Cerebrovascular Haemodynamic Parameters:

reproducibility and changes following acute stroke

Doctor of Medicine Thesis

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Table of Contents

Page

List of Tables

List of Figures

List of Abbreviations

ACCESS	Acute Candesartan Cilexetil Therapy in Stroke Survivors
ACEi	angiotensin converting enzyme inhibitor
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARI	autoregulatory index
BASC	Blood pressure in Acute Stroke Collaborative
BMI	body mass index
BMS	between subjects mean sum of squares
BP	blood pressure
CBF	cerebral blood flow
CBFV	cerebral blood flow velocity
CEA	carotid endarterectomy
CHHIPS	Control of Hypertension and Hypotension In the acute Post Stroke period
CI	confidence intervals
CO_2	carbon dioxide
COSSACS	Continue Or Stop Post Stroke Antihypertensives Collaborative Study
CPP	cerebral perfusion pressure
CrCP	critical closing pressure
CT	computed tomography
dCA	dynamic cerebral autoregulation
Dx	Diastolic correlation coefficient index
ECG	electrocardiogram
EEG	electroencephalogram

ENOS	Efficacy of Nitric Oxide in Stroke
ESO	European Stroke Organisation
EUSI	European Stroke Initiative
FFT	fast Fourier transform
HOPE	Heart Outcomes Prevention Evaluation
ICA	internal carotid artery
ICC	intraclass correlation coefficient
ICH	intracerebral haemorrhage
INTERACT	INTEnsive blood pressure Reduction in Acute Cerebral haemorrhage Trial
INWEST	Intravenous Nimodipine West European Stroke Trial
IQR	inter-quartile range
JNC 7	7th report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure
LACS	lacunar syndrome
LREC	Leicestershire research ethics committee
MAP	mean arterial pressure
MRI	magnetic resonance imaging
mRS	modified Rankin scale
MS –DOS	Microsoft disk operating system
Mx	Mean correlation coefficient index
NIHSS	National Institute of Health stroke scale
NINDS	National Institute of Neurological Disorders and Stroke
OCSP	Oxfordshire community stroke project
$PaCO_2$	partial pressure of carbon dioxide

PACS	partial anterior circulation syndrome
PET	positron emission tomography
POCS	posterior circulation syndrome
PROGRESS	perindopril protection against recurrent stroke study
Q	flow
RAP	resistance area product
rCBF	regional cerebral blood flow
RMS	Residual error mean sum of squares
rtPA	recombinant tissue plasminogen activator
SCAST	Scandinavian Candesartan Acute Stroke Trial
SD	standard deviation
SEM	standard error of measurement
SPECT	single photon emission computed tomography
Sx	systolic correlation coefficient index
t	time
TACS	total anterior circulation syndrome
TCD	transcranial Doppler
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
UHL R+D	University Hospitals Leicester Research + Development
WHO	World Health Organisation
WMS	within subject sum of mean squares
XeCT	xenon computed tomography

Study Declaration

The design, organisation and administration of this study were performed by the author with the advice of Professors Thompson Robinson and Ronney Panerai, University of Leicester. The recruitment and study of all subjects was undertaken by the author with the assistance of Emily Atkins. The data handling and statistical analysis were performed by the author. Dr Suzanne Rafelt provided statistical advice. The data analysis software was developed by Professor Ronney Panerai and the Department of Medical Physics, University of Leicester. I confirm that unless otherwise acknowledge or referenced all original work contained within this Thesis is my own.

Ethical Declaration

The original research contained within this Thesis was performed in accordance with the principles stated in the Declaration of Helsinki, and the conduct of the research accorded to the principles of good clinical practice. Consent was obtained according to the requirements of the multi-centre and local research ethics committees. Management of all data was in compliance with the Data Protection Act.

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Chapter 1: Introduction

1.1 Introduction

This Thesis will discuss the importance of stroke disease, and review the existing literature regarding acute stroke blood pressure (BP) changes and management. It will also review methods of measuring cerebral autoregulation, and the effects of stroke, hypertension, and antihypertensive therapy on cerebral autoregulation.

Using an established method of measuring cerebral autoregulation this Thesis will examine the reproducibility of this method in a study of healthy volunteers. The same measurement technique will then be used to examine the effects of ageing on cerebral autoregulation in a cohort of healthy volunteers. The effects of acute stroke and early recovery on cerebral autoregulation will then be studied and compared to healthy controls. In addition it will consider the potential effects of stroke type, clinical features, and history of hypertension on cerebral autoregulation post-stroke.

1.2 Stroke Disease

Stroke is defined clinically as a rapidly developing focal neurological deficit lasting greater than 24 hours or causing death, which is attributable to a vascular cause[1]. Stroke is common, remaining the third commonest cause of death worldwide with approximately 20% of patients being dead within one month of first stroke[2]. It is a significant cause of disability and health resource use in the developed world. Despite improved access to specialist stroke services and public education campaigns epidemiological studies suggest that the incidence of stroke remains largely unchanged[3]. Stroke has recently been identified as a priority area for UK government funding, with the publication of the Department of Health National

Stroke Strategy in December 2007 identifying key areas for education and service improvement[4].

The incidence of stroke varies between populations and increases with age, but community-based studies suggest an age-standardised annual incidence for first-ever stroke of between 238 and 627 per 100,000[5].

Risk factors for stroke disease include hypertension, increasing age, cigarette smoking, atrial fibrillation, diabetes mellitus and obesity.

1.2.1 Classification of Stroke

Stroke encompasses a range of clinical syndromes, and it is important to establish the underlying aetiology as this has implications for prognosis, future stroke risk and optimising subsequent management. Timely neuroimaging allows reliable distinction between cerebral infarction and cerebral haemorrhage, and may be helpful in determining aetiology in some cases. Stroke may be classified clinically, neuroradiologically, or by aetiology.

1.2.2 Clinical Classification of Stroke

Stroke may be classified according to clinical features, and the most widely used classification for this purpose is the Oxford Community Stroke Project (OCSP) classification[6], which uses clinical features to classify stroke according to the likely arterial territory affected. The triad of hemiparesis (or hemisensory loss), higher cortical dysfunction such as dysphasia or inattention, and homonymous hemianopia is classified as a total anterior

circulation syndrome (TACS), while a syndrome of two out of these three features (or isolated higher cortical dysfunction) is classified as a partial anterior circulation syndrome (PACS). Syndromes of pure hemiparesis or hemisensory loss, sensori-motor loss or ataxic hemiparesis are classified as lacunar syndromes (LACS). Syndromes attributable to the posterior circulation such as brainstem or cerebellar signs, or isolated homonymous hemianopia, are classified as posterior circulation syndromes (POCS). The OCSP was a community based study of patients with first stroke (confirmed or likely cerebral infarcts were included, while those with definite intracerebral haemorrhage (ICH) were excluded, though CT scanning was not performed in every case), but the classification is now widely used in hospital, it is straightforward to apply and has acceptable inter-observer reliability[7]. The OCSP classification is summarised in Appendix 1.

Clinical evaluation alone cannot reliably distinguish between ischaemic stroke and intracerebral haemorrhage, neuroimaging is required.

1.2.3 Neuroradiological classification of stroke - Ischaemic Stroke

Cerebral infarction accounts for 80-85% of all strokes in the U.K. Previously ischaemic stroke has been considered a single disease, however it has become increasingly clear that there is a spectrum of clinical and pathological subtypes.

Early changes which may be present on CT scan include a dense middle cerebral artery (MCA), loss of basal ganglia definition, loss of the insular ribbon, a region of hypodensity,

and sulcal or ventricular effacement. Later CT may show an area of hypodensity in the arterial territory affected.

Ischaemic stroke may not always be visible on CT, particularly if performed early after symptom onset, however if the history and clinical signs are appropriate and CT excludes haemorrhage then the likely diagnosis is of ischaemic stroke and should be treated as such.

1.2.4 Neuroradiological classification of stroke – Intracerebral Haemorrhage

ICH accounts for around 10-15% of first ever strokes, and confers a worse prognosis than ischaemic stroke, with 30 day mortality reaching up to 50%. (Subarachnoid haemorrhage tends to occur in a younger age group, and in those with saccular aneurysms in the circle of Willis, and it is not considered in further detail in this thesis). CT scan is the investigation of choice to confirm or exclude ICH and will detect up to 100% of ICH if performed early enough, however the characteristic appearances of haemorrhage may be lost within 5-7 days from symptom onset[8].

ICH is usually defined as being lobar (arising in the temporal, parietal, occipital or frontal lobes(s)), or deep (arising around the basal ganglia or brainstem). It has long been thought that hypertension is more associated with deep haemorrhage, and a recent meta-analysis found hypertension to be almost twice as common in patients with deep compared to lobar haemorrhage in studies including around 4000 patients[9] with ICH.

Along with hypertension other important risk factors for ICH include excess alcohol, male gender, increasing age and anticoagulant use. Cerebral amyloid angiopathy is also a risk factor for ICH, and the association appears to be stronger for lobar than deep intracerebral haemorrhage[10]. Cerebral amyloid angiopathy is characterised pathologically by amorphous fibrillar protein (amyloid) deposition in the walls of small and medium cerebral arteries, which predisposes to vessel rupture. It is strongly associated with increasing age, but not specifically with hypertension. ICH secondary to cerebral amyloid angiopathy tends to be recurrent, lobar, and multi-focal, and although the diagnosis is confirmed post-mortem gradient echo MRI may now allow a 'probable' diagnosis to be made ante-mortem[11].

1.2.5 Aetiological Classification of Stroke

The TOAST classification was developed to improve classification of ischaemic stroke into clinically relevant subtypes with good inter-rater reliability[12]. Unlike the OCSP classification[6] the TOAST[12] classification takes into account not only clinical information but also the results of relevant investigations including neuroimaging, cardiac investigations, carotid artery imaging, and haematological investigation. Broadly speaking ischaemic stroke may be classified as being due to large artery atherosclerosis, cardioembolism, small vessel occlusive disease, or rarer causes using the TOAST classification. The TOAST classification of ischaemic stroke is presented in Table 1.1[12].

Table 1.1 The TOAST Classification of Ischaemic Stroke[12]

TOAST stroke subtype classification	Clinical features	Neuroimaging	Supporting Features	Other
Large artery atherosclerosis	Cortical impairment (e.g. dysphasia, neglect) or Cerebellar or brainstem signs	Significant stenosis or occlusion of major brain artery, Cortical/cerebellar infarct or subcortical infarct >1.5cm	Carotid artery stenosis >50% History of same-territory TIA Peripheral vascular disease	No evidence of cardioembolic cause
Cardioembolism	May be similar to above	May be similar to above	History of TIA in a different territory or history of a systemic occlusive vascular event Identifiable high or medium risk source of cardioembolus	No evidence of large artery atherosclerosis as cause
Small vessel occlusion (lacunae)	Lacunar syndrome (motor/sensory/sensorimotor involvement affecting ≥2 out of arm/face/ leg, ataxic hemiparesis)	Subcortical or brainstem infarction <1.5cm	History of hypertension, diabetes	No evidence of large artery atherosclerosis or cardioembolic cause
Other determined aetiology	Clinical features of acute ischaemic stroke	CT/MRI consistent with acute ischaemic stroke	Diagnostic evidence of a rare cause, e.g. vasculopathy, haematological disorder, procoaguable state	No evidence of large artery atherosclerosis or cardioembolic cause
Undetermined aetiology	Clinical features of acute ischaemic stroke	CT/MRI consistent with acute ischaemic stroke	Lack of diagnostic evidence, or diagnostic evidence for >1 subtype	No likely cause identified, or more than one possible cause (e.g. atrial fibrillation and ipsilateral carotid stenosis > 50%)

Table adapted from original reference

1.3 Hypertension as a risk factor for stroke

Arterial hypertension affects from 20% to 30% of the world population and is the most prevalent modifiable risk factor for stroke[13]. There is a continuous and consistent association between both systolic and diastolic BP and the risk of cerebrovascular disease[14], which is independent of other risk factors. The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC 7) considered that vascular risk begins with BP values of 115/75 mmHg, and that the risk doubles with each increase of 20/10 mmHg[15]. The Framingham Heart study showed that BP values of >120/80 mmHg were associated with a higher risk of cardiovascular disease[16]. A recent meta-analysis of >40 randomized controlled trials of BP-lowering, which included >188,000 participants indicated that a 10 mmHg reduction in systolic BP would be associated with a 31% reduction in risk of stroke[17] . Initial evidence of the positive and continuous association between BP and the risk of stroke came from North American and European populations[18]. More recently, a similar association has been demonstrated in Asian populations, although the slope of the relationship appears to be somewhat steeper for Asian than White populations[19;20], possibly due, at least in part, to the relatively higher incidence of haemorrhagic stroke in Asian populations. The relationship between BP and stroke risk has been demonstrated for all age groups studied. While the strength of the association becomes attenuated with increasing age, it is still strong and continuous among those aged 70 years or more[20].

As age increases systolic BP continues to rise at least into the eighth decade, whereas diastolic BP reaches a plateau early in the sixth decade then declines. Systolic BP level is directly related to the risk of stroke, particularly after age 65 years.

There has been considerable debate over the shape of the association curve between BP and stroke. Some cohort data appear to demonstrate a J-shaped curve[21;22], and it has been suggested that this relationship indicates that BP can be lowered too far and that cerebral blood flow will then be compromised, leading to ischemia. It is more likely to reflect deteriorating health accounting perhaps for both falling BP and a greater likelihood of a cardiovascular event. Prevention trials such as PROGRESS[23] and HOPE[24] have found no evidence of a J-curve association across a wide range of BP levels. The majority of BP lowering studies support a log-linear association and indicate that a potential J-curve relationship should not detract attention from the major benefits of BP lowering.
Hypertension is an important factor in the development of atherosclerosis, which leads to the development of plaques within large and medium sized artery walls. Necrosis or rupture of these plaques leads to thrombus formation, which can cause either direct vessel occlusion or embolisation. Small vessel disease is characterised by occlusion of a single cortical perforating artery, giving rise to a 'lacunar' syndrome. This may occur in isolation, or may be associated with more widespread small vessel arteriopathy or leukoariosis. Hypertension is associated with small vessel disease and this association appears to be stronger than for large artery atherosclerosis. A recently published study of small vessel disease, large vessel disease, and controls, found an odds ratio of 3.43 (95%CI 2.32-5.07, $p<0.001$) for the presence of hypertension in small vessel compared to large vessel stroke[25]. In addition

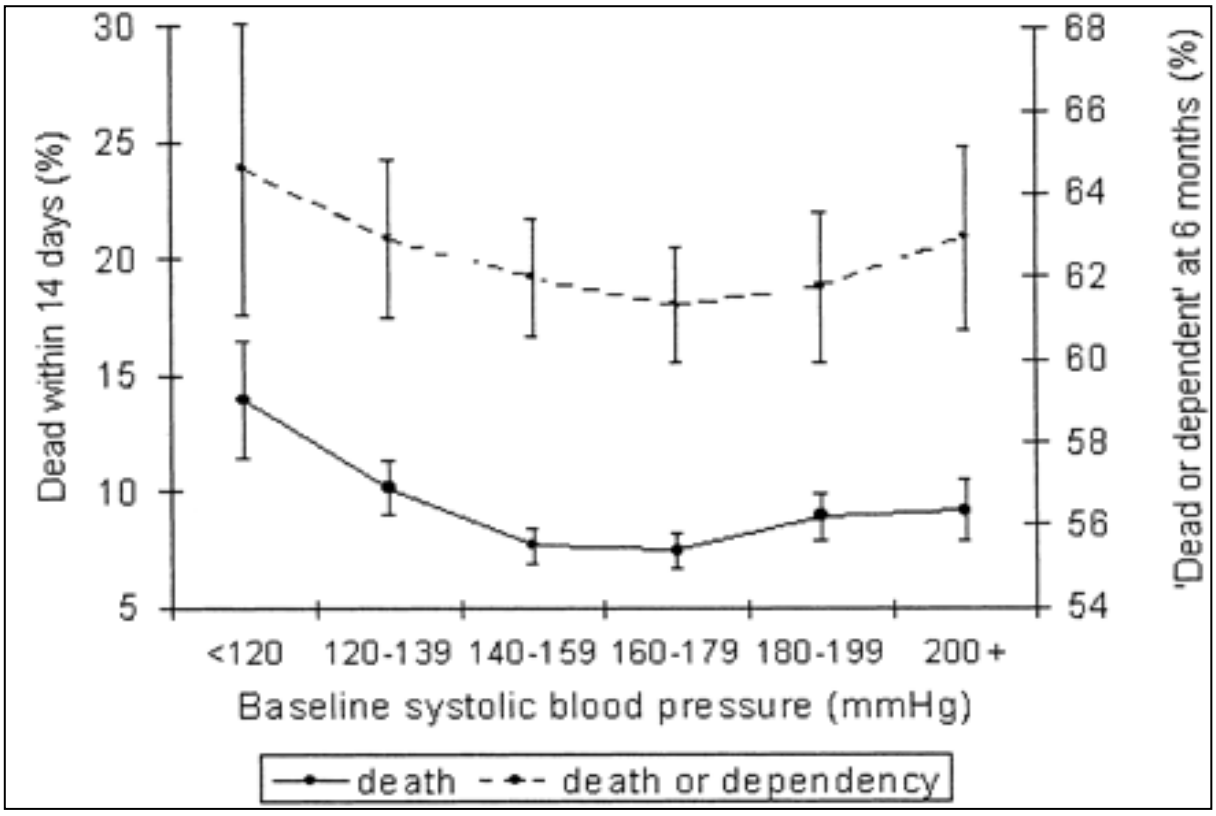
hypertension is a risk factor for the development of atrial fibrillation[26] and ischaemic heart disease, both of which are commonly implicated in cardioembolic stroke.

1.4 Acute Stroke BP

Several observational studies have illustrated the changes which occur in blood pressure following acute stroke. Around 46% of patients with acute stroke have a history of hypertension, but around 69% will have a systolic BP ≥170mmHg at the time of admission[27], and around 80% will have a BP considered hypertensive by World Health Organisation (WHO) criteria (>140/90mmHg). The mechanism for this is not entirely clear, nor is it clear whether this is a physiological response to improve perfusion to adjacent ischaemic tissue, or whether it is a detrimental side-effect with the potential to worsen cerebral oedema. BP levels tend to fall spontaneously over four to seven days even without treatment, returning to pre-stroke levels in around two thirds of patients[28].

It has been postulated that very high BP immediately post stroke may be detrimental, equally very low BP may be thought to worsen outcome. In fact both are true. In a review of 17 398 ischaemic stroke patients enrolled in the International Stroke Trial a U-shaped curve of systolic BP versus both early mortality (at 14 days) and late death and dependency (at six months) is demonstrated[28]. For each 10mmHg systolic BP below 150mmHg there was a 17.9% increase in early death, and for every 10mmHg systolic BP above 150mmHg there was a 3.8% increase in early death (see figure1.1)[28].

Figure 1.1 Systolic Blood Pressure and outcome after Stroke[28]



Proportion of patients who died within 14 days (solid lines), or were dead or dependent at 6 months (dashed lines) by baseline SBP.
Circles and squares indicate the mean percentage of patients who had died within 14 days and patients who had died or were dependent at 6 months, respectively, within each blood pressure subgroup; 95% CIs are represented by T bars.
Reproduced from original reference

A systematic review of BP post stroke (ischaemic and haemorrhagic) and outcome is in keeping with this observation, adding that high systolic BP, mean arterial BP (MAP) and diastolic BP are all associated with increased death and dependency after stroke[29].

In addition to the effect of BP on mortality, several authors have investigated the potential relationship between BP and other outcomes including stroke recurrence and functional outcome. It has been shown that higher diastolic BP and higher pulse pressure on 24 hour monitoring post stroke are associated with an increased risk of stroke recurrence, and also that higher systolic BP following acute ischaemic stroke is associated with poorer early (ten

day) and late (six month) functional outcome in terms of modified Rankin score[30] (though this latter finding was not independent of initial stroke severity). Another study demonstrated that patients with higher systolic and diastolic BP following acute ischaemic stroke actually had a *better* functional outcome at 90 days, but patients with a baseline systolic BP >185mmHg or diastolic BP >110mmHg were excluded[31].

The relationship between BP and outcome following ICH appears to be less clear. Most studies have been relatively small, often retrospective, and without standardised BP treatment. One retrospective review of 87 patients with ICH found patients with lower MAP at presentation (≤145mmHg versus >145mmHg) and lower MAP at 2-6 hours from admission (≤125mmHg versus >125mmHg) had more favourable outcomes in terms of death or severe morbidity at 30 days[32], the majority received some antihypertensive therapy (usually nifedipine or sodium nitropusside). A larger series (1701 patients) found MAP to be higher for those who had fatal versus non-fatal intracerebral putaminal or thalamic haemorrhage, but no such association in cerebellar, subcortical or pontine haemorrhage[33]. The volume of ICH is an important determinant of outcome[34], and there is increasing evidence that haematoma expansion is also associated with increased mortality[35], but these factors do not appear to be directly related to BP.

1.4.1 Blood Pressure Management in Acute Stroke

As discussed, elevated BP values (>140/90 mmHg) are present in up to 80% of patients with acute stroke[36;37] while nearly one in four patients presents with markedly raised systolic BP >180 mmHg. The elevation in BP may be secondary to the stress of the cerebrovascular

event, a full bladder, nausea, pain, pre-existing hypertension, a physiological response to hypoxia or a response to increased intracranial pressure. In a majority of patients, a decline in BP occurs within the first hours after stroke even without any specific medical treatment. The BP often falls spontaneously with non-pharmacological measures.

However, the optimal management of arterial hypertension following acute stroke has not been established and remains an issue of on-going debate. Theoretical reasons for lowering BP include reducing the formation of cerebral oedema, lessening the risk of haemorrhagic transformation of infarction, preventing further vascular damage and forestalling early recurrent stroke. Conversely, there is a concern that aggressive treatment of BP may lead to neurological worsening by reducing perfusion pressure to ischaemic areas of the brain in a situation of impaired cerebral autoregulation.

Unfortunately, data from randomized controlled trials are limited and inconclusive when considering whether lowering BP during the first hours of ictus is beneficial in stroke patients. The Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study, a prospective double-blind, placebo controlled, randomised phase II trial, evaluated the use of an angiotensin II receptor blocker in acute ischaemic stroke patients with severely elevated BP levels (SBP>180 mmHg and/or DBP>105 mmHg). Preliminary data from 432 patients demonstrated that oral candesartan reduced a composite secondary endpoint (all cause mortality and vascular events) by 52.5%[38]. It should be noted though that the trial was stopped prematurely with a neutral finding for its primary endpoint (total mortality and disability at 3 months). In a small randomised study, Eames et al[39] found no major reduction in BP among patients treated with bendrofluazide, and they concluded that this agent was

not effective in treating hypertension after stroke, though its use appeared safe. In contrast, β-blockers, such as propranolol and atenolol achieve a greater BP fall compared to placebo. However, these have been associated with a non-significant increase in mortality and decrease in neurological and functional outcome at 6 months compared to placebo[40;41]. The safety of labetalol, a combined β- and α-adrenergic antagonist, in rapidly and effectively reducing BP has been demonstrated in the NINDS thrombolysis trial[42], though its use was non-randomised. The administration of calcium channel antagonists during the acute stage of ischaemic stroke has neutral effect on functional outcome or survival, according to the conclusions of a review from the Blood Pressure in Acute Stroke Collaboration (BASC)[40]. The INWEST trial demonstrated that functional outcome was worsened in parallel with the degree by which BP was reduced using calcium channel antagonists intravenously[43]. The recent CHHIPS pilot study[44] of BP lowering in acute stroke (predominantly ischaemic) using lisinopril, labetalol or placebo did not demonstrate a significant difference in the primary endpoint of death and dependency at two weeks, but there did not appear to be excess neurological deterioration in the actively treated group despite a significant fall in BP. There was a trend towards reduced 3 month mortality in the combined treated groups versus placebo which reached borderline statistical significance (p=0.05).

The recent intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT) pilot study[45] assessed the safety and efficacy of intensive BP lowering versus standard treatment within 6 hours of ICH in a total of 404 patients, and found early intensive BP lowering to be feasible and well-tolerated, as well being associated with a reduction in haematoma expansion. However the study was not powered to detect a difference in terms of outcome.

Thus large, well-designed prospective randomised trials are needed to clarify the management of arterial hypertension after acute stroke. The results of currently ongoing trials (Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS)[46], Efficacy of Nitric Oxide in Stroke (ENOS) trial[47], the Scandinavian Candesartan Acute Stroke Trial (SCAST), and the main phase INTERACT 2 may provide some answers to some of the former unresolved issues.

The European Stroke Initiative (EUSI, now European Stroke Organisation (ESO)) [48] and the Stroke Council of the American Stroke Association[49] have released scientific statements and guidelines regarding the management of hypertension in the setting of acute ischemic stroke. Both authorities recommend that BP should not be lowered in ischaemic stroke patients who are not otherwise candidates for thrombolysis (grade C recommendation). Threshold BP values demanding immediate medical interventions are recommended by consensus. More specifically, pharmacological intervention is indicated if repeated BP readings reveal systolic BP values >220 mmHg and diastolic BP >120 mmHg. In patients eligible for thrombolytic therapy systolic BP values >185 mmHg or diastolic BP values >110 mmHg should be actively treated and maintained at desired levels (<185/110 mmHg) during and after rtPA infusion. Situations that might require urgent antihypertensive therapy independent of BP levels include acute myocardial infarction, severe left ventricular heart failure, aortic dissection, acute renal failure, acute pulmonary oedema and hypertensive encephalopathy.

Guidelines for treatment of elevated BP levels in patients with intracerebral haemorrhage are more aggressive than in ischaemic stroke[50]. Accordingly, systolic and diastolic BP levels

should be maintained below 180 and 105 mmHg, respectively. Blood pressure levels should be lowered carefully in a monitored setting with close and continuous observation of BP values and using an easily titrable, short-acting agent, such as labetalol. Extreme (>20%) reductions in BP levels ought to be avoided.

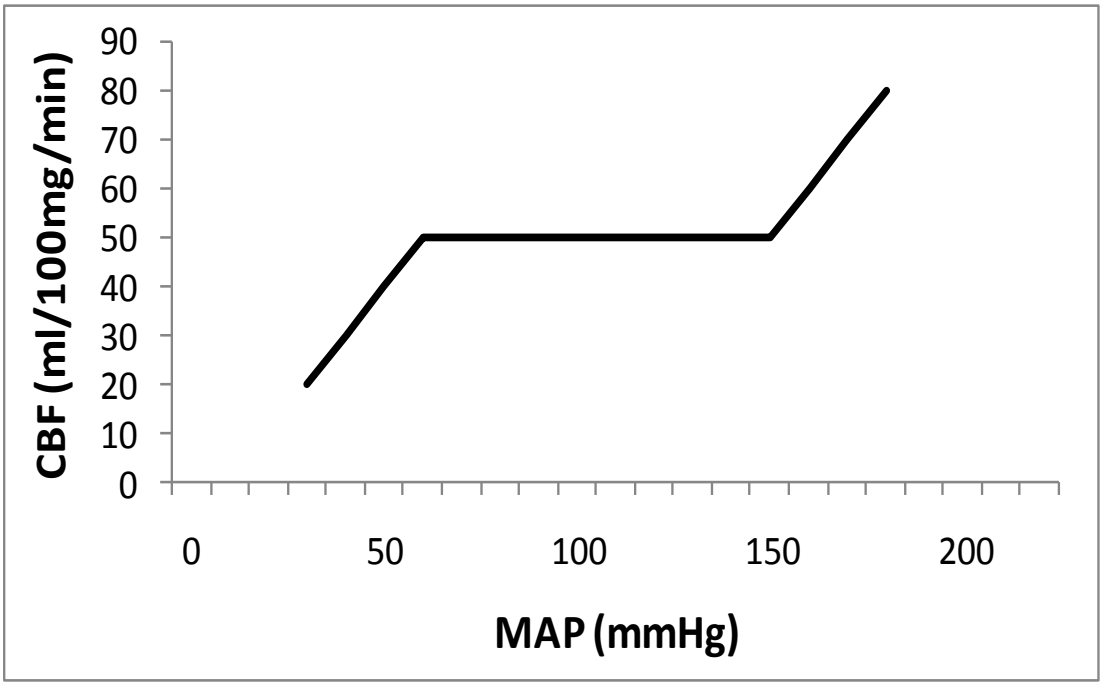
1.5 Cerebral Autoregulation

Cerebral autoregulation is the mechanism(s) by which cerebral blood flow is maintained despite changes in cerebral perfusion pressure (CPP), and can be defined as being static (responding gradually to long term changes) or dynamic (responding to acute changes). Static cerebral autoregulation reflects how efficient the autoregulatory mechanisms are over time, whereas dynamic cerebral autoregulation (dCA) describes the ability to restore cerebral blood flow following a sudden change in perfusion pressure (i.e. before static autoregulation has occurred). Under normal physiological conditions cerebral blood flow (CBF) is around 50ml/100g/min, and this can usually be maintained across a wide range of blood pressures (MAP of 60-160mmHg), this is illustrated schematically in figure 1.2. There are thought to be several factors involved in cerebral autoregulation, including cerebrovascular resistance, local endothelial factors, metabolic factors, and possibly neurogenic factors within the cerebral vasculature.

Cerebral autoregulation is important for a number of reasons. It provides a protective homeostatic mechanism to prevent cerebral hypoxia and ischaemia in situations of systemic hypotension, whether physiological (e.g. vasodilatation due to raised temperature), pathological (e.g. sepsis, myocardial ischaemia), or pharmacological (e.g. blood pressure lowering for reduction of cardiovascular risk). Similarly it prevents cerebral damage resulting

from systemic hypertension. Cerebral autoregulation is known to be impaired in a number of pathological settings, but the prognostic relevance of this is uncertain, and it is also unclear whether cerebral autoregulation may be a target for therapeutic manipulation. These seem to be important areas for further study, and as will be discussed newer, non-invasive means of measuring cerebral autoregulation make this a realistic possibility.

Figure 1.2 Cerebral autoregulation: CBF across a range of MAP



1.5.1 Cerebral Blood Flow and Cerebral Blood Flow Velocity

CBF, as mentioned earlier, is usually maintained within strict limits across a wide range of physiological variables such as a change in CPP. However CBF is difficult to measure directly, and attempts have been made to find an acceptable clinically relevant surrogate which can be measured non-invasively. CBF can be measured using invasive techniques such as electromagnetic flowmetry, which requires cannulation of major extra-cranial arteries such

as the internal carotid artery (ICA). However there are few clinical situations when this would be considered acceptable, and the advent of transcranial Doppler (TCD) ultrasound has offered a promising alternative[51].

It is clearly important to establish how well TCD assessment of cerebral blood flow velocity (CBFV) correlates to actual CBF. Lindegaard and colleagues studied seven patients undergoing carotid endarterectomy (CEA) (two with staged coronary artery bypass procedures), and found a strong correlation between directly measured ICA flow using electromagnetic flowmetry and middle cerebral artery (MCA) flow velocity measured using TCD suggesting that in anaesthetised adults the two methods provide comparable information[52].

Halsey et al studied a series of 13 high-risk patients undergoing carotid endarterectomy, using labelled xenon (Xe^{133}) administered into the common carotid artery to assess regional cerebral blood flow (rCBF) via a scintillation detector and TCD to assess mean MCA flow velocity[53]. They found good correlation between rCBF and CBFV when rCBF was <20ml/100g/min, but wide variation and poor correlation at higher values. Simultaneous electroencephalograph (EEG) monitoring was used to identify cerebral ischaemia (seen as a suppression of EEG activity) at the time of carotid clamping, and it is of interest to note that change in rCBF as measured using Xe^{133} corresponded more closely than CBFV with EEG changes. The authors concluded that the two methods are not directly comparable, but provide complimentary information. rCBF provided information about cerebral blood flow at a cortical level while CBFV showed good correlation with haemodynamic events and can provide continuous information, unlike measures of rCBF.

Bishop et al studied a series of seventeen patients undergoing carotid endarterectomy, again using intravenous Xe^{133} with a scintillation detector to measure CBF, and TCD to measure maximum CBFV in the MCA[54]. They induced hypercapnia by increasing the inspired CO_2 concentration to 5% in order to impair cerebral autoregulation, and compared change in CBF with change in CBFV. They found wide variability in results at rest both in terms of flow and velocity, but there was excellent correlation between change in flow and velocity after CO_2 inhalation, which was highly significant (correlation coefficient $r=0.849$, $p<0.001$), and the authors concluded that while CBFV does not provide an exact measure of CBF it provides an accurate reflection of any change in CBF.

Newell and colleagues studied a small series of patients (n=7) undergoing elective orthopaedic surgery, and used electromagnetic flowmetry to directly measure ICA flow, and TCD to assess maximum CBFV in the MCA to assess autoregulatory responses to induced BP change (using the thigh cuff method, which is described in more detail below). There was no significant difference ($p=0.97$) in responses in cerebral autoregulation when measured with the flowmeter or with TCD, again suggesting that CBFV provides an accurate reflection of changes in CBF[55].

In combination these studies suggest that CBFV as measured by TCD is an acceptable non-invasive means of assessing relative changes in CBF.

The relationship between flow and velocity in a vessel is described by the equation

$$Q=V_{av} \times A$$

where Q is the blood flow in ml, V_{av} is the average velocity in cm/s, and A is the lumen area in cm^2. This equation relies on the assumption that flow is laminar and that the diameter of the vessel remains constant. In order for TCD assessment of CBFV to be an acceptable means of assessing CBF therefore the diameter of the insonated vessel (in this case usually the MCA) must remain constant. The correlation between flow and velocity in the above studies suggests that any change in MCA diameter during recordings was negligible.

Poiseuille's Law gives the relationship between laminar flow in a cylinder, with flow being proportional to the fourth power of the cylinder's radius. Thus it is apparent that very small changes in cylinder (or vessel) diameter would lead to significantly higher changes in flow. Giller et al[56] studied MCA diameter in 12 patients undergoing craniotomy and demonstrated only small variation in MCA diameter (<4%) despite alterations in mean BP and end-tidal CO_2. Smaller arteries showed a considerably higher degree of variation (up to 21%). More recently Serrador demonstrated alterations in CBFV measured with TCD following induced hypo- and hypercapnia and lower body negative pressure, but no change in MCA diameter measured using MRI[57].

It is important to note however that these studies, though widely quoted, contain relatively small numbers of subjects, and do not provide conclusive reassurance regarding the stability of MCA diameter. In addition they do not take into account potential effects of stroke and vasoactive medications on MCA size, and thus it remains a limitation of TCD measurement of MCA velocity that there is an assumption of constant MCA diameter.

1.5.2 Methods of Measuring Cerebral Autoregulation

The assessment of CA requires a reproducible means of measuring CBF or CBFV while simultaneously measuring changes in arterial BP. Static CA can be assessed by inducing

gradual changes in BP, such as by the continuous iv infusion of pressor agents[58], or the gradual inflation of thigh cuffs[59]. Assessment of dCA however requires rapid short-term fluctuations in BP against which change in CBF or CBFV may be measured, such as the sudden release of thigh cuffs previously inflated to suprasystolic pressures for several minutes. Tiecks et al[58] compared static CA (using iv phenylephrine to induce a gradual increase in BP) with dCA (using the thigh cuff release method) in anaesthetised patients with intact auoregulation and impaired autoregulation (induced by the administration of isoflurane), and found good correlation between the two methods. It is likely however that different factors mediate responses to static and dynamic stimuli, as Dawson et al demonstrated that dynamic but not static CA is impaired following acute ischaemic stroke[59]. In their study thigh cuff inflation and hand grip were used as pressor stimuli for static CA, and the thigh cuff release method described by Tiecks as a stimulus for dynamic CA.

'Indicator methods' of measuring CBF include labelled isotope administration (eg Xe^{133}) with scintillation detection, and more recently single photon emission CT (SPECT) scanning. These methods allow quantification of rCBF and provide information on CBF at the level of the cerebral microcirculation, but provide a snapshot view rather than a continuous estimate over time.

TCD provides continuous information on CBFV in the basal arteries and provides excellent time resolution, allowing correlation with rapid and short-term fluctuations in arterial BP.

1.5.3 Measurement Techniques

Historically dCA has been measured using induced changes in arterial BP (and hence cerebral perfusion pressure) while measuring the rate of return to baseline of CBF or CBFV. Methods used to induce change in BP include the thigh cuff release previously described, lower body

negative pressure, postural change (such as rapid sit-to-stand), Valsalva manoeuvre, and cold pressor stimulus (immersion of the hand in cold water). Each of these methods induces a measurable step change in arterial BP which can be related to changes in CBFV in either the time or frequency domain.

Panerai et al studied the patterns of CA to dynamic tests and to spontaneous fluctuations in arterial BP in 56 healthy volunteers. Their results suggest that different dynamic tests exert different magnitudes of sympathetic activation, but autoregulatory index (ARI) and impulse response measures were independent of the type of manoeuvre performed[60]. They also reported no significant difference in results derived from dynamic testing and spontaneous BP fluctuations, though this was a preliminary study.

The dynamic methods described so far have some limitations, namely they can be time consuming, they promote sympathetic activation which may influence any responses observed, and subjects may find them painful. In addition there are groups of patients in whom a sudden induced fall in BP may be undesirable, including those with heart failure, autonomic failure, and significant carotid stenosis.

This has prompted interest in the use of spontaneous BP fluctuations occurring at rest as the stimulus against which to measure cerebral autoregulation. Several authors have used spontaneous fluctuations in arterial BP to assess dynamic cerebral autoregulation in neonates[61], patients with significant carotid stenosis[62;63] and following acute ischaemic stroke[64], using both the time and frequency domain, and this method is now generally accepted as a practical alternative to induced step changes of BP for measurement of cerebral autoregulation.

1.5.4 Analysis of Dynamic Cerebral Autoregulation – Frequency Domain

dCA may be assessed in either the frequency domain or the time domain. Transfer function analysis is the most widely used technique in the clinical study of dCA in the frequency domain. Transfer function analysis is a mathematical means of examining a relationship between input and output in a linear system. It was first proposed by Giller[65] that dCA could be modelled by transfer function analysis with BP as the input and CBFV as the output. Interrogation of a system using transfer function analysis yields valuable information about the properties of the system (in this case the integrity of the dCA) across a range of frequencies. This system approach relies upon the assumption that input and output are linearly related. It is likely that some of the factors influencing dCA, such as $PaCO_2$[66] do not behave in an entirely linear manner, but under stable physiological conditions the use of small spontaneous fluctuations in BP make it possible to assume linearity in this method[67;68] Fast Fourier transform (FFT) is an algorithm used to compute the discrete Fourier transform and its' inverse, and is a means by which a series of values e.g. a time series may be decomposed into components of different frequencies (or harmonics). FFT is a means by which a time series may be interrogated in the frequency domain by transfer function analysis. This allows realisations of the system's properties in the frequency domain, i.e. it describes the system's gain and phase.

Giller[65] reported his initial results in terms of coherence, i.e. the degree of coupling between the output and input signals. The rationale for this is that intact dCA would result in low coherence due to factors other than BP exerting an effect on dCA, while if CBFV was dependent on BP (in a situation of impaired dCA) the coherence would be higher (approaching 1). However there is no consensus what the cut-off between good and poor

coherence, nor which particular frequency in which to study coherence. In addition low coherence may represent lack of a relationship between input and output, but it may also reflect a poor signal-to-noise ratio.

Further work has developed this method, with increasing interest in other frequency parameters such as gain and phase. The gain is the ratio of the amplitude of the output signal to the input signal, and so indicates the magnitude of change in CBFV that is due to a change in BP. Gain alone is not a reliable measure of cerebral autoregulation.

The phase is equivalent to the shift in radians (or degrees) that would be required to align input (BP) with output (CBFV) at a given frequency, and so gives an indication of the relative timing of the two signals. The magnitude of the phase response may be an indicator of the integrity of the autoregulatory response, with lower phase suggesting less efficient dCA[68;69]. This has been demonstrated in a number of conditions, including occlusive cerebrovascular disease[70], arteriovenous malformation[70] and carotid stenosis[62]. In one study phase was not found to be significantly lower in patients with acute minor stroke compared to control, though there was a trend to reduced phase on the affected side[64]. There are some limitations to the use of phase as a measure of CA. The first of these is the problem of 'wrap-around'. This is exhibited when the value of phase is greater than π radians, and the signal 'wraps around' the y-axis, and is therefore estimated as a negative value giving a false result. Another limitation is that phase may be very much affected by rate of respiration, with several studies of cerebral autoregulation using phase requiring a fixed rate of respiration (often 6 breaths per minute or 1Hz). This raises the possibility that these results

demonstrate not only the integrity of cerebral autoregulation but also potentially the effects of altered respiration, and consequent changes in CO_2 and BP upon cerebral autoregulation.

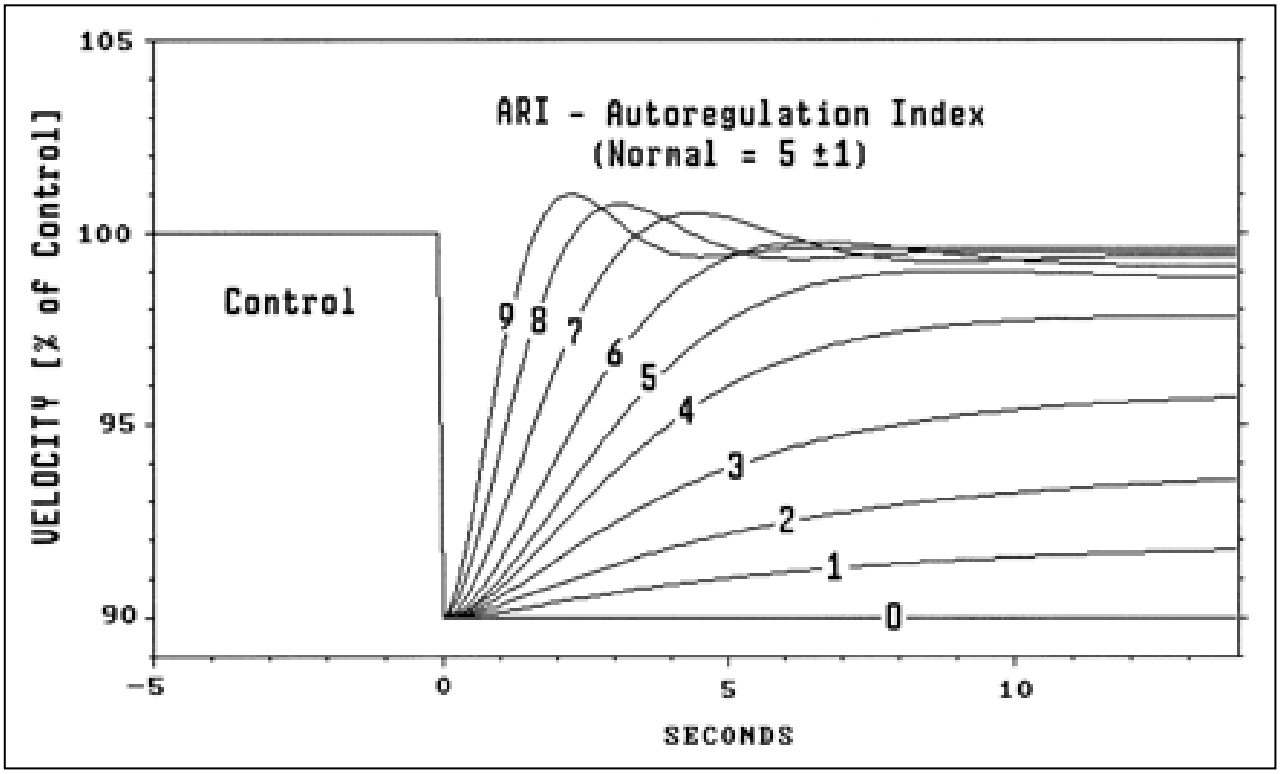
1.5.5 Analysis of Cerebral Autoregulation – Time Domain

The impulse response is derived by inverse Fourier transform of the transfer function, and describes the output as a response to a brief input (or impulse). It provides information about the relationship between CBFV and ABP in response to a sudden step-like change in ABP. The CBFV step response provides information regarding the system's coherence, gain and phase but in the time domain, and has the advantage that it is unaffected by 'wrap-around'. The CBFV step response can be estimated by numerical integration of the impulse response in the time domain.

Tiecks et al described a set of equations for CBFV response to a step-like fall in BP induced by thigh cuff deflation from which ARI can be calculated, with 0 representing absence of autoregulation i.e .CBF dependent on CPP, (a 'pressure-passive relationship') up to 9 being best measurable autoregulation[58], these curves are shown in Figure 1.3.

Figure 1.3 Responses of cerebral autoregulation model to a step change in BP[58]

Reproduced from original reference



It has subsequently been shown that the impulse response from spontaneous fluctuations in ABP at rest may be used to calculate the CBFV step response, from which ARI can be estimated[63]. This is done by comparison of the calculated step response with Tiecks' model curves and selecting the 'best-fit' 0-9. The least square error or the correlation coefficient may be used as measures of fitting, with a correlation coefficient >0.5 suggesting an acceptable level of agreement between the actual step response and the predicted curve. Other parameters in the time domain may also provide useful information regarding the integrity of dCA, including critical closing pressure (CrCP) and resistance area product (RAP). CrCP is defined as the arterial pressure below which small vessels collapse and forward blood flow becomes zero, which in the cerebral circulation is equivalent to the sum of intracranial pressure and the contributions of vascular smooth muscle tone[71]. There has

been interest in the use of CrCP as a measure of cerebrovascular tone and as a component of cerebral autoregulation[71;72]. CrCP can be estimated from the first harmonic for arterial BP and CBFV[71], and is expressed in mmHg. Resistance area product is an index of cerebrovascular resistance, which is equal to the total cerebrovascular resistance x cross-sectional area of the vessel[73], and is determined as the inverse of the linear regression slope between instantaneous CBFV and ABP relationship for each cardiac cycle[67;73], it is expressed in mmHg.s/cm.

1.5.6 Reproducibility of dCA Measurement

It is worth noting that despite the many recent advances in measurement of cerebral autoregulation using TCD and spontaneous fluctuations in BP there is no published work regarding its reproducibility in the same subject over time (i.e. the intra-subject variability), or how this relates to the inter-subject variability. Mahony et al[74] measured dCA using the thigh cuff method up to six times in 16 subjects to establish the variability of the test and any accommodation that may occur. Using analysis of variance (ANOVA) they found no significant difference between measures and there was no evidence of physiological accommodation with repeated testing. The investigators conclude that three sequential thigh cuff releases are sufficient to determine dCA. These were recordings performed on a single visit however, and do not give us an indication of the variability within the same subject over time. Birch et al[75] studied the reproducibility of dCA using two strengths of lower body negative pressure in five healthy subjects on eight separate occasions (with two recordings at each visit). Their results are reported in the frequency domain, and they report a consistently positive phase on repeated testing, with less variability when the stronger

vacuum was used. Unfortunately subject discomfort and concerns regarding safety may limit the wider applicability of this technique, particularly in studies involving acutely unwell patients. Smielewski[76] et al assessed the repeatability of dCA measured using transient ipsilateral carotid artery compression on a single occasion in 11 healthy volunteers, and concluded that for arterial compression ≥5 seconds the index of autoregulation was reproducible, and showed similar variation in response to changes in CO_2 as the more established thigh cuff method. However there are methodological concerns in that the stimulus to autoregulation is not quantifiable, as well as safety concerns regarding the use of this technique in patients with carotid artery disease.

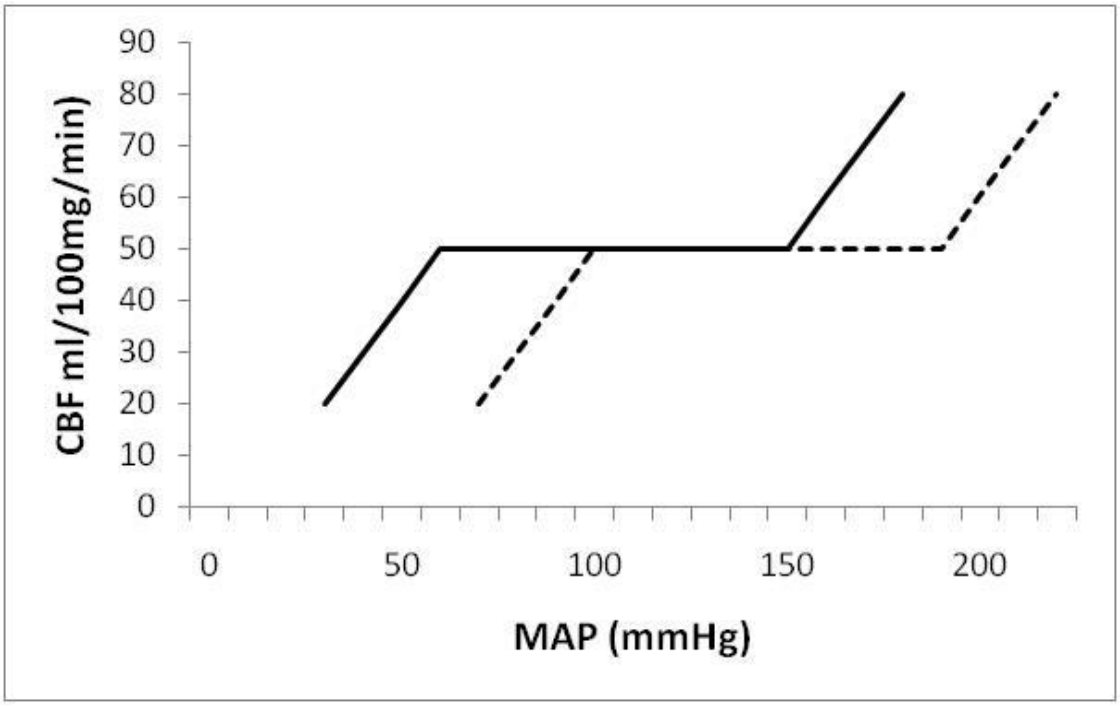
It is unclear to what extent dCA derived from spontaneous fluctuations in BP may vary during a single recording period or between recordings in the same subject. Thus when this method is used some attempt should be made to estimate the effects of intra-subject variability upon results, in order to avoid drawing erroneous conclusions. This information is essential to interpret the results of clinical studies since any change occurring as a result of a disease or a treatment must be greater than the intrinsic variability of the test. Further study of this measurement would also assist the planning of future clinical studies of dCA using this method.

1.6 Cerebral autoregulation in hypertension

There appears to be adaptation of cerebral autoregulation in patients with hypertension, and the lowest MAP before symptoms of cerebral hypoperfusion appear is also higher in patients with hypertension than in normotensive patients[77]. This right shift in the

autoregulatory curve, as illustrated in figure 1.4, appears to be reversible to some extent when hypertension is treated[78], but it is likely that hypertension over a long time leads to permanent changes in vascular structure which may lead to an irreversible raising of the MAP threshold for cerebral autoregulation. There is a large body of evidence that treating hypertension reduces vascular morbidity and mortality, and certainly antihypertensive therapy should be considered for most patients at significant risk of vascular events. However the majority of BP lowering trials have focussed on vascular endpoints, and there exists some controversy over whether certain outcomes in certain groups may be adversely affected with aggressive BP lowering, such as the development or worsening of cognitive impairment in those with small vessel cerebrovascular disease[79]. It is possible that this may be seen where antihypertensives lower the MAP below the altered threshold of cerebral autoregulation in patients with longstanding hypertension. Initial treatment of severe hypertension should be aimed at a gradual reduction rather than a sudden fall to levels considered 'normotensive', as this may precipitate symptoms of cerebral ischaemia (or infarction) which may be due to hypoperfusion secondary to the altered threshold for cerebral autoregulation.

Figure 1.4 Right shift in autoregulatory curve in hypertension



Solid line = normotensive subjects, Broken line = hypertensive subjects
Adapted from original reference[78]

1.7 Effects of antihypertensive treatment on cerebral autoregulation

Several authors have studied the effects of treating hypertension on cerebral autoregulation. Contrary to what one might expect, these have shown a trend to unchanged or improved cerebral autoregulation following treatment. They have however tended to be small scale studies, using a variety of different hypotensive agents, and using a variety of methods to study CBF or CBFV.

In the early 1980s one group studied the effects of treating hypertension in spontaneously hypertensive rats using minoxidil, hydralazine and propranolol, compared with placebo-treated hypertensive and normotensive rats[80]. CBF and cerebral oxygen metabolic rate were measured under hypotensive conditions, and those receiving antihypertensive therapy

showed preserved autoregulation while it was significantly decreased in those receiving placebo.

More recently in humans, Zhang and colleagues studied the effects of antihypertensive therapy at baseline, after 1-2 weeks of treatment and after 3-4 months of treatment with an angiotensin 2 receptor blocker (losartan) and a thiazide diuretic (hydrochlorthiazide)[81]. Patients were defined as having mild or moderate hypertension and were treated to a target of <140/90 mmHg, using 24 hour ambulatory monitoring to monitor BP control. CBFV was assessed using TCD at rest and during head-up tilt. CBFV was unchanged following short and long term antihypertensive treatment. Those who were classified as having moderate hypertension actually appeared to have enhanced CA at baseline, in that change in CBFV in response to spontaneous fluctuations in BP was attenuated in this group, returning to levels similar to the normotensive (untreated) control group after 3-4 months treatment. The study was however small (n=21, controls=9), patients were young (mean age 47 and 49 years for mild and moderate hypertension respectively), and patients with severe hypertension (>180/110 mmHg) were excluded.

Lipsitz et al[82] studied three groups of patients all >65 years, who were either normotensive, treated hypertensive (BP<140/90mmHg), or with previously uncontrolled hypertension (SBP>160mmHg) at baseline. Those with uncontrolled hypertension received treatment with an ACE inhibitor (lisinopril) +/- a thiazide (hydrochlorthiazide), if not tolerated they received a calcium channel blocker (nifedipine) or an angiotensin 2 receptor blocker. Treatment was not standardised in the treated hypertensive group. In addition to examining carotid distensibility, cerebral autoregulation was assessed using TCD to measure CBFV on sit-to-

stand testing and cerebrovascular reactivity to carbon dioxide. The fall in CBFV in response to standing was similar in all three groups, both at baseline and after 6 months. A BP of <140/90mmHg was achieved at six months in all patients in the uncontrolled hypertension group. Lowering of BP in this group was associated with a significant increase in CBFV, suggesting that effective treatment of hypertension may lead to improvement in CBF.

1.8 Cerebral Autoregulation in Acute Stroke

dCA has been shown to be impaired following acute stroke, with a reduced ability to maintain constant cerebral blood flow in response to sudden fluctuations in BP[83], while static autoregulation does not appear to be affected in the same way. Several authors have found a fall in dynamic autoregulatory indices following acute stroke (<96 hours from onset)[59;83;84]. Immink et al[84] studied dynamic cerebral autoregulation following acute ischaemic MCA stroke and acute lacunar stroke, and found impairment of dCA in the affected hemisphere only in MCA stroke, but global impairment following lacunar stroke. Dawson et al[59] found no difference between affected and unaffected hemisphere in patients with acute ischaemic stroke when all subtypes were analysed together, both hemispheres had significantly reduced ARI compared to controls. This finding was reproduced by Eames et al[83], who again found no inter-hemispheric difference (affected versus unaffected) in dCA following acute stroke. Reinhard et al[64] however found no significant impairment of dCA following acute stroke, but the patients were all studied earlier and all had minor stroke (NIHSS 6 ± 4). There appears to be a difference in the effects of different stroke subtypes on dCA, however not all studies have looked in detail at this aspect and some were

underpowered to allow subgroups to be studied in detail. Reinhard showed impaired cerebral autoregulation in ipsilateral severe carotid artery stenosis, which rapidly recovered following carotid revascularisation[85]. It remains unclear to what extent dynamic cerebral autoregulation recovers following acute stroke. While there is some evidence that reduced dCA confers a worse prognosis in patients with head injury[86] it remains uncertain what the prognostic significance of impaired dCA following acute stroke may be.

1.9 Antihypertensive Therapy and Cerebral Autoregulation following Acute Stroke

There are a few small studies examining the effects of antihypertensive therapy on cerebral autoregulation post-stroke. It may be postulated that in a situation of already impaired cerebral autoregulation, where CBF is dependent on systemic arterial BP, that the introduction of antihypertensive therapy may further impair CBF, a potentially hazardous situation.

Waldemar et al[87] studied the effects of a rapid acting ACE inhibitor, captopril, (peak antihypertensive effect occurs within 1-1.5 hours of oral administration) on rCBF in 12 patients within 5 days of stroke. They used SPECT scanning pre- and one hour post oral drug administration to identify possible changes in CBF. They found no significant alteration in rCBF, but nor was there a significant fall in BP.

Lisk et al[88] studied a series of 16 patients within 72 hours of onset of MCA territory ischaemic stroke who were randomised to antihypertensive treatment with nicardipine (n=5), captopril (n=3), clonidine (n=2), or placebo (n=6), and used SPECT scanning to assess

CBF. They found a significant negative correlation between SPECT MCA flow and mean arterial pressure, in that CBF increased to a lesser extent by day 3 in those with lower MAP, though this did not correlate with neurological impairment as determined by the NIHSS score. Nonetheless the authors advise caution in using calcium channel blockers to lower MAP following acute stroke due to risk of impairing cerebral perfusion.

Eames et al[39] randomised thirty-six hypertensive patients ten days post-stroke to receive bendrofluazide 2.5mg od or matching placebo for a period of 28 days. There was no demonstrated fall in BP in those receiving active treatment, but those in the placebo group had an overall rise in BP at 28 days (mean rise 13/6mmHg). Bendrofluazide did not appear to have any detrimental effect on cerebral autoregulation, as measured by TCD, compared with placebo treatment. Nazir et al[89] studied the effects of perindopril versus placebo in a group of twenty five patients with recent stroke (4-8 days from ictus), using TCD and SPECT scanning to assess global and regional CBF, in addition to assessing effects on renal perfusion. All of their patients were defined as normotensive prior to trial entry (DBP 70-90mmHg on consecutive recordings). Again they found a non-significant fall in BP at 14 days, though an acute-phase fall in MABP of 12mmHg compared to placebo was shown at 1-10 hours post-first dose. No significant difference was demonstrated in global or regional cerebral perfusion in the perindopril-treated group compared to placebo, and there was in fact a non-significant trend to increased ICA flow in the active treatment group at the time of peak drug effect.

Willmot et al[90] administered transdermal GTN or placebo to 18 patients randomised within 5 days of onset of stroke, CBF was measured using xenon CT (XeCT), and MCA velocity measured using TCD, while central BP was estimated using a Sphygmocor. This group found

a significant fall in systolic BP and a non-significant fall in diastolic BP in those receiving GTN compared to placebo, but without any associated change in regional or global CBF. Hatazawa et al[91] examined cerebral perfusion reserve using PET scanning in patients with a history of previous minor stroke within the preceding 5 years who had been randomised to receive either perindopril 4mg od (n=9) or placebo (n=10). They found a significant increase in cerebral perfusion reserve in the treatment group compared to the placebo group though there was no significant difference in BP between the 2 groups. This was a small study, but raises interesting questions about the potential mechanisms involved, and also as to whether prior treatment with ACE inhibitors (or other vasoactive agents) may be beneficial in limiting ischaemic damage following acute stroke. As previously discussed it is important to note that in studies using TCD to assess CBFV that this method relies on the assumption that the insonated vessel diameter (i.e. MCA diameter) remains constant during examination. Thus further information is required on the potential intracerebral vasodilatation caused by different antihypertensive agents used in order to judge the validity of such results. In general however these studies suggest that early initiation of some antihypertensive agents post-stroke may be safe in selected patients without detrimental effects on dynamic cerebral autoregulation, but further conclusive work in this area is required. To date there is no published work exploring the effects of prior antihypertensive therapy on dynamic cerebral autoregulation in the acute post-stroke period, nor whether continuing or stopping antihypertensive therapy following acute stroke has any effect on rate of recovery or absolute recovery of autoregulation. Such studies would help further our understanding of the factors involved in cerebral autoregulation in hypertension and acute stroke, and the potential effects of different classes of antihypertensive therapy.

1.10 Cerebral Autoregulation and Ageing

It has been suggested that cerebral autoregulation declines with ageing[92], leading to a reduced tolerance to postural change and increased risk of syncope[93], and worse outcomes following brain injury[94]. However other authors have demonstrated little or no difference in cerebral autoregulation when comparing older and younger subjects[95-97]

Important methodological differences exist between these studies, making direct comparison of results less straightforward. It is possible that some of these studies were not adequately powered to reveal changes in cerebral autoregulation between age groups. There is also the difficulty of overcoming inter-subject variation in studies which rely upon comparison between two unrelated or unmatched groups[98].

1.11 Hypotheses

This Thesis will test the following hypotheses:

- ***i.*** That dynamic cerebral autoregulation can be measured reliably from spontaneous fluctuations in BP using transfer function analysis to derive the ARI
- ***ii.*** That ARI will be of acceptable reliability to allow calculation of sample size for future study
- ***iii.*** That dynamic cerebral autoregulation will become less efficient with healthy ageing
- ***iv.*** That dynamic cerebral autoregulation will demonstrate early recovery following acute ischaemic stroke
- ***v.*** That the effect of acute ischaemic stroke on dynamic cerebral autoregulation will be independent of a prior history of hypertension

1.12 Aims of MD

The aims of this Thesis are as follows:

i. To assess the reliability of dCA using spontaneous fluctuations in BP, with reference to sample size and planning of future studies

ii. To assess the effects of ageing on dCA in a group of healthy volunteers.

iii. To determine the changes in dCA following acute stroke (within 48 hours of onset) and early recovery (two weeks) compared to controls

iv. To determine whether dCA after acute stroke is affected by a prior history of hypertension.

Chapter 2: Methods

2.1 Methods

This section will describe the general methods used for data collection and analysis which are common to each of the studies. Specific detailed methodology relevant to individual studies, including statistical analysis, will be discussed in more detail in the appropriate Chapters.

2.2 Cerebral Autoregulation - Data Collection

Simultaneous bilateral recording of middle cerebral artery (MCA) blood flow velocity was performed using TCD with 2MHz probes using a Viasys Companion III, with the subject lying supine on a couch. The vessel was located via the temporal bone window, and identified as the MCA by the waveform[51], its depth, velocity, the direction of flow, and the vessel's traceability (its presence at different depths). A specifically designed head frame was used to secure the ultrasound probes in position and to minimise movement. The temporal bone window is illustrated in figure 2.1. The properties of the MCA and other major intracranial vessels are summarised in table 2.1.

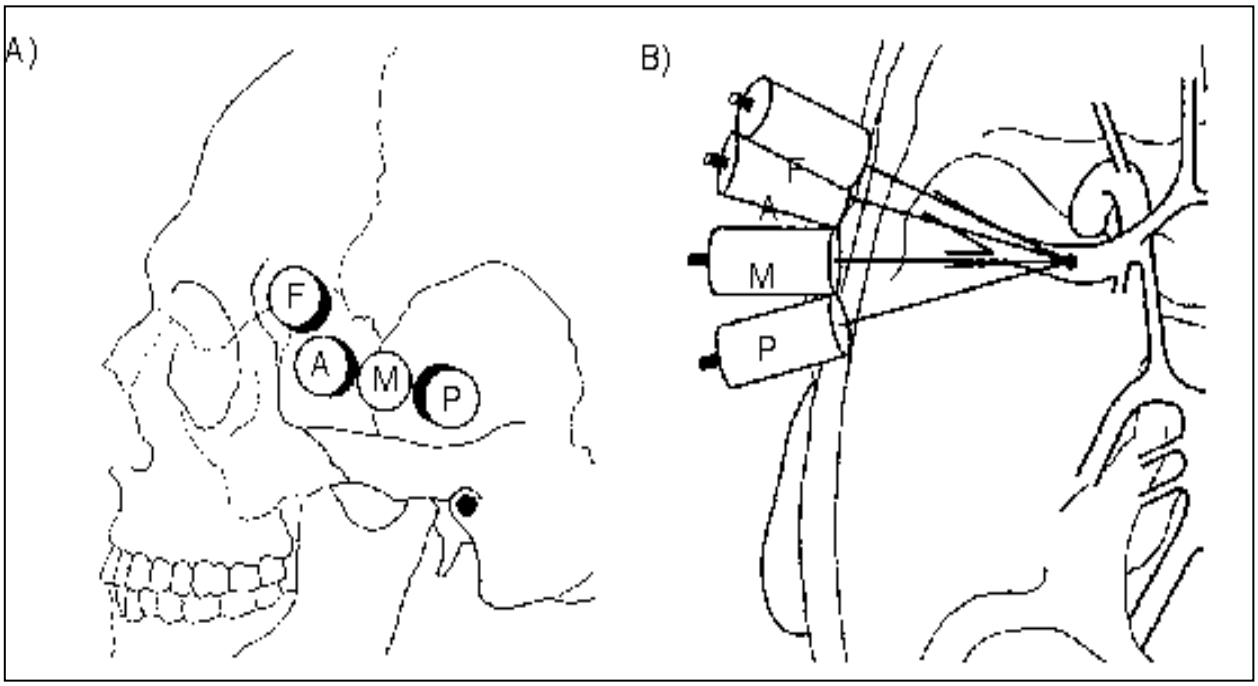
Table 2.1: Intracranial Artery Identification using Transcranial Doppler [99]

Artery	Depth of Sample Volume	Direction of Flow	Mean Velocity
Middle cerebral artery (MCA)	30-60 mm	Towards probe	55 +/- 12 cm/sec
Anterior cerebral artery (ACA) (A1)	60-80 mm	Away from probe	50 +/- 11 cm/sec
MCA/ACA bifurcation	55-65 mm	Bidirectional	variable
Posterior cerebral artery (PCA) (P1)	60-70 mm	Towards probe	39 +/- 10 cm/sec

Table adapted from original reference

Figure 2.1 Temporal acoustic window[100]

Reproduced from original reference. F – frontal, A – anterior, M – middle, P – posterior



2.2.1 Blood Pressure and Heart Rate

Non-invasive measurement of blood pressure was undertaken using a servo-controlled plethysmograph (Finapres 2300, Ohmeda, USA), the cuff being attached to the middle finger of the non-dominant hand and the arm supported at heart level. Use of the Finapres to measure spontaneous fluctuations in BP from which to assess dCA has previously been validated, and shown to have reasonable agreement with dCA measured from more invasive intra-aortic BP measurement[101]. Finapres is good at detecting trends in BP and spontaneous fluctuations, but the absolute agreement with intra-arterial brachial measurement is less good[102]. Brachial blood pressure was therefore also checked using a UA-767 BP machine, with the average of three values recorded. Heart rate was recorded with a three-lead surface ECG monitor.

2.2.2 Data Recording

All recordings were undertaken in a quiet research laboratory, with minimal external stimuli, room temperature was maintained relatively constant at ~24^0 C, and patients were asked to maintain a stable respiratory rate during each recording.

Once a stable baseline had been achieved (<10% variation in BP and CBFV) three recordings were made, each lasting a minimum of 5 minutes. Data were recorded directly from the TCD, Finapres and ECG onto a dedicated research computer using custom-designed physiological data acquisition software (*Physidas*) from the Medical Physics Group, University of Leicester. Each file was anonymised and named using a coded sequence from which the subject and examination number could be derived by the researcher. During each period of recording the Finapres servo was switched off, and a calibration signal was recorded at the start of each recording. In between each recording the servo was switched back on, and an adequate time interval allowed before making subsequent recordings. The TCD output was configured to give the maximum velocity envelope for both velocity channels, and these were standardised as output1 = right MCA and output 2 = left MCA. Recordings were transferred on CD to a dedicated editing/analysis computer.

2.3 Data Editing and Analysis

Data were edited and analysed using customised software specifically designed for this use by the Medical Physics Group, University of Leicester, which runs on an MS-DOS based system.

2.3.1 Data Editing

The Finapres calibration signal was used to calibrate arterial BP measurements, and this signal was then removed. CBFV channels were visually inspected, and spikes were manually removed by linear interpolation. Visual assessment of the data quality was made looking specifically at the shape and quality of the CBFV waveform and the presence of large spikes or noise. The Finapres waveform was inspected for drift (which can occur if the Servo has been off for some time or if the subject's finger becomes cold), non-physiological changes in BP again led to data rejection. The R-R interval was marked using the ECG trace, which was visually inspected to ensure correct marking. In cases where the ECG appeared unreliable (e.g. due to poor skin contact or interference) the editing software permitted R-R marking from the Finapres trace.

Following CBFV spike removal a median filter was applied, followed by a zero-phase eighth order Butterworth low-pass filter, and data were then re-sampled at 0.2 seconds to create a uniform time base. Following editing as above a fast Fourier transform was applied to the data, thus transferring from the time domain into the frequency domain. The input variable was selected as arterial blood pressure, with the output variable being right or left MCA blood flow velocity.

2.3.2 Frequency Domain Parameters

The resultant data were further inspected for quality to ensure accuracy of any results. The coherence was acceptable if it was >0.5 in higher frequencies (even if only in a narrow band), while lower coherence at lower frequencies was accepted. Coherence that was very low throughout prompted review and possible rejection of the data. The impulse response was accepted if a narrow central response was displayed at t=0. If large amplitude oscillations were present which were equivalent in height to the central impulse peak this was a further reason for data rejection. The step response was used as a third measure of data quality following fast Fourier transform. The step response should start from a positive value and exhibit a steep upslope in the first 3 seconds, and should be physiologically plausible. Examples of acceptable coherence, impulse response and step response are illustrated in Figures 2.2-2.4.

Figure 2.2 Acceptable Coherence between BP and CBFV

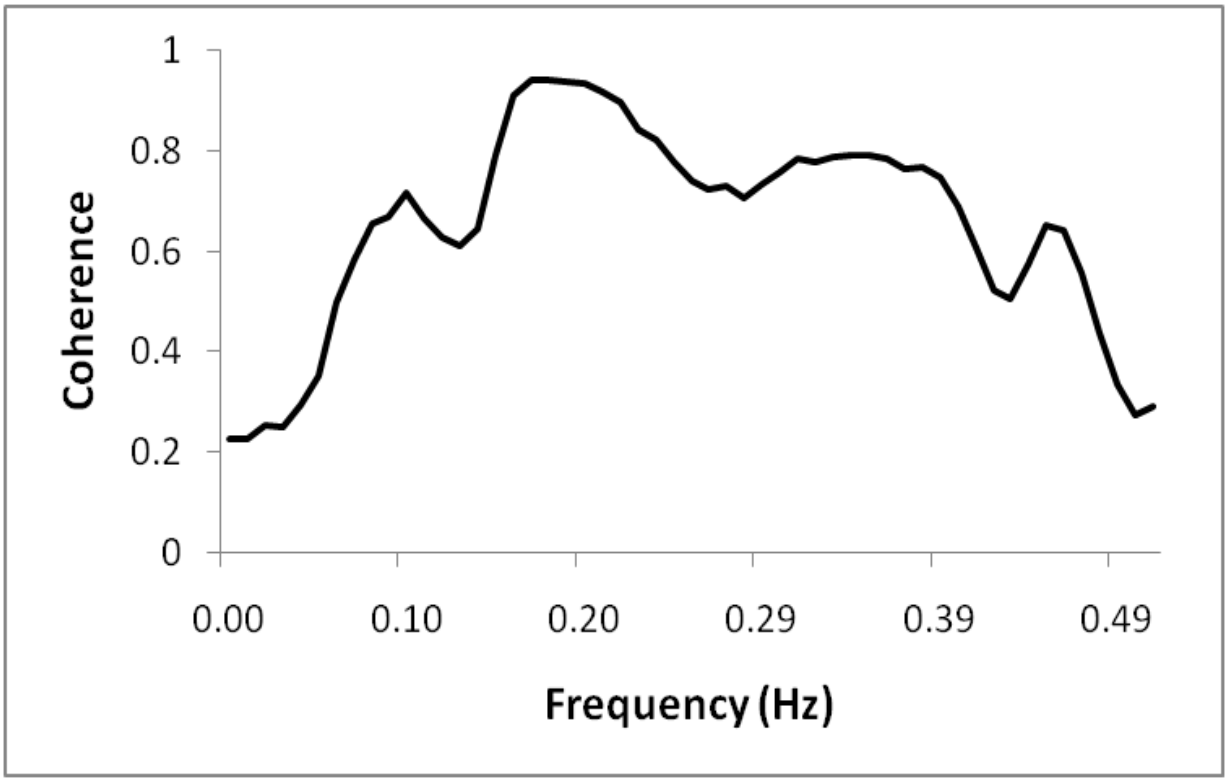


Figure 2.3 Acceptable CBFV Impulse Response

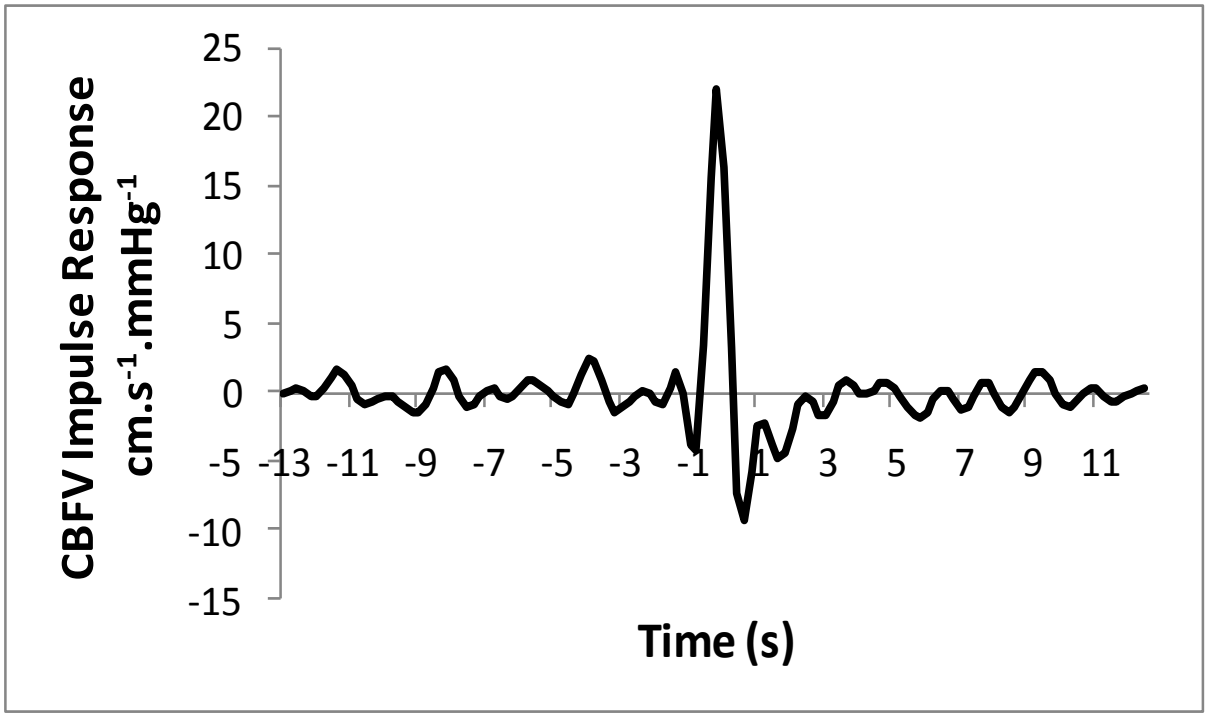
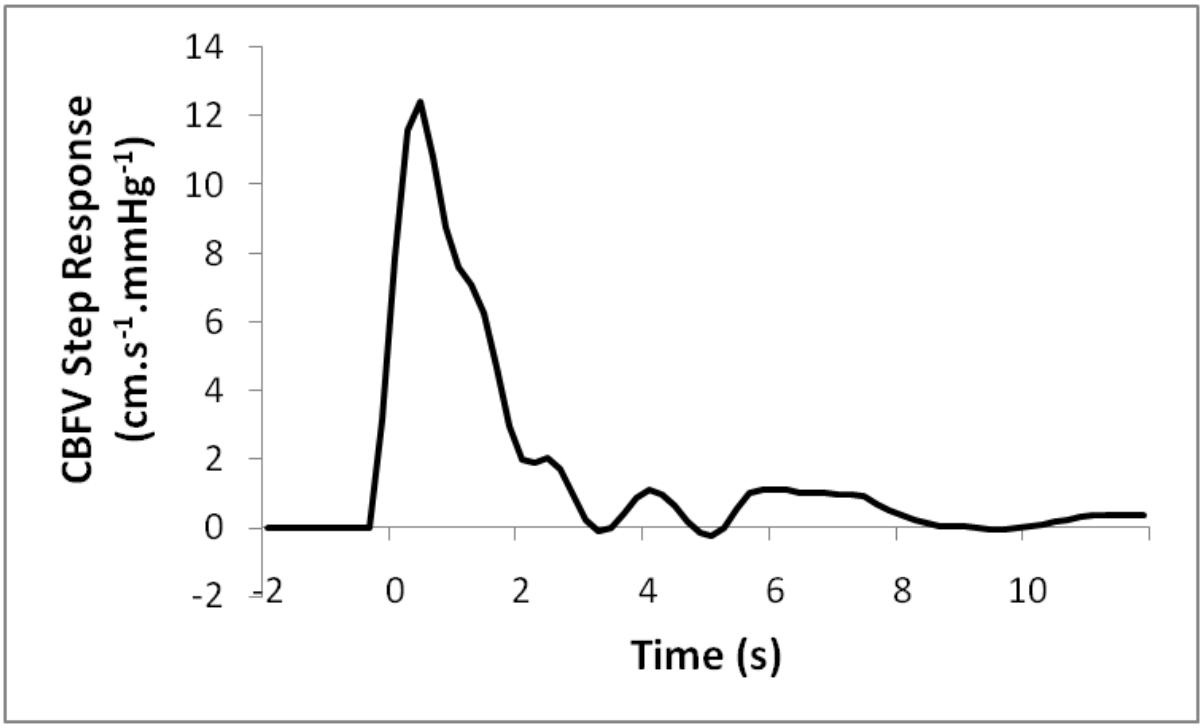


Figure 2.4 Acceptable CBFV Step Response



As described in 'data collection' a minimum of three recordings were made at each visit. This usually allowed three separate estimates of R and L CBFV (except when data were rejected due to poor quality or artefact e.g. from Finapres drift). An averaging analysis programme was used to review individual files and then obtain auto- and cross-spectral estimates, and gave the option to accept or reject outlying results. For all variables (coherence, impulse response, step response) outlying results were carefully inspected prior to accepting the data. The coefficient of variance (i.e. the standard deviation÷mean) was expected to be less than or equal to 1. If the coefficient of variance was greater than 1 individual files were inspected, and if each contributed equally to the variance they were included. If however a single file appeared to disagree with the other results any 'rogue' files were rejected.

2.3.3 Time Domain Parameters and ARI

The step response was derived by inverse Fourier transform (integration) of the impulse response. This represents a realisation of the frequency parameters in the time domain. This was matched using the least squares method to the 'best fit' autoregulatory index (ARI) from the model described by Tiecks[58]. Each of Tiecks's model curves were selected and compared for fitting with the step response for each recording. The 'best fit' of the model curves is the one which most closely matches the rate of change and return to baseline of the CBFV observed in each recording. A correlation coefficient was calculated, giving an idea of how closely the best fit curve mirrored the actual step response derived from the recording. The correlation coefficient describes the relation between the actual step response with its corresponding model response, and this was used as a further measure of data quality – if the correlation coefficient was less than 0.5 these results were rejected as it was felt that the derived ARI was unreliable. Figure 2.5 illustrates acceptable and poor agreement between a derived step response and the best fit ARI curve.

Figure 2.5a Good agreement between model ARI and derived CBFV step response

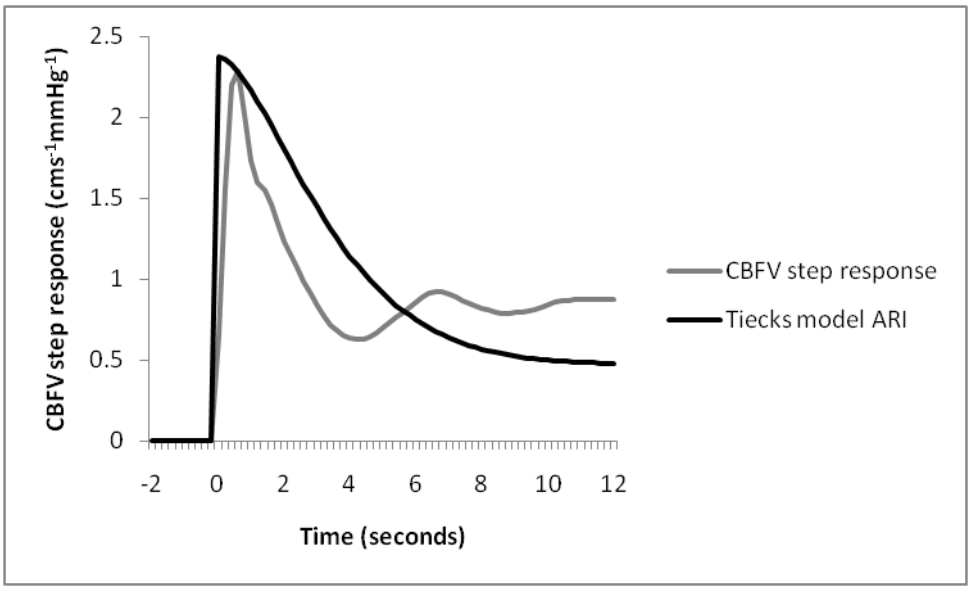
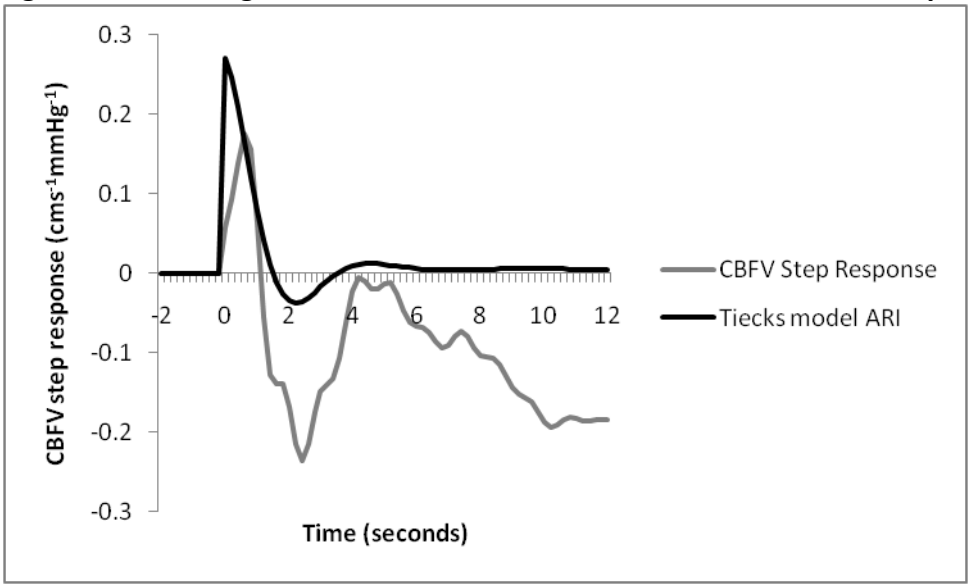


Figure 2.5b Poor agreement between model ARI and derived CBFV step response



Note that the magnitude of the change in CBFV is less important than the direction of change and the rate of return to baseline in terms of determining the ARI value. In example a) the step response and model ARI curves are very similar in morphology and the speed with which they return to 0, whereas in example b) there is a non-physiological drop in step response which fails to return to baseline, and as a result the model ARI curves are all a very poor fit. Thus in example b) the data is not of a quality to allow interpretation in terms of ARI and the correlation with each of the model ARI curves is extremely poor.

Chapter 3: Reliability of dynamic cerebral autoregulation measurements using spontaneous fluctuations in blood pressure

Aim: To assess the reliability of dynamic cerebral autoregulation using spontaneous fluctuations in BP, with reference to sample size and planning of future studies

3.1 Volunteer Selection

Volunteers for the intrasubject variability study were recruited from members of staff. Each subject gave written informed consent to participation and recording of anonymised data. The study was approved by the local research ethics committee and by the Trust research and development department (LREC 07/Q2501/83, UHL R&D 10314; LREC 07/Q2501/122, UHL R&D 10328).

3.2 Volunteer Characteristics

The following characteristics were collected for each of the volunteers:
Age, gender, body mass index (BMI = weight in kg ÷ height in metres^2), resting BP, time of day of recording, and time (in days/hours) since last recording. No subjects had a history of vascular risk factors, nor were they taking any regular medications. No subjects were known or suspected to have carotid stenosis.

Four consecutive measurements were made at five day intervals over a period of 20 days. Measurements were made at the same time of day and under the same measurement conditions for each subject, and subjects were asked to maintain similar behaviour (e.g.

exertion, caffeine intake, abstinence from alcohol) prior to each recording in order to minimise external factors affecting cerebral autoregulation.

3.3 Data Collection

Data collection, editing and analysis were performed using the method described previously. In addition to examining ARI, the critical closing pressure (CrCP) and resistance area product (RAP) were also studied. Frequency domain parameters were examined during data analysis, but reproducibility of dCA results was examined in the time domain only.

3.4 Statistical Methods

The intrasubject variability in ARI, CrCP and RAP was compared with that of SBP, DBP and HR in order to provide commonly used clinical measures for reference. Each parameter was examined for normality, those which were non-normally distributed (i.e. non-homoscedastic variables) were log-transformed using the natural logarithm prior to statistical analysis. Using the method described by Pinna[103] repeated measures analysis of variance (ANOVA) was used to estimate the standard error of measurement (SEM):

$$SEM = \sqrt{WMS}$$

(WMS = within-subject sum of mean squares). SEM is given as an index of absolute reliability. The intra-class correlation coefficient (ICC) was then calculated from the ANOVA table using the formula described by Shrout and Fleiss[104]

$$ICC = [BMS - RMS] / [BMS + (\kappa-1)RMS]$$

(BMS = between-subject mean sum of squares, RMS = residual error mean sum of squares, κ=no. of repeated observations), and 95% confidence intervals (CI) were calculated. Those

parameters which were log-transformed were back transformed using the anti-logarithm. The 95% CI for homoscedastic variables represent the range within which the difference between subsequent measurements would be expected to lie solely as a result of intrasubject variability, while for the non-homoscedastic variables the 95% CI represent the expected ratio of subsequent measurements to the first measurement. The coefficient of variation was also calculated as SEM ÷ overall mean for each parameter (expressed as %). ICC is given as an index of relative reliability.

The interpretation using the above statistical methods is as follows: high values of SEM represent low absolute reliability, indicating large random variation within an individual. On the other hand, ICC is a measure of relative reliability as it expresses the amount of intra-subject variability in relation to corresponding values of inter-subject variability, thus reflecting the ability of a measurement or parameter to discriminate between different individuals. ICC ≥0.8 is considered to indicate good to excellent reliability[103].

3.5 Results

Ten volunteers (5 male) with a mean age of 37.5 years (range 21 – 56) were recruited. Each had three recordings at each of four visits giving a total of 120 recordings for each side. Thirteen recordings (7 R and 6 L) were rejected due to artefact or poor data quality; these were distributed at random across the group. Demographics for the subjects are presented in Table 3.1. All subjects who took part were R-handed.

Table 3.1 Subject Characteristics: Reproducibility Study

Age (years)	Gender	BMI (kg/m^2)	SBP (mmHg)	DBP (mmHg)	HR (bpm)
37.5 ± 9.2	5 Male : 5 Female	22.9 ± 3.0	117 ± 8	69 ± 9	64 ± 10

Individual mean values of CBFV and ARI are presented in Figures 1 and 2. Table 3.2 presents the mean ± SD of haemodynamic parameters for each visit, as well as the overall mean ± SD for the 4 visits. Repeated-measures ANOVA did not show any significant differences in mean values of the parameters in Table 3.2 on different visit days. CBFV and RAP were found to be non-homoscedastic and required log-transformation prior to statistical analysis. CrCP was found to be non-normally distributed even after log-transform, and was therefore not analysed further.

Table 3.2 Haemodynamic parameters by visit

	Visit 1	Visit 2	Visit 3	Visit 4	Overall
ARI Right	5.8 ± 1.1	5.9 ± 0.8	5.8 ± 1.3	6.3 ± 0.9	6 ± 1.2
ARI Left	5.7 ± 1.1	5.6 ± 1.1	5.8 ± 1.0	6.2 ± 0.9	5.9 ± 1.2
ARI R-L	0.4 ± 0.4	0.6 ± 0.5	0.3 ± 0.4	0.3 ± 0.5	0.4 ± 0.4
CBFV R (cm/s)	69.6 ± 25.4	65.9 ± 19.7	70.6 ± 29.1	67.3 ± 22.8	68.3 ± 23.6
CBFV L (cm/s)	66.1 ± 10.5	61.3 ± 15.0	63.2 ± 14.3	63.9 ± 12.7	63.6 ± 12.8
RAP Right (mmHg.s/cm)	1.2 ± 0.4	1.3 ± 0.5	1.2 ± 0.6	1.2 ± 0.4	1.2 ± 0.5
RAP Left (mmHg.s/cm)	1.1 ± 0.3	1.4 ± 0.6	1.3 ± 0.5	1.3 ± 0.4	1.3 ± 0.5
CrCP Right (mmHg)	7.8 ± 6.0	11.7 ± 8.6	10.7 ± 11.4	10.6 ± 8.9	10.2 ± 8.7
CrCP Left (mmHg)	9.4 ± 6.4	10.5 ± 8.2	11.1 ± 10.1	12.2 ± 9.3	10.8 ± 8.4
Systolic BP (mmHg)	119 ± 9	115 ± 9	117 ± 5	117 ± 9	117 ± 8
Diastolic BP (mmHg)	71 ± 9	69 ± 9	68 ± 9	67 ± 9	69 ± 9
HR (bpm)	64 ± 7	65 ± 14	61 ± 7	63 ± 9	64 ± 10

All results presented as mean ± SD

The absolute (SEM) and relative (ICC) reliability for haemodynamic and autoregulatory parameters are presented in Table 3.3. The implications of the SEM and its 95% confidence limits (Table 3.3) for the reproducibility of the ARI and other parameters are discussed below. The coefficient of variation (CV) of SEM, also shown in Table 3.3, is more appropriate to make comparisons of reproducibility between different parameters.

Table 3.3 SEM and ICC for Haemodynamic and Autoregulatory Indices

	SEM	95% CI	Coefficient of Variation (%)	ICC	95% CI
ARI R	0.739	-2.048, 2.048	12.3	0.51	0.19, 0.81
ARI L	0.784	-2.172, 2.172	13.3	0.43	0.12, 0.77
ARI R-L	0.410	-1.130, 1.130	102.5	n/a	n/a
CBFV R (cm/s)	1.092	0.783, 1.278	1.7	0.91	0.79, 0.97
CBFV L (cm/s)	1.086	0.796, 1.256	1.7	0.86	0.68, 0.96
RAP R (mmHg.s/cm)	1.201	0.602, 1.661	100.0	0.75	0.50, 0.92
RAP L (mmHg.s/cm)	1.198	0.605, 1.652	92.0	0.70	0.42, 0.90
SBP (mmHg)	4.311	-11.950, 11.950	3.7	0.68	0.39, 0.89
DBP (mmHg)	3.550	-9.854, 9.854	5.1	0.82	0.62, 0.95
HR (bpm)	6.123	-16.971, 16.971	9.6	0.56	0.25, 0.84

CBFV showed the lowest CV, followed by SBP and DBP. RAP and the ARI R-L difference showed very high CV (Table 3.3). For the ARI R-L difference, this was expected due to the relatively low mean values of the difference. The CV for the ARI was an order of magnitude greater than that of CBFV, but, on the other hand, not too dissimilar than what was observed for heart rate.

The highest ICC values were also obtained for CBFV, followed by diastolic BP; the lowest values resulted for ARI. However, for reasons that will be discussed below, the corresponding 95% CI were fairly broad, suggesting that these estimates were not entirely robust. Similarly to the CV, the ARI ICC and its 95% CI was comparable to the corresponding figures for HR. Of interest is the much higher values of ICC obtained for RAP.

The low SEM and high ICC observed for CBFV can be explained by the individual values given in Fig. 3.1. The reduced CV followed from the highly stable intra-subject values recorded for the 4 visits. In addition, the ability to discriminate between different subjects (e.g. subjects #2 and #4), led to the high values of ICC estimated for CBFV. A slightly different picture emerged for the ARI (Fig. 3.2). Although several subjects showed very stable values for all 4 visits, 4 subjects (right MCA) and 5 subjects (left MCA) had greater inter-visit variability. The lack of stability of the ARI for these subjects contributed to the relatively high SEM and CV in Table 3.3. The fact that the ARI values for these subjects also 'criss-crossed' the values of the more stable subjects (Fig. 3.2) also reduced the ability of the ARI to discriminate between subjects thus leading to the relatively low values of ICC given in Table 3.3.

The absolute value (magnitude) of ARI R-L was considered, but not the direction of the difference (i.e. values of ARI R-L are shown as a positive integer, though the difference may be R>L or L>R). The actual difference ARI R-L is shown in Figure 3.3.

Figure 3.1a CBFV R across serial visits

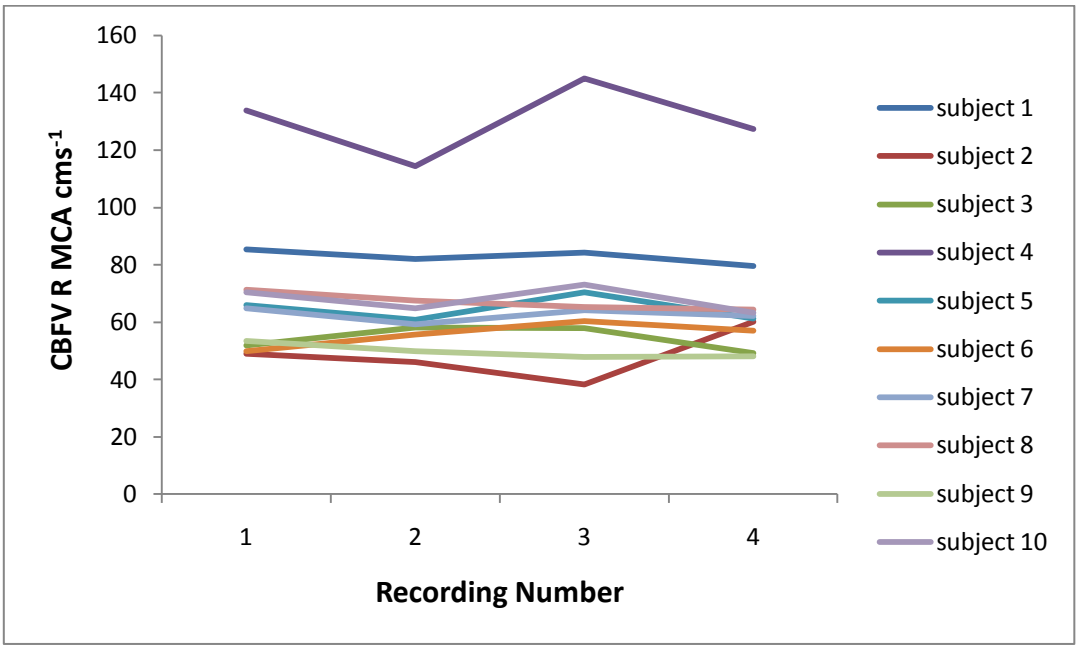
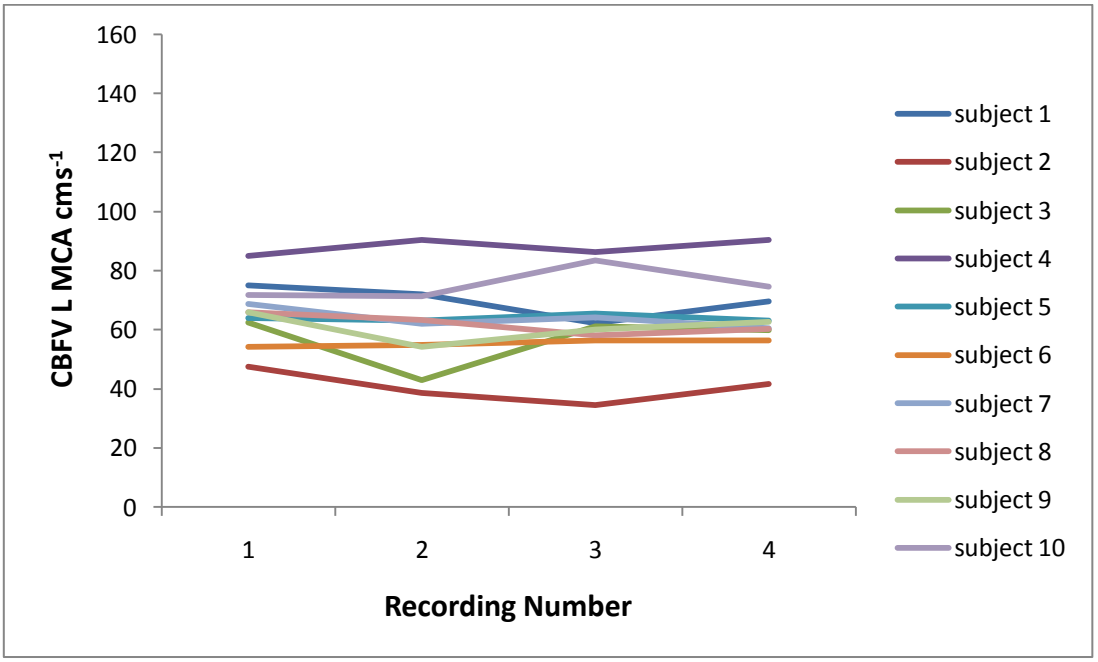


Figure 3.1b CBFV L across serial visits



The cause of the markedly elevated R MCA velocities in subject 4 is not clear.

Figure 3.2a ARI R across serial visits

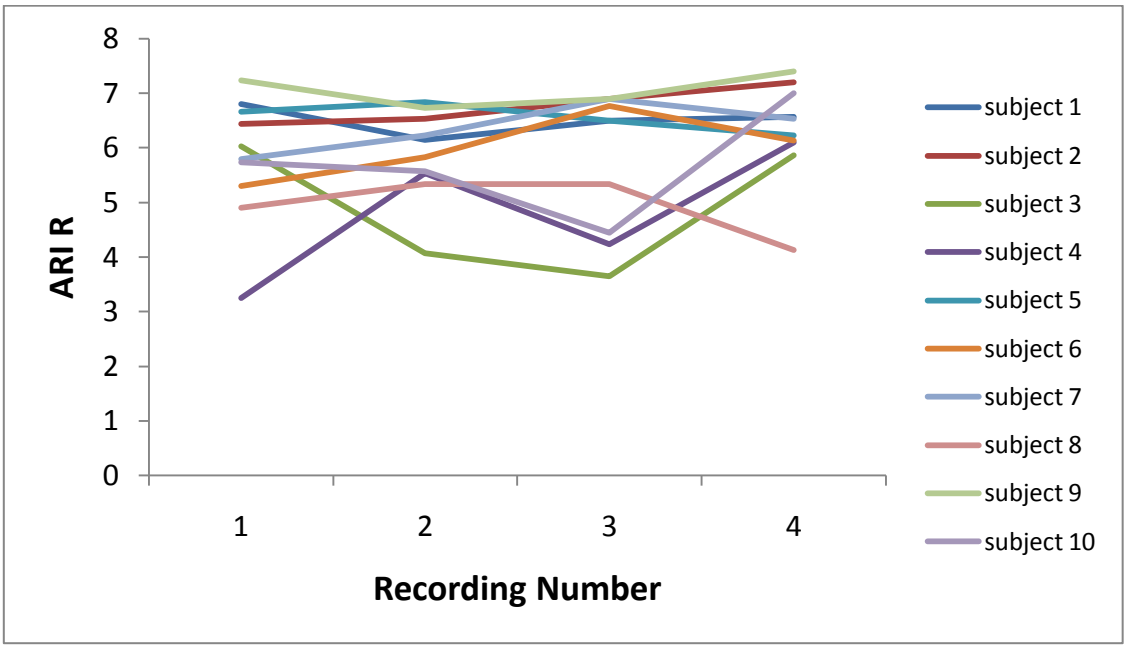


Figure 3.2b ARI L across serial visits

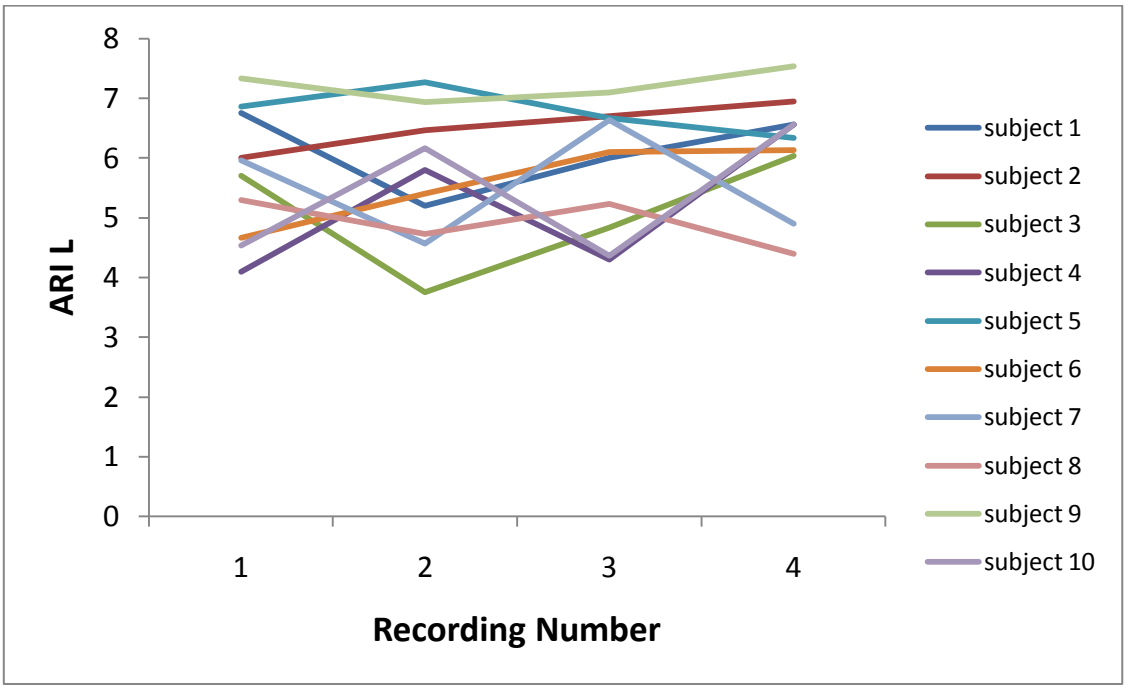
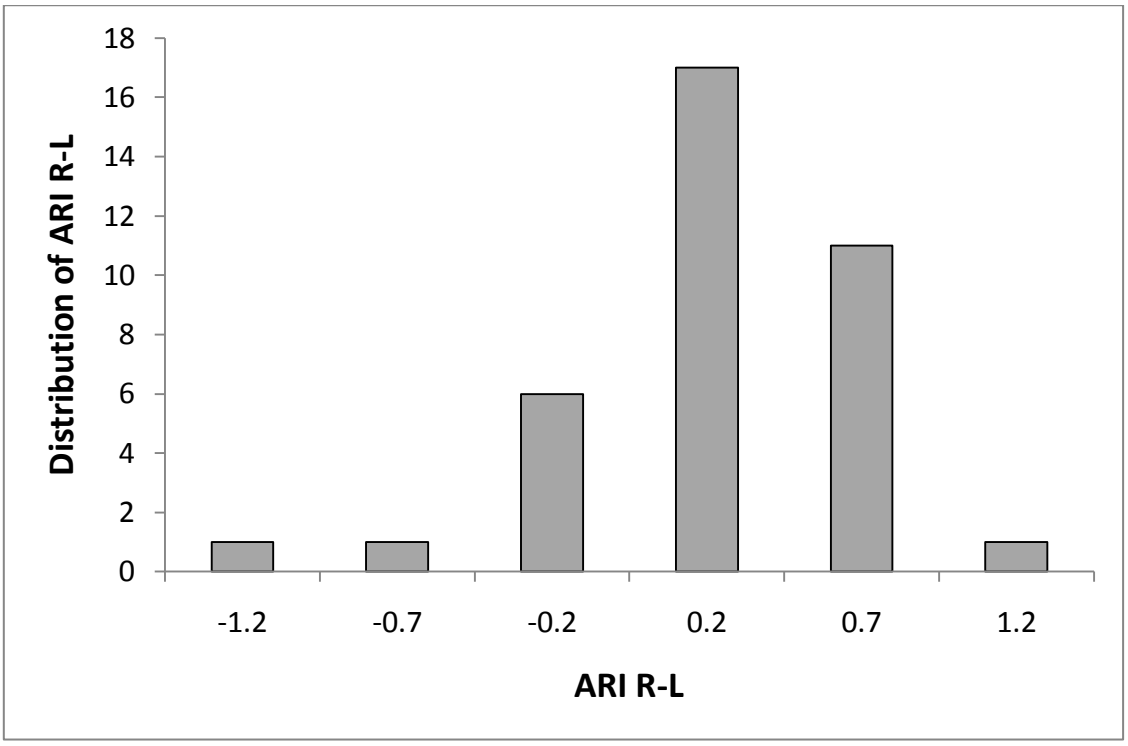


Figure 3.3 Inter-hemispheric difference in ARI (ARI R – ARI L)



3.5.1 Sample size estimation

The relatively small sample size of this study (n=10) limits the precision of the estimates presented in Table 3.3. In particular, the 95% confidence limits of the ICC tend to be fairly wide for low estimated values of ICC, as in the case of ARI. Applying the values presented by Walter et al [105] more than 180 subjects would be needed to guarantee that the ICC is greater than 0.3 for these parameters, with 80% power at α =0.05. For other parameters showing relatively high values of ICC, such as CBFV, the sample size of n=10 already guarantees that the estimated ICC in Table 3.3 is greater than 0.7 [105]. Although much larger sample sizes are required to improve estimates of 95% CI for parameters with estimated ICC <0.5, smaller sample sizes can be predicted for clinical studies aimed at detecting changes in ARI. Based on the ANOVA's mean within-subjects sum of squares of 2.82 (ARI R) (data not shown), the

sample size for each group would be 44.6/ $(\Delta ARI)^2$ for detecting a difference of ΔARI between the two groups with 80% power at $\alpha = 0.05$ [106]. Therefore, for ΔARI=1.0, 45 subjects would be needed in each group, whilst only 11 subjects would be required to detect a change of 2 units in ARI. The above formula for calculating sample sizes may be useful to other investigators designing studies of dCA based on the ARI estimated from spontaneous fluctuations in BP.

3.6 Discussion

Despite the increasing use of TCD for the assessment of cerebral autoregulation using spontaneous fluctuations in BP there have been no previous studies looking at the intrinsic variability of this measurement. This is clearly of importance in order to accurately interpret apparent differences noted in dCA in different clinical situations and further study into its reliability has been advocated[67].

In this study repeated measurements were made on ten healthy volunteers under identical circumstances using strict data collection and analysis protocols in order to assess variability within one visit across serial visits, and between subjects.

Despite potential limitations with probe positioning on different visits, CBFV turned out to be the most reliable of all parameters studied showing superior absolute (i.e. SEM) and relative (i.e. ICC) reliabilities than more established haemodynamic measurements such as SBP, DBP and HR. The relatively lower reliability observed for the ARI and RAP were to be expected due to the mathematical estimation processes involved in their calculation. The

same would possibly apply to CrCP, but this was not assessed due to the lack of normality even after log-transformation. RAP had a high CV and SEM, suggesting it may be quite variable, though the ICC was higher than for ARI. The instantaneous relationship between ABP and CBFV and be characterised by the linear model ABP=a+b(CBFV), where a is the pressure axis intercept (or CrCP) and b is the cerebrovascular resistance (thought to be an important component of dCA)[61]. Given that CBF is equal to the product of CBFV and the cross sectional area of the insonated vessel (i.e.$Q=V_{av} \times A$) it has been suggested that the ABP-CBFV relationship may also be described in terms of the RAP, and its use as a measure of cerebrovascular resistance and CA has been suggested previously[73]. For this reason future work looking at the sensitivity of RAP to reflect changes in dCA would be of interest[61;107].

The observation that the numerical values of CV and ICC for the ARI are similar to those of HR (Table 3.3) provide a 'feeling' for the physiological variability of ARI, but very different considerations apply to its reliability in clinical applications. The low ICC values for ARI (Table 3.3) suggest that this parameter may not discriminate well between relatively young healthy subjects, but it is still possible that ARI will show good sensitivity and specificity to discriminate against individuals with impaired autoregulation, for example those with values of ARI<4.0 (Fig. 3.2). Nevertheless, the longitudinal variability observed in approximately half of the subjects (Fig. 3.2) should be a warning against putting too much reliance on single punctual measurements of ARI. In contrast to other studies of reliability of clinical parameters, measurements were recorded during four visits, rather than the usual test-retest approach [104]. Since the number of tests multiplies the residual mean error (RMS) in the denominator of equation (2), this means that this particular design represented a much

harsher situation to estimate the ICC for parameters that had RMS of the order of 20% of the BMS, as was the case with the ARI.

The second important consideration follows from the 95% limits of agreement obtained for the ARI (Table 3.3) since there appears to be no consensus regarding what is considered a significant change (increase or decrease) in ARI value. Previous work on ARI in patients at risk of impaired cerebral autoregulation has concentrated on identification of a statistically significant difference between ARI in patient and control groups, without pre-specifying an 'acceptable' ARI value or the magnitude of any predicted change. Tiecks et al[58] demonstrated in ten healthy patients undergoing elective surgery a fall in ARI from 4.8±1.0 (propofol anaesthesia) to 2.3±1.3 (isofluorane anaesthesia) ($p<0.01$), thus the observed mean difference in ARI between 'intact' and 'impaired' was 2.5. It can be seen from the confidence limits of the SEM that a difference >2.048 is unlikely to be explained by intrasubject variability, and thus it is likely that although some physiological variability may have occurred the observed difference does at least in part reflect a real difference in ARI (in this case between propofol and isofluorane treatment). Dawson et al[59] found the ARI of controls to be higher than those in Tiecks' group, with acute stroke patients having an affected hemisphere ARI 4.1±3.3 compared to 6.2±2.3 in the healthy control group. In their study a mean difference of 2.1 was observed between acute stroke and controls, again this is greater than the confidence limits of the SEM suggesting that there was a real difference in ARI between the two groups. White et al[108] found a similar difference when studying patients with significant carotid disease compared to healthy controls, with ARI 3.3±2.2 in those with significant carotid disease compared to 6.3±1.1 in the control group ($p=0.0001$), i.e. a mean difference in ARI of 3. Notwithstanding studies that reported large differences in

ARI, many others have obtained differences that fall within the 95% CI for SEM and therefore could be reflecting purely random variation rather than a true difference. One recent example was the assertion that ARI is reduced in the morning as compared to values taken the previous evening [109].

As discussed in the Results it is possible to estimate sample size for future studies, with a sample size of 11 subjects per group required to detect a difference in ARI ≥2, or a sample of 45 subjects per group to detect a difference in ARI ≥ 1 between groups. These estimates correlate well with the clinical studies mentioned above, where differences in ΔARI > 2.0 were observed with sample sizes that were not adequate to detect smaller differences.
It remains unclear to what extent there is an inter-hemispheric relationship in changes in ARI. This is of particular relevance in the study of acute stroke, where comparison may be made between 'affected' and 'unaffected' hemisphere. This study demonstrated over serial recordings that there was little mean change in ARI R-L, and that an absolute difference >1.13 would have to exist between hemispheres to be considered 'real'. Dawson demonstrated an ARI of 4.1±3.3 in the affected hemisphere and 4.8±3.3 in the unaffected hemisphere following acute ischaemic stroke, i.e. a difference of 0.5[59]. This relatively small value fell well within the confidence limits for the test-retest difference (Table 3.3) and for this reason might be expressing intra-subject variability, rather than inter-hemispheric asymmetry of dCA due solely to stroke. The distribution of ARI R-L in Figure 3.3 shows that in healthy subjects with no history of cerebrovascular disease inter-hemispheric difference in ARI is normally distributed and centred around zero (mean = 0.12, SD=0.6, min -1.2, max 1.7). This further supports the use of the mean ARI in control subjects where the mean is derived from both sides, as was performed in the control group in the acute stroke study.

3.6.1 Limitations of Study

There are a few limitations to this study. There is no end-tidal CO_2 measurement, which may have been helpful to examine CBFV and ARI more closely. However subjects were free from respiratory disease and were all non-smokers, and, as they maintained a constant respiratory rate, significant fluctuations in CO_2 would not have been expected. In support of this, CBFV which is highly sensitive to changes in CO_2 demonstrated very little variability. The CBFV measured using TCD can only be expected to represent CBF if the diameter of the insonated vessel (in this case the MCA) remains constant. Giller[56] examined MCA diameter in patients undergoing craniotomy and demonstrated little variation (<4%) in the diameter of the proximal MCA despite considerable fluctuation in mean arterial pressure and CO_2. In addition depth, power, and location of temporal window were the same at each visit and probes were secured using an adjustable head frame in order to try and ensure uniformity of signals and avoid insonation of smaller vessels which have shown considerably greater variation in diameter (up to 21%). Although transducer repositioning could contribute to longitudinal variability, the excellent absolute and relative reliabilities observed for CBFV suggested that this was not the case.

A further limitation of this study was the age of the subjects (mean 37.5 years), which limits the extrapolation of these results to other groups such as neonates and the elderly, both of whom may for various reasons demonstrate wider variability than shown here. Caution should therefore be exercised before applying these results to other patient groups, such as older subjects, or following stroke, as it may be that these conditions introduce a greater

magnitude of inherent variability – in which case then potentially much larger samples may be required.

Results were presented in the time domain only, though the frequency parameters coherence, phase and gain were carefully examined during data analysis, and the impulse response incorporates information from the frequency domain. There has been uncertainty regarding selection of frequency in which to report frequency parameters. Some authors suggest using the region of maximum coherence in the low frequency region (0.07-0.15Hz)[85] Zhang et al used transfer function analysis to examine dCA in ten healthy subjects both at rest and following sudden thigh cuff deflation. They examined a relatively large frequency range (0.07-0.3Hz) and found an 'intermediate' frequency range of [0.07-0.2Hz] they felt reflected a high-pass filter model for the relationship between ABP and CBFV, and chose this frequency range for assessment of dCA by transfer function analysis in subsequent work. This region was characterised by high coherence, high gain, and reducing phase. In addition to frequency selection there are limitations to the use of phase such as the problem of wraparound[110], and gain alone is not a reliable measure of dCA in the presence of a normal phase[111]. Thus this current study does not provide direct evidence of the reproducibility of frequency domain parameters in the measurement of dCA.

3.6.2 Summary

This study demonstrates excellent absolute and relative reliability of CBFV, while ARI is of comparable reliability to the measurement of HR. These results demonstrate that ARI has acceptable reproducibility to be used for serial measurements over time. They also demonstrate a 'normal range' of ARI measurements in healthy volunteers, and suggest that

under steady state conditions there is minimal inter-hemispheric difference in ARI. In addition it is possible from these results to estimate sample sizes which would be required to detect a real difference in ARI between unmatched groups, allowing for intersubject variability.

Chapter 4: Evolution of dynamic cerebral autoregulation over 10 year follow-up

Aim: To assess the effects of ageing on dynamic cerebral autoregulation in a group of healthy volunteers

4.1 Recruitment

Subjects were identified from departmental staff in 1997-8 and were followed up in 2008. At the time of the first recording all were free from illness and none were taking any medication. Information regarding the occurrence of any illness or major physiological event (e.g. pregnancy) and medication use was collected at the follow-up visit. The study had local research ethics approval (LREC 4808 and LREC 07/Q2501/83) and all subjects gave written informed consent.

4.2 Data Collection

Two baseline recordings per subject, each lasting ten minutes, were performed in 1998 by Dr S Foster, and were used in this study with her kind permission. Three baseline recordings were performed in 2008, each lasting five minutes. A Sci-Med QVL-120 TCD machine was used in 1998, in 2008 a Viasys Companion III was used. Data collection, editing and analysis were performed using the methods described above.

As the recordings from 1998 were made only on the RMCA the same was done in 2008 to allow comparison. In addition to expressing results in terms of the ARI, cross- and auto-spectral averaging was used to estimate representative values for coherence, gain and phase

at the two time points. CBFV and BP signals were normalised by the mean, and are expressed as % of the mean.

4.3 Statistical Methods

Since the groups were pair-matched the ARI values for 1998 and 2008 were compared using a Student's paired t-test. Statistical significance was assumed for $p<0.05$. Frequency domain parameters (coherence, gain, phase) were plotted by year (1998 vs 2008), and differences at 0.05 Hz between 1998 and 2008 were examined using a Student's paired t-test.

4.4 Results

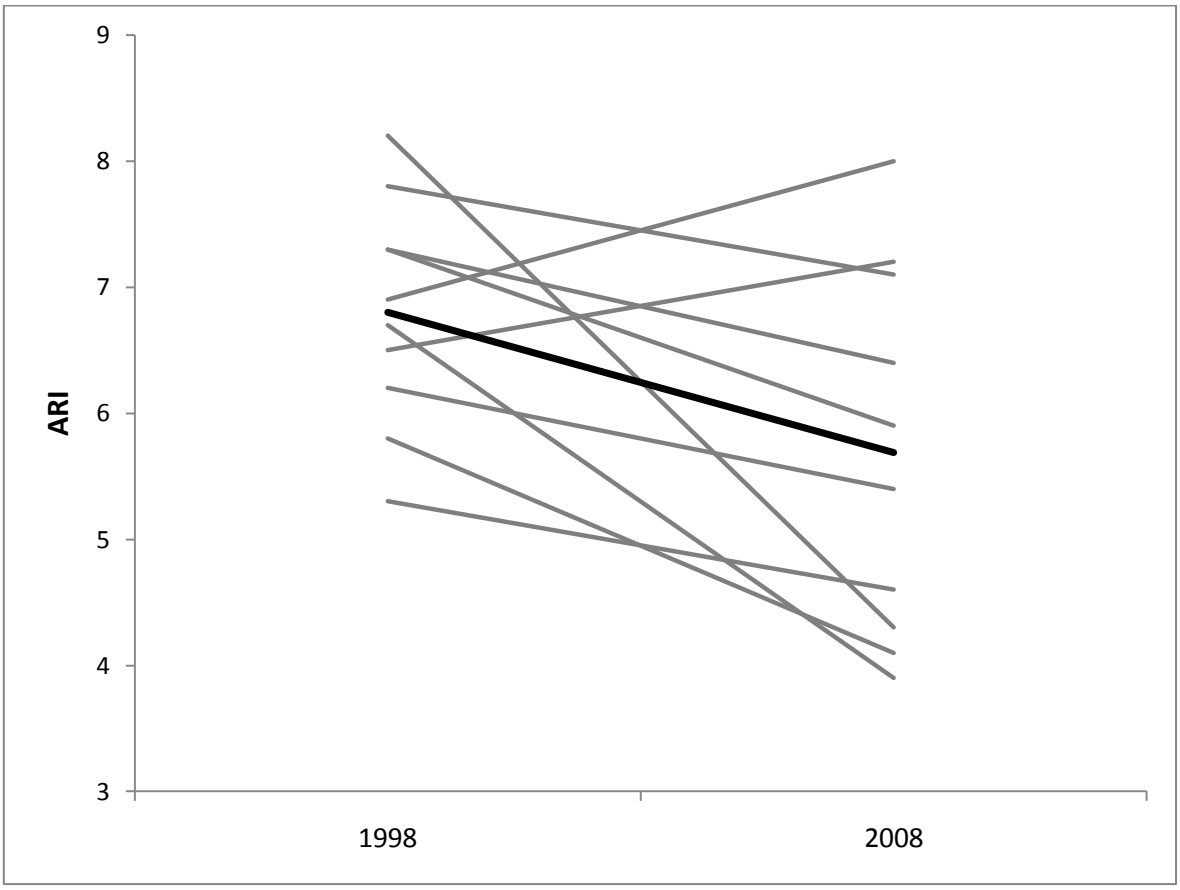
Ten subjects were identified, mean age 35.5 years (range 24-51) in 1998 (7 male). In 1998 all were healthy and free from any medication, all were non-smokers. In 2008 one had developed mild hypertension (treated with an ACE-inhibitor), while another of the subjects had been hospitalized due to an autoimmune condition in 2002, though was in remission at the time of the follow-up recording. One female was 6 months pregnant at the time of recording. Subject characteristics are summarized in Table 4.1. Mean CBFV in 1998 was 59.8cm.s^{-1} (±8.5) and in 2008 was 64.1cm.s^{-1} (±5.1), this difference was not statistically significant. Average $BP_{finapres}$ was 153/86mmHg (±29/13), dropping to 125/68mmHg (±20/15) in 2008.

Table 4.1 Subject characteristics: 10 year follow-up study

Subject	Gender	Age in 2008(years)	$BP_{Finapres}$ 1998 (mmHg)	$BP_{Finapres}$ 2008 (mmHg)	BP_{cuff} 2008 (mmHg)	BMI 2008 kg/ m^2	Significant physiological events between 1998-20
1	M	42	141/86	123/59	118/83	24	n/a
2	M	47	171/103	148/93	142/79	26	n/a
3	F	38	131/68	112/50	107/76	23	normal pregnancy 2007
4	M	51	161/90	104/51	103/70	24	autoimmune condition (in remission since 2003)
5	M	47	122/68	99/56	126/75	22	n/a
6	M	41	145/80	125/68	112/72	25	n/a
7	M	61	143/83	108/66	139/76	24	hypertension (ACEi)
8	M	57	223/110	136/76	126/76	22	n/a
9	F	34	163/88	161/88	101/64	23	normal pregnancies 2000, 2003, 2006
10	F	35	128/80	127/67	115/69	23	pregnant (2008 recording)

Mean ARI in 1998 was 6.8 (range 5.4-8.2), and in 2008 was 5.7 (range 4.0-8.0) (p=0.021), which represents a fall of 16%. Individual changes in ARI are displayed graphically in Figure 4.1. Two subjects showed a rise in ARI while it fell in the remaining eight.

Figure 4.1 Autoregulation index (ARI) for 1998 and 2008 for each subject (grey line) and mean population values (black line)



Frequency domain parameters for the whole group are shown in Figures 4.2-4.4, and the CBFV step responses are shown in Figure 4.5. Paired t-tests at 0.05Hz showed a significant difference for coherence (p=0.018). The return to baseline of the CBFV step response was averaged over 2-10s. Difference in the mean averaged step response between 1998 and 2008 was also statistically significant (p=0.045).

Figure 4.2 Mean coherence function for 1998 (thick continuous line) and 2008 (thick broken line) and corresponding SEM (thin lines)

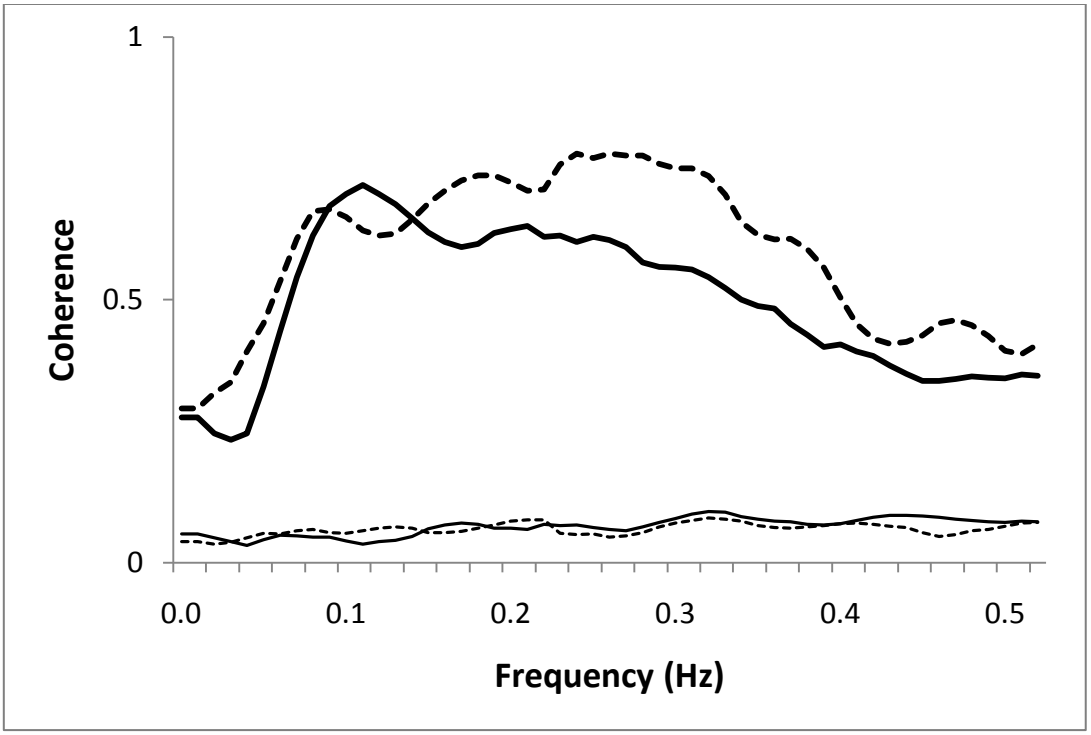


Figure 4.3 Mean transfer function amplitude (gain) frequency response for 1998 (thick continuous line) and 2008 (thick broken line) and corresponding SEM (thin lines)

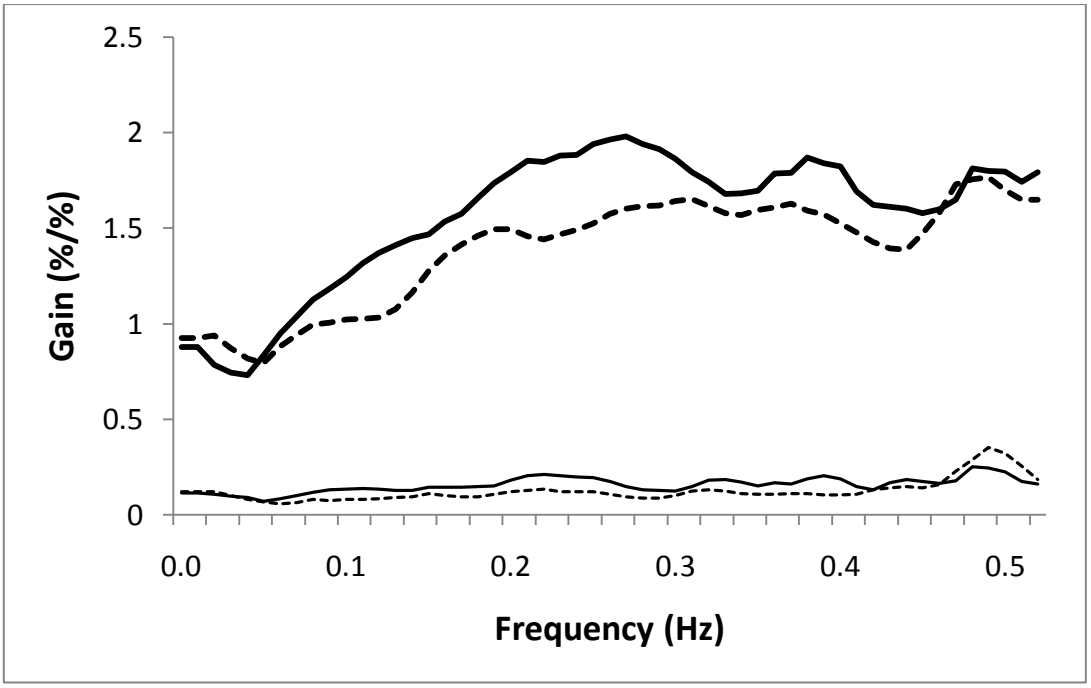


Figure 4.4 Mean transfer function phase frequency response for 1998 (thick continuous line) and 2008 (thick broken line) and corresponding SEM (thin lines)

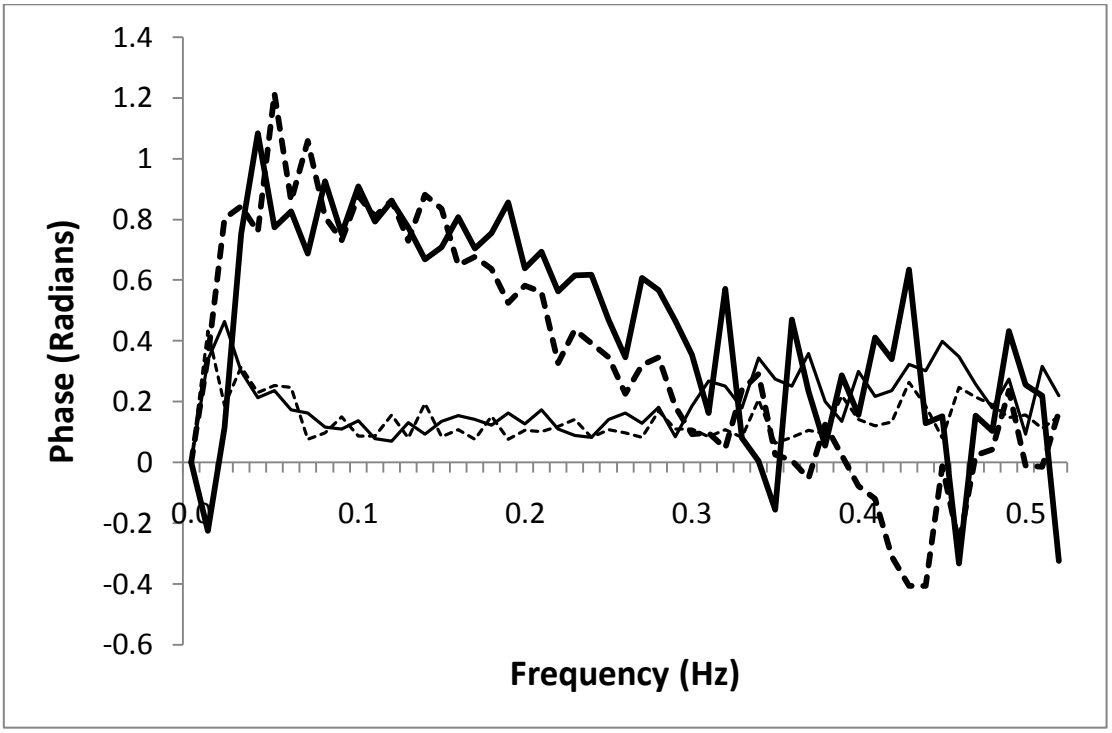
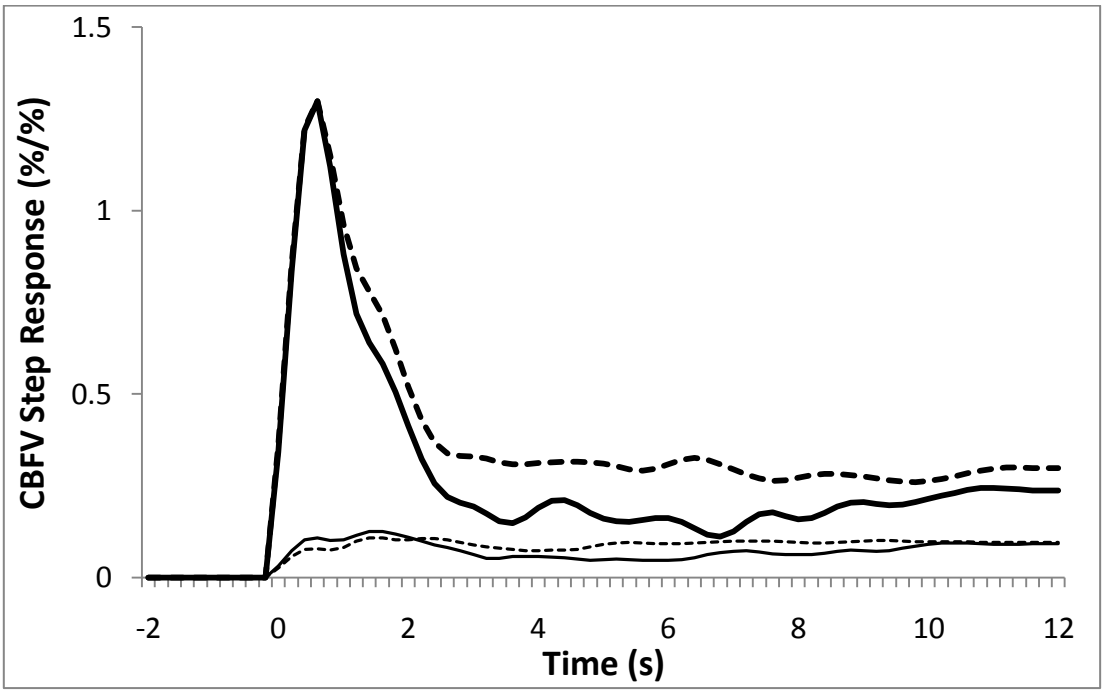


Figure 4.5 Mean CBFV step response for 1998 (thick continuous line) and 2008 (thick broken line) and corresponding SEM (thin lines)



4.5 Discussion

To date this is the first study to assess the effects of ageing on dCA in a long-term follow-up. Overall, the results suggest a reduction in the efficiency of dCA. In addition to a significant reduction in a well known index of dCA (ARI)[58], frequency domain estimates of coherence function in the very-low frequency region (0.05 Hz) were significantly higher in 2008, compared to corresponding values in 1998, an indication of depressed cerebral autoregulation[65]. Furthermore, the CBFV step response also showed less efficient return to baseline values in 2008 (Fig. 4.5). Other transfer function parameters, such as the amplitude (gain) and phase frequency responses did not show significant differences during the 10-year period. Phase has been shown to be a sensitive index of loss of dCA in clinical studies[70;112], but its high variability at each harmonic, and the phenomenon of 'wrap-around'[110], as observed in the 1998 phase response (Fig. 4.4), might have reduced its sensitivity to detect small differences within a group of healthy subjects. Unlike phase, gain has not been widely accepted as an index of dCA, and as mentioned in the previous Chapter it has been shown to have poor discriminative value in the presence of normal values of phase[111]. For these reasons, the CBFV step response is a much more robust estimate of dCA, since it integrates all the gain and phase information, for the complete frequency spectra, and it can be easily interpreted in comparison with the classical thigh cuff test[113] and the template step response curves proposed by Tiecks et al[58].

Our findings are relevant because of the negative results of previous studies looking into the influence of ageing on cerebral autoregulation[94;114-116]. One important methodological difference is that previous studies compared a young and an older group, whilst this study looked at intra-subject differences, thus using each subject as his/her own control. By doing

so, this removed the influence of inter-subject variability which could have masked the relatively small reduction in efficiency of cerebral autoregulation which was detected over a 10 year period. The lack of an effect of ageing on dCA suggested by previous studies was puzzling, since many other physiological mechanisms, such as the baroreflex, tend to decline with ageing. It is possible that previous studies did not have sufficient statistical power to detect the small change in dCA performance that we found[98]. As seen from the previous study of reproducibility of dCA a sample size of 45 young and 45 older subjects would be required in order to see a difference in ARI >1 between groups, allowing for inter-subject variability, while a follow-up study of this design overcomes that issue.

From a conceptual perspective, these findings add to current knowledge of human cerebrovascular physiology and also have important implications for patient management. Future studies are needed, involving a larger group of subjects, to determine if CA declines with age at a constant rate, or if there is a breaking point after which the age related loss of CA is accelerated or attenuated.

4.5.1 Limitations of the study

It is possible that larger differences in dCA efficiency over a 10-year period could have been found with a larger and older group of subjects. Despite the small sample, having each subject as his/her own control led to enough sensitivity to detect a loss of dCA with age as reflected by the time- and frequency-domain estimates of dCA (Figs. 4.1, 4.2 & 4.5). Over the 10 year period covered by the study, one subject developed mild hypertension and other was in remission from an autoimmune disease with acute manifestation in 2002, though

neither had any impact on lifestyle at the time of recording. At the time of the second examination, another subject was 6 months pregnant. There is no evidence in the literature to suggest that dynamic CA is altered by mild hypertension or normal pregnancy[117;118]. Moreover, if these three subjects with health related events in the 10 year duration of the study were removed, the difference in ARI (ΔARI 1998-2008) would increase to 1.41 (instead of ΔARI=1.1 for all subjects) and remain significant (p=0.023).

The usual concern about the influence of MCA diameter changes on the relationship between CBFV and absolute flow does not strictly apply in this study because changes in CBFV were normalized by mean values, as were the changes in BP. Different TCD equipment were used to perform measurements 10-year apart, but the resulting values of mean CBFV for each subject were not significantly different. Again, any differences in mean CBFV between 1998 and 2008 would not have affected results due to the normalization performed. Unfortunately, BP measurements with sphygmomanometry were not performed in 1998 for comparison with the 2008 values. Since the 2008 values were all indicative of normotension (Table 4.1), there is no reason to believe that these subjects would have had much different values in 1998, or that minor changes in BP could have led to the observed differences in CA during this period.

4.5.2 Change in BP over 10 years

Finapres values of systolic and diastolic BP were significantly higher in 1998 than in 2008. The reasons for the difference are not clear. Several studies reported biases in absolute systolic/diastolic BP values recorded with the Finapres, in comparison with intra-vascular recordings, but changes in Finapres BP have been shown to follow changes in intra-arterial

BP, including spontaneous fluctuations in BP used to assess dynamic CA[101]. It is unlikely that all ten subjects being studied demonstrated a physiological fall in BP over the ten year period, and it may be explained in part by ageing of the Finapres. As previously mentioned the lack of sphygmomanometer BP measures from 1997-8 makes it difficult to determine whether a real change in BP occurred over this time. Another factor of relevance is that different researchers performed the 1998 and 2008 recordings, and it is possible that there were differences in cuff sizing or arm positioning between investigators.

Normalization of BP fluctuations by the mean BP recorded with Finapres removed any biases that could result from differences in mean BP levels. Moreover, the high values of coherence recorded for frequencies above 0.1 Hz (Fig. 4.2), provide reassurance about the reliability of BP and CBFV changes.

4.5.3 Summary

This is the first study to assess the effects of ageing on dCA over long-term follow-up. The use of each subject as their own control eliminates the potential for inter-subject variability, which may have confounded previous studies. The findings demonstrate a decline in dCA in both frequency and time domain analysis, and persist after removal of subjects with potentially confounding conditions.

Chapter 5: Dynamic cerebral autoregulation following acute stroke and early recovery

Aim: To determine the changes in dynamic cerebral autoregulation following acute stroke (within 48 hours of onset) and early recovery (two weeks) compared to controls

5.1 Recruitment

Patients were identified from admissions to Leicester General Hospital with a clinical diagnosis of acute stroke. All patients were identified and recruited by the researcher (FB). All patients participating gave written informed consent, and the study was approved by the local research ethics committee and by the Trust research and development department (MREC 02/4/51 LREC 6837m, LREC 07/Q2501/83, UHL R&D 10314). Ethical approval was initially granted as a substudy of the ongoing Continue Or Stop post Stroke Antihypertensives Collaborative (COSSACS) study. Volunteers were approached from outpatient clinics, relatives of participating patients, and a bank of relatives, staff, and people who had previously expressed an interest in taking part in the department's research.

Patients were eligible to participate if they were alert (<2 on NIHSS score 1a, details of NIHSS score are shown in Appendix 2), had a clinical diagnosis of stroke with onset within the last 48 hours (if onset time was unknown, e.g. on waking, then last known time without symptoms was used as time of onset), were able to swallow, and gave informed consent. Patients and volunteers were excluded if they were in atrial fibrillation, or if they had coexisting illness with a life expectancy less than six months.

5.2 Patient Characteristics

Information collected for each patient included age, sex, time of onset of symptoms, and the stroke syndrome was classified using the Oxford Community Stroke Project (OCSP) classification[6] (this is summarised in Appendix 1). Dependency was assessed using the modified Rankin scale and the Barthel index (these are described in more detail in Appendices 3 and 4). Risk factors for stroke were recorded, including diabetes, history and duration of hypertension, history of prior stroke or cardiovascular disease, and smoking history. Prior medication use was also recorded, specifically use of antihypertensive agents and statins. Any change in antihypertensive therapy was noted at the follow-up visit, specifically whether prior antihypertensive therapy had been continued or stopped, or whether additional treatment had been introduced. The same data were collected from volunteers, with the exception of information related to acute stroke.

Neuroimaging was performed in all patients as part of their routine clinical care and their results were recorded along with carotid ultrasound imaging where available. Neuroimaging results were classified as showing corresponding infarct, haemorrhage, small vessel disease, normal scan, or other. If neuroimaging revealed a stroke mimic such as tumour or demyelination these patients were excluded. The type of stroke was defined as ischaemic or primary intracerebral haemorrhage, with ischaemic strokes being classified into pathological subtypes according to the TOAST criteria[12]. Carotid ultrasound results were categorised as showing significant carotid stenosis (≥70% lumen), or no significant carotid stenosis (<70% lumen), and as being ipsilateral or contralateral (i.e. the carotid attributable to the affected hemisphere, or the unaffected hemisphere). All carotid ultrasounds were performed by

trained sonographers using the grading system suggested by Sidhu[119]. The criteria for different grades of carotid stenosis are shown in Table 5.1. Finally data on mortality six months post-stroke was collected from hospital or GP records. In accordance with the ethical approval follow-up data was not collected for volunteer subjects.

Table 5.1: Doppler Ultrasound Criteria for Grading Internal Carotid Artery (ICA) Diameter Reduction[119]

Diameter Reduction (%)	PSV (cm s^{-1})	EDV(cm s^{-1})	PSV_{ICA}/PSV_{CCA}
0-29	<100	<40	<3.2
30-49	110-130	<40	<3.2
50-59	>130	<40	<3.2
60-69	>130	40-110	3.2-4.0
70-79	>230	110-140	>4
80-95	>230	>140	>4
96-99		'String Flow'	
100		'No Flow'	

Table adapted from original reference. PSV=peak systolic velocity, EDV=end-diastolic velocity, ICA=internal carotid artery, CCA=common carotid artery.

5.3 Data Collection

Data collection, editing and analysis were performed using the method described previously. Patient recordings were made at baseline (ideally <48 hours from symptom onset) and two weeks later, volunteers attended only once. Three five minute recordings were made at each visit. The Finapres was recorded on the affected side for patients and on the non-dominant

hand for volunteers. ARI is described in terms of $ARI_{affected}$ and $ARI_{unaffected}$ for the stroke patients, each of these is the mean value for that hemisphere on that visit. Volunteers attended only once, and their results are expressed as ARI which is the overall mean across both hemispheres. Previous studies have adopted a similar method for assessing dCA in a control group, having found no significant inter-hemispheric difference in dCA[64;83].

5.4 Statistical Methods

Demographic information including age, sex and resting BP are described for patients and controls, and compared for any significant differences between the two groups. Stroke patients were considered as a group and then pre-specified sub-groups of interest were compared, namely patients with a history of hypertension vs patients with no prior history of hypertension- see Chapter 6) and stroke subtype (by OCSP classification).

Data were plotted and examined for normality. Where variables were normally distributed differences between continuous variables were compared using a t-test, and where they were not normally distributed a Mann-Whitney U-test was used. Differences in categorical variables (e.g. smoker, diabetic, history of previous stroke) were assessed using Chi-square test (where the numbers were low Fisher's exact test was used). Normally distributed continuous variables are presented as mean (±standard deviation (SD), range), and non-normally distributed variables are presented as median (inter-quartile range (IQR), range). Forward selection of potentially significant covariates was performed, and statistically significant results were adjusted for significant covariates using analysis of covariance (ANCOVA). Statistical significance was assumed for $p<0.05$.

ARI was considered as a continuous variable. It is possible that there exists a 'threshold of normality', above which ARI is considered to be 'normal', below which it is considered to be 'impaired' or 'reduced'. Tiecks et al[58] demonstrated a mean ARI of 5 in a cohort of healthy volunteers, which fell to a mean of 2.3 following isofluorane (which has been shown to impair cerebral autoregulation in a dose-dependent manner), while Junger et al[120] found a mean ARI of 4.7 in a cohort of healthy volunteers using similar methods. Based on these previous studies an ARI of 4 was selected as an arbitrary cut-off above which to consider ARI 'normal', and comparisons were repeated between groups and controls to identify particular groups containing an excess of patients with 'reduced' ARI.

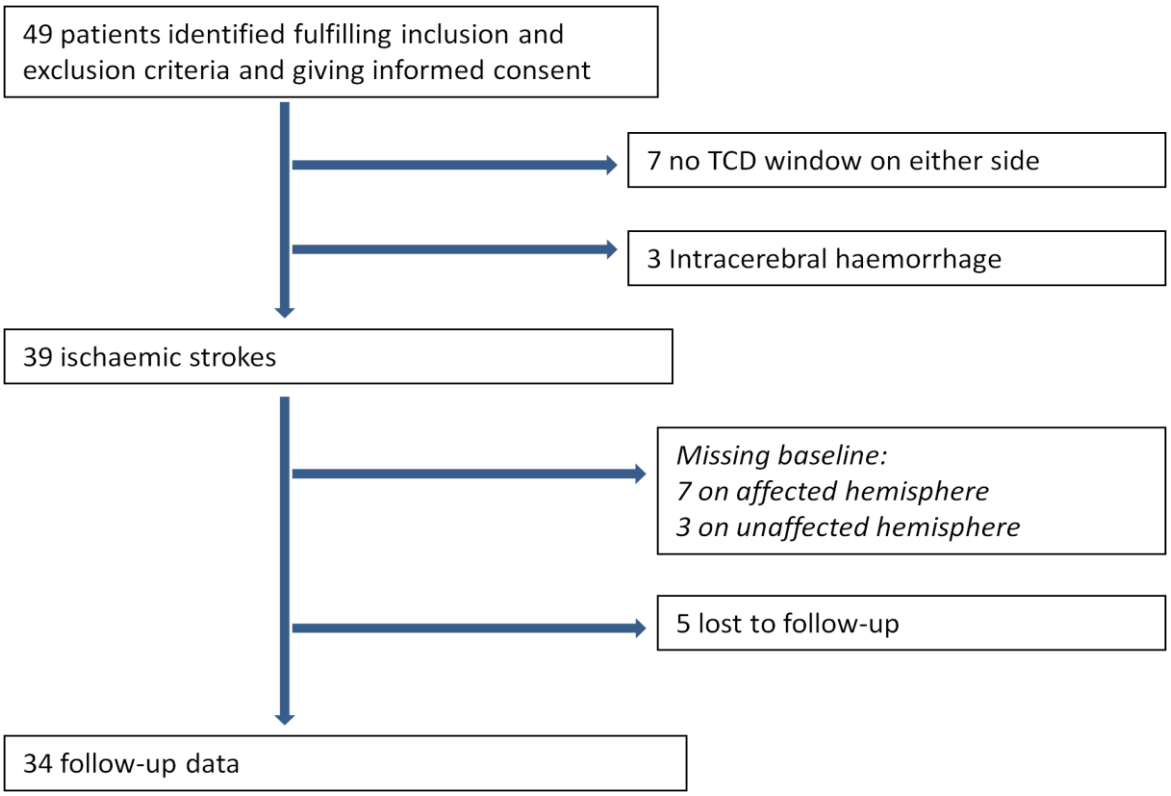
5.5 Results

5.5.1 Subjects

A total of 49 patients fulfilled the inclusion and exclusion criteria and gave informed consent between March 2007 and November 2008. Seven of these had no transtemporal acoustic window, and thus no TCD signals could be obtained, these subjects were excluded from further analysis. These subjects were all female, but did not differ significantly in terms of age, stroke type or severity, BP or heart rate from the rest of the group.

42 patients with acute stroke (27 male, 15 female) therefore underwent recordings of MCA CBFV, beat-to-beat BP and HR. Mean age of subjects was 68.5 years (s.d. 10.4, range 48-91). Three patients had intracerebral haemorrhage (ICH), 39 had ischaemic stroke. As the number with ICH was small these were analysed separately. All patients who gave consent are summarised in figure 5.1.

Figure 5.1 Outcome of consented patients



5.5.2 Ischaemic Stroke

39 patients with ischaemic stroke were studied at median 42 hours from stroke onset (IQR 36-49, range 6-105), and again 14 days later (median time from onset to follow-up 378 hours, IQR 369- 386, range 360-394). Five patients did not attend for follow-up, four of whom were male, they did not differ significantly from the rest of the group in terms of stroke severity or other demograhics.

5.5.3 Controls

A group of control subjects underwent recordings following the same protocol, but these were performed on a single occasion only. 20 controls were recruited from friends, relatives and departmental staff. Six of these were excluded due to unilateral or bilateral transtemporal acoustic window failure or poor signal quality leading to data rejection. In addition data were available from departmental volunteers who had been studied previously using the same methods. These were selected to ensure that the groups were balanced in terms of age, sex and BMI. They were selected based on age and sex but blinded to ARI. A total of 24 controls (16 male, 8 female) were available for comparison.

5.5.4 Demographics

SBP, DBP, HR and BMI were normally distributed. The distribution of results for strokes and controls are shown in Figures 5.2-5.4.

Figure 5.2a Systolic BP stroke (baseline)

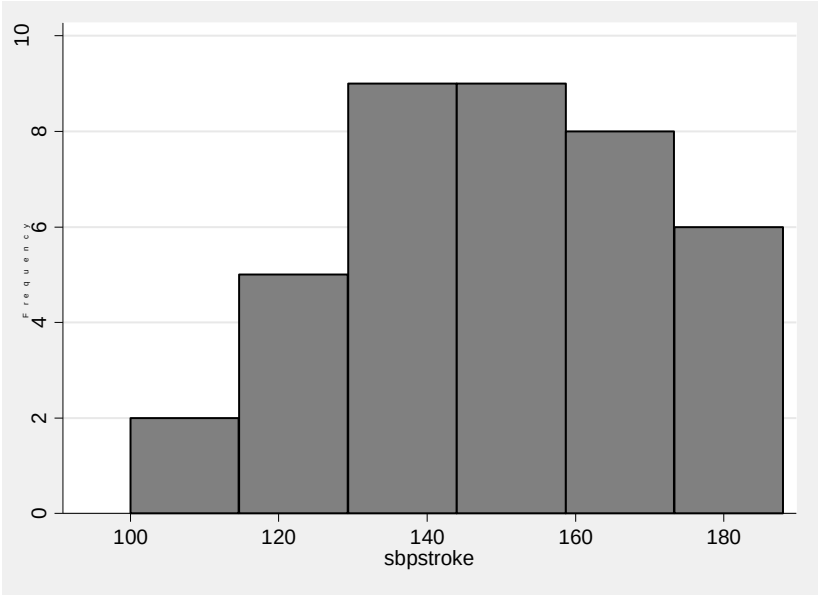


Figure 5.2b Systolic BP controls

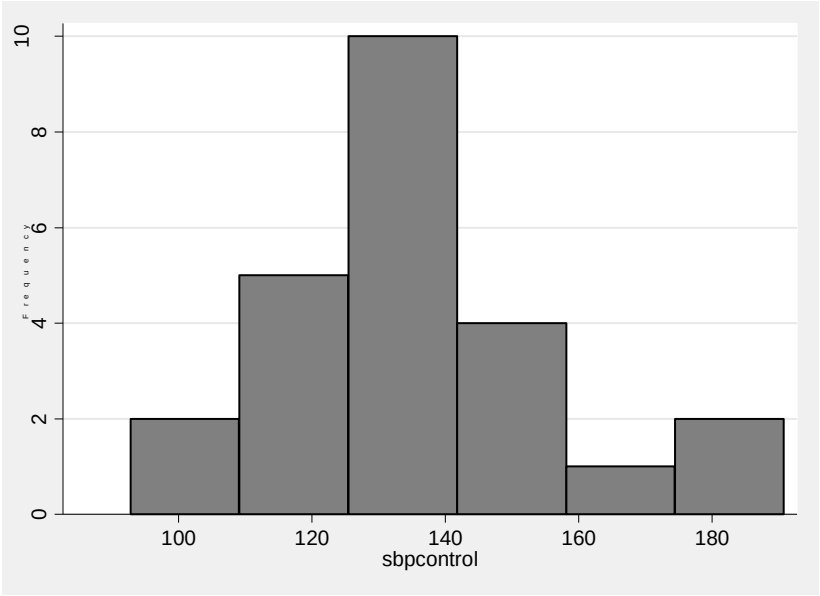


Figure 5.3a Diastolic BP stroke (baseline)

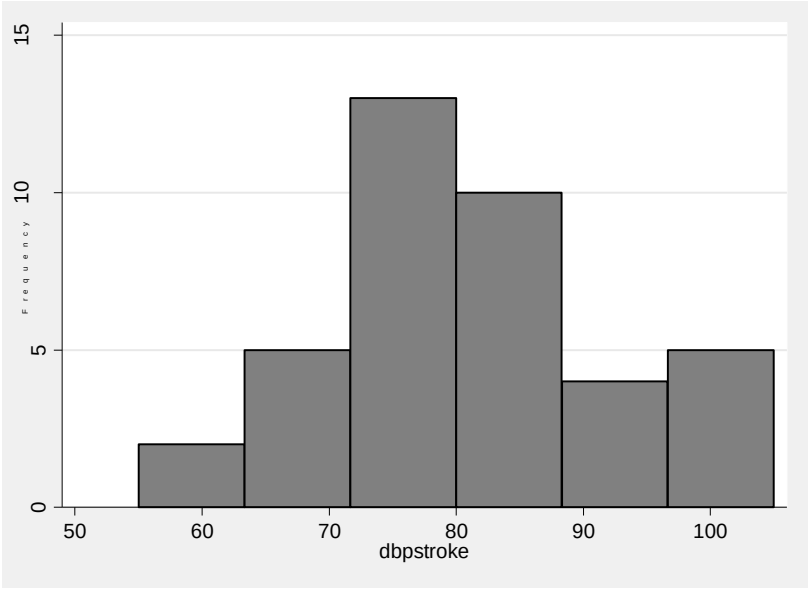


Figure 5.4b Diastolic BP controls

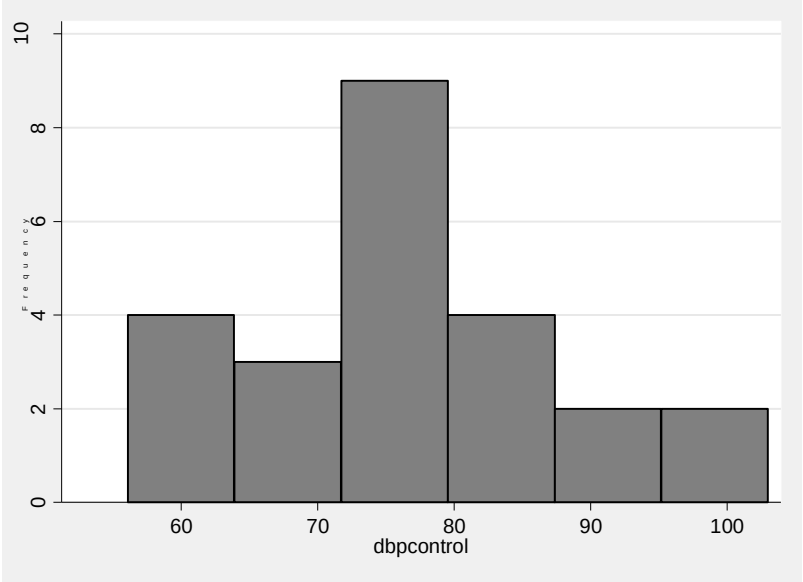


Figure 5.4a Heart rate stroke

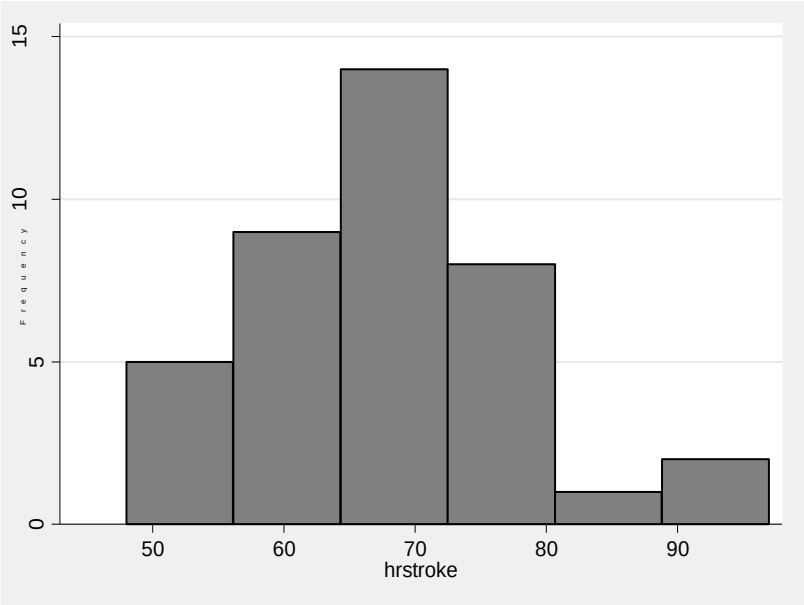
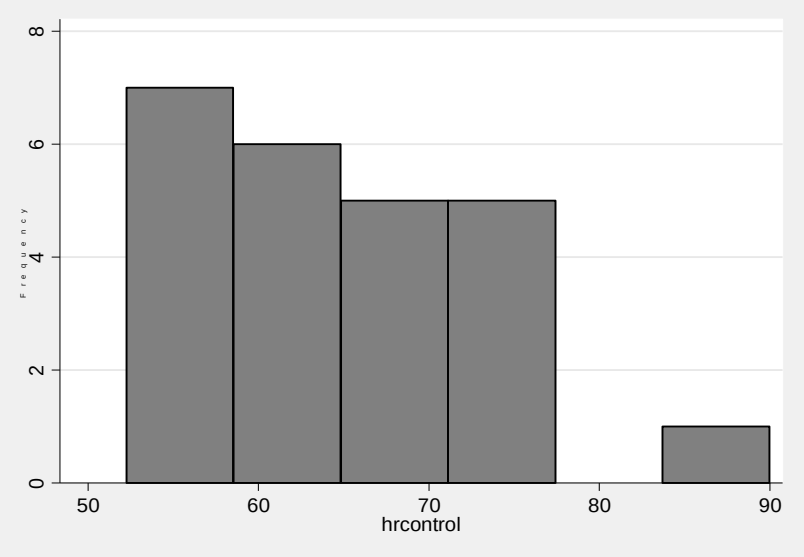


Figure 5.4b Heart rate controls



The demographics of controls and stroke patients are shown in tables 5.2 and 5.3 below:

Table 5.2 Demographics of Controls vs Ischaemic Stroke patients (Continuous Variables)

	Control Mean (±SD; Range)	Stroke baseline	P-value† control = stroke baseline	Stroke follow-up	p-value control = stroke follow-up
Age (years)	65.5 (±8.7; 46-79)	69.2 (±10.4; 48-91)	P=0.15	69.1 (±10; 49-91)	P=0.15
SBP (mmHg)	135 (±23; 93-191)	149 (±22; 100-188)	P=0.02	143 (± 17; 106-181)	P=0.15
DBP (mmHg)	77 (±11; 56-103)	81 (±12; 55-105)	P=0.14	78, (±10; 68-113)	P=0.79
HR (bpm)	64 (±9; 52-90)	68, (±11; 48-97)	P=0.12	68 (±14; 46-99)	P=0.74
BMI (kg/m^2)	25 (±4; 20-36)	27.5 (±5; 17-39)	P=0.06	27 (±4; 17-35)	P=0.06

†t-test to determine differences between normally distributed continuous variables

Table 5.3 Demographics of Controls vs Ischaemic Stroke patients (Categorical Variables)

	Control	Stroke baseline	P-value† control = stroke baseline	Stroke follow-up	p-value control = stroke follow-up
Sex (M:F)	16:8	26:13	P=1.0	22:12	P=0.97
Smoker (N:Ex:Y)	15:8:1	10:22:7	P=0.01	10:18:6	P=0.03
Diabetic (No:Yes)	22:2	34:5	P=0.70	29:5	P=0.45
Statin (No:Yes)	23:1	16:23	P=0.001	10:24	P=0.001
Previous stroke (No:Yes)	24:0	29:10	P=0.007	27:7	P=0.018

†Chi^2 test for categorical variables (Fisher's exact test used if <5 in any cell)

Patients and controls were well balanced for age, sex and BMI. SBP was significantly higher in patients than controls at baseline but not at follow-up, while DBP and HR were not significantly different between the two groups. There were significantly more smokers and ex-smokers in the stroke group compared to controls. The incidence of diabetes did not differ significantly between the two groups. Statin use was significantly more frequent in the stroke group.

5.5.5 Stroke Severity

Baseline modified Rankin score was a median of 3 (IQR 2-4, range 0-5), and Barthel index a median of 17 (IQR 10-20, range 4-20). Baseline NIHSS was a median of 3 (IQR 2-6, range 0-15). The occurrence of NIHSS=0 was possible due to the inclusion of patients with CT confirmed acute ischemic stroke but with rapidly resolving symptoms. Barthel index, modified Rankin score and NIHSS were found to be non-normally distributed. According to the OCSP classification there were 17 LACS, 15 PACS, 3 TACS, 3 POCs, and 1 unclassified.

5.5.6 Cerebral Autoregulation after Acute Stroke

The mean ARI of controls was 5.7. The mean ARI in the affected hemisphere at baseline was 4.4. This was significantly lower than controls, p=0.001 (mean difference -1.3). No significant confounders were identified using the forward selection method (variables entered into the model were SBP, smoking, statin use, history of previous stroke, and significant carotid stenosis). However in view of the significant difference in these parameters in stroke patients compared to controls analysis of covariance was performed, adjusting for each of

these variables. The adjusted p-value = 0.025, adjusted mean difference -1.3, (95% CI -2.48,-0.18).

The mean ARI of the unaffected hemisphere at baseline was 5.2, and this was not significantly different from control. The ARI in the affected hemisphere was significantly lower than in the unaffected hemisphere at baseline (p=0.006). All ARI values are summarised in Table 5.5 below.

There was wide range of time from onset to recording, but no correlation was found between ARI and time from onset to recording (affected hemisphere Spearman rank correlation=0.01, p= 0.57, unaffected hemisphere Spearman rank correlation=0.21, p=0.201). The distribution of ARI by time from onset to recording is shown in Figure 5.5.

Figure 5.5a ARI by Time from onset to recording (affected hemisphere)

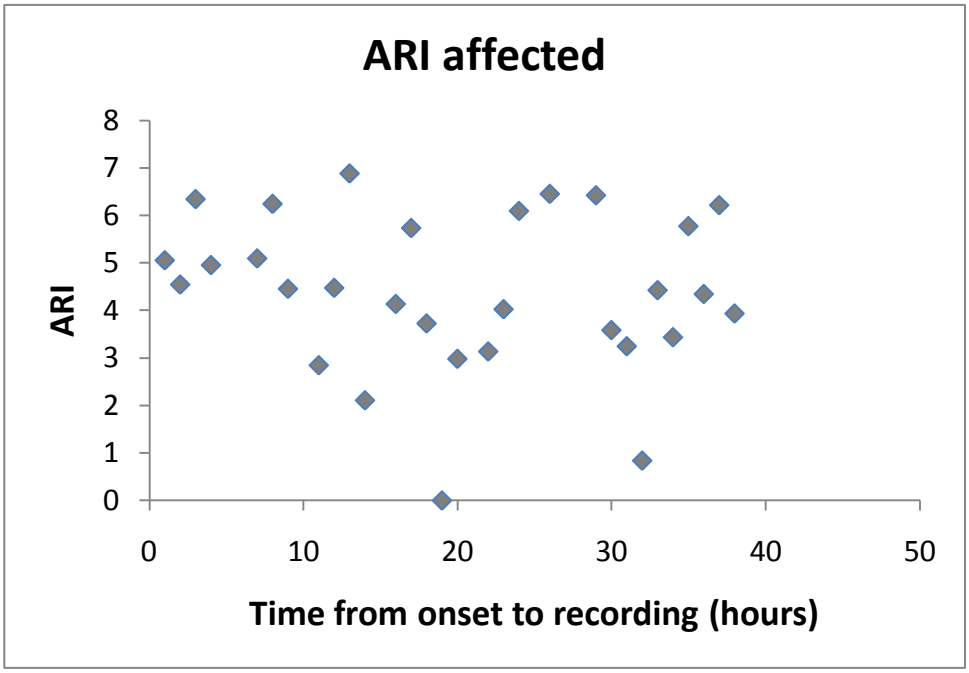
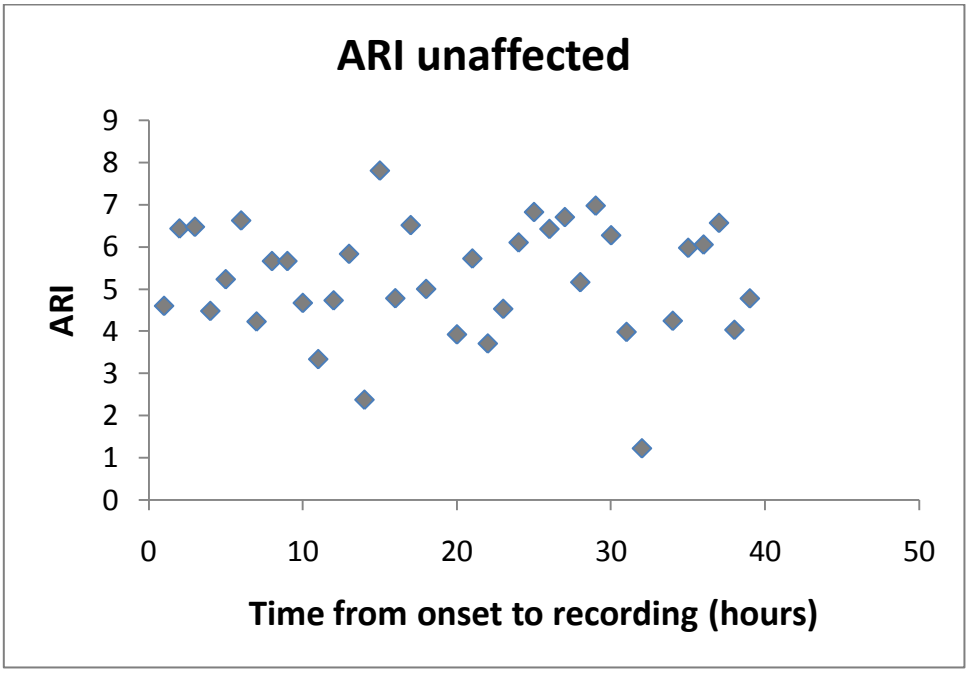


Figure 5.5b ARI by Time from onset to recording (unaffected hemisphere)



5.5.7 Change from baseline to follow-up

The functional and neurological changes which occurred between baseline and follow-up are shown in table 5.4.

Table 5.4 Neurological and Functional Status at Baseline and Follow-up

	Stroke Baseline Median (IQR; range)	Stroke Follow-up	p-value change from Baseline-Follow-up†
NIHSS	3 (2-6; range 0-15)	1 (0-2; 0-8)	P=0.0005*
mRS	3 (2-4; 0-5)	2 (1-3; 0-4)	P=0.051
Barthel	17 (10-20; 4-20)	19 (16-20; 7-2)	P=0.031*

† Mann-Whitney U-test used to assess change in non-normally distributed continuous variables

There was a significant fall in NIHSS and a significant rise in Barthel index between baseline and follow-up. Fall in modified Rankin score was of borderline statistical significance.
The change in SBP, DBP and HR from baseline to follow-up is shown in table 5.1. SBP fell from baseline to follow-up, though this did not reach statistical significance (p=0.2). DBP and HR did not differ significantly between baseline and follow-up.

Statin use had increased from 41% to 71% by follow-up. Of those who were lost to follow-up 4/5 were not on a statin at the time of their stroke, however the use of statins at 2 weeks post stroke in those who were lost to follow-up is unknown.

One patient was found to have significant ipsilateral ICA stenosis, and underwent carotid endarterectomy before the follow-up visit. This patient's ARI results were not included in the follow-up analyses, the rationale for this is discussed below.

Mean ARI in the affected hemisphere at follow-up was 5.0, this remained lower than control and this was of borderline statistical significance (p=0.055). There was a rise in ARI in the affected hemisphere from baseline to follow-up, but this was not statistically significant. Mean ARI in the unaffected hemisphere at follow-up was 5.1, which was lower than at baseline but was not significantly different from control. The fall from baseline to follow-up was not statistically significant. The difference in ARI between affected and unaffected hemispheres at follow-up was no longer statistically significant at follow-up.

The overall change in ARI from baseline to follow-up in the affected and unaffected hemispheres by individual subject is shown in Figure 5.6. The overall ARI results for affected and unaffected hemispheres at baseline and follow-up are shown in Table 5.5.

Table 5.5 ARI results at baseline and follow-up

	ARI (±SD), Δ from control, (95% CI for Δ)	p-value against control	p-value change from baseline	Inter-hemispheric Δ, (95% CI for Δ), p-value
Control	5.7 (1.3)	-	-	-
Affected Hemisphere (baseline)	4.4 (1.7), -1.3 (-2.1,-0.5)	P=0.001	-	0.6, (0.1,0.8), P=0.006
Adjusted†	*-1.3 (-2.2,-0.13)*	*P=0.028*		
Unaffected Hemisphere (baseline)	5.2 (1.4), -0.5 (-0.2,1.1)	P=0.1	-	-
Affected Hemisphere (follow-up)	5.0 (1.7), -0.7 (-0.2,1.5)	P=0.06	P=0.18	0.1, (-0.4,0.5), P=0.93
*Adjusted**	*0.1 (-1.7,1.9)*	*P=0.92*		
Unaffected Hemisphere (follow-up)	5.1 (1.5), -0.6 (-0.2,1.3)	P=0.08	P=0.76	-
*Adjusted**	*0.59 (-1.9, 1,1)*	*P=0.56*		

†Adjusted for potential covariates SBP, smoking, statin use, and history of previous stroke

*Adjusted for ipsilateral baseline ARI

Figure 5.6a Change in ARI from baseline to follow-up (affected hemisphere)

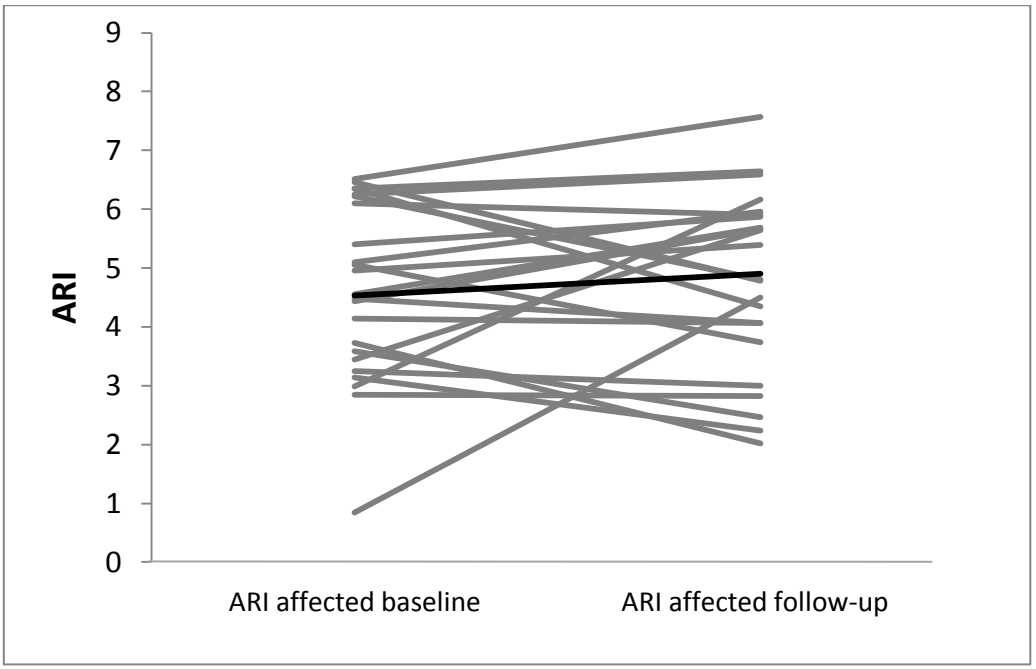
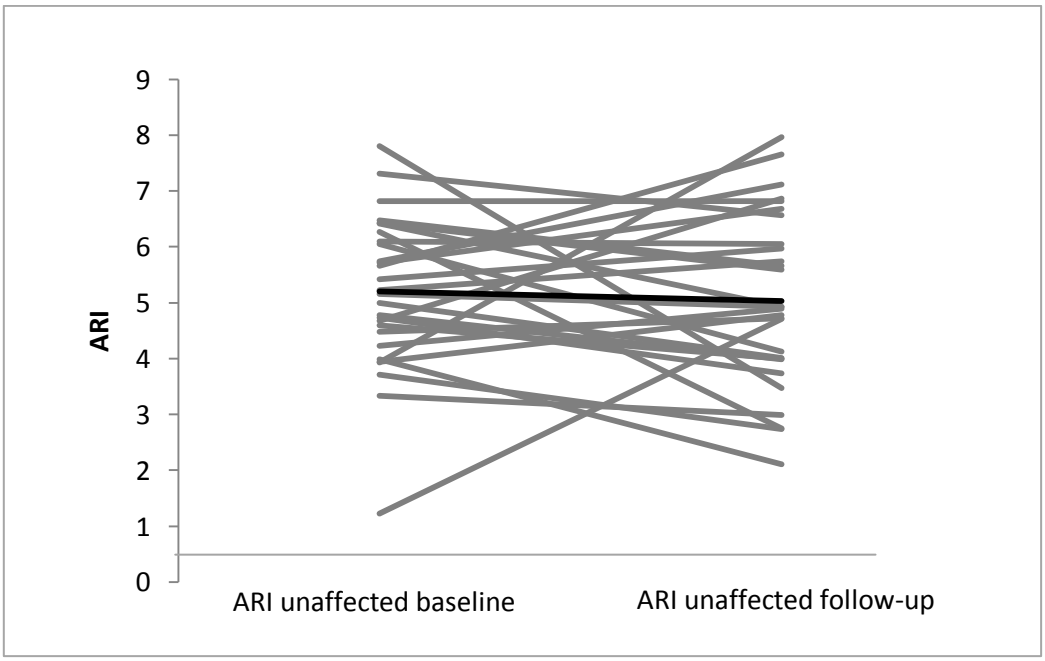


Figure 5.6b Change in ARI from baseline to follow-up (unaffected hemisphere)



5.5.8 ARI within 'Normal Range'

The proportion of subjects with an ARI <4 or ≥4 was examined at baseline and follow-up, and this again demonstrated significantly lower ARI in the affected hemisphere at baseline which did not persist to follow-up. It also demonstrated a trend towards rise in ARI in the affected hemisphere and fall in ARI in the unaffected hemisphere from baseline to follow-up (though these were not statistically significant). These are presented in Table 5.6.

Table 5.6 ARI below 'normal' threshold

	Control	Affected Hemisphere baseline	Unaffected Hemisphere baseline	Affected Hemisphere follow-up	Unaffected Hemisphere follow-up
Number of Subjects with ARI <4	2/24	11/30	6/37	6/24	7/31
% with ARI <4	8%	37%	16%	25%	23%
Fisher's exact test for difference from control	n/a	P=0.02	P=0.32	P=0.25	P=0.27

5.5.9 Stroke Subtype

The effect of stroke subtype on ARI was examined. One patient was unclassified by OCSP and three were classified as POCS, these were excluded from the analysis. Patients with LACS syndrome were considered as one group, while PACS and TACS were combined to form the other group. No significant effect of stroke type on either hemisphere was noted at baseline, or in the unaffected hemisphere at follow-up. In the affected hemisphere at follow-up there was a statistically significant effect of stroke type on ARI with a lower ARI in the PACS/TACS group compared to LACS (mean ARI PACS/TACS 3.7, mean ARI LACS 4.7, p=0.03). However following Bonferroni correction for multiple tests (affected hemisphere baseline and follow-

up, unaffected hemisphere baseline and follow-up) this result is no longer statistically significant (p=0.12).

Patients with a lacunar stroke and evidence of small vessel disease on CT scan (n=6) were then considered as a 'small vessel' group, while those with PACS/TACS and evidence of a cortical infarct on CT (n=13) were considered as a 'large vessel' disease. As can be seen from Table 5.7 there was considerable overlap between clinical stroke type (OCSP classification) and radiological (CT) diagnosis. For this reason it was decided to select patients who fitted into both a clinical and radiological classification of stroke type in order to examine possible effects of stroke type on dCA. This did however result in much smaller patient numbers in each group.

There was no significant difference in ARI between 'small vessel' and 'large vessel' in either hemisphere at baseline or at follow-up. There was no pattern of change in ARI from baseline to follow-up according to stroke subtype (OCSP classification or 'small vessel' vs 'large vessel'). The distribution of patients according to OCSP classification and CT result is shown in Table 5.7.

Table 5.7 Breakdown of OCSP subtype by CT finding†:

OCSP Classification	CT result		
	Corresponding Infarct	Small Vessel Disease	Normal Scan
LACS	6	6	5
PACS	10	4	1
TACS	3	-	-
POCS	2	1	-

†1 missing value as unclassified by OCSP, CT scan showed acute basal ganglia infarct

5.5.10 ARI and Neurological/Functional Outcome

In order to establish whether change in ARI was related to outcome 'change in ARI' = $ARI_{Follow-up}$-$ARI_{Baseline}$ was calculated for each hemisphere, along with 'change in NIHSS', 'change in mRS', and 'change in Barthel'. The interpretation of these values is as follows: if change in ARI is positive this indicates that ARI has increased from baseline to follow-up. If 'change NIHSS' or 'change mRS' were negative this indicates neurological or functional improvement (as a higher result on either scale is worse), while the reverse is true in the case of Barthel index. If patients were lost to follow-up or had no signal/rejected ARI data at either baseline or follow-up they were not included in the plots. In the affected hemisphere the number with ARI data at baseline and follow-up was 23 (out of the 34 patients who were followed up); in the unaffected hemisphere this number was 30.

Change in neurological or functional status was then plotted against change in ARI, and these are shown in Figures 5.7-5.9. As can be seen from the figures there did not appear to be a correlation between change in ARI and change in neurological or functional outcome. At six month follow-up 2/39 patients had died. In view of the small numbers it is not possible to examine a correlation between ARI and mortality.

Figure 5.7a Change in NIHSS against change in ARI (affected hemisphere)

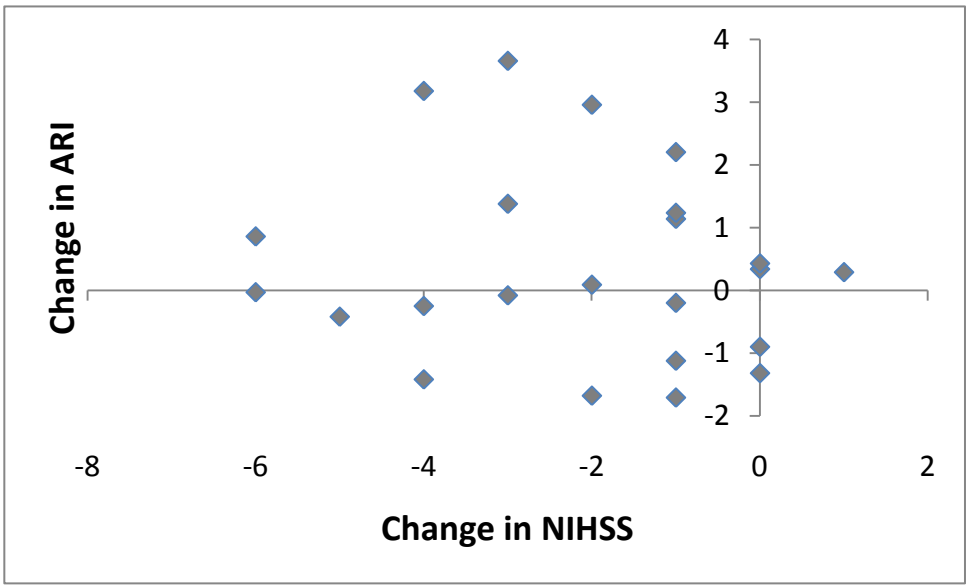


Figure 5.7b Change in NIHSS against change in ARI (unaffected hemisphere)

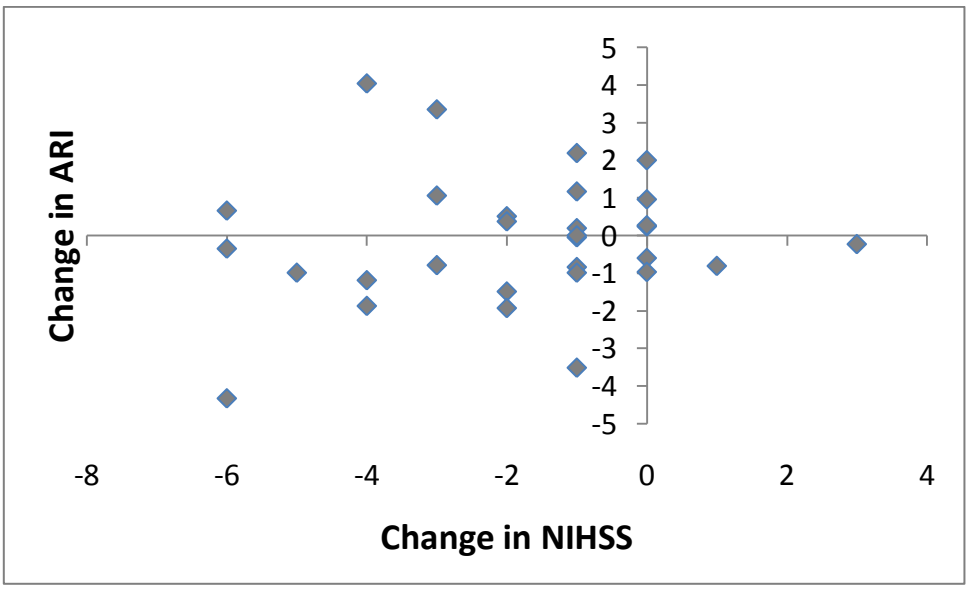


Figure 5.8a **Change in mRS against change in ARI (affected hemisphere)**

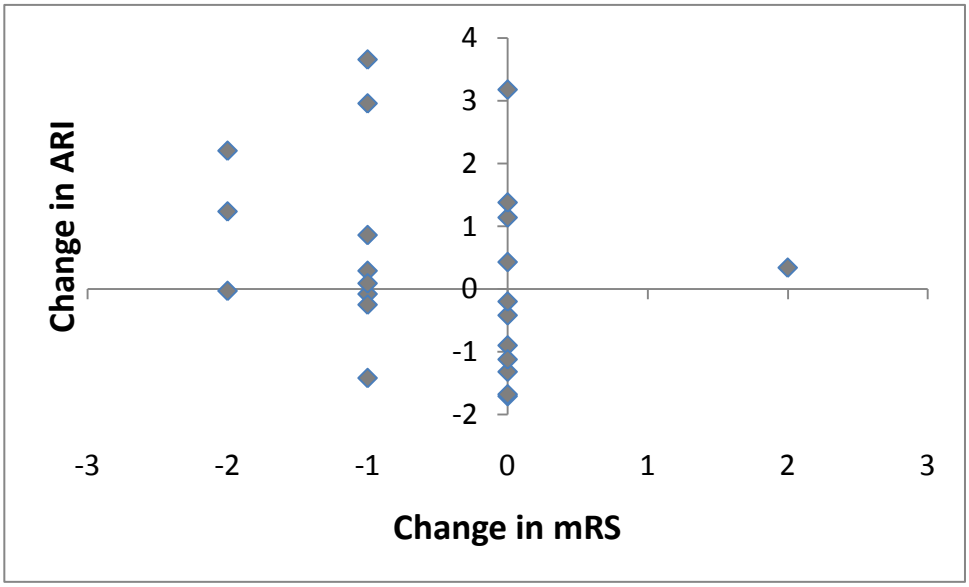


Figure 5.8b **Change in mRS against change in ARI (unaffected hemisphere)**

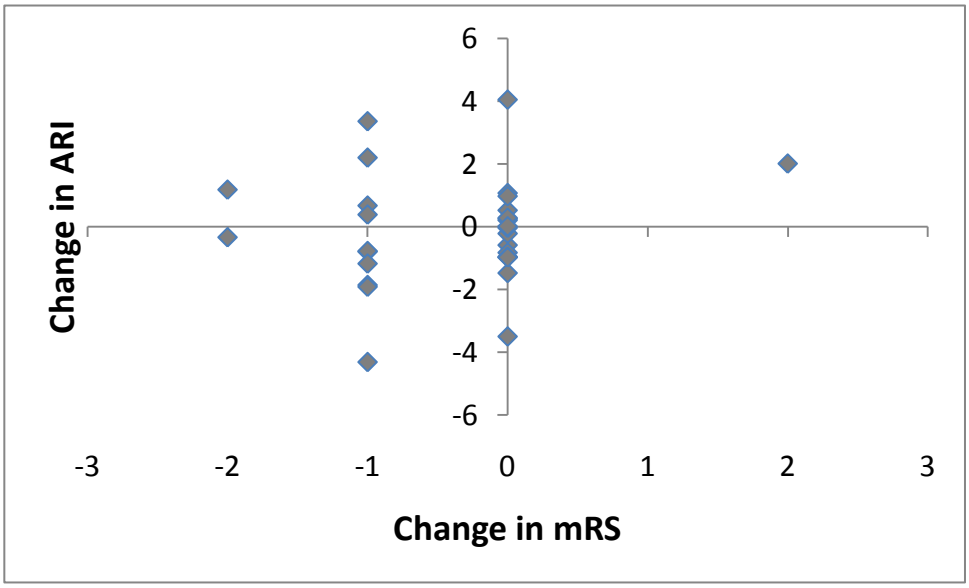


Figure 5.9a Change in Barthel against change in ARI (affected hemisphere)

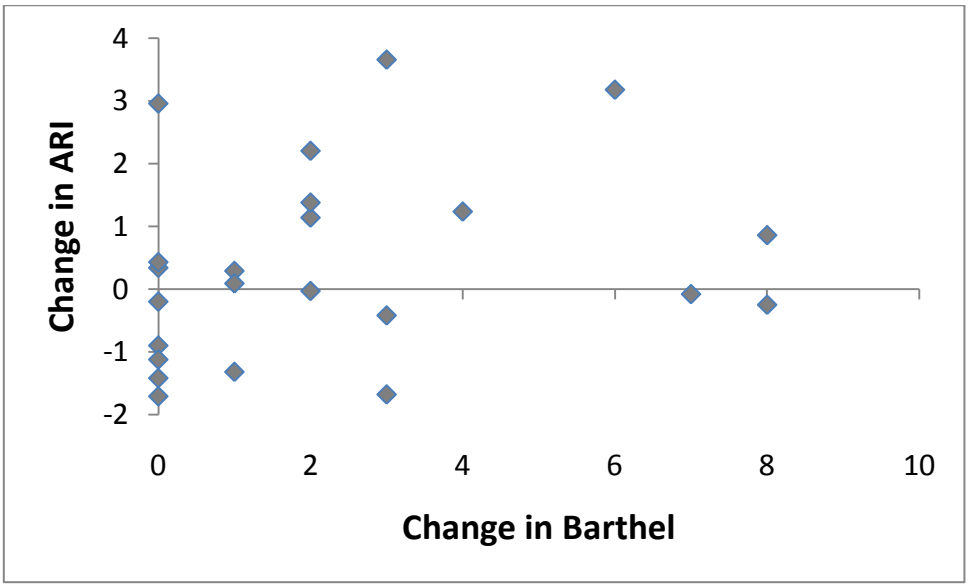
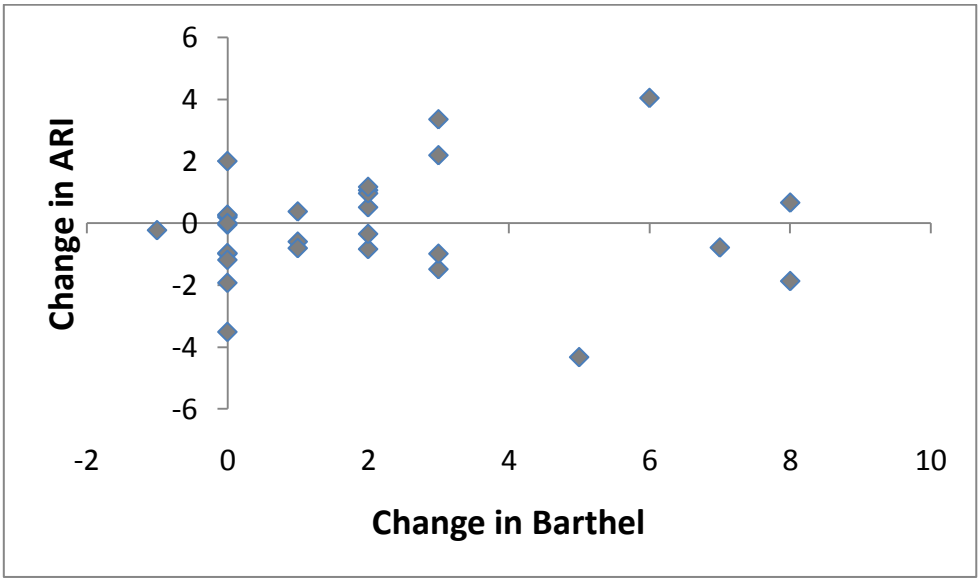


Figure 5.9b Change in Barthel against change in ARI (unaffected hemisphere)



5.5.11 Intracerebral Haemorrhage

Three patients who took part in the study were found to have had an intracerebral haemorrhage (1 male, 2 female). In view of the small number statistical analysis of this subgroup has not been performed. Demographics for this group are shown in Table 5.8, neurological and functional status in Table 5.9 and their ARI results are shown in Table 5.10.

Table 5.8 Demographics ICH Patients

	Baseline Mean (range)	Follow-up
Age (years)	59 (53-63)	-
SBP (mmHg)	145 (117-183)	140 (132-154)
DBP (mmHg)	81 (64-97)	74 (65-92)
HR (bpm)	70 (65-76)	65 (61-69)
BMI (kg/m^2)	35 (27-41)	-
Smoker (No/Ex/Yes)	1:1:1	-
Diabetic (No/Yes)	2:1	-
Statin (No/Yes)	2:1	2:1
Previous stroke (No/Yes)	2:1	-

Table 5.9 Neurological and Functional Status ICH patients

	Baseline Median (range)	Follow-up
NIHSS	6 (all 3 patients)	2 (2-4)
mRS	3 (1-4)	2(1-2)
Barthel	16 (11-20)	19 (19-20)

Table 5.10 ARI ICH patients at Baseline and Follow-up

	Baseline Median (range)	Follow-up
Affected Hemisphere	3.9 (2.0-4.1)	4.4 (4.3-5.8)
Unaffected Hemisphere	5.3 (4.3-6.9)	5.6 (3.7-6.1)

5.6 Discussion

This study demonstrates reduced ARI in the affected hemisphere following acute ischaemic stroke both acutely (within 48 hours) and at 2 week follow-up, though this was no longer statistically significant at follow-up. The ARI of the unaffected hemisphere was not significantly different from control at baseline or follow-up. There was no obvious correlation between change in ARI and neurological or functional recovery. Stroke subtype did not appear to affect ARI, though subgroups were small.

5.6.1 dCA in Acute Ischaemic Stroke

The finding of this current study of impairment in dCA acutely following ischaemic stroke is in keeping with previous studies[59;83;84]. The consistent finding of reduced dCA following acute ischaemic stroke in different studies using different measurement techniques (induced changes in BP[59] , spontaneous fluctuations in BP[64;83;84],ARI[59;83], phase[84]), suggests that this impairment is real, and is likely to be a direct consequence of stroke. It does not however help discriminate between methods of measuring dCA in terms of sensitivity and specificity. Reinhard et al[64] in contrast found no impairment in dCA following acute ischaemic stroke

(mean 22 hours from ictus) using phase and the autoregulatory index Mx as measures of cerebral autoregulation. Mx is a correlation coefficient between mean ABP and mean CBFV during spontaneous fluctuations in BP. It is worth noting that they examined patients earlier than in the other studies, which raises that possibility that the disruption in autoregulatory mechanisms takes time to develop. This hypothesis is supported by their subsequent observation that a significant reduction in Mx was noted a few days later (day 5 post ictus, see table 5.11).

5.6.2 Recovery of dCA following Acute Stroke

The present study demonstrates a reduction in dCA acutely following stroke in the affected hemisphere, which appears to have risen after an interval of two weeks (though the ARI had not quite reached that of healthy controls). As mentioned above Reinhard et al[64] demonstrated a fall in dCA over the first few days following acute ischaemic stroke (from day 1 to day 5). The present findings in addition to the published literature suggest that dCA impairment and possible recovery following acute stroke is a dynamic process, with impairment evident within the first day or two following acute stroke, persisting to day 5[64] and day 10[121], but starting to return to controls values by day 14.

Eames et al[83] examined patients once only, within 72 hours from onset (though the distribution of delay from onset to recording is unclear) using similar methods to the present study. The observed ARI in their study (stroke patients: 3.2 and 3.8 for transient BP rise and fall respectively, controls: 4.5, 4.7) are lower than in the present study, the reasons for this are not entirely clear. Interestingly they found no significant difference between the affected

and unaffected hemispheres, and so present their ARI results as the mean of both hemispheres for both strokes and controls.

It is possible that their patients were studied close to 72 hours from onset, and that there is, as suggested by Reinhard[64], a fall in dCA over the first few days following acute stroke. Thus the reduction in ARI seen in the affected hemisphere in the present study may represent a point on a downward curve, rather than a trough value of ARI.

Dawson et al[121] studied a group of patients a median of 2 days from onset after ischaemic stroke and again at a median of 10 days. They found significant reduction in ARI in the affected hemisphere both at baseline and follow-up. Interestingly they also noted a small non-significant fall in ARI in the unaffected hemisphere from baseline to follow-up, similar to what was observed in the current study. Their methodology was different, using bilateral thigh cuff release as the stimulus for dCA, but they report their results in terms of ARI. It is worth noting in Dawson's study that the ARI in the affected hemisphere did not demonstrate any rise between day 2 (3.9±3.1) and day 10 (3.9±2.8). It may be that recovery in autoregulatory mechanisms had not begun, or may reflect a difference in the population studied (for example they had a higher proportion of PACS/TACS than in the present study, and neuroimaging information is not provided). The differences in dCA results according to time from onset in these studies is summarised in table 5.11.

Table 5.11 dCA in acute stroke versus control, by time from onset to recording

Study	Time from Symptom Onset	Eligible Patients	Measure of dCA	Difference (Stroke v Control)
Reinhard[64] (study 1)	Mean 22 hours	Ischaemic MCA stroke, n=33	Mx, Dx, phase	No difference: Mx (0.19 v 0.2) phase (44˚ v 48˚)
Dawson[59] (baseline)	Mean 2.1 days	First ischaemic stroke, n=54	ARI (thigh cuff release)	ARI affected hemisphere (4.1 v 6.2), p<0.05* ARI unaffected hemisphere (4.8 v 6.2), p<0.05*
Immink[84]	<72 hours	First ischaemic MCA (n=10) or lacunar stroke (n=10)	Phase	Ipsilateral ↓ in LF† phase MCA, (26˚ v 56˚), p<0.05* Bilateral↓in phase lacunar, (32˚ and 33˚ v56˚), p<0.05*
Eames[83]	<72 hours	First ischaemic stroke, n=56	ARI (spontaneous fluctuations in BP)	ARI (3.2 v 4.5) for BP rise, p=0.003* ARI (3.8 v 4.5) for BP fall, p=0.03*
Reinhard[64] (study 2)	Mean 134 hours	Ischaemic MCA stroke, n=29	Mx, Dx, phase	Mx 0.27, change from baseline (22 hours) p<0.05 phase: no difference
Dawson[121] (follow-up)	Mean 10 days	First ischaemic stroke, n=30	ARI (thigh cuff release)	ARI affected hemisphere (3.9 v 6.2), p<0.05* ARI unaffected hemisphere (4.6 v 6.2), p<0.05*

* statistically significant from control, †LF = low frequency

Reinhard et al[122] studied at mean 20 hours, 64 hours and 112 hours from onset of symptoms a group of ischaemic stroke patients who had received thrombolysis with rtPA , and divided patients into 'good outcome' and 'poor outcome' groups. They found worsening impairment in dCA in terms of both Mx and phase in the affected hemisphere of those with a poor

outcome, but did not detect any difference between those with good outcome and healthy controls at any of the three visits.

The current study demonstrates impairment in cerebrovascular haemodynamic control following acute ischaemic stroke, though this appears to be improving by 2 week follow-up. This is of relevance particularly to guide the appropriate time to introduce antihypertensive therapy. There is compelling evidence that antihypertensive therapy, particularly with ACE inhibition, lowers the risk of vascular events, but the majority of secondary preventative studies have introduced therapy later than the first two weeks after stroke[123-125]. The current study is too small to draw a final conclusion and did not specifically look at introduction of antihypertensive therapy following acute stroke; further work in this area would help to answer the questions raised.

5.6.3 Mechanisms affected in impaired dCA

Cipolla[126] et al studied MCA myogenic activity in groups of rats following MCA occlusion and varying degrees of reperfusion. Myogenic reactivity (which is a marker of alteration in vascular smooth muscle tone) is thought to play a role in maintaining CBF. They demonstrated a fall in myogenic reactivity as reperfusion duration (i.e. as the length of time from ischaemia to full restoration of blood flow) increased, suggesting that time taken to reperfuse tissue may influence this part of the cerebral autoregulatory mechanism. Varying degrees of ischaemia and reperfusion may affect not only the extent but also the timing of

any impairment in dCA detected, though this has not been established clearly in humans, and in any case would be difficult to characterise directly.

It has been demonstrated that patients with significant carotid artery stenosis/occlusion have significant ipsilateral impairment in CA[127], and furthermore that revascularisation in significant stenosis leads to rapid return to near normal values (when reassessed at a mean of 3 days post-revascularisation)[85]. From the present study the same does not seem to hold following acute ischaemic stroke, where the ARI of the affected hemisphere had increased by 2 week follow-up, but was still lower than controls (5.0 vs 5.7, p=0.06) . This is perhaps not surprising, but raises interesting points regarding the putative mechanisms underlying healthy CA and the distinctive effects of various insults on individual mechanisms.

In patients with significant carotid stenosis impairment in dCA is probably due to chronic low flow through a region of increased vascular resistance and a reduced capacity for any further relaxation of vasomotor tone, and it may be that the sudden improvement seen following revascularisation is due to a marked fall in the vascular resistance. It is interesting to note that in Reinhard's study of dCA in patients with significant carotid stenosis or occlusion previously symptomatic patients demonstrated significantly worse dCA in terms of phase and gain (following transfer function analysis) than asymptomatic patients. However this difference was not apparent when the correlation coefficients Sx, Dx and Mx were assessed[127]. This suggests that separate mechanisms occur in stroke disease giving rise to more prolonged impairment in dCA. From a physiological point of view it is possible that in

patients with acute ischaemic stroke there is disruption of cortical autoregulatory mechanisms such as local myogenic, metabolic or possibly neurogenic factors, and it may be that some or all of these factors demonstrate gradual recovery. Where there is a large volume of infarcted tissue the metabolic requirements of that region will be reduced and so metabolic factors may contribute less to maintaining CBF in that hemisphere.

Work in healthy anaesthetised cats investigated the relative contributions of myogenic and metabolic autoregulatory responses and found metabolic responses seemed to predominate under normal circumstances[128]. There are postulated to be other mechanisms by which cerebral autoregulation is maintained, including possible neurogenic factors, and the relative contributions of different mechanisms in cerebral arteries in healthy and ill humans requires further study.

As CPP=MAP-intracranial pressure (ICP) any effect of acute stroke on ICP may in turn alter CPP and hence CBF unless there is a sufficient compensatory rise in MAP. ICP is not routinely measure in patients with acute stroke, and requires invasive manometry. However in acute stroke there may be evidence of intracerebral oedema on neuroimaging, which is likely to cause raised ICP. It is likely that larger strokes will have a greater degree of associated oedema, and hence are more likely to cause a rise in ICP. As discussed later the population included in this study tended to have less severe strokes, and so although ICP was not measured directly we would not expect significant changes in ICP. This may be of importance

however in a group with more severe stroke, where ICP may become a crucial determinant of cerebral perfusion pressure.

5.6.4 dCA and thrombolysis

The current study did not look at the effects of thrombolysis on changes in dCA following acute ischaemic stroke, largely because a thrombolysis service was established only once several patients had been recruited into the study.

Infeld et al[129] studied changes in cerebral perfusion using SPECT scanning before and after administration of iv streptokinase (n= 15) or placebo (n=9) in patients with acute ischaemic stroke taking part in the Australian Streptokinase Trial. They demonstrated in those who received streptokinase that there was an excess of non-nutritional perfusion (so-called 'luxury perfusion') compared to those receiving placebo, and also that non-nutritional perfusion was associated with poorer functional outcome. A study of the mechanisms of rtPA in rats compared the effects of rtPA and placebo on the myogenic activity of the MCA in normal and ischaemic conditions[130]. This demonstrated impaired cerebrovascular resistance in both ischemic and non-ischaemic arteries infused with rtPA, and there appeared to be an additive effect when rtPA was administered into the ischaemic vessel. These studies raise the possibility that thrombolytic agents may themselves adversely affect CA.

Reinhard et al[122] studied the effects of rtPA on dCA in 16 patients with acute MCA occlusion compared to minor strokes not receiving rtPA and a healthy control group, using Mx and phase. They found no difference in dCA between successfully thrombolysed patients

compared to non-thrombolysed minor strokes or controls, though Mx was significantly higher (i.e. higher correlation between CBFV and BP and therefore impaired dCA) and phase was significantly lower in the affected hemisphere of those who were thrombolysed and demonstrated poor clinical outcome. These suggest that rtPA itself does not play a role in the further disruption of dCA following acute ischaemic stroke, and that the impairment in dCA is directly due to stroke.

5.6.5 dCA by Stroke Subtype

The current study did not identify any significant influence of clinical or radiological stroke subtype on ARI. However this should be viewed in light of the small numbers in each group, giving rise to the possibility of type 2 statistical error (the failure to detect a real difference when one exists). Subgroups were small when the groups were compared by aeitiology ('large vessel and 'small vessel' ischaemic stroke). 72% of patients with a PACS or TACS syndrome had evidence of a corresponding infarct on CT scan (the remainder had small vessel disease (22%) or a normal CT scan (6%, 1 patient)). However, of patients with a LACS syndrome 35% had small vessel disease, 35% had a corresponding infarct, and 30% had a normal CT scan. The lack of MRI studies in the majority of patients reduces the sensitivity of the comparison between 'small vessel' and 'large vessel' disease; it is certainly possible for example that lacunar infarction may have been demonstrated on MRI in a significant number of the LACS patients with a normal CT scan.

We were unable to characterise the patients in this study using the TOAST classification due to lack of necessary information in several cases (usually due to missing echocardiography or haematological investigations). As the TOAST classification uses clinical, neuroradiological and other information it is more robust as an aetiological classification, and it is possible that comparison by TOAST classification may have revealed a difference between subgroups.

Immink et al[84] have previously shown a difference in the pattern of dCA impairment following acute ischaemic stroke relative to stroke type, which were defined as MCA stroke or lacunar stroke based on clinical findings and subsequent CT/MRI. Their study used phase as a measure of dCA and so is not directly comparable to the current study, but they demonstrated global impairment in dCA in patients with lacunar stroke but ipsilateral impairment only in MCA territory stroke. Eames et al[83] found no significant difference in dCA relative to stroke subtype as determined by OCSP classification.

It seems likely that different subtypes of stroke will affect dCA in different ways. A lacunar infarct may be the first clinical manifestation of on-going small vessel cerebrovascular disease, and so one may speculate that impairment in dCA may be more global, while a single large artery occlusion giving rise to a TACS or PACS syndrome may cause disruption of ipsilateral dCA but may not be expected to cause impairment on the unaffected hemisphere.

There is further uncertainty as to whether autoregulatory mechanisms will be similarly disrupted in posterior circulation strokes, and if this study were to be repeated perhaps those patients should not be included in analysis (or if numbers permit perhaps studied as a separate group).

5.6.6 Limitations of the present study

5.6.6.1 TCD Window Failure

In this study bilateral TCD window failure was demonstrated in 7/49 potentially eligible stroke patients, all of whom were female. This is in keeping with other studies using TCD, and represents a limitation of TCD in certain subjects. Bos et al[131] demonstrated a TCD window failure rate of nearly a quarter of healthy older subjects undergoing TCD as part of the Rotterdam study into haemodynamic parameters and stroke risk (741/3008 subjects). In their cohort, as in this, being female was associated with an increased likelihood of window failure. They also found increasing age to be a risk for window failure though that was not the case in our cohort of stroke patients, possibly due to the smaller sample size in the current study.

5.6.6.2 Rationale for Removal of ARI post CEA

One subject with a non-disabling ischaemic stroke was found to have significant ispilateral carotid stenosis, and in keeping with current guidelines underwent CEA within 2 weeks from stroke. It has previously been demonstrated that cerebral autoregulation is impaired in ipsilateral significant carotid artery stenosis[108;127], and moreover that carotid revascularisation (CEA or stenting) results in rapid improvement in cerebral autoregulation approaching pre-operative values on the unaffected side[85]. For this reason the ARI of the subject described above was not included in the data analysis at follow-up, as inclusion of their results may have led to a falsely raised ARI for the group at follow-up. In addition inclusion of these results may have confounded interpretation of follow-up results as it

would be impossible to separate out effects of revascularisation against possible effects of stroke recovery. Carotid revascularisation would not be expected to influence systemic haemodynamics (SBP, DBP, HR) or recovery from stroke in terms of functional or neurological status (NIHSS, mRS, Barthel) and these results for this subject were included in the analysis at follow-up.

Baseline recordings were made as soon as possible following hospital admission, sometimes prior to vascular imaging. It could be argued that the baseline results for this patient should not have been included in the analysis either, as it is not possible to determine the relative contributions of stroke and carotid stenosis to any impairment in dCA. However adjustment of baseline results for significant carotid stenosis was performed, and this did not alter results. ARI results for this patient are shown in table 5.12.

Table 5.12 ARI of patient with significant ipsilateral carotid stenosis, pre and post CEA

ARI	Baseline	2 week follow-up (9 days post CEA)
Affected hemisphere	4.0	5.0
Unaffected hemisphere	4.5	5.8

5.6.6.3 Stroke Severity

The overall stroke population in this study tended to have had minor strokes, as evidenced by their NIHSS and mRS scores. This is likely to be a reflection of the recruitment criteria for the COSSACS study, which required patients to be alert and able to swallow. In fact there is no reason why dysphagic patients should have been excluded from the present study, except for the inclusion of this in the original Ethics approval. Clearly this limits the applicability of these results to patients with more disabling stroke, as they are under-represented in the study population. If this study were to be repeated then all attempts should be made to include patients with more severe stroke.

5.6.6.4 Separate Analysis of Ischaemic Stroke and ICH

It has been demonstrated by several authors that dCA is impaired following acute ischaemic stroke[59;83;84], however there is less work available regarding the potential effects of ICH on dCA, and the mechanisms involved may differ. Thus in order to avoid further heterogeneity in the stroke group ischaemic stroke and ICH were analysed separately. It had been hoped initially that these two groups could be compared, however small numbers with ICH (n=3) prohibit statistical analysis. ICH is a less common cause of acute stroke than cerebral ischaemia, so it is perhaps unsurprising that fewer patients with ICH were recruited.

5.6.7 Summary

ARI was significantly lower in the affected hemisphere at baseline in ischaemic stroke patients compared to age- sex- and BMI-balanced controls, and was significantly lower in the affected compared to the unaffected hemisphere at baseline. At follow-up there was no significant difference in ARI between ischaemic stroke patients and controls. There was significant neurological and functional recovery in the stroke group, but change in ARI did not appear to correlate with neurological and functional recovery. ARI appeared to be lower in the affected hemisphere at follow-up in the PACS/TACS group compared to the LACS group, but following adjustment for multiple testing this was not statistically significant. No significant effect was found for small vessel versus large vessel ischaemic stroke, but the numbers in each group were small.

Chapter 6: Dynamic cerebral autoregulation following acute ischaemic stroke: comparison of patients with and without a history of hypertension

Aim : To determine whether dCA after acute stroke is affected by a prior history of hypertension

This is a sub-study of the work described in detail in Chapter 5. This Chapter looks specifically at ischaemic stroke patients in terms of whether or not they had a prior history of hypertension treated with conventional antihypertensive agents.

6.1 Subjects

Subjects were identified and studied as described in Chapter 5.

6.2 Results

Of 39 patients with acute ischaemic stroke 26 patients were receiving regular antihypertensive therapy prior to their stroke, while the remaining 13 were antihypertensive naïve. The demographics of the two groups are shown in table 6.1. The two groups did not differ significantly at baseline in terms of age, sex, smoking status, SBP, DBP, HR, diabetes, incidence of carotid stenosis, or stroke severity. There were significantly more patients with a history of previous stroke and significantly more on statin therapy prior to stroke in the previously hypertensive group compared to those with no clear history of hypertension.

Table 6.1 Baseline characteristics of patients by prior antihypertensive therapy

	Baseline		P-value between groups†
	History of Hypertension	No history of hypertension	
Age	69 (±10; 48-91)	69 (±10; 49-84)	P=0.93
Sex (M:F)	17:9	9:4	P=1.0
SBP (mmHg)	151 (±24; 100-188)	145 (±17; 115-188)	P=0.44
DBP (mmHg)	81 (±13; 55-105)	83 (±12; 60-140)	P=0.99
HR (bpm)	69 (±13; 48-97)	68 (±7, 56-79)	P=0.84
NIHSS	4 (2-7; 0-11)	3 (1-3; 0-15)	P=0.23
mRS	3 (2-4; 0-4)	3 (2-3; 0-5)	P=0.34
Barthel	14 (10-19; 4-20	17 (16-20; 4-30)	P=0.13
BMI (kg/m^2)	27 (±5; 17-39)	27 (±4, 21-35)	P=0.63
Smoker (No:Ex:Yes)	7:16:3	3:6:4	P=0.38
DM (No:Yes)	22:4	12:1	P=0.65
Statin (No:Yes)	14:12	11:2	P=0.04
Ipsilateral Carotid Stenosis ≥70% (no: yes: occluded, n/a)	20:2:1:3	11:1:0:1	P=0.88
Previous Stroke	10	1	P=0.04

Normally distributed variables described as Mean (±SD; range); Non-normally distributed variables described as median (IQR; range)

† differences between categorical variables tested using Chi^2 or Fisher's exact test (age, smoker, DM), t-test used for normally distributed continuous variables (SBP, DBP, HR, BMI), Mann-Whitney U-test used for non-normally distributed continuous variables (NIHSS, mRS, Barthel)

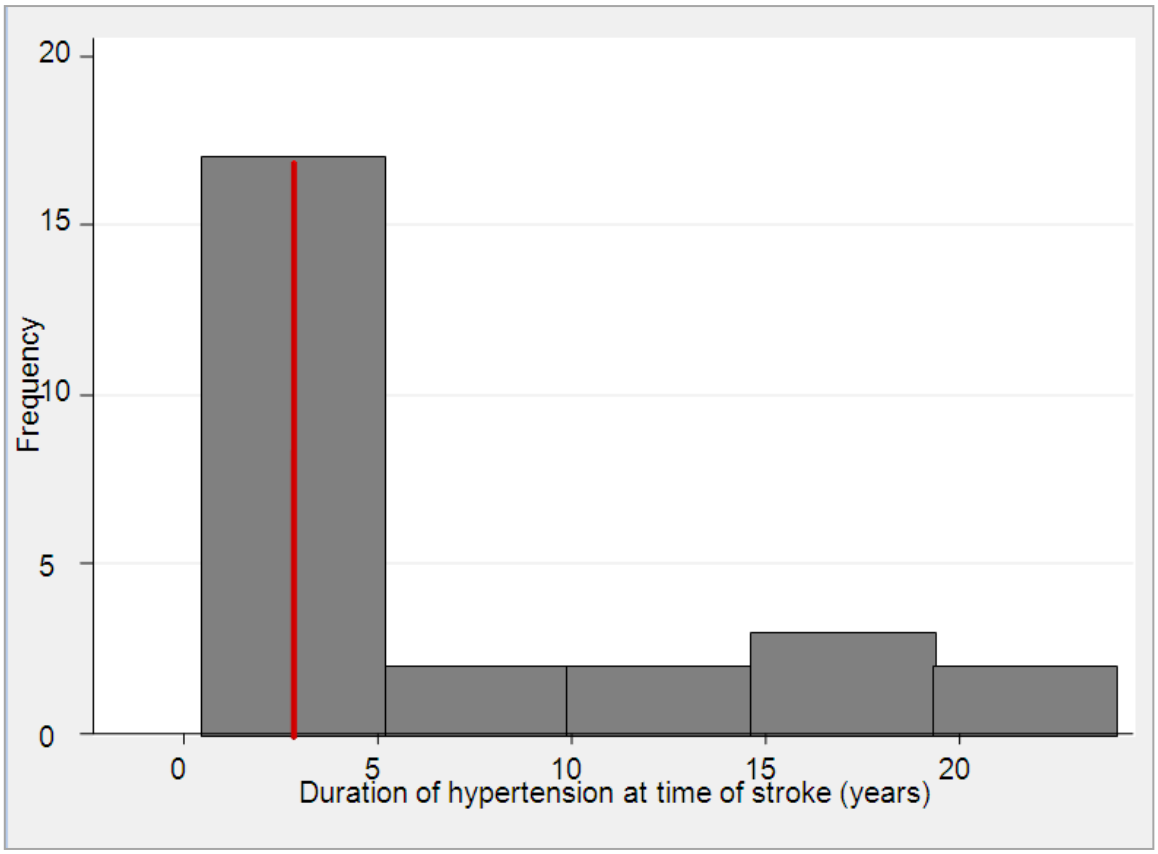
Anithypertensive agent use in those with a history of hypertension varied widely; nine patients were on a single agent, nine were on two agents, and the remaining eight were on three or more agents. The classes of medication used are summarised in table 6.2.

In the treated hypertensive group, median time from onset of hypertension was 42.5 months, (IQR 17.3-111, range 6-288), as shown in figure 6.1.

Table 6.2 Antihypertensive agents in the treated hypertensive group

Treatment Class		Number of Patients
ACEi		2
A2RB		1
α blocker		0
β blocker		2
Calcium channel blocker (CCB)		1
Thiazide Diuretic		3
ACEi + CCB		3
CCB + β blocker		2
CCB + Diuretic		1
ACEi + β blocker		1
A2RB + β blocker		1
ACEi + Diuretic		1
Combination:	three agents	5
	four agents	2
	five agents	1

Figure 6.1 Duration of antihypertensive therapy in the antihypertensive treated group at time of stroke



Median Duration = 3.5 years (red line)

6.2.1 Cerebral Autoregulation after acute stroke: treated hypertensives versus no history of hypertension

ARI was lower in both the affected and unaffected hemispheres in those with a history of hypertension, though the difference was not statistically significant. The ARI results for the two groups at baseline by affected and unaffected hemisphere are shown in table 6.3.

Table 6.3 ARI by prior antihypertensive treatment

	History of hypertension	No history of hypertension	Mean Difference (95% CI)	p-value difference between the two groups
Mean ARI Baseline Affected Hemisphere	4.1	5.2	1.1 (-0.2, 2.4) *Adjusted mean difference† 1.4 (-0.5,2.8)*	P=0.10 *Adjusted† P=0.2*
Mean ARI Baseline Unaffected Hemisphere	4.9	5.8	0.9 (-0.1, 1.8) *Adjusted mean difference†1.8 (- 0.1,2.1)*	P=0.07 (-0.1,1.8) *Adjusted P=0.08*

† Adjusted for statin use and history of previous stroke

6.2.2 Change from Baseline to Follow-up

Five patients were lost to follow-up. As described above patients who were receiving regular antihypertensive therapy prior to stroke were considered as a 'treated' group, and remained in this group at follow-up regardless of changes to treatment following hospital admission. Of those lost to follow-up three were in the previously treated group, while two were antihypertensive naïve. Over the two weeks five patients in the previously treated group had their antihypertensive medication stopped; no-one in the antihypertensive naïve group had been started on antihypertensive therapy by follow-up. Changes in BP and HR from baseline to follow-up are shown in table 6.4. SBP fell in both groups, but remained higher in the antihypertensive treated group (though these differences were not statistically significant). DBP and HR were similar at baseline and follow-up.

There was no significant difference between the groups in terms or neurological or functional recovery at two week follow-up; change in NIHSS, mRS and Barthel from baseline to follow-up are shown in table 6.5.

Table 6.4 Change in haemodynamic parameters from baseline to follow-up, by antihypertensive treatment

	Treated hypertensive		P-value change from baseline	No history of hypertension		P-value change from baseline	P-value between groups at follow-up
	baseline mean (±SD)	follow-up		baseline	follow-up		
SBP (mmHg)	151 (24)	146 (17)	P=0.46	145 (19)	136 (14)	P=0.18	P=0.07
DBP (mmHg)	81 (13)	79 (11)	P=0.46	81 (12)	78 (6)	P=0.47	P= 0.93
HR (bpm)	69 (13)	69 (16)	P=0.90	68 (7)	66 (8)	P=0.69	P=0.61

Table 6.5 Change in Neurological and Functional status from baseline to follow-up, by antihypertensive treatment

		Baseline Median (IQR; range)	Follow-up	p-value treated vs no history of hypertension at follow-up
Treated hypertensive	NIHSS	4 (2-7; 0-11)	1 (1-3; 0-8)	-
	mRS	3 (2-4; 0-4)	2 (1-3; 0-4)	-
	Barthel	14 (10-19; 4-20)	19 (16-20; 7-20)	-
No history of hypertension	NIHSS	3 (1-3; 0-15)	1 (0-2; 0-6)	P=0.38
	mRS	3 (2-3; 0-5)	1 (1-3; 0-4)	P=0.38
	Barthel	17 (16-20; 4-30)	20 (19-20; 9-20)	P=0.19

As shown in table 6.6 ARI at follow-up in the affected hemisphere was 4.5 in the treated group, compared to 6.1 in the group previously not receiving antihypertensives, this was statistically significant (p=0.03). In the unaffected hemisphere ARI was again lower in the treated group, 4.9, than in the previously normotensive group, 5.8, but this did not reach statistical significance (p=0.11).

The forward selection method was used to identify potentially significant covariates. Those entered into the model were SBP, DBP, statin use prior to stroke, statin use at time of follow-up, previous stroke, and carotid stenosis. Only statin use at the time of follow-up was a significant covariate, and after adjustment for this the difference between ARI in the affected hemisphere in the treated vs previously normotensive groups was no longer statistically significant. ARI results at follow-up by group are summarised in table 6.6.

Table 6.6 ARI at Follow-up; Treated vs Antihypertensive Naïve

	History of hypertension	No history of hypertension	Mean Difference (95% CI)	p-value difference between the two groups
Mean ARI Follow-up Affected Hemisphere	4.5	6.1	1.5 (0.2, 2.8) *Adjusted†1.0 (-0.7,2.7)*	P=0.03 *P=0.2*
Mean ARI Follow-up Unaffected Hemisphere	4.9	5.8	0.9 (-0.2, 2.1)	P=0.11

†Adjusted for statin use at time of follow-up

6.3 Discussion

Reduction in dCA was most marked in patients with a history of treated hypertension compared to the previously normotensive group. This was observed in both affected and unaffected hemispheres both at baseline and at follow-up, though results were statistically significant only in the affected hemisphere at follow-up and did not remain significant following adjustment for potentially significant covariates. The pattern of reduced ARI is consistent in both hemispheres at both time points in the treated hypertensive group compared to the previously normotensive group, as well as being physiologically plausible, though as the differences in ARI between the two groups are not statistically significant it is possible that the observed difference is an effect of chance.

6.3.1 Possible mechanisms for reduced dCA in hypertensive patients

6.3.1.1 Antihypertensive Therapy

The observed results may be due to the antihypertensive agents used. In the current study however the small numbers taking only one class of agent and the relatively high proportion of people on combinations of agents (65% were receiving two or more agents) makes statistical analysis very difficult. As mentioned in the introduction most of the current evidence surrounding the effects of individual antihypertensive agents on cerebral autoregulation comes from small studies[132-135] using heterogeneous methods to assess dCA, thus making their interpretation and comparison difficult.

It is also possible that the relatively low ARI values seen in the treated hypertensive group were due to the effects of BP lowering per se, rather than the individual agents used. As mentioned in Chapter 5 CPP=MAP-ICP. If a rise in ICP occurs then a compensatory rise in MAP will maintain CPP and hence CBF. If however antihypertensive therapy prevents a rise in MAP then CPP will fall, CBF will fall, and autoregulatory mechanisms may fail to compensate adequately.

6.3.1.2 Chronic Hypertension

The two groups compared in this study were a hypertensive group and group with no history of hypertension. The observed difference in dCA between groups may be directly due to the effects of hypertension on dCA, in that they may reflect an inability of people with chronic

hypertension to withstand a further insult to CBF at lower MAP because of a right shift of autoregulatory curve (see Figure 1.4). The lack of significant difference in SBP acutely post-stroke does not necessarily reflect differences in the steady-state BP between groups, as a rise in BP following acute stroke is well-recognised regardless of prior antihypertensive treatment[136]. However at 2 week follow-up the SBP in the treated group had fallen from 151 to 146mmHg, while in the antihypertensive naïve group it had fallen from 145 to 136 mmHg, and the difference in SBP between treated and naïve groups at follow-up reached borderline statistical significance (P=0.07).

6.3.2 Change from baseline to follow-up

As described in Chapter 5 ARI for the patient group increased in the affected hemisphere by 2 week follow-up, and was no longer significantly different from control. This, along with previous work on dCA at different time points following acute ischaemic stroke, raises the possibility of a dynamic pattern of autoregulatory impairment following acute stroke, with an initial fall and subsequent recovery. This has implications for those patients already receiving antihypertensive therapy prior to stroke, as the results of this study suggest this group demonstrate relatively worse dCA; previous work suggests that at least 40% of patients with acute stroke are already receiving antihypertensive therapy[137]. Thus it raises the question of whether continuing or stopping antihypertensive therapy will influence the change in dCA observed, and furthermore what the clinical significance of this may be.

6.3.3 Previous work

There is little published work which looks at the effects of a prior history of hypertension or prior antihypertensive therapy on CA following acute stroke. Dawson et al studied dCA in 54 patients with acute stroke, of whom 15 had previously been receiving antihypertensive therapy. They found no difference in ARI between the groups, nor did they observe any difference in BP between the two groups (mean SBP at baseline 163mmHg in both groups)[121]. It is worth noting that since their study was done the BP threshold for diagnosing and treating hypertension have fallen and the extent to which BP is lowered has increased[138].

6.4 Definition of Groups

As discussed patients were defined as being either on antihypertensive treatment or antihypertensive naive. The major limitation of this is that hypertension may be silent for many years prior to diagnosis, and some of the patients in the antihypertensive naive group may have had undiagnosed hypertension. A true comparison between hypertensive and normotensive individuals presenting with acute stroke would be challenging to design, but the inclusion of a patient group with hypertension alone (without stroke) may have helped answer questions about the relative contributions of hypertension per se and stroke to the dCA impairment that was demonstrated.

6.5 Summary

There was a trend towards lower ARI in the treated hypertensive group compared to those without a history of hypertension in both the affected and unaffected hemispheres at baseline and at follow-up. The difference was statistically significant in the affected hemisphere at follow-up, though this did not persist after adjustment for significant covariates (statin use at follow-up).

Chapter 7: Conclusions

7.1 Reproducibility of dCA

This study is the first to look at reliability of ARI derived from spontaneous fluctuations of BP. This method clearly has advantages for the study of acutely ill patients where it may be undesirable or impossible to perform haemodynamic manoeuvres such as thigh cuffs, lower body negative pressure or carotid artery compression. This study demonstrated that mean CBFV is highly reproducible and that serial ARI measurements are of acceptable reliability for clinical study if strict data collection and analysis protocols are followed. These results help to answer questions regarding the reproducibility of assessment of cerebral autoregulation using spontaneous fluctuations of BP, and in addition they help to address the issue of sample size calculation for future clinical studies using this method. It is estimated that to accurately detect a difference in ARI of ≥1 a sample size of 45 subjects per group would be required, while to detect a difference of ≥2 only 11 per group would be required. The group studied were relatively young healthy adults, and it may be that different age groups (e.g. neonates or the very old) exhibit wider variability in dCA, this should be considered before using the current results to plan sample size for studies in these groups.

If this study was to be performed again a simpler test re-test approach may be reasonable, though a larger cohort of subjects should be included. In terms of generalisability the results of this study are applicable to a young healthy group. As most work concerning cerebral autoregulation involves examining the effects of disease states, attempts should perhaps be made to repeat the study in a more representative study population, for example an older group or a group with hypertension.

7.2 Changes in cerebral autoregulation over ten years

Recordings of CBFV and BP in a group of subjects after a time interval of 10 years have shown a small but significant decline in dCA, which may have been missed by previous studies of the effects of ageing on dCA which used a different design. Future research in this area should focus on the influence of advanced age on the loss of dynamic CA and whether this decline can be influenced by risk factors for cerebrovascular disease.

The findings of this study are at odds with previous studies examining the effects of ageing on cerebral autoregulation. This may reflect the study design, which allows comparison between the same subjects after an interval of time. However in view of the small sample size it is possible that this represents a chance finding.

The study would have benefited from further measurement of dCA within the study period, for example annual measurements, to better examine a trend. Furthermore there have been some changes in methodology since the first study was performed, including the routine collection of brachial BP with a cuff, and the recording of height, weight and BMI. As both BP and BMI may influence dCA it would have been useful to have these data available from 1998.

As in the previous study, the data collected are for a relatively young, healthy population, and caution should be exercised in the interpretation of results. While the study looks at an interval of 10 years healthy ageing it does not provide direct information on vascular risk factors or vascular ageing and potential effects on cerebral autoregulation. These are areas where further study would be very useful to try and quantify the relative contributions of age per se and other vascular risk factors to any change in cerebral autoregulation.

7.3 dCA following acute stroke and early recovery

ARI was significantly lower in the affected hemisphere at baseline in ischaemic stroke patients compared to age- sex- and BMI-balanced controls, and was significantly lower in the affected compared to the unaffected hemisphere at baseline. At follow-up the ARI in the affected hemisphere remained low compared to controls but this difference was no longer statistically significant. Due to low numbers comparison between ischaemic stroke and intracerebral haemorrhage were not possible.

These results are consistent with the majority of studies in the published literature, and suggest a stroke-specific insult to dCA, with the current study suggesting that this may demonstrate some recovery with time. It remains unclear however whether one method of measuring dCA is more accurate at detecting impairment in this patient group. In addition it remains unclear whether impairment in dCA following acute ischaemic stroke is of prognostic significance, and whether it may be a therapeutic target.

A limitation of the study is the relatively minor stroke severity of the study population. This is probably attributable to the study design, which began as a sub-study of the on-going COSSACS study. While the exclusion of dysphagic patients was necessary for the COSSACS study there was no other reason for excluding them from the study of cerebral autoregulation, and future studies should endevour to include patients with more severe stroke.

A further potential limitation is the lack of MRI or TOAST classification, both of which may have helped with stroke classification, for example when trying to identify differences between large and small artery stroke disease.

Patients with atrial fibrillation were also excluded because the data analysis techniques rely on a measure of change in CBFV relative to each cardiac cycle, as measured from the R-R interval, and this is inaccurate when the ECG trace is irregular and gives rise to false estimates of dCA. This limitation is common to other techniques used to model dCA. Atrial fibrillation is a common cause of ischaemic stroke, and the use of different mathematical modeling techniques to permit the study of dCA in this group should be explored further.

7.4 Dynamic cerebral autoregulation following acute ischaemic stroke: comparison of treated hypertensive patients with antihypertensive naïve patients

There was a trend towards lower ARI in the treated hypertensive group compared to those without a history of hypertension in both the affected and unaffected hemispheres at baseline and at follow-up. The difference was statistically significant in the affected hemisphere at follow-up, though this did not persist after adjustment for significant covariates (statin use at follow-up). These findings should not detract from the evidence-based benefits of antihypertensive therapy. Future work looking at the effects of individual antihypertensive agents on dCA would further our understanding of these findings and may assist in the choice of antihypertensive for particular patients following acute stroke.

This study emphasises the importance of hypertension as a potentially major factor in determining the efficiency of dCA. The study would have benefited from a second control

group of subjects with hypertension but without stroke disease, in order to try and determine the relative contributions of stroke and hypertension to impairment in dCA. The study also raises questions regarding the mechanism of stroke in patients with hypertension. It is impossible to know, for example, whether dCA was impaired in these patients before their stroke.

In conclusion the findings of this Thesis contribute to current understanding of cerebral haemodynamics; their measurement, the extent to which variability of measurements may influence reproducibility and sample size planning, and the effects of ageing and stroke on cerebral haemodynamics. Future work in this area may benefit from the suggestions which arise as improvements to the present studies. It is hoped that further work in the areas suggested will expand our current understanding of cerebral haemodynamics, and the roles of ageing, hypertension and stroke disease.

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Appendices

Appendix 1: OCSP classification[6]

Patients presenting with a stroke can be classified into the following according to their symptoms and signs:

1. TACS – Total anterior circulation syndrome
2. PACS –Partial anterior circulation syndrome
3. LACS – Lacunar syndrome
4. POCS – Posterior circulation syndrome

If neuroimaging confirms an infarct I for infarct may be substituted for S for syndrome.

Classification depends on 3 main features –

- Unilateral motor or sensory involvement (face/arm/leg)
- Visual involvement - hemianopia or quadrantanopia or visual neglect
- Higher cerebral dysfunction (dysphasia, dyscalculia, visuospatial disorder/inattention/neglect).

Features	**Classification**
All 3 present or Drowsy + unilateral weakness (visual + higher cerebral involvement assumed)	TACS
2 out of 3 present Isolated speech or visual involvement Motor or sensory involvement affecting only one of face/arm/leg	PACS
Motor/Sensory/sensorimotor ≥2 out of face/arm/leg affected Ataxic hemiparesis	LACS
Cerebellar syndrome or brainstem involvement	POCS

Appendix 2: National Institute of Health Stroke Scale (NIHSS)

1a Level of consciousness	0 Alert 1 Not alert but can be woken by voice 2 Not alert but can be woken by pain 3 Cannot be woken
1b Questions *What month is it? How old are you?*	0 Answers both questions correctly 1 Answers 1 question correctly 2 Answers neither question correctly or does not answer
1c Commands *Close your eyes. Make a fist.*	0 Performs both correctly 1 Performs 1 correctly 2 Performs neither correctly or does not perform
2 Gaze *Horizontal gaze*	0 No gaze palsy 1 Partial gaze palsy 2 Complete gaze palsy
3 Visual Fields	0 No visual loss 1 Partial hemianopia 2 Complete hemianopia 3 Bilateral hemianopia (includes cortical blindness)
4 Facial Palsy	0 No facial palsy 1 Minor paralysis, flattened naso-labial fold 2 Major paralysis of lower half of face 3 Paralysis of whole face (on one or both sides)
5a Motor arm: Left 5b Motor arm: Arm	0 Can elevate arm at 90^0 for 10 seconds 1 Drifts, but does not hit bed 2 Some effort against gravity but can't hold or maintain 3 No effort against gravity 4 No movement
6a Motor leg: Left 6b Motor leg: Right	0 Can elevate leg at 30^0 for 5 seconds 1 Drifts, but does not hit bed 2 Some effort against gravity but can't hold or maintain 3 No effort against gravity 4 No movement
7 Limb ataxia	0 No ataxia 1 Present in 1 limb 2 Present in 2 limbs
8 Sensory	0 No sensory loss 1 Mild-moderate sensory loss 2 Total sensory loss
9 Best language	0 No aphasia 1 Mild-moderate aphasia 2 Severe aphasia 3 Mute
10 Dysarthria	0 Normal 1 Mild-moderate dysarthria 2 Severe dysarthria
11 Extinction/Inattention	0 Normal 1 Visual/tactile/spatial inattention 2 Inattention in > 1 modality

Appendix 3: Modified Rankin Scale

Grade	Description
0	No symptoms
1	Minor symptoms, no limitation in lifestyle
2	Minor symptoms, some limitation in lifestyle but does not affect ability to look after self
3	Moderate handicap, symptoms which limit independence or restrict lifestyle. Able to walk 50 yards without assistance
4	Moderately severe handicap, requires significant but not constant assistance
5	Severe handicap, requires constant assistance

A score of 6 may be allocated for patients who have died

Appendix 4: The Barthel Index

Function	Description
Bathing	0 dependent 1 independent (including bath/shower transfers)
Bladder	0 incontinent/catheterised 1 occasional accident 2 continent
Bowels	0 incontinent 1 occasional accident 2 continent
Dressing	0 dependent 1 needs help 2 independent
Feeding	0 unable 1 needs help 2 independent
Grooming	0 needs help with personal care 1 independent
Mobility	0 immobile 1 wheelchair independent 2 walks with help of one person 3 independent
Stairs	0 unable 1 needs help (verbal, physical, aid) 2 independent up and down
Toilet use	0 dependent 1 needs some help 2 independent
Transfers	0 unable, no sitting balance 1 major help (physical, one or two people) 2 minor help (verbal or physical) 3 independent

Appendix 5: Publications arising from Thesis

Original Article: Reliability of dynamic cerebral autoregulation measurement using spontaneous fluctuations in blood pressure. Clinical Science (2009) 166:513-20. **Fiona G. Brodie**, Emily R. Atkins, Thompson G. Robinson, Ronney B. Panerai

Original Article: Longterm changes in dynamic cerebral autoregulation: a 10 year follow up study. Clinical Physiology and Functional Imaging (2009) doi 10.1111/j.1475-097x.2009.00880.x. **Fiona G. Brodie**, Ronney B. Panerai, Stephanie Foster, David H. Evans, Thompson G. Robinson

Abstract (poster) European Stroke Conference 2009: Dynamic cerebral autoregulation is impaired acutely following ischaemic stroke but demonstrates early recovery. Cerebrovascular Diseases (2009) 27 (Supplement 6) 210 (15) doi 10.1159/000221781. **F.G. Brodie**, R.B. Panerai, T.G. Robinson

Abstract (platform) European Stroke Conference 2009: Dynamic cerebral autoregulation is impaired in treated hypertensive patients compared to antihypertensive naïve patients following acute ischaemic stroke. Cerebrovascular Diseases (2009) 27 (Supplement 5) I-XXVII doi 10.1159/000221784. **F.G. Brodie**, R.B. Panerai, T.G. Robinson

Abstract (poster) European Stroke Conference 2008: Cerebral blood flow velocity and cerebral autoregulation following intracerebral haemorrhage in a patient with ipsilateral carotid artery occlusion. Cerebrovascular Diseases (2008) 25 (Supplement 2) 118 (52). **F.G. Brodie**, E.R. Atkins, R.B. Panerai, T.G. Robinson