbra. Therefore, a widely applicable method to assess dynamic CA in acute stroke patients is required that does not induce any autonomic disturbance and can be applied to the vast majority of stroke patients. Towards this end I used spontaneous transient BP stimuli selected from rest recordings to examine dynamic CA in the second experimental chapter. In Chapter 4 fifty-six CT or MRI diagnosed ischaemic stroke patients were recruited within 72 hours of ictus and pair-matched with 56 controls for age, sex and MAP. Aaslid's analysis [306] was applied to spontaneous transient pressor and depressor BP changes selected from 10-minute rest recordings of Finapres BP and bilateral MCA TCD signals. A global impairment of dynamic CA in acute ischaemic stroke patients compared to controls was detected, confirming previous work using the THC method. As can be seen in Chapters 5 and 6 the THC technique is poorly tolerated, mainly because it is uncomfortable, although some patients are too large for the cuffs and using spontaneous transient BP stimuli avoids these problems. In addition to being more widely applicable, the use of rest recordings avoids the possibility of the response to discomfort, including altered breathing patterns and increased sympathetic activity, from confounding the measurement of dynamic CA. However, even using this method, 16% of the recordings did not yield a BP transient suitable for analysis. In some cases there were no BP transients larger than 5 mmHg but in other cases ectopic beats invalidated the analysis. To be clinically useful and for

research purposes a universally applicable and more reproducible method for measuring dynamic CA should still be sought.

In the final 2 experimental chapters the effects of bendrofluazide on cerebral and systemic haemodynamic parameters are investigated. In acute stroke, systemic BP levels are raised ($>160/90$ mmHg) in about 80% of patients [319], half of whom have a history of hypertension [32]. The BP tends to fall spontaneously over the next 7-10 days [116;117;319] but remains in the hypertensive range in a third of cases and most studies have found an association between high initial BP in the acute post-ictal phase and poor outcome [31;169;262]. This does not necessarily imply that to artificially lower BP would be beneficial and so far there are no large randomised controlled trials to clarify this but in the few small studies there are β -blockers and CCB appear to worsen outcome [302]. Bendrofluazide was chosen for this work as it fulfils many of the characteristics of an ideal antihypertensive for this situation: it is known to be effective in lowering BP with few side effects, has a gradual onset of antihypertensive effect avoiding a precipitous fall in BP, it is effective in the primary and secondary prevention of stroke and bendrofluazide is already in common use by 69% of patients admitted to hospital with an acute ischaemic stroke who are already receiving antihypertensive medication (data from the Stroke Register for the University Hospitals of Leicester NHS Trust).

In chapter 5 forty-one CT or MRI diagnosed acute ischaemic stroke patients with mild to moderate hypertension, based on 24-hour ABPM recordings, were recruited within 96 hours of ictus. All underwent cerebral autoregulatory studies on recruitment and 7 days later, during which time they were randomised in a double blind, placebo controlled, parallel group trial to oral bendrofluazide 2.5mg daily or matching placebo. Cerebral autoregulatory studies were performed during two 10-minute rest

periods and 2 THC manoeuvres, allowing BP, BP and PI variability, dynamic and static CA and cardiac BRS to be calculated before and after the 7 days of treatment with bendrofluazide or placebo. No significant change in BP or any other haemodynamic parameter was found over the study period and neither static nor dynamic CA in the active treatment or the placebo groups differed significantly after 7 days of treatment. It is likely that onset of antihypertensive activity of bendrofluazide is too slow to be useful in this setting although active treatment did not have any significant adverse effect on CA, independent of its antihypertensive effects. It is concluded from this that if BP reduction is required in the acute post-ictal phase of ischaemic stroke, bendrofluazide is ineffective and the use of other antihypertensive agents, possibly ACE inhibitors should be considered.

In chapter 6 thirty-six CT or MRI diagnosed acute ischaemic stroke patients with mild to moderate hypertension, using the same diagnostic criteria as in chapter 5, were recruited 10 days post ictus. A group of 12 never-treated hypertensive, otherwise healthy, controls were also enrolled. Twenty-four hour ABPM recordings were performed in patients and controls and they underwent cerebral autoregulatory studies, as described in chapter 5. The stroke patients were studied on recruitment, 10 days post-ictus, and 28 days later, during which time they received oral bendrofluazide 2.5mg daily or matching placebo, again as a double blind, randomised, parallel group study. The controls were studied in a double blind, randomised, placebo controlled crossover study, each of the 2 periods of the crossover lasting 4 weeks, and randomly received oral bendrofluazide 2.5mg daily or matching placebo during the first 4 weeks and the alternative treatment during the second 4 weeks. The effects of bendrofluazide 2.5mg oral or matching placebo over 28 days in the subacute post-ictal phase of ischaemic stroke on BP, BP and PI variability, static and dynamic CA and cardiac

BRS were calculated and the effects on systemic BP levels and variability, static and dynamic CA and cardiac BRS were compared to the never treated hypertensive control group.

Bendrofluazide again did not reduce BP levels in stroke patients during the 4 week treatment period but in the placebo treated stroke patients BP rose by 13/5 mmHg and in the control group there was a significant decrease in SBP levels with active treatment. No change in static or dynamic CA, BP variability or cardiac BRS was seen with either active or placebo treatment in strokes or controls during the study period but the effects of BP reduction on static and dynamic CA remain to be tested.

In acute ischaemic stroke an increase in sympathetic activity probably has a strong influence in increasing systemic BP levels but bendrofluazide, which acts mainly through volume depletion, has no effect on autonomic balance, and this, in addition to its slow onset of antihypertensive activity, may partly explain the failure of bendrofluazide to lower BP over both the 1 and 4 week treatment periods.

No change in static or dynamic CA was seen in stroke patients over the course of 7 or 28 days in either the active treatment groups independent of its antihypertensive action, or in the placebo groups, nor was any change in BP or PI variability or cardiac BRS seen in either the active treatment or placebo groups during those time periods.

Although the effect of lowering BP remains to be investigated these results confirm previous findings [60] that there is no measurable improvement in dynamic CA over the 14 days after stroke but extends the time period studied to 38 days. This is an important finding as, although antihypertensive therapy is now proven in the secondary prevention of stroke, it remains unclear as to how soon post-ictus it is safe to start treatment and this may be influenced by the continued impairment of dynamic CA.

7.2 Shortcomings of the study.

Shortcomings of the study have been discussed in each chapter. In chapter 3 the causes of death were not recorded and, although suggested to be associated with arrhythmias and cardiac disease, this is unproven. However, it would be extremely difficult to verify a sudden death as due to an arrhythmia, especially after a patient has been discharged back into the community.

The measurement of dynamic CA, even when using spontaneous transient BP changes, was not applicable in nearly a fifth of patients, leaving the remainder with unknown dynamic ARI. This is inherent to the analysis and, while more widely usable and reproducible techniques for measuring dynamic CA are under development, the currently available methods were used to the best of their potential. Previous work found relatively low reproducibility of Aasliids analysis when applied to THC and it has been suggested that it should be repeated 3 times to gain the best results [179] whereas in this work only 2 THC manoeuvres were performed on each patient to limit the total length of the recordings.

The size of the studies do not allow the effects of stroke size, site and position on CA and cardiac BRS to be studied in relation to these variables.

7.3 Final Conclusions.

Cardiac BRS is lower in acute ischaemic stroke patients compared to controls and is a useful indicator of long-term prognosis. Reduced cardiac BRS may increase the potential for later coronary artery events, the commonest cause of death in those who survive longer than a few weeks, and potentially therapeutic interventions that can

improve cardiac BRS such as ACE inhibitors may be important in the post-stroke period. The initial elevation in BP seen in many acute stroke patients may be partly influenced by the increase sympathetic nervous system activity associated with impaired cardiac BRS.

Following acute ischaemic stroke there is a global impairment of dynamic CA that may interact with the abnormal systemic homeostasis to affect outcome. Spontaneous transient BP stimuli can be successfully used to measure dynamic CA in most acute ischaemic stroke patients with minimal disturbance or discomfort to the patient.

Although the proportion of patients where this method was unsuccessful in measuring dynamic CA was lower than with the THC method, more widely applicable techniques still need to be developed.

The impairment of Dynamic CA following acute ischaemic stroke allowing CBF to be pressure passive, means that any reduction in systemic BP levels in the acute post-ictal phase should be slow to avoid the risk of compromising perfusion of the potentially viable ischaemic penumbra. The safety and efficacy of bendrofluazide, which is known to be effective in primary and secondary prevention of stroke, have not previously been tested in acute stroke. However, it appeared that bendrofluazide was ineffective in lowering BP over 7 or 28 days in the acute post-ictal phase of stroke but did not adversely affect other important systemic and cerebral haemodynamic parameters such as dynamic and static CA or cardiac BRS. Dynamic and static CA did not improve over 7 days in the acute post-ictal phase or over 28 days in the subacute phase and further serial studies are needed to clarify whether, and over what time period, CA does improve after stroke, and how other antihypertensives affect this.

7.4 Future Studies.

Cardiac BRS has been demonstrated to be a prognostic indicator following acute stroke but larger studies of cerebral autoregulation are required to investigate whether static or dynamic CA is also of prognostic significance and to study the effects of stroke type (lacunar vs. large artery) and position (side or site) on these parameters. The need also remains for large well-designed studies into the effect of lowering BP in the acute post stroke period on prognosis as highlighted in the Cochrane report [302]. The effects of different agents such as ACE inhibitors on systemic and cerebral haemodynamics in acute stroke and on prognosis with particular attention to their effects on autonomic balance could be studied. ACE inhibitors regulate release of noradrenaline from sympathetic nerve terminals [156] but whether they reduce central sympathetic neural outflow in has not been clarified [102]. In the both myocardial infarction and congestive heart failure, but not in normal controls or hypertensive patients [103;106], ACE inhibitors have been demonstrated to reduce markers of sympathetic activity and improve cardiac BRS and this is likely to be associated with improved outcome attributed to ACE inhibitors in these conditions. However, the effect of ACE inhibitors on sympathovagal balance following acute stroke is unknown. It will be interesting to see the results of studies already underway, such as CHIPS (a randomised control pilot study of the effect of lisinopril on BP, cardiac BRS and CA in the acute post-stroke period), to see whether treatment with an ACE inhibitors following acute stroke improves cardiac BRS, but more importantly whether it improves outcome.

It remains to be seen whether a concurrent improvement in systemic BP level and sympathovagal balance depending on the specific drug used is important as seems likely.

Although β -blockers and CCBs have been demonstrated to restore autonomic balance in some conditions [100;198], in view of the findings of BASC [302] that both drugs appeared to worsen outcome when given in the acute post ictal phase, it would not be appropriate to test them for their effects on systemic and cerebral haemodynamic parameters in acute stroke.

Other drugs thought to improve cardiac BRS but without affecting systemic BP, possibly by modulation of the endothelial NO system, include statins [235] and it would be interesting to investigate whether they may have a beneficial effect in the treatment of acute stroke although no studies are presently addressing this specific question to my knowledge.

In view of work suggesting the involvement of NO in dynamic CA [327] it is possible that drugs such as ACE inhibitors or statins may also modify CA but this also remains to be investigated.

In order to pursue these aims a widely applicable and reproducible method to measure CA is still needed to allow more sensitive and accurate assessment of the changes following stroke, their interaction with BP parameters, the timescale of possible recovery and prognostic implications. Work on refining spectral analysis techniques and developing novel techniques for the measurement of CA is underway.

A huge amount of work remains to be done and in the pursuit of a detailed understanding of stroke and the development of therapeutic strategies to minimise the consequences

Appendix I: Stroke Classification and Stroke Scales.

1. Oxford Community Stroke Project (OCSP) Clinical Classification of Stroke.

Total Anterior Circulation Stroke Syndrome.

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).

This syndrome is most likely to be a result of occlusion of the proximal stem of the MCA, causing ischaemia in both deep and superficial MCA territory, and caused by embolism (possibly cardiac in origin) or spread of thrombus from a more proximal occlusion. Following TACI there is a high mortality rate and poor functional outcome with 60% dead and only 4% independent at 1 year in the original OCSP study population [18].

Partial Anterior Circulation Stroke Syndrome.

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.

Partial anterior circulation infarcts are due to thromboembolic occlusions of the upper or lower division of the MCA, individual MCA branch occlusions, isolated anterior cerebral artery infarctions or striatocapsular infarctions. Early recurrence after PACI is common, over 30% at 3 months with 45% of patients were dead or dependent after 1 year [18].

Lacunar Stroke Syndrome..

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.

Predictive of small lacunar infarction in the basal ganglia or pons thought to be caused by intrinsic disease of a single basal perforating artery, either by lipohyalinosis or microatheroma and are less likely to be embolic. Patients with lacunar syndromes tend to have poor recovery of function and, although there is a 9% recurrence rate throughout the first year[18], there is commonly progressive small vessel disease and cognitive decline, and recurrence rate increases with longer follow up.

Posterior Circulation Stroke Syndrome.

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.

Cases where there is disturbance of higher cortical function alongside any of the above should be considered to be POCS.

In this case it is difficult to identify which specific vessels are occluded but evidence suggests that thrombosis in-situ is probably about 4 times more common as the cause of the occlusion than embolism [18]. Over 60% of patients with posterior circulation infarcts are independent at 30 days but a high rate of early recurrent stroke is a feature of this syndrome [18].

2. The National Institute of Health 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.

3. Modified 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.

4. Barthel Index.

TASK	DESCRIPTION	SCORE
Feeding	Independent	10
	Food needs to be cut	5
	Dependent	0
Moving bed to chair including sitting up	Independent	15
	With minimal help	10
	Able to sit but maximum assistance to transfer	5
	Unable	0
Personal toilet: wash face, comb hair, shave, clean teeth	Independent	5
	Needs help	0
Getting on and off toilet, handling wipe, flush.	Independent	10
	Needs help	5
	Unable	0
Bathing self	Independent	5
	Needs Help	0
Walking on a level surface (or propel wheelchair if unable to walk).	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: including tying shoes, fastening buttons	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: Local Ethical Committee letters of approval for studies reported in this thesis.

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Melanie Sursam
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Leicester General Hospital

Dear Dr Robinson

The effects of antihypertensive treatment on haemodynamic and cerebral autoregulatory function in the post stroke period - our ref. no. 4814

Further to your letter dated 10 March to Dr N Seare, Research Manager at Leicester General Hospital, you will be pleased to know that the Leicestershire Ethics Committee has approved your request to undertake the above-mentioned research.

Your attention is drawn to the attached paper which reminds the researcher of information that needs to be observed when ethics committee approval is given.

Yours sincerely

M. Sursam

R F Bing pp.
Chairman
Leicestershire Ethics Committee

(NB All communications relating to Leicestershire Ethics Committee must be sent to the Committee Secretariat at Leicestershire Health)



Melanie Sursham
Direct Dial 0116 2588610
07 November 1995

Professor J F Potter

Department of Medicine for the Elderly
Glenfield Hospital



LEICESTERSHIRE HEALTH

Gwendolen Road, Leicester LE5 4QF

Tel: (0116) 273 1173 Fax: (0116) 258 8577

Dear Professor Potter

Static and dynamic changes in cerebral vasoregulation following acute ischaemic stroke and outcome - our ref. no. 3982

Further to your application dated 2 October, you will be pleased to know that the Leicestershire Ethics Committee at its meeting held on the 3 November, 1995 approved your request to undertake the above-mentioned research conditional upon the patient information leaflet being revised to make it less complex as it is felt unlikely that patients in the immediate post stroke period would be able to assess fully and understand the information they were being given. The Committee would be grateful for your comment on this point. It is suggested that you may wish only to approach patients who have no cognitive impairment following their stroke and/or you may wish to involve relatives in the consent process.

I would remind you, however, that your research project has been given approval only in relation to its acceptability from an ethical point of view. If, subsequently, departure from the methodology outlined in your protocol is contemplated, the Ethics Committee must be advised in order that the proposed changes may be approved. Also a report should be made to the Ethics Committee if any significant adverse reactions are noted during the course of the study. In addition, any NHS resource implications of your project must be discussed with the appropriate Trust Chief Executive. Similarly, it may be that the research project has implications for other disciplines and, if so, you are advised to discuss them with the appropriate departmental manager. Researchers should also be able to assure the Ethics Committee that satisfactory arrangements have been made for the labelling, safe storage and dispensation of drugs and pharmaceutical staff are always willing to provide advice on this.

Researchers' attention is also drawn to correspondence from the Regional Director of Public Health dated 28 January, 1991 relating to Clinical Trials which sets out revision of the procedures to be followed, and the Clinical Trials Indemnity Letter and Deed of Guarantee. Researchers should ensure that these indemnity arrangements have been complied with.

Researchers intending to study selective groups of patients in the community are reminded that their first approach should be to the individual patient's general practitioner to ascertain whether the particular patient was suitable for inclusion in the study. Equally, when the researcher contacts the patient it should be emphasised that the approach is made with the knowledge of the General Practitioner, with whom the patient may discuss this research, if the patient so wished.

Yours sincerely

M. Sursham

for Director of Public Health

LEICESTERSHIRE HEALTH AUTHORITY

Director of Public Health
and District Medical Officer
Dr. G. M. Morgan MB, BS, MRCP, MFPHM, DRCOG, MHSM

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Your ref:
My ref:

AEC/MS

10th May, 1993

Dear Dr. Potter,

Autonomic Function and Short-term and Long-term Blood Pressure
Variability following Acute Stroke

Further to your application dated 19th April, 1993, you will be pleased to know that the Ethical Committee at its meeting held on the 7th May, 1993 approved your request to undertake the above-mentioned research.

I would remind you, however, that your research project has been given approval only in relation to its acceptability from an ethical point of view. If, subsequently, departure from the methodology outlined in your protocol is contemplated, the Ethical Committee must be advised in order that the proposed changes may be approved. Also a report should be made to the Ethical Committee if any significant adverse reactions are noted during the course of the study.

In addition, any NHS resource implications of your project must be discussed with the appropriate Chief Executive/Unit General Manager. Similarly, it may be that the research project has implications for other disciplines and, if so, you are advised to discuss them with the appropriate departmental manager. Researchers should also be able to assure the Ethical Committee that satisfactory arrangements have been made for the labelling, safe storage and dispensation of drugs and pharmaceutical staff are always willing to provide advice on this.

Researchers' attention is also drawn to correspondence from the Regional Director of Public Health dated 28th January, 1991 relating to Clinical Trials which sets out revision of the procedures to be followed, and the Clinical Trials Indemnity Letter and Deed of Guarantee. Researchers should ensure that these indemnity arrangements have been complied with.

Researchers intending to study selective groups of patients in the community are reminded that their first approach should be to the individual patient's general practitioner to ascertain whether the particular patient was suitable for inclusion in the study. Equally, when the researcher contacts the patient it should be emphasised that the approach is made with the knowledge of the General Practitioner, with whom the patient may discuss this research, if the patient so wished.

Yours sincerely,

G.M. Morgan

Director of Public Health and
District Medical Officer. PPMs

Dr. J. F. Potter,
Senior Lecturer,
Department of Medicine for the Elderly,
Leicester General Hospital.

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