UNIVERSITY OF LEICESTER

# The Impact of Cerebral Perfusion Strategies on Cerebral Haemodynamics in Acute Ischaemic Stroke

**Thesis submitted for the degree of**

**Doctor of Philosophy**

by

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# Abstract

Title: The Impact of Cerebral Perfusion Strategies on Cerebral Haemodynamics in Acute Ischaemic Stroke

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Background:

Ischaemic stroke (IS) is a devastating neurological disease. It is a significant global public health problem, placing enormous burden on patients, relatives, the health care system, and society as a whole. It is generally accepted that cerebral haemodynamics, and associated parameters, are impaired following ischaemic stroke (IS). Recently, a wide range of cerebral perfusion strategies have been introduced. These aim to improve perfusion to the ischaemic penumbra and to restore cerebral blood flow, thereby enhancing neurological and functional recovery. Understanding how these strategies affect cerebral haemodynamics may give us the necessary understanding to optimise individualised stroke management, aiming to prevent secondary perfusion-related injury and to minimise its potential devastating impacts.

Objectives:

This thesis aimed to determine how non-pharmacological (head positioning changes) and pharmacological (pressor therapy and intravenous thrombolysis) affect cerebral haemodynamic and associated parameters, specifically cerebral autoregulation, in acute ischaemic stroke (AIS) patients, and whether such changes are associated with neurological and functional improvements.

Methods:

This dissertation presents a systematic review and four inter-related studies, as follows:

1) The systematic review synthesises findings from twenty studies which examined the feasibility, safety and clinical effectiveness of using pressor agents as induced hypertension therapy in AIS (Chapter 3);

2) A reproducibility study on how gradual changes in head positioning (GHP) affect cerebrovascular physiology in healthy older subjects (Chapter 5);

3) A prospective observational study on how GHP affect systemic and cerebral haemodynamic parameters in healthy controls and patients with AIS, up to 90 days post stroke symptom onset (Chapter 6);

4) A prospective observational study on using rapid head positioning (RHP) as a new dynamic cerebral autoregulation (dCA) paradigm, in both healthy controls and patients with AIS (Chapter 7);

5) A feasibility study evaluating changes in systemic and cerebral haemodynamic parameters during, and immediately after, intravenous thrombolysis (IVT) and up to 90 days post stroke symptom onset in AIS patients who received IVT (Chapter 8).

Conclusions:

This PhD thesis carefully scrutinised various pharmacological and non-pharmacological perfusion strategies used in AIS, their impact on cerebral haemodynamics and associated parameters change. It also demonstrated beautifully how AIS patients act differently when compare to controls in different paradigm measurements. The heterogeneous nature of CA impairment and recovery, and the time course of CA changes in AIS, provide

valuable information in facilitating personalised post-stroke recovery plan. Further large-scale, prospective studies are needed in order to translate such important information into day-to-day clinical setting.

# Acknowledgements

*'When one door closes another door opens; but we so often look so long and so regretfully upon the closed door, that we do not see the ones which open for us.'*

*Alexander Graham Bell, 1903*

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*This thesis is dedicated to everyone who has ever suffered a stroke.*

# Contributorship

The overall organisation, and administration of the research studies included in this thesis was performed by the author with the advice and guidance of Professor Thompson Robinson, Professor Ronney Panerai and Dr Victoria Haunton, University of Leicester. Additional contributors for each chapter are listed below.

Chapter 3: The systematic review protocol, literature search, data extraction, data analysis and writing up were undertaken by the author. Dr Nikil Patel, post-doctoral researcher at the University of Leicester, was the second reviewer for the systematic review. Professor Thompson Robinson, Professor Ronney Panerai and Dr Victoria Haunton provided critical review of the study report.

Chapters 5 and 7: The study design, recruitment, transcranial Doppler measurements, and write up were performed by the author with guidance from Professor Thompson Robinson, Professor Ronney Panerai and Dr Victoria Haunton. The data analysis software was written and developed by Professor Ronney Panerai and the Medical Physics Group, University of Leicester. All data analysis was performed by the author using this software. Professor Ronney Panerai regularly reviewed the quality of the data collection, the subsequent analysis, and provided advice and support if needed. All statistical analyses were performed by the author.

Chapter 6: The study design, recruitment, transcranial Doppler measurement, and write up were performed by the author with guidance from Professor Thompson Robinson, Professor Ronney Panerai and Dr Victoria Haunton. The data analysis software was written and developed by Professor Ronney Panerai and the Medical Physics Group, University of Leicester. All data analysis was performed by the author using this software. Professor Ronney Panerai regularly reviewed the quality of the data collection, the

subsequent analysis and provided advice and support if needed. Dr Mintu Nath provided support and assistance for the statistical analysis in this result chapter.

Chapter 8: The study design, transcranial Doppler measurement, and write up were performed by the author with guidance from Professor Thompson Robinson, Professor Ronney Panerai and Dr Victoria Haunton. The recruitment of all subjects was undertaken by the author, with the assistance of Dr Osian Llwyd. The data analysis software was written and developed by Professor Ronney Panerai and the Medical Physics Group, University of Leicester. All data analysis was performed by the author using this software. Professor Ronney Panerai regularly reviewed the data collection, the subsequent analysis and provided guidance if needed. The statistical analysis was performed by the author.

The author confirms that unless otherwise acknowledged or referenced all work in this thesis is original and her own work.

# List of Publications

This is a current list (26th November 2020) of manuscripts, abstracts and presentation which have resulted from work performed as part of the thesis.

**Work published in peer-reviewed journals**

- **Lam MY**, Haunton VJ, Robinson TG, Panerai RB. Does gradual change in head positioning affect cerebrovascular physiology? Physiological Reports. 2018; 6(3). doi: 10.14814/phy2.13603.

- **Lam MY**, Haunton VJ, Robinson TG, Panerai RB. Dynamic cerebral autoregulation measurement using rapid changes in head positioning: experiences in acute ischaemic stroke and healthy controls populations. American Journal of Physiology – Heart and Circulatory Physiology. 2019; 316(3); H673-H683. doi: 10.1152/ajpheart.00550.2018

- **Lam MY**, Haunton VJ, Panerai RB, Robinson TG. Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study. PLoS One. 2020; 15(9). doi: 10.1371/journal.pone.0238620

- **Lam MY**, Haunton VJ, Nath M, Panerai RB, Robinson TG. The effect of head positioning on cerebral haemodynamics: experiences in mild ischaemic stroke. *Journal of the Neurological Sciences. 2020; 419;117201*

- **Lam MY**, Haunton VJ, Panerai RB, Robinson TG. Pressor therapy in acute ischaemic stroke – a systematic review update. *(In preparation)*

## Conference abstracts (oral presentations)

- **Lam MY**, Haunton VJ, Robinson TG, Panerai RB. Rapid changes in head positioning: a new paradigm of dynamic cerebral autoregulation? Experience in acute ischaemic stroke and healthy subjects. 8th International Meeting on Cerebral Haemodynamic Regulation (CARNet), Oxford, UK, 18th to 19th June 2018.

- **Lam MY**, Haunton VJ, Nath M, Panerai RB, Robinson TG. Time varying cerebral autoregulation in response to gradual transition in head positioning: experiences in acute ischaemic stroke and healthy control populations. 13th UK Stroke Forum Conference (UKSF), Telford, UK, 4th to 6th December 2018.

## Conference abstracts (poster presentations)

- **Lam MY**, Haunton VJ, Robinson TG, Panerai RB. Feasibility of dynamic cerebral autoregulation testing using transient changes in head positioning. 6th International Meeting on Cerebral Haemodynamic Regulation (CARNet), Boston, USA, 28th June to 2nd July 2016.

- **Lam MY**, Haunton VJ, Robinson TG, Panerai RB. The effects of head positioning on beat-to-beat cerebral haemodynamics in healthy controls. 6th International Meeting on Cerebral Haemodynamic Regulation (CARNet), Boston, USA, 28th June to 2nd July 2016.

- **Lam MY**, Haunton VJ, Robinson TG, Panerai RB. The effects of head positioning on beat-to-beat cerebral haemodynamics in healthy controls – a reproducibility study. 7th International Meeting on Cerebral Haemodynamic Regulation (CARNet), Berlin, Germany, 1st April 2017.

- **Lam MY**, Haunton VJ, Panerai RB, Robinson TG. Head position affects cerebral autoregulation in ischaemic stroke. 4th European Stroke Organisation Conference (ESOC), Gothenburg, Sweden, 16th to 18th May 2018.

- **Lam MY**, Haunton VJ, Panerai RB, Robinson TG. Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study. 5th European Stroke Organisation Conference (ESOC), Milan, Italy, 22nd to 24th May 2019.

- **Lam MY**, Haunton VJ, Robinson TG, Panerai RB. Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study. 9th International Meeting on Cerebral Haemodynamic Regulation (CARNet), Leuven, Belgium, 12th to 13th September 2019
- **Lam MY**, Haunton VJ, Robinson TG, Panerai RB. Pressor Therapy on Acute Ischaemic Stroke – A Systematic Review Update. ESO-WSO Joint Stroke Conference, 7th to 9th November 2020

## Co-author publications

- Intharakham K, Panerai R, Katsogridakis E, **Lam MY**, Llwyd O, Salinet ASM, Nogueira R, Haunton VJ, Robinson TG. Can we use short recording for assessment of dynamic cerebral autoregulation? A sensitivity analysis study in acute ischaemic stroke and healthy subjects. Physiological Measurement. 2019; 40(8). doi: 10.1088/1361-6579/ab39d3.

- Llwyd O, Haunton VJ, Salinet ASM, Nath M, **Lam MY**, Saeed NP, Brodie F, Robinson TG, Panerai RB. Can we assess dynamic cerebral autoregulation in stroke patients with high rates of cardiac ectopicity? Medical & Biological Engineering & Computing. 2019; doi: 10.1007/s11517-019-02064-0.

- Llwyd O, Salinet ASM, Panerai RB, **Lam MY**, Saeed NP, Brodie F, Bor-Seng-Shu E, Robinson TG, Nogueira RC. Cerebral Haemodynamics following acute ischaemic stroke: effects of stroke severity and stroke subtype. Cerebrovascular Disease Extra. 2018;8(2). doi: 10.1159/000487514.

- Nogueira R, **Lam MY**, Llwyd O, Salinet ASM, Bor-Seng-Shu E, Panerai RB, Robinson TG. Cerebral autoregulation and response to intravenous thrombolysis for acute ischaemic stroke. Scientific Reports. 2020; doi:10.1038/s41598-020-67404-9

- Sands E, Wong L, **Lam MY**, Panerai RB, Robinson TG, Minhas JS. The effects of gradual change in head positioning on the relationship between systemic and cerebral haemodynamic parameters in healthy controls and acute ischaemic stroke patients. Brain Sciences. 2020; 10(9) doi: 10.3390/brainsci10090582

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# List of Abbreviations

| | |
|---|---|
| 20-HETE | 20-Hydroxy-Eicosatetraenoic Acid |
| $^{99m}$TC-HMPAO | Technitium-99m and hexamethylpropyleneamine oxime |
| $^{99m}$TC-ECD | Technitium-99m and ethyl cysteinate dimer |
| AA | Arachidonic Acid |
| ABP | Arterial Blood Pressure |
| ACA | Anterior Cerebral Artery |
| AF | Atrial Fibrillation |
| AH | Affected Hemisphere |
| AHA | American Heart Association |
| AIC | Akaike Information Criterion |
| AIS | Acute Ischaemic Stroke |
| ARI | Autoregulation Index |
| ASA | American Stroke Association |
| ASL | Arterial Spin Labelling |
| ASPECTS | Alberta Stroke Programme Early CT Score |
| ATP | Adenosine Triphosphate |

| | |
|---|---|
| AUC | Area Under The Curve |
| AVERT | A Very Early Rehabilitation Trial |
| BAO | Basilar Artery Occlusion |
| BBB | Blood Brain Barrier |
| BIC | Bayesian Information Criterion |
| BMI | Body Mass Index |
| BOLD | Blood Oxygenation Level Dependent |
| BP | Blood Pressure |
| BPV | Blood Pressure Variability |
| CA | Cerebral Autoregulation |
| CADASIL | Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy |
| CARASIL | Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leucoencephalopathy |
| CARNet | Cerebral Autoregulation Research Network |
| CAS | Carotid Artery Stenting |
| $Ca^{2+}$ | Calcium ion |
| CBF | Cerebral Blood Flow |

| | |
|---|---|
| CBV | Cerebral Blood Velocity |
| CCS | Causative Classification of Stroke |
| cGMP | Cyclic Guanine Monophosphate |
| CGRP | Calcitonin Gene-related peptide |
| CHANCE | Clopidogrel in High Risk Patients with Acute Non-disabling Cerebrovascular Events |
| CLOTBUST-HF | Combined Lysis of Thrombus in Brain Ischaemia with Transcranial Ultrasound and Systemic T-PA-Hands-Free |
| CO | Cardiac Output |
| $CO_2$ | Carbon Dioxide |
| CNS | Central Nervous System |
| CPP | Cerebral Perfusion Pressure |
| CrCP | Critical Closing Pressure |
| CS | Conscious Sedation |
| CSA | Cross Sectional Area |
| CT | Computed Tomography |
| CTA | Computed Tomography Angiography |

| | |
|---|---|
| CVC | Central Venous Catheter |
| CVP | Cerebral Venous Pressure |
| CVRea | Cerebrovascular Reactivity |
| CVR | Cerebrovascular Resistance |
| CVRi | Cerebrovascular Resistance Index |
| DBP | Diastolic Blood Pressure |
| DALYs | Disability Adjusted Life Years |
| dCA | Dynamic Cerebral Autoregulation |
| DH | Dominant Hemisphere |
| DOACs | Direct Oral Anticoagulants |
| DOH | Department of Health |
| DSC | Dynamic Susceptibility Contrast |
| ECG | Electrocardiogram |
| ECP | External Counterpulsation |
| ECASS | European Co-operative Acute Stroke Study |
| ED | Emergency Department |
| EET | Epoxyeicosotrienoic |
| ESO | European Stroke Organisation |

| | |
|---|---|
| ESUS | Embolic Stroke of Undetermined Source |
| $ETCO_2$ | End Tidal Carbon Dioxide |
| FFT | Fast Fourier Transform |
| FINAPRES | FINger Arterial PRESsure |
| fMRI | functional Magnetic Resonance Imaging |
| FN | False Negative |
| FP | False Positive |
| GA | General Anaesthesia |
| GHP | Gradual Head Positioning |
| $H^+$ | Hydrogen Ion |
| HASU | Hyperacute Stroke Unit |
| HeadPosT | Head Position in Stroke Trial |
| HF | High Frequency |
| HR | Heart Rate |
| HUT | Head-Up Tilt |
| IA | Intra-arterial |
| IAT | Intra-arterial Thrombolysis |
| ICH | Intracerebral Haemorrhage |

| | |
|---|---|
| ICP | Intracranial Pressure |
| IH | Induced Hypertension |
| IS | Ischaemic Stroke |
| IST | International Stroke Trial |
| ITU | Intensive Treatment Unit |
| IV | Intravenous |
| IVT | Intravenous Thrombolysis |
| $K^+$ | Potassium ion |
| LAC | Lacunar Circulation |
| LF | Low Frequency |
| LVO | Large Vessel Occlusion |
| MAP | Mean Arterial Pressure |
| MCA | Middle Cerebral Artery |
| MELAS | Mitochrondrial Myopathy, Encephalopathy, Lactacidosis and Stroke |
| MELT | The Middle Cerebral Artery Embolism Local Fibrinolysis Intervention Trial |
| MeSH | Medical Subjects Headings |

| | |
|---|---|
| MRA | Magnetic Resonance Angiography |
| MRI | Magnetic Resonance Imaging |
| mRS | Modified Rankin Scale |
| MT | Mechanical Thrombectomy |
| MTT | Mean Transit Time |
| Mx | Mean Velocity Index |
| NAH | Non Affected Hemisphere |
| NDH | Non Dominant Hemisphere |
| NIHSS | National Institutes of Health Stroke Scale |
| NINDS | National Institutes of Neurological Disorders and Stroke |
| NIRS | Near-Infrared Spectroscopy |
| NO | Nitric Oxide |
| NPE | Norepinephrine |
| NVC | Neurovascular Coupling |
| OCSP | Oxford Community Stroke Project |
| PAC | Partial Anterior Circulation |
| $PaCO_2$ | Partial Pressure of Carbon Dioxide |

| | |
|---|---|
| $PaO_2$ | Partial Pressure of Oxygen |
| PCA | Posterior Cerebral Artery |
| PCT | Perfusion Computed Tomography |
| PE | Phenylephrine |
| PET | Positron Emission Tomography |
| PHYSIDAS | Physiological Data Acquisition System |
| Pi | Pulsatility Index |
| PMD | Power Motion Mode Doppler |
| POC | Posterior Circulation |
| POINT | Platelet-orientated Inhibition in New TIA and Minor Ischaemic Stroke |
| PROACT | Prolyse in Acute Cerebral Thromboembolism II |
| RAP | Resistance Area Product |
| rCBF | Regional Cerebral Blood Flow |
| rCBV | Regional Cerebral Blood Velocity |
| rCMRO2 | Regional Cerebral Metabolic Rate of Oxygen |
| RHP | Rapid Head Positioning |
| ROC | Receiver Operating Characteristics |

| | |
|---|---|
| rOEF | Regional Oxygen Extraction Fraction |
| RoR | Rate of Recovery |
| r-proUK | recombinant Prourokinase |
| rtPA | Recombinant Tissue Plasminogen Activator |
| SAE | Serious Adverse Event |
| SAH | Subarachnoid Haemorrhage |
| SBP | Systolic Blood Pressure |
| sCA | Static Cerebral Autoregulation |
| SD | Standard Deviation |
| sICH | Symptomatic Intracerebral Haemorrhage |
| SITS-ISTR | The Safe Implementation of Thrombolysis in Stroke - International Stroke Thrombolysis Register |
| SITS-MOST | The Safe Implementation of Thrombolysis in Stroke Monitoring Study |
| Sn | Sensitivity |
| SNR | Signal to Noise Ratio |
| Sp | Specificity |
| SPECT | Single Photon Emission Computed Tomography |

| | |
|---|---|
| ST | Standard Therapy |
| STENTIS | Safety and Efficacy of NeuroFlow in Acute Ischaemic Stroke |
| SV | Stroke Volume |
| SVR | Systemic Vascular Resistance |
| TAC | Total Anterior Circulation |
| TARDIS | Triple Antiplatelet for Reducing Dependency After Ischaemic Stroke |
| TBI | Traumatic Brain Injury |
| TCD | Transcranial Doppler |
| TCM | Takotsubo Cardiomyopathy |
| TFA | Transfer Function Analysis |
| TIA | Transient Ischaemic Attack |
| TN | True Negative |
| TOAST | Trial of ORF 10172 in Acute Stroke Treatment |
| TP | True Positive |
| UA | Undetermined Aetiology |
| UHL | University Hospitals of Leicester NHS Trust |

| | |
|---|---|
| UK | United Kingdom |
| VIP | Vasoactive Intestinal Peptide |
| VKA | Vitamin K Antagonists |
| VLF | Very Low Frequency |
| V/Q | Ventilation/Perfusion |
| WHO | World Health Organisation |

# Chapter 1. Research Introduction

## 1.1 Introduction

It is well established that cerebral blood flow (CBF) regulation, metabolism and associated haemodynamic parameters are impaired following ischaemic stroke (IS) (1-3). This may lead to hypertension-related reperfusion injuries, such as cerebral oedema and symptomatic intracerebral haemorrhage (sICH), and hypotension-associated secondary ischaemia, all of which are associated with poorer prognosis and clinical outcomes. Recently, a wide range of cerebral perfusion strategies have been introduced which aim to improve CBF and cerebral haemodynamics. Assessing the effect of these strategies on cerebral haemodynamics may therefore provide a better understanding of how to manage stroke disease and reduce secondary brain injury. This introductory chapter will concentrate on the clinical aspects of stroke, focusing on stroke epidemiology, pathophysiology, risk factors and the different types of cerebral perfusion therapies. It will then discuss the definition, mechanisms, and methods of measurement of cerebral haemodynamics to understand how they relate to IS disease.

## 1.2 Stroke

### 1.2.1 A Historical Perspective of Stroke

The history of stroke disease begins in ancient Mesopotamia, as early as the second millennium BC (4). Humban-nimena III, the Elamite King (ruler, 692 BC to 689 BC) suffered symptoms described as ‘his mouth was locked so that he could not speak’, which would fit with the modern description of stroke. He was left incapacitated for almost a year which resulted in the Assyrians winning the battle and re-invading the City of Babylon (5).

Hippocrates (460 BC to 370 BC), the father of western medicine, recognised the phenomenon of sudden onset of paralysis, loss of consciousness and speech deficit. He invented the word 'apoplexy', meaning 'in the sense of being struck down at lightning speed' (6). Galen (131 AD to 201 AD), a Greek physician, founder of experimental physiology, further expanded on Hippocrates' theories, with the belief that there is an "accumulation of black bile or phlegm, described as dense humors, causing stagnation of 'animal spirit' (blood or blood components) in the arteries of the brain" (7, 8). This was widely accepted for many centuries and it was only until the 1600s, when Johann Jakob Wepfer (1620-1695), a Swiss pathologist, identified post-mortem signs of cerebral haemorrhage in patients who had died from what was then called 'cerebral apoplexy'. Galen's theories were thus finally overthrown (9). Wepfer also reported that 'apoplexy' could be due to occlusive arterial disease by demonstrating carotid thrombus in the autopsies of nuns (10). Furthermore, he managed to illustrate the arterial polygon of the brainstem in detail, which laid the foundation of the Circle of Willis (11, 12). Rudolf Virchow (1821-1902), a German pathologist and statesman, subsequently identified thrombotic and embolic components of 'apoplexy' (13). He recognised the interaction between blood and arterial walls and the consequences of CBF impairment, and invented the term 'ischaemia' (14). The underlying pathophysiology of stroke disease identified by Wepfer and Virchow provides the basis of stroke classification in modern medicine.

### 1.2.2 Definition

The traditional definition of stroke, provided by the World Health Organisation (WHO), is the "*abrupt onset of focal (or global, as in subarachnoid haemorrhage) disturbance of cerebral function, with symptoms lasting for 24 hours or longer, or leading to death, with no apparent cause other than that of vascular origin"* (15). If the symptoms and signs resolve within 24 hours the event is defined as Transient Ischaemic Attack (TIA)

(16). However, stroke and TIA are on the same disease spectrum, both involving interruption in cerebral perfusion with resulting tissue damage. Furthermore, they share the same aetiologies, risk factors, and primary and secondary prevention strategies (17). These traditional definitions of stroke and TIA were formulated more than 30 years ago when diagnostic neuroimaging and effective treatments were not available. It is also important to note that the arbitrary establishment of the '24-hour' cut-off point was chosen without extensive support from the literature (18), and that most the TIAs resolve within an hour rather than lasting several hours (19, 20). Recent studies also suggest that up to a third of traditional 24-hour TIA patients, in particular those who have symptoms lasting longer than an hour, will have restricted diffusion lesions in the Magnetic Resonance Imaging (MRI) (21-23) whereas up to 20% of minor IS patients may have negative diffusion weighted MRI (24). All of these suggest that using time-based definitions may be inaccurate in reflecting end-organ injury. As a result, the American Heart Association (AHA) and the American Stroke Association (ASA) issued consensus statements using tissue-based rather than time-based definitions, and supporting the revised definition of TIA as '*a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without acute infarction*' (25). If the episode of neurological dysfunction is associated with infarction it will be defined as Central Nervous System (CNS) infarction, irrespective of the duration of symptoms (26). However, these statements await endorsement; using these definitions would certainly result in an increase in stroke incidence (27), in particular silent CNS infarction (28), which is associated with a significant risk of subsequent cognitive impairment (29, 30), dementia (31) and recurrent stroke (32, 33). Despite this, using such definitions remains challenging to the clinician: areas with limited access to advanced neuroimaging

may have difficulty in diagnosing IS and distinguishing between TIA and stroke patients.

### 1.2.3 Epidemiology of Stroke

Stroke is a significant public-health burden globally with an enormous impact on patients, their families, healthcare systems and societies (34, 35). Worldwide, it is the leading cause of disability (35), the second most common cause of death after ischaemic heart disease and the third leading cause of disability adjusted life years (DALYs) (35). In 2016, stroke accounted for 5.5 million deaths, equivalent to 10% of all deaths worldwide (35). Using the Framingham Study data, Seshadri and colleagues estimated that by the age of 75, the lifetime risk of stroke will be 1 in 6 for men and 1 in 5 for women (36), though a recent epidemiological study suggested the lifetime risk of stroke has increased to 1 in 4 for both men and women (37). In the United Kingdom (UK) alone, there are approximately 100,000 new stroke cases per annum, which equates to roughly one every five minutes (38). Although stroke is a disease of older people, up to 30% of strokes occur in people under the age of 65 (39), which represents approximately half of the total DALYs from stroke (40).

A systematic review carried out by Feigin and colleagues suggested that the incidence of stroke over the last four decades has reduced by approximately 40% in developed countries. However, the incidence of stroke in developing countries has almost doubled (41) and continues to rise (40). In developing countries, age-standardised stroke mortality rates in both those aged under and over 75 are significantly higher (212% and 33% respectively) compared to developed countries, and studies suggest that by 2020, stroke mortality rates worldwide will double (39). It is thought that such strong geographic variation could be explained by health and demographic transitions (42), genetic

predisposition (43), expanding ageing populations and suboptimal stroke risk factor management (44, 45).

### 1.2.4 Global and Regional Impact of Stroke

Stroke results in a significant cost to both healthcare and social care systems. It imposes a serious impact on long-term disability, and also mortality. There is a 25% mortality rate (46), and this can increase up to 40% in some low to middle income countries (47). Moreover, up to 50% of stroke survivors are left with permanent disability (48-50). The cumulative risk of stroke recurrence within 5 years ranges from 14% to 25% (51-55) with recurrent stroke increasing the risk of disability, institutionalisation (56), total hospitalisation costs, (57) and fatality rates (58, 59). Stroke costs approximate £9 billion in the UK, equivalent to 5% of total National Health Service (NHS) expenditure, of which direct costs account for approximately 49% of the total, whereas the informal care costs, and resultant productivity losses are responsible for 27% and 24%, respectively (60). Importantly, in the UK, the estimated stroke costs vary considerably between patients; in the first five years it could vary fivefold between patients who have the lowest and highest care costs (61). The significant incidence and prevalence rates, together with the serious consequences of stroke disease resulted in the Department of Health (DOH) issuing the consultation document "Reshaping Stroke Care" – which highlights stroke as a clinical priority, and stresses the importance of identifying key areas for stroke education and service development (62).

### 1.2.5 Types of Stroke

There are three types of stroke disease: IS (80%), intracerebral haemorrhage (ICH - 10%) and subarachnoid haemorrhage (SAH) (5%). The remaining 5% are of undetermined type (63). Each of these have different aetiologies (64-67), risk factor profiles, management

regimes (68) and outcomes (69, 70). There is also an ethnic disparity of stroke subtypes in which the incidence of IS, ICH and SAH can be up to three-fold higher in the Black and minority ethnic population compared to Caucasians (71-75). The Black, Hispanic and Asian populations also have a significantly higher proportion of stroke attributable to ICH compared to the Caucasian population (76-79). Recently, a prospective, multi-centre, case-control study has been carried out, aiming to identify the genetic variation on ICH risk among different ethnicities (80).

### 1.2.6 Stroke Risk Factors

Traditionally, stroke risk factors can broadly be divided into modifiable and non-modifiable risk factors (81); hypertension (82) and increasing age (81) being reported as the strongest modifiable and non-modifiable risk factors, respectively. However, it is important to remember that only 60 to 80% of strokes are attributable to these so called 'traditional risk factors' (83). Indeed, studies have identified several non-traditional risk factors, such as sleep apnoea and homocysteine, and found that by including these factors it may be possible to explain up to 90% of stroke incidence (82). Table 1.1 outlines the risk factors for stroke disease.

**Table 1.1** Modifiable and non-modifiable stroke risk factors (81-88).

| | **Ischaemic Stroke** | **Intracerebral Haemorrhage** | **Subarachnoid Haemorrhage** |
|---|---|---|---|
| Non-modifiable Risk Factors | Increasing Age,<br>Male Sex,<br>Race,<br>Ethnicity,<br>Genetic (CADASIL, CARASIL, Moya-moya, Fabry disease, MELAS, Marfan, Ehlers-Danlos (89)<br>Family History. | Increasing Age,<br>Male Sex,<br>Race,<br>Ethnicity,<br>Genetic (CAA, COL4A1) (90). | Increasing Age,<br>Female Sex,<br>Race,<br>Ethnicity,<br>Intracranial Artery Dissection. |
| Modifiable Risk Factors | Blood pressure,<br>Smoking, Diet,<br>Alcohol Consumption,<br>Physical Inactivity,<br>Serum Cholesterol,<br>Fibrinogen,<br>Diabetes,<br>Atrial Fibrillation,<br>Myocardial Infarction,<br>Carotid Artery Disease. | Blood Pressure,<br>Smoking, Diet,<br>Alcohol Consumption,<br>Physical Inactivity,<br>Drugs (Anticoagulants, Anti-Platelet Agents, Thrombolytic Agents),<br>Substance Misuse,<br>Vascular Malformation,<br>Cerebral Amyloid Angiopathy. | Blood Pressure,<br>Smoking,<br>Cerebral Aneurysm,<br>Vascular Malformation,<br>Bleeding Disorders,<br>Vasculitis,<br>Substance Misuse,<br>Cerebral Amyloid Angiopathy. |
| Non-traditional Risk Factors | Obesity,<br>Metabolic Syndrome,<br>Sleep Apnoea,<br>Chronic Inflammation,<br>Chronic Kidney Disease,<br>Nutrition,<br>Psychosocial Stress,<br>Ratio of Apolipoprotein B To A1,<br>Homocysteine,<br>Air Pollution. | Psychosocial Stress. | |

This thesis will primarily focus on IS disease, in contrast to TIA and stroke caused by ICH or SAH.

### 1.2.7 Pathophysiology of Stroke

As mentioned in the previous section, IS is by far the most common type of stroke. There are five different types of IS: large artery atherothromboembolism, embolism (e.g. cardiac embolism), small vessel occlusive disease, uncommon stroke (e.g. connective tissue disease, venous thrombosis, arterial dissection, systemic hypoperfusion) and stroke of undetermined cause (cryptogenic stroke) (91), of which a subgroup is now defined as embolic stroke of undetermined source (ESUS) (92). IS is a highly unstable, complex and dynamic process. Its pathophysiology can be explained at a molecular, cellular, tissue and organ level. Various research studies, including animal models and the use of novel imaging techniques, enable us to build a depth of understanding of the underling pathophysiology of stroke, helping us to ultimately identify suitable preventive measures and targets for therapeutic intervention.

**Cerebral Ischaemic Effects at the Cellular Level**

The brain has a limited energy reserve and is completely dependent on aerobic metabolism to deliver oxygen, nutrients and removal of waste products of metabolism. As a result, cerebral tissue is exceptionally vulnerable to the effects of ischaemia. An initial vascular (i.e. atherosclerotic plaque), cardiac (i.e. left atrial thrombus as a results of atrial fibrillation), or haematological event (i.e. sickle cell disease), results in the formation of local thrombus with subsequent occlusion in the cerebral artery and interruption to the brain blood supply distal to this point. This leads to a neurochemical process called the ischaemic cascade. Generally speaking, the ischaemic cascade begins with cerebral focal hypoperfusion, depletion of oxygen and glucose, accumulation of lactate via anaerobic glycolysis, and subsequent intracellular energy failure (93, 94). This is rapidly followed by excitotoxicity secondary to the release of glutamate and aspartate,

leading to the influx of intracellular calcium (95, 96), which triggers ionic imbalances (97), mitochondrial dysfunction, activation of free radicals (98, 99), post-ischaemia inflammation, and finally apoptosis of the peripheral neurons, glial and endothelial cells (100). These are co-ordinated and inter-related events which result in ischaemic necrosis and cerebral dysfunction (Figure 1.1)

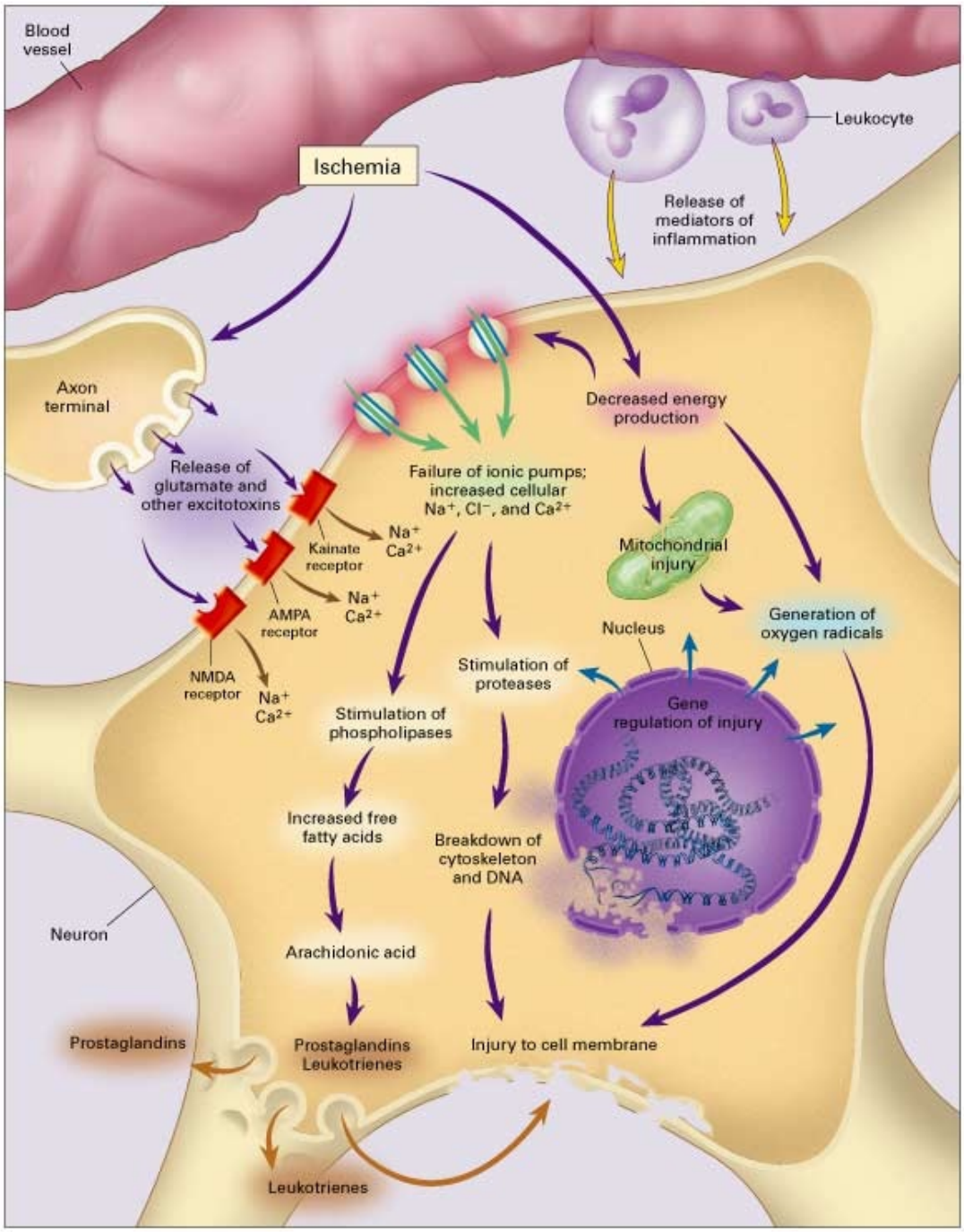


**Figure 1.1** The ischaemic cascade [reproduced from (101), with permission].

## Cerebral Ischaemic Effects at a Tissue Level

Cerebral ischaemia does not only cause deleterious effects at the cellular level, but also damages the structural integrity of both the brain tissue and cerebral blood vessels. Release of enzyme proteases such as matrix metalloproteinases (102), and accumulation of bradykinin (103), vascular endothelial growth factor (104) and thrombin (105) all lead to the breakdown of the blood-brain barrier (BBB), resulting in the formation of vasogenic oedema. This causes secondary brain injury by local compression of the microcirculation and raised intracranial pressure (ICP) (106).

## The Ischaemic Core and Penumbra

In IS, the extent of the damage is dependent on the CBF that is able to pass through and reach the distal tissue, either through the incomplete occluded cerebral vessels, reperfusion, or collaterals. Within a few minutes of cerebral ischaemia, the region of the brain tissue exposed to the most dramatic CBF interruption becomes rapidly and irreversibly injured leading to necrotic cell death (107). This area is called the ischaemic core, and by definition, it is electrically silent and beyond therapeutic rescue. This area is typically characterised by a CBF as low as 10mL/100g/min (108). Surrounding the ischaemic core, is an area called the penumbra which is functionally impaired, but structurally intact, i.e. it is characterised by electrical failure, but preservation of membrane polarisation, energy metabolism and oxygen extraction (107, 109-111). It is classically characterised by less severely impaired CBF (15 to 40ml/100g/min) (108). The cerebral penumbra is therefore the main target for therapeutic intervention as successful salvage in this area is associated with neurological improvement and recovery. However, it only remains viable for a short period of time and is at risk of infarction if not salvaged quickly enough, emphasising the urgency of acute stroke management.

### 1.2.8 Classification of Stroke

It is important to have a validated and well-designed stroke classification system as this enables clinicians to exclude any stroke mimics, plan precise investigations, make treatment decisions, and instigate preventative strategies. Accurate and reproducible assignments of the underlying mechanisms of stroke disease are also important in both clinical trials and epidemiological studies. However, to formulate such classifications is a complex task as stroke is a heterogeneous syndrome with multiple underlying pathologies.

There are several approaches to stroke classifications specifically: clinical, aetiological, phenotypic and neuroradiological.

**Clinical Classification of Stroke**

The Oxford Community Stroke Project (OCSP) classification is one of the examples of a clinical stroke classification system (112). It relies exclusively on clinical features to classify stroke according to the likely arterial vascular territory involved, without considering the potential aetiology (113). It is easy to carry out in different clinical settings even if relevant investigations cannot be performed. OCSP categorises stroke syndromes into four subtypes: total anterior circulation (TAC), partial anterior circulation (PAC), lacunar (LAC) and posterior circulation (POC). The code of the last letter could be S (Syndrome: indeterminate pathogenesis), I (Infarct) and H (Haemorrhage). Using the OCSP classification, the location and the extent of the infarct (114), mortality rates and outcome (115) can be predicted, but not individual stroke risk factors and underlying mechanisms (116).

**Aetiological Classification of Stroke**

Trial of ORF 10172 in Acute Stroke Treatment (TOAST) is one of the most widely accepted aetiological classifications of stroke. It was initially designed to improve standardisation of stroke subtype classification in a multi-centre randomised clinical trial (91). It takes into account not only the clinical features of the stroke, but also information from relevant investigations such as neuroimaging, carotid artery imaging, cardiac investigations and haematological investigations. Vascular risk factors, risk of recurrence and stroke prognosis can all be identified according to stroke subtypes using the TOAST classification (117). There are five major categories of stroke subtypes that are established in TOAST: large artery athero-thromboembolism, embolism (e.g. cardiac embolism), small vessel occlusive disease, uncommon stroke, and stroke of undetermined cause (cryptogenic stroke). Since the introduction of TOAST, it is now not only applied in randomised controlled trial settings, but also in epidemiological and genetic studies (118, 119). However, it is not uncommon that IS patients have multiple coexisting aetiologies [e.g. atrial fibrillation (AF) and carotid artery disease] and, under the TOAST classification, this group of patients will be classified as 'cause undetermined', together with those patients who have not yet been investigated thoroughly.

The Causative Classification of Stroke (CCS) is an automated, evidence-based classification system constructed using the same concept as TOAST. By harmonising multiple aspects of the diagnostic stroke evaluation in a systematic manner, it is able to divide the most likely stroke aetiologies into five major subtypes which are similar to the TOAST categories (120, 121). It takes into account any specific cardiac and vascular pathologies, together with imaging and clinical parameters when estimating stroke risk. The CCS offers subtype information in two different formats: the causative subtype and

phenotypic subtype, in which the causative subtype is further divided into 'evidence, probable or possible', allowing the investigators to reduce the chance of categorising patients into the undetermined cause, and therefore, increase the level of confidence to the users (122).

**Phenotypic Classification of Stroke**

ASCO classification is one of the examples of phenotypic classification of stroke in which 'A' stands for atherosclerosis, 'S' stands for small vessel disease, 'C' stands for cardiac source and 'O' stand for other cause (113). ASCO phenotyping has recently been upgraded to ASCO-D in which 'D' stands for dissection (123). Unlike the TOAST classification system, which characterises only the most likely cause, ASCO takes into account stroke aetiology and presence of underlying disease. The likelihood of each phenotype is divided by the grade of severity and level of evidence (Table 1.2). As it grades all morbidity present in the patient, it manages to capture the overlap between diseases and identifies the potentially causal relationship between the IS and diseases (124, 125).

**Table 1.2** Methods of ASCO-D classification [adapted from (126)].

| Grades of pathology | Levels of diagnostic evidence |
|---|---|
| **1** Definitely a potential cause of the index stroke | **A** Direct demonstration by gold standard diagnostic tests or criteria |
| **2** Causality uncertain | **B** By indirect evidence or less sensitive or specific tests or criteria |
| **3** Unlikely a direct cause of the index stroke (but disease is present) | **C** By weak evidence |
| **0** Absence of disease | |
| **9** Insufficient work up, patient cannot be graded | |

## Neuroradiological Classification of Ischaemic Stroke

Hyperdense middle cerebral artery (MCA), loss of grey-white matter differentiation, cortical hypodensity with associated parenchymal swelling and gyral effacement are some of the early radiological features of IS on Computed Tomography (CT) scanning. The Alberta Stroke Programme Early CT Score (ASPECTS) was introduced in the year 2000 to offer a standardised detection and reproducible grading system in CT to assess the extent of hypodensity of the MCA territory in acute ischaemic stroke (AIS) patients (127). It is a strong prognostic indicator, equivalent to using clinical stroke severity assessments such as the National Institutes of Health Stroke Scale (NIHSS) score and disability scales such as Modified Rankin Scale (mRS). It is also a strong predictor of functional outcome (128, 129), fatality rate, and reperfusion rate when used in the context of intravenous thrombolysis. The European Co-operative Acute Stroke Study (ECASS) highlighted the importance of assessing early CT ischaemic changes to predict the benefit

from intravenous thrombolysis (130) and ASPECTS has since been widely used by both neuroradiologists and stroke physicians.

Several studies have been carried out to investigate the agreement between different stroke classifications and whether they would be able to reduce the proportion of patients classified as undetermined cases. Table 1.3 shows the level of agreement between different stroke classifications, the inter-rater reliability, and reduction of the proportion of patients with undetermined aetiology respectively. Selecting correct stroke classification systems, and taking caution when combining or comparing such classification systems is essential when analysing outcomes in both clinical practice and research settings.

| Stroke classification | Level of agreement | Inter-rater reliability | Reduction in the proportion of patients with undetermined aetiology |
|---|---|---|---|
| **CCS and TOAST** (131-133) | From moderate (131) to excellent agreement (132, 133). | | Conflicting results: some studies suggested CCS assigned fewer patients as undetermined aetiology (132), whilst others do not (133). |
| **ASCO and TOAST** (132, 134, 135) | Moderate to good agreement except undetermined aetiology (134) which had good to excellent agreement (132, 135). | | No significant reduction in patients classified as undetermined aetiology (132, 134). |
| **CCS and ASCO** (132) | From good to excellent agreement (132). | | Reduction in patients classified as undetermined aetiology (132). |
| **CCS, TOAST and ASCO** (136, 137) | Moderate agreement: different classification systems differed in their capability in assigning subtypes according to aetiologies, though all three systems exhibit similar discrimination in mortality rate at 90 days post stroke onset (136). | | CCS assigned fewer patients as undetermined aetiology (136). CCS and ASCO assigned fewer young patients (age<59 yrs old) as undetermined aetiology (137). |
| **CCS** (121, 122) | | High inter-rater reliability (κ range 0.8-0.9) (121, 122). | |
| **TOAST** (138-141) | | Moderate inter-rater reliability (κ range 0.41-0.56) (138-141). | |
| **ASCO** (132, 135) | | High inter-rater reliability (κ range 0.92-1) (132, 135). | |

| | | | |
|---|---|---|---|
| **OCSP**<br>(117) | | Moderate inter-rater reliability<br>($\kappa = 0.54$) (117). | |

**Table 1.3** Level of agreement, inter-rater reliability, and proportion of patients in undetermined aetiology among different stroke classification systems.

### 1.2.9 Prognostic Factors following Stroke

Recovery from AIS is influenced by a variety of biological and environmental factors. Age, stroke subtype and severity, pre-stroke mRS, and lesion site and size are some of the well-established predictors of stroke survival (142-147). However, many other prognostic factors such as metabolic disturbances, hyperglycaemia, inter-current infection and cerebral oedema have also been proposed (148-154). Although adequate control of these abnormal parameters could improve the viability of ischaemic neuronal tissue and therefore stroke outcome (155), approximately only 50% of the recovery can be explained by the predictors describe above (156). Recent studies have suggested using neurophysiological biomarkers (e.g. electroencephalography, transcranial magnetic stimulation) to assess cortico-spinal tract function, or neuroimaging biomarkers to assess the descending motor pathway to increase the sensitivity in predicting post stroke motor recovery and outcome (157).

Several clinical studies and systematic reviews have suggested that increased blood pressure variability (BPV) in acute and sub-acute phases of stroke is associated with adverse cerebrovascular outcomes (158-163). Importantly, this also applies to AIS patients who received endovascular treatment (164-166), particularly those who have poor collateral circulation (167). It has been suggested that cerebral autoregulation (CA) impairment, reduction of cardiac baroreceptor sensitivity, and autonomic nervous system impairment could be the underlying causes of increased BPV (168-170). A meta-analysis carried out by Manning et al. assessed the effect of BPV on functional outcomes, demonstrated that systolic BPV, particularly during the acute phase of IS, is associated with poorer long-term functional outcomes (171).

There is also a suggestion that CBF, and its associated haemodynamic parameters, may provide valuable information regarding the progression of IS, the cerebral tissue outcome and therefore the ultimate prognosis (172, 173). When CBF reduces to 25ml/100g/min symptoms of cerebral hypoperfusion may occur. However, it is only when perfusion flow falls below 10ml/100g/min that neurological signs become prominent (174). Therefore, early assessment of CBF and associated haemodynamic parameters may help to identify, and provide therapeutic strategies for, neuro-critical patients who are prone to developing ischaemic brain lesions and secondary brain injury.

## 1.3 Cerebral Haemodynamic Regulatory Mechanisms

### 1.3.1 Cerebral Autoregulation (CA), Neurovascular Coupling (NVC) and Cerebrovascular Reactivity (CVRea)

The brain accounts for 2% of body weight yet requires 20% of total body oxygen consumption (≈3.5ml/100g/min) and receives 15% of the total cardiac output (CO) (175, 176). The brain is extremely sensitive to oxygen deprivation: cessation of CBF for only a few minutes can result in irreversible ischaemic brain damage. The brain has limited energy reserves and therefore a constant blood supply to the cerebral circulation is essential in order to support its high metabolic demand, meet nutritional needs, and ensure homeostasis (177). Cerebral haemodynamics have important regulatory mechanisms which maintain cerebral homeostasis. There are three main defence mechanisms responsible for cerebral perfusion adjustment; the sensitivity to arterial partial pressure of oxygen ($PaO_2$) and partial pressure of carbon dioxide ($PaCO_2$) changes, known as cerebrovascular reactivity (CVRea), the effectiveness of cerebral autoregulation (CA) and the matching of CBF to localised metabolic needs termed neurovascular coupling (NVC).

**Cerebral Autoregulation**

When Mogen Fog used the cranial window technique demonstrated by Forbes and Wolff (178), he observed changes in the pial artery of feline brains in response to blood pressure (BP) manipulation, finding that an increase in systemic BP was followed by vasoconstriction whereas a decrease in systemic BP was followed by vasodilatation (179, 180). Kety and Schmidt subsequently developed an inert gas method, a technique which monitors arterial-venous gas difference, allowing quantitative measurement of CBF to be carried out in human settings for the first time (181). However, it was not until 1959, when Lassen compiled data from more than 370 subjects of induced hyper- and hypotension in man, and concluded that CBF remains relatively constant over a wide range of BP (the so-called autoregulation plateau), that the concept of CA was finally established (182). It is important to remember that, this plateau was plotted using the results from multiple studies. Each data point on the curve is derived from independent subjects and therefore represents inter-, but not intra-, individual relationships (183). Furthermore, subjects either had a pathological condition or medications were used to maintain mean arterial pressure (MAP), and these factors were subsequently known to have an effect on CA (184).

Autoregulation is defined as the intrinsic capacity of an organ to maintain constant blood flow despite changes in arterial perfusion pressure. Autoregulation occurs in many vascular beds, but is particularly well developed in the brain. CA is a physiological protective mechanism of the cerebral vasculature in order to maintain stable CBF, both regional and global, despite changes in cerebral perfusion pressure (CPP). CPP is usually defined as the difference between the MAP and the mean cerebral venous pressure (CVP) (185). However, CVP is normally low (2-5mmHg), difficult to measure, and is directly influenced by intracranial pressure (ICP). Therefore, CPP can also be defined as the difference between MAP and ICP, that is:

$$CPP = MAP - ICP \qquad \textit{Equation 1.1}$$

MAP can be estimated as diastolic BP (DBP) + 1/3 pulse pressure and is usually approximately 90 mmHg in a normal healthy subject. Conversely ICP, under normal CPP, is usually not higher than 10 mmHg and therefore CPP is mainly dependent on the MAP.

CPP can also be defined as the pressure gradient across the CBF. That is, CBF is directly proportionally to perfusion pressure but inversely related to Cerebrovascular Resistance (CVR):

$$CBF = CPP/CVR \qquad \textit{Equation 1.2}$$

$$CBF = (MAP - ICP)/CVR \qquad \textit{Equation 1.3}$$

When CA is intact, CBF remains approximately constant, and CVR changes according to changes in the CPP.

Poiseuille's law would be applicable to describe the relationship between CBF, CPP and CVR in a cylindrical vessel, as flow is directly proportional to the perfusion pressure and the fourth power of the vessel's radius. It is inversely proportional to length and blood viscosity.

$$CBF = CPP\pi r^4 / 8\,\eta L \qquad \textit{Equation 1.4}$$

r = Vessel radius

ŋ = Blood viscosity

L = Vessel length

It is important to note that Poiseuille's law applies to steady laminar flow of Newtonian fluids in cylindrical tubes. However, whole blood contains red and white cells and protein

elements, which are non-Newtonian and able to aggregate in low-flow states (186). Therefore, caution is needed to ensure the equation is applicable under the conditions in the study.

CA is affected mainly by the arterioles and precapillary sphincters. These are small resistance vessels which are responsible for approximately 85% of total CVR. According to Poiseuille's law, a small change in the cerebral arterioles radius will result in a significant change in CBF.

When CA is intact, normal CBF is kept constant at 50ml/100g/min over the range of MAP from 60 mmHg to 160 mmHg. This is illustrated schematically in Figure 1.2 (182, 185). This occurs as a response of cerebral adjustments in CVR secondary to BP changes. There is a regional heterogeneity in the brain in which grey matter CBF can be up to four times higher than white matter (187, 188). Both upper and lower limits of CA are, however, not fixed and can be influenced by pharmacological agents and systemic and intracranial pathological conditions (185, 189-191). For example, in chronic hypertensive patients, the lowest MAP before cerebral hypoperfusion symptoms appear is higher than in normotensive patients. This results from a right shift in the autoregulatory curve, as illustrated in Figure 1.3. Several studies have suggested that the right shift may be able to return to the normal pressure range to some extent after prolonged effective antihypertensive treatment (189, 192, 193). However, more common is that the chronic hypertension results in permanent changes in vascular structure which lead to the irreversible raising of the MAP threshold for CA. Therefore, careful introduction of antihypertensive medications, especially in those who have severe hypertension, is required as aggressive antihypertensive treatment may result in lowering of the MAP

below the altered threshold of CA, leading to brain injuries such as cerebral ischaemia or infarction secondary to the hypoperfusion.

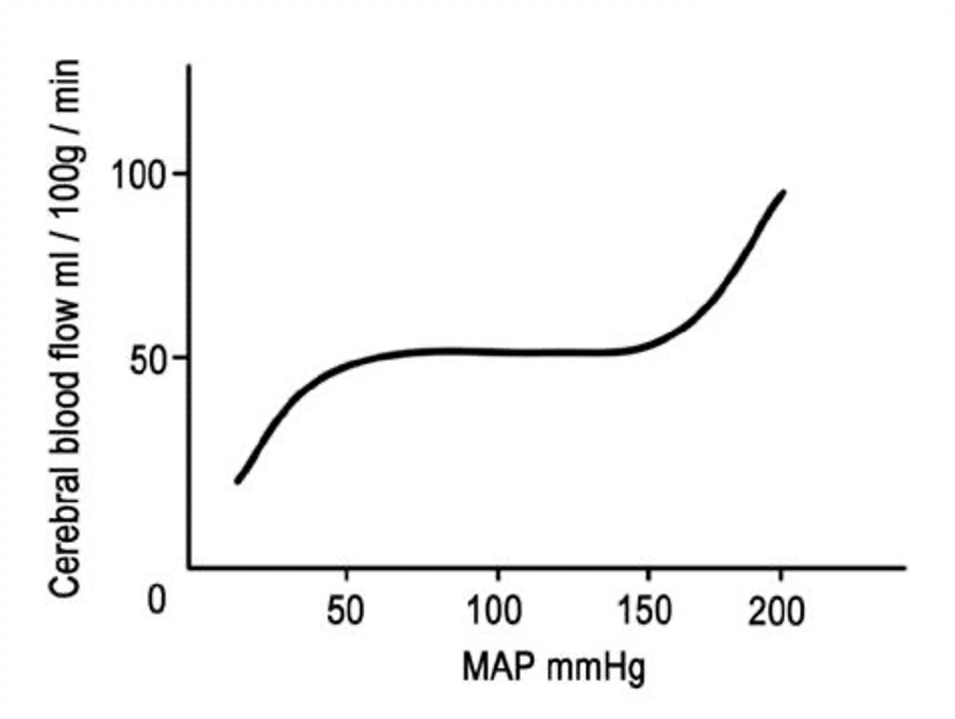


**Figure 1.2** Relationship between CBF and MAP in intact cerebral CA [adapted from (194)].

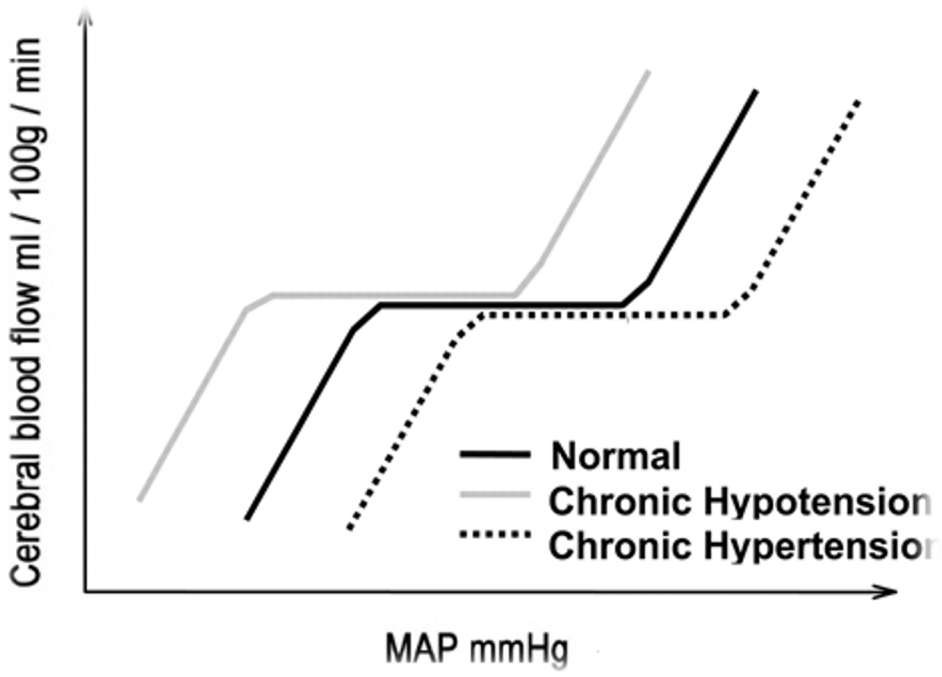


**Figure 1.3** Cerebral autoregulation curve during chronic hypotension and chronic hypertension [adapted from (195)].

CA is said to have failed when the MAP range exceeds the compensatory vasoconstriction or vasodilatation capacity with a resulting pressure-passive relationship between MAP and CBF, i.e. if the MAP falls below the lower limit (<50 mmHg), ICP will decrease as CPP is lowered, vascular radius reaches the point of maximal dilatation and subsequently collapses when the MAP further declines. This results in a steep increase in CVR; CBF will therefore be passively reduced and hypoperfusion may result. At the other end of the spectrum, if the MAP rises above the upper limit (>160 mmHg), vascular radius reaches the point of maximal constriction in which it is no longer able to limit the blood flow; breakdown of BBB and cerebral oedema will eventually result. Therefore, the brain becomes vulnerable to secondary injury such as ischaemic or hyperaemic changes if CPP is not able to match metabolic demands.

**Neurovascular Coupling**

More than a century ago, Angelo Mosso investigated patients with skull defects and found that emotional stimuli or cognitive tasks could result in local CBF changes (196-198). A landmark publication by Roy and Sherrington subsequently concluded that *'the vascular supply of the brain can be varied locally in response to the local variations in functional activity'*, i.e. when the regional cerebral activity increases, so does CBF. Roy and Sherrington attributed the change in the cerebral vessel calibre and the regional blood flow feedback mechanisms to 'chemical products of the cerebral metabolism' (199). This is known as functional hyperaemia or neurovascular coupling (NVC) - a spatial and temporal relationship between local neural activity and the corresponding CBF changes (200).

Despite several decades of enquiry, mechanisms of NVC are still not fully understood. However, it is certain that, like CA, NVC is a complex, co-ordinated phenomenon and

there is not a single cell type, agent or mechanism which can explain the entire process. Traditionally, it was believed that neuronal activation generates metabolic signals (i.e. hypoxia, hypoglycaemia, hypercapnia) (201) and vasoactive agents [i.e. nitric oxide (NO), adenosine, eicosanoids] which are solely responsible for CBF changes (199, 202). However, studies have shown that inhibition of any one of these vasoactive products does not contribute to a complete attenuation of the CBF response (203-205). Manipulation of the oxygen and glucose supply also does not result in significant CBF changes (206-210). Furthermore, the time course of vasoactive metabolite diffusion is not consistent with the rapid response observed in the cerebral arteries upon neuronal activation, which is typically delayed by 1-2 seconds and peaks at 4-6 seconds (211). This all suggests that exclusive dependence on vasoactive metabolites cannot produce as rapid and site-specific CBF changes as those evoked by neuronal activation.

There is a growing body of evidence to suggest that CBF is directly coupled to neuronal activity rather than to local energy needs (208), with the suggestion that several cellular and molecular signalling pathways, in particular, neuron-to-astrocyte signalling, have a major role in linking the neurotransmitter activity to vascular responses (212, 213). These complex signalling mechanisms involve perivascular neurons, glial (astrocytes, microglia, oligodendrocytes) and vascular cells (endothelium, smooth muscle cells), which are together referred to as the neurovascular unit (Figure 1.4), along with local metabolites such as $H^+$, $K^+$, NO and adenosine, to safeguard the cerebral micro-circulation homeostasis (214-217).

Blood flow to the brain was first conducted through pial arteries, which is either in the subarachnoid space or located on the surface of the brain. Pial arteries are surrounded by cerebrospinal fluid and consist of *tunica intima* (an endothelial cell layer and internal

elastic lamina), *tunica media* (smooth muscle cells and some collagen and elastin fibres) and an outermost layer called *tunica adventitia* (which consists of collagen, fibroblast and perivascular neuron) (218). These arteries give rise to the penetrating arterioles which enter from the surface of the brain into parenchyma and become parenchymal arterioles. The penetrating arterioles are separated from neurons and astrocytes by the Virchow-Robin Space. As parenchymal arterioles penetrate deeper into the brain, the Virchow-Robin space disappears and the vascular basement membrane makes direct contact with the astrocyte end-feet, which terminate as an extensive capillary network (219, 220) (Figure 1.4). These capillaries are surrounded by the pericytes which have unique contractile properties and are responsible for altering capillary calibre (214, 221). The change of the calibre controls the local blood flow and therefore, the supply of oxygen and glucose.

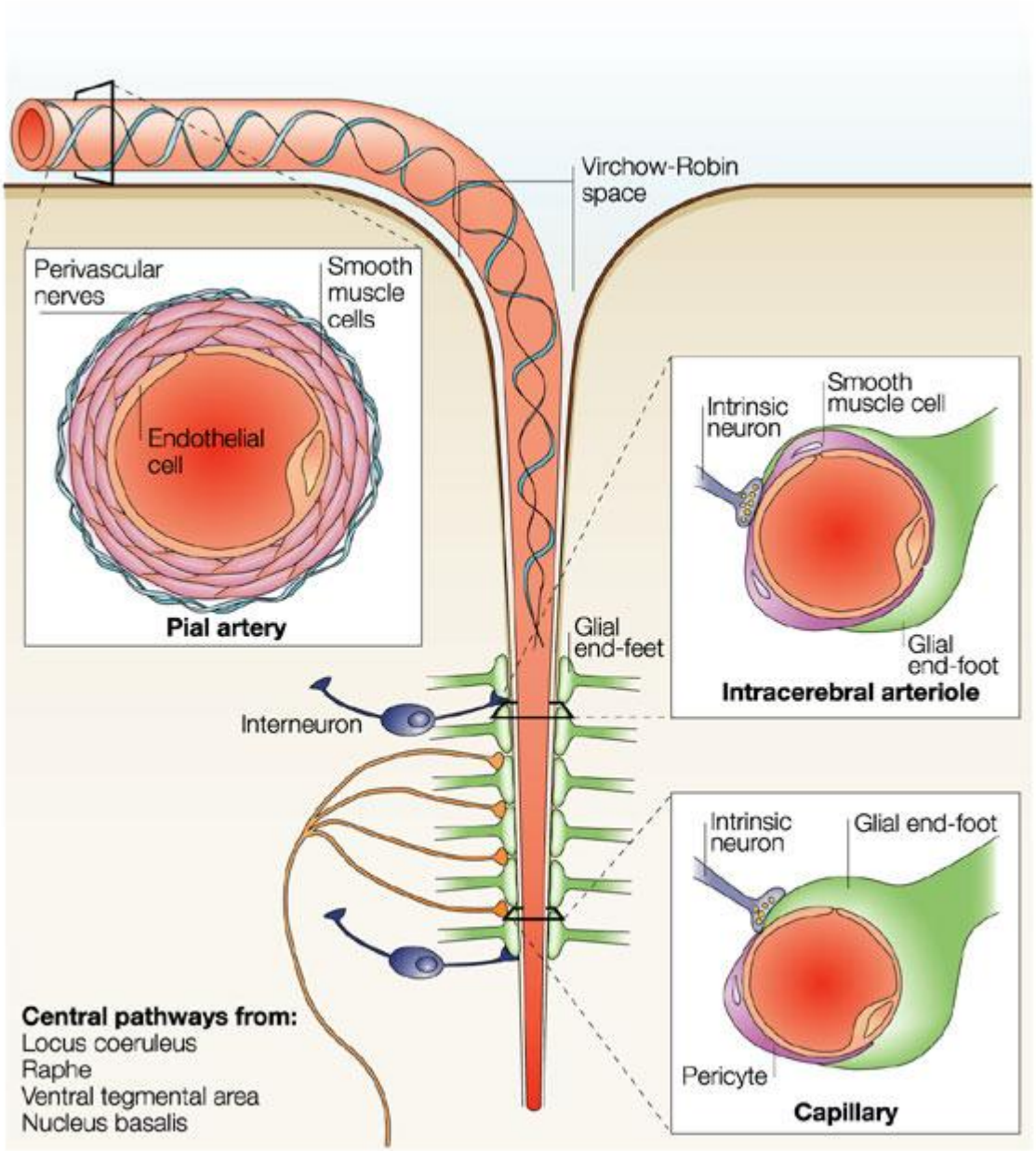


**Figure 1.4** The Neurovascular Unit [adapted from (214), with permission].

Recent evidence suggests that astrocytes play a vital role in regulating neuronal activity (222-225). They appear to be responsible for up-regulating tight junction proteins, monitoring ion and water homeostasis, and most importantly, CBF regulation (226). Astrocytes have abundant synapses which means they can be stimulated by neuronal activity. The close proximity of endothelial cells to astrocyte-end feet within microvessels, and the support of astrocyte and neurons, allows a direct communication between the microvessels to the neurons they supply, and signal to the smooth muscle cells that control vessel diameter (227).

Neural activity stimulates excitatory neurotransmitter release (i.e. glutamate) at synapses; the neurotransmitter will activate the metabotropic glutamate receptors in the cortical astrocytes (228). This results in an influx of intracellular $Ca^{2+}$ in astrocytes, leading to the $Ca^{2+}$-dependent stimulation of phopholipase $A_2$, and subsequent conversion of arachidonic acid (AA) into its vasodilator metabolites such as prostaglandins and epoxyeicosotrienoic acid (EET). Some AA also reaches vascular smooth muscle cells which contain enzymes CYP4A, this then subsequently generates vasoconstrictor 20-hydroxy-eicosatetraenoic acid (20-HETE) (229, 230). The competition between vasodilatation and vasoconstriction depends on $PaO_2$, with lower $PaO_2$ favouring vasodilatation (231). The rise of intracellular $Ca^{2+}$ also results in the opening of large conductance $Ca^{2+}$ activated potassium ($K^+$) channels in the astrocyte end-feet, leading to the increase of extracellular $K^+$ concentration, which hyperpolarizes smooth muscle cells causing vasodilatation. Astrocytes are also responsible for lactate production by metabolising glucose via glycolysis; lactate subsequently increases hydrogen ion ($H^+$) concentration, and therefore further facilitates vasodilatation (232).

Neurons can also signal directly to blood vessels via glutamate mediated signalling which leads to the production of NO and/or prostaglandin with resulting vasodilatation (233, 234). Furthermore, NO also binds and inactivates the CYP4A enzyme, therefore switching off the 20-HETE production. Astrocytes therefore act as a mediator by delivering vasodilatory prostanoids, while neuronal NO acts as a modulator of this process.

### 1.3.2 Mechanisms

CA is accomplished through a complex interplay of a variety of mechanisms allowing the brain to match its blood supply and metabolic demands both regionally as well as globally. Although these underlying mechanisms are not fully understood, and considerable controversy exists, various theories such as myogenic, chemical, metabolic and neurogenic control have been proposed (185, 190, 235, 236).

**The Myogenic Hypothesis**

Smooth muscle cells of small arteries and arterioles in the cerebral vasculature alter the resting myogenic tone, enabling vasoconstriction or vasodilatation in response to changes in transmural pressure. This is known as the 'Bayliss effect' (237), and contributes to CBF autoregulation (185). Support for this myogenic hypothesis is provided by the autoregulatory response being carried out within a few seconds and completed within 30 seconds after the transmural pressure of the resistance vessels changes. The myogenic mechanism primarily acts through a $Ca^{2+}$-dependent pathway in which depolarisation of the smooth muscle cell membrane occurs in response to an increase in transmural pressure, with the resultant $Ca^{2+}$ influx via the opening of voltage-operated $Ca^{2+}$ channels (238-240). The rise in intracellular $Ca^{2+}$ increases myosin light-chain phosphorylation and actin polymerisation, altering the state of the actin and myosin filaments within the

smooth muscle cells and promoting vasoconstriction (241). A reversed phenomenon would be observed in response to the decrease of transmural pressure. There are also some suggestions that several signalling pathways, such as Protein Kinase C and RhoA-Rho Kinase are stimulated in response to an increased transmural pressure, resulting in an enhancement of the calcium sensitivity during the myogenic reactivity process (242, 243).

Cerebral vessel response to shear stress increases the activity of NO synthase which results in generation of NO from L-arginine (244, 245). NO stimulates soluble guanylate cyclase in vascular smooth muscle, leading to an increase in the intracellular cyclic guanine monophosphate (cGMP). This in turn results in protein Kinase G activation and relaxation of vascular smooth muscle via the activation of $K^+$ channels (246-248).

**Chemical and Metabolic Hypothesis**

The metabolic hypothesis states that CBF reduction stimulates the release of vasoactive metabolites, which in turn reduce the vascular resistance and therefore, dilatation of the cerebral arteries and restoration of the blood flow. Therefore, it could be simply another manifestation of NVC. Carbon dioxide, oxygen, $H^+$, K+ and adenosine have all been proposed to have such a role.

**Adenosine**

Adensosine, a purine nucleoside, is responsible for CBF regulation via neuronal and synaptic activity. It is a potent vasodilator produced during Adenosine Triphosphate (ATP) catabolism, and is well known to be involved in NVC (203). An earlier study showed that cerebral adenosine concentration doubles with only moderate BP reduction (249). Intravenous infusion of adenosine results in marked cerebral vasodilation and an increase in CBF by opening of the ATP-sensitive $K^+$ channel (250). Caffeine, an

adenosine antagonist, demonstrates significant CBF reduction in both normal volunteers and IS patients (251, 252), which all suggests that adenosine may have a role in CBF regulation.

**Arterial Partial Pressure of Carbon Dioxide ($PaCO_2$)**

Arterial $PaCO_2$ is one of the most important systemic regulators of CBF, known as $CO_2$ cerebrovascular reactivity (CVRea) (253). Hypercapnia results in cerebral vasodilatation, with a resultant increase in regional perfusion and therefore, CBF. Conversely, hypocapnia results in cerebral vasoconstriction and CBF reduction (254). Changes in $PaCO_2$ exert an intense effect on cerebral perfusion whereby every 1mmHg change in $PaCO_2$ could result in up to a 4% change in CBF during normocapnic ventilation, and approximately a 2% change in CBF during hyperventilation (255-257). This is likely due to an increase in tissue proton ($H^+$) concentration which results in a reduction of extracellular pH in response to the increase of $PaCO_2$, leading to a raise in potassium concentration and vasodilatation in an attempt to increase CBF (258). Interestingly, $PaCO_2$ has shown to affect cerebral blood velocity (CBV) faster than the dynamic Cerebral Autoregulation (dCA) (259). Several studies have shown hyperventilatory hypocapnia can temporarily restore CA by redistributing blood flow from normal responsive regions of the brain to the ischaemic area. This has been shown in both pathologically and pharmacologically induced settings (260-262).

**Arterial Partial Pressure of Oxygen ($PaO_2$)**

As detailed in the previous section, the brain requires adequate CBF to meet its metabolic demand. CBF is coupled with cerebral oxygen metabolism in order to ensure adequate oxygen delivery both at rest and in response to different physiological activities. Therefore, it is unsurprising that during acute hypoxia, that cerebral vasodilatation occurs

leading to an increase in CBF. Such a phenomenon would, however, only occur when tissue $PO_2$ falls to approximately 50 mmHg (i.e. outside the physiological range of $PO_2$). In this situation, in CBF can increase by up to 400% from resting levels (263). Several mechanisms, such as ATP-sensitive $K^+$ channels, NO, adenosine, and arachidonic acid metabolites have all been implicated as mediators of this process (264).

**Neurogenic**

The role of neurogenic involvement in the control of CBF remains obscure and controversial. The cerebral vessels are innervated by both intrinsic and extrinsic systems of nerve fibres. The intrinsic system refers to the nerve arising within the brain, whereas the extrinsic system refers to those arising outside of the brain parenchyma. The intrinsic system consists of vascular fibers arising from the nucleus basalis, locus coeruleus and raphe nucleus. These can all modulate CBF changes, either by altering vascular tone directly or via stimulation of perivascular interneurons or glial cells (226, 265). The extrinsic system consists of sympathetic (originates from the superior cervical ganglion), parasympathetic (originates from the sphenopalatine, otic and internal carotid ganglia) and the trigeminal nerve (originates from the trigeminal ganglion) (248). Sympathetic innervation has little effect in normal conditions but is involved in protecting the brain during acute hypertensive episodes (266). The sympathetic nervous system exerts its vasomotor function in the larger cerebral resistance vessels, whereas CA is predominately carried out on the smaller resistance vessels. Sympathetic stimulation results in the release of norephephrine and neuropeptide Y and leads to vasoconstriction of the larger resistance vessels; the smaller resistance vessels which are located further downstream will dilate as an autoregulatory response to keep blood flow constant, providing the arterial pressure

is within the autoregulatory range, the opposite takes place if the sympathetic tone is reduced (267).

Similar to sympathetic innervation, the parasympathetic nerve supply also has no effect on CBF under normal conditions. However, under certain pathological circumstances parasympathetic stimulation results in the release of acetylcholine, vasoactive intestinal peptide (VIP), NO and leads to cerebral vasodilatation (226). A study carried out by Kano et al. suggested that the autonomic parasympathetic fibers explicitly offer a protective role in the pathophysiology of focal cerebral ischaemia (268). This is also confirmed by Koketsu and colleagues who demonstrated that an increase in the volume of infarction is observed after lesioning of the parasympathetic innervation to the Circle of Willis in spontaneously hypertensive rats (269).

Sensory fibres originating from the trigeminal ganglion are responsible for the release of calcitonin gene-related peptide (CGRP), a potent vasodilator (270). It is the only sensory afferent in the cerebral circulation and contributes to the increased CBF seen in a wide range of pathological conditions such as seizure, meningitis and cortical spreading depression (271-273). Studies also suggest that there is a regional heterogeneity in the extrinsic system in terms of innervation patterns, density, and cerebral arterial response to neurotransmitters. This could explain why there are varying degrees of vasoconstriction and metabolic needs in different cerebral vascular territories (274-276). Zhang et al. found that ganglion blockage induces significant dCA change, with a profound reduction in the CBV, suggesting that autonomic neural control of the cerebral circulation is involved in CBV regulation (277). However, such observations have not been reproduced in orthostasis (278). Furthermore, autonomic denervation was able to alter CA (279), but not CBF, in animal studies (280), suggesting that the role of autonomic

neural control in the cerebral circulation is far more complex than previously speculated (277).

### 1.3.3 Measurement Techniques

**Blood Pressure Measurement**

The use of an invasive arterial catheter system via radial or brachial artery is considered to be the gold standard in continuous BP measurements. However, this is rarely appropriate in clinical practice or research, save for in high dependency settings (281). Standard sphygmomanometer, Dinamap ™ and Finapres™ (FINger Arterial PRESsure) are some of the examples of non-invasive methods which can be used to assess BP relating to CBF changes. Finapres™ was introduced in the 1980s; it was the first non-invasive continuous beat-to-beat BP monitoring system designed on the volume clamp method described by Penaz, and the Physiocal (abbreviation for Physiologic Calibration), an automated self-calibration algorithm by Wessling et al. (282). The volume clamp method is built on the development of dynamic pulsatile unloading of the finger arterial wall. Total finger arterial blood volume is measured by a small, inflatable finger cuff with a built-in infrared photoplethysmograph. The arterial blood volume under the cuff is kept constant, so called 'set point', by modulating the cuff pressure via a fast electropneumatic servo system in response to arterial pressure changes during every heartbeat. The continuously changing cuff pressure is measured electronically and displayed as the pressure waveform. 'Physiocal' then periodically adjusts the set point in order to maintain the unloaded arterial volume and hence make the applied external pressure the same as the intravascular pressure (283). Finometer® (Figure 1.5), Portapres® (Portable version of Finapres) (Figure 1.6) and Nexfin® (Figure 1.7) are some of the examples of Finapres successor devices. These devices have previously been validated with regard to their

accuracy and precision in measuring absolute BP in different physiological and pathological settings (284-290). However, some studies suggest there could be discrepancy in terms of baseline parameter values (291), and satisfactory validity may not be achievable in certain pathological conditions (292, 293), highlighting the importance of choosing BP measurement apparatus in both research and clinical settings.

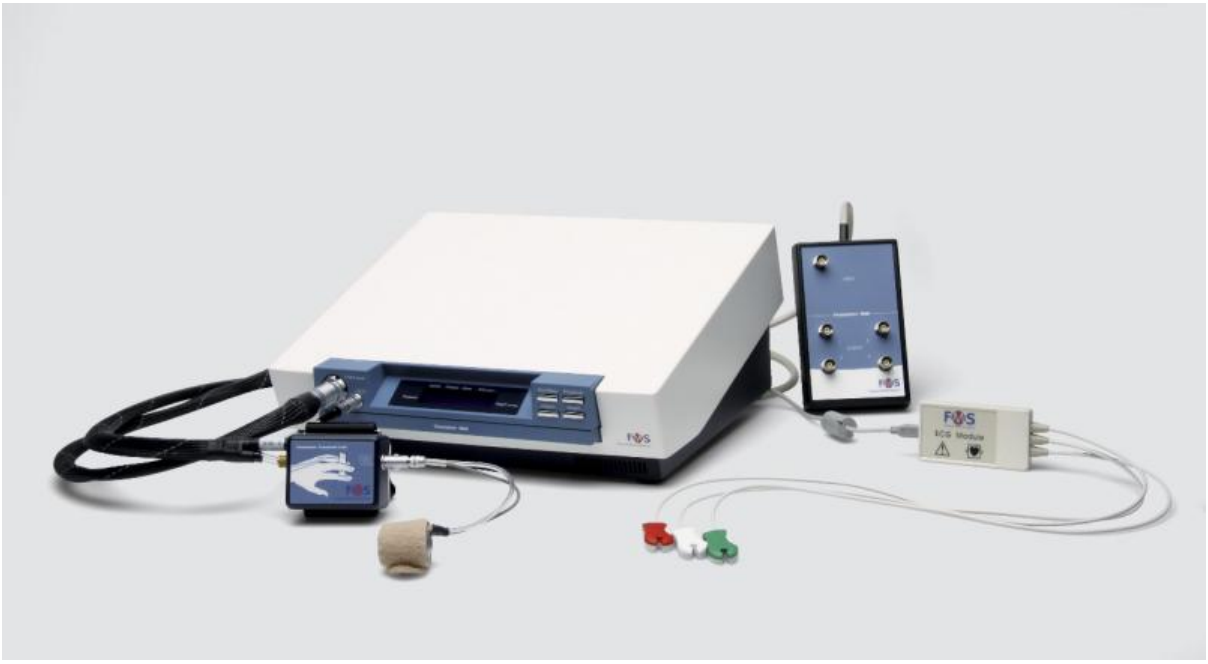

**Figure 1.5a** The Finometer® MIDI (Now discontinued)

Reproduced from http://www.smartmedical.co.uk/, with permission.


**Figure 1.5b** The Finometer® NOVA

Reproduced from http://www.smartmedical.co.uk/, with permission.

**Figure 1.6** The Portapres® (Now discontinued)

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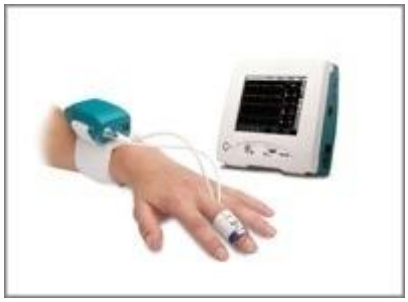

**Figure 1.7** The Nexfin®

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## Cerebral Blood Flow and Cerebral Blood Velocity Measurement

There are a number of measurement techniques which have been used to assess CBF. The inert gas and the indicator dilution technique (i.e. $^{133}$Xenon, $^{85}$Kryton and nitrous oxide) were used in estimating CBF during the early stages of CA studies (294). These are invasive, and CBF values are measured at a single MAP value over several minutes, reducing measurement reproducibility, making it time consuming, and prone to technical error. Furthermore, the extra-cranial circulation cannot be totally separated from the intra-cranial circulation and, therefore, these methods have been used to investigate the overall, rather than regional, static autoregulatory response (184). Electromagnetic flow studies require cannulation of extra-cranial vessels such as the internal carotid artery and this is unacceptable in current clinical practice. Near-infrared spectroscopy (NIRS), Positron Emission Tomography (PET), blood oxygenation level dependent (BOLD) contrast in functional Magnetic Resonance Imaging (fMRI) and single Photo Emission Computed Tomography (SPECT) are some of the non-invasive imaging techniques that can be used to assess cerebral haemodynamics; each of these imaging modalities have different underlying mechanisms, measurement parameters, and strengths and weaknesses. Tables 1.4a and 1.4b gives an overview of some of the CBF and CBV measurement techniques.

| | Inert Gas Method | Indicator Dilution Method | Electromagnetic Flowmetry | Near-Infrared Spectroscopy (NIRS) |
|---|---|---|---|---|
| **Description** | Based on Fick's Principle<br>Assumption of arterial-venous inert tracer difference is inversely proportional to the volume of CBF | Venous dilution of indicator<br>Regional CBF can by estimated by using multiple radiation detectors | Blood flow will be measured using the electro-magnetic flowmeters. | Optical monitoring technique that derives concentration changes of oxy- and deoxy-haemoglobin<br>Marker of changes in CBF in the form of Tissue Oxygenation Index |
| **Beside assessment** | Yes | Yes | No | Yes |
| **Emergency assessment** | Yes | Yes | No | Yes |
| **Contrast Material** | $N_2O$ | $N_2O$, $^{85}Kr$, $^{133}Xe$ | No | None |
| **Radiation exposure** | No | Yes but small | No | Yes |
| **Route of administration** | Inhalation $N_2O$<br>Arterial and jugular venous sample obtained subsequently to analyse $N_2O$ concentration | Intravenously,<br>intra-arterial,<br>inhalation | Intra-arterial (e.g. internal carotid artery, subclavian artery) | Non-invasive |
| **Assessed Parameters** | Global CBF,<br>$CMRO_2$,<br>$CMR_{glu}$,<br>$CMR_{lac}$, | Global CBF and regional CBF | Global CBF | CBF, CBV |
| **Strengths** | Inexpensive<br>Repeatability<br>Quantitative measurement<br>Simultaneous measurement of cerebral haemodynamic parameters | Has been used since the early studies of CA, technique has been validated in various studies. | Able to measure blood flow to and from the brain continuously<br>Device can be attached to the blood vessels for prolonged periods of time without affecting other cerebral haemodynamic parameters | Continuous real time data<br>Very easy to apply<br>High temporal and spatial resolution |

| | Inert Gas Method | Indicator Dilution Method | Electromagnetic Flowmetry | Near-Infrared Spectroscopy (NIRS) |
|---|---|---|---|---|
| **Weaknesses** | Time consuming<br>Low temporal resolution<br>Does not allow regional CBF measurement<br>There is an assumption of symmetrical venous drainage of the brain which is not truth in more than 50% of the subjects | Time consuming<br>Low temporal and spatial resolution<br>Potential problem of extra-cranial sampling | Invasive: require cannulation in extra- cranial blood vessels<br>Impractical in clinical settings | Expensive, complexity of the signals, may not directly related to CBF |

**Table 1.4a** Overview of CBF and CBV measurement techniques (I) (184, 294-296)

**CA: Cerebral Autoregulation**

**CBF: Cerebral Blood Flow**

**CBV: Cerebral Blood Velocity**

**CMR: Cerebral Metabolic Rate**

**$CMRO_2$: Cerebral Metabolic Rate of Oxygen**

**ICP: Intracranial Pressure**

**$^{85}Kr$: Krypton**

**NIRS: Near-Infrared Spectroscopy**

**$^{133}Xe$: Xenon**

| | Positron Emission Tomography (PET) | Single Photon Emission Computed Tomography (SPECT) | Xenon-enhanced CT | MRI Dynamic susceptibility Contrast (DSC) | Dynamic Perfusion Computed Tomography (PCT) | Arterial Spin Labelling (ASL) | Transcranial Doppler (TCD) Ultra-sonography |
|---|---|---|---|---|---|---|---|
| **Description** | Pairs of gamma rays emitted indirectly by a positron emitting radionuclide, which is introduced into the body on a biologically active molecule. | Radioisotope passes through the BBB and metabolised by neuronal and glial cells Radioisotope measures CBF using tomographic images through detection of scattered photos | Lipophilic radioactive tracer diffuses through BBB, using modified Kety-Schmidt to calculate CBF | Measurement of the T2 during first pass of an exogenous, paramagnetic, non-diffusible contrast agent through the capillary bed | Intravenous bolus infusion of iodinated contrast material First-pass tracer methodology used to measure cerebral haemodyna-mics | Using electromagnetically labelled arterial blood water as the endogenous diffusible tracer to measure CBF | Doppler Shift: measure velocity of red blood cells in relatively large cerebral artery |
| **Beside assessment** | No | Yes | No | No | No | No | Yes |
| **Emergency assessment** | No | Yes, although it takes approximate 30 minutes to create $^{99m}$Tc –HMPAO compound | Yes | Yes | Yes | Yes | Yes |

| | Positron Emission Tomography (PET) | Single Photon Emission Computed Tomography (SPECT) | Xenon-enhanced CT | MRI Dynamic susceptibility Contrast (DSC) | Dynamic Perfusion Computed Tomography (PCT) | Arterial Spin Labelling (ASL) | Transcranial Doppler (TCD) Ultra-sonography |
|---|---|---|---|---|---|---|---|
| **Contrast Material** | $C^{15}O_2$, $H_2{}^{15}O$, $^{15}O_2$ | $^{99m}$Tc –HMPAO<br>$^{99m}$Tc-ECD | Stable, non-radioactive Xenon gas | Gadolinium Chelate | Iodinated contrast material | None | None |
| **Radiation exposure** | Yes | Yes | Yes but small | No | Yes (but less than standard unenhanced CT) | None | None |
| **Route of administration** | Intravenous route | Intravenous route | Inhalation stable Xenon gas | Intravenous route | Intravenous route | Non-invasive | Non-invasive |
| **Assessed Parameters** | Global CBF rCBF, rCBV, rOEF, $CMRO_2$, glucose metabolism | Global and rCBF | Global and rCBF | CBF, CBV, MTT, TTP | CBF, CBV, MTT, TTP | CBF | CBV, ICA |
| **Strengths** | Accurate quantitative measurement | Does not require sedation<br>Simple semi-quantitative method<br>Does not require head stabilisation | Accurate quantitative technique<br>Can be repeated at 15-minute intervals, allowing CBF measurement in response to intervention | Intolerance to Gadolinium chelates is rare.<br>Repeatability<br>can be combined with other anatomic imaging to provide comprehensive information in one examination<br>Longitudinal assessment of tissue perfusion and metabolism | Good spatial resolution, data can be mapped with anatomic images<br>Multiple Cerebral Haemodynamics could be measured | Good Spatial resolution<br>Multiple repeated measurement easily to be performed<br>No contrast allergy issue | Simple and low cost<br>Can provide frequent and continuous measurement<br>High temporal resolution<br>Useful in recording cerebral emboli |

| | Positron Emission Tomography (PET) | Single Photon Emission Computed Tomography (SPECT) | Xenon-enhanced CT | MRI Dynamic susceptibility Contrast (DSC) | Dynamic Perfusion Computed Tomography (PCT) | Arterial Spin Labelling (ASL) | Transcranial Doppler (TCD) Ultra-sonography |
|---|---|---|---|---|---|---|---|
| **Weakness** | Expensive<br>Limited to research settings rather than in routine clinical practice<br>Long acquisition time<br>Sensitive to patient motion<br>Exposure to significant radiation dose | Poor spatial resolution compared to CT and MRI Semi-quantitative analysis only<br>Requires co-registration with CT or MRI scan | Head stabilisation with inflatable restraints is necessary<br>Sedative effect of the Xenon gas may not suitable for neurologically impaired patients<br>Long acquisition time, limited number of measurements could be obtained | MRI contraindications | Contrast allergy<br>Limited cerebral coverage | Poor signal to noise ratio<br>Long acquisition time<br>CBF results could be affected by the relatively long arterial transit time and limited water diffusibility<br>MRI contraindication<br>Very sensitive to subject movement (background suppression techniques have been introduced recently to correct this problem) | Assess CBV but not CBF<br>Limited to observations of large vessel flow velocities<br>Approximate 15% subjects do not have acoustic windows<br>Operator dependent<br>Assumption that insonated vessel diameter remains constant during assessment<br>Anatomical variation within the Circle of Willis making interpretation of signals difficult |

**Table 1.4b** Overview of CBF and CBV measurement techniques (II) (1, 184, 295-302).

**$^{99m}$Tc– HMPAO: Technitium-99m and hexamethylpropyleneamine oxime**

**$^{99m}$Tc– ECD: Technitium-99m and ethyl cysteinate dimer**

**ASL: Arterial Spin Labelling**

**BBB: Blood Brain Barrier**

**CBF: Cerebral Blood Flow**

**CBV: Cerebral Blood Velocity**

**CT: Computed Tomography**

**DSC: Dynamic Susceptibility Contrast**

**ICA: Internal Carotid Artery**

**MRI: Magnetic Resonance Imaging**

**MTT: Mean Transit Time**

**NIRS: Near-Infrared Spectroscopy**

**PET: Positron Emission Tomography**

**rCBF: Regional Cerebral Blood Flow**

**rCBV: Regional Cerebral Blood Velocity**

**rCMRO$_2$: Regional Cerebral Metabolic Rate of Oxygen**

**rOEF: Regional Oxygen Extraction Fraction**

**TCD: Transcranial Doppler**

**TTP: Time to Peak**

**Transcranial Doppler (TCD) ultrasonography**

Doppler ultrasound was first introduced in the 1950s to assess velocity in the systemic blood vessels (303, 304). However, it was not the ideal choice for assessing intracranial vessels at that time as the thickness of skull greatly attenuated the penetration of ultrasound waves. It was not until the 1982 when Aaslid et al. demonstrated using the frequency range of 1-2MHz, which is significantly lower than the conventional frequencies of 3-12 MHz, applied onto an area of the skull where the bone is sufficiently thin for ultrasound energy to penetrate (so called acoustic windows), that satisfactory measurement of the direction and velocity of blood flow in the cerebral blood vessels could be studied (305).

There are four different acoustic windows which can be used in the assessment of intracranial arteries: transtemporal, transorbital, sub-occipital, and submandibular (Figure 1.8). The transtemporal window is the most commonly used window in the assessment of CA as it allows easy insonation of the middle cerebral arteries (MCAs), anterior cerebral arteries (ACAs) and posterior cerebral arteries (PCAs). The principle of TCD follows the same principle as other Doppler ultrasound; being based on the Doppler effect, a theory first enunciated by Austrian Physicist Christian Andreas Doppler in 1942. Generally speaking, a change in the frequency of a wave, as of sound or light (source) and the observer are in motion relative to each other; the frequency increasing when the source and observer are nearing each other and decreasing when they move apart (306). The TCD probe emits sound waves that are reflected off moving red blood cells in large vessel with a frequency shift that is directly proportional to the velocity of the scattering elements. The intensity of the signal represents the number of blood cells travelling at a given velocity that are reflecting the ultrasound beam back to the transducer (307-309).

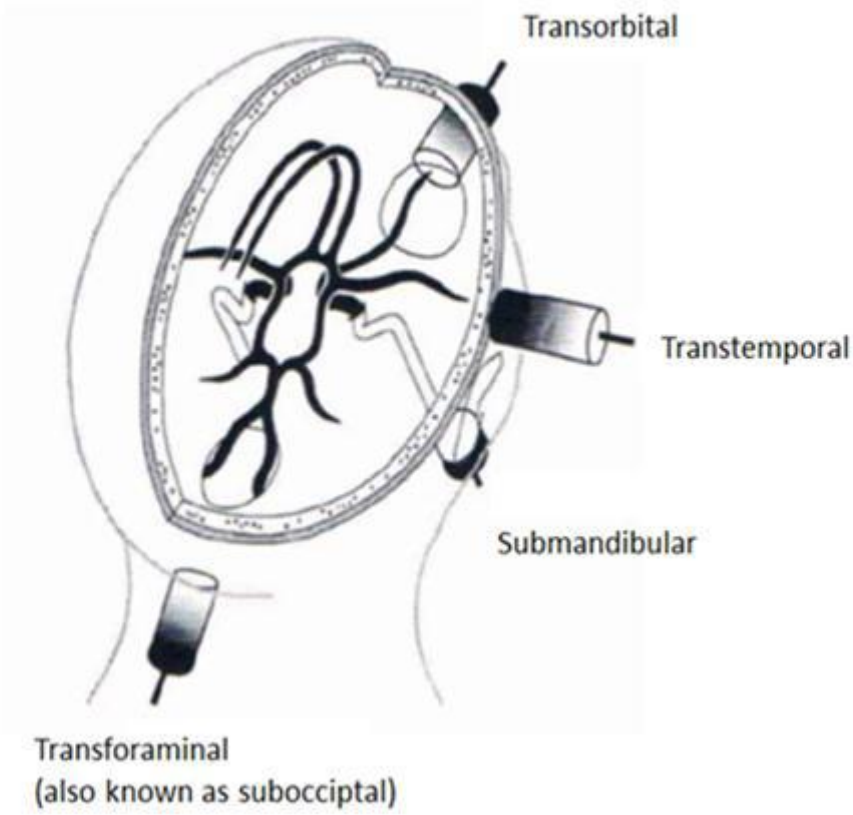



**Figure 1.8** The four main acoustic windows in assessing intracranial arteries [adapted from (310)].

TCD is non-invasive, cost effective and provides superior temporal resolution in the bedside setting (311). TCD generates reproducible values in both healthy controls and disease populations (312). Apart from being a widely accepted tool in assessing CA (313-315), TCD is recognised as a valid tool in detecting emboli during perioperative settings (316, 317). In head injury patients, TCD can also be used to detect vasospasm, act as an indicator of severity (318), and can also be used to confirm brain death (319, 320). TCD is a well-established technique in diagnosing cerebral arterial occlusion in AIS (321-323), the evaluation of collateral flow, the monitoring of subsequent arterial reperfusion after thrombolysis (307, 324) and detecting paradoxical embolism (patient foramen ovale) in

cryptogenic stroke (325-327). A meta-analysis carried out by Stolz and colleagues in acute stroke studies, recruiting at least 20 patients, has reported that early (< 6 hours) TCD ultrasound confirmed, complete MCA recanalisation, is an important marker of good outcome. This was evidenced by clinical improvement within 48 hours or functional independence at 3 months (328); suggesting that TCD plays an important role in providing prognostic information and also informing therapeutic decision making. Several *in vitro* studies have suggested that TCD can act as an adjunctive therapy for clot dissolution in AIS patient, simply by applying the low intensity ultrasound to enhance enzymatic effect of clot-busting agents, altering the fibrin structure and increased binding of intravenous thrombolysis (IVT) to fibrin (329-333). However, the Combined Lysis of Thrombus in Brain Ischaemia Using Transcranial Ultrasound and Systemic T-PA-Hands-Free (CLOTBUST-HF) study did not demonstrate any clinical benefit in using TCD as an adjunct of ultrasound enhanced thrombolysis (sono-thombolysis) (334), and it is not recommended in current AIS management guidelines (335).

There is a concern among clinicians that performing TCD prior to and during administration of IVT is associated with a delay in initiation of IVT compared to using non-contrast CT alone. A prospective cohort study was carried out in 244 AIS patients who received IVT (336). Of these 244 AIS patients, 116 patients (47.5%) underwent non-contrast CT, 79 (32.4%) underwent non-contrast CT and Computed Tomography Angiography (CTA), and 49 (20.1%) underwent non-contrast CT and TCD prior to IVT administration. There was a significant increase in door-to-needle time in the CTA but not in the TCD group. However, a recent study by Mazya et al., who looked at approximately 10 years of data from the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR), reported the door-to-needle time was significantly higher in AIS patients with pre-IVT TCD (74 mins vs. 60 mins;

p<0.001), suggesting TCD should only be performed during and after IVT infusion in order to avoid treatment delays (337).

There are several assumptions and limitations when using TCD in CA assessment. First, TCD measures CBV but not the absolute volumetric CBF and there is therefore an assumption that changes in CBV reflects changes in CBF (338). These assumptions have been explored in several studies which have confirmed that using TCD to measure CBV is a reliable and practical surrogate for direct CBF measurement (339-342). However, a recent study carried out by Coverdale and colleagues demonstrated that the cross sectional area (CSA) of MCA changes under hyper- and hypo-capnic conditions, and therefore CBV may underestimate CBF in such situations (343). Furthermore, when measuring CBV using TCD, there is an assumption that the diameter of the insonated vessels is kept constant. Although such an assumption has been found to be valid in various studies (341, 344, 345), some studies have also shown that the conduit vessels do, in fact, change diameter in various settings (343, 346-348). Secondly, only the larger cerebral arteries are able to provide an adequate CBV measurement. These arteries tend to supply a relatively large cerebral region, and therefore TCD gives an index of global, rather than local, stimulus response (338). Thirdly, it is important to note that age and sex could affect the 'normative' CBV value, and therefore, caution should be taken when analysing such results (349). Fourthly, the quality of TCD assessment relies on the operator's technical skills and anatomical knowledge. Familiarity with cerebral artery anatomy, insonation depths and CBV can significantly increase the quality and validity of the measurement. Finally, in the presence of laminar flow, the velocity of blood through a vessel is parabolic in shape, i.e. with the fastest velocity in the centre of the vessel. The reflected Doppler frequency shift will consequently comprise a distribution of frequencies, rather than a single value. One of the approaches in extracting meaningful velocity values is to apply

the Fast Fourier Transform (FFT) algorithm to short segments (typically $\Delta t$=5 ms) of the raw Doppler shifted signal, and the maximum or mean velocity is calculated from the maximum or intensity weighted mean $\Delta t$, respectively (350, 351). The velocity distribution, the maximum velocity envelope and the intensity-weighted mean are normally displayed as a colour coded sonogram (Figure 1.9).

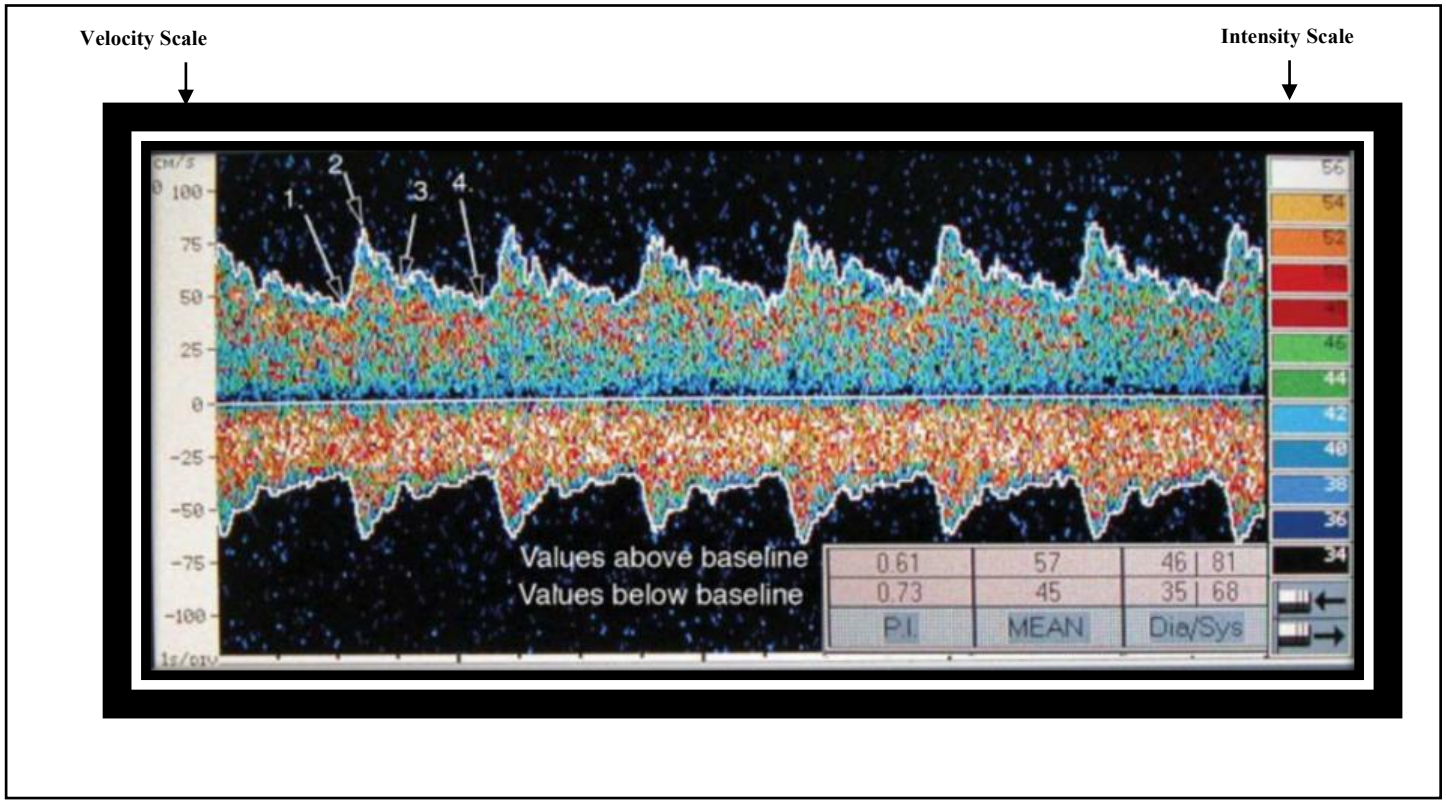



**Figure 1.9** Transcranial Doppler (TCD) sonogram, adapted from (352).

**1: Beginning of systole** **2: Peak Systole** **3: Diacrotic notch** **4: End diastole**

**PI: Pulsatility Index** **Dia/Sys: Diastolic and Systolic Blood Flow Velocity**

**Mean: Mean Blood Flow Velocity**

### 1.3.4 Methods for assessing Cerebral Autoregulation

CA can be assessed as either a *static* (sCA) or *dynamic* (dCA) phenomenon. sCA reflects the steady-state relationship between the gradual change of CBF and MAP, demonstrating the adaptation of CVR to the new, stable BP reading (182). If CVR does not change with MAP manipulation, CA is said to be impaired. sCA studies the outcome of the autoregulatory process (efficiency) over a period of time, but not the latency of the process itself (353, 354). dCA reflects the ability of CBF to recover following a rapid and transient alteration in perfusion pressure, usually over a period of seconds. In other words, it is the ability of CVR to change in response to the dynamic changes of BP (355, 356). Therefore, dCA addresses both the latency and the outcome of the autoregulatory response to the BP manipulation.

CA measurement is a complicated process as there are many physiological variables (i.e. BP, $PaCO_2$) that can affect CBF. CA is a very fast acting homeostatic mechanism and, therefore, the method for measuring autoregulatory response should ideally have excellent temporal resolution. It is important to remember that there are technical limitations to each of the measurement methods previously described. As such, there is not a single method that can be defined as the 'gold standard' (184, 357). sCA can be assessed by using vasoactive medications such as phenylephrine (PE) and norepinephrine (NPE) that have a limited effect on cerebral vasculature, or non-pharmacological manoeuvres such as Head-Up Tilt (HUT) to introduce a step change in mean BP. However, downfalls of these techniques are inconvenience and the risk posed to patients by BP manipulation. sCA is also vulnerable to confounding by the occurrence of spontaneous non-BP-related variability which could also affect CBF and therefore CA.

The time-consuming nature of procedures and the need for invasive pharmacological interventions has resulted in researchers seeking alternative ways to assess CA.

The Valsalva manoeuvre (358-360), lower body negative pressure (361, 362), bilateral thigh cuff technique (355), posture change (363-366), cold pressor stimulus (367, 368) and transient hyperaemia (achieved by compressing participants' carotid artery briefly) (369, 370) are some of the examples of non-pharmacological manoeuvres which can be used to assess dCA. Although the temporal relationship and the dynamic properties of CA can be easily assessed using the above techniques, it may be uncomfortable, impractical and even unacceptable to carry these out on patients. Difficulties in providing a consistent BP fall, and the possibility of inducing sympathetic activation, are some other drawbacks of these techniques. More recently, spontaneous fluctuations in BP at rest have been used as an autoregulatory stimulus in assessing dCA (169, 363, 371-373). Panerai et al. demonstrated there is a good correlation of Autoregulation Index (ARI) derived from an induced BP reduction between the thigh cuff technique and spontaneous fluctuations in BP (374). Additionally, Brodie and colleagues demonstrated satisfactory absolute and relative reliability of spontaneous fluctuations in BP and subsequent change in CBV in ARI measurements (375). However, there is ongoing debate regarding whether dCA should be measured by induced or spontaneous BP fluctuation (376, 377); Tzeng and colleagues have demonstrated poor correlation between different dCA measures using spontaneous BP fluctuation (378), and several studies have also suggested that CA reproducibility was improved when increased variability was induced in mean BP (379, 380), highlighting that limited signal-to-noise ratio (SNR) may not be able to produce robust CA measurements (376). Table 1.5 summarises the different approaches which can be used in the assessment of CA.

| | Valsalva manoeuvre | Periodic Breathing | Bilateral Thigh Cuff Inflation | Lower-body negative pressure | Postural Change | Cold Pressor Stimulus | Isometric exercise | Transient Hyperaemia | Spontaneous fluctuations of BP |
|---|---|---|---|---|---|---|---|---|---|
| **Description** | BP reduction as a result of elevation of intra-thoracic and intra-abdominal pressure induced by straining, which subsequently leads to reduction in venous return, CO and BP, and ultimately causing baroreflex mediated vasoconstriction | Period of pause in breathing followed by a series of rapid, shallow breathing | Rapid deflation of cuffs around thighs after an inflation lasting approximate 2 minutes. Peripheral resistance is reduced leading to a BP drop which acts as an autoregulatory stimulus | Reducing the atmospheric pressure surrounding the lower limbs leads to a reduction of extravascular pressure, dilatation of the veins and therefore increases lower limb blood flow | Sit to stand<br>Squatting<br>HUT | Placing a hand in ice water | Hand grip | Compressing subject's carotid artery for a brief period of time | BP oscillations ranging from 0.02 to 0.4Hz during normal daily activities |
| **Strengths** | Easy to perform<br>Can be performed in bedside settings | Easy to perform, does not require any extra medications<br>Can be performed in bedside settings | Can assess dCA in supine position, suitable for patients who are bedbound and in a neuro-critical state | Measurement can be made continuously and therefore ideal for monitoring trends over a defined time period<br>High vacuum level shows good reproducibility | HUT is a satisfactory method in assessing syncope<br>Sit to stand induces depressor change in both BP and CBV secondary to the underlying cardiopulmonary baroreflex mechanisms and represent daily physiological response | Easy to perform | Easy to perform<br>Can be performed in bedside settings | Easy to perform<br>Can be performed in bedside settings | Does not require medication or procedure to introduce BP oscillations<br>Has been carried out in neonates, head-injured, significant carotid stenosis and AIS patients. |

| | Valsalva manoeuvre | Periodic Breathing | Bilateral Thigh Cuff Inflation | Lower-body negative pressure | Postural Change | Cold Pressor Stimulus | Isometric exercise | Transient Hyperaemia | Spontaneous fluctuations of BP |
|---|---|---|---|---|---|---|---|---|---|
| **Weaknesses** | Valsalva Manoeuvre leads to increase in end-tidal $CO_2$ which is one of the important CBF regulators<br>Increased intra-thoracic pressure can lead to increased intracranial pressure which can subsequently affect physiological parameters that are responsible for CBF regulation | Leads to increments in tidal volume and hypocapnia<br>Difficulty in performing in patients with cognitive impairment or lung disease | Cuff inflation can cause pain<br>Activation of sympathetic pathways which can confound the interpretation of results<br>Induced BP change may not be suitable in certain group of patients i.e. heart failure, autonomic failure, carotid artery disease | Uncomfortable procedure that older and unwell patients may find difficult to tolerate<br>Not suitable in obese subjects | Not suitable for subjects who have difficulty in mobilising | Heterogeneous CBV response | Heterogeneous CBV response | Not suitable for subjects who have significant carotid artery disease | In some subjects the BP variability may not be high enough to induce satisfactory BP oscillation and therefore, estimation of dCA |

**Table 1.5** Methods for assessing CA (169, 184, 355, 356, 359, 361, 362, 364-370, 374, 379, 381, 382).

**BP: Blood Pressure** **CBV: Cerebral Blood Velocity**

**CA: Cerebral Autoregulation** **CO: Cardiac Output**

**CBF: Cerebral Blood Flow** **dCA: dynamic Cerebral Autoregulation** **HUT: Head Up Tilt**

### 1.3.5 Methods for assessing Cerebrovascular reactivity (CVRea) and Neurovascular Coupling (NVC)

CVRea can be assessed by measuring changes in CBF in response to hyper- and hypo-ventilation which results in hypocapnia and hypercapnia, respectively (253). Assessment in NVC can be achieved by using different functional activation paradigms to stimulate different cortical areas in normal healthy brains. Cerebral activation can be achieved through various cognitive tasks such as language, writing, speaking, visual stimulation and sensorimotor activities (200, 383-390). This results in a corresponding CBF increment in the feeding bed arteries, secondary to the increased regional demand for oxygen, glucose and other metabolites (391). Generally speaking, cognitive activities tend to induce global CBF changes due to the involvement of large number of cortical areas, whereas sensorimotor activities tend to induce regional CBF changes.

### 1.3.6 Analysis of Cerebral Autoregulation (CA)

With either induced or spontaneous changes in BP, the relationship between BP and CBF has to be quantified. However, there are many interactions between different input variables and it is this multivariate characteristic of CBF regulation which makes it very challenging to predict the response to a BP change. In this section, the most common analysis techniques used to quantify dCA, specifically Frequency Domain Analysis and Time Domain Analysis, will be discussed. It is important to note that both of these methods describe the relationship between BP and CBF as if it is linear (363, 381, 392). Laguerre expansion of Volterra kernels (393), principal dynamic mode (394) wavelet analysis (395), autoregressive and multimodal pressure-flow analysis (396) and dynamic support vector machine (397) are some of the examples of recently developed more complex mathematical models to allow for non-linear CA analysis. It is important to

acknowledge that, for all of these models, the assumption that they measure CA is always a simplification.

**Frequency Domain analysis**

Variations of a particular frequency in the input signal (ABP) are transmitted as signals of the same frequency in the output (CBV), and such relationships can be evaluated using the method of transfer function analysis (TFA). This was first proposed by Giller who performed it in both healthy controls and SAH patients (398).

The Transfer Function H($f$) between the two signals is calculated as:

$$H(f) = G_{PV}(f) / G_{PP}(f) \qquad \textit{Equation 1.5}$$

Where $G_{PV}(f)$ is the smoothed cross-spectra of BP and CBV and $G_{PP}(f)$ is the smoothed autospectra of BP.

TFA is based on the Welch's method and uses FFT to decompose stationary input and output signals into sums of sinusoidal waves of multiple frequencies (0-0.5Hz). Several parameters, such as coherence, gain and phase shift are used to quantify CA. Coherence represents the fraction of output power that can be linearly explained by the corresponding input power at each frequency, and its ranges between 0 and 1. It is analogous to the squared correlation coefficient and can be estimated by:

$$\gamma^2(f) = \left| G_{PV}(f) \right|^2 / G_{VV}(f)\, G_{PP}(f) \qquad \textit{Equation 1.6}$$

Where $G_{VV}(f)$ is the smoothed autospectra of CBV.

Values of coherence approaching 1 indicate a high SNR and/or a univariate linear input-output relationship. On the other hand, a value of coherence approaching zero indicates

that there is a non-linear input-output relationship, poor SNR or the presence of other variables influencing the output (351). According to the International Cerebral Autoregulation Research Network (CARNet) white paper, several factors such as number of windows, degree of overlapping and spectral smoothing, could all affect the threshold of coherence, highlighting should not have a single cut-off value adopted to all the studies (357).

Gain, or transfer magnitude, quantifies the magnitude of the output signal (CBV) in comparison to the input signal (BP). It represents the damping effect of CA on the magnitude of the BP oscillations. Gain alone is not a reliable measure of CA as the absolute value of gain can be easily affected by the baseline value of CBV (i.e. MCA diameter) and BP. This issue can be overcome by using normalised gain, which is the product of gain and CVR. In general, an increase in gain suggests impaired CA, whereas a low gain suggests an efficient CA.

The phase shift represents the displacement of the output waveform (CBV) relative to input waveform (BP), i.e. it measures the time delay between the input (BP) and the output (CBV) at a given frequency. When CA is intact, changes in CBV occur faster than the changes in BP. As such, the CBV oscillation appears to lead BP oscillation. The phase shift can be expressed as degrees from $0^0$ to $360^0$, or in radians from 0 to $2\pi$. A positive phase shift indicates there is an intact CA as the CBV changes before BP whereas if the phase shift that is close to 0 indicates there is no time delay between BP and CBV, suggesting CA is impaired. There are some limitations when using phase as a parameter to assess CA integrity. Firstly, if the value for phase is greater than $\pi$ Radians, it results in the signal 'wrapping around' the Y-axis and therefore produces a falsely negative result. Another limitation is that phase can be affected by the rate of respiration, although

several studies which have used phase as a parameter to assess CA integrity have fixed the rate of respiration (381, 399). However, it may be extremely difficult to carry out such a restriction in clinical research, especially in patients with underlying cognitive impairment.

Due to the time delay required to initiate cerebrovascular adaptation to the changes in perfusion pressure, CBV regulation tends to be more effective in LF BP changes (0.02 to 0.20Hz). Therefore, the cerebral autoregulatory feedback control system acts as a high-pass filter, damping effectively only VLF BP changes and allowing high frequency BP changes to be transmitted to CBV (400), as VLF (0.02-0.07 Hz), LF (0.07-0.20 Hz), and HF (0.20- 0.50 Hz) (372).

**Time Domain analysis**

As the name suggests, time domain analyses study various physical parameters [CBV, BP, heart rate (HR), $EtCO_2$] with respect to time. Traditionally, the efficiency of dCA can be assessed by the time of CBV recovery after a single sudden change in BP challenge, known as rate of recovery (RoR) (355). However, same as other metrics, RoR does not take CSA between CBF and CBV into account. CVR, cerebrovascular resistance index (CVRi), pulsatility index (PI) and correlation coefficient are some of the examples of quantifying CA using time domain methods. CVR acts as a regulator between the transfer of BP input signal to the CBV output signal. It is the resistance of small cerebral vessels distal to the site of insonation and can be defined as:

$$CVR = BP_{mean} / CBF_{mean} \qquad \textit{Equation 1.7}$$

The total brain weight is taken into account when using CBF to calculate CVR, however, in TCD studies where total brain weight is lacking, cerebrovascular resistance index (CVRi) can be used to quantify dCA instead:

$$CVRi = BP_{mean} / CBV_{mean} \qquad \textit{Equation 1.8}$$

Gosling's pulsatility index (PI) is defined as the difference between systolic and diastolic extremes of CBV divided by the mean of CBV, and can also be used to reflect CVR (401). In a steady state condition, PI is directly proportional to CVRi but inversely proportional to CBV. However, such a relationship could not reproduced in pathological settings. Therefore, the PI cannot serve as an adequate parameter to assess dCA.

Mean Velocity Index (Mx), a cross-validated index of CA was first described by Czosnyka and colleagues in head injury patients (402). It can be determined by calculating the correlation coefficient between consecutive time-averaged (every 3 minutes) samples of slow, spontaneous fluctuations in CBV and CPP. Lang et al. subsequently reported a modified Mx index, correlating BP rather than CPP with CBV (403), in which a strong correlation between the two indices and outcome in head injury was found. A positive Mx indicates a positive association between CBV and CPP and therefore impaired CA. On the other hand, a zero or negative Mx indicates there is an absent or negative association, suggesting functioning CA. Mx can be repeated along the time window of correlation, acting as a continuously monitored variable and indicating CA changes with time. Mx has been demonstrated to have prognostic value in various pathological conditions such as traumatic brain injury (TBI), carotid stenosis, haemorrhagic and IS (404-406).

**Autoregulation Index (ARI)**

By studying dCA using the thigh cuff release technique, sCA responses with intact autoregulation during propofol anaesthesia (no effect on CA) and during high-dose isoflurane anaesthesia (known to impair CA in a dose-dependent manner), Tiecks et al. demonstrated that dCA yielded similar results to sCA in healthy individual settings, thus demonstrating a good correlation between the two methods (356), although a recent study carried out by de Jong and colleagues overthrew this idea (407). Using the alterations in CVRi in relation to the change in BP, Tiecks et al. proposed a concept of ARI: a second order differential equation which consists of three main parameters: a time constant, a damping factor, and an autoregulatory gain. Initially, ARI was only defined from the response to the thigh cuff manoeuvre; TFA is subsequently used to quantify the dynamic relationship between the input (BP) and output signal (CBV). The inverse Fourier transform of the gain and phase can subsequently estimate the CBV response to a sudden change in BP, termed impulse response, in the time domain manner. The impulse response is then used to calculate the CBV step response and generate ten hypothetical CBV step response curves, ranging from 0 to 9 (Figure 1.10). A value of ARI equal to zero suggests the absence of CA as CBV follows BP in the exact time course manner (a pressure-passive relationship). On the other hand, an ARI value of 9 represents the best measurable CA response (356). A recent meta-analysis of TFA in AIS studies, suggested that ARI and phase, but not gain, demonstrated significant differences in comparison with controls (408). In AIS patients, it is generally accepted that an ARI $\leq$ 4 represents impairment in CA (349, 409).

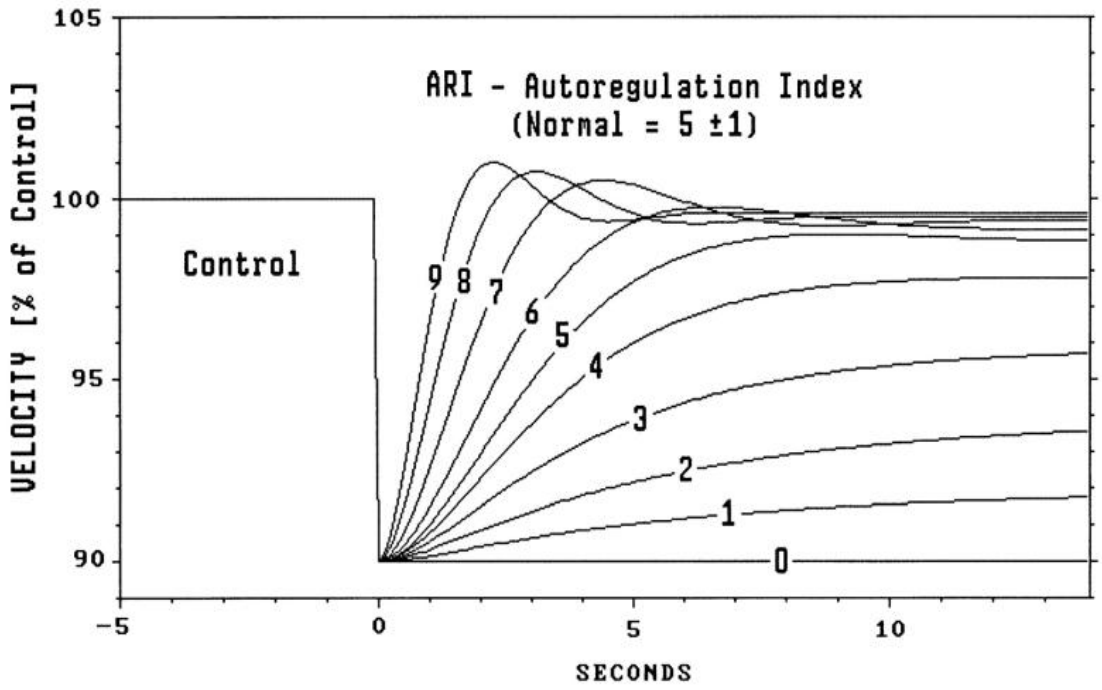



**Figure 1.10** The Autoregulation Index [adapted from (356), with permission].

Critical closing pressure (CrCP) and resistance area product (RAP) are two other parameters that can be used to assess CA validity in time domain settings. CrCP, expressed as mmHg, indicates the value of BP at which CBF ceases. It is the point where transmural pressure is not sufficient to counteract the active tension imposed by the smooth muscle and therefore, the corresponding vessels collapse and blood flow ceases (410, 411). Similar to other parameters used in the time domain analysis, estimation of CrCP can only occur if the pressure-flow relationship is considered to be linear. Therefore, the estimates of CrCP can only reflect the apparent values, rather than the true value, when CBF or CBV becomes zero. Similarly to CBV, 'normative values' of CrCP could also be affected by age (349). RAP is an index of vascular resistance; it is the inverse of the linear CBV-BP relationship slope, and is the product of CBV and the corresponding vessel's CSA. It has been suggested that CrCP reflects intracranial pressure, arterial tone and the metabolic mechanisms involved in underlying CBF

regulation, whereas RAP could be associated with the corresponding myogenic mechanism (411-413).

### 1.3.7 Cerebral Autoregulation and Ischaemic Stroke

The integrity of CA in the setting of IS, in particular, during acute vessel occlusion and the reperfusion phase is of significant clinical importance. Following cerebral ischaemia, when a blood vessel is cleared of occluding intraluminal thrombus, either spontaneously or therapeutically, there will be a short phase of hyperperfusion, known as post-ischaemic hyperaemia, followed by a secondary prolonged phase of delayed hypoperfusion, in which the reduction of the brain blood flow is often below the pre-ischaemic level (414-416). The duration of post-ischaemic hyperaemia is often directly proportional to the duration of the ischaemia (417). Impairment in CVR mechanisms (418, 419), imbalance between local vasodilators and vasoconstrictors (420) and stagnation of blood flow in post-capillary venules (421) are some of the theories that have been proposed to explain the underlying pathophysiology of delayed hypoperfusion.

Numerous studies have investigated CA in the post-acute stroke setting. However, the conclusions drawn from these studies have been inconsistent. In particular, the influence of impaired haemodynamics on improvement of clinical cerebral function over time remains uncertain, such that the clinical application of the results of these studies is still not fully understood. A systematic review of TCD autoregulation in AIS revealed considerable heterogeneity in autoregulation methodology and time points of measurement (2). Moreover, the number of patients recruited tended to be small, with various types and location of infarction, making robust analysis and interpretation difficult. Therefore, further studies and research are needed to investigate the relationship between CA and IS.

It is generally accepted that impairments in dCA are usually seen after AIS (2, 408), though a recent study carried out by Salinet et al. suggested cerebral autoregulatory impairment only occurs in moderate (median NIHSS =9) to severe stroke (median NIHSS > 18), with preserved CA in the acute period associated with improved functional outcome at 3 months (422). Immink and colleagues studied dCA following AIS and demonstrated that dCA impairment is only found in the affected hemisphere (AH) in the MCA stroke patient, but bilaterally following lacunar stroke (423). These observations are supported by Guo et al., (424), highlighting cerebral microangiopathy could occur in lacunar stroke which results in global CA changes (425). On the other hand, other studies suggest dCA is not only impaired in the AH (local dysautoregulation), (373) but also in the non-affected hemisphere (NAH) (global autoregulatory dysfunction) following AIS (158, 169, 353, 406, 426-429). Reinhard et al. found that dCA impairment in the AH is associated with larger infarct size and when CA impairment extends to the NAH during the acute stage of stroke it is associated with poorer clinical outcome (430). It has also been suggested that milder but more global autoregulatory dysfunction probably evolves during the first-days following AIS (430). Such observations are supported by Castro et al. who demonstrated CA impairment in AIS (AH) is associated with cerebral haemorrhage and oedema at 24 hours post stroke symptom onset (431), and worsening functional outcome at 3 months (432).

Several TCD studies have been undertaken within the first few days following AIS, finding that bilateral disturbance in dCA is observed in the MCA, lasting for at least 2 weeks, independent of stroke subtype and severity (158, 169, 353, 433). However, this was not observed in the evaluation of sCA, suggesting that these two processes may be controlled by different underlying mechanisms, and that dCA may be more sensitive in detecting CA impairment in AIS when compared to sCA (158).

There are also conflicting results regarding the course of CA over time following stroke. Studies have suggested that bilateral CA impairment occurs in both the sub-acute and chronic phases of IS (353, 434). Kwan et al. studied the CA time course in stroke and found that there was bilateral CA impairment in the acute phases (less than 7 days) with subsequent improvement from the sub-acute phase onwards (6 weeks post onset) (382). Salinet et al. carried out serial TCD assessment of CA in AIS patients over a 3-month period, and reported that there was a reduction in bilateral CBV response in the acute phase, followed by CBV increase in the NAH at one month, and then a progressive return to a normal CBV response pattern by 3 months. On the other hand, Salinet et al. also found that CA was not impaired acutely, and a significant reduction in ARI was only seen by week 2, with subsequent improvement over time (427). It is important to remember that the size of all these studies is small, and therefore power is limited to permit detailed subgroup analyses. Moreover, as mentioned in the previous section, when using TCD in assessing CA in stroke patients, a small MCA infarct could lead to severe focal CA impairment without global autoregulatory dysregulation detected in the MCA main stem. Therefore, more studies using haemodynamic monitoring techniques, especially those with a high spatial resolution, [e.g. functional MRI (fMRI)], are needed in order to provide a better understanding in this particular field. Table 1.6 summarises some important TCD studies which have used time and frequency domain analyses in assessing AIS patients.

| Study | Number of patients/ controls | Patients characteristics | Mean/Median admission NIHSS | Time of assessment | Assessment Methods | Which hemisphere affected? | Main findings |
|---|---|---|---|---|---|---|---|
| Dawson 2000 (158) | 54 IS<br>61 Controls | IS: 69±11.7 yrs<br>Controls: 67±9.7 yrs | 8±3.6 | Mean 2.1±1.3 days | Isometric handgrip (sCA)<br>Thigh cuff manoeuvre (dCA) | Both | dCA, but not sCA was impaired when compared to controls. |
| Eames 2002 (169) | 56 IS<br>56 controls | IS: 70±9 yrs<br>Controls: 69±7 yrs | Unknown | < 72 hrs post stroke onset | Spontaneous BP | Both | dCA is globally impaired when compared to controls. |
| Kwan 2004 (382) | 10 MCA IS | 73±11yrs | Unknown | < 7 days post stroke onset | Isometric handgrip | Both | No significant difference in phase and gain when compared to both hemispheres, improving CA (increase phase and decrease gain) over 3 months post stroke symptom onset. |
| Immink 2005 (423) | 10 MCA IS<br>10 Lacunar IS<br>20 Controls | MCA IS: 63±3 yrs<br>Lacunar IS: 59± 5 yrs<br>Controls: 57±2 yrs | MCA IS: 17±2<br>Lacunar IS: 9±1 | < 72 hrs post stroke onset | Spontaneous BP | MCA IS: AH<br>Lacunar IS: both | dCA impaired bilaterally in lacunar IS but only AH in MCA IS. |
| Reinhard 2005 (373) | 33 IS | 61±12 yrs | IS: 4.5±3.8 | 22±11 hrs post stroke onset | Spontaneous BP | Both | dCA is not significantly affected in subacute stage. |

| Study | Number of patients/ controls | Patients characteristics | Mean/Median admission NIHSS | Time of assessment | Assessment Methods | Which hemisphere affected? | Main findings |
|---|---|---|---|---|---|---|---|
| Gommer 2008 (434) | 29 Lacunar IS (only 19 cases analysed) | Median: 67 (40-80) yrs | Unknown | Median 93 (50-190) days | Spontaneous BP, Acetazolamide infusion | None | dCA is not impaired. |
| Reinhard 2008 (404) | 16 MCA IS (with IVT) | 67±12 yrs | 14±3 | 20±9 hrs | Spontaneous BP | AH | Patients with unsuccessful recanalisation had impairment in dCA over first 5 days post stroke symptom onset. |
| Atkins 2010 (433) | 19 IS<br>17 TIA<br>22 Controls | IS: 67 ± 11 yrs<br>TIA: 62 ± 11 yrs<br>Controls: 65 ± 8 yrs | Median NIHSS 3 (2-6) | Median 36 hrs (24-48) | Spontaneous BP | AH | Impairment in dCA observed in mild ischaemic stroke, but not TIA at baseline. |
| Saeed 2013 (426) | 22 IS (11 Cortical vs. 11 Subcortical)<br>10 Controls | Cortical IS: 65±19 yrs<br>Subcortical IS: 60±18 yrs<br>Controls: 59±15 yrs | Not available | <48 hrs post stroke symptom onset | Spontaneous BP<br>Thigh Cuff manoeuvre | Both | No significant differences between hemisphere in controls, subcortical and cortical IS. Cortical IS has lower ARI compared to subcortical IS. |
| Guo 2014 (435) | 15 LAA<br>21 SVD<br>20 controls | LAA:44.7±13.1 yrs<br>SVD: 54.1±9.7 yrs<br>Controls: 42.2±13.7 yrs | LAA: 7.1±4.7<br>SVD: 3.8±2.8 | 5-10 days post stroke symptom onset | Spontaneous BP | LAA: AH<br>SVD: global | In LAA IS, dCA impairment only observed in AH, but bilaterally in SVD IS. |
| Salinet 2014 (427) | 15 IS<br>22 Controls | IS: 62.4±9 yrs<br>Controls: 62.2±7.5 yrs | 7.8±4.8 | <72hrs post stroke symptom onset | Spontaneous BP<br>Passive elbow movement (NVC) | Both | ARI deceased at 2 weeks, and returned to control levels during recovery (1-3 months). |

| Study | Number of patients/ controls | Patients characteristics | Mean/Median admission NIHSS | Time of assessment | Assessment Methods | Which hemisphere affected? | Main findings |
|---|---|---|---|---|---|---|---|
| Tutaj 2014 (436) | 6 UA IS<br>14 Controls | IS: 66±9 yrs<br>Controls: 62±10 yrs | Median: 4 (2.5-6.5) | < 72 hrs post stroke symptom onset | Deep Breathing | NAH | dCA is impaired in NAH during acute phase of the disease. |
| Guo 2015 (424) | 46 MCA IS<br>25 PCA IS<br>30 Controls | MCA IS: 54±9.5 yrs<br>PCA IS: 53±10 yrs<br>Controls: 54±10.6 yrs | MCA IS: 3.74±1.9<br>PCA IS: 3.88±1.69 | Up to 6 months follow up | Spontaneous BP | Both | Bilateral dCA impairment in lacunar IS, irrespective of the location of territory involved. |
| Petersen 2015 (437) | 28 IS<br>29 Controls | IS: 68.4±17.1 yrs<br>Controls: 54.9±9 yrs | 12±6.5 | 1.3±0.5 days post stroke symptom onset | Spontaneous BP | AH | CA impairment (AH) occurs within first week of stroke symptom onset, and normalises by second week. |
| Castro 2017 (431) | 46 IS | 73±12 yrs | Median NIHSS 14 (9-22) | < 6 hrs post stroke symptom onset | Spontaneous BP | AH | CA impairment (reduction in phase) observed in patients with cerebral haemorrhage and oedema, within 24 hrs of post stroke symptom onset, normalised by 3 months. |
| Castro 2017 (432) | 30 IS | 69±13 yrs | Median 9 (5-15) | < 6 hrs post stroke symptom onset | Spontaneous BP | AH | CA Impairment (reduction in phase) associated with worse functional outcome at 3 months. |

| Study | Number of patients/ controls | Patients characteristics | Mean/Median admission NIHSS | Time of assessment | Assessment Methods | Which hemisphere affected? | Main findings |
|---|---|---|---|---|---|---|---|
| Xiong 2017 (428) | 60 IS (LAA=30, SVD=13, LAA and SVD=17) 16 Controls | LAA: 61.5 (52.8-71.5) yrs SVD: 68.0 (61.5-79.0) yrs LAA and SVD: 69.0 (60.0-74.5) yrs Controls: 59.0 (57.3-61.8) yrs | LAA: 5.0 (3.8-8.0) SVD: 4.0 (3.0-5.5) LAA and SVD (6.0-9.0) | < 16 days post stroke symptom onset | Spontaneous BP | Both | dCA is bilaterally impaired in IS with LAA. Coexisting LAA and SVD show worse dCA impairment. |
| Ma 2018 (429) | 67 IS (LAA = 12 SVD= 47 UA=8) | 52.8±10.2 yrs | 6.0±3.3 | < 3 days post stroke symptom onset | Spontaneous BP | Both | Bilateral dCA impairment observed in acute and subacute phase. IS who received IVT tended to have better dCA in the acute phase. |
| Truijen 2018 (438) | 39 IS 17 Controls | IS: 68±12 yrs Controls: 64±7 yrs | 8±6 | <48 hrs post stroke symptom onset | Head positioning changes | Both | dCA performance was not significantly different between groups or hemispheres. |

**Table 1.6** Important TCD studies assessing CA status in AIS patients. Mean ± SD or median (Interquartile range).

**AH: Affected Hemisphere**

**BP: Blood Pressure**

**CA: Cerebral Autoregulation**

**dCA: dynamic Cerebral Autoregulation**

**IS: Ischaemic Stroke**

**IVT: Intravenous Thrombolysis**

**LAA: Large Artery Atheromatous**

**MCA: Middle Cerebral Artery**

**NAH: Non-affected Hemisphere**

**NIHSS: National Institutes of Health Stroke Scale**

**NVC: Neurovascular Coupling**

**sCA: Static Cerebral Autoregulation**

**SVD: Small Vessel Disease**

**TIA: Transient Ischaemic Attack**

**UA: Undetermined Aetiology**

### 1.3.8 Neurovascular Coupling and Ischaemic Stroke

Although NVC is known to be impaired in AIS and neurodegenerative disorders, such as Alzheimer's disease (200), limited data are available regarding the relationship between NVC, stroke subtype and associated aetiologies. Salinet et al. recruited 61 AIS participants, within 48 hours of stroke symptom onset, and carried out a passive elbow paradigm to assess NVC status. She demonstrated NVC impairment during acute phase of the disease, irrespective of the stroke subtype and severity (422). Following AIS, incremental CBF change produced by functional activation is decreased. This leads to an inadequate matching of CBF to neural activity which in turn leads to damage to neuron and glial cells (216). This decreased flow phenomenon could be attributed to a reduction in capillary diameter secondary to astrocyte end-foot swelling (439), defects in arteriole vasodilatation mechanisms (440, 441), or failure of pericyte relaxation secondary to oxidative stress (442), which leads to the absence of ATP to pump calcium out of the cell. This results in pericytic rigor making the capillaries too small for the passage of red blood cells (443).

There is also a suggestion that following AIS, neuronal activity is not coupled to regional CBF and CBV changes to the same degree as in healthy subjects. Lin et al. carried out a functional TCD study to evaluate NVC in a clinically asymptomatic cortical area in patients with large intracranial artery stenosis and small vessel disease. Both groups showed similar degrees of NVC impairment, in particular in large intracranial artery stenosis patients, there were no significant differences in terms of the degree of NVC impairment in both AH and NAH. This suggests that there is a possibility that NVC impairment extends to clinically asymptomatic vascular territories outside the infarct area (444). Several BOLD fMRI studies which studied NVC in post-IS patients have found

that they can either have transient missing BOLD signals (445) or lower BOLD signal change (in both AH and NAH), when compared to healthy controls (446). However, it has still not been possible to correlate imaging findings with post-stroke clinical outcome (447).

## 1.4 Cerebral Perfusion Strategies in Acute Ischaemic Stroke Disease

Recanalising the occluded intracranial arteries is one of the primary aims in the treatment of hyperacute stroke. Deprivation of CBF will ultimately lead to cell necrosis, and early recanalisation will limit the extent of infarction and lead to an associated improvement in clinical outcome. Several strategies have been suggested recently to improve cerebral perfusion following AIS, these strategies can be divided into pharmacological, such as pressor therapy, intravenous (IV) and intra-arterial (IA) thrombolysis or non-pharmacological therapy, such as mechanical thrombectomy (MT), partial aortic occlusion, external compression system and head positioning adjustment. However, there is limited information regarding the effect of the above perfusion strategies on cerebral haemodynamics following IS. Several advanced neuroimaging modalities, including CT perfusion, MRI diffusion-perfusion imaging, SPECT and PET, have been introduced in the last decades and provide valuable information regarding the degree of reversibility of ischaemic injury, discriminating between the infarct core and potential salvageable penumbra, and estimating the size and location of the occlusive intracranial lesion. Although these modalities are becoming increasingly available in clinical settings, current international guidelines still recommend non-contrast CT as the primary imaging modality for the initial evaluation of patients with suspected stroke (335).

### 1.4.1 Cerebral Perfusion Strategy Targeting Intracranial Occluded Vessels

**Antiplatelet therapy**

Individuals who suffer IS or TIA and not requiring anticoagulation (i.e. in sinus rhythm), should be given antiplatelet therapy for secondary prevention; Aspirin, Clopidogrel, Dipyridamole, Triflusal and Cilostazol are some examples (335, 448). Loading does of antiplatelet (i.e. 300mg of Aspirin or Clopidogrel) are required during the acute phase of IS order to provide maximal inhibiting effect in platelet aggregation. The Anti-Platelet Trialists' collaboration meta-analysis reported a 25% reduction in non-fatal stroke (449). The safety and efficacy of using Aspirin in AIS have been demonstrated in both large clinical trials (450, 451) and a Cochrane review (452); though there was a small but definite bleeding risk, the benefits outweigh the hazards (452). Importantly, low dose Aspirin (75-162 mg OD) was as effective as higher daily dose (> 162mg OD) (453). Comparative trials have shown that Aspirin plus modified-release Dipyridamole (RR= 0.82%; 95% CI=0.74-0.91) (454-456), and Clopidogrel monotherapy (RR=0.91%; 95% CI=0.84-0.97) are equally effective at reducing stroke risk, with both options superior to Aspirin monotherapy (457). Triflusal shows similar efficacy in reducing stroke risk when compared to Aspirin, but with fewer adverse events (458). This observation is also supported by a recent randomised controlled trial, which allocated stable coronary artery disease or non-cardioembolic IS patients either on Triflusal 300mg BD, 600mg OD or Aspirin 100mg OD for 12 months. Results demonstrated Triflusal has a similar efficacy (95% CI=-1.1 to 3.5) and better safety profile when compared to Aspirin (459). A recent meta-analysis demonstrated Cliostazol reduces the recurrent stroke risk when compared with Aspirin (50mg OD) plus Dipyridamole (400mg OD) (OR=0.75; 95% CI=0.52-1.02)

or Clopidogrel alone (75mg OD) (OR=0.76; 95% CI=0.51-1.05), though it did not reach statistical significance (453).

Several trials have investigated the use of Aspirin and Clopidogrel in combination, compared to Aspirin or Clopidogrel as monotherapy in AIS. Although some studies suggest there is no significant potential benefit in using dual antiplatelet in AIS (460, 461), and it is also associated with increased risk of haemorrhage (462), other studies suggest there is a benefit in terms of reduction in stroke recurrence at 90 days in patients who have minor stroke, TIA (463) or carotid artery disease (464). The CHANCE (Clopidogrel in High Risk Patients with Acute Non-disabling Cerebrovascular Events) was a double-blinded, randomised controlled trial, looking at using dual antiplatelet therapy (Aspirin plus Clopidogrel) within 21 days post stroke symptom onset, followed by Clopidogrel alone to 90 days, in Chinese patients with mild stroke (NIHSS $\leq$ 3) or high risk TIA ($ABCD^2 \geq 4$). The study demonstrated that the primary outcome of recurrent stroke at 90 days was favoured in dual antiplatelet therapy rather than Aspirin alone, without significantly increase in haemorrhagic risk (465). However, the POINT (Platelet-orientated Inhibition in New TIA and Minor Ischaemic Stroke) randomised trial, looking at using dual antiplatelet (Clopidogrel 600mg on day 1 followed by 75mg OD and Aspirin 50-325mg OD) or Aspirin only (50-325mg OD) in patients with mild stroke (NIHSS $\leq$ 3) or high risk TIA ($ABCD^2 \geq 4$), study was discontinued prematurely, it demonstrated reduced recurrent stroke events with dual antiplatelets (hazard ratio=0.75; 95% CI=0.59 to 0.95; p=0.02), it was associated with significant major bleeding risk (hazard ratio= 2.32; 95% CI=1.10 to 4.87; p=0.02) (466). Furthermore, the TARDIS (Triple Antiplatelets for reducing dependency after ischaemic stroke) trial was terminated prematurely as it demonstrated using intensive triple antiplatelet therapy (Aspirin,

Clopidogrel and Dipyridamole) was associated with significantly increased risks of bleeding, without reducing the incidence of recurrent and severity of IS and TIA (467).

**Anticoagulant therapy**

Both AIS and TIA patients who are found to be in persistent, permanent or paroxysmal non-valvular AF, or where there is an identified cardiac source of embolus, should be considered for anticoagulation (32, 335). The vitamin K antagonist (VKA), Warfarin, is an anticoagulant widely used in various clinical settings. Similar to antiplatelet therapy, treatment should be initiated only after ICH is excluded. There is no superior effect of using anticoagulation in non-cardiac IS patients. Moreover, this is associated with an increased risk of haemorrhage and is therefore not recommended (468-470).

Recently, the direct oral anticoagulants (DOACs) [Dabigatran (471) , Rivaroxaban (472), Edoxaban (473) and Apixaban (474)] have been approved for both primary and secondary IS prevention in non-valvular AF. Recent Cochrane reviews and meta-analysis suggest that, in both primary and secondary IS prevention, DOACs demonstrate similar efficacy with lower sICH risk when compared to VKA (475, 476). Similar to VKA, there is no superior effect of using DOACs in non-cardiac IS patients (477). Due to the potential risk of haemorrhagic transformation in those with large infarcts, in individuals with disabling stroke, anticoagulation treatment (VKA or DOACs) should be deferred for 14 days (with Aspirin 300mg used in the interim) (335, 478), whilst in those with non-disabling stroke and TIA treatment may be commenced sooner (4-14 days), at the discretion of the treating clinician (335, 448).

**Intravenous Recombinant Tissue Plasminogen Activator (IV rtPA)**

Thrombolytic therapy (IVT) is a widely approved treatment for AIS. Currently, the only thrombolytic drug licensed for use in AIS is Alteplase, which is given at a dose of 0.9mg/kg (maximum dose 90mg). 10% of the total dose is given as a bolus injection, and the remaining 90% infused over one hour (335). Recently, several randomised controlled trials have been carried out to investigate other promising thrombolytic agents (479-481). The landmark National Institute of Neurological Disorders and Stroke (NINDS) rtPA Trial, in which more than 600 patients with AIS were treated either with placebo, or IVT within 3 hours of the stroke symptom onset showed that for those AIS patients treated with IVT, at least 30% were more likely to have minimal or no disability at 3 months, with an acceptable risk of sICH and no significant difference in mortality (482, 483).

The Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) was a large scale, prospective registry study which looked at approximate 6500 AIS patients from 285 centres, comparing those who were treated with 0.9mg/kg IV Alteplase, within 3 hours of symptoms onset to those who were treated with the same dosage of IV Alteplase, but within 3-4.5 hours of symptoms onset (484). These registry data suggest both groups show similar rates of functional independence (mRS of 0-2) (58% of patients treated within 3-4.5 hours of symptom onset compare to 56.3% of patients treated within 3 hours of symptom onset; p= 0.42) and recovery (mRS of 0-1) (40.5% compare to 39.9%; p=0.79). Moreover, the rates of sICH and mortality are similar between the two groups, suggesting it could be safe to use IV Alteplase in AIS patients up to 4.5 hours of the symptom onset.

The Third European Co-operative Acute Stroke Study (ECASS III) was a randomised controlled trial, and demonstrated AIS patients, administered IV Alteplase 3-4.5 hours

post stroke symptom onset, were significantly more likely to have a favourable outcome (mRS ≤ 1) when compared to placebo (OR=1.34; 95% CI=1.02-1.76; p=0.04), though the risk of sICH was also greater in IV Alteplase group (2.4% vs. 0.2%; p=0.008) (130).

Emberson et al. undertook a meta-analysis of nine randomised trials, comparing IVT versus placebo or standard acute stroke regimes. Of 6765 patients, results showed that IVT is associated with significant functional outcome improvement when treatment is given within 4.5 hours of stroke symptom onset. Moreover, the earlier the treatment is given, the greater the proportional benefit (OR=1.75; 95% CI=1.35-2.27), highlighting the importance of giving IVT is an urgent manner (485).

Despite extension of the therapeutic time window and improvements in neuro-radiological imaging which have increased IVT rates, up to 15% of IS occur during sleep with unknown time of onset (486, 487); i.e. patients are not eligible for IVT according to current guidelines (335). The WAKE-UP Study was a multi-centre, investigator blind, randomised controlled trial, looking at AIS patients with unknown time of stroke onset, but with a positive MRI DWI-FLAIR mismatch, and randomised to either IVT or placebo. Results suggested patients receiving IVT had better functional outcome (mRS≤1) when compared to controls (53.3% vs. 41.8%; OR=1.61; 95% CI=1.17-2.23; p=0.003), without significant increase sICH rate (2% vs. 0.4%; OR=4.95; 95% CI=0.57-42.87; p=0.15), suggesting with appropriate multimodal imaging, IS patients with unknown onset time could also benefit from IVT (488).

**Pharmacological Endovascular Intervention: Intra-arterial thrombolysis (IAT)**

Intra-arterial thrombolysis (IAT), usually carried out by an interventional neuro-radiologist, could act as an alternative for AIS patients who are not eligible for IVT. In IAT, cerebral angiography is performed to localise the occluded intracranial artery, and

an intra-arterial thrombolytic agent is delivered locally through a percutaneous micro-catheter. One of the advantages of using IAT is that a smaller but highly localised dose of the thrombolytic agent can be directly delivered to the thrombus, which in turn, could reduce the risk of local and systemic haemorrhagic complications. IAT can also be used as the adjuvant therapy with mechanical clot retrieval devices.

Prolyse in Acute Cerebral Thromboembolism II (PROACT II) was a prospective, randomised, multicentre control trial, using recombinant Prourokinase (r-proUK) plus Heparin, versus Heparin alone, to treat MCA (M1 and M2) occlusion within 6 hours of stroke symptom onset. Comparison of IAT plus Heparin (n=121) versus Heparin only group (n=59) showed that those treated with IAT and Heparin were more likely to have an improved 90-day clinical outcome (mRS score 0 to 2, 40% vs. 25%; p=0.06). Recanalisation rates were also significantly higher in the IAT group (66% vs. 18%; p=0.001). Although IAT is associated with an increased risk of sICH in the first 7 days (10% vs. 2%; p=0.06), there was no significant difference in total ICH rates by day 10, and IAT resulted in a non-significant reduction in 90-day mortality (25% vs. 27%; p=0.80) (489).

The Middle cerebral artery Embolism Local fibrinolysis intervention Trial (MELT) was a multicentre, randomised controlled trial, which assessed the safety and efficacy of using IA Urokinase infusion in AIS patients within 6 hours of symptom onset. This study was prematurely terminated due to the approval of IV rtPA use for AIS in Japan. The primary end point, defined as mRS 0-2 at 90 days, was non-significantly higher in the IA Urokinase group when compared to the controls (49.1% vs. 38.6%; OR=1.54; 95% CI=0.73-3.23; p=0.345). However, excellent functional outcome, a pre-specified secondary end point, defined by 90-day mRS of 0-1, was significantly higher in the IA

Urokinase group (42.1% vs. 22.8%; OR=2.46; 95% CI=1.09-5.54; p=0.045). In addition, significantly more IA Urokinase patients achieved NIHSS 0 or 1 at 90 days compared to controls (35.1% vs. 14.0%; OR= 3.311; 95% CI=1.334-8.813; p=0.017) (490).

**Intravenous Thrombolysis versus Intra-arterial Thrombolysis**

To date, there have been only a few studies which have directly compared the safety and efficacy of IAT to IVT. Lindsberg and colleagues looked at 420 patients who suffered basilar artery occlusion (BAO) and treated either with IVT or IAT. Despite a higher recanalisation rate in the IAT group compared to the IVT group (65% vs. 53%; p=0.05), there were no significant differences in death, dependency or satisfactory clinical outcomes (491). Nam et al. undertook a meta-analysis of randomised control trials comparing the safety and efficacy of IAT with either standard medical treatment or IVT following AIS, and reported that IAT compared to standard medical treatment showed a significant increase in sICH (RR=3.90; 95% CI=1.41-10.76; p=0.006), but a significant reduction in functional dependence (RR=0.80; 95% CI=0.67-0.95; p=0.01) and no difference in mortality (RR=0.82; 95% CI=0.56-1.21; p=0.32). However, when IAT was compared to IVT, there were no differences in sICH, functional dependency and mortality rates (492). By comparison, another meta-analysis undertaken by Ma and colleagues suggested that IAT was associated with a significantly better functional outcome, as defined by mRS, (OR=3.28; 95% CI=1.91-5.65; p=0.001), and lower mortality rate (OR= 0.40; 95% CI=0.17 to 0.92; p=0.032) when compared to IVT (493). These contrasting results could be explained by the small and heterogeneous nature of the included studies, and significant differences from symptom onset to treatment.

**Mechanical Endovascular Intervention**

IMS III (494), SYNTHESIS EXPANSION (495) and MR RESCUE (496) were three prospective, multicentre, randomised controlled trials, looking at older generation endovascular devices and first use of stent retrievers, when in combination with IVT versus IVT alone. All three trials reported neutral results on clinical outcome, which may have related to long delays between symptom onset and intervention, mechanical thrombectomy (MT) used as a sole intervention regime, use of older generation devices, and, most importantly, patient selection criteria (497, 498). As will be discussed later in this section, endovascular intervention is suitable for AIS patients with large intracranial artery occlusion, though IMS III and SYNTHESIS EXPANSION did not mandate CTA/MR Angiography (MRA) to define large vessel occlusion (LVO). Accordingly, 21% and 8.3% of patients in the IMS III and SYNTHESIS EXPANSION interventional arms, respectively, did not receive any intervention (either due to absence of large intracranial artery occlusion, dissection, or distally located thrombus which was inaccessible to endovascular intervention) (494, 495). In the SYNTHESIS EXPANSION trial, there was no specific NIHSS score threshold for patient recruitment. Results showed that 36% of patients had an NIHSS score <11, which may have reduced the ability to detect an incremental benefit of endovascular treatment (495).

More recent studies have used specific imaging techniques and/or scores for patient selection, as well as new generation stent retriever devices, and have confirmed significant benefit from endovascular therapy over IVT alone; ESCAPE (499), EXTEND-IA (500), MR CLEAN (501), REVASCAT (502), SWIFT-PRIME (503), THERAPY (504) and THRACE (505) are some of the important trials (506-508). Furthermore, two recent randomised controlled trials have demonstrated that, in a

selected group of patients with appropriate multimodal imaging, the therapeutic window for MT could extend up to 16-24 hours (509, 510). Of note, all of the trials have shown similar sICH risk and 90-day mortality rates, with a substantial reduction in 90-day disability. Importantly, more than 80% of trial patients were initially treated with IVT, and therefore, currently national stroke consensus statements recommend endovascular thrombectomy as an adjunct to IVT, or as a sole treatment in AIS patients not eligible for IVT (335, 511). Table 1.7 summarises the key trials of mechanical endovascular therapy.

| Trial | Patients (Intervention vs. control) | Age (Intervention vs. control) | Time of onset to treatment (Intervention vs. IVT) | Imaging used | Inclusion NIHSS | IVT used in intervention group? | Stroke aetiology | Revascularisation rate (Intervention) | mRS 0-2 (Intervention vs. control) | sICH (Intervention vs. control) | 90 day mortality rate (Intervention vs. control) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **IMS III** (494) | 434 vs. 222 | 69 (23-89) vs. 68 (23-84) (yrs) | 5 vs. 3 (hrs) | CTA was used infrequently until the late stage of the study | ≥10 Or 8-9 with CTA evidence of occlusion | Yes | ICA, M1, M2 (MCA), VA, BA | 23%-44% | 40.8% vs. 38.7% | 6.2% vs. 5.9% | 19.1% vs. 21.6% |
| **MR RESCUE** (496) | 64 vs.54 | 64±12.8 vs. 67.6±16.5 (yrs) | 8 vs. 4.5 (hrs) | CTA/MRA | ≥6 | IAT is allowed as rescued therapy | ICA, M1, M2 (MCA) | 27% | 18.8% vs. 20.3% | 4.7% vs. 3.7% | 18.8% vs. 24.1% |
| **SYNTHESIS EXPANSION** (495) | 181 vs. 181 | 66±11 vs. 67±11 (yrs) | 3.45 (3.14-4.20) vs. 2.45(2.20-3.20) (hrs) | CTA/MRA Can also have MRI DWI, CTP, MRP | Not specific | Not IVT, but some received IAT | No specific site of occlusion | Not reported | 30.4% vs. 34.8% | 6% vs. 6% | 14.4% vs. 9.94% |
| **MR CLEAN** (501) | 233 vs. 267 | 65.8 (54.5-76) vs. 65.7 (55.5-76.4) (yrs) | 260 (210-313) vs. 196 (149-266) (hrs) | CTA MRA DSA | ≥2 | IAT in majority intervention group | ICA, M1, M2 (MCA), A1,A2 (ACA) | 58.7% | 32.6% vs. 19.1% | 7.7% vs. 6.4% | 18.9% vs. 18.4% |
| **ESCAPE** (499) | 165 vs. 150 | 71 (60-81) vs. 70 (60-81) (yrs) | 241 (176-359) vs. 125 (89-183) (mins) | CT and CTA | >5 | Yes, if eligible (72.7%) | ICA, MCA (proximal occlusion) | 72.4% | 53.0% vs. 29.3% | 3.6% vs. 2.7% | 10.4% vs. 19.0% |

| Trial | Patients (Intervention vs. control) | Age (Intervention vs. control) | Time of onset to treatment (Intervention vs. IVT) | Imaging used | Inclusion NIHSS | IVT used in intervention group? | Stroke aetiology | Revascularisation rate (Intervention) | mRS 0-2 (Intervention vs. control) | sICH (Intervention vs. control) | 90 day mortality rate (Intervention vs. control) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **SWIFT PRIME** (503) | 98 vs. 98 | 65.0±12.5 vs. 66.3±11.3 (yrs) | 224 (165-275) vs. 188 (130-268) (mins) | CTP or MRP | 8-29 | Yes | M1,M2 (MCA), ICA | 88% | 60% vs. 35% | 0% vs. 3.1% | 9% vs. 12% |
| **EXTEND-IA** (500) | 35 vs. 35 | 68.6±12.3 vs. 70.2±11.8 (yrs) | 210 (166-251) vs. 145 (105-180) (mins) | CTA, MRA, DSA, CTP | Not specific | Yes | M1, M2 (MCA), ICA | 89% | 71% vs. 40% | 0% vs. 6% | 9% vs. 20% |
| **REVASCAT** (502) | 103 vs. 103 | 65.7±11.3 vs. 67.2±9.5 (yrs) | 269 (201-340) vs. 105 (86-137.5) (mins) | CTA/MRA Confirmation of occlusion ASPECT ≥ 7 on non-contrast CT ASPECT ≥ 6 DWI MRI | > 6 | Yes, if eligible (72.8%) | ICA, M1 (MCA) | 65.7% | 43.7% vs. 28.2% | 1.9% vs. 1.9% | 18.4% vs. 15.5% |
| **THERAPY** (504) | 108 vs. 55 | 67±11 vs. 70±10 (yrs) | 227 (184-263) vs. 102 (80-154) (mins) | CT, CTA | ≥8 | Yes | ICA, M1, M2 (MCA) | Not reported | 38% vs. 30% | 9.3% vs. 9.7% | 12% vs. 24% |
| **THRACE** (505) | 204 vs. 208 | 66 (54-74) vs. 68 (54-75) (yrs) | 250 (210-290) vs. 153 (124-180) (mins) | CTA/MRA | 10-25 | IAT in intervention group | ICA, M1, M2 (MCA) | 69% | 53% vs. 42% | 2% vs. 2% | 12% vs. 13% |
| **DEFUSE** (509) | 92 vs. 90 | 70 (59-79) vs. 71 (59-80) (yrs) | 11:28 vs. 10:44 (hrs) | CTP/ MRP and CTA/MRA | ≥6 | Yes, if eligible (11%) | ICA/ MCA | 78% | 45% vs. 17% | 7.6 % vs. 4.4% | 14% vs. 26% |

| Trial | Patients (Intervention vs. control) | Age (Intervention vs. control) | Time of onset to treatment (Intervention vs. IVT) | Imaging used | Inclusion NIHSS | IVT used in intervention group? | Stroke aetiology | Revascularisation rate (Intervention) | mRS 0-2 (Intervention vs. control) | sICH (Intervention vs. control) | 90 day mortality rate (Intervention vs. Control) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **DAWN** (510) | 107 vs. 99 | 69.4±14.1 vs. 70.7±13.2 (yrs) | 12.2 vs. 13.3 (hrs) | CTA/MRA | ≥10 | Yes, if eligible (5%) | ICA, M1, M2 (MCA) | 77% | 49% vs. 13% | 6% vs. 3% | 16% vs. 18% |

**Table 1.7** Summary of the key MT trials (494-496, 499-505, 509, 510). Data present Mean ± SD or median (IQR).

**BA: Basilar Artery**
**CTA: CT Angiography**
**CTP: CT Perfusion**
**DSA: Digital Subtraction Angiography**
**DWI: Diffusion Weight Imaging**
**FR: Flow Restoration**
**ICA: Internal Carotid Artery**
**IAT: Intra-arterial Thrombolysis**
**IVT: Intravenous Thrombolysis**
**MCA: Middle Cerebral Artery**
**MRP: MR Perfusion**
**sICH: symptomatic Intracerebral Haemorrhage**
**VA: Vertebral Artery**

### 1.4.2 Cerebral Perfusion Therapy Targeting Ischaemic Penumbral Area

As mentioned in the previous section, the narrow therapeutic time window means that the effectiveness of IVT is critically time-dependent (512). IVT results in recanalisation of the occluded artery in only approximately 50% of patients (513), and is moreover associated with risk of both systemic and cerebral haemorrhage. On the other hand, endovascular intervention is only suitable for approximately 4% to 10% of AIS patients (498). Therefore, as well as attempts to treat major vessel occlusion, improving CBF, particularly to the penumbral area, via the collateral circulation is another potential therapeutic approach in AIS. Collateral circulation refers to a pre-existing but alternative conduit, that allows perfusion of the target tissue when the principal conduit is blocked. The arterial collateral circulation can be divided into the primary (arterial segments in the Circle of Willis) and the secondary (leptomeningeal or pial collaterals) pathway (514). A number of pharmacological and non-pharmacological interventions have been proposed to improve CBF in the penumbral area, acting as a neuroprotective, collateral therapeutic strategy. Pressure augmentation using pressor agents, partial aortic occlusion system, external compression system, and head position adjustments are some examples. The use of pressor therapy in AIS patients will be described in more detail in the subsequent chapter, whereas the remaining techniques will be described in the following sections.

**Partial Aortic occlusion and external compression system**

The idea of partial aortic occlusion, a redistribution of the systemic blood volume from the splanchnic circulation to the cerebral circulation was initially tested in animal studies in the 1980s (515). Partial aortic occlusion is the physiological equivalent to a sudden increase in cardiac afterload. An increase in afterload could result in a decrease in CO and increase in BP, and it is the increase in BP that may result in a beneficial effect in the

context of impaired CA in AIS, i.e. when CBF depends predominately on arterial pressure (516).

A number of non-pharmacological 'mechanical' interventions have been proposed to improve CBF in the penumbral area (517). The Safety and Efficacy of NeuroFlow in Acute Ischaemic Stroke (STENTIS) trial investigated the effects of a partial aortic occlusion system to increase perfusion on clinical outcomes in 515 patients within 14 hours of symptom onset, failing to demonstrate any benefits on the 3-month global disability scale primary outcome (515), though post-hoc analyses suggested that patients aged >70 years presenting within 5 hours of onset with a NIHSS score 8 to 14 had improved outcomes (518). This was demonstrated by a consistent decrease in both all-cause and stroke-related mortality, without an increase in severe disability (519). Emery et al. carried out a multicentre, open-label pilot study to look at using partial aortic occlusion in AIS patients post IVT. Of those 22 patients, no cases reported sICH but there were 41% (n=9) cases with asymptomatic petechial haemorrhagic transformation within 7 days of treatment. Despite a significant number of procedure-related adverse events (groin haematoma/bleeding; 45.5%; n=10; femoral pseudo-aneurysms; 13.6%; n=3), 17 of 22 (77%) patients had significant neurological improvement (defined as more than 4 points NIHSS score reduction at 90 days), suggesting partial aortic occlusion appeared safe and could act as an adjunct to IVT (520). However, there was no control group in this study and the small sample size warrants further study to look at the efficacy and feasibility of this intervention in the clinical setting.

External counterpulsation (ECP) is another non-invasive mechanical intervention that uses electrocardiogram (ECG)-triggered pressure during ventricular diastole delivered by air-filled cuffs around the lower vascular tree to enhance blood flow to cardiac and

systemic circuits; one proof-of-concept study reporting a favourable trend for improvement in NIHSS score for AIS with large vessel occlusive disease receiving early (week 1 to 7) treatment (521). Lin et al. carried out a systematic review to look at the safety and efficacy of using ECP in AIS patients. A reliable conclusion was not achieved due to the poor quality of methodology and data collection (522). A retrospective study was subsequently carried out to look at more than 200 AIS patients who had large artery atherosclerotic disease, of whom 155 received at least 10 sessions of ECP compared to 52 AIS patients receiving standard medical treatment. Results indicated that 70.5% of completely ECP-treated, 46.5% of in-completely ECP-treated and only 38.5% of standard medical care patients had a good functional outcome (defined as 90-day mRS 0-2). However, those patients enrolled to the ECP group tended to be younger and with a lower baseline NIHSS score. Both of these factors, together with the duration of ECP, have been shown as an independent predictor of favourable outcome (523). Xiong et al. carried out a retrospective pilot study to look at approximate 70 AIS patients within 7 days of stroke symptoms onset, bilateral MCA TCD was performed before, during, and after the ECP session. Results suggested that those patients with a poor functional outcome (mRS 3-6) at 6 months tended to have a higher baseline NIHSS score despite a longer duration of ECP. Higher ipsilateral cerebral augmentation index was also independently associated with an unfavourable outcome (524). Tian et al. recruited 46 IS patients, approximately 5 days post stroke symptom onset and 14 healthy controls. ECP was performed for 35 sessions (1 hour each) within 7 weeks, and results suggested ECP increased BP and CBV and reduced beat-to-beat BPV at the same time, arguing ECP could improve the clinical outcome in IS patients by reducing BPV (525).

## Head Positioning

A simple way of increasing CBF in the collateral circulation and of augmenting blood flow to the ischaemic penumbra might be to lower the head of AIS patients into a 'lying flat' ($0^{o}$) position. Several observational studies have investigated the effects of head positioning on CBF in a healthy population; Edlow and colleagues reporting significant reductions in MCA CBF with $30^{o}$ head-up tilt compared to the supine position, consistent across all age groups (526). However, there are few studies on the effect of head positioning on CBF following AIS, with a systematic review concluding that there was insufficient evidence to make any recommendation (527). In order to quantify the strength of the association of head positioning on CBF, a meta-analysis of recent studies which measured MCA CBV using TCD ultrasound has been undertaken. Results showed that moving the head from $30^{o}$ to $0^{o}$ was associated with an increased MCA CBV of 8.3cm/s (95% CI=5.34 to 11.28) (528).

## Adverse effect of lying flat position in AIS

There is a common concern among clinicians that there may be adverse consequences to 'lying flat' ($0^{o}$), such as a risk of aspiration pneumonia, pulmonary oedema, raised ICP and delayed mobilisation. Dysphagia, older age, mRS $\geq$ 4, cognitive impairment (529) and mechanical ventilation (530) are some of the risk factors of post stroke aspiration pneumonia. However, it is only in mechanically ventilated patients that the risk of pneumonia appears higher when lying flat compared to sitting up (531, 532). Palazzo and colleagues carried out a prospective study to look at the risk of pneumonia associated with lying flat ($0^{o}$) in 333 AIS patients who were treated with IVT. Only a small percentage (4.5%) of patients suffered pneumonia from the lying flat position after

thrombolysis, suggesting the avoidance of the lying flat position due to concerns of pneumonia may be unjustified (533).

A cross-sectional survey study was carried out to review the current head position practice for AIS patients among 298 physicians from 16 countries. Most of the participants (71%) are uncertain of the best head position in the AIS patients and there was no written protocol specifying the preferred head position for AIS in over half (53.9%) of the hospitals, suggesting there is a lack of consensus about the best strategy regarding head position for the AIS patient (534). Therefore, the Head Position in Stroke Trial (HeadPost) Study was a multi-centre, prospective, cluster randomised, cross-over, blinded outcome assessment trial, which compared the effects of 'lying flat ($0^{o}$) with 'sitting up ($\geq 30^{o}$) head position applied in the first 24 hours of hospital admission for patients presenting within 12 hours of AIS onset, to investigate any improvement in terms of neurological status (defined as NIHSS score), functional dependency (defined as mRS) and mortality rate (535). Further details regarding the HeadPoST study will be explained in the subsequent chapters (Chapters 5 and 6).

## 1.5 Summary

Stroke is a global public-health burden, results in enormous costs to both healthcare and social care systems, and is associated with significant disability and mortality. There are three main types of stroke disease, and they are associated with similar but not identical modifiable and non-modifiable risk factors. IS is the most common type of stroke and there are a number of classification systems available to enable us to exclude stroke mimics and to guide treatment. There are a number of important regulatory mechanisms to maintain homeostasis of cerebral haemodynamics, including CA, NVC and CVRea. It is generally accepted that these regulatory mechanisms are impaired following AIS.

However, as discussed in this introduction, there are a number of non-pharmacological and pharmacological strategies to improve cerebral perfusion following AIS, for example: IVT, MT or improving CBF to the penumbral area via the collateral circulation, i.e. partial aortic occlusion or head position adjustment. In assessing the relative benefits and risks of these various strategies, it is important to have a more detailed mechanistic understanding, and in particular a detailed assessment of their effects on CBF and the underlying cerebral haemodynamic regulatory mechanisms. Such studies will form the basis of this thesis; the next chapter outlining the key objectives to be tested in the following study chapters.

# Chapter 2. Aims and Objectives of this Thesis

The overall objective of this PhD thesis is to determine how various cerebral perfusion (pharmacological and non-pharmacological) strategies and assessment [gradual head positioning (GHP) and rapid head positioning (RHP)] paradigms affect cerebral haemodynamics, in particular CA and associated parameters, in AIS disease, and whether such changes are associated with improvements in neurological and functional outcome.

The following section outlines the research questions that are addressed in this thesis, and summarises the methods used:

**Pharmacological perfusion strategies – pressor agents and intravenous thrombolysis (IVT)**

***What is the existing evidence for using pressor agents in acute ischaemic stroke?***

This is addressed in a systematic review of the use of pressor agents as induced hypertension (IH) therapy in AIS (Chapter 3). This systematic review explores the feasibility, safety and clinical effectiveness of using pressor agents in AIS, and whether they can be used as an adjunct in IVT and MT.

**Non–Pharmacological perfusion strategies – head positioning changes**

***How does head positioning changes affect cerebral haemodynamics, in particular, CA, in AIS patients?***

The above question is addressed by two chapters in this thesis; first, a reproducibility study reports how GHP changes affect cerebrovascular physiology, most importantly, CA

in healthy controls, and whether such changes demonstrate reproducible results (Chapter 5). Next, a prospective, observational study evaluates how GHP changes affect systemic, and cerebral haemodynamic parameters between controls and AIS patients, up to 90 days post stroke symptom onset (Chapter 6).

**Cerebral Haemodynamic Assessment Paradigm – gradual head positioning vs. rapid head positioning**

The author proposed GHP could act as a clinical treatment, this is achieved by placing participants in an either prolonged lying flat (0°) or sitting up (30°) head position. As mentioned in the previous question, an observational study was carried out to assess haemodynamic parameter changes and neurological recovery in AIS patients in GHP (Chapter 6). The author also proposed RHP could induce dynamic variation in both systemic and cerebral haemodynamic parameters, which might be able to differentiate between clinical states (i.e. mobilisation vs. bed resting). RHP was also undertaken in controls and AIS patients, to look at haemodynamic parameter changes and whether such a technique could improve sensitivity and specificity in assessing dCA, and therefore, act as a new dCA paradigm (Chapter 7).

***How do cerebral haemodynamics, in particular CA, respond in AIS patients who receive IVT?***

This is addressed by a prospective, observational, feasibility study, looking at the temporal relationship of CA, and associated systemic and cerebral haemodynamic parameters, during and immediately after IVT treatment in AIS patients, and up to 3 months post stroke symptom onset (Chapter 8).

# Chapter 3. Pressor Therapy in Acute Ischaemic Stroke – A Systematic Review Update

One of the aims in hyperacute IS treatment is to recanalise the occluded intracranial arteries, and therefore, to improve CBF and CPP. However, incomplete recanalisation, and therefore, poor neurological recovery is repeatedly observed in AIS patients despite receiving IVT, IAT or MT. Small groups of AIS patients may present with low BP during the acute stage of the disease or with worsening neurological symptoms correlated with BP reduction. Such a group of patients could benefit from IH as an individualised, pharmacological perfusion regime. The last systematic review of pressor therapy in 2006 highlighted limited evidence of clinical efficacy of IH in AIS (536). Given the advancement of hyperacute IS treatment in the last decade, this chapter will re-assess the safety and clinical efficacy of this important, and yet overlooked treatment regime in AIS.

## 3.1 Introduction

As mentioned in Chapter 1, hypertension is the leading modifiable risk factor in IS (82). Several epidemiological studies have documented an association between hypertension and IS risk. Lawes and colleagues reviewed more than 425,000 participants in 58 cohort studies, and demonstrated that there was a log-linear association between systolic BP (SBP) (>115 mmHg) and IS incidence. For every 10 mmHg reduction in SBP, there was a 54% (95% CI=53-56%), 36% (95% CI=34-38%) and 25% (95% CI=22-28%) stroke risk reduction in the age groups of <60, 60-69 and ≥70 years, respectively (537). Lewington and colleagues carried out a meta-analysis, looking at approximately 950,000 individuals in 61 prospective observational studies and suggested that, for individuals in

the age 40-69 years group, every 20 mmHg difference in SBP or 10mmHg difference in DBP would result in a 2-fold increment in stroke mortality (538).

AIS patients often present with elevated BP during the hyperacute stage, particularly those with pre-existing hypertension (539). Qureshi and colleagues carried out a survey study and looked at the data collected from more than 660 emergency departments (ED) in 50 states and the District of Columbia in the US, and found that approximately 70% of AIS patients admitted to ED had SBP >140 mmHg (540). The International Stroke Trial (IST) enrolled more than 17,000 AIS participants, in which more than 80% and 27% had a SBP ≥140 and ≥180 mmHg, respectively (541). Although such hypertensive responses are commonly observed, it is difficult to determine whether these represent a natural compensatory mechanism, i.e. to improve perfusion in the ischaemic penumbra, or whether it represents a maladaptive response that leads to secondary reperfusion injury. Importantly, multiple observational studies have reported that elevated BP is associated with cerebral oedema (542), hyper-perfusion haemorrhage (543) and worsening functional outcome in IS (544).

It is generally accepted that there is a U-shaped relationship between BP and AIS functional outcome, i.e. both BP extremities could result in detrimental effects for death and disability (541, 545-549). In a retrospective analysis of the IST, patients who had SBP 140-179 mmHg had the lowest possibility of developing significant disability (mRS >2) or death at 6 months, but when SBP was above 150 mmHg, for every 10 mmHg increase in SBP, there was a 3.6% and 4.2% increase in mortality and recurrent stroke, respectively. On the other hand, hypotension also resulted in a detrimental effect in IS, for every 10 mmHg SBP reduction below 150 mmHg, there was more than a 17% increase in mortality (541). Castillo and colleagues looked at more than 300 AIS patients, and

suggested 180/100 mmHg as the optimal BP during the acute phase of the disease. They also pointed out that for every 10 mmHg above or below SBP 180 mmHg, there was a 25% and 40% increase, respectively, in the risk of poor functional outcome (547).

Therefore, management of acute stroke BP is a matter of some debate. For example, a meta-analysis carried out by Bath et al., looking at 26 trials with more than 17,000 AIS patients, indicated that there was insufficient evidence to suggest BP lowering provided acute beneficial effect (550). Furthermore, the study of Castillo et al. also demonstrated that patients with SBP reduction greater than 20 mmHg had the largest final infarct volumes (547). One of the explanations for this observation could be that CA is impaired following AIS, with extreme values of BP resulting in a passive relationship between CPP and CBF. Consequently, post-stroke hypotension could be related to infarct progression and neurological deterioration. Overall, numerous well designed clinical trials (551-556) that have focused on identifying the optimal BP in AIS patients have not resulted in definite conclusions on BP management in AIS. Nonetheless, in the longer-term, management of hypertension is important, with Arima and colleagues carrying out a randomised, placebo-controlled trial to study any beneficial effects of BP lowering in more than 6,000 IS or TIA patients, and demonstrating that BP reduction was associated with concomitant reductions in stroke recurrence (557).

Although the majority of AIS patients present with elevated BP during the acute phase, as previously highlighted, there is a small group of AIS patients presenting with relatively low BP, with risk of cerebral hypo-perfusion; such a group of AIS patients may require a more individualised, rather than standardised AIS perfusion regime. Hence, induced hypertension (IH) could be a promising adjuvant therapy in such cases, aiming to enhance CPP and CBF, expedited collateralisation, preservation of the ischaemic penumbra, and

therefore overall neurological function. Several animal studies have successfully demonstrated that BP elevation is associated with increased CBF, and some studies also demonstrated associated functional neuronal recovery as measured by neurophysiological tests (558-562). Noteworthy, in clinical settings, IH has been widely used for management of delayed cerebral ischaemia after SAH, either alone, or in combination with haemodilution and hypervolaemia, constituting the so called triple H therapy (563). Use of IH was first reported in AIS patients by Shanbrom and Levy, in patients with fluctuating neurological deficits followed by persistent neurological deterioration, in whom subsequent improvement was noted after IH using IV NPE (564). Over the last couple of decades, some small pilot studies have reported that IH reduces the degree of neurological dysfunction during AIS (565) or improves CBF and neurological function during the subacute phase (566). However, there is still a lack of randomised controlled trials to explore this therapeutic option. At present, both the ASA and European Stroke Organisation (ESO) guidelines recommend that only in exceptional cases, a stroke physician could consider prescribing vasopressors to improve CBF, with close neurological and cardiac monitoring (Class IIb, Level of evidence C) (567, 568). One possible explanation of underuse of such a regime could be due to the adverse consequences of extreme hypertension and also the small, but significant side effects from pressors; for example: digital ischaemia, cardiac arrhythmia, myocardial ischaemia and acute renal injury (569).

More than a decade ago, Mistri et al. carried out a systematic review to assess the evidence for IH in AIS, and suggested that since the majority were small pilot studies with different trial methodologies, it was difficult to draw reliable conclusion regarding the harms and benefits of such an approach in AIS (536). However, as new studies have been reported in an era of increasing reperfusion options, including IVT and MT, it was important

revisiting this topic. Therefore, the aim of this chapter is to look at the current evidence on the feasibility, safety and clinical efficacy of using pressor agents in AIS, in particular whether they can be used as an adjunct to IVT and MT hyperacute IS treatment.

## 3.2 Methods

### 3.2.1 Search Strategies

A systematic literature search was conducted in the following bibliographical databases: AMED, CINAHL, EMBASE, MEDLINE, Web of Science, SCOPUS and The Cochrane library. All studies published in English from January 2005 to July 2019, and featuring adult human participants, were included for review. The systematic review was updated in December 2019 prior to submission. A literature search was undertaken from January 2005 as Mistri and colleagues' systematic review covered until 2006 (536). Medical Subjects Headings (MeSH Terms) or subcategories available on the search database were used in order to increase the sensitivity of the search. Bibliographies of selected articles were screened for additional relevant articles. Search terms are listed in Appendix 1.

### 3.2.2 Study Selection

Given the relative paucity of literature in this field, case reports, case studies and case series were also included. Conference abstracts and studies where the type of pressor agent was not specified were excluded. All references were evaluated by two independent reviewers [Dr Man Yee Lam (ML) and Dr Nikil Patel (NP)]. Abstracts for all results were reviewed and relevant studies were selected for further detailed analysis. Should disagreement occur between investigators, the full text of the article was reviewed. Included studies were independently evaluated as full papers by two reviewers against the inclusion and exclusion criteria (ML, NP). Studies generating multiple publications from the same participant cohort were reported only once. As the majority of the studies

included were case reports, study quality was assessed using a separate checklist adapted from author for case reports (570) (Table 3.1) and the rest of the studies (571) (Table 3.2), were assessed separately. The overall methodological quality of each study is presented in Tables 3.3 and 3.4. Searches were exported to EndNote X8 to build a master file for all references.

Inclusion criteria

1) Adult aged ≥ 18 years;

2) English literature;

3) Diagnosis of IS disease as defined by standard criteria;

4) Name of pressor agent present

Exclusion criteria

1) Aged under 18 years;

2) Non-English Literature

3) Non-IS disease patients;

4) No pressor agent as listed above

### 3.2.3 Data Extraction

The following data were extracted for the review:

1) General Information

- Researcher performing data extraction
- Date of data extraction
- Identification features of the study

- Record number

- Author

- Title

- Citation

- Type of Publication

2) The Study characteristics

- Aims and objectives
- Study design
- Total sample size
- Recruitment procedures used
- Study inclusion/exclusion criteria, if any

3) Participant characteristics

- Demographic characteristics (age, sex)
- Stroke severity (NIHSS, mRS)
- BP (Baseline and/or during symptom progression)
- Imaging used to confirm diagnosis
- Type of IS

4) Intervention

- Name of pressor agent
- Reasons of pressor agent given
- Dosage, timing and duration of the intervention
- Any concomitant treatment during intervention
- Target BP during intervention
- Volume expansion, if any

5) Outcome/results

- Any adverse event
- Factors associated with good outcome

- Follow up interval
- Final functional outcome, if any

Evaluation of publication bias was not feasible because of heterogeneity and the fact that most of the studies included were case reports and case series. Table 3.5 outlines the study design, participant characteristic and details of the pressor regimen. Table 3.6 outlines the BP characteristics, any adverse events related to the pressor agent and functional outcome.

**Table 3.1** Study quality checklist (case reports)

| Intervention assessed | Criterion | Letter |
|---|---|---|
| **Background** | | |
| Introduction | Brief summary of the case with appropriate medical literature referencing | A |
| Patient description | Patient's characteristics are described in details (age, sex) | B |
| Clinical findings | Relevant physical examination findings are clearly documented | C |
| Timeline | Important dates and times in this case are clearly documented (can present as graph/table) | D |
| **Investigation and follow up** | | |
| Diagnostic assessment | Diagnostic methods and reasoning are clearly documented | E |
| Intervention | Types of pressor agent, route of administration and any rationale of changes in intervention | F |
| Follow-up and outcomes | Summarise the clinical course of follow-up visits including any adverse event and functional outcome | G |
| **Discussion** | | |
| Strength and limitation | Strengths and limitations of the study are presented and discussed, supported by relevant literature | H |
| Total: | | 8 points |

**Table 3.2** Study quality checklist (remaining studies)

| Intervention assessed | Criterion | Letter |
|---|---|---|
| **Background and methods** | | |
| Aims/ hypothesis | Aims/ hypothesis of the study are clearly described in the introduction/methods section | A |
| Description of the study population | Participant characteristics are described in details (e.g. age, sex, co-morbidities) | B |
| Medical ethics review and informed consent | Study has ethical approval from the relevant committee and informed consent taken from study participants | C |
| Sample size calculation | Sample size is calculated at the beginning of the study | D |
| Inclusion and exclusion criteria | Inclusion and exclusion criteria are clearly documented | E |
| Statistical association between dependent and independent variables | Methods for assessing outcome between pressor agent and functional outcome are clearly defined | F |
| Statistical validation of relationship between dependent and independent variables | Association between pressor agent used and outcome assessed for statistical significance | G |
| Timing and duration of pressor therapy | Timing and duration of pressor therapy are clearly stated | H |
| **Results** | | |
| Specification of relevant patient characteristics | Patient characteristics described: age, sex, stroke severity, pressor agent, BP | I |
| Adjustment for confounding factors | Analyses adjusted appropriately to consider confounding factors | J |
| Main outcome | Main outcome is presented in graph and/or table | K |
| **Discussion** | | |
| Strength and limitation | Strengths and limitations of the study are presented and discussed, supported by relevant medical literature | L |
| Total | | 12 points |

## 3.3 Results

### 3.3.1 Search Results

The initial search yielded 4808 references. Following removal of duplicates and title/abstract screening, 210 references remained for full text review (Figure 3.1). Twenty studies were suitable for inclusion, of which three were randomised controlled trials (572-574), two were case series (575, 576), four were retrospective studies (577-580), nine were case reports (581-589), and two were observational studies (590, 591).

### 3.3.2 Quality Assessment

There were no disagreements in quality assessment between reviewers. Median checklist quality score was 7.5 (range 6-8) and 10 (range 8-12) for case reports and the remaining studies, respectively. This reflects the heterogeneity in study quality, and incomplete reporting of key criteria in the majority of the studies.

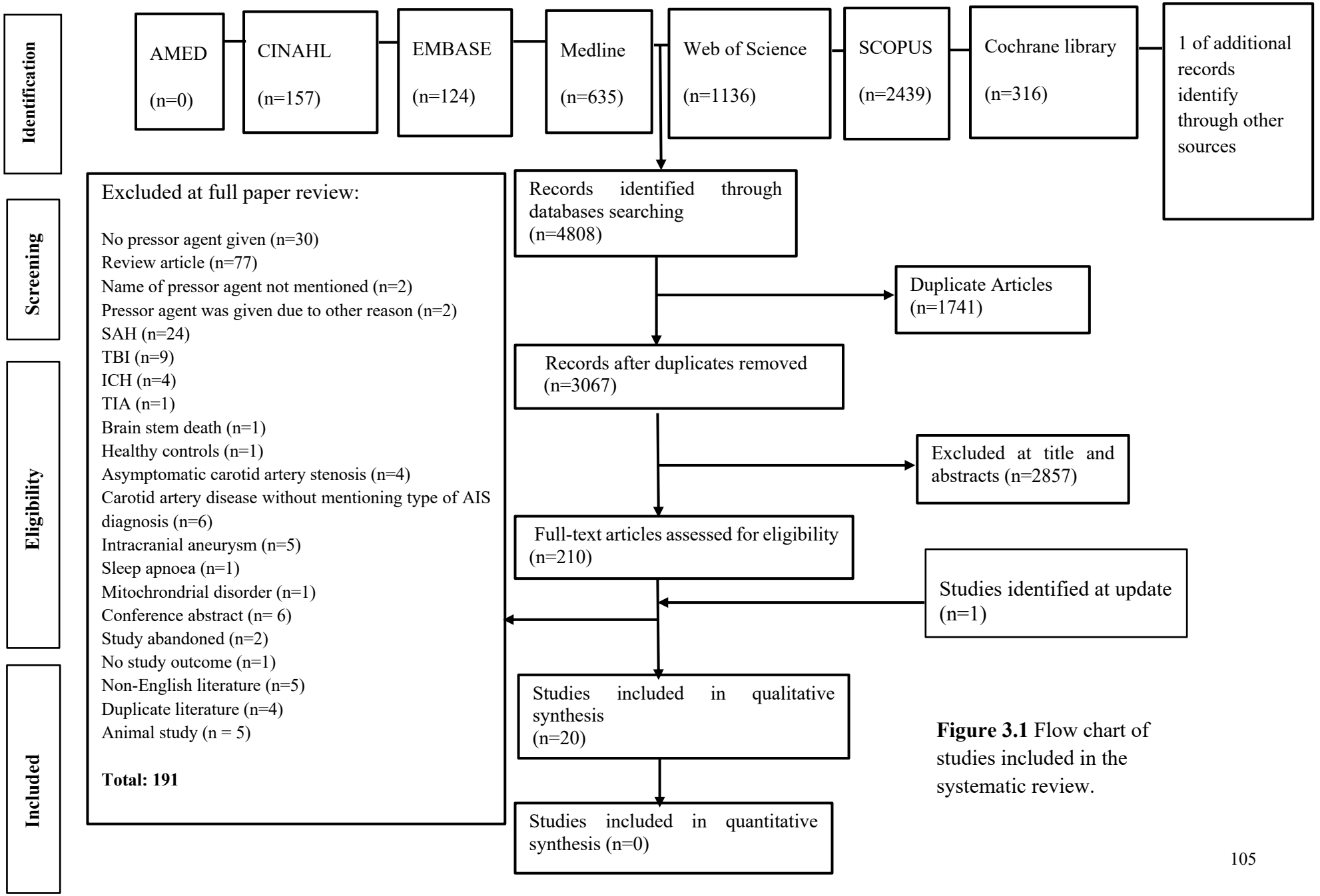



**Figure 3.1** Flow chart of studies included in the systematic review.

**Table 3.3** Quality assessment of included studies (case reports)

| Study | Criterion | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **A** | **B** | **C** | **D** | **E** | **F** | **G** | **H** | **Total score** |
| Bogoslovsky 2006 (581) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Chalela 2005 (582) | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 6 |
| Janjua 2005 (583) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Kim and Kang 2007 (584) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Kim 2018 (585) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Machida 2018 (586) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Nakagawa 2016 (587) | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 6 |
| Shah 2008 (576) | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| Stead 2008 (588) | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| Verro and Chow 2009 (589) | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 7 |

**Table 3.4** Quality assessment of included studies (remaining studies)

| Study | Criterion | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **A** | **B** | **C** | **D** | **E** | **F** | **G** | **H** | **I** | **J** | **K** | **L** | **Total score** |
| Bang 2019 (574) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 12 |
| Delgado 2016 (577) | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 9 |
| Kang 2017 (578) | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 11 |
| Koenig 2006 (579) | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 10 |
| Lee 2019 (591) | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 11 |
| Lim 2011 (580) | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 10 |
| List 2013 (575) | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 8 |
| Mundiyanapurath 2016 (590) | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 8 |
| Nasi 2019 (572) | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 11 |
| Rasmussen 2018 (573) | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 10 |

### 3.3.3 Participant Characteristics

There were a total of 597 IS patients, with study sample sizes ranging from 1 to 121 patients. Patients receiving IH ranged from 30 to 94 years, with 255 of 438 patients male (58.2%); three studies not stating sex as either not mentioned in the study (590), or participants who did not receive IH, were also included (572, 573). Radiological imaging (e.g. CT or MRI) was used to confirm infarction in all participants. Majority of the studies reported the NIHSS for categorising stroke severity, ranging from 1 to 22 (572-576, 578-581, 584, 588, 590-592), though some studies used imaging markers, such as location, degree of occlusion and presence of LVO to define the severity of the disease, including MRI/MRA (582, 585-587, 589) and arteriography (583). It was not possible to define stroke severity for one study (577). The ischaemic lesion was located in the ACA (n=3) (573, 575, 582), MCA (n= 9) (573, 575, 576, 581, 584, 587-590), internal border (n=1) (585), vertebrobasilar (n=2) (583, 586) or small perforating artery (lacunar) (n=2) (578, 580). Three studies did not specify the precise location of the lesion (572, 577, 579). Two studies used LVO and small vessel occlusion to describe the ischaemic lesion location (574, 591) and two studies presented the pre-admission mRS (574, 581).

Fourteen studies used either isolated SBP (572-574, 578, 580, 590), both SBP and DBP (581, 584, 586, 587, 589, 591), or MAP (573, 576, 579, 581, 591), to describe baseline BP. Details of BP characteristics (baseline BP, BP during symptoms progression and target BP) are listed in Table 3.6. Two studies did not report target BP for IH intervention (577, 585). Eleven studies conducted follow up, which ranged from 1 week to 12 months post stroke symptom onset (572-574, 576, 581, 583-587, 591).

### 3.3.4 Pressor Agents

The majority of the studies used PE (573, 574, 576-582, 584, 585, 588, 589, 591) or NPE (572, 575, 590) as the sole pressor agent. Concomitant use of pressor agents was reported in the following studies: PE and NPE (576, 583); Ephedrine and Dopamine (586); Etilefrine and Dopamine (587); and PE, Dopamine and Midodrine (579).

In general, pressors were given as an IV infusion [either via central venous catheter (CVC) or peripherally] (574, 577, 578, 580, 581, 584, 586, 587, 589, 591), though in four studies the pressor agent was given as a single bolus only [Ephedrine (586) and Etilefrine (587)] or a bolus followed by infusion (588, 590). Only Midodrine was given orally as a pressor agent (579). First dose of the pressor agent ranged from approximately 5 to 84 hours post stroke symptom onset, and duration of pressor treatment ranged from 15 hours up to 14 days. Concomitant volume expansion was most commonly IV crystalloid (572, 578-582, 584, 585, 588, 589, 591), though Hydroxyethyl starch (584), Fludrocortisone (579) and red blood cells (586) were also used.

Individual pharmacological strategies will now be presented in more details, though the information available in respect of indication, dose and duration of mono- or combination therapy, outcome and safety, is limited by that described in the individual studies. However, all available information has been presented in these categories to allow direct comparison between agents where possible.

**Phenylephrine (PE)**

PE is a selective α1-adrenergic receptor agonist. It increases BP and systemic vascular resistance (SVR) by peripheral vasoconstriction in a dose-dependent manner (593). Unlike other pressor agents (e.g. NPE, Epinephrine and Dopamine), the absence of a β1

chronotropic and inotropic effect makes it less likely to induce a tachyarrhythmia (594, 595). PE is prominent in the peripheral, and relatively sparse in the cerebrovasculature, hence, it increases MAP without causing profound cerebral vasoconstriction (596). Its feasibility of administration, safety profile and tolerability have been well established (597). PE has a short half-life (approximately 5 minutes) with a duration of action of approximately 20 minutes. As it may reduce stroke volume (SV) and CO over prolonged use, it is usually indicated for patients with preserved cardiac function.

PE was used for the following reasons in the studies reviewed: (i) outside IVT therapeutic window (574, 581, 585); (ii) partial recanalisation post MT (576, 589); (iii) fluctuating/worsening symptoms which correlated with BP variation (582, 583, 588); (iv) early neurological deterioration, which usually defined as an increase in NIHSS ≥2 points (574, 591); and (v) prolonged haemodynamic compromise (577, 584). Both Kang (578) and Lim (580) carried out similar retrospective case studies, recruiting 25 and 52 participants, respectively, looking at using PE as the IH agent in lacunar stroke patients (defined as a solitary infarct in the perforating arterial territory on MRI DWI) with motor progression. PE was given and titrated until target BP was reached (SBP: 220 mmHg or 20% increased from admission SBP), and tapered down after symptoms had stabilised for 24 hours. With respect to outcomes, studies reported that IH was associated with reduced of length of hospital stay (Lim et al. p=0.047), neurological improvement, as assessed by the NIHSS score (Lim et al. p=0.044 and Kang et al. p=0.004), and improved functional outcome, as assessed by discharge mRS (Lim et al. p=0.042 and Kang et al. p=0.036). In respect of adverse effects in 287 patients confirmed receiving PE monotherapy, headache (n=6) (574), palpitation (n=1) (574), urticaria (n=1) (574), haemorrhagic transformation (n=4) (589, 591), sinus bradycardia or pause (n=6) (591), mild pain and erythema around the infusion site (n =1) (577), dysuria (n=3) (578, 580), sICH (n=1) (574), vasogenic

oedema (n=1) (591), pulmonary hypertension (n=1) (591), renal failure (n=1) (591) and transient chest tightness (n =3) (580) were the most commonly reported.

Bang and colleagues carried out a multicentre, prospective, randomised, open label, blinded-endpoint trial, looking at non-cardioembolic IS stroke patients (NIHSS 4 to 18), within 24 hours of symptom onset. Patients were either ineligible for recanalisation therapy (IVT, MT) or developed progressive stroke (defined as NIHSS ≥2), and subsequently randomised to IH (n=76) or control group (n=77). PE was given and titrated until target BP was reached [SBP: 200 mmHg or 20% increased from admission SBP or neurologic improvement observed (defined as NIHSS score improved with ≥ 2)]. PE infusion tapered down after 24 hours of neurologic stabilisation in responder or after 60 minutes at the maximum PE dosage (160ml/hr) or upper SBP limit in non-responders. With respect to outcome, significant neurologic improvement (p=0.001) and favourable shift of NIHSS (OD=2.17; 95%CI=1.19-3.92; p=0.011) were observed in IH group. However, there was no significant differences of functionally independent (mRS <2) at 90 days between IH and control group (p=0.114) (574).

**Norepinephrine (NPE)**

Unlike PE, NPE is a potent α1-adrenergic receptor agonist with modest β agonist effect (β1 > β2) (598). Though it can exhibit adverse vasoconstrictor effects on the collateral cerebral circulation, these effects are limited due to a lower sensitivity and density of α-adrenergic receptors (596). Therefore, it can be given safely to maintain CPP without comprising CBF. With its limited chronotropic effects, NPE primarily increases BP with minimal impact on CO and HR (569, 594). However, prolonged use of NPE can lead to detrimental consequences, such as cardiac myocyte toxicity (599). Similar to PE, it behaves in a dose-dependent manner (600).

NPE was used for the following reasons in the studies reviewed: (i) BP-related symptom progression (575, 583); (ii) partial recanalisation post MT (576); and (iii) to achieve target BP (572, 590). NPE use was associated with adverse effects, including sICH (572, 590), acute coronary syndrome (572) and symptomatic bradycardia (572).

One study, that of Nasi and colleagues (572), assessed NPE for IH therapy in a randomised controlled trial to investigate the efficacy of early SBP manipulation in AIS, which also included BP reduction (IV Esmolol and Nitroprusside), where appropriate, to reach target BP. 218 non-thrombolysed AIS patients within 12 hours of symptom onset were randomised to three target BP groups (Group 1: 140-160 mmHg; 2: 161-180 mmHg; and 3: 181-200mmHg), of which 90 patients (41%) received NPE. A significantly higher proportion of sICH was observed in patients allocated to the highest target BP group (Group 3, p=0.049). Patients who had evidence of mismatch on neuroimaging, and either received IH therapy or no manipulation (p=0.043), were more likely to have a good clinical outcome. However, for patients without mismatch, there were no differences in outcomes irrespective of pressor, depressor or no SBP manipulation (p=0.26). Overall, there were no significant differences in terms of functional outcome (p=0.27) or mortality (p=0.40) between groups.

**Dopamine**

Dopamine is a monoamine neurotransmitter. It is a NPE and PE precursor which acts on both dopaminergic and adrenergic receptors in a dose-dependent manner (594). At a lower dose (0.5-2 microg/ kg body weight/ min), it acts on the dopaminergic D1 receptors, causing vasodilatation in the renal, mesenteric, cerebral and coronary vasculatures. At a moderate dose (2-10 microg/kg body weight/min), Dopamine acts on both dopaminergic and β1-adrenergic receptors, resulting in increased cardiac contractility, SV, CO and HR.

At higher doses (> 10 microg/kg body weight/min), it acts on the α-adrenergic receptors, which leads to vasoconstriction and increased SVR (569).

In the studies assessed, Dopamine was mainly used for BP-related symptom progression (586, 587) and to achieve target BP (579), often in conjunction with other agents [e.g. PE and Midodrine (579), Ephedrine (586) or Etilefrine (587)].

**Midodrine**

Midodrine is a selective, α-adrenergic receptor agonist, resulting in arterial and venous constriction and subsequently increases in BP (601). As it acts peripherally, it does not affect central nervous system activity nor pulmonary or renal function (602). It is a prodrug; after oral or IV administration, it converts to its pharmacologically active metabolite, de-glymidodrine (603). It acts rapidly and reaches maximal plasma concentration within an hour, with the duration of action lasting for approximately 4 to 6 hours (602). Avoidance of concomitant use with monoamine oxidase inhibitor is required as this could lead to hypertensive crises (601).

Koenig and colleagues carried out a retrospective case study, looking at AIS patients who had MRI-confirmed ischaemic abnormalities within 7 days of symptom onset. Patients were either treated with pressors (n=46) (PE, Dopamine or Midodrine with volume expanders) or underwent standard therapy (ST) (n = 54). Patients treated with pressors tended to have LVO ($p<0.003$), higher frequency of intracranial and extracranial arterial stenosis ($p=0.0002$), and greater volume of diffusion-perfusion mismatch ($p=0.005$). Patients in the IH group were also more likely to be admitted to ITU (42% vs. 28%; no p value given) and have a longer length of stay ($p=0.005$) than those who received ST (579).

**Ephedrine**

Ephedrine is a synthetic, non-catecholamine agonist acting on α, β1 and β2-adernergic receptors. It predominately exhibits β agonist effect (604), and this results in increased BP and CO (605). Compared to PE, it has slower onset and longer duration of action. Ephedrine has limited efficacy and in order to achieve target BP, additional dosage may be required (606). Repeated dosage could demonstrate diminished response, known as tachyphylaxis, secondary to depletion of NPE supplies and receptor blockade (607). For further details of Ephedrine use, please refer to subsequent section (Sections 3.3.6 and 3.3.8).

**Etilefrine**

Compared to PE and NPE, Etilefrine is a lesser known pressor agent. It is a sympathomimetic agonist, acting on both α and β (β1 > β2) adrenergic receptors (608). This leads to an increase in SV, CO and BP, causing positive inotropic and chronotropic effects. It is commonly used in orthostatic hypotension (609) and priapism in sickle cell disease patients (610, 611). For further details of Etilefrine use, please refer to subsequent section (Section 3.3.7).

### 3.3.5 Pressor Therapy used as an adjunct to IVT and IAT

Three studies reported the use of pressor therapy as an adjunct to sole IVT (583, 589) and IAT (584). In a case report, Janjua and colleagues reported a 39-year-old man who initially presented with right-sided facial numbness and hemiparesis. The patient later developed locked in syndrome and despite the administration of Aspirin, IV Heparin and PE, symptoms continue to progress. IVT was delivered subsequently and terminated after two-thirds of the infusion was given, as marked neurological improvement and

satisfactory BP were observed. Patient was discharged home with minimal sixth nerve palsy and no adverse events were reported (583). In another case report, Verro et al. reported a 54-year-old man who suffered left MCA infarct, treated with IVT. MRI performed 24 hours later demonstrated persistent MCA occlusion, and in view of persistent low BP and high risk of infarction extension, IV Heparin and PE were given with serial CT monitoring. This treatment regimen was terminated on day 4 as the latest CT demonstrated moderate haemorrhagic transformation. However, the patient's condition deteriorated the following day and a further CT showed significant infarct extension affecting the entire MCA territory. The patient was subsequently discharged to a nursing home with dense hemiplegia and aphasia (mRS = 5) (589).

Finally, in another case report, Kim and Kang reported a 68-year-old man who suffered a left MCA infarct. His condition deteriorated 4 days following initial symptom onset, with altered mental status, severe global aphasia, gaze palsy and profound right-sided hemiparesis. IAT (100,000 unit of Urokinase), IV normal saline and Hydroxyethyl starch were given without significant improvement. Subsequently, PE was given as an infusion and the neurological deficits improved slowly over the next 24 hours. The patient was finally discharged home with excellent functional outcome and no adverse event was reported.

### 3.3.6 Pressor Therapy used as an adjunct to MT

Several studies have reported the use of pressor agents in AIS patients who underwent MT, with IVT as bridging therapy. The main indication for pressor therapy use was given as partial recanalisation post MT (576) and to achieve target BP (573, 590). Agents were given either during (573, 590) or post MT (576). Pressor agents were more commonly used in patients who underwent general anaesthesia (GA) than conscious sedation (CS),

presumably because hypotension tended to occur more frequently in the GA setting (612, 613).

Mundiyanapurath and colleagues carried out a prospective observational study on 64 AIS patients, ranging in age from 59 to 81 years, who underwent MT with GA. Hypotension directly after intubation was treated with NPE bolus and infusion (590), with 98.4% of patients requiring pressor therapy during MT. Of note, higher cumulative NPE dose ($p=0.003$), as well as older age ($p=0.013$) and presence of ICH ($p=0.001$) were independent risk factors for an unfavourable outcome (mRS >2). Importantly, the adverse effect of NPE on outcome was independent of MT procedural time ($p=0.719$). The negative relationship between NPE dosage and functional outcome observed in this prospective observational study could reflect haemodynamic instability; patients with more severe strokes possibly having more profound hypotension, and requiring higher dosage of NPE with longer duration to restore BP. Interestingly, this study did not demonstrate any significant effects of BP level per se on functional outcome (590).

Rasmussen et al. carried out a prospective, open-labelled, randomised controlled trial on 128 AIS patients who had an anterior circulation stroke with LVO. Patients were randomised to MT either under GA (n=65) or CS (n=63). Target BP (SBP $\geq$ 140 mmHg and MAP $\geq$ 70 mmHg) was maintained during the procedure by PE or Ephedrine. Patients in the GA group had lower procedural BP ($p<0.001$), and therefore, were more likely to receive pressor therapy than the CS group ($p<0.001$). However, BP variables were not related to neurological outcome at 90 days, and no adverse events related to pressor therapy were observed (573).

Shah and colleagues reported three patients who had proximal MCA occlusion (NIHSS 15 to 20) undergoing MT with IVT bridging therapy. Post MT imaging demonstrated

partial recanalisation, and pressor therapy was given to raise MAP. All patients were discharged with lower NIHSS (1 to 7) with no adverse events reported (576).

### 3.3.7 Pressor Therapy used as an adjunct in Carotid Endarterectomy/Stenting

Two studies reported the use of pressor therapy in AIS patients who required carotid artery procedures (575, 587). List et al. carried out an observational case series to look at AIS patients with occlusive carotid artery disease. Two patients received carotid endarterectomy and stenting (CAS), respectively. Both received pressor therapy due to BP-related worsening neurological deficits and maintained target BP (SBP 160-190 mmHg). All patients had successful intervention and satisfactory CBF improvement without adverse events (575).

Nakagawa and colleagues reported an AIS patient who underwent CAS, with Etilefrine and Dopamine given during the procedure due to hypotension. Post-procedure ECG demonstrated significant cardiac ischaemic changes and raised cardiac enzyme markers, with normal plasma Epinephrine and NPE, but markedly raised Dopamine levels. Subsequently, an echocardiogram was performed which confirmed Takotsubo cardiomyopathy (TCM), though follow-up demonstrated improved cardiac function (587).

### 3.3.8 Pressor Therapy used as an adjunct to Extra-intracranial Bypass

Three studies reported the use of pressor agents in AIS patients who underwent extra-intracranial bypass (575, 585, 586). In the three patients, aged 30 to 66 years, included in these studies, pressor therapy was given either prior to (575, 585) or post procedure (586) because of BP-related worsening symptoms. All patients were discharged with good neurological recovery and no adverse events were reported.

| Study | Study Design | Patient numbers IH/ ST | Patient characteristics (IH/ST) | Imaging used | Reasons of IH | Any concomitant AIS treatment | Type of AIS | Pressor agents | Details of pressor agent | Time of pressor given | Duration of pressor given | Any volume expansion/ haemodilution treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bang 2019 (574) | Prospective, randomised trial | 76 vs. 77 | 62.7±12.9 vs. 69.9±12.3 | MRI DWI | Ineligible of recanalisation therapy or progressive stroke | | Only defined as LVO or small vessel occlusion | PE | 10ml/hr, maximum 160ml/hr | At least 24 hrs, tapered off after 24 hrs in responder or 60mins at maximum dose of upper SBP in non - responder | Median: 5 days | |
| Bogoslovsky 2006 (581) | Case report | 1 | 72 yrs old Female | CTP- Perfusion/ diffusion mismatch CTA -1cm thrombus in right MCA | Unknown onset time (wake up stroke) | Pre-admission antihypertensive medication was stopped during IH | Cardiac-embolic right MCA occlusion | PE | 0.5mg/hr up to 3.5mg/hr | > 8 hrs of symptom onset (4 hrs after admission) | 4 days | IV crystalloid 3000ml/day |
| Chalela 2005 (582) | Case report | 1 | 76 yrs old Male | MRI confirmed with perfusion/ diffusion mismatch MRA: Left A2 occlusion | Fluctuating symptoms correlate with MAP variation | | ACA infarct | PE | | | | IV crystalloid |

| Study | Study Design | Patient numbers IH/ ST | Patient characteristics (IH/ST) | Imaging used | Reasons of IH | Any concomitant AIS treatment | Type of AIS | Pressor agents | Details of pressor agent | Time of pressor given | Duration of pressor given | Any volume expansion/ haemodilution treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Delgado 2016 (577) | Retrospective record review | 5 | Mean age: 62 yrs | | Decision made by intensivist. Sudden drop of BP in patients who cannot receive a CVC | | Only mentioned as ischaemic stroke | PE | Administered peripherally, infusion rate up to 2µg/ (kg min), mean dosage 0.53 µg/(kg min) | | Mean duration: 14.29 hrs (range 1-54.3 hrs) | |
| Janjua 2005 (583) | Case report | 1 | 39 yrs old male | Arterio-graphy revealved hypoplastic left VA, distal occluded right VA with dissection and compromised basilar flow | Recurrent lock-in syndrome in 2 hrs, each last approximately 10 mins (32 hrs post initial symptom onset) | Aspirin 300mg IV Heparin and IVT | Pontine ischaemia secondary to vertebra-basilar dissection | PE and NPE | | > 24 hrs | 72 hrs | |

| Study | Study Design | Patient numbers IH/ ST | Patient characteristics | Imaging used | Reasons of IH | Any concomitant AIS treatment | Type of AIS | Pressor agents | Details of pressor agent | Time of pressor given | Duration of pressor given | Any volume expansion/ haemodilution treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kang 2017 (578) | Retro-spective case study | 25 vs. 41 | 66.0±10.9 vs. 68.1±9.1 (yrs) Male: 52% vs. 58.5% | MRI DWI showed solitary infarct <20mm diameter, affected area was in the perforating arterial territory | Evidence of motor progression | | Lacunar infarct with motor progression | PE | Induction rate 0.5mg/hr, then titrate every 4 hrs to reach target BP | | Tapered down after motor stabilisa-tion for 24 hrs | IV saline 40ml-80ml/hr in both groups |
| Kim and Kang 2007 (584) | Case report | 1 | 68 yrs old Male | MRA: occlusion in left proximal MCA Repeat MRI showed new scattered lesions in the left MCA territory | Prolonged haemodynamic compromise | Antiplatelet IAT | Left MCA infarct with a large perfusion defect | PE | 60 µg/min | Day 4 of hospital admission | Approx. 40 hrs | IV saline 100ml/hr and hydroxyethyl starch 40ml/hr |
| Kim 2018 (585) | Case report | 1 | 61 yrs old female | MRI: subacute infarction in the left internal border and loss of signal within the left ICA | Symptoms onset > 7 hrs | Dual antiplatelet (Aspirin and Clopidogrel) Extra-cranial and intra-cranial bypass | Left internal border infarction | PE | | | | IV fluid |

| Study | Study Design | Patient numbers IH/ ST | Patient characteristics | Imaging used | Reasons of IH | Any concomitant AIS treatment | Type of AIS | Pressor agents | Details of pressor agent | Time of pressor given | Duration of pressor given | Any volume expansion/ haemodilution treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Koenig 2006 (579) | Retro-spective case study | 46 vs. 54 | 63±15 vs. 65±13 (yrs)<br>Male: 56% vs. 56% | MRI performed confirmed abnormal-lities of acute ischaemia | Within 7 days of symptom onset | 19 (4.1%) received IV heparin, all withholding existing anti-hypertensive | Any type of AIS | PE Dopamine Or oral Midodrine | | 6.5±8.0 hrs (range 0.5 to 40 hrs) after MRI | | IV Fluid Fludrocortisone |
| Lee 2019 (591) | Obser-vational study | 121<br>vs.<br>121 | IH: 65.9±12.7 (yrs)<br>Male: 60% | Not Mentioned | Early neurological deterioration (NIHSS ≥2), or (NIHSS >1) with physician's decision | | Only defined as LVO or small vessel occlusion | PE | 0.3µg/kg/ min and titrate every 30 to 60 mins | | Mean 5.8±2.7 days | IV saline |
| Lim 2011 (580) | Retro-spective case study | 52 vs. 30 | 62.5±12.2 vs. 64.9±10.8 (yrs)<br>Male: 50% vs. 46.6% | MRI DWI – solitary infarct <20mm in diameter and affected area is in the perforating arterial territory | Evidence of motor progres-sion and physician's decision | | Lacunar syndrome with motor progression | PE | 0.5mg/hr and titrate every 4 hr to reach target BP | | Taper down after motor stabilisa-tion for 24 hrs | IV saline 40 to 80ml/hr |

| Study | Study Design | Patient numbers IH/ ST | Patient characteristics | Imaging used | Reasons of IH | Any concomitant AIS treatment | Type of AIS | Pressor agents | Details of pressor agent | Time of pressor given | Duration of pressor given | Any volume expansion/ haemodilution treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| List 2013 (575) | Case series study | 6 | Mean age: 70.5 ±7.27 (yrs), 5 Male | US confirmed intracranial collateral flow activation and proximal occlusion or high grade stenosis of the ICA | BP-related worsening neuro-logical deficits, profound post-stenotic flow patterns in the affected MCA | 1 x Extra-cranial and Intra-cranial bypass<br>1 x carotid endarterectomy<br>1 x carotid stenting | Acute MCA-ACA watershed infarctions or MCA inner border zone infarction | NPE | | Within 24 hours of symptom onset | 1 to 14 days | |
| Machida 2018 (586) | Case report | 1 | 30 yrs old Female | MRI showed left temporal lobe infarction, occlusion in the ICA bilaterally and PCA | Suspected Benzold-Jarischi reflex and autonomic dysfunction results cerebral ischaemia | Superficial temporal artery to MCA anastomosis | Moya-moya patient with autonomic dysfunc-tion | Ephedrine and Dopamine | Ephedrine: 8mg Dopamine: 5-10 µg/kg/min | Dopamine: approx. 105 mins post-surgery Ephedrine: approx. 160 mins post-surgery | | Red blood cells in an albumin infusion |
| Mundiyana purath 2016 (590) | Prospec-tive observa-tional study | 64 | Age range 59-81 yrs old | All patients received CT and CTA or MRI and MRA | To maintain SBP in a target range during MT | IVT, IAT, MT | AIS due to occlusion of ICA or MCA | NPE | Bolus followed by infusion (1.7-16.7µg/ min) | When BP dropped below the target range | | |

| Study | Study Design | Patient numbers IH/ ST | Patient characteristics | Imaging used | Reasons of IH | Any concomitant AIS treatment | Type of AIS | Pressor agents | Details of pressor agent | Time of pressor given | Duration of pressor given | Any volume expansion/ haemodilution treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nakagawa 2016 (587) | Case report | 1 | 79 yrs old Female | MRI showed multiple right precentral and postcentral gyrus infarct CTA: severe stenosis in right ICA | BP dropped during CAS | Dual antiplatelet therapy (Clopidogrel and Cilostazol) Carotid stenting | Right MCA infarct | Etilefrine and Dopamine | Etilefrine: 1mg Dopamine: 12 µg/kg/min | During CAS | 24 hrs | |
| Nasi 2019 (572) | Random-ised controlled Trial | 218 * Group 1: 77 Group 2: 75 Group 3: 66 In total, 90 patients received IH | Group 1: 68±12 Group 2: 69±11 Group 3: 67±11 (yrs) (p=0.64) Male: Group 1: 56% Group 2: 57% Group 3: 47% | CT to confirm diagnosis of AIS | If BP did not reach the target range | Antiplatelet | Non-thrombolysed AIS within 12 hrs of onset | NPE | | 5 hrs from hospital admis-sion. Target SBP needed to be reached within 3 hrs | 24 hrs of manipulation | IV saline |

| Study | Study Design | Patient numbers IH/ ST | Patient characteristics | Imaging used | Reasons of IH | Any concomitant AIS treatment | Type of AIS | Pressor agents | Details of pressor agent | Time of pressor given | Duration of pressor given | Any volume expansion/ haemodilution treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rasmussen 2018 (573) | Prospective parallel group, open-label randomised controlled trial | GA= 65<br>CS = 63<br>Pressor received:<br>GA: 64/65<br>CS: 36/63 | Mean age: 71.4±11.4 (yrs)<br>Male: 51.6% | MRI DWI to confirm cerebral infarction | Did not reach target BP | IVT and MT | Anterior circulation stroke with LVO | PE or Ephedrine | | | | |
| Shah 2008 (576) | Case series | 3 | Pt:1 58, male<br>Pt:2 75, male<br>Pt:3 94, female (yrs) | CT and CTA revealed proximal MCA occlusion | Partial recanalisation post MT | IVT and MT | Pt 1 Right MCA infarct<br>Pt 2 Right MCA infarct<br>PT 3 Right MCA infarct | Pt 1: PE<br>Pt 2: PE and NPE<br>Pt 3:PE | | | | |
| Stead 2008 (588) | Case report | 1 | 63<br>Female | CTA: occlusion in right ICA<br>Doppler: high grade stenosis in right ICA | Fluctuated GCS and NIHSS score | | Right MCA infarct | PE | Bolus (50mcg) followed by infusion 140mcg/min | | 36 hrs | IV saline |

| Study | Study Design | Patient numbers IH/ ST | Patient characteristics | Imaging used | Reasons of IH | Any concomitant AIS treatment | Type of AIS | Pressor agents | Details of pressor agent | Time of pressor given | Duration of pressor given | Any volume expansion/ haemodilution treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Verro and Chow 2009 (589) | Case report | 1 | 54 (yrs) Male | CT: left MCA infarct MRA: Left MCA occlusion | Partial recanalisation after IVT and persistent low BP | IVT IV heparin | Left MCA infarct | PE | 40-180 mcg/min | | 72 hrs | IV N saline |

**Table 3.5** Summary of study design, patients and pressor agent characteristics in IH studies

**ACA: Anterior Cerebral Artery**

**AIS: Acute Ischaemic Stroke**

**BP: Blood Pressure**

**CAS: Carotid Artery Stenting**

**CT: Computer Tomography**

**CTA: Computer Tomography Angiography**

**CTP: Computer Tomography Perfusion**

**CVC: Central Venous Catheter**

**CS: Conscious Sedation**

**GA: General Anaesthesia**

**GCS: Glasgow Coma Scale**

**ICA: Internal Carotid Artery**

**IH: Induced Hypertension**

**IV: Intravenous**

*** Group 1 identified as BP range 140-160mmHg**

**Group 2 identified as BP range 161-180mmHg**

**Group 3 identified as BP range 181-200mmHg**

**IVT: Intravenous Thrombolysis**

**LVO: Large Vessel Occlusion**

**MCA: Middle Cerebral Artery**

**MRA: Magnetic Resonance Angiography**

**MRI: Magnetic Resonance Imaging**

**MRI DWI: Magnetic Resonance Imaging Diffusion Weight Imaging**

**MT: Mechanical Thrombectomy**

**NPE: Norepinephrine**

**PCA: Posterior Cerebral Artery**

**PE: Phenylephrine**

**SBP: Systolic Blood Pressure**

**US: Ultrasound**

**VA: Vertebral artery**

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Bang 2019 (574) | IH vs. ST 7.6±3.8 vs. 5.6±3.7 | IH vs. ST 144.2±18.5 vs. 146.5±16.8 | | | | | | Increased baseline SBP by 20% , aim SBP <200mmHg | 1x (sICH and oedema)<br>6x headache<br>1x palpitation<br>1x urticaria | | IH group had better early neurologic improvement (Unadjusted) (p=0.001), favourable shift of NIHSS (p=0.011), but not functionally independent at 90 days (mRS <2) (p=0.114). 5 ICH at follow up visits |
| Bogoslovsky 2006 (581) | 14 | 150 | 72 | 98 | | | | Increased MAP by 20% within 1 hr of IH and maintained at 120 mmHg | None reported | | 4 hrs after IH NIHSS: 12<br>MRI performed 25 hrs post IH: subtle sign of cortical infarction, NIHSS at discharge = 7<br>10 months mRS = 2 |
| Chalela 2005 (582) | | | | | | | Range from 91 to 110 | MAP elevated to 142 mmHg during IH | None reported | | MRI before and after IH demonstrated perfusion deficit decreased by 40% (from 50 to 30ml), but no change in cerebral blood volume |

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Delgado 2016 (577) | | | | | | | | | 1 minor complication reported as pain and erythema around the infusion site | | |
| Janjua 2005 (583) | | | | | | | | Increased SBP to 220 mmHg, aiming to maintain between 175-185 mmHg | | | MRI performed 24 hrs post IH showed a left paramedian pontomedullary infarct with minimal haemorrhage. Patient discharged home with no weakness and mild 6$^{th}$ nerve palsy only. |

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kang 2017 (578) | PE vs. Non-PE: 4.0±2.1 vs. 4.0±3.1 (p=0.955) | PE vs. Non-PE 139.1±18.5 vs. 150.4±21.5 (p=0.033) | | | PE vs. Non-PE 127.6±20.3 vs 127.4±18.2 (p=0.963) | | | Increased SBP to 220mmHg or 20% increased from admission BP | 1 = dysuria | NIHSS reduction (p=0.006), successful BP elevation during treatment (≥ 20%) (p=0.002) and increased of pulse wave velocity (OR= 1.004; 95% CI=1.001-1.008; p=0.018) | IH group had significantly lower NIHSS (p=0.036) and mRS (p=0.004) at discharge |
| Kim and Kang 2007 (584) | Admission: 4 Day 4: 12 | 128 | 73 | | 87 | 52 | | 150/80 mmHg | None reported | | NIHSS dropped from 12 to 0, no recurrent neurological symptoms for the following 1 year period |

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Kim 2018 (585) | | | | | | | | | | | Right sided weakness improved after 24 hours post IH, new onset of intermittent amaurosis fugax-superficial temporal artery to cortical MCA bypass performed. Patient discharged with mRS =1. |

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Koenig 2006 (579) | IH vs. ST: 8.4±5.1 vs. 7.1±4.9 | | | IH vs. ST 106 vs. 100 | | | | Only 35% of IH group achieved MAP augmentation by 10-20% above admission baseline BP. | IH: 4 (2 x ICH, 1 x hypertensive encephalopathy and 1 x pulmonary oedema) ST: 4 (2x MI and 2x pulmonary oedema) | | IH group had higher proportion of large vessel disease (52 vs. 11%) (p<0.003), ICA/ECA stenosis (80 vs. 27%) (p=0.0002) and were more likely to be admitted to ITU (42 vs. 28%). The length of stay was longer in IH group (p=0.005) Larger volume of diffusion-perfusion mismatch in IH (p=0.005) Discharge NIHSS 3 vs. 4 (p=0.121) |

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lee 2019 (591) | IH vs. ST: 5(3-7) vs. 3(1-6) | IH vs. ST: 152.3±25.4 vs. 144.6±21.5 | | | | | | 15 to 25% increase from baseline SBP, with maximum SBP of 220mmHg | IH: 12<br><br>(3 x HT; 5 x sinus bradycardia;<br><br>1x sinus pause; 1x vasogenic oedema; 1x renal failure; 1x pulmonary hypertension)<br>SH: 9<br><br>(6 x HT; 1x sinus pause; 1x renal failure; 1 x pulmonary hypertension) | | IH group had greater resolution of neurological deficit (highest NIHSS – discharge NIHSS) ($p<0.001$) at discharge, but ST group has significant higher proportion of favourable mRS (≤3) at discharge ($p<0.001$), but no differences between two groups at 3 months ($p=0.059$) |

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lim 2011 (580) | IH vs. ST: 1.00±1.25 vs. 0.63±0.89 (p=0.163) | IH vs. ST: 161.7±24.8 vs. 168.0±31.9 (p=0.326) | | | IH vs. ST: 140.6±18.4 vs. 160.2±24.2 (p<0.001) | | | SBP: 220mmHg or 20% increase from baseline SBP. | IH: 5 (3 x transient chest tightness and 2x dysuria) Standard: (1x transient chest tightness) normal ECG and cardiac enzyme in both group (p=0.407) | *Model 1: History of hypertension (OR=5.05; CI 95% =1.33-19.28; p=0.018); Model 2: History of hypertension (OR 7.11; CI 95%=1.43-35.31 p=0.016) successful BP elevation (OR=8.13; 95% CI=1.49-44.45; p=0.016) and motor stabilisation time (OR=0.51; 95% CI= 0.29-0.87; p=0.015) | NIHSS at discharge: IH vs. ST: 1.01±1.47 vs. 1.86 ± 1.92 (p=0.042) Length of stay: IH 13.1±7.0 vs. ST 18.6± 17.3 (p=0.047) mRS (0-2) at discharge: IH 62% vs. ST 50% (p=0.044) |

*Model 1: BP elevation ≥ 10%  Model 2: BP elevation ≥ 20%

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| List 2013 (575) | 2.83±1.07 | | | | | | | Target SBP: 160-190mmHg | | BP elevation is associated with increased cerebral blood volume in the AH MCA and PCA | 1x extra-intracranial bypass<br>1x carotid endarterectomy<br>1x carotid stenting<br>1x stabilised with antihypertensive<br>1x malignant MCA infarct<br>1x symptoms worsen when IH withdrawal |
| Machida 2018 (586) | | 110 | 60 | | 90 | 50 | | BP raised to 180/85 mmHg | | | GCS improved from 7 to 14, discharged 3 weeks post operation. HUT performed post discharged confirmed vasopressor type autonomic dysfunction |

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mundiyanapurath 2016 (590) | Range : 13-22 | Range: 125-178.5 | | | | | | SBP: 140-160 mmHg | 11% of sICH in unfavourable outcome group (mRS >2) (p=0.078) | Lower age (p=0.013), absence of ICH (p=0.001), lower NPE dose used (p=0.001). | BP dropped > 20mmHg in 51% patients but no statistical differences between good and bad outcome groups |
| Nakagawa 2016 (587) | | 136 | 68 | | 70-90 | | | SBP > 90 mmHg | Patient developed Takotsubo Cardiomyopathy after CAS | | Confirmed Takotsubo cardiomyopathy<br>Initial Echo showed LV hypokinesis and apical akinesis, dopamine stopped and repeat Echo showed improved ejection fraction and akinesis. |

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nasi 2019 (572) | Median (IQR)<br>Group 1: 7 (3-16)<br>Group 2: 8 (4-16)<br>Group 3: 8 (3-16)<br>(p= 0.56) | Median (IQR)<br>Group 1: 166(144-185)<br>Group 2: 163 (140-189)<br>Group 3: 169 (151-203)<br>(p=0.19) | | | | | | Group 1: 140-160 mmHg<br>Group 2: 161-180 mmHg<br>Group 3: 181-200 mmHg<br><br>70% in Group 1, 61% in Group 2 and 60% in Group 3 achieved target SBP. | Significant higher proportion of sICH in group 3 (9%) compare to group 1 (1%) and group 2 (3%) (p=0.049). ACS: 1.3% and 6% in group 2 and 3, respectively. Symptomatic bradycardia (1.5%) in Group 3. | Better outcome in positive mismatch patient and received BP increment or no manipulation (p=0.043) Patients with negative mismatch had no difference in outcomes related to up or down manipulation. | No differences in terms of good outcome at 90 days (mRS <2) (p=0.27) and mortality (p=0.40) between groups. |

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rasmussen 2018 (573) | Median (IQR)<br>18 (14-21)<br>GA: 18 (13-21)<br>CS: 17 (15-21)<br>p=0.84 | GA: 164±24.7<br>CS: 163±27.1<br>p=0.83 | | GA: 110±17.0CS: 108±18.4<br>p=0.48 | | | | SBP ≥140 mmHg and MAP ≥70 mmHg | | | GA group had lower procedural MAP, SBP and higher BPV than CS group (all p<0.001). More patients in GA group required vasopressor. (p<0.001). No difference between BP variables and neurological outcome at 90 days. |
| Shah 2008 (576) | Pt 1: 20<br>Pt 2: 15<br>Pt 3: 18 | | | Pt 1: 96<br>Pt 2: 87.3<br>Pt 3: 93 | | | | MAP 20% above the baseline | | | Pt 1: NIHSS was 7 and 0 at 24 hrs and 3 months, respectively. mRS was 0 at 3 months.<br>Pt 2: 3 months NIHSS and mRS was 0 and 1, respectively.<br>Pt 3: Discharge NIHSS and mRS was 1 and 4, respectively. |

| Study | Admission NIHSS | Baseline SBP (mmHg) | Baseline DBP (mmHg) | Baseline MAP (mmHg) | SBP during symptom progression (mmHg) | DBP during symptom progression (mmHg) | MAP during symptom progression (mmHg) | Target BP (mmHg) | Adverse event | Factors associated with good outcome | Outcomes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Stead 2008 (588) | NIHSS: 9 and increased to 17 when symptoms worsen | | | | | | | MAP: range 110-120 mmHg | | | Completely resolution of left hemisphere less than an hour. Completely normal neurological examination on day 4. |
| Verro and Chow 2009 (589) | | 119 | 86 | | 105 | 60 | | 150-170/80-90 mmHg | Repeat CT showed moderate haemorrhagic transformation | | PE stopped after 72 hrs, BP dropped to 90/40mmHg. Repeat CT showed extension of infarct in entire MCA territory, required mannitol for cerebral oedema. |

**Table 3.6** Summary of BP characteristics, adverse events and final functional outcome

**AF: Atrial Fibrillation**
**AH: Affected Hemisphere**
**AIS: Acute Ischaemic Stroke**
**BP: Blood Pressure**
**CAS: Carotid Artery Stenting**
**CS: Conscious Sedation**
**CTP: Computer Tomography Perfusion**
**CTA: Computer Tomography Angiography**
**CVC: Central Venous Catheter**
**ECHO: Echocardiogram**
**EVT: Endovascular Therapy**
**GA: General Anaesthesia**
**HT: Haemorrhagic Transformation**
**HUT: Head Up Tilt**
**IAT: Intra-arterial Thrombolysis**
**ICA: Internal Carotid Artery**
**ICH: Intracerebral Haemorrhage**
**IH: Induced Hypertension**
**LVO: Large Vessel Occlusion**
**MAP: Mean Arterial Pressure**
**MI: Myocardial Infarction**
**MRA: Magnetic Resonance Angiography**
**MRI: Magnetic Resonance Imaging**
**mRS: Modified Rankin Scale**
**MT: Mechanical Thrombectomy**
**NIHSS: National Institutes of Health Stroke Scale**
**NPE: Norepinephrine**
**PCA: Posterior Cerebral Artery**
**PE: Phenylephrine**
**SBP: Systolic Blood Pressure**
**sICH: Symptomatic Intracerebral Haemorrhage**
**ST: Standard Therapy**

***Group 1 identified as BP range 140-160mmHg**
**Group 2 identified as BP range 161-180mmHg**
**Group 3 identified as BP range 181-200mmHg**

## 3.4 Discussion

The aim of this systematic review was to investigate the evidence of feasibility, safety and clinical effectiveness in using pressor agents as IH therapy in AIS. IH seems feasible in AIS in certain clinical scenarios. However, the small number of included studies from the original search strategies (20 studies from 4808 abstracts reviewed), highlights the limited nature of the current evidence base, and therefore, the low use of such a strategy by stroke physicians is not unsurprising. As the majority of data are derived principally from case reports and case series, it also cannot be seen to be representative or typical of clinical practice. As such, no definite conclusions can be drawn regarding the clinical effectiveness of using IH in AIS settings. However, the included studies do suggest there could be benefits in this particular group of AIS patients, pointing to the need for randomised interventional studies.

### 3.4.1 Clinical Efficiency

Overall, clinical efficacy in IH has been demonstrated in selected groups of AIS patients, in particular in the following categories:

1) Fluctuating symptoms that correlate with BP variation (≥ SBP 20mmHg differences) and resulting in haemodynamic instability (575, 582, 584, 588);

2) Deteriorating symptoms despite the administration of standard AIS treatment (574, 578, 580, 591);

3) Outside the therapeutic window for IVT/MT (or where such services are not available), in particular to those with salvageable but underperfused cerebral tissue (574, 579, 581, 585);

4) Ipsilateral extensive extracranial or intracerebral vessel stenosis/occlusion (583, 586);

5) Achievement of target BP (e.g. > SBP 140mmHg or 20% higher from the baseline SBP) during AIS-related procedures (e.g. CAS, MT) (572, 573, 577, 587, 590);

6) Incomplete recanalisation after AIS-related procedures (e.g. IVT, MT) (576, 589);

As mentioned in the previous section, the lacking of relevant randomised data to inform guidelines, necessitates limited use in association with close monitoring (e.g. HDU/ITU settings), and extensive specialist input could explain the low pick up rate of such regime.

Similar to the systematic review carried out by Mistri and colleagues (536), this review has also demonstrated that PE is the most widely used pressor agent in IH therapy. This likely reflects familiarity with its use over several decades, including in various anaesthesia procedures (e.g. spinal surgery) to correct hypotension, and its established side effect profile. As mentioned in the previous section, its α1-adrenergic agonist property means it is less likely in induce tachyarrhythmias and other cardiovascular adverse effects. Nevertheless, it should be administered in patients who have preserved cardiac function and without significant history of cardiovascular disease.

### 3.4.2 Adverse Events

A number of adverse events were reported in the studies, though the majority were minor, including dysuria (578, 580), transient chest tightness (578, 580), headache (574), palpitation (574), urticaria (574), and erythema around the infusion site (577). sICH (574, 579, 590), haemorrhagic transformation (574, 589-591), vasogenic oedema (591), hypertensive encephalopathy (579), sinus bradycardia and pause (591), renal failure (591), and pulmonary oedema (579) are more serious adverse events, also reported in

studies. However, information is sparse and it is therefore difficult to conclude whether these adverse events directly lead to less favourable functional outcome.

In the study carried out by Koenig et al., patients in the IH group were more likely to be admitted to ITU with longer hospital length of stay (p=0.005) (579). One possible explanation could be that patients in the IH group in this study tended to have more severe disease, as evidenced by a higher proportion of LVO (and hence, higher NIHSS) and diffusion-perfusion mismatch; this is supported by Bang et al (574) and Lee et al (591). whose studies also demonstrated higher proportion of LVO and NIHSS in the IH group (574, 591). Accordingly, pressor therapy was more likely to be given due to haemodynamic instability, hence requiring closer monitoring in an ITU/HDU setting. Importantly, in the study carried out by Koenig et al., there were no significant differences in median NIHSS score between IH and ST groups, at admission, 24, 48, 72 hours and discharge (p=0.121). Four adverse events in both groups were also reported: IH (ICH = 2, hypertensive encephalopathy =1, pulmonary oedema =1) and ST (myocardial infarction =2, pulmonary oedema =2). Overall, only 35% patients in the IH group achieved target BP (579).

Whilst in the study carried out by Nasi and colleagues, there was a significant proportion of sICH, acute coronary syndrome and symptomatic bradycardia in participants who were allocated to the higher target BP (Group 3) than the other groups (Group 1 and 2) (572). However, of note, it was not possible to identify participants who had adverse events whether undergoing pressor, depressor or no BP manipulation. Therefore, it is not possible to draw a firm conclusion that all such events were due to NPE use (572). There was also a lack of individual baseline BP recordings in this study (572), and hence, participants who could have a fairly low baseline BP (prone to developing left shift of

CA) and randomised to a higher BP group (group 2 or 3). This could result in a profound BP change, causing detrimental effect on CA and subsequently secondary reperfusion injury. It is also important to note that the 24-hour target SBP was sustained in only 70%, 61%, and 60% of patients in Group 1, 2 and 3, respectively (572).

The case reported by Nakagawa et al. suggested that the higher dose of Dopamine infusion used in AIS patients during CAS could lead to TCM, though the condition was reversible following termination of pressor therapy (587). Nevertheless, caution should be used in patient selection, with close monitoring required when using such a regime in AIS.

### 3.4.3 Study Limitations

There are several limitations to this systematic review. Similar to other systematic reviews, this study is limited by reporting bias, although published data has been collected in respect of IH, its indication, patients characteristics, IH-associated complications and final functional outcome. However, it is likely that some relevant information was not published, which reduces the strength of the conclusions of this review. Another major limitation is the inconsistency of reporting among published reports. Moreover, the majority of included studies were retrospective observational studies and case reports with relatively small sample sizes. Accordingly, it was not possible to perform meta-analyses of the clinical efficacy of IH in AIS.

In addition, the treatment algorithms used were often different with respect to pressor agents used, dosage, time, and duration to event and subsequent monitoring. This resulted in moderate heterogeneity, and the quality evidence of analysed outcomes was likely unreliable as a result of the small sample sizes of available studies. Despite the increasing use of IVT and MT which may increase the likelihood of need for pressor therapy because

of sedation-induced hypotension, there is still a lack of good quality, randomised, controlled trials, with reported outcomes of all-cause morbidity and mortality, length of hospital stay and adverse events in using IH in order to provide a firm guidance on how best to manage low BP in AIS in such situations.

### 3.4.4. Consideration for Future Studies

Due to poor study quality, small sample size of included studies and possible reporting bias, the current review could not provide definitive evidence on clinical efficacy on pressor treatment in AIS patients. As most of the included studies are case reports and case series, participant binding was not possible to carry out. In the future, high quality, prospective, randomised controlled trials with sufficient sample sizes should be considered. Measures such as using computer programme to randomise patients, use of outcome assessor blinded to allocation, standardised procedures to all the intervention and control arms, adherence to the allocated treatment and reporting any deviation from standardised procedures could all minimise bias. Furthermore, the included studies reported a wide variety of pressors, with variable dosage, duration and timing of initiation. Future studies should consider using single pressor agent, preferably phenylephrine as it has a well-known pharmacokinetic and safety profile, and has been widely used in different medical settings. Finally, as mentioned in Section 3.4.1, several groups of AIS patients seem to benefit from IH and can be provided safely, so future studies should initially focus on these groups of patients, assessing its safety, clinical efficacy, neurological and functional recovery, and subsequently extend to other AIS patients if necessary.

## 3.5 Conclusion

In conclusion, there is low quality evidence to suggest IH is feasible and safe in a selected group of AIS patients, with acceptable side effect profile, though current evidence is from underpowered studies that carry a high risk of bias. Large-scale, well-designed definitive trials with randomised evidence are required as to whether IH could translate into improved neurological recovery. Overall, this systematic review suggests that careful patient selection will be crucial to optimise the clinical outcome. In particular, the definition of hypotension should be individualised, according to the patient's premorbid BP, other co-morbidities and stroke subtype. It may not be practical to define a specific BP threshold or target for all AIS patients at which IH therapy should be considered, therefore, this could certainly argue whether assessing such patients' cerebral haemodynamic status, using appropriate imaging, such as TCD, to analyse flow response patterns in AIS patients and to evaluate the individual extent of dCA changes could guide us in using IH or other perfusion strategies in AIS, which will be discussed in subsequent chapters.

# Chapter 4. Research Methods

To have an in-depth understanding on how cerebrovascular physiology changes in controls under different circumstances and to interpret the natural history in IS patients, it is essential and important to have accurate haemodynamic measurements. In this chapter the techniques used in the studies undertaken in this thesis for the non-invasive assessment of beat-to-beat BP monitoring, $ETCO_2$ measurement and CBV will be described. General research protocols, scientific methods used to obtain data, and the recording, editing and analysis will also be outlined. For the specific details relating to the recruitment of subjects, and individual research protocols, please refer to Chapters 5 to 8.

## 4.1 Non-invasive beat-to-beat blood pressure monitoring (Finometer®)

Details of non-invasive beat-to-beat BP monitoring, including the background, the volume clamp method and the Physiocal algorithm have already been described in Chapter 1, Section 1.3.3. For internal consistency, a Finometer® MIDI (Finapres Medical Systems; Amsterdam, Netherlands) (Figure 1.5a) was used in each study presented in this thesis. The finger cuff of the Finometer® MIDI was placed on the middle finger of the non-dominant hand in controls, and the non-hemiparetic hand in AIS patients (Figure 4.1).

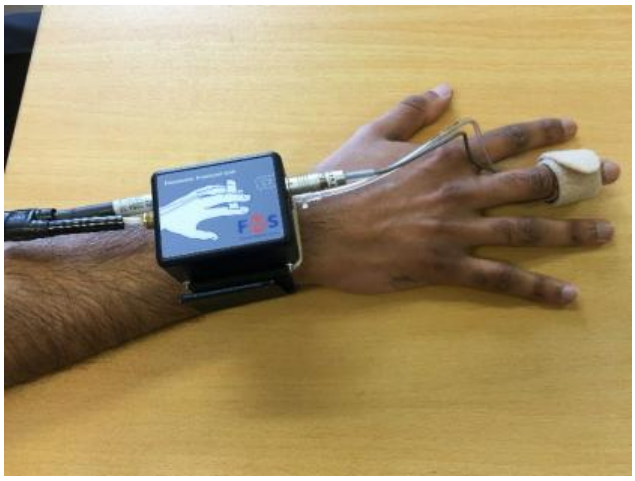


**Figure 4.1** Correct application of the Finometer® MIDI.

### 4.1.1 Validation

The accuracy and reliability of the Finometer®, and its predecessor the Finapres®, have been assessed in a variety of physiological and pathological conditions. These include utility in different ethnicities (287), resting states (282), under anaesthesia (614-617), during pregnancy (618), hypertension (618), and situations which result in marked changes in arterial BP [i.e. surgical interventions (619), hand-grip manoeuvre (284), cold pressor test (284) and valsalva straining (620)]. However, conflicting data were shown in these studies. Using the re-sampling technique, Silke and McAuley (286) carried out a study to evaluate the data of approximately 450 patients, to review the performance of the Finapres® when compared to intra-arterial BP monitoring. Their results suggest that there is little systematic bias in the Finapres® reading, and that the Finapres® device can provide an accurate estimate of DBP and MAP, but not SBP when compared to the intra-arterial recording. Silke and McAuley therefore suggest that calibration against a reliable reference arterial pressure is required in order to minimise this offset error. However, Kim et al. have carried out a systematic review comparing different types of non-invasive continuous arterial pressure devices with invasive continuous BP monitoring. Their

results have shown that, overall, random-effect pooled bias and standard deviation can be up to -1.6 ± 12.2.mmHg in SBP, 5.3 ± 8.4mmHg in DBP, and 3.2 ± 8.4mmHg in MAP, suggesting the potential inaccuracies of using such non-invasive devices are larger than had previously been defined as acceptable (621). It is, however, important to note that such results are generated by combining several types of non-invasive BP devices, rather than the Finometer® alone. Moreover, their review evaluated the older Finapres® and not the Finometer® MIDI or NOVA. Jones et al. demonstrated that the Finometer® MIDI has greater accuracy and reliability than the older Finapres®; assessing 3,000 sets of continuous BP measurements from 15 patients who underwent elective spinal surgery and compared the non-invasive BP values generated from the Finometer® MIDI to invasive arterial BP readings (622). Results suggested the Finometer® MIDI was statistically and clinically more accurate than the older version. However, they also highlighted that correct cuff application is the key to achieving accurate BP measurements (623).

One of the main and important advantages of using the Finometer® is it can provide excellent continuous BP monitoring which follows direct arterial pressure values more accurately than other non-invasive intermittent oscillometric BP devices. It is able to provide excellent reflection of the physiological changes, and not only during an established manoeuvre (i.e. thigh cuff deflation) (288). Recently, there have been a large number of studies which have used the Finometer® MIDI to assess dCA in various situations. Petersen et al. (624) used both the Finometer® MIDI and an invasive radial catheter to monitor BP in acute brain injury patients. They found that although there was a significant difference in absolute values for mean phase shift and mean velocity index, there was a good correlation between the dCA estimation. Bindra et al. (625) also used the Finometer® MIDI and NIRS (which required invasive arterial BP monitoring) to assess dCA in ITU patients with differing pathologies. They found that there was good

agreement in assessing ARI and inter-hemispheric CA asymmetry between both techniques. This evidence, together with the previous studies which have studied dCA using the older Finapres® to assess CA, supports the use of the Finometer® MIDI for non-invasive BP monitoring in cerebral haemodynamic studies (288, 626, 627).

### 4.1.2 Operational Aspects

As mentioned in Chapter 1, Section 1.3.3, both Finapres® and Finometer® operate under the principle of the arterial volume clamping technique. Hence, it is important to remember that finger cuff size (623), position (628), peripheral vasoconstriction and cold digits (614, 629) can all affect measurement accuracy. It may be difficult to obtain satisfactory finger pressure in patients who suffer significant vascular disease, arthritis, or Raynaud's disease (282). Therefore, choosing the correct finger cuff, and taking care to place the finger cuff over the proximal interphalangeal joint with the sensor on the lateral side of the finger is crucial. Warming the hand can improve vasoconstriction and finger temperature, and accuracy of measurement (630, 631).

The discrepancy in BP between the Finometer® and intra-arterial pressure in the brachial artery is mainly due to the pressure gradient of arterial blood flow in the arms and hands. This results in differences, not only in BP level, but also in pulse waveforms. The Finometer® is able to overcome this by reconstructing the brachial pressure from the finger pressure and applying a correction algorithm to compensate for the differing pressure gradient over the arm arteries (632-634). The discrepancy can be further minimised by placing the arm at the heart level during study measurement (282).

As mentioned previously, Physiocal® periodically adjusts the set point in order to maintain the applied external pressure at the same level as the intravascular pressure. However, periodic interruption by the Physiocal® can result in a loss of important

information, in particular during highly dynamic BP changes (i.e. rapid changes of head positioning). This problem can be resolved by temporarily switching off the Physiocal® during the recording. It is however important to ensure that Physiocal® is switched on at the start of each measurement in order to ensure that an adequate calibration has been made.

Although invasive BP monitoring still remains the gold standard for continuous BP measurement, it is important to note that there are risks associated with its use including thrombosis, embolism, arterial rupture, infection and relatively high cost. Therefore, non-invasive beat-to-beat BP monitoring can be used as an acceptable alternative.

## 4.2 Measurement of Partial Pressure Carbon Dioxide ($PaCO_2$)

As discussed in Chapter 1, Section 1.3.1, arterial $PaCO_2$ is one of the most important systemic regulators of CBF and CBV, and it exhibits a profound effect on CA, NVC and CVRea. Therefore, it is essential to monitor arterial $PaCO_2$ when assessing cerebral haemodynamics. However, arterial $PaCO_2$ is measured by invasive arterial blood gas sampling. Away from the intensive care environment, where invasive arterial lines can be inserted as part of standard clinical care, it is impractical and unethical to use such a technique for continuous arterial $PaCO_2$ monitoring in research and general clinical ward settings. In the last 40 years, $ETCO_2$ monitoring has become an attractive method as it is non-invasive and relatively inexpensive (635). Moreover, studies have shown that $ETCO_2$ is found to be an accurate method of estimating $PaCO_2$ in different populations (636-639). Therefore, it is generally accepted that $ETCO_2$ can act as a surrogate for $PaCO_2$.

### 4.2.1 Measurement of End-Tidal Carbon Dioxide ($ETCO_2$)

$ETCO_2$ is normally expressed as either mmHg, or percentage, and corresponds to the maximum level at the end of expiration. Infrared light absorption and mass spectrometry

are the two methods that are most commonly used in measuring $ETCO_2$ (640). Of these, the infrared light absorption technique has been most widely used for measuring $ETCO_2$ in cerebral haemodynamic research. Infrared capnography is operated under either mainstream or side-stream settings. In the mainstream setting, the $CO_2$ sensor is built into an adaptor, inline and close to the endotracheal tube (airway). In the side-stream setting, the $CO_2$ sensor is located away from the airway and the expired gas is continuously aspirated from subjects via a nasal or nasal-oral cannula. The side-stream setting is best suited for non-intubated patients (641). In this thesis, the capnograph (Capnocheck Plus, Smith Medical, Minnesota, USA) was operated in the side-stream setting.

### 4.2.2 Infrared Waveform Capnograph

In the infrared waveform capnography, an infrared light beam with a specific wavelength (4.3μm) is projected through the expired gas sample to fall on a photoelectric sensor. Since the degree of light absorption is exponentially dependent on the $CO_2$ concentration, the higher the $CO_2$ concentration in the expired gas the less light will reach the sensor, thus resulting in a change in the voltage output. This is displayed as a waveform in the monitor which is representative of the $CO_2$ level at each phase of the respiratory cycle (Figure 4.2 and Figure 4.3).

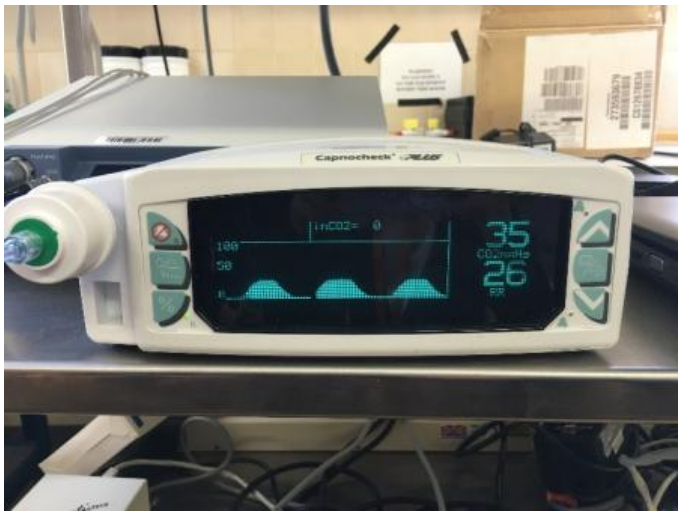


**Figure 4.2** Capnograph showing breath-by-breath waveforms of $ETCO_2$.

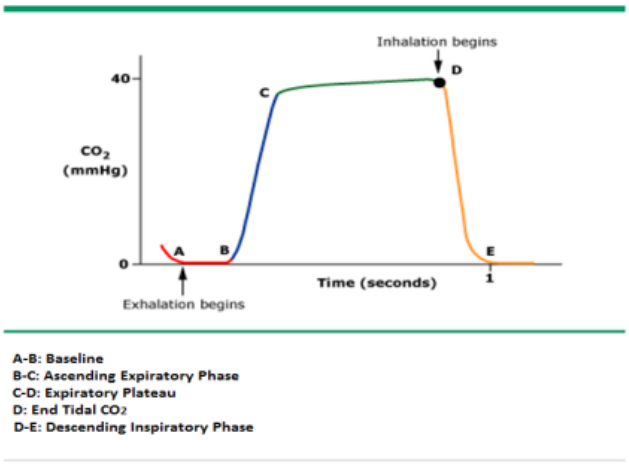



**Figure 4.3** The normal end-tidal $CO_2$ waveform [adapted from (642), with permission].

## 4.3 Transcranial Doppler (TCD) Ultrasound

The background and the underlying physical principles of TCD have previously been described in Chapter 1, Section 1.3.3. As already stated, there are four different acoustic windows that can be used in the assessment of intracranial arteries. For consistency, the transtemporal window was used for insonation of the intracranial arteries in each study reported in this thesis. The transtemporal window is located just above the zygomatic arch, in front of the tragus of the ear where the temporal bone is generally thinner. Power motion mode TCD (PMD) (Viasys Companion III, Natus Medical Incorporated, California, USA) was used as it can simultaneously display the intensity and direction of the blood flow signal. Two transducers operating at 2MHz were positioned on the temporal bone. The ACA, MCA and PCA were subsequently identified according to the direction of the blood flow relative to the probes, and the depths, waveforms and characteristics of the signal as summarised in Table 4.1. For the studies presented in this thesis, only the proximal segment of MCA was insonated, and bilaterally, if possible. The TCD transducers were also standardised as channel 1 for right hemisphere MCA and channel 2 for the left hemisphere MCA.

| Artery | Depth (mm) | Direction of flow | Mean CBV ($cm.s^{-1}$) | Response to ipsilateral carotid compression |
|---|---|---|---|---|
| MCA | 30-60 | Towards the probe | 55±12 | Obliteration<br>Diminished |
| MCA/ACA Bifurcation | 55-65 | Bidirectional | | ACA: Obliteration<br>Diminished<br>Reversal<br>MCA: Obliteration<br>Diminished |
| ACA | 60-80 | Away from the probe | 50±11 | Obliteration<br>Diminished<br>Reversal |
| PCA (P1) | 60-75 | Towards the probe | 39±10 | Obliteration<br>Diminished<br>Reversal |
| PCA (P2) | 60-75 | Away from the probe | 40±10 | No change<br>Diminished |

**Table 4.1** Summary of depth, direction of flow and mean CBV of the major intracranial vessels [adapted from (643)].

Once the MCA signal has been identified, it is important to reduce the depth gradually (up to 30mm) and then increase it again (up to 65mm) in order to ensure the signal pattern and the velocity amplitude has been optimised. In a difficult scenario, common carotid artery compression can be performed to distinguish different intracranial arteries: by using two fingers to compress down and away from the trachea. If the insonated vessel is supplied by the common carotid artery, a diminished, obliterated or reversed blood flow will be observed, otherwise a normal or augmented blood flow will be produced. However, such a technique is not appropriate in the acute stroke setting due to the possibility of cerebral and peripheral circulation instability (643). It is also important to note that the mean velocity value varies with age and sex, specifically the value tends to diminish with increasing age, and females tend to have slightly higher values compared to males (644). Other physiological factors, for example, blood viscosity (haematocrit), BP, $CO_2$, mental motor task and assessment environment can also have a significant impact on the blood flow velocity values (645).

Of note, even when the transmission power of the ultrasound has been maximised, 15-30% of subjects do not have an adequate temporal window, making TCD assessment and recording impossible. Studies have shown that inadequate temporal windows are more common in older age and female subjects, and non-Caucasian populations (646-649).

## 4.4 Research Protocol

In this thesis, all studies were either carried out in the Hyperacute Stroke Unit (HASU), or in a dedicated research laboratory, which was at a controlled temperature (20-24°C) with minimal external stimuli, in the University Hospitals of Leicester NHS Trust (UHL), Leicester, UK. Prior to attending the assessment, participants avoided excessive caffeine, alcohol, food intake and strenuous exercise for at least four hours (Apart from participants in Visit 1, Chapter 8). Effort was made to ensure all participants' assessments were carried out at a similar time of the day at all visits. BP signal was calibrated at the beginning of each recording, using the brachial BP readings taken by an OMRON 705IT sphygmomanometer (Figure 4.5). Beat-to-beat non-invasive BP was measured continuously using the Finometer® MIDI device (Finapres Medical Systems; Amsterdam, Netherlands) attached to the middle finger of the non-dominant (controls)/ non-hemiparetic (AIS patients) hand. The servo-correcting mechanism of the Finometer® MIDI was switched on then off prior to measurements. The cuff was held at heart level to minimise any orthostatic pressure difference between finger and heart.

A 3-lead ECG was used to record HR. Respiratory rate and $ETCO_2$ was monitored using an infrared capnograph (Capnograph Plus, Smith Medical, Minnesota, USA) attached to a nasal cannula, using TCD ultrasonography (Viasys companion III, Natus Medical incorporated, California, USA). 2MHz transducers were positioned on the temporal bone and the proximal segment of the MCA was identified according to the depth, waveform and characteristics of the signal (305). The depth, power, velocity and location of the

temporal window were documented in each participant to ensure the same measuring parameters were used at subsequent visits. A custom made head frame was used to secure the ultrasound probes in position and to minimise movement (Figure 4.6). Details of the individual research protocols are reported in Chapters 5 to 8.


**Figure 4.4** OMRON 705IT sphygmomanometer.

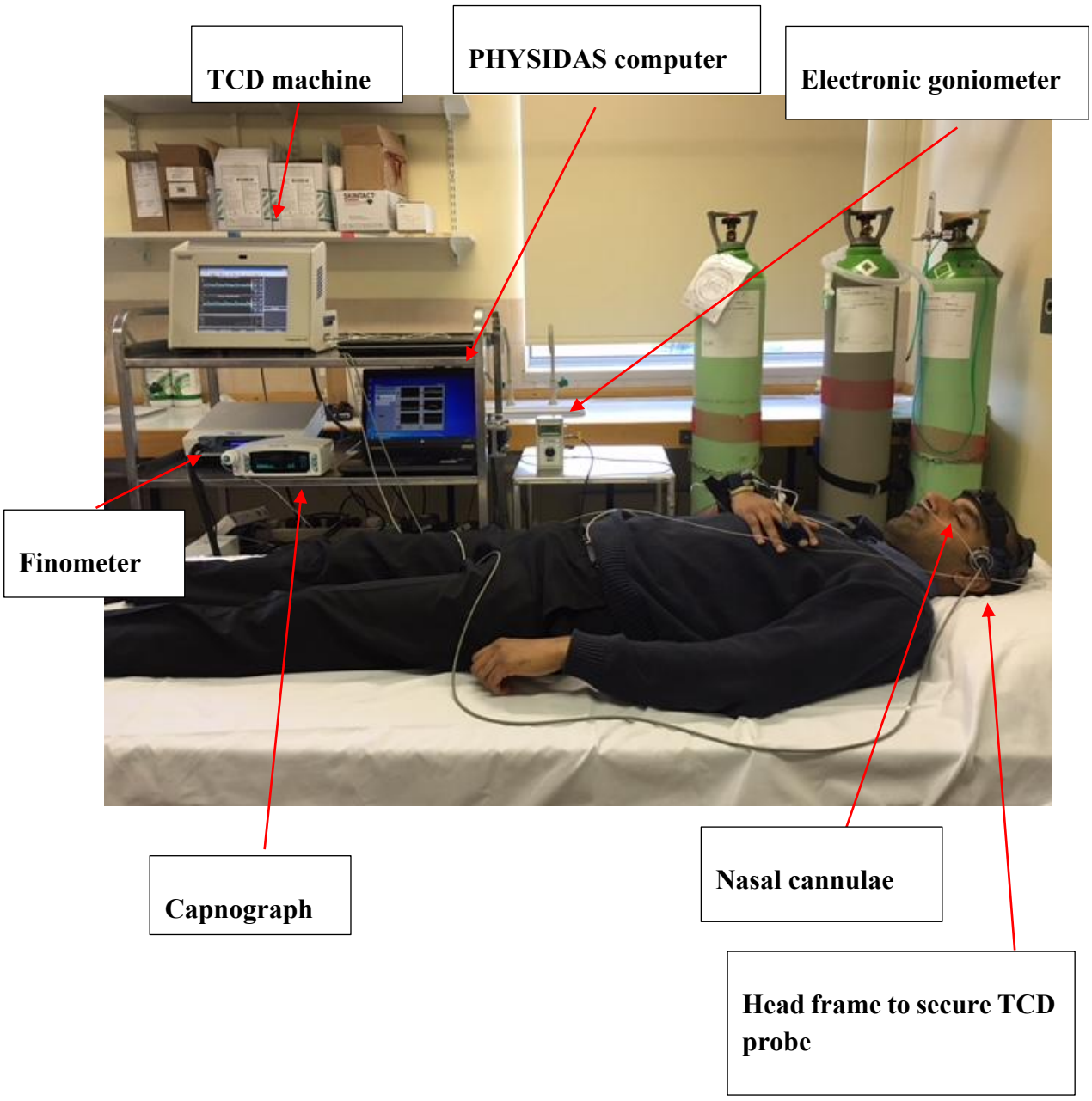



**Figure 4.5** Equipment set up for the continuous recordings of CBV, beat-to-beat BP, HR and $ETCO_2$.

## 4.5 Data Acquisition and Editing

### 4.5.1 Data Collection and Recording

Data collected as part of the research protocol (i.e. BP, ECG, CBV, $ETCO_2$ and electronic goniometer signals) were simultaneously recorded onto a physiological data acquisition system (PHYSIDAS, Department of Medical Physics, UHL NHS Trust, UK) for subsequent off-line analysis (Figures 4.6 and 4.7). All signals were sampled at 500 samples/s and all the recorded files were named using a specific code sequence, allowing the anonymity of individual participants, but the easy identification of specific files by the researcher.

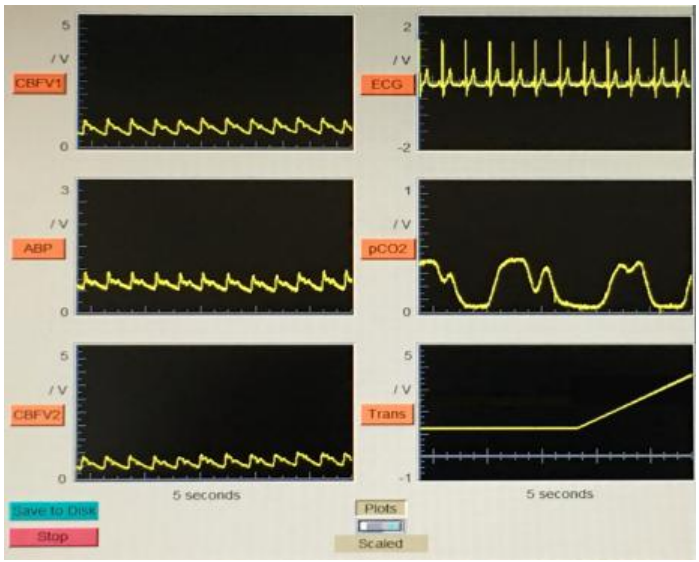
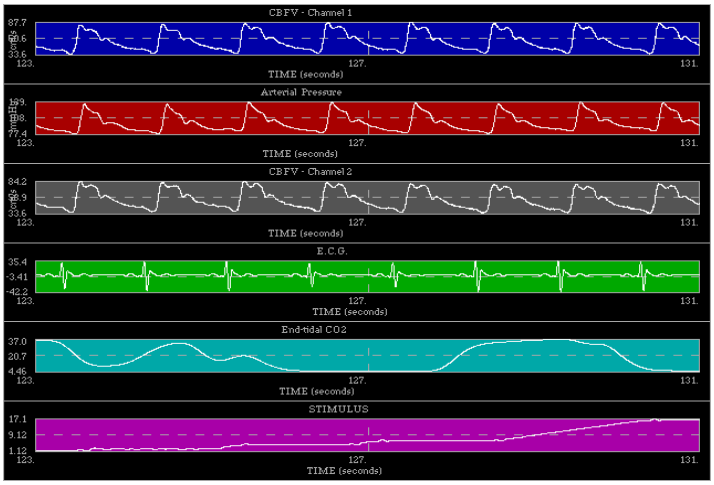



**Figure 4.6** PHYSIDAS screenshot. The transducer channel (Trans) shows the electronic goniometer signal measuring the head position as it changes from 0° to 30°. The y-axis provides the voltage range for each variable, these were then calibrated off-line.

### 4.5.2 Data Editing and Analysis

Data editing was carried out using an in-house MS DOS based programme, designed by the Department of Cardiovascular Sciences, University of Leicester, Leicester, UK (Professor RB Panerai). Figure 4.8 shows an example of typical data recording in the MS DOS based software programme.




**CBV channel 1**

**BP**

**CBV channel 2**

**ECG**

**$ETCO_2$**

**Electronic goniometer showing head positioning changes**

**Figure 4.7** The MS DOS data-editing screenshot.

BP waveform was inspected for any drift (Figure 4.9) and all signals were subsequently visually inspected to identify any artefacts and noise; narrow spikes (<100ms) being removed by linear interpolation (Figure 4.10). Recordings were rejected if there was BP drift, excessive artefact, noise or poor quality CBV signals (Figure 4.11).

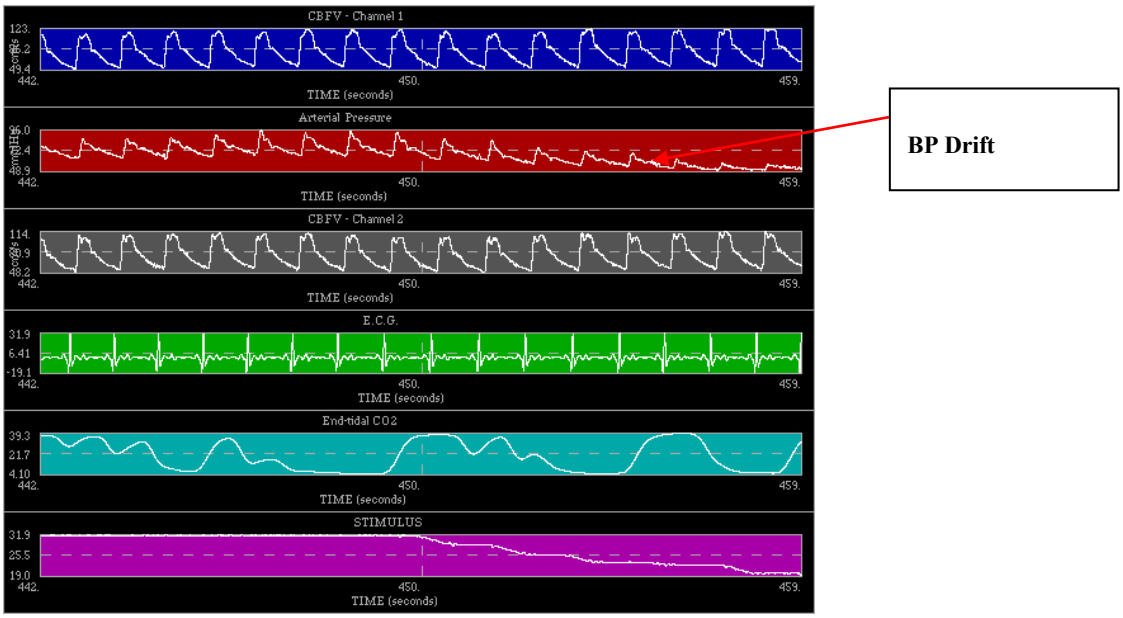



**Figure 4.8** MS DOS screenshot showing loss of BP Finometer signal.

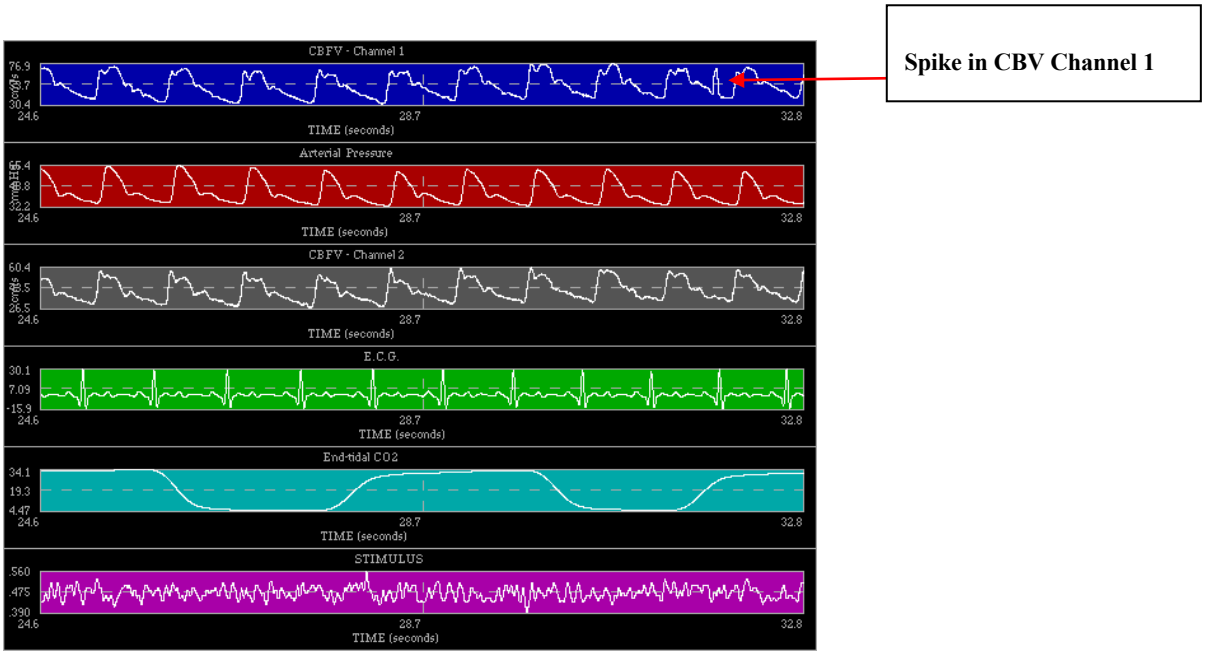



**Figure 4.9** MS DOS screenshot showing spike in the diastolic phase of the channel 1 CBV.

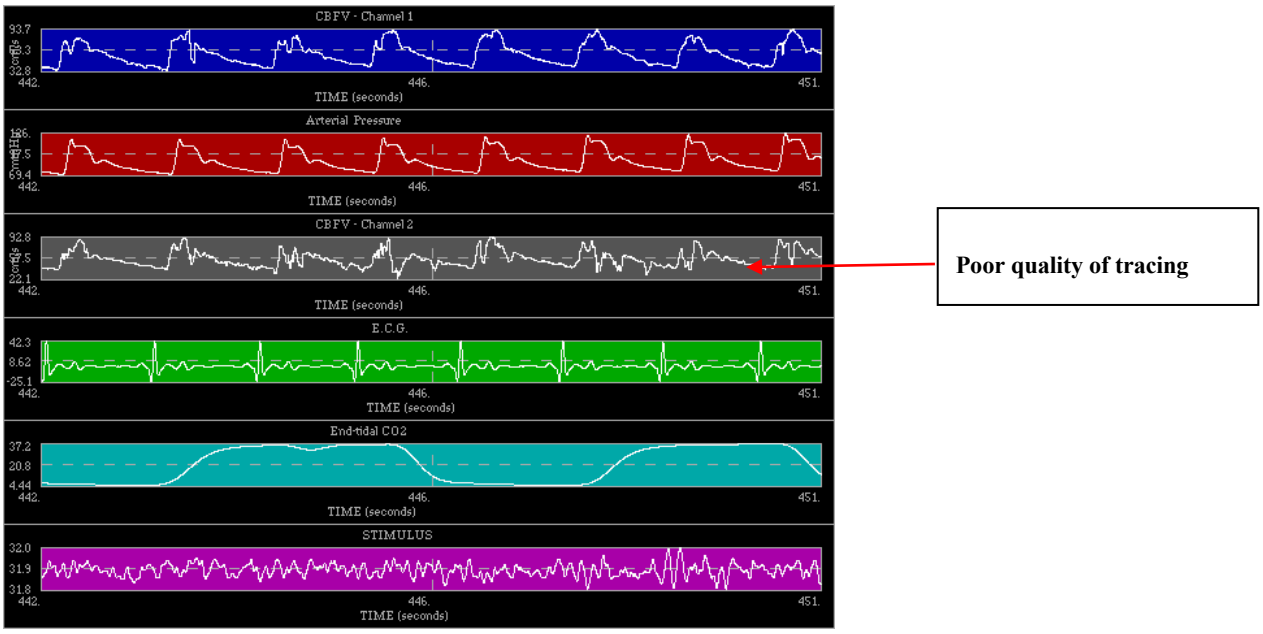



**Figure 4.10** MS DOS screenshot showing poor quality signal in channel 2 CBV. In this case the channel 2 CBV was not included in the analysis.

The CBV signals were subjected to a median filter. All signals were then low pass filtered with a zero-phase, Butterworth filter with cuff-off frequency of 20Hz. The R-R interval (the interval between two consecutive heartbeats in the ECG monitoring) was then automatically marked from the ECG tracing, and continuous HR was plotted against time. Any ectopic beats which resulted in spikes in the signal were identified by visual inspection of every QRS complex by the researcher, which were then manually corrected by the linear interpolation of R-R intervals for the time points at which they occurred. Occasionally, due to the poor quality of tracing, HR could not be calculated using the ECG, in these cases cardiac cycles were marked using the BP tracing as an alternative.

Mean, systolic/diastolic values of BP and CBV, HR, RAP and CrCP were calculated for each cardiac cycle and linear interpolation was used to obtain estimates of $ETCO_2$ synchronised to the end of each cardiac cycle. CrCP and RAP were obtained by the first harmonic method (411); these parameters being calculated to reflect the instantaneous

CBV-BP relationship changes that accompany changes in head positioning (GHP and RHP) or during IVT.

Subsequent data analysis for the individual studies reported in this thesis, together with specific software and statistical considerations, are reported in the relevant chapters.

# Chapter 5: Does Gradual Change in Head Positioning Affect Cerebrovascular Physiology? A Reproducibility Study in Healthy Older Subjects

*"Non-reproducible single occurrences are of no significance to science."*

*- Karl Popper, 1959*

As mentioned in Chapter 3, IH was introduced as one of the pharmacological perfusion strategies in AIS. However, such a regime is only suitable for small groups of patients, with limited evidence to demonstrate its safety profile and clinical efficacy. On the other hand, placing patients in a lying flat (0°) head position could be one of the simplest, non-pharmacological perfusion strategies in an AIS setting; it is easy to perform and requires minimal participant co-operation, and is ideal in a critical care setting.

It is generally agreed that optimal head positioning is an important consideration in AIS management regime. However, there is limited literature investigating the effect of head positioning changes on cerebrovascular physiology in AIS. Lowering head positioning could be achieved by either gradual, prolong lying flat (0°) head positioning (GHP) or rapid changes (30s) from lying flat (0°) to sitting up (>30°) head positioning (RHP). This chapter will focus on assessing CA and associated haemodynamic responses during GHP changes in control participants, and most importantly, whether such changes could be reproduced in subsequent visits.

## 5.1 Introduction

As mentioned in Chapter 1, section 1.4, IVT (335, 650) and MT (335, 511, 651) are the main licensed hyperacute reperfusion stroke regimens; aiming to recanalise occluded intracranial arteries, to optimise recanalisation following LVO. Although recent studies

have demonstrated a longer time window and broader inclusion criteria for AIS patients that may benefit from these strategies (488, 510, 652), due to the economic cost and logistic considerations, many low-income countries and remote areas may still find them challenging to implement into everyday clinical practice.

Traditionally, AIS patients are nursed with elevation of the head (≥ 30°), aiming to prevent aspiration pneumonia, and to reduce ICP, therefore avoiding hypertension-related reperfusion damage (653). However, one way of augmenting CBF to the collateral circulation and ischaemic penumbra would simply involve lowering the head of AIS patients into a 'lying flat (0°) head position. Until now, limited literature, with inconsistent results, has been reported in respect of the effect of changing head position on cerebrovascular physiology. Moreover, there is limited information about whether such changes persist following changes in head positioning. Some studies were inconclusive (654, 655), whilst others favoured lying flat (528, 656, 657), or head elevation (653, 658). In AIS patients, Wojner-Alexandrov et al. (657) reported an approximate 20% increase in MCA mean velocity when head position changed from 30° to 0°. However, this study did not separately report on AH and NAH. Hunter et al. (659) only observed impaired CBF in the AH (in the incompletely recanalised group), but not the completely recanalised group or NAH, whereas Aries et al. (660) suggested there was significant CBV reduction in the AH, when head position changed from lying flat to upright (70°), but not the half-sitting position (45°). Though approximately 50% of AIS patients received IVT in this latter study, no comment on any difference between the completed and incompletely recanalised groups was made.

The Head Position in Stroke Trial (HeadPoST) study was an international, prospective, multicentre, cluster-randomised study which demonstrated that head positioning ('lying-flat' or 'sitting-up') did not alter functional outcome in AIS (535). However, the low

admission NIHSS score (median 4), and significant proportion of lacunar strokes (30.2%) and stroke mimics (4.9%) may have reduced power in advocating a specific head position strategy to augment collateral blood flow and ischaemic penumbral perfusion in LVO stroke. The A Very Early Rehabilitation Trial (AVERT) (661) was a multicentre, randomised controlled trial, enrolling more than 2,000 ischaemic and haemorrhagic stroke patients who were assigned to receive either very early mobilisation or usual care. Results suggested that intensive early mobilisation (upright position) was associated with an unfavourable 90 day functional outcome. A possible mechanism is that early mobilisation, particularly in severe stroke (i.e. NIHSS>16), may result in reduced CBF secondary to acute stroke-associated impairment in CA, adversely impacting on penumbral viability and consequently clinical outcome (528). At present, there is no consensus agreement and specific recommendations are lacking regarding the head positon in which AIS patients should be nursed (567, 662).

To understand cerebral haemodynamic changes in response to head positioning in an AIS population, it is first important to study in control group to determine the normal physiological response. Therefore, the aim of this chapter was to investigate the extent of CBV change, and associated systemic and cerebral haemodynamic parameters, during a gradual change from a lying flat (0°) to sitting up (30°) head position in a control population, and whether such changes persist after change of the head positioning. The author also tested the hypothesis that the findings could be reproduced between visits.

## 5.2 Methods

### 5.2.1 Research Participants

The study was conducted in accordance with the Declaration of Helsinki (2000) and was approved by the Wales Research Ethics Committee 1, UK (Reference: 15/WA/0328). Clinical Trial.gov unique identifier number: NCT02932540.

A total of 18 volunteers were recruited from the University of Leicester, Leicester, UK and by poster advertisement at the UHL, Leicester, UK. Participants' handedness was determined by Edinburgh Inventory (663). All participants had no history of cerebrovascular disease, atrial fibrillation, diabetes or autonomic disturbance. Additional exclusion criteria included participants who practiced yoga regularly, and female participants who were pregnant, lactating, or planning pregnancy during the course of the study. Female participants who were pre-menopause and currently on any form of contraception, during menstruation or post-menopause were eligible. Participants who had mild, controlled hypertension or any other cardiovascular disease were acceptable as representative of active, but otherwise healthy, older participants.

All participants gave written informed consent and were aware of the right to withdraw from the study at any point of time without prejudice.

### 5.2.2 Measurements

Recordings were performed as described in Chapter 4, Section 4.4. All parameters were recorded over a 5-min baseline (5-min FLAT) recording period, with participants in the lying flat (0°) head position on a standard hospital bed. The recumbent angle was measured with an electronic goniometer built in-house (Department of Medical Physics, UHL, Leicester, UK). Thereafter, another 2-min recording was carried out while the

participant was still in the lying flat (0°) head position; afterward, the recumbent angle was changed from 0° to 30° over 30s (UP phase); another 5-min recording was carried out while participants were in the 30° head position (5-min SIT); thereafter, the recumbent angle was changed from 30° back to 0° over 30s (DOWN phase); another 2-min recording was carried out when the participant was in the lying flat (0°) head position (Figure 5.1). This manoeuvre was repeated twice at each visit. Each participant attended two visits.

### 5.2.3 Data Analysis

Data analysis was performed as described in Chapter 4, Section 4.5. In this chapter, mean BP, RAP and CrCP were compensated for changes in head height by subtracting DH-T*0.735*sin θ ° where θ is head angle from the horizontal, ranging from 0° to 30° and DH-T is the heart to temporal window distance in each participant.

After beat-to-beat data were spline interpolated and resampled at 5Hz to produce signals with a uniform time base, mean values of all cerebral and systemic haemodynamic variables, lasting 30s were extracted, these were expressed as time point 1 (T1) (80-110s), time point 2 (T2) (160-190s), time point 3 (T3) (400-430s) and time point 4 (T4) (490-520s), respectively. The 5-min FLAT and SIT periods and time points T1-T4 are represented in Figure 5.1.

Details of ARI have been described in Chapter 1, Section 1.3.6. In summary, the CBV response to a hypothetical step change in BP was derived by TFA, using the parameter settings recommended by the CARNet (357). Each of the 10 template CBV step responses proposed by Tiecks et al. (356) was compared with the estimated step response and the ARI value corresponding to the best fit, assessed by the minimum mean square error, was adopted for each of the 5-min recordings corresponding to the FLAT (0°) and SIT (30°)

positions and time points 1, 2, 3, and 4 (T1-T4). The main advantage of using ARI as compared to using either gain or phase from TFA is that it automatically incorporates the influences of both gain and phase, for the entire frequency response, without the need to select specific frequency bands.

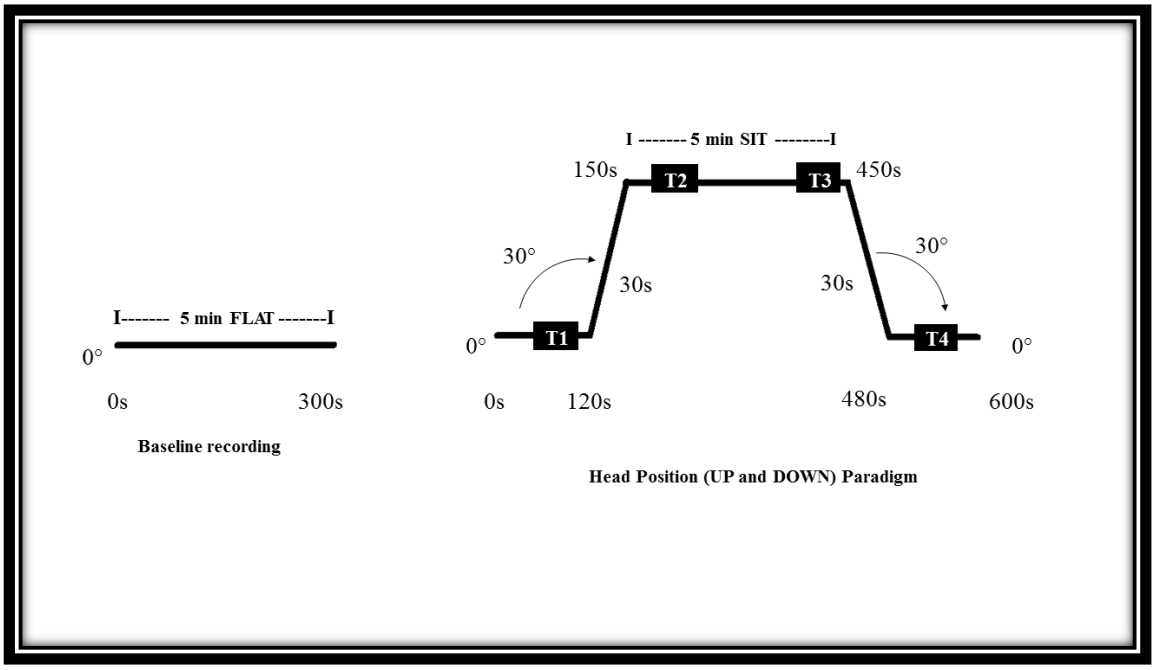



**Figure 5.1** Schematic representation of 5-min FLAT and SIT periods, and selected time points (T1, T2, T3, and T4) used to extract mean parameter values in the head positon paradigm with gradual elevation of the head from 0° to 30° and return to horizontal.

### 5.2.4 Statistical Analysis

Data were assessed for normality using the Shapiro-Wilk test. All normally distributed data are presented as mean ± standard deviation, and continuous skewed data are presented as median [interquartile range].

A paired t-test or Wilcoxon sign-ranked test was adopted to identify any inter-hemispheric differences. In the absence of inter-hemispheric differences, values were averaged from both hemispheres. For those participants who only had unilateral measurements, that value was used. As baseline 0° (5-min FLAT) recordings were performed once and the 10-min GHP paradigm was performed twice in each visit, the GHP paradigm readings were averaged prior to statistical comparison with the baseline 0° (5-min FLAT) reading.

Two-way repeated measures ANOVA was undertaken to assess the effects of head position (5-min FLAT vs. 5-min SIT), time (T1-T4) and reproducibility (visit 1 vs. visit 2) separately. The Tukey post hoc test was used to perform individual comparisons when ANOVA showed significant effects. A significance level of $p \leq 0.05$ was adopted for all results. Statistical analyses were performed using TIBCO Statistica (version 13.0, Statistica, Dell).

### 5.2.5 Sample Size Calculation

A formal sample size calculation was not possible for this specific study. However, following the approach previously described by Brodie et al. a sample of 11 healthy older subjects would be required to detect an ARI difference of 2 units with 80% power to at the 5% significance level (375).

## 5.3 Results

Eighteen participants (10 females) were recruited, though suitable transtemporal windows could not be found in two female participants who were removed from the study. Therefore, 16 controls of mean age 57 years (range 26 to 87) were included in the analysis. Three participants were aged < 50 years old. All participants attended both assessment visits a mean of 12 ± 8 days apart. Four participants only had a single transtemporal window (two right, two left). According to the Edinburgh Handedness inventory (663), 15 participants were right-handed and one participant was left-handed. Details of other participant demographic parameters are reported in Table 5.1.

| | |
|---|---|
| **Participant (n)** | **16** |
| **Age (years )** | **57±16** |
| **Sex (female), n %** | **8 (50.0)** |
| **Handedness (right), n%** | **15 (93.8)** |
| **Body mass index (BMI) kg.m$^{-2}$** | **24±4** |
| **Smoker (n)** | |
| **Yes** | **1** |
| **Ex** | **2** |
| **No** | **13** |
| **Past Medical History** | |
| **Hypertension (n) %** | **5 (31.3)** |
| **Medication** | |
| **Antihypertensive therapy** | **5 (31.3)** |

**Table 5.1** Demographic characteristics of healthy older subjects. Data are number of cases (n) or mean ± standard deviation (SD)

### 5.3.1 Baseline Data

Baseline CBV values at visit 1 were 53.9 ± 15.6 $cm.s^{-1}$ and 53.0 ± 12.6 $cm.s^{-1}$ for the dominant hemisphere (DH) and non-dominant hemisphere (NDH), respectively. Corresponding values for visit 2 were 52.4 ± 12.3 $cm.s^{-1}$ and 51.3 ± 12.7 $cm.s^{-1}$. There were no significant differences in mean baseline CBV values between visit 1 and 2 for either hemisphere (DH, p=0.57; NDH, p=0.41). In addition, no significant differences in inter-hemispheric CBV baseline were found for the 12 subjects who had bilateral recordings ($1^{st}$ visit, p=0.42; $2^{nd}$ visit, p=0.38). Therefore, averaged values were used in subsequent analyses. No significant differences were found for systemic parameters (BP, HR, and $ETCO_2$) and other cerebral haemodynamic parameters (CrCP and RAP) at baseline between the two visits (Table 5.2).

### 5.3.2 Effects of Head Position (5-min FLAT and SIT)

Systemic and cerebral haemodynamic parameters averaged over 5-min FLAT and SIT head positions are given in Table 5.2 for each visit. BP, CBV and CrCP values were reduced in the SIT head position at both visits 1 and 2, respectively (BP: 8.3 ± 7.4% and 11.0 ± 11.3%, p<0.001; CBV: 4.5 ± 3.3% and 4.1 ± 3.5%, p<0.0005; CrCP: 14.1 ± 7.8% and 15.5 ± 14.0%, p<0.0005). No significant differences in ARI (p=0.86; p=0.1) and other systemic or cerebral haemodynamic parameters, averaged over 5 min, were seen due to head position or between visits, respectively (Table 5.2).

| Parameters | Controls visit 1 (n=16) | | Controls visit 2 (n=16) | | P value (Head Position effect) | P value (Visit effect) |
|---|---|---|---|---|---|---|
| **Head Position** | **5-min FLAT (0°)** | **5-min SIT (30°)** | **5-min FLAT (0°)** | **5-min SIT (30°)** | | |
| BP (mmHg) | 89.1±12.1 | 81.8±8.0 | 89.6±11.3 | 79.8±11.4 | **<0.001** | 0.39 |
| Heart Rate (bpm) | 65.7±9.9 | 65.1±9.7 | 65.3±11.3 | 5.1±11.0 | 0.42 | 0.89 |
| End-tidal $CO_2$ (mmHg) | 38.4±4.7 | 37.3±4.6 | 39.3±3 | 39.5±1.7 | 0.39 | 0.38 |
| CBV ($cm.s^{-1}$) | 53.5±13.6 | 51.1±13.8* | 51.9±12.2 | 49.7±12.9# | **<0.0005** | 0.66 |
| CrCP (mmHg) | 39.0±10.4 | 32.5±9.2* | 40.1±11.0 | 32.9±11.4# | **<0.0005** | 0.77 |
| RAP ($mmHg.s.cm^{-1}$) | 0.94±0.30 | 1.02±0.32 | 0.95±0.27 | 0.99±0.32 | 0.13 | 0.93 |
| ARI | 5.64±1.42 | 5.47±1.10 | 6.00±1.37 | 6.12±1.00 | 0.86 | 0.10 |

**Table 5.2** Systemic and cerebral haemodynamic parameters for FLAT (0°) and SIT (30°) head positions for two repeated visits.

Values are mean ± SD for 5 min segments of data. P values from two-way ANOVA for the difference between 5-min FLAT and SIT head positions and between visit 1 and 2. BP, blood pressure; bpm, beats per minute; CBV, cerebral blood velocity; CrCP, critical closing pressure; RAP, resistance area product; ARI, autoregulation index.

* Tukey post hoc compared to FLAT head position $P < 0.05$ in visit 1. # Tukey post hoc compared to FLAT head positon $P < 0.05$ in visit 2.

### 5.3.3 Temporal Pattern of Systemic Haemodynamic Responses

Representative recordings during GHP are shown in Figure 5.2, and population averages are given in Figures 5.3-5.5. With the exception of HR and $ETCO_2$, all other parameters showed significant changes across selected time points (T1-T4) for both visits (Table 5.3). Of note, most parameters showed relatively large transient changes during UP and DOWN phases, even in cases when the T1-T4 ANOVA did not indicate an overall significant F-value (Figures 5.6-5.9).

During the UP phase (120 to 150s), there was a profound MAP reduction (Figure 5.3A, 87.8 ± 11.0 to 78.0 ± 10.3 mmHg), followed by a gradual increase (78.0 ± 10.3 to 82.0 ± 11.3 mmHg, Tukey's p=0.04) over 25s. MAP remained plateaued during subsequent SIT period (175 to 450s). During the DOWN phase (450 to 480s), there was a non-significant trend towards recovery, compared to the UP phase (Figure 5.3A, 80.7 ± 11.0 to 84.3 ± 11.6 mmHg) which continued to increase for further 30s (84.3 ± 11.6 to 86.0 ± 10.9mmHg) and reached its plateau for the remaining 90s measurement.

There was a non-significant increase in HR during both UP (Figure 5.3B, 64.8 ± 10.6 to 66.5 ± 11.8 bpm) and DOWN phases (66.2 ± 11.1 to 67.6 ± 11.7 bpm) over 20s. Otherwise, HR remained stable throughout the 10-min measurement. As mentioned previously, no significant differences were seen across time points (T1-T4) (Table 5.3).

There was a subtle reduction in $ETCO_2$ during UP (Figure 5.4A, 38.2 ± 4.0 to 37.3 ± 3.7 mmHg) and DOWN phase (38.4 ± 3.6 to 37.9 ± 3.4 mmHg). Otherwise, similar to HR, $ETCO_2$ remained stable throughout the 10-min measurement and there were no significant differences observed across any time points (T1-T4) (Table 5.3).

### 5.3.4 Temporal Pattern of Cerebral Haemodynamic Responses

During the UP phase, CBV showed an initial bilateral steep decline (Figure 5.4B, DH 51.1 ± 13.6 to 47.4 ± 11.9 cm.s$^{-1}$; NDH 52.8 ± 14.5 to 49.8 ± 13.4 cm.s$^{-1}$; DH Tukey's p=0.0005, NDH Tukey's p=0.001) over 30s, followed by a plateau during the 5-min SIT period (150s to 450s). During the DOWN phase (450 to 480s), there was a non-significant trend towards recovery, compared to the UP position (Figure 5.4B, DH 48.8 ± 12.6 to 50.1 ± 13.7 cm.s$^{-1}$; NDH 49.3 ± 12.9 to 52.4 ± 14.6 cm.s$^{-1}$). The magnitude of the CBV change during the UP phase was more profound when compared to the DOWN phase.

Similar to CBV, there was an initial bilateral steep decline in CrCP during the UP phase (Figure 5.5A, DH 38.02 ± 11.93 to 29.64 ± 12.4 mmHg; NDH 39.07 ± 11.59 to 30.76 ± 12.50 mmHg; DH Tukey's p=0.0001, NDH Tukey's p=0.001) over 30s, followed by a plateau during the SIT period. During the DOWN phase, there was also a significant rise towards recovery (Figure 5.5A, DH 31.78 ± 11.96 to 38.06 ± 12.14 mmHg; NDH 32.71 ± 11.79 to 38.92 ± 12.31 mmHg; DH Tukey's p=0.0001, NDH Tukey's p=0.002).

With respect to RAP, there was a non-significant increase during the UP phase (Figure 5.5B, DH 1.02 ± 0.37 to 1.09 ± 0.34 mmHg.s.cm$^{-1}$; NDH 0.91 ± 0.29 to 0.98 ± 0.32 mmHg.s.cm$^{-1}$), followed by a plateau during the SIT period. Whilst during the DOWN phase (450 to 480s), there was a non-significant reduction towards recovery (Figure 5.5B, DH 1.04 ± 0.36 to 0.98 ± 0.35 mmHg.s.cm$^{-1}$; NDH 0.97 ± 0.32 to 0.90 ± 0.31). This reduction trend continued for approximately another 10s (DH 0.98 ± 0.35 to 0.94 ± 0.33 mmHg.s.cm$^{-1}$; NDH 0.90 ± 0.31 to 0.86 ± 0.27 mmHg.s.cm$^{-1}$) before slowly returning to baseline.

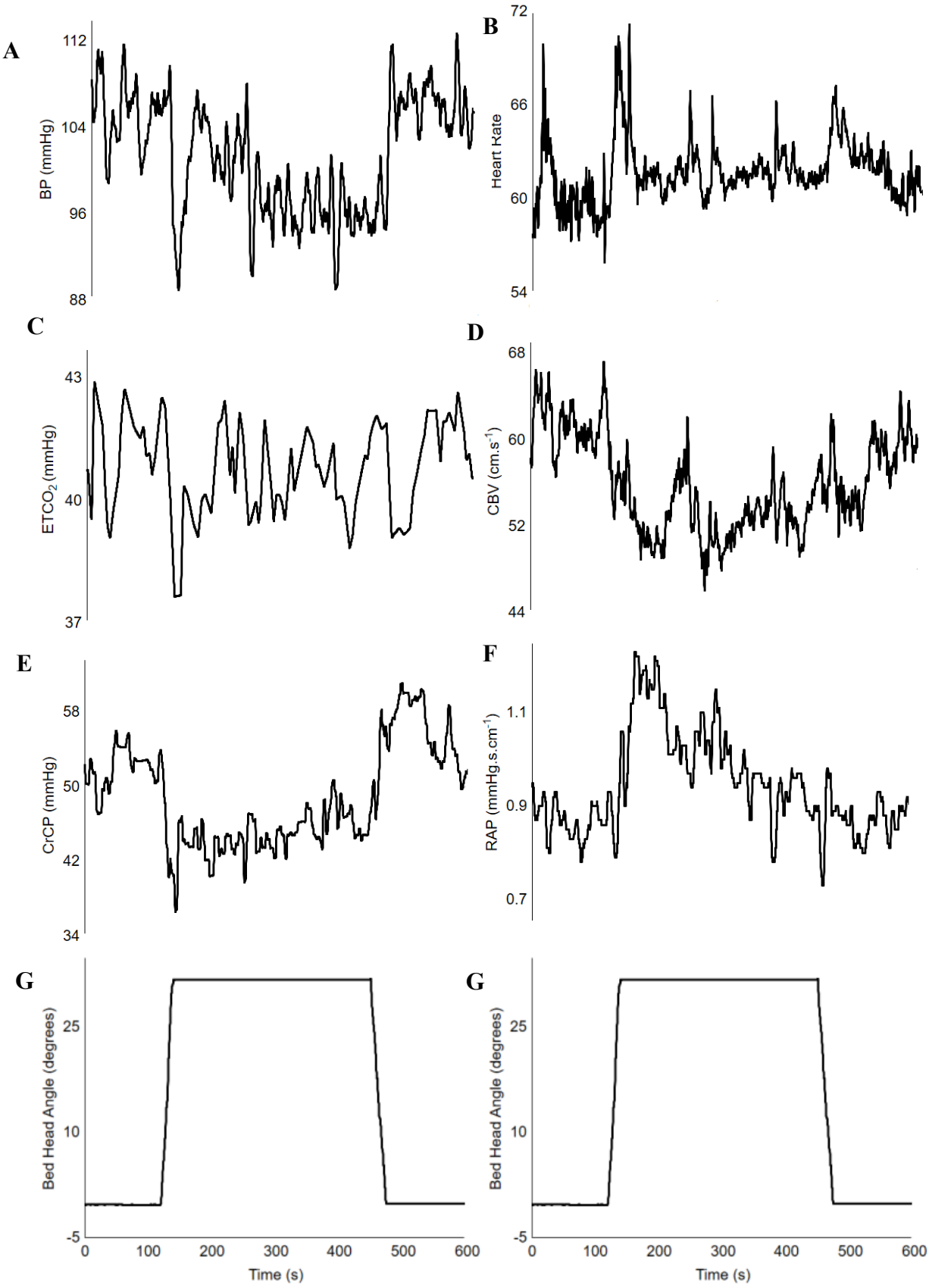



**Figure 5.2** Representative recordings of BP (A), HR (B), $ETCO_2$ (C), dominant hemisphere CBV (D), CrCP (E), RAP (F) during gradual change of head positioning, as indicated by the bed head angle (G).

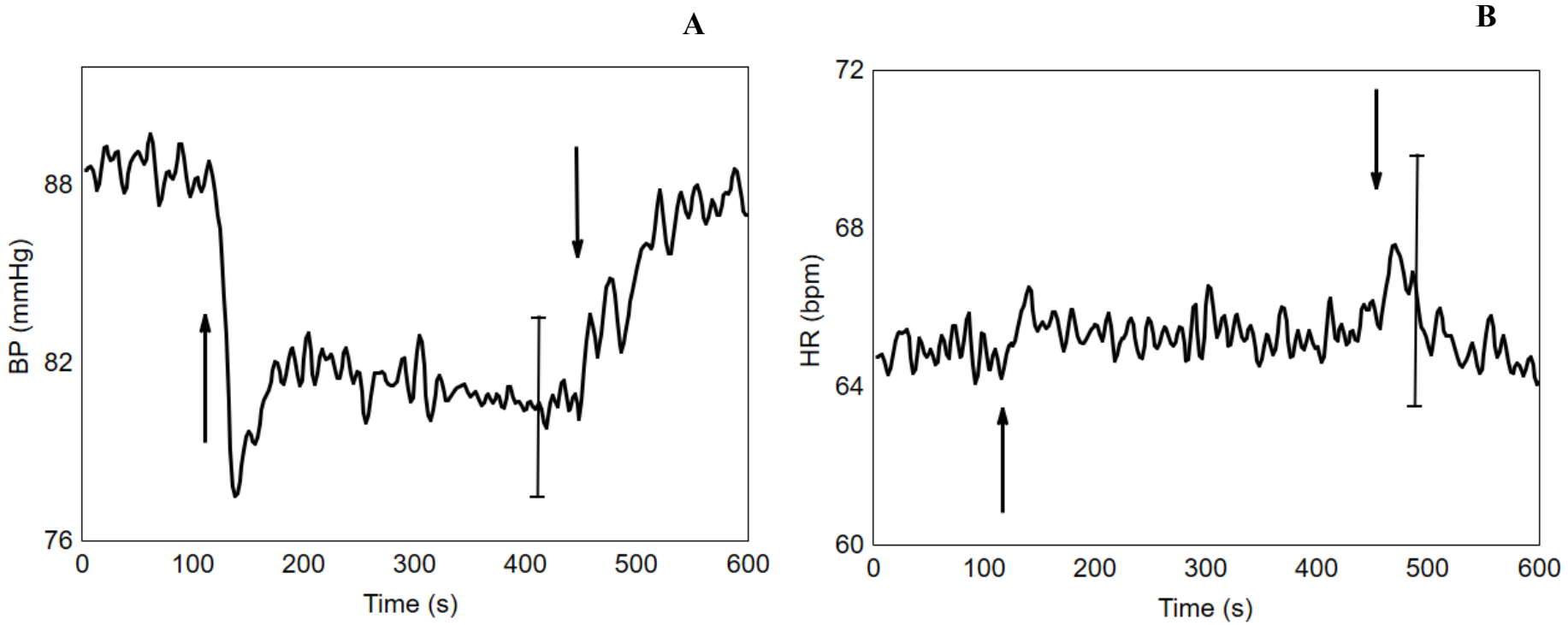



**Figure 5.3** Population averages of BP (A) and HR (B) during gradual change of head positioning. Upward arrow shows the point when the head position changed from 0° to 30° (UP phase) and downward arrow from 30° to 0° (DOWN phase). For clarity, the error bar represents only the largest ± 1 SE at the point of occurrence.

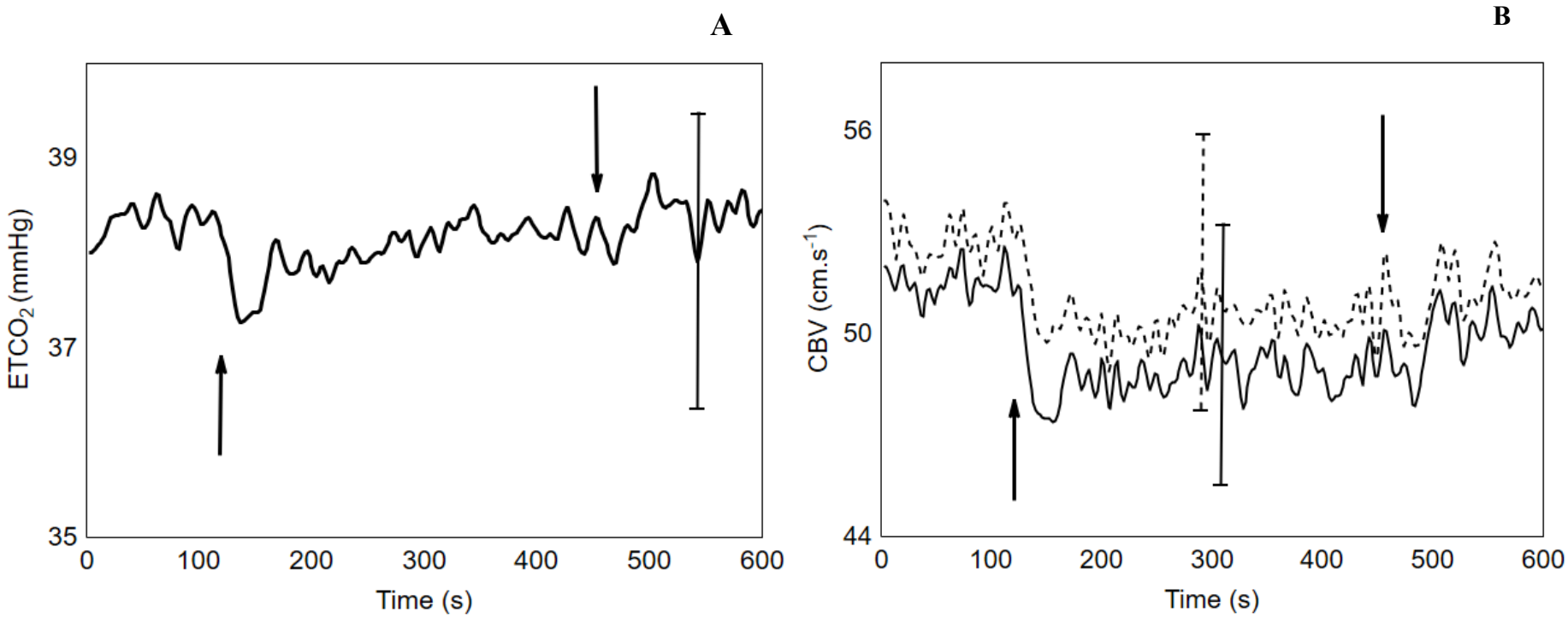



**Figure 5.4** Population averages of $ETCO_2$ (A) and CBV (B) during gradual change of head positioning. Upward arrow shows the point when the head position changed from 0° to 30° (UP phase) and downward arrow from 30° to 0° (DOWN phase). Dominant hemisphere (DH) (continuous line) versus non-dominant hemisphere (NDH) (dotted line). For clarity, the error bar represents only the largest ± 1 SE at the point of occurrence.

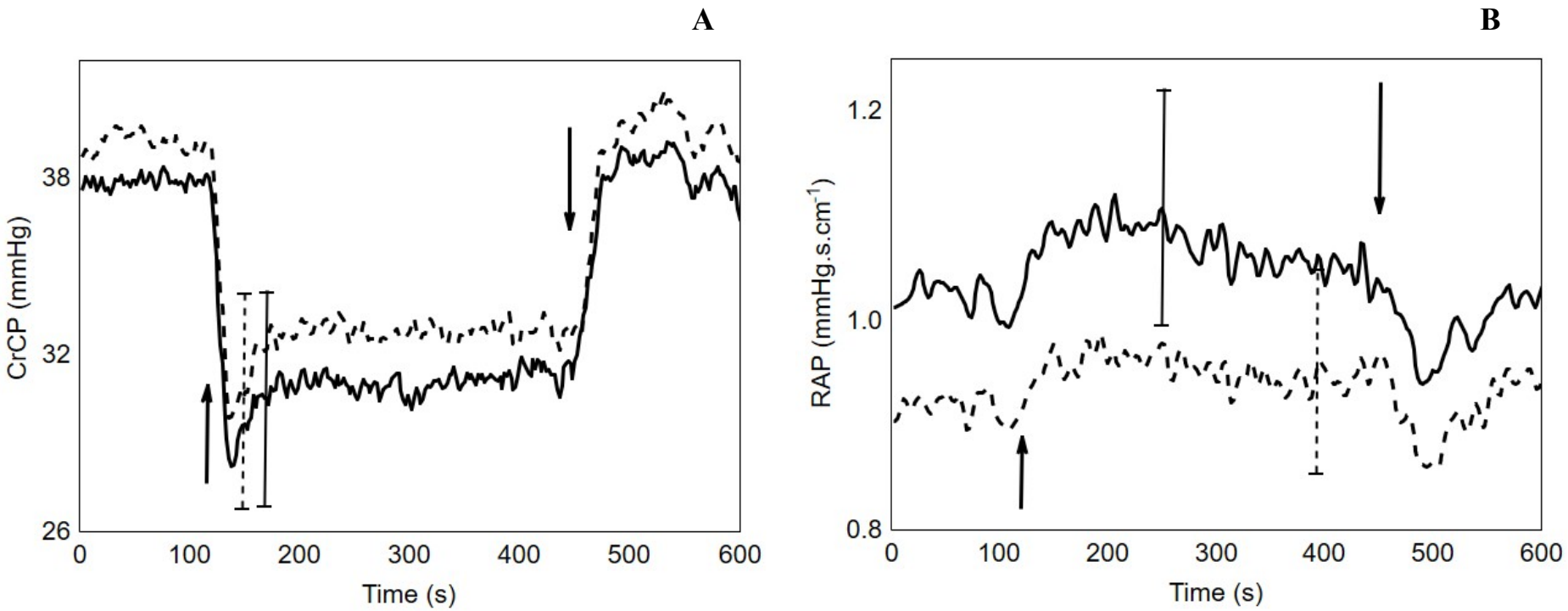



**Figure 5.5** Population averages of CrCP (A) and RAP (B) during gradual change of head positioning. Upward arrow shows the point when the head position changed from 0° to 30° (UP phase) and downward arrow from 30° to 0° (DOWN phase). Dominant hemisphere (DH) (continuous line) versus non-dominant hemisphere (NDH) (dotted line). For clarity, the error bar represents only the largest ± 1 SE at the point of occurrence.

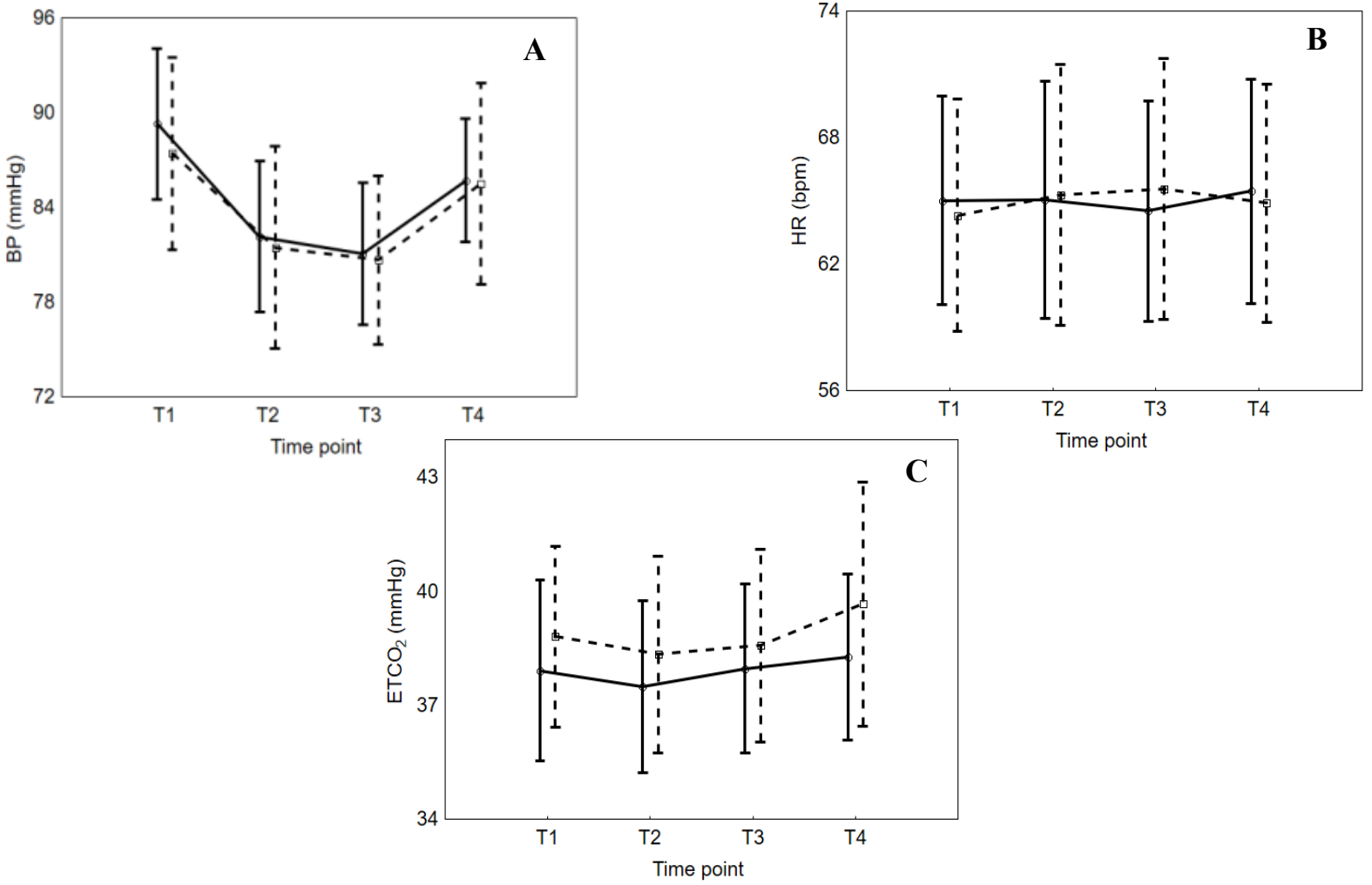



**Figure 5.6** Effects of visit on the changes in BP (A), HR (B) and $ETCO_2$ (C). First visit (continuous line) versus second visit (dotted line). Vertical bar denotes 95% confidence interval.

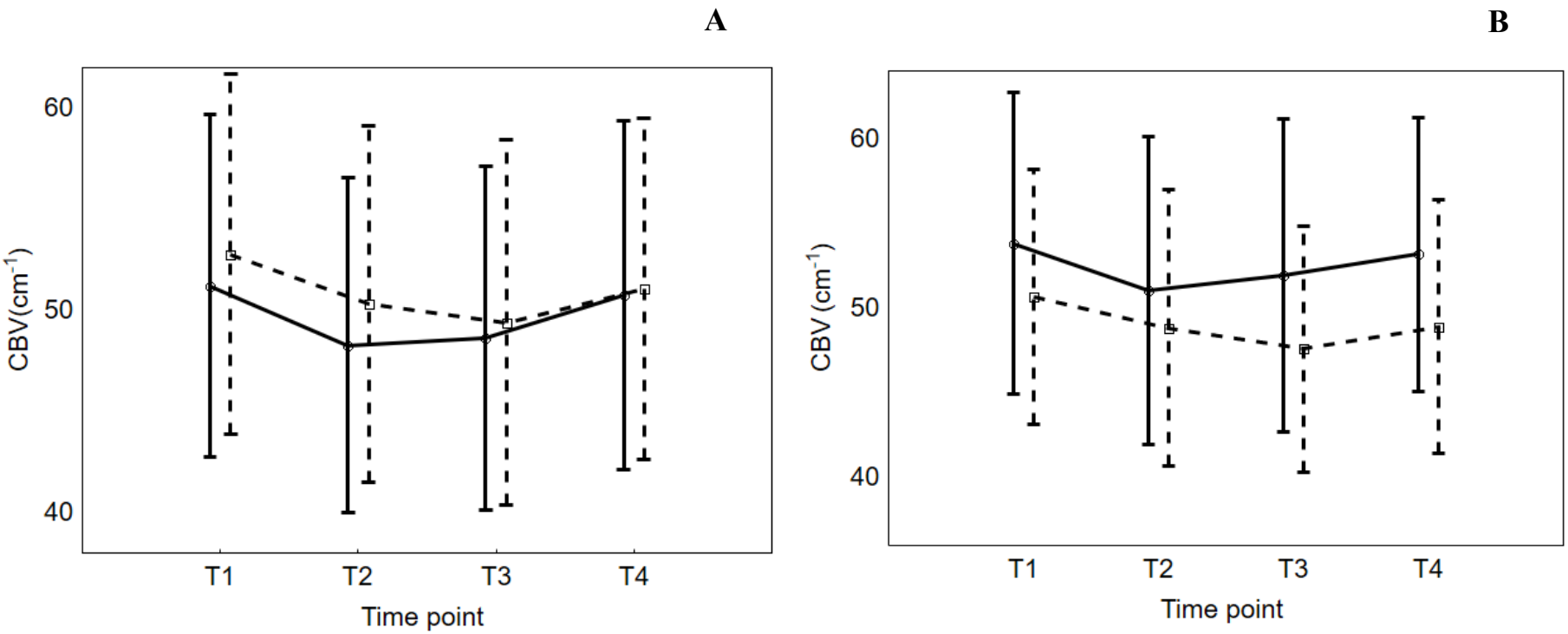



**Figure 5.7** Effects of visit on the changes in CBV (A and B). First visit (continuous line) versus second visit (dotted line). Dominant hemisphere (A) versus non-dominant hemisphere (B). Vertical bar denotes 95% confidence interval.

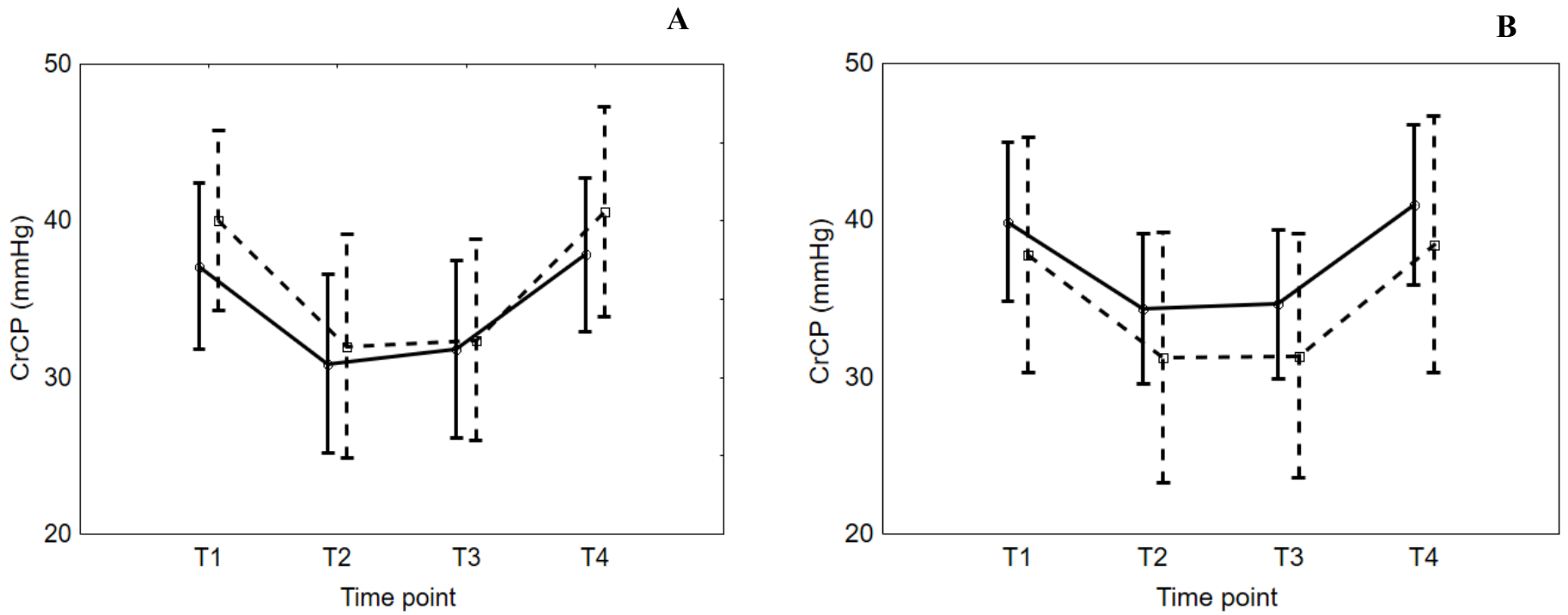



**Figure 5.8** Effects of visit on the changes in CrCP (A and B). First visit (continuous line) versus second visit (dotted line). Dominant hemisphere (A) versus non-dominant hemisphere (B). Vertical bar denotes 95% confidence interval.

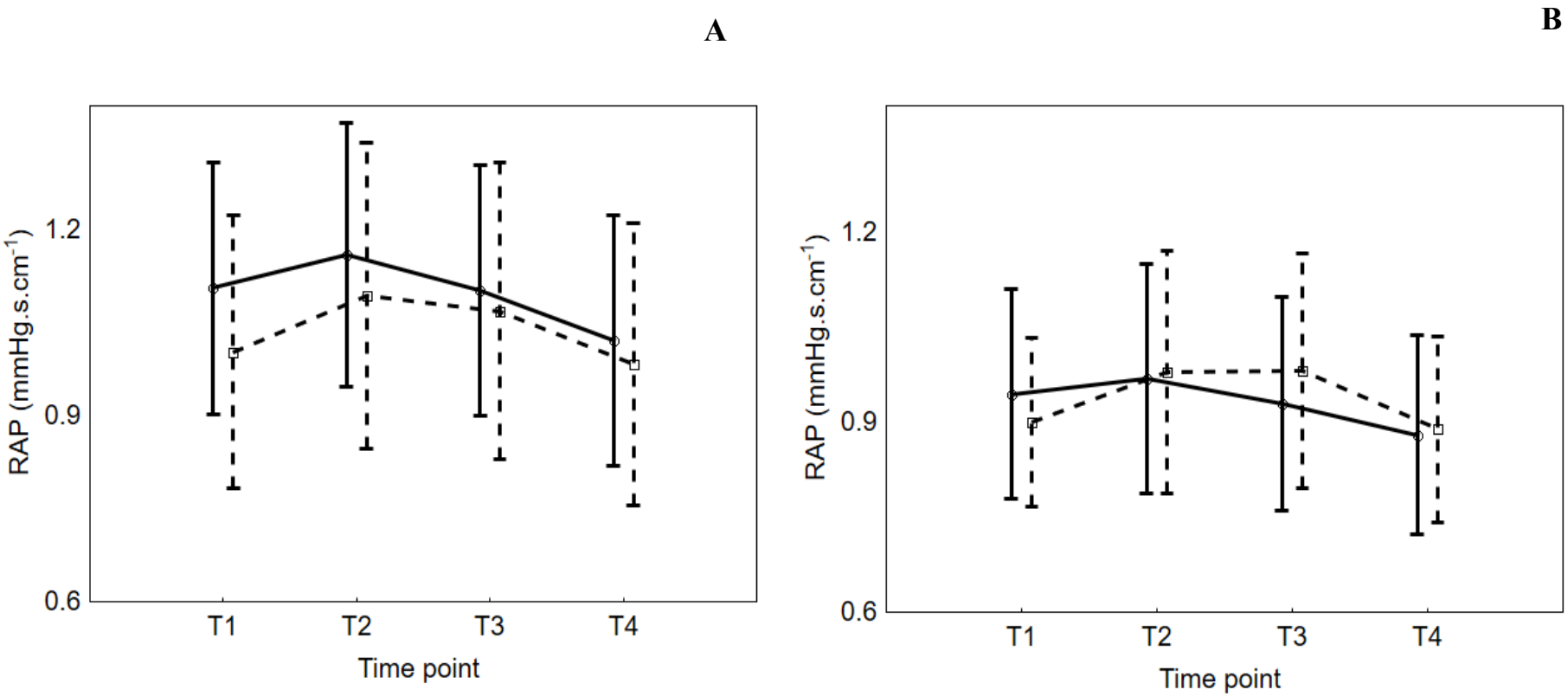



**Figure 5.9** Effects of visit on the changes in RAP (A and B). First visit (continuous line) versus second visit (dotted line). Dominant hemisphere (A) versus non-dominant hemisphere (B). Vertical bar denotes 95% confidence interval.

### 5.3.5 Reproducibility of the Head Position Paradigm across Two Separate Visits

Paradigm-synchronised population averages are shown in Figures 5.6-5.9 for the selected T1-T4 time points at both visits 12 ± 8 days apart. Though $ETCO_2$, CBV (NDH), CrCP (NDH) and RAP (DH), showed differences in baseline values, there were no significant differences in overall temporal patterns in any parameters between visits (Table 5.3).

| Parameters | Visit | T1 | T2 | T3 | T4 | P value (Time point effect) | P value (visit effect) |
|---|---|---|---|---|---|---|---|
| BP (mmHg) | 1 | 89.3 ± 8.6 | 82.2 ± 8.6* | 81.0 ± 8.1* | 85.7 ± 7.1* | **<0.001** | 0.70 |
| | 2 | 87.4 ± 11.0 | 81.5 ± 11.6 | 80.7 ± 9.7* | 85.5 ± 11.5 | | |
| HR (bpm) | 1 | 65.0 ± 9.3 | 65.1 ± 10.6 | 64.5 ± 9.8 | 65.5 ± 10.0 | 0.76 | 1.00 |
| | 2 | 64.3 ± 10.4 | 65.3 ± 11.6 | 65.6 ± 11.6 | 64.9 ± 10.6 | | |
| $ETCO_2$ (mmHg) | 1 | 37.9 ± 4.0 | 37.5 ± 3.7 | 38.0 ± 3.7 | 38.3 ± 3.6 | 0.39 | 0.38 |
| | 2 | 38.8 ± 4.0 | 38.3 ± 4.3 | 38.6 ± 4.2 | 39.7 ± 5.3 | | |
| DH CBV ($cm.s^{-1}$) | 1 | 51.2 ± 13.4 | 48.3 ± 13.0* | 48.6 ± 13.4 | 50.7 ± 13.6 | **<0.005** | 0.77 |
| | 2 | 52.4 ± 12.9 | 49.3 ± 13.0* | 48.7 ± 13.2 | 50.4 ± 12.3 | | |
| NDH CBV ($cm.s^{-1}$) | 1 | 53.8 ± 14.7 | 51.0 ± 15.1* | 51.9 ± 15.3* | 53.2 ± 13.4 | **<0.001** | 0.68 |
| | 2 | 50.7 ± 12.5 | 48.8 ± 13.5 | 47.6 ± 12.0* | 48.9 ± 12.4 | | |
| DH CrCP (mmHg) | 1 | 37.1 ± 8.8 | 30.9 ± 9.4* | 31.8 ± 9.4* | 37.9 ± 8.1 | **<0.001** | 0.60 |
| | 2 | 40.0 ± 9.5 | 32.0 ± 11.8* | 32.4 ± 10.6* | 40.6 ± 11.1 | | |
| NDH CrCP (mmHg) | 1 | 39.9 ± 8.8 | 34.4 ± 8.3* | 34.7 ± 8.2* | 41.0 ± 8.9 | **<0.001** | 0.60 |
| | 2 | 37.8 ± 13.0 | 31.3 ± 13.9* | 31.4 ± 13.5* | 38.5 ± 14.2 | | |
| DH RAP ($mmHg.sec.cm^{-1}$) | 1 | 1.11 ± 0.34 | 1.16 ± 0.35 | 1.10 ± 0.33 | 1.02 ± 0.33ǂ | **0.002** | 0.56 |
| | 2 | 1.00 ± 0.36 | 1.09 ± 0.41 | 1.07 ± 0.40 | 0.98 ± 0.38ǂ | | |
| NDH RAP ($mmHg.sec.cm^{-1}$) | 1 | 0.94 ± 0.29 | 0.97 ± 0.31 | 0.93 ± 0.29 | 0.88 ± 0.27ǂ | **0.033** | 0.89 |
| | 2 | 0.90 ± 0.23 | 0.98 ± 0.33 | 0.98 ± 0.32 | 0.89 ± 0.25ǂ | | |

**Table 5.3** Systemic and cerebral haemodynamic parameters at selected time points.

Data are mean ± SD, P-values from two-way ANOVA for effect of time (T1-T4) and visit. BP, blood pressure; bpm, beats per minutes; CBV. cerebral blood velocity; CrCP, critical closing pressure; RAP, resistance area product; ARI, autoregulation index; DH, dominant hemisphere; NDH, non-dominant hemisphere. *Tukey post hoc P<0.05 compared to T1. ǂ Tukey post hoc P<0.05 compared to T2.

## 5.4 Discussion

### 5.4.1 Main Findings

In this chapter, the effects of GHP on both systemic and cerebral haemodynamic parameters were demonstrated in a group of healthy older subjects, that could be regarded as a suitable control group for studies of AIS. Over two visits, BP, CBV, and CrCP were significantly reduced in the 5-min SIT compared to 5-min FLAT position. No other significant changes in systemic or cerebral haemodynamics were detected, and this was consistent over both visits. However, over a 10-min GHP paradigm, significant transient changes were seen in the majority of systemic and cerebral haemodynamic parameters, including CBV, RAP and CrCP, particularly in association with the 30s UP and DOWN phases. Again, these changes were reproducible over two visits.

Though reproducibility of cerebral and circulatory responses to postural change in healthy subjects (664), healthy older participants (665), and patients with syncope (666) have previously been reported, to the best of our knowledge, this is the first study to provide a detailed description of the cerebral and systemic haemodynamic changes taking place during GHP paradigm, including reproducibility of key parameters before, during and after a gradual change in head positioning. Of considerable relevance, dCA, as expressed by the ARI index, was not affected by a change from 0° to 30° head position in this healthy older group, which is important for future longitudinal studies of such changes in a diseased population, including studies of AIS patients during the acute and recovery periods, which are going to be explored in the subsequent chapter.

### 5.4.2 Effects of Head Position on Systemic Haemodynamics and $ETCO_2$

In the absence of other similar studies in the literature, comparisons are only possible with related studies, such as changes in posture induced by tilt. These show broad

general agreement with the temporal pattern of HR, BP, and $ETCO_2$ during the 10-min GHP paradigm (667-671). Though this study recruited a wide age range group, the majority of participants were aged over 50, where the normal physiological responses to head position changes are blunted in ageing, with alterations in circulatory response, changes in autonomic function, and reduction in the efficiency of the muscle pump all contributing to a delay in compensatory mechanisms (672, 673). Interestingly, despite a BP drop during the UP phase, the author did not observe a significant compensatory HR increase, which may relate to previous studies having a faster postural change (3 to 6s) (668, 674) compared to this study (30s), and therefore may have reduced the magnitude of any physiological responses (675). Furthermore, HUT (70°) and standing have previously been utilised (667, 668, 670), in contrast to the 0° to 30° changes used in this study, which are more typical of the changes seen in an acute medically unwell bed-bound patient population.

A mild, but consistent, $ETCO_2$ reduction is noted during both UP and DOWN phases. Hypocapnia secondary to posture change has been previously demonstrated in tilt studies (670, 671); with hyperventilation (676), reduction in venous return, increase in functional residual capacity (677), and ventilation-perfusion (V/Q) mismatch (678) hypothesised as possible explanations.

### 5.4.3 Effect of Head Position on Cerebral Haemodynamics

As suggested in Section 5.1 above, CA is important in maintaining CBF/CBV during posture changes through various mechanisms (185, 190, 679). Rosner and Coley (656) previously reported that even moderate head elevation could compromise CPP and therefore, CBF. The temporal pattern of CBV changes found in this study was in keeping with former studies (680, 681). Romero and colleagues (680) carried out a HUT study on nine healthy male volunteers (mean age 23 ± 0.5 years), during both euhydration and

dehydration and found that the percentage of CBV reduction during HUT was consistent and statistically non-significant between both conditions. Garrett et al. (681) carried out a study of 18 young healthy volunteers (seven male and 11 female, mean age 26 ± 9 years), and observed a 13% reduction in CBV when changing from a supine (0°) to seated (90°) position.

As mentioned previously, both CrCP and RAP are variables derived from the instantaneous relationship between BP and CBF/CBV (411). CrCP represents the BP at which cerebral blood vessel collapse and therefore, CBF ceases. It reflects ICP, arterial tone and the metabolic mechanisms involved in underlying CBF regulation. It is generally accepted during head elevation, due to the head-to-foot hydrostatic pressure, improvement of cerebral venous drainage results in reductions in CPP and ICP, in both healthy and disease states (656, 682-684). On the other hand, RAP is an index of cerebrovascular resistance (CVR); the inverse of the linear CBV-BP relationship slope, and has been suggested as an indicator of myogenic control (411-413). The temporal pattern of RAP changes in response to head elevation (Figures 5.5B, 5.9A and B) seems to support this interpretation where the gradual reduction in RAP, following a profound fall in BP, maintains a relatively constant CBV during the 5-min head UP. Despite these phasic changes, no significant differences in RAP were observed between averaged 5-min FLAT and SIT positions. This was supported by Robertson et al. (685) who looked at CrCP and RAP in supine lying, sitting and standing position among young and old participants (n = 80). Their study demonstrated a non-significant rise in RAP but significant CrCP reduction, particularly in healthy older adults (n = 22, aged 72 ± 6 years) and adults with uncontrolled hypertension (n = 12, aged 76 ± 6 years), suggesting CrCP played a dominant role in response to posture change. Castro and colleagues (686) recruited 13 healthy young volunteers, aged 26 ± 9 years, and performed a reading task

in supine, sitting and HUT positions, and reported a significant reduction in MCA CBV, and an associated significant increase in CrCP from supine to HUT, but no such change in RAP.

In this study, ARI values were not influenced by postural change. Similarly, Lefthériotis et al. (687) reported no ARI differences between supine and 40° head upright tilt positions, nor did Carey et al. (688) during 30-min HUT in younger (n = 25, aged 28 ± 8 years) and older healthy volunteer (n = 25, aged 69 ± 10 years) populations. To explain such diverse changes, with reductions in CBV, an integrated multivariate model, possibly including the contributions of $PaCO_2$, ICP, and sympathetic nervous system activity should be considered.

### 5.4.4 Clinical Implications

Previous studies have used a variety of techniques to investigate haemodynamic parameters in response to postural change, for example: supine to sitting (689), squatting (690), standing (691), or HUT (692). The author designed an electronic goniometer, a novel method, to provide continuous recording of head angle on a standard hospital bed, and such a method enables medically unstable and cognitively impaired patients to comply with the protocol; ideal for AIS patient studies. The author chose 0° to 30° head positions in this study, as these are the commonest head positions that AIS patients are nursed at in day-to-day clinical settings. In addition, the GHP paradigm was sufficient to elicit measureable changes in systemic and cerebral haemodynamic responses, that were reproducible. This will enable longitudinal changes to be investigated in disease populations, as well as the potential beneficial and detrimental effects of physiological manipulations in the acute and recovery periods of illness, which will be investigated further in subsequent chapters.

### 5.4.5 Study Limitations

The study has a number of limitations. First, only non-stroke volunteers were included, though the author did allow participants with controlled hypertension, similar to those seen in an AIS population, were recruited. Noteworthy, the ARI values for this group (Table 5.2), are in excellent agreement with values reported in the literature for healthy subjects (349, 356), thus suggesting that volunteers had normal dCA. Secondly, though a wide age range (26-87 years) of non-stroke control subjects were included, only three participants were aged under 50 years old, which may confound the study results. However, van Beek et al. (300), using a variety of methods to assess dCA in elderly populations, did not find an influence of ageing on dCA. Thirdly, as mentioned in Section 5.2.5, a formal size calculation was not possible since no previous data were available from similar studies. However, the study sample size of 16 participants would have an 80% power to detect an ARI difference of 2 units at 5% significance level (375). Accordingly, it is difficult to draw meaningful conclusions in respect of more subtle cerebral haemodynamic regulatory responses to GHP paradigm. Therefore, with only 16 subjects, it is possible that changes in ARI of less than 2 units may have been missed. Future studies should focus on an older population with a larger number of participants. Fourthly, due to the relatively small sample size with multiple testing, the positive and negative results we observed in this study could be due to Type I and II errors, respectively. Finally, within visit reproducibility was not explored, though consistency of systemic and cerebral haemodynamic responses between visits, including at four time-points during GHP paradigm, was demonstrated. It was assumed that intra-visit reproducibility was very high, and repeated measurements were used to improve results and to ensure at least one good set of data in each session.

## 5.5 Conclusion

This study chapter demonstrated dCA, as assessed over a 5-min time interval, was not affected by GHP, but there were static changes in BP, CBV, and CrCP that were reproducible on repeated visits approximately two weeks apart. Of relevance, with the exception of HR and $ETCO_2$, most other parameters (BP, CBV, CrCP, RAP) showed dynamic changes in response to head elevation or return of the lying flat (0°) head position, with reproducible results. Understanding these systemic and cerebral haemodynamic changes due to head position provides a depth of understanding how these responses behave differently between controls and AIS patients, which may provide important information for patient management, and this will be discussed in the next chapter.

# Chapter 6: The Effect of Gradual Changes in Head Positioning on Cerebral Haemodynamics: Experiences in Acute Ischaemic Stroke and Controls

## 6.1 Introduction

To understand the effects of GHP on AIS and associated functional outcome, it is worthwhile to study the relationship between GHP and CA. In Chapter 5, the author has demonstrated reproducible significant static changes, and also profound transient changes in key haemodynamic parameters when head position was changed from 0° to 30°, and vice versa, without significant change in CA in healthy older subjects. Given that AIS patients may show different responses to changes in head position, this chapter will consider: 1) alterations in CA, and associated systemic and cerebral haemodynamic parameters, between AIS patients and controls in the 'lying-flat (0°)' head position; 2) whether such changes are similar to those observed during GHP; 3) the temporal relationship of such parameters in response to GHP changes over 90 days following AIS; and 4) whether it is feasible to stratify the best timing for post-stroke mobilisation, and therefore, to provide an individualised AIS treatment regime.

## 6.2 Methods

### 6.2.1 Research Participants

Details of the controls participant's screening, inclusion and exclusion criteria have been previously reported in Chapter 5, section 5.2.1.

A total of 19 AIS patients were recruited from the UHL HASU within 24 hours of symptom onset. Patients with complete resolution of symptoms within 24 hours of symptom onset (TIA), mRS greater than 3 (693), and co-morbidity with an anticipated life expectancy less than 3 months were excluded from the study. OCSP (69), NIHSS

(694) and mRS were used to assess clinical stroke subtype, stroke severity, and pre-morbid functional dependence, respectively. Similar to control subjects, AIS participants' handedness was determined by the Edinburgh inventory (663). All AIS patients received pharmacological treatment, including antithrombotic, anticoagulant, antihypertensive, and statin therapy according to local hospital protocols.

Both controls and AIS participants who practice yoga regularly and female participants who were pregnant, lactating, or planning pregnancy were excluded from the study.

All participants or their personal consultee provided written informed consent and were aware of the right to withdraw from the study at any point without prejudice.

### 6.2.2 Measurements

Details of the experimental procedures has been previously described in Chapter 5, section 5.2.2. For AIS patients, acute, subacute, and chronic phase assessment were undertaken at approximately 24 hours, 7, and 90 days following stroke symptom onset, respectively.

### 6.2.3 Data Analysis

Details of data analysis has been previously described in Chapter 5, section 5.2.3.

### 6.2.4 Statistical Analysis

As baseline 0° (5-min FLAT) recordings were performed once and the 10-min GHP paradigm was performed twice in both controls and AIS patients at each visit, the GHP paradigm readings were averaged prior to the statistical comparison with the baseline 0° (5-min FLAT) readings.

The data on systemic and cerebral haemodynamic variables were analysed using a separate linear mixed effect model. The model included the following explanatory variables as fixed effects: age, sex (male and female), group (controls and AIS patients), cerebral hemispheres [affected/dominant hemisphere (AH)/(DH) and non-affected/non-dominant hemisphere (NAH)/(NDH)], head positioning (5-min FLAT and 5-min SIT) as well as two-way interaction effect of group and head positioning. Additionally, we explored linear mixed effect models exclusively on the data from the AIS patients to evaluate the effect of visit (Visits 1, 2 and 3) as well as two-way interaction effect of time of visit and head positioning, other diagnostic history and co-morbidities. All models included a random intercept term for each patient. The global F-statistic, Akaike's information criterion (AIC) and Bayesian information criterion (BIC) were used to perform the model selection and only the outcomes from the final model are presented here. All statistical tests were two-sided with type 1 error rate (p-value) of 0.05 to determine statistical significance and were performed using the R packages nlme and lme4 in R software environment (version 3.4) and TIBCO Statistica, version 13.0 (Statistica, Dell).

## 6.3 Results

### 6.3.1 Baseline Data

Eighteen controls and 19 AIS participants were recruited; satisfactory insonation of temporal windows was not possible in two controls and 4 AIS participants. Therefore, 16 controls (8 female) of mean age 57 years (range 26 to 87) and 15 AIS patients (7 female) of mean age 69 years (range 45 to 82) were included in the analysis. Eleven AIS patients completed all acute, sub-acute and chronic visits at 13.3 ± 6.9 hrs, 4.8 ± 3.2 days and 93.9 ± 11.5 days, respectively. None of the AIS patients received IVT. All participants

tolerated the GHP paradigm and no side effects were reported in the study. Participant characteristics are summarised in Table 6.1.

| Participant (n) | Controls (n=16) | AIS (n=15) |
|---|---|---|
| Age (years) | 57±16 | 69±8.2 |
| Sex (female), n (%) | 8 (50.0) | 7 (46.7) |
| Handedness (right), n (%) | 15 (93.8) | 14 (93.3) |
| Body mass index (BMI) $kg.m^{-2}$ | 24±4 | 27±5 |
| Past medical history, n (%) | | |
| Hypertension (n) | 5 (31.3) | 8 (53.3) |
| Diabetes mellitus (n) | 0 (0) | 2 (13.3) |
| Hypercholesterolaemia (n) | 0 (0) | 6 (40) |
| Ipsilateral ICA stenosis† (n) | NA | 2 (13.3) |
| Bilateral ICA stenosis‡(n) | NA | 1 (6.7) |
| NIHSS admission | NA | 5 [3-5] |
| Visit 2 | NA | 1.5 [1-3] |
| Visit 3 | NA | 0 [0-1] |
| mRS pre admission | NA | 0 [0] |
| Visit 2 | NA | 1 [0-2] |
| Visit 3 | NA | 0 [0-1] |
| OCSP classification | | |
| TACS | NA | 2 |
| PACS | NA | 5 |
| LACS | NA | 5 |
| POCS | NA | 3 |

**Table 6.1** Demographic characteristics of controls and AIS participants

Data are number of cases (n), mean ± standard deviation (SD) or median [interquartile range]

AIS: acute ischaemic stroke; BMI: Body mass index; ICA: Internal carotid artery; mRS: Modified Rankin Score; NA: Not assessed; NIHSS: National Institutes of Health Stroke Scale; LACS: lacunar syndrome; PACS: partial anterior circulation syndrome; POCS: posterior circulation syndrome; TACS: total anterior circulation syndrome

[†]defined as 10-30% of reduction in diameter

[‡]defined as 40-70% and 10-20% of reduction in diameter in the ipsilateral and contralateral internal carotid artery, respectively

### 6.3.2 AIS vs. Controls: Effects of Head Position (5-min FLAT and SIT)

A representative recording during GHP paradigm for an AIS patient is shown in Figure 6.1, and population averages for both controls and AIS patients are shown in Figures 6.2 -6.5.

The two-way interaction effect between head position (5-min FLAT and SIT) and group (AIS and controls) was assessed, however, there was no evidence that interaction of head position and group was statistically significant for systemic and cerebral haemodynamic parameters.

Compared to control subjects, AIS patients were significantly more hypertensive ($p=0.005$) (Figure 6.2A), hypocapnic ($p <0.001$) (Figure 6.2C), and had significantly lower CBV ($p=0.02$) (Figures 6.3A and 6.3B), and higher RAP ($p=0.004$) (Figures 6.5A and 6.5B) in both head positions (Table 6.2).

Patients on average had reduced BP ($p<0.001$) (Figure 6.2A) and CrCP ($p=0.009$) (Figures 6.4A and 6.4B) in 5-min SIT head position at all three visits (Table 6.2). Significant differences in CBV were seen in controls when changing from 5-min FLAT to SIT head position (dominant [DH] and NDH, $p<0.05$) (Figures 6.3A and 6.3B) (Table 6.2), but not in AIS patients.

Of note, in AIS patients, a significant reduction in ARI was observed in both AH and NAH, from 5-min FLAT to SIT head position, at all three visits ($p=0.018$) (Table 6.2).

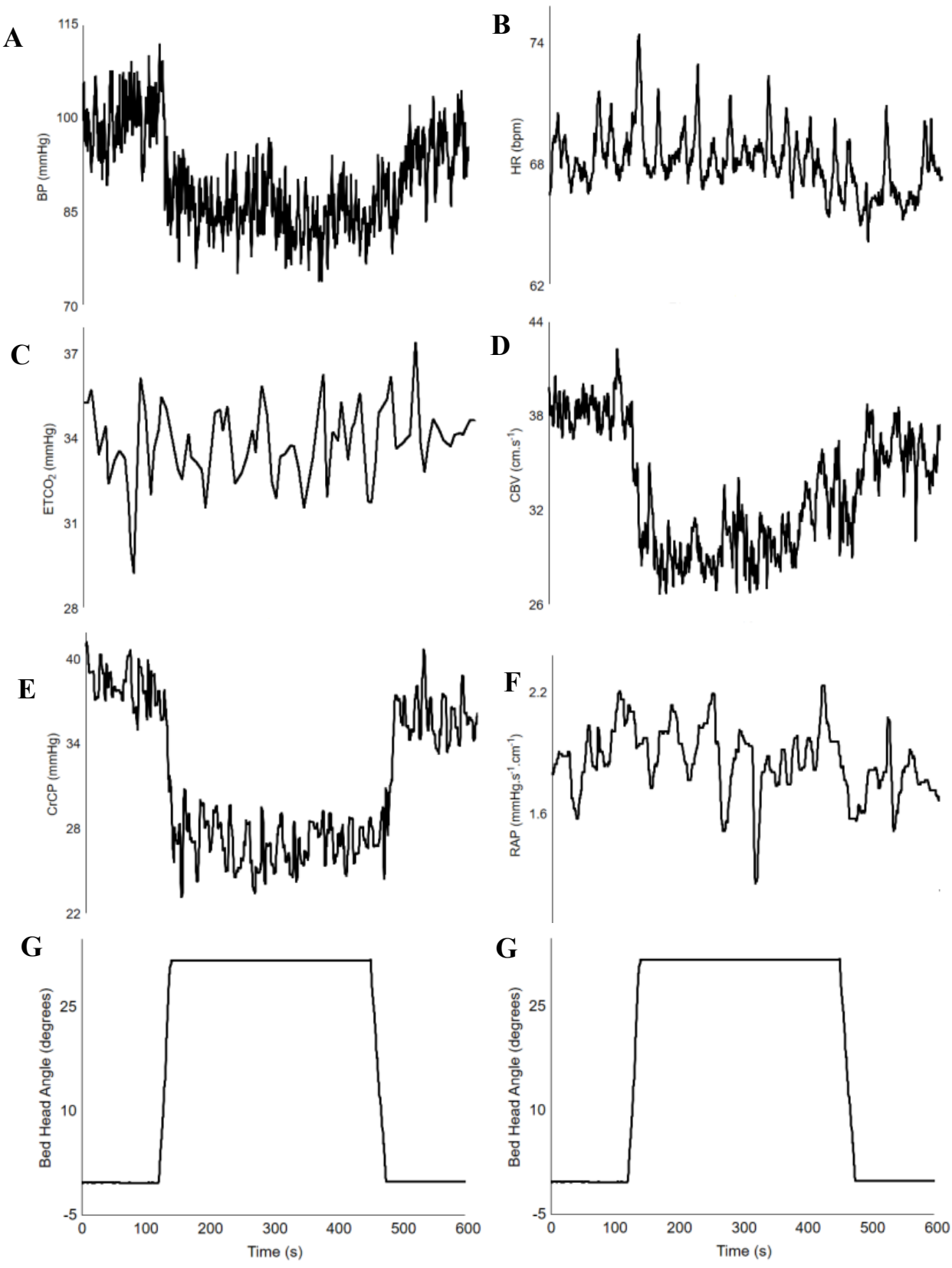



**Figure 6.1** Representative recordings of BP (A), HR (B), $ETCO_2$ (C), affected hemisphere CBV (D), CrCP (E) and RAP (F) during gradual change of head positioning, as indicated by the bed head angle (G), for an AIS participant.

| **Parameters** | **Controls Visit 1 (n = 16)** | | **Controls P value (head position effect)** | **AIS Visit 1 (n = 15)** | | **AIS Visit 2 (n =12)** | | **AIS Visit 3 (n=13)** | | **AIS P value (hemi-spheric effect)** | **AIS P value (head position effect)** | **AIS P value (visit effect)** | **AIS P value (visit and head position interaction)** | **P value (Controls Visit 1 vs. AIS Visit 1)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Head Position** | **5-min FLAT (0°)** | **Average of 5-min SIT (30°)** | | **5-min FLAT (0°)** | **Average of 5-min SIT (30°)** | **5-min FLAT (0°)** | **Average of 5-min SIT (30°)** | **5-min FLAT (0°)** | **Average of 5-min SIT (30°)** | | | | | |
| BP (mmHg) | 89.1±12.1 | 81.8±8 | **<0.001** | 101.0± 17.0 | 90.8±7.1 | 93.8±11.6 | 86.9±10.7 | 95.3±11.0 | 86.4±10.5 | NA | **<0.001** | 0.09 | 0.90 | **0.005** |
| Heart rate (bpm) | 65.7±9.9 | 65.1±9.7 | 0.34 | 68.4± 15.0 | 67.8±14.2 | 62.8±14.3 | 62.7±14.9 | 65.2±15.8 | 61.8±10.5 | NA | 0.71 | **0.04** | 0.99 | 0.24 |
| End-tidal $CO_2$ (mmHg) | 38.4±4.7 | 37.3±4.6 | 0.30 | 33.5± 2.7 | 33.0±2.6 | 31.8±6.9 | 34.4±2.3 | 33.6±4.3 | 34.5±2.7 | NA | 0.90 | 0.46 | 0.12 | **<0.001** |
| CBV (AH or DH) ($cm.s^{-1}$) | 53.0±12.6 | 50.2±14.1 | **0.001** | 38.3± 14.4 | 37.0±13.9 | 41.8±14.3 | 40.7±11.7 | 38.1±14.5 | 39.3±10.7 | 0.34 | 0.90 | 0.45 | 0.98 | **0.02** |
| CBV (NAH or NDH) ($cm.s^{-1}$) | 53.9±15.0 | 51.3±12.7 | **0.05** | 43.4± 14.9 | 43.6±14.0 | 41.4±9.4 | 41.9±9.2 | 41.1±8.9 | 42.0±4.8 | | | | | |
| CrCP (AH or DH) (mmHg) | 39.3±11.4 | 31.9±8.2 | **<0.001** | 35.9± 17.9 | 29.1±15.7 | 32.0±15.6 | 27.1±11.3 | 37.2±21.9 | 30.8±14.4 | **<0.001** | **0.009** | 0.20 | 0.60 | 0.77 |
| CrCP (NAH or NDH) (mmHg) | 38.8±10.7 | 33.1±7.8 | **0.012** | 37.4± 13.4 | 35.4±12.8 | 39.3±11.2 | 34.0±7.2 | 40.2±18.4 | 37.4±11.9 | | | | | |
| RAP (AH or DH) ($mmHg.sec.cm^{-1}$) | 1.01±0.32 | 1.11±0.35 | 0.11 | 2.00±0.97 | 1.97±0.88 | 1.70±0.84 | 1.57±0.75 | 1.68±0.81 | 1.61±0.57 | | | | | |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RAP (NAH or NDH) (mmHg.sec.cm$^{-1}$) | 0.86±0.29 | 0.95±0.3 | 0.55 | 1.62±0.70 | 1.44±0.53 | 1.35±0.38 | 1.35±0.44 | 1.29±0.42 | 1.23±0.24 | **<0.001** | 0.18 | **0.026** | 0.81 | **0.004** |
| ARI (AH or DH) | 5.57±1.53 | 5.12±1.4 | 0.62 | 5.43±2.03 | 4.17±1.75 | 4.29±1.12 | 3.31±1.72 | 4.92±1.56 | 4.36±1.24 | 0.10 | **0.018** | **0.02** | 0.39 | **0.009** |
| ARI (NAH or NDH) | 5.70±1.46 | 5.80±1.29 | 0.37 | 5.55±1.80 | 4.23±1.71 | 4.38±1.98 | 4.31±1.80 | 5.60±1.53 | 5.25±1.84 | | | | | |

**Table 6.2** Systemic and cerebral haemodynamic parameters for FLAT (0°) and SIT (30°) head positions in controls and AIS participants.

Values are mean ± SD for 5 min segments of data. P values from the mixed-effects general linear model between 5-min FLAT and SIT head position and between controls (Visit 1) and in AIS (Visit 1, 2 and 3).

AH, affected hemisphere; AIS, acute ischaemic stroke; BP, blood pressure; bpm, beats per minute; CBV, cerebral blood velocity; CrCP, critical closing pressure; DH, dominant hemisphere; NAH, non-affected hemisphere, NDH, non-dominant hemisphere; RAP, resistance area product; ARI, autoregulation index.

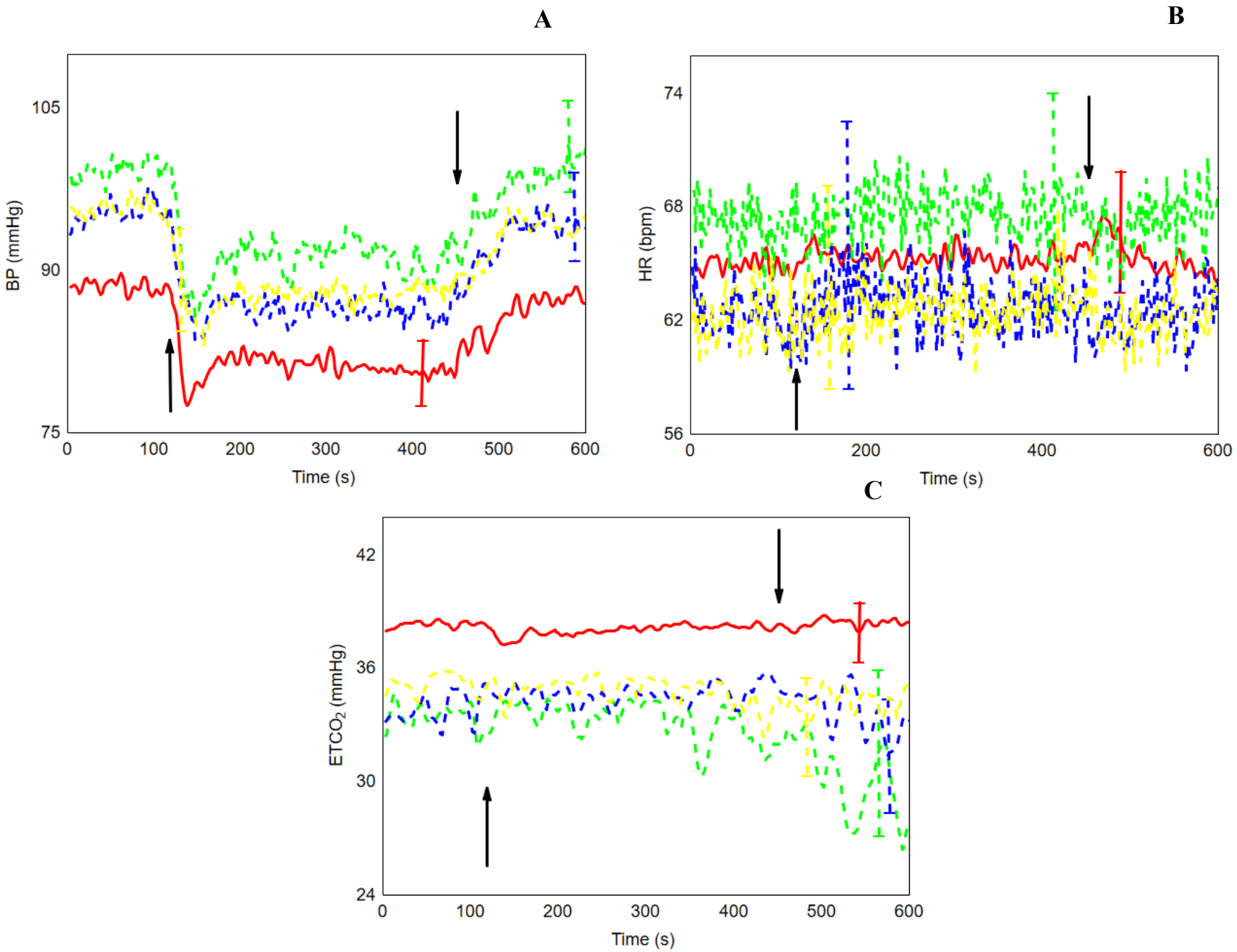

A
B
C
BP (mmHg)
105
90
75
0
100
200
300
400
500
600
Time (s)
HR (bpm)
74
68
62
56
0
200
400
600
Time (s)
ETCO2 (mmHg)
42
36
30
24
0
100
200
300
400
500
600
Time (s)

**Figure 6.2** Population averages of BP (A), HR (B) and $ETCO_2$ (C), in controls (continuous line) and AIS participants (dotted line) during gradual change of head positioning. Upward arrow shows the point when the head position changed from 0° to 30° (UP phase) and downward arrow from 30° to 0° (DOWN phase). Controls (red continuous line) versus AIS first (green dotted line), second (blue dotted line) and third visits (yellow dotted line). For clarity, the error bar represents only the largest ± 1 SE at the point of occurrence.

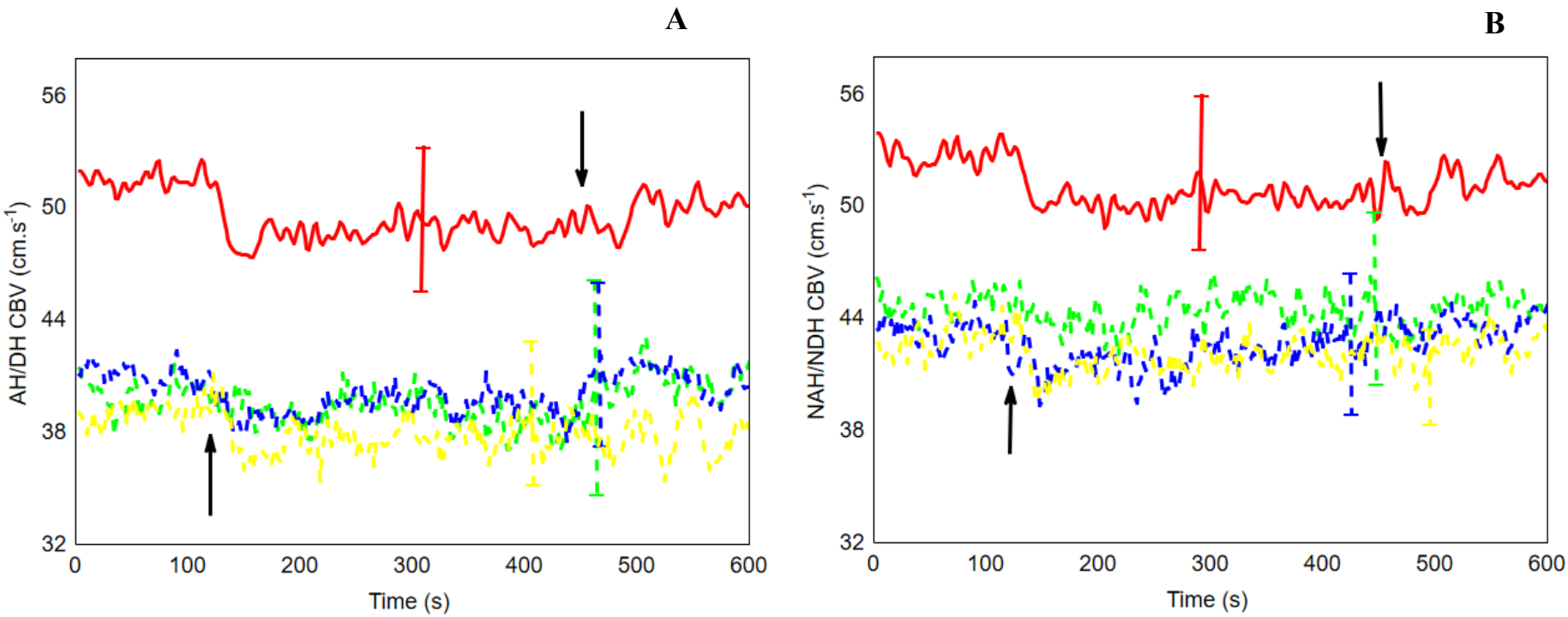



**Figure 6.3** Population averages of CBV (A and B) in controls (continuous line) and AIS participants (dotted line) during gradual change of head positioning. Upward arrow shows the point when the head position changed from 0° to 30° (UP phase) and downward arrow from 30° to 0° (DOWN phase). Controls (red continuous line) versus AIS first (green dotted line), second (blue dotted line) and third visits (yellow dotted line). Affected/dominant hemisphere (A) versus non-affected/non-dominant hemisphere (B). For clarity, the error bar represents only the largest ± 1 SE at the point of occurrence.

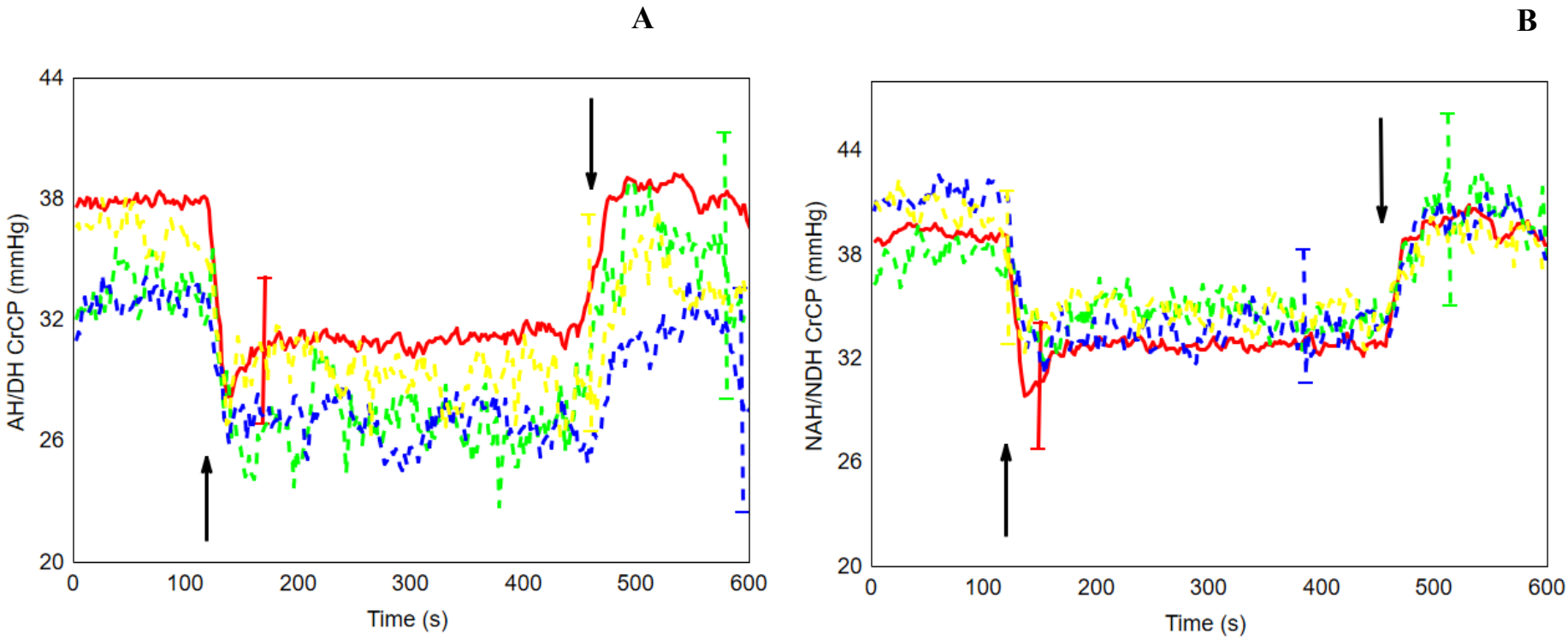



**Figure 6.4** Population averages of CrCP (A and B) in controls (continuous line) and AIS participants (dotted line) during gradual change of head positioning. Upward arrow shows the point when the head position changed from 0° to 30° (UP phase) and downward arrow from 30° to 0° (DOWN phase). Controls (red continuous line) versus AIS first (green dotted line), second (blue dotted line) and third visits (yellow dotted line). Affected/dominant hemisphere (A) versus non-affected/non-dominant hemisphere (B). For clarity, the error bar represents only the largest ± 1 SE at the point of occurrence.

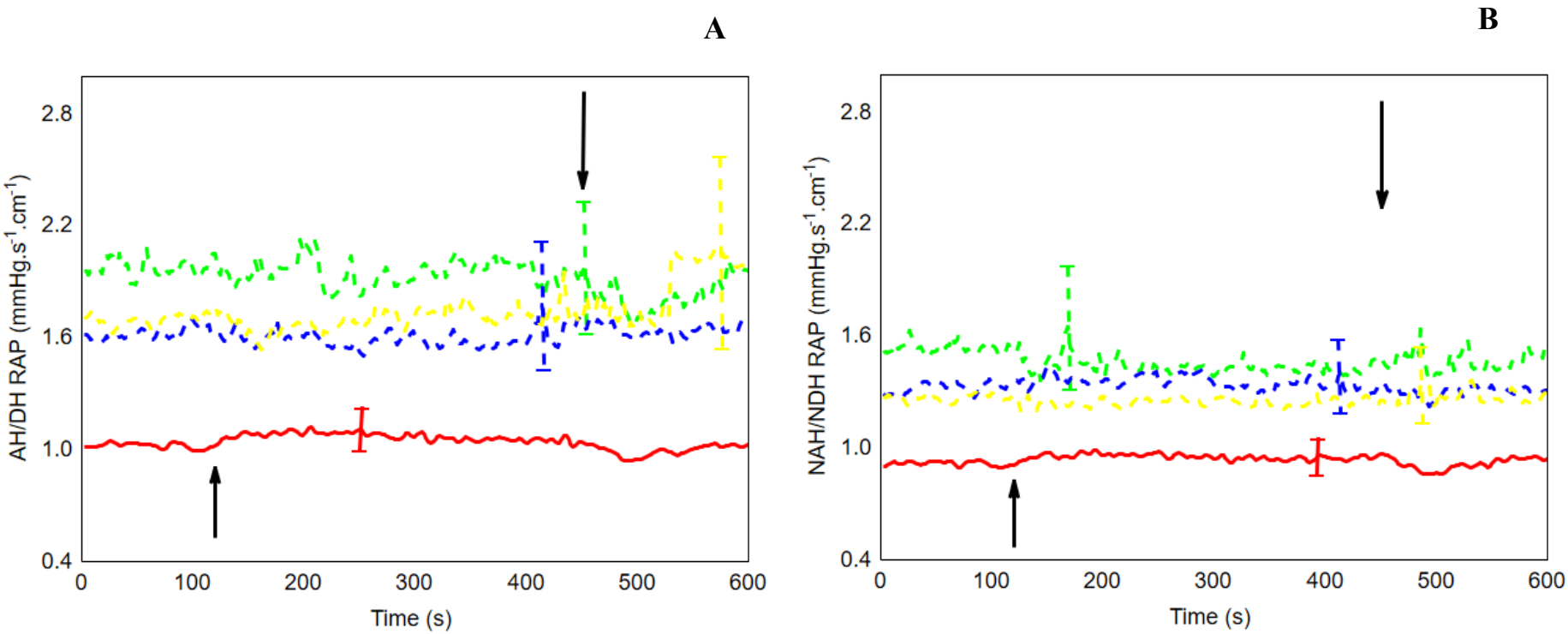



**Figure 6.5** Population averages of RAP (A and B) in controls (continuous line) and AIS participants (dotted line) during gradual change of head positioning. Upward arrow shows the point when the head position changed from 0° to 30° (UP phase) and downward arrow from 30° to 0° (DOWN phase). Controls (red continuous line) versus AIS first (green dotted line), second (blue dotted line) and third visits (yellow dotted line). Affected/dominant hemisphere (A) versus non-affected/non-dominant hemisphere (B). For clarity, the error bar represents only the largest ± 1 SE at the point of occurrence.

### 6.3.3 Inter-hemispheric Haemodynamic Differences in AIS

Regardless of head positioning, lower AH CrCP ($p<0.001$) and higher AH RAP ($p<0.001$) were observed compared to NAH, in both 5-min FLAT and SIT head positions at all visits. However, inter-hemispheric differences in CBV and ARI were not statistically significant (Table 6.2).

### 6.3.4 Haemodynamic Parameter Changes during AIS Recovery

Significant reductions in HR ($p = 0.04$) (Figure 6.2B) and RAP ($p = 0.026$) (Figures 6.5A and 6.5B) were observed over 90 days following stroke onset (Visit 1 to 3). The mean ARI significantly ($p =0.006$) reduced by 1.2 units at Visit 2 compared with Visit 1. The mean ARI although numerically reduced at Visit 3, was not statistically significant ($p =0.071$). No significant differences were seen in other systemic and cerebral haemodynamic parameters in AIS patients over the follow-up period (Table 6.2).

The two-way interaction effect of visits (Visit 1 to 3) and head positions (5-min FLAT and SIT) was assessed, however there was no evidence that interaction of visit and head position was statistically significant for systemic and cerebral haemodynamic parameters.

## 6.4 Discussion

### 6.4.1 Main Findings

This study chapter looked at cerebral haemodynamic responses to GHP, in controls and AIS patients over 90 days post stroke onset. When compared to controls, at 5-min FLAT head positon (Visit 1), AIS patients were significantly hypertensive and hypocapnic with lower CBV and higher RAP. This is broadly in agreement with previous literature (422, 695-697).

### 6.4.2 Effects of head positioning between AIS and controls

Compared to 5-min FLAT head position, both AIS and controls demonstrated a reduction in BP and CrCP, without significant changes in HR and $ETCO_2$ during the 5-min SIT head position. As mentioned in Chapter 5, BP reduction during sitting up position is widely recognised (667, 668, 698), and reflects systemic vasodilatation caused by the cardiopulmonary baroreflex activation, leading to reduced CO, increased peripheral vascular resistance and passive translocation of blood from the thorax. On the other hand, conflicting results regarding CrCP response to 'head-up' tilt have been reported (685, 699-701). Reduced CrCP on 'sitting-up' could be due to reduced cerebrovascular tone, secondary to increased $ETCO_2$ and CBV. These study chapter results demonstrated a reduction in CrCP without significant changes in $ETCO_2$ and CBV and therefore, may reflect a compensatory process to preserve CBV.

Unlike controls, where CBV reduced during 5-min SIT head position, no such changes were observed in AIS. Conflicting results have been previously reported, with AH CBF, measured by near-infrared spectroscopy (438, 660, 702) or diffuse correlation spectroscopy (702, 703), variably demonstrating reduced (438, 660, 703), paradoxically increased (703) or even significant variability in response during head position change

from 0° to 30° (702). Conversely, AH CBV, measured by TCD, shows a reduction (657, 659, 660, 704) or no change (703) when head position angle is increased. These conflicting results are likely related to small sample sizes with significant heterogeneity in study methodology and measurements. Certainly, it is likely that a wide range of contributing factors, such as measurement timing, stroke severity and subtype and recanalisation status, could explain the high variability in response to head positioning following AIS.

Significant reduction in ARI was observed following AIS during 5-min SIT head position, across all 3 visits, suggesting CA impairment could occur when head angle is increased, regardless of the stage of recovery. Truijen and colleagues investigated 39 AIS patients with near infrared spectroscopy and/or TCD, and demonstrated an inverse relationship between CA performance and CBF (as measured by NIRS), but not CBV (as measured by TCD) in response to head positioning (438). Our findings support reduced CA during 'sitting-up' head position, such that very early mobilisation following AIS may be detrimental, as suggested in the AVERT Trial (661).

### 6.4.3 The Natural History of AIS

Our study did not demonstrate any significant CBV changes, in both hemispheres and head position, across all three visits. Previous studies have shown conflicting results, with increased (373, 427), biphasic (437) or unchanged (429) CBV over repeated measurements. Ma and colleagues carried out serial TCD assessments in 67 AIS patients, and demonstrated no significant changes of CBV (AH and NAH) across two visits (visit 1: days 1-3 and visit 2: days 7 -10), compared to controls (429).

As mentioned in Chapter 1, Section 1.3.7, it is generally accepted that CA is impaired after IS (158, 169, 373, 423, 432, 435), particularly in more severe stroke (median NIHSS >9) (422), though onset varies from hours to weeks. This likely represents significant heterogeneity in terms of stroke subtype, imaging modalities, time from symptom onset and CA assessment methodologies. In this study chapter, though lower CA was not demonstrated acutely, ARI (AH and NAH) reduction was demonstrated at visit 2, with improvement by visit 3 (3 months post stroke onset), in keeping with Salinet and colleagues (427). However, unlike the former study, a reduction in $ETCO_2$ and mild improvement in AH CBV during 5-min FLAT (0°) head position was observed in Visit 2 compared with Visit 1. This observation could be explained by the ischaemic cascade in the infarcted area after AIS, leading to cerebral hypoperfusion, depletion of oxygen, local acidosis, mitochondrial dysfunction, activation of free radicals and therefore apoptosis of the peripheral neurons, glial, and endothelial cells. This would ultimately lead to arteriolar dysfunction at the ischaemic site and spread to the peri-infarct and remote areas later in the post-stroke interval (705). Furthermore, this study was not specifically designed to evaluate neuronal activation and NVC between controls and AIS patients led to a mismatch in CBV and tissue metabolic requirements, ultimately affecting the CA and ARI results. It is also important to take into account the significant hypocapnia observed in AIS. $CO_2$ is known as a powerful modulator in CA, hypocapnia could lower CBV and ICP, and restoration of cerebral penumbral homeostasis, and, hence, improve CA. Therefore, caution must be taken when interpreting such results.

### 6.4.4 Clinical Implications

Effective and co-ordinated rehabilitation is important in optimising post-stroke recovery (706). It is generally accepted that rehabilitation should be initiated in the acute hospital setting, though the AVERT study has suggested a higher morbidity and mortality in patients who received very early mobilisation when compared to standard care (661). This may relate to the consequences on penumbral viability related to adverse cerebral haemodynamics, which may be further aggravated by a premature upright position, as demonstrated in this study. When compared to those in the AVERT Trial, which demonstrated that very early mobilisation following AIS (NIHSS ≥ 16) may be detrimental, our AIS cohort had relatively mild stroke disease (mean NIHSS=5). Given that no significant changes in CBV were observed in this cohort when moved from 5-min FLAT to SIT head position, together with a satisfactory stroke recovery at 3 months (median mRS=0), it could be argued that changes in head positioning may have a clinically detrimental impact on severe, but not mild, AIS patients. Monitoring of cerebral haemodynamic parameters may thus be important in making informed personalised decisions about very early mobilisation; its timing, intensity and the maximum positional changes that may be tolerated.

### 6.4.5 Study Limitations

The study has a number of limitations. Firstly, control subjects were younger with lower BMI compared to AIS patients, though CA is unaffected by age (300, 688), and the linear mixed effect model has already taken the age variables into account. Secondly, as a pilot study, the patient number was relatively small, with significant heterogeneity in stroke subtype and severity increasing the chances of type II error. Future studies should recruit a larger cohort with higher NIHSS severity. Thirdly, the author undertook a MCA TCD

study, providing global CBV values, and excluding the possibility of subtle regional changes in response to GHP. Other intracerebral arteries, for example, the PCA and ACA, could lead to different results in different stroke subtypes (e.g. PCA measurements in POCS). Fourthly, the author assessed dCA using the ARI proposed by Tiecks et al. (356) and the underlying model relies on MAP, but not ICP. The author did not take into account changes in ICP and venous outflow in our study because of difficulties in recording these measurements by noninvasive means. Nevertheless, it is possible that these variables could influence dCA. To address these uncertainties, future studies would need to involve patients in critical care in which invasive measurements of ICP and venous outflow would be possible.

## 6.5 Conclusion

The study chapter provided evidence of the feasibility of using TCD to measure cerebral haemodynamic changes during GHP in AIS patients. Reduced ARI but without significant changes in CBV were observed during head positioning changes in mildly affected, and well recovered AIS patients, suggesting that head up position could be a safe option in such a cohort. The clinical implication of these changes warrants further study to determine optimal head positioning and the timing of rehabilitation following AIS.

# Chapter 7: Dynamic Cerebral Autoregulation Measurement Using Rapid Changes in Head Positioning: Experiences in Acute Ischaemic Stroke and Controls

Chapters 5 and 6 have demonstrated the feasibility of using TCD to measure cerebral haemodynamic changes during GHP in mildly affected AIS and control participants. However, prolonged bed rest could result in reduction of BPV, so this may consequently not be the best method for assessing dCA. RHP, a manoeuvre which involves rapid changes (30s) of head positioning, could lead to more dynamic changes in BPV and cerebral perfusion, and better for the assessment of dCA. This study chapter will focus on the feasibility of undertaking RHP in AIS, in particular, whether such a paradigm could increase sensitivity and specificity in assessing dCA, thus making it a better CA assessment protocol when compared to GHP.

## 7.1 Introduction

There is a growing clinical interest in the role of dCA in AIS patients, as it could provide valuable information regarding prevention, causation, progression, and outcome prediction (2, 430). CA is an important mechanism in maintaining stable CBF in the ischaemic penumbra area in order to avoid any secondary intracranial hypertension-related hyperfusion or ischaemic-related hypofusion injury, and therefore, improvement in the neurological recovery and functional outcome (1). Despite the relevance of assessing CA, ideally in its dynamic response, a gold standard technique for this purpose is still missing (376, 377). Spontaneous BP fluctuations at rest have been used as a stimulus in assessing dCA (169, 373). It has been validated in health and disease, including carotid artery disease (707) and SAH (708). However, there is ongoing concern

regarding a potential lack of variability in BP and CBV (380) and therefore a limited SNR to produce a robust dCA assessment (376).

Therefore, the ideal dCA assessment should need minimal participant co-operation and be able to provide consistent BP change, and yet, with limited alteration of autonomic nervous activity and breathing pattern (and hence $PaCO_2$). It is also important to note that uncomfortable procedures could make these manoeuvres difficult and impractical to implement in some clinical settings and patient populations. There is continued research interest in the development of alternative techniques that are able to assess CA integrity but are also suitable for acutely unwell and potentially medically unstable patient populations, such as those in AIS. There is already extensive literature available on systemic and cerebral haemodynamic responses to postural change (526, 709). Rapid head positioning (RHP) changes, a manoeuvre easily undertaken using a standard hospital bed that does not require participant co-operation, could be used to induce larger mean BP changes to spontaneous fluctuations at rest. In this chapter, the hypothesis that RHP can be induced by raising and lowering the head rest of the hospital bed was tested, and that this was well tolerated by control subjects and AIS patients. The aim was also to demonstrate that RHP leads to increased BPV when compared with spontaneous BP fluctuations at supine rest. Finally, effects of RHP on sensitivity (Sn) and specificity (Sp) of ARI, one of the main indices of dCA (356), to detect dCA impairment in AIS patients, compared with assessments performed at rest, was investigated.

## 7.2 Methods

### 7.2.1 Research Participants

Details of control and AIS participants were described in Chapter 5, Section 5.2.1 and Chapter 6, Section 6.2.1, respectively. In brief, a total of 18 control participants were

recruited from the University of Leicester, Leicester, UK and from the outpatient clinics at the UHL. A total of 19 AIS patients were recruited from the UHL HASU within 24 hours of symptom onset.

### 7.2.2 Measurements

Recording were performed as described in Chapter 4, Section 4.4. Two separate 5-min recordings were performed in each participant, at each visit, lying on a standard hospital bed. First, a baseline 5-min measurement was carried out with the participants in the lying flat (0°) head position. The second 5-min recording comprised a 2-min lying flat (0°) head position followed by four rapid changes from lying flat (0°) to sitting up (30°), then back to lying flat (0°) over 15s, and finally another 2-min with the participant in the lying flat (0°) head position (Figure 7.1).

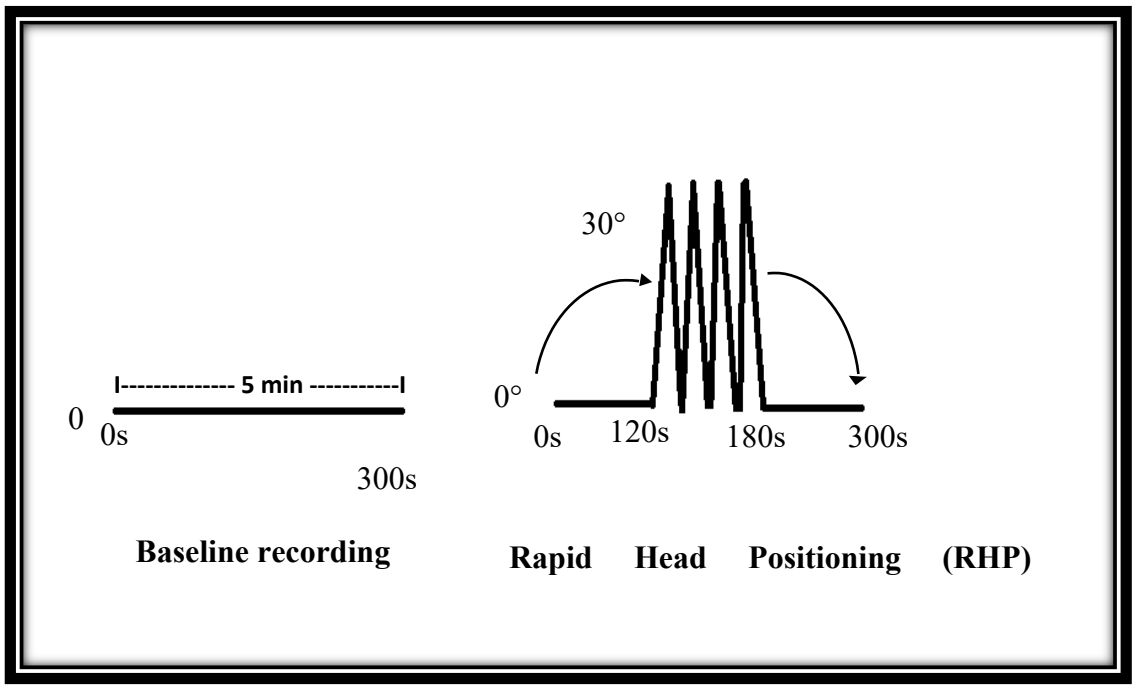



**Figure 7.1** Schematic representation of a 5-min baseline recording and a 5-min recording including the 1-min long RHP paradigm.

### 7.2.3 Data Analysis

Data analysis was performed as described in Chapter 4, Section 4.5 and Chapter 5, Section 5.2. Same as Chapter 5, mean BP, RAP and CrCP were compensated for changes in head height by subtracting DH-T*0.735*sinθ where θ is head angle from the horizontal, ranging from 0° to 30° and DH-T was the heart to temporal window distance in each participant.

Mean values of all systemic and cerebral haemodynamic parameters during 5-min baseline recording and from 60s to 240s in the RHP paradigm were extracted.

It is important to note that the segment duration used in study Chapters 5 and 6 was 5 min in both baseline and GHP, but in this Chapter the segment duration was 5 min in baseline recording and 180s in RHP paradigm. As a result, the author reduced the Welch overlapping windows (number of points) from 512 to 256 in both the 5 min baseline recording and 180s RHP paradigm in order to make such recordings directly comparable.

### 7.2.4 Statistical Analysis

As described in Chapter 5, Section 5.2.4, parameter distributions were assessed using the Shapiro-Wilk normality test. All normally distributed continuous variables are presented as mean ± SD, and non-Gaussian variables are presented as medians [interquartile ranges].

Baseline demographics and main physiological parameters were compared between control subjects and AIS patients using an independent Student t-test for normally distributed parameters and a Mann-Whitney test for non-Gaussian data. Corresponding paired t-tests were adopted in control subjects to identify baseline differences between visits. In the absence of differences, values were averaged between visits for comparison

with AIS patients. Repeated measures ANOVAs, were undertaken to test both systemic and cerebral haemodynamic parameters in AIS patients between visits. Bonferroni corrections were applied to multiple-comparison tests (710). For each visit, Fisher's cumulative P value was adopted to identify spectral regions that were uniformly different during RHP compared with baseline. A value of $p < 0.05$ was adopted to indicate statistical significance.

Sensitivity (Sn) and specificity (Sp) were used as measures of ARI performance in detecting RHP-induced dCA changes (711).

Sn was calculated as follows:

$$Sn = TP/ (FN + TP) \qquad \textit{Equation 7.1}$$

Where TP represents a true positive (impaired dCA) and FN represents false negative.

Sp was estimated as follows:

$$Sp = TN/ (FP + TN) \qquad \textit{Equation 7.2}$$

Where TN represents true negative (intact dCA) and FP represents false positive.

The area under the receiver-operating characteristic (ROC) (712) curve was used to evaluate the ability to discriminate between AIS patients and control subjects and during the RHP recordings. The ROC curve was plotted by successively using all discrete values of ARI between 0 and 9 as thresholds for separating AIS patients from control subjects.

An area under the curve (AUC) of 0.5 indicates no discrimination, whereas 1.0 indicates perfect discrimination.

Statistical analysis were performed using TIBCO Statistica (version 13.0, Statistica, Dell).

## 7.3 Results

### 7.3.1 Baseline Data

As in Chapter 6, Section 6.3.1, 16 controls (8 women) with a mean age of 57 years (range 26 to 87) and 15 AIS patients (7 women) with a mean age of 69 years (range 45-82) were included in the analysis. Control subjects attended both assessment visits with a mean of 12 ± 8 days apart, with 11 AIS patients completing all acute, subacute, and chronic visits at 13.3 ± 6.9 hrs, 4.8 ± 3.2 days, and 93.9 ± 11.5 days, respectively. All participants were able to complete both baseline and RHP paradigms without difficulty, and none of the participants declined the invitation to return for subsequent measurements after Visit 1. The small number of AIS patients that were not able to perform the RHP manoeuvre during subsequent visits resulted from their inpatient transfer to another hospital for ongoing rehabilitation, although 4.2% and 8.3% of controls and AIS recordings, respectively, were rejected because of poor quality of the CBV and/or BP signals.

For participant characteristics (Controls and AIS) please refer back to Chapter 6, Table 6.1. A representative recording of 5-min baseline and RHP is shown in Figure 7.2.

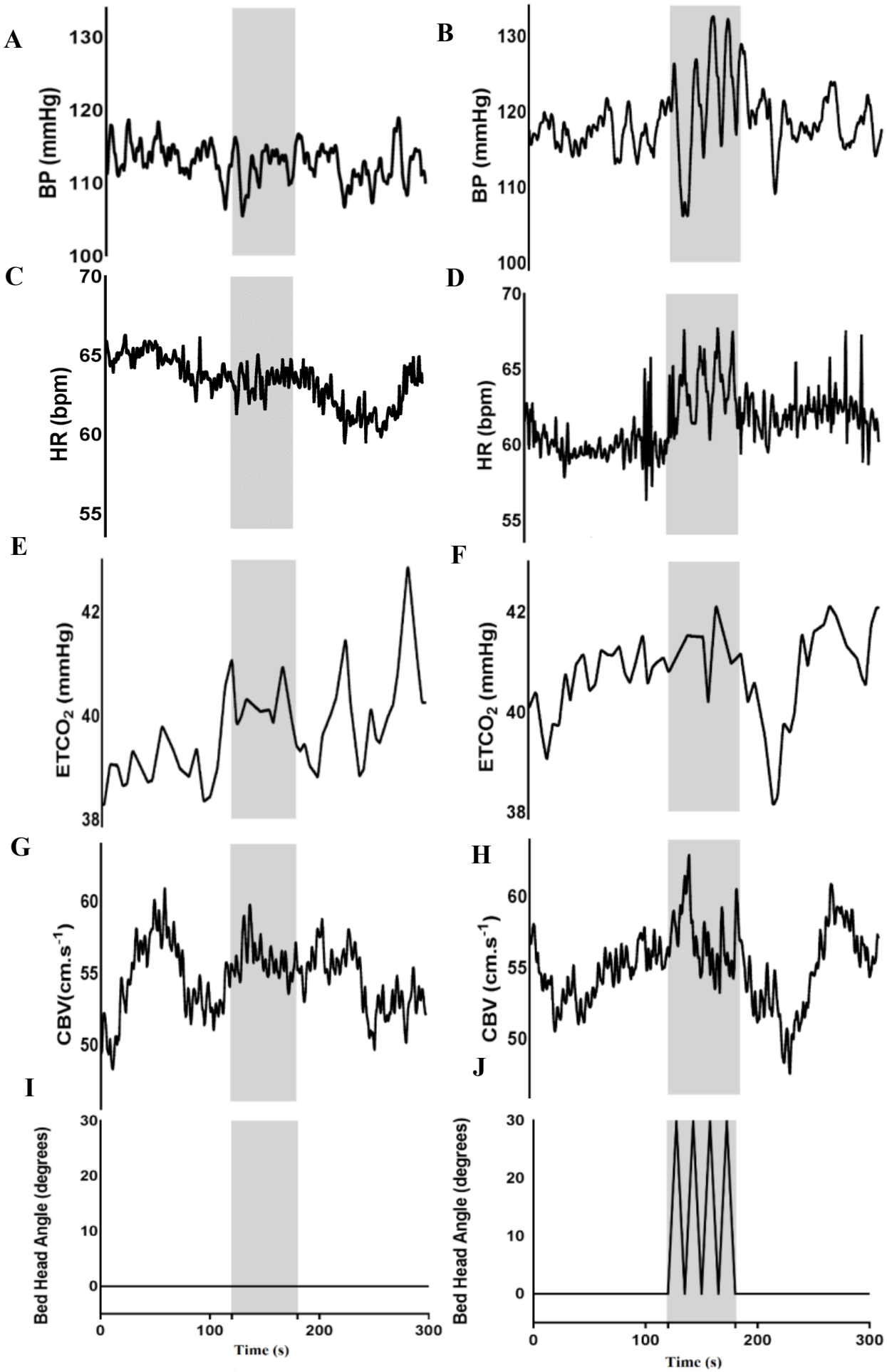

A
B
C
D
E
F
G
H
I
J
BP (mmHg)
HR (bpm)
ETCO2 (mmHg)
CBV(cm.s-1)
CBV (cm.s-1)
Bed Head Angle (degrees)
Time (s)
130
120
110
100
70
65
60
55
42
40
38
50
30
20
10
0
100
200
300

**Figure 7.2** Representative recording of BP (A and B), HR (C and D), $ETCO_2$ (E and F), and dominant hemisphere CBV (G and H) during 5-min baseline recording (A, C, E, G and I) and 5-min rapid head positioning (RHP; B, D, F, H, and J), as indicated by the bed head angle (I and J). The light grey area corresponds to the 120-180s time in which the RHP paradigm took place.

No significant baseline differences were seen in systemic or cerebral haemodynamic parameters between both visits for control subjects; therefore, data were averaged for subsequent comparisons with AIS patients. As mentioned in Chapter 6, Section 6.3.2, at baseline, patients with AIS at visit 1 had significantly higher MAP ($p = 0.011$) (Table 7.1 and Figure 7.3A), AH ($p < 0.0001$) and NAH RAP ($p < 0.0001$) (Table 7.1 and Figures 7.6A and 7.6B). A lower $ETCO_2$ ($p < 0.0024$) (Table 7.1 and Figure 7.3C) and AH CBV ($p < 0.01$) were also observed when compared to controls at Visit 1 (Table 7.1 and Figure 7.4A). At subsequent visits, $ETCO_2$ (Visits 2 and 3, $p < 0.001$) was consistently lower in AIS patients (Table 7.1 and Figure 7.3C). Both AH and NAH CBV were significantly lower at Visit 3, but not Visit 2 (Visit 3: AH CBV $p = 0.0031$ and NAH CBV $p = 0.0086$) when compared to controls (Table 7.1 and Figures 7.4A and 7.4B). On the other hand, both AH and NAH RAP were significantly higher when compared to controls (Visit 2: AH RAP $p = 0.002$; Visit 3: AH RAP $p = 0.0008$; and Visit 2: NAH RAP $p = 0.0002$ and Visit 3: NAH RAP $p = 0.0008$) (Table 7.1 and Figures 7.6A and 7.6B). The ARI was significantly lower at visit 2, in both AH ($p = 0.04$) and NAH ($p = 0.03$), but not at Visits 1 and 3 (Table 7.1 and Figures 7.7A and 7.7B) when compared to control subjects. Apart from AH ($p = 0.04$) and NAH RAP ($p = 0.03$), repeated measures ANOVA showed no significant effect of time (Visits 1, 2, and 3) on any of the systemic or cerebral haemodynamic parameters in AIS patients (Table 7.1 and Figures 7.3-7.7).

### 7.3.2 Effects of RHP

Similar to baseline recordings, during RHP, $ETCO_2$ was significantly lower in AIS patients at all visits (Visits 1, 2, and 3, $p < 0.0001$) compared with controls (Table 7.2 and Figure 7.8C). There was an increase in AH RAP at Visit 1 ($p = 0.007$) when compared to controls, but this was not reproduced in the NAH nor at other visits (Table 7.2 and Figures 7.11A and 7.11B). Otherwise, no other significant differences were seen in both systemic

and cerebral haemodynamic parameters between AIS patients at all visits and control subjects in response to RHP (Table 7.2 and Figures 7.8-7.12).

Beat-to-beat BPV during 5-min baseline and RHP was expressed as the power spectral density shown in Figures 7.13 and 7.14, respectively. BPV resulting from the RHP paradigm was significantly higher compared with baseline at both visits (both $p < 0.001$) in control subjects (Figure 7.13), but not in AIS patients at any of the three visits (Figure 7.14). In a subgroup of control subjects who were aged 68 years old or above ($n = 7$), BPV during RHP was still significantly higher compared with baseline at both visits (Visit 1: $p = 0.021$ and Visit 2: $p = 0.023$).

### 7.3.3 ROC Curve

No significant differences in ARI were seen in baseline and RHP recordings, between DH and NDH (control subjects) and AH and NAH (AIS patients). As a result, data were averaged for subsequent ROC analysis. The ROC curve had AUCs of 0.53 and 0.54 for the baseline and RHP recordings, respectively, thus showing no significant discrimination between AIS patients and control subjects.

| Parameters | Controls (n=16) | AIS Visit 1 (n=15) | AIS Visit 2 (n=12) | AIS Visit 3 (n=13) | AIS P Value (Visit effect) |
|---|---|---|---|---|---|
| BP (mmHg) | 89.5 ± 11.6 | 101.0 ± 17.0$^{*}$ | 93.8 ± 11.6 | 95.3 ± 11.0 | 0.40 |
| Heart Rate (bpm) | 65.5 ± 10.5 | 68.4 ± 15.0 | 62.8 ± 14.3 | 65.2 ± 15.8 | 0.79 |
| End-Tidal $CO_2$ (mmHg) | 38.9 ± 3.5 | 33.5 ± 2.7$^{*\dagger}$ | 31.8 ± 6.9$^{*\dagger}$ | 33.6 ± 4.3$^{*\dagger}$ | 0.70 |
| CBV (AH or DH) ($cm.s^{-1}$) | 52.7 ± 12.2 | 38.3 ± 14.4$^{*}$ | 41.8 ± 14.3 | 38.1 ± 14.5$^{*}$ | 0.43 |
| CBV (NAH or NDH) ($cm.s^{-1}$) | 52.6 ± 13.6 | 43.4 ± 14.9 | 41.4 ± 9.4 | 41.1 ± 8.9$^{*}$ | 0.75 |
| CrCP (AH or DH) (mmHg) | 39.0 ± 10.3 | 35.9 ± 17.9 | 32.0 ± 15.6 | 37.2 ± 21.9 | 0.76 |
| CrCP (NAH or NDH) (mmHg) | 40.3 ± 11.1 | 37.4 ± 13.4 | 39.3 ± 11.2 | 40.2 ± 18.4 | 0.79 |
| RAP (AH or DH) ($mmHg.sec.cm^{-1}$) | 1.01 ± 0.32 | 2.00 ± 0.97$^{*\dagger}$ | 1.70 ± 0.84$^{*\dagger}$ | 1.68 ± 0.81$^{*\dagger}$ | **0.04** |
| RAP (NAH or NDH) ($mmHg.sec.cm^{-1}$) | 0.89 ± 0.27 | 1.62 ± 0.70$^{*\dagger}$ | 1.35 ± 0.38$^{*\dagger}$ | 1.29 ± 0.42$^{*\dagger}$ | **0.03** |
| ARI (AH or DH) | 5.75 ± 1.53 | 5.43 ± 2.03 | 4.29 ± 1.12$^{\ddagger}$ | 4.92 ± 1.56 | 0.42 |
| ARI (NAH or NDH) | 5.95 ± 1.40 | 5.55 ± 1.80 | 4.38 ± 1.98$^{\ddagger}$ | 5.60 ± 1.53 | 0.79 |

**Table 7.1** Systemic and cerebral haemodynamic parameters during baseline recordings between controls and AIS participants.

Values are means ± SD for 5-min segments of data. Baseline data for control subjects are the average of both visits. AH, affected hemisphere; AIS, acute ischaemic stroke; ARI, autoregulation index; CBV, cerebral blood velocity; CrCP, critical closing pressure; DH, dominant hemisphere; NAH, non-affected hemisphere; NDH, non-dominant hemisphere; RAP, resistance area product.

P values from repeated measures ANOVA are for the baseline recordings difference between AIS in Visits 1, 2, and 3.

* $p < 0.017$ by an independent t-test to compare controls and AIS between different visits.

† $p < 0.0024$ by an independent t-test to compare controls and AIS between different visits (after Bonferroni correction).

‡ $p < 0.05$ by Mann-Whitney U-test to compare controls and AIS between different visits.

| Parameters | Controls (n=16) | AIS Visit 1 (n=15) | AIS Visit 2 (n=12) | AIS Visit 3 (n=13) | AIS P Value (Visit effect) |
|---|---|---|---|---|---|
| BP (mmHg) | 89.1 ± 12.2 | 94.5 ± 15.4 | 92.6 ± 10.3 | 91.4 ± 11.7 | 0.18 |
| Heart Rate (bpm) | 64.9 ± 9.1 | 65.3 ± 17.1 | 62.5 ± 15.0 | 62.3 ± 14.9 | 0.98 |
| End-Tidal $CO_2$ (mmHg) | 38.6 ± 2.7 | 31.8 ± 4.1$^{*\dagger}$ | 34.2 ± 2.5$^{*\dagger}$ | 33.2 ± 5.5$^{*\dagger}$ | 0.63 |
| CBV (AH or DH) ($cm.s^{-1}$) | 49.3 ± 13.1 | 38.4 ± 16.9 | 45.1 ± 18.6 | 37.0 ± 12.5 | 0.36 |
| CBV (NAH or NDH) ($cm.s^{-1}$) | 51.1 ± 12.8 | 44.4 ± 14.9 | 43.5 ± 10.0 | 42.6 ± 7.0 | 0.95 |
| CrCP (AH or DH) (mmHg) | 37.1 ± 7.5 | 36.2 ± 20.8 | 27.1 ± 16.7 | 36.2 ± 20.5 | 0.45 |
| CrCP (NAH or NDH) (mmHg) | 40.4 ± 9.3 | 36.4 ± 15.9 | 34.1 ± 13.7 | 36.3 ± 16.6 | 0.76 |
| RAP (AH or DH) ($mmHg.sec.cm^{-1}$) | 1.12 ± 0.34 | 1.73 ± 0.65$^{*}$ | 1.60 ± 0.91 | 1.52 ± 0.54 | 0.79 |
| RAP (NAH or NDH) ($mmHg.sec.cm^{-1}$) | 0.99 ± 0.29 | 1.29 ± 0.65 | 1.26 ± 0.43 | 1.25 ± 0.35 | 0.32 |
| ARI (AH or DH) | 5.67 ± 1.79 | 4.28 ± 3.27 | 4.91 ± 2.37 | 4.92 ± 2.20 | 0.77 |
| ARI (NAH or NDH) | 6.10 ± 1.78 | 4.90 ± 2.82 | 4.97 ± 2.38 | 5.0 ± 1.81 | 0.92 |

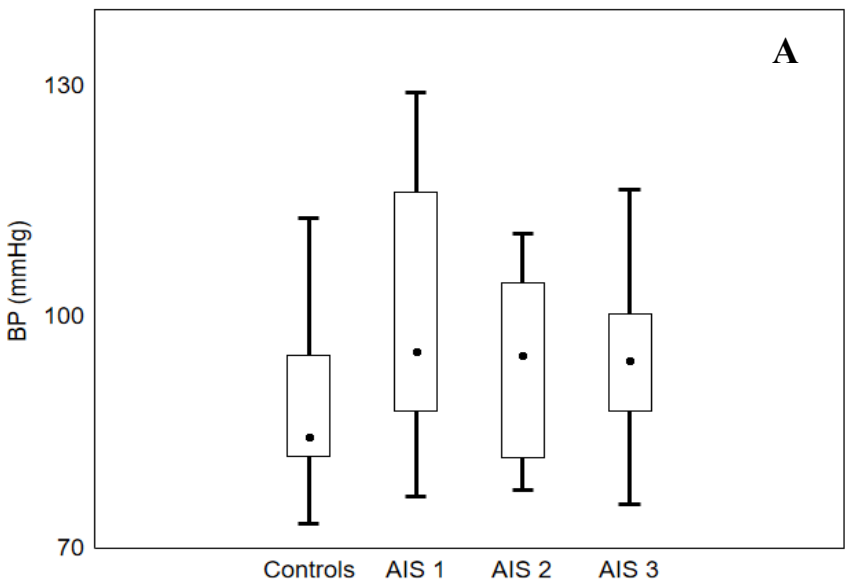
**Table 7.2** Systemic and cerebral haemodynamic parameters during RHP between controls and AIS participants.

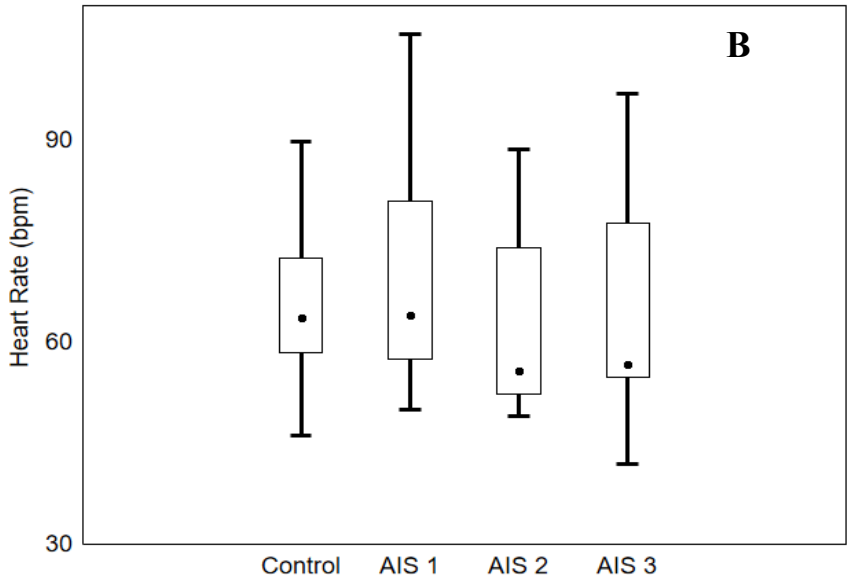
Values are expressed as means ± SD for the 60s to 240s segments of data. Baseline data for controls are the average of both visits. AH, affected hemisphere; AIS, acute ischaemic stroke; ARI, autoregulation index; CBV, cerebral blood velocity; CrCP, critical closing pressure; DH, dominant hemisphere; NAH, non-affected hemisphere; NDH, non-dominant hemisphere; RAP, resistance area product; RHP, rapid head positioning.

P values from repeated measures ANOVA are for the RHP recording difference between AIS in Visits 1, 2, and 3.

* $p < 0.017$ by an independent t-test to compare controls and AIS between different visits.

† $p < 0.0024$ by an independent t-test to compare controls and AIS between different visits (after Bonferroni correction).


A
130
100
70
BP (mmHg)
Controls
AIS 1
AIS 2
AIS 3


B
90
60
30
Heart Rate (bpm)
Control
AIS 1
AIS 2
AIS 3

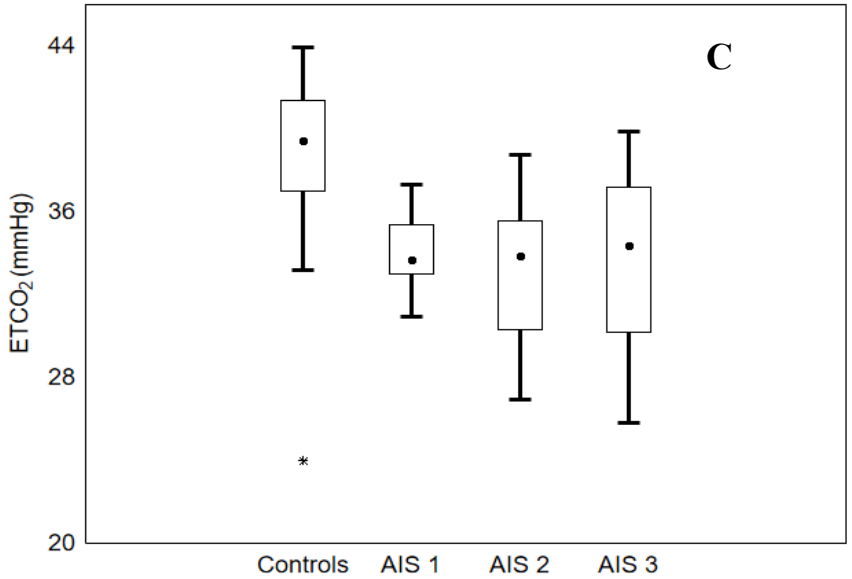

C
44
36
28
20
ETCO2 (mmHg)
*
Controls
AIS 1
AIS 2
AIS 3

**Figure 7.3** Box plots showing the median, interquartile range, and maximum and minimum values of the baseline recordings in BP (A), HR (B), and $ETCO_2$ (C) between controls and AIS participants. AIS 1, AIS Visit 1; AIS 2, AIS Visit 2; AIS 3, AIS Visit 3.

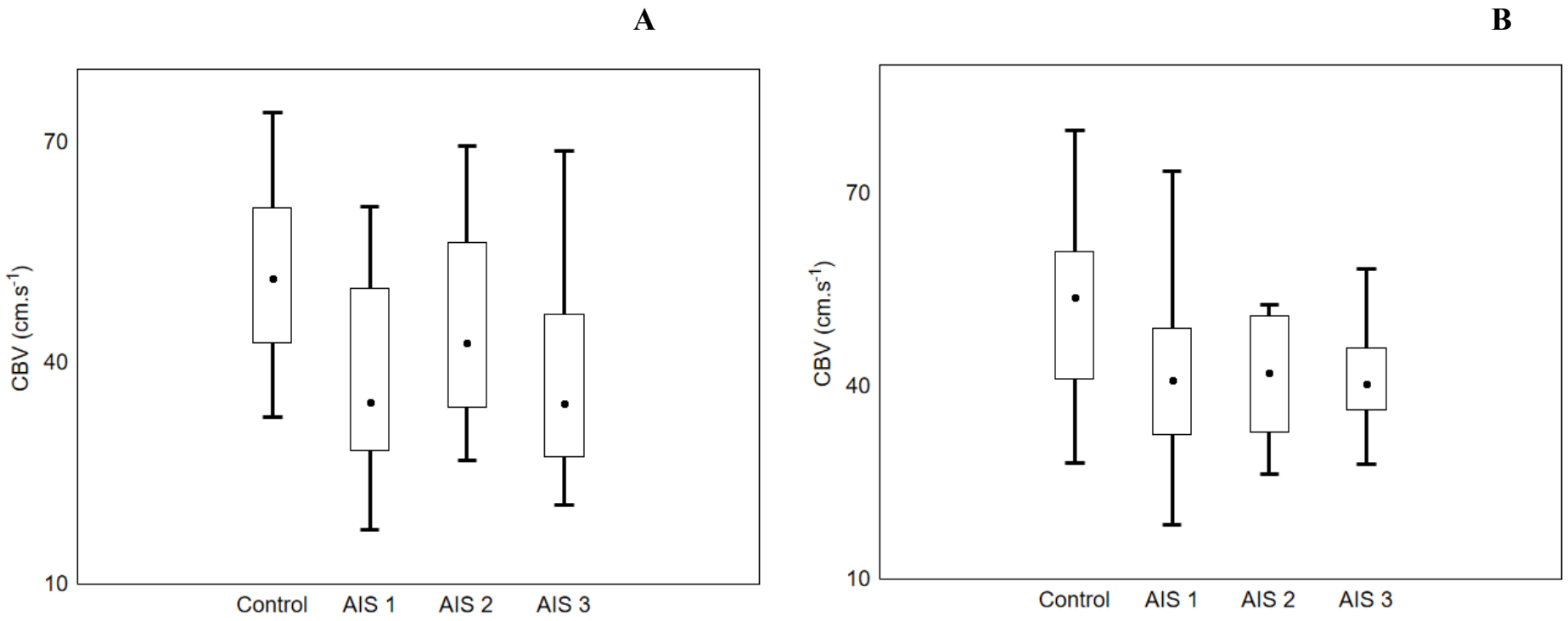



**Figure 7.4** Box plots showing the median, interquartile range, and maximum and minimum values of the baseline recordings in dominant and affected hemisphere CBV (A), and non-dominant and non-affected hemisphere CBV (B) between controls and AIS participants. AIS 1, AIS Visit 1; AIS 2, AIS Visit 2; AIS 3, AIS Visit 3.

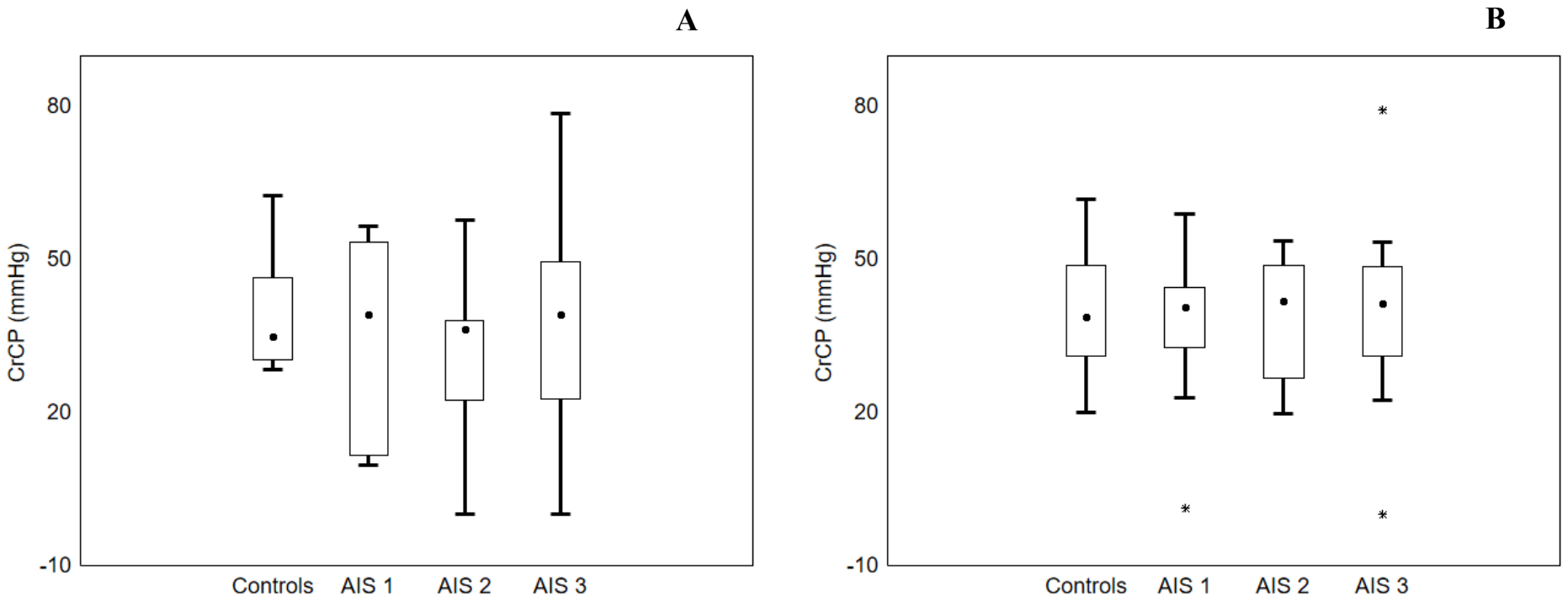



**Figure 7.5** Box plots showing the median, interquartile range, and maximum and minimum values of the baseline recordings in dominant and affected hemisphere CrCP (A), and non-dominant and non-affected hemisphere CrCP (B) between controls and AIS participants. AIS 1, AIS Visit 1; AIS 2, AIS Visit 2; AIS 3, AIS Visit 3.

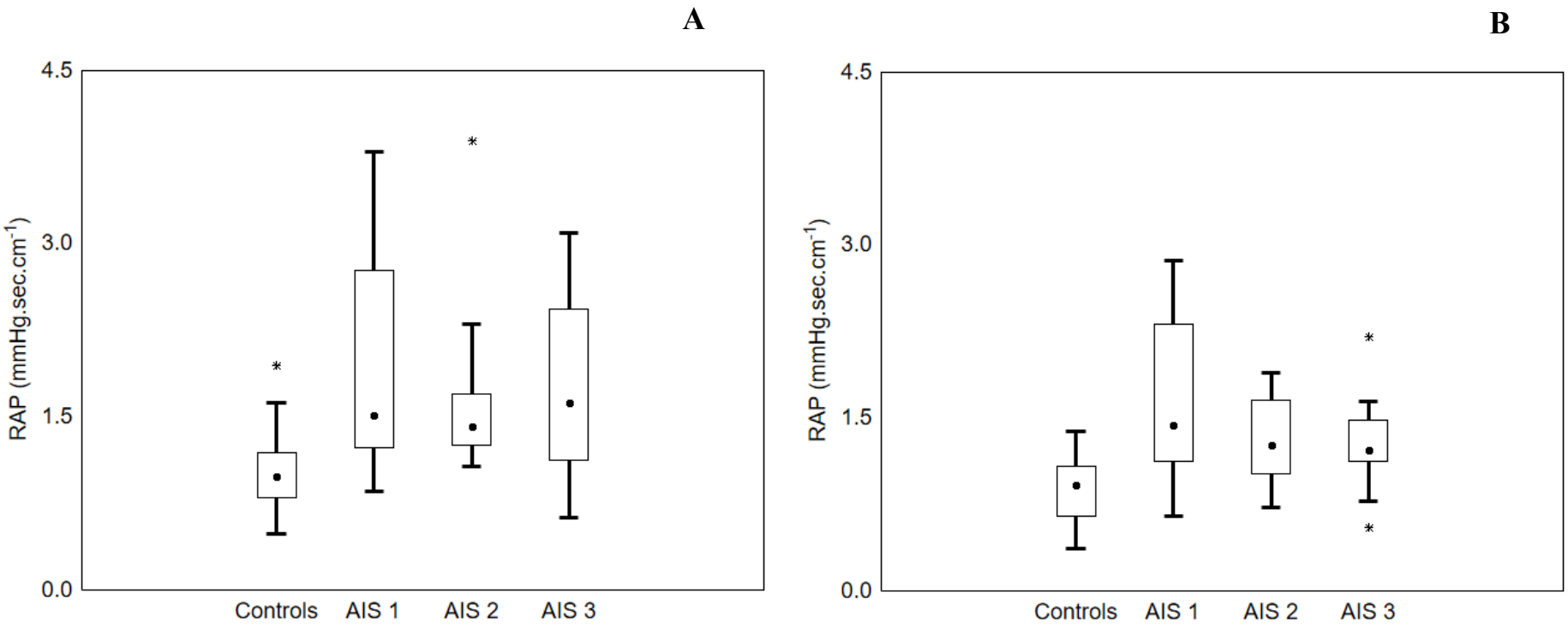



**Figure 7.6** Box plots showing the median, interquartile range, and maximum and minimum values of the baseline recordings in dominant and affected hemisphere RAP (A), and non-dominant and non-affected hemisphere RAP (B) between controls and AIS participants. AIS 1, AIS Visit 1; AIS 2, AIS Visit 2; AIS 3, AIS Visit 3.

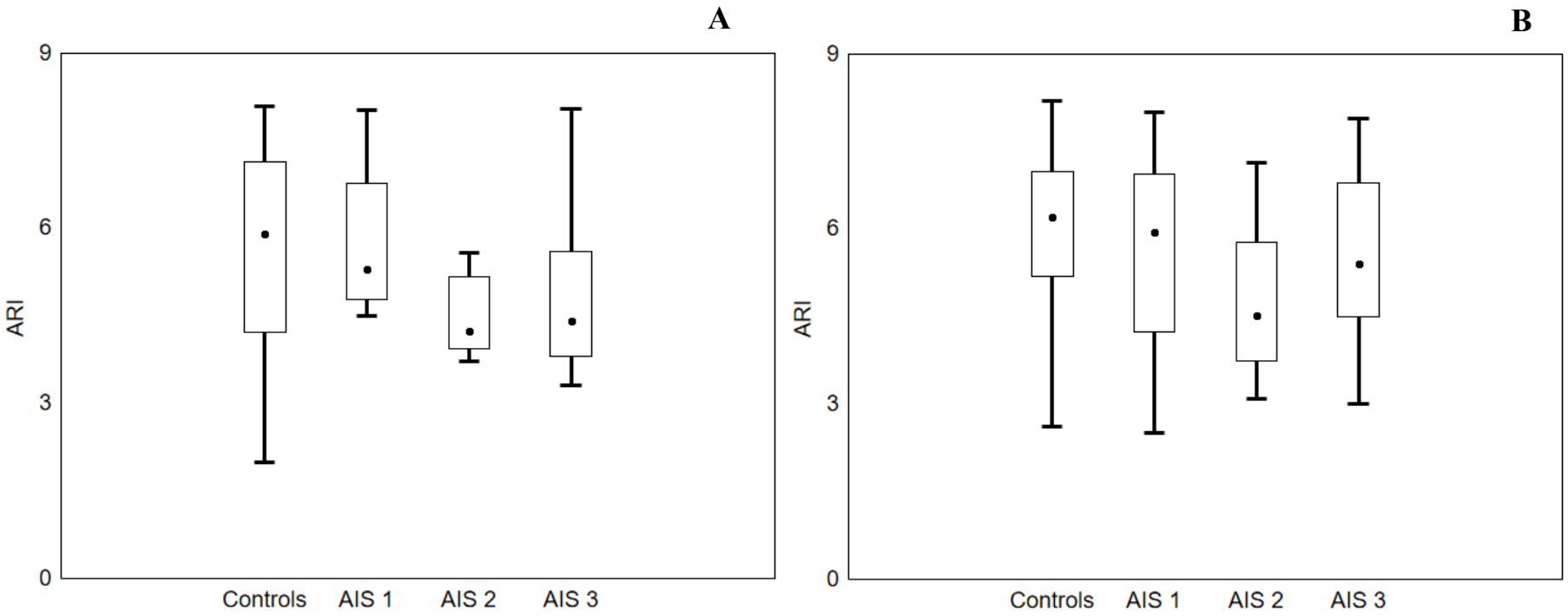



**Figure 7.7** Box plots showing the median, interquartile range, and maximum and minimum values of the baseline recordings in dominant and affected hemisphere ARI (A), and non-dominant and non-affected hemisphere ARI (B) between controls and acute AIS participants. AIS 1, AIS Visit 1; AIS 2, AIS Visit 2; AIS 3, AIS Visit 3.

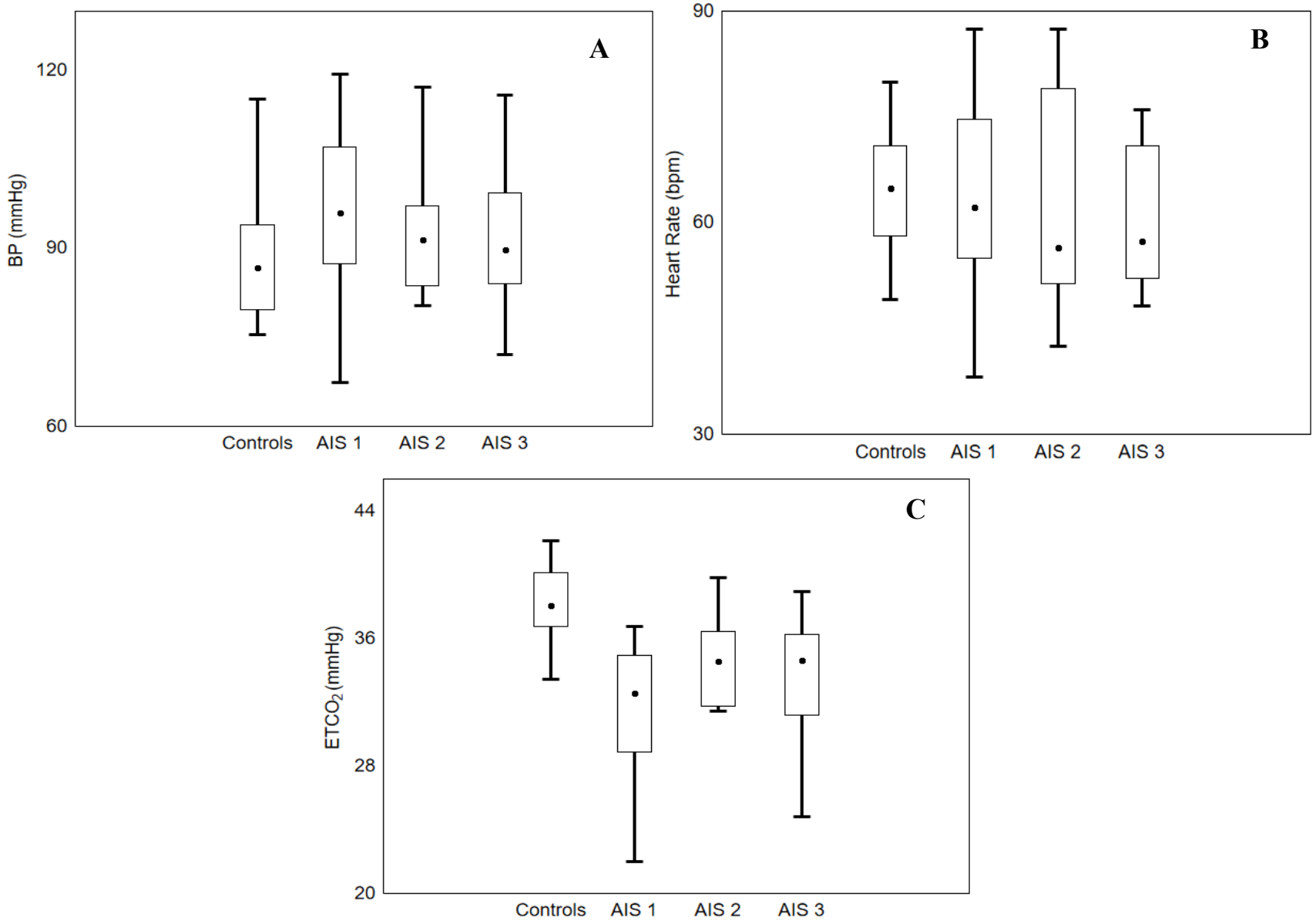

A
BP (mmHg)
120
90
60
Controls
AIS 1
AIS 2
AIS 3
B
Heart Rate (bpm)
90
60
30
Controls
AIS 1
AIS 2
AIS 3
C
ETCO2 (mmHg)
44
36
28
20
Controls
AIS 1
AIS 2
AIS 3

**Figure 7.8** Box plots showing the median, interquartile range, and maximum and minimum values of the rapid head positioning (RHP) recording in BP (A), HR (B), and $ETCO_2$ (C) between controls and AIS participants. AIS 1, AIS Visit 1; AIS 2, AIS Visit 2; AIS 3, AIS Visit 3.

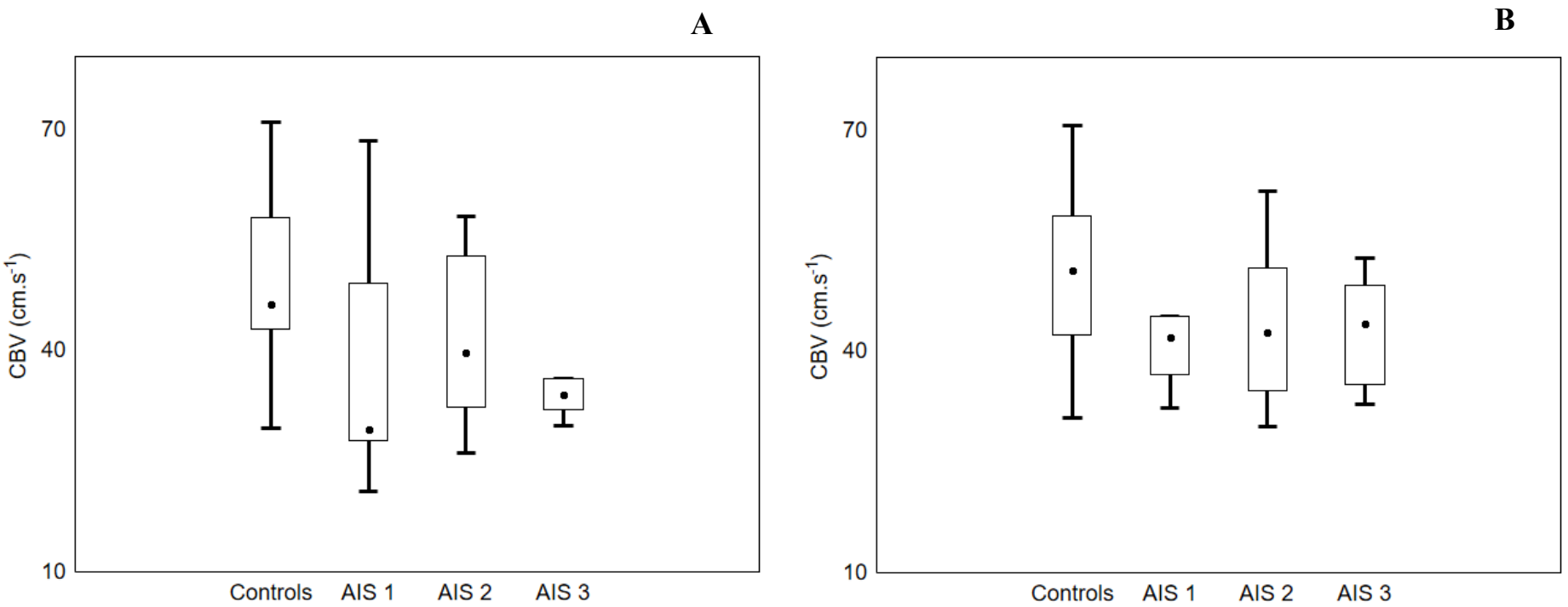



**Figure 7.9** Box plots showing the median, interquartile range, and maximum and minimum values of the rapid head positioning (RHP) recording in dominant and affected hemisphere CBV (A), non-dominant and non-affected hemisphere CBV (B) between controls and AIS participants. AIS 1, AIS Visit 1; AIS 2, AIS Visit 2; AIS 3, AIS Visit 3.

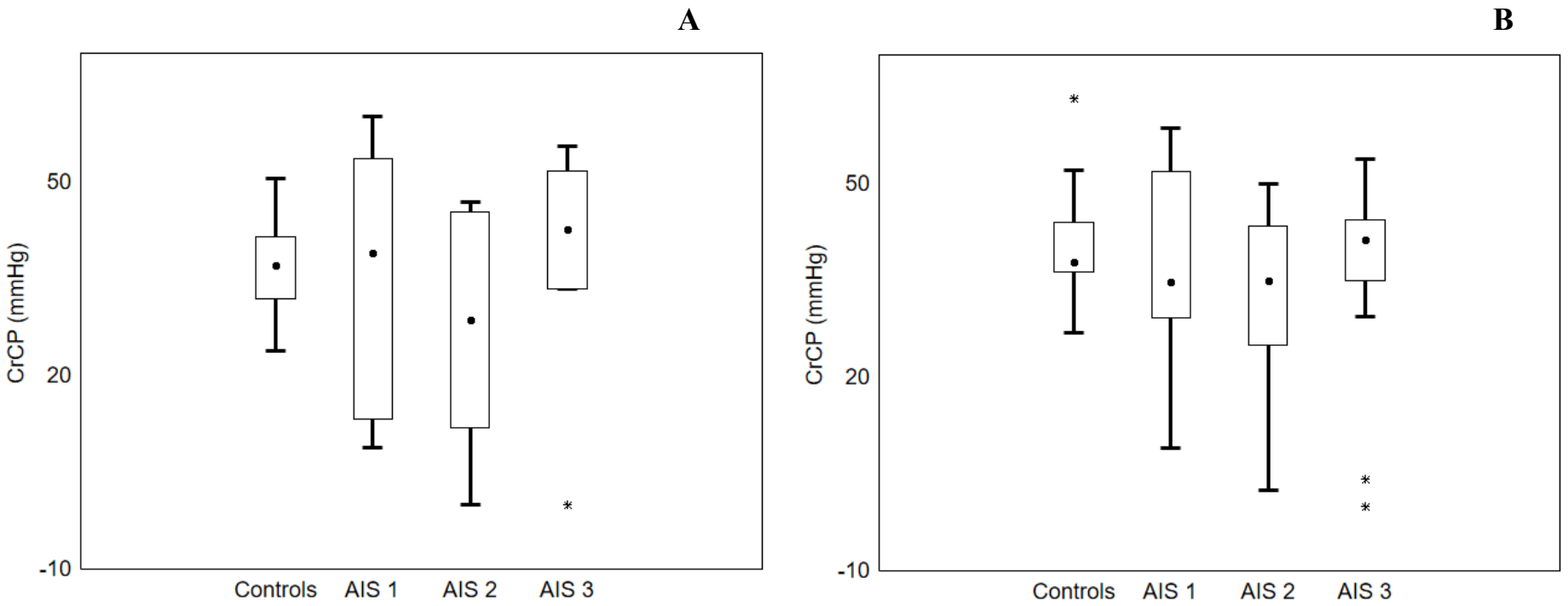



**Figure 7.10** Box plots showing the median, interquartile range, and maximum and minimum values of the rapid head positioning (RHP) recording in dominant and affected hemisphere CrCP (A), non-dominant and non-affected hemisphere CrCP (B) between controls and AIS participants. AIS 1, AIS Visit 1; AIS 2, AIS Visit 2; AIS 3, AIS Visit 3.

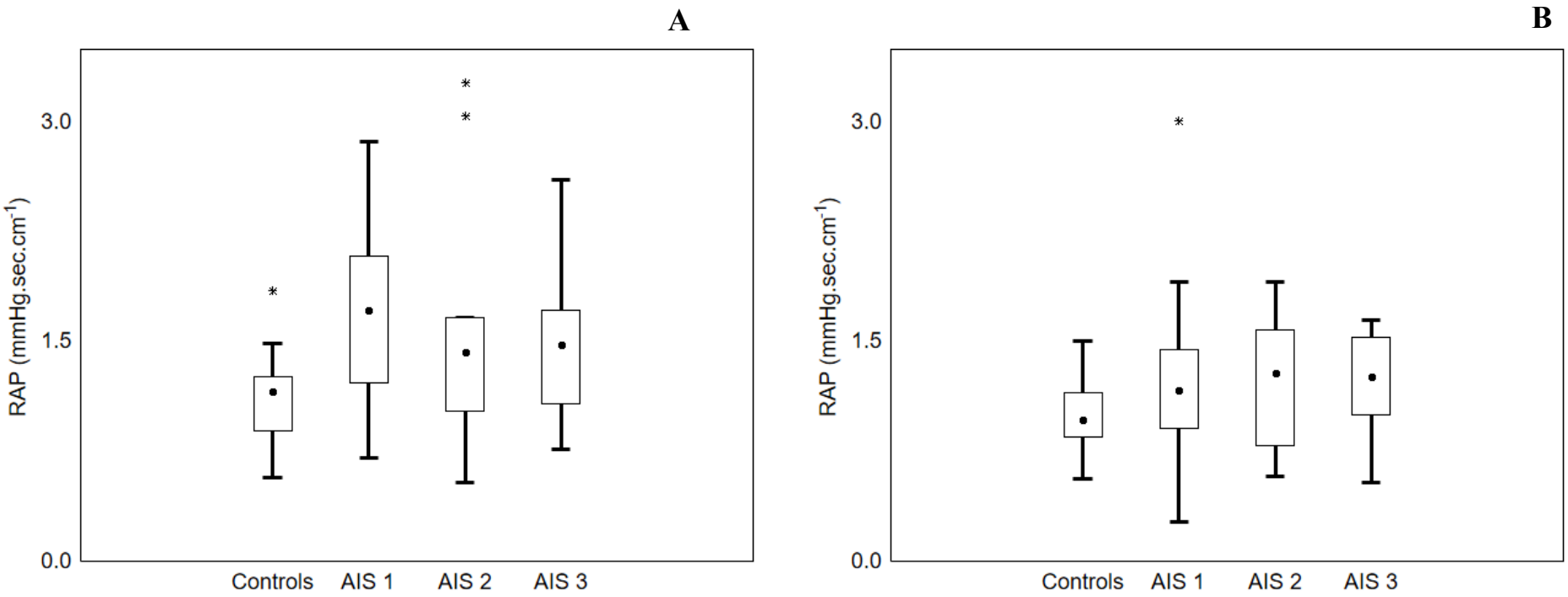



**Figure 7.11** Box plots showing the median, interquartile range, and maximum and minimum values of the rapid head positioning (RHP) recording in dominant and affected hemisphere RAP (A), non-dominant and non-affected hemisphere RAP (B) between controls and AIS participants. AIS 1, AIS Visit 1; AIS 2, AIS Visit 2; AIS 3, AIS Visit 3.

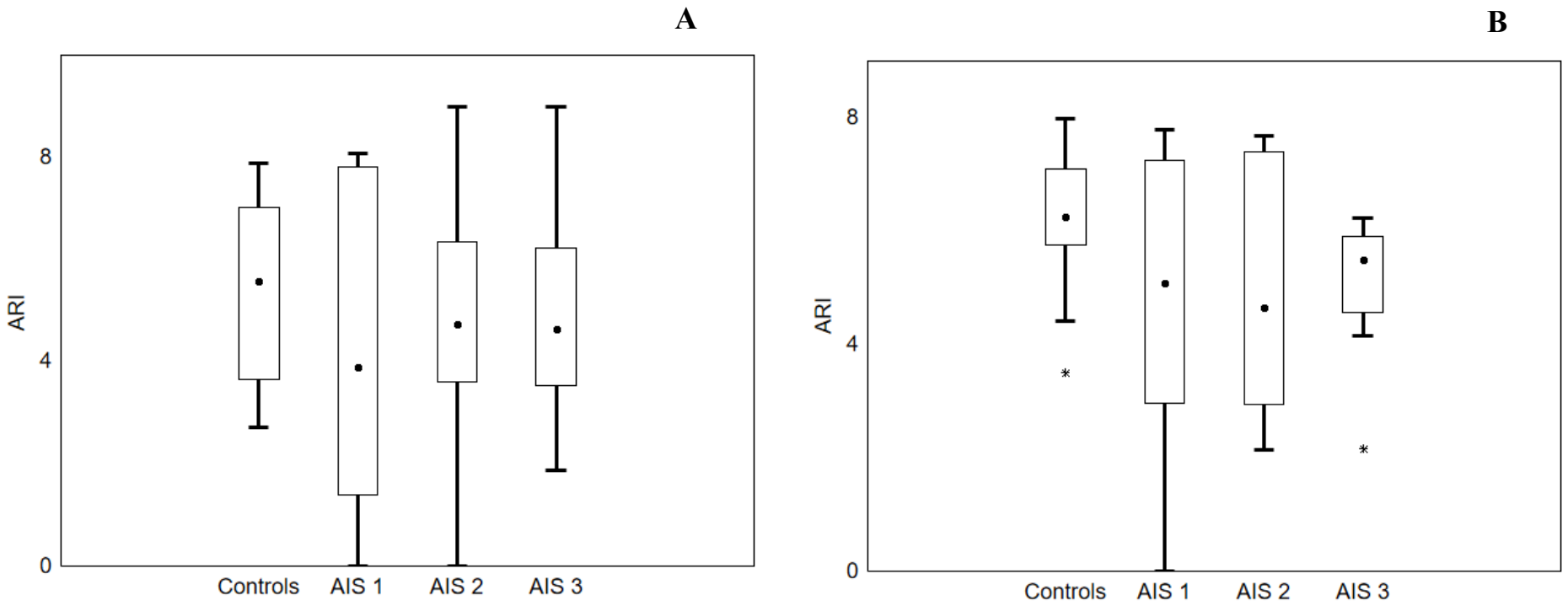



**Figure 7.12** Box plots showing the median, interquartile range, and maximum and minimum values of the rapid head positioning (RHP) recording in dominant and affected hemisphere ARI (A), non-dominant and non-affected hemisphere ARI (B) between controls and AIS participants. AIS 1, AIS Visit 1; AIS 2, AIS Visit 2; AIS 3, AIS Visit 3.

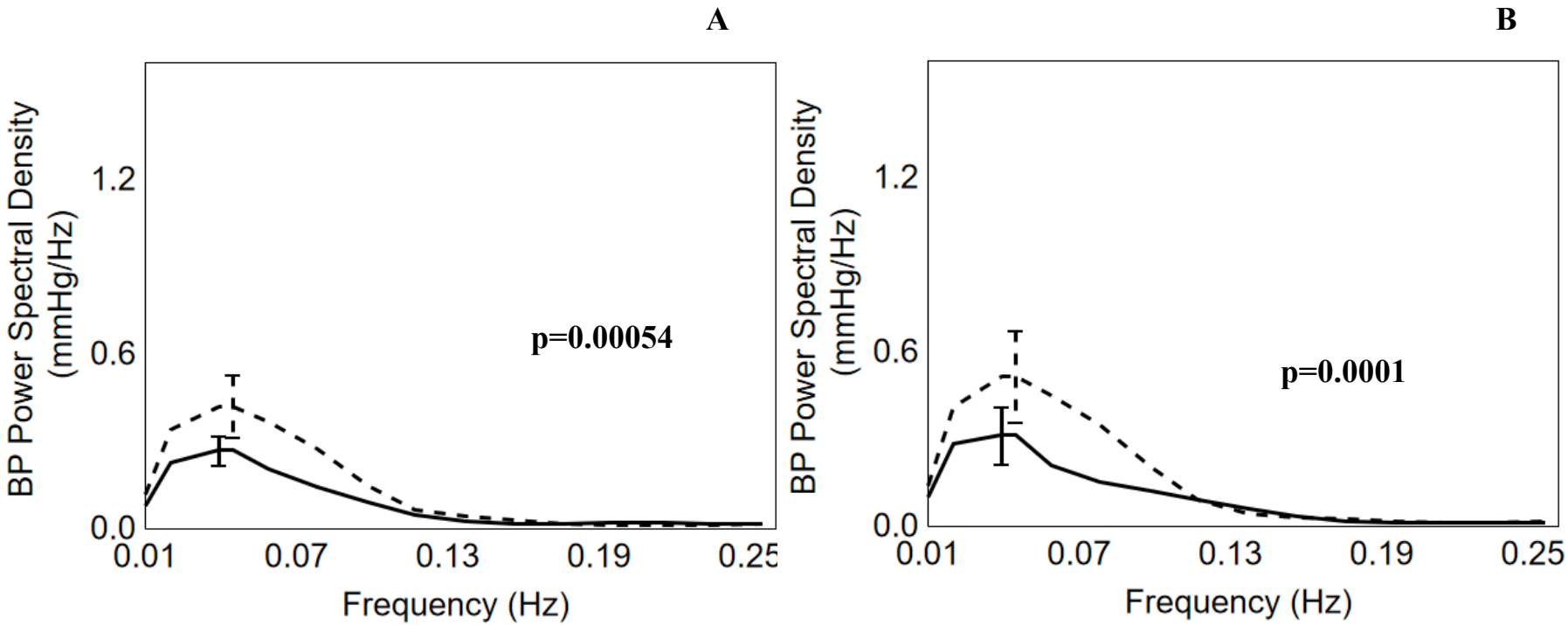
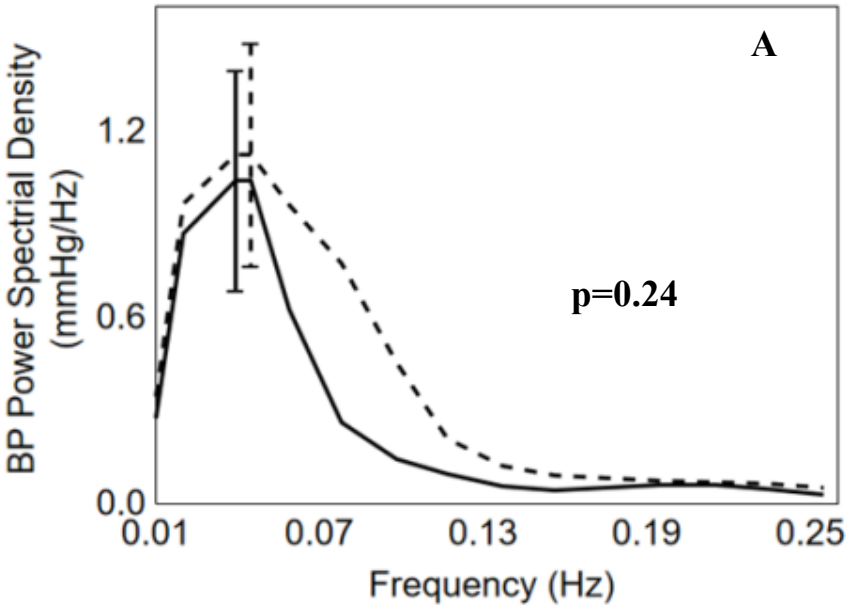
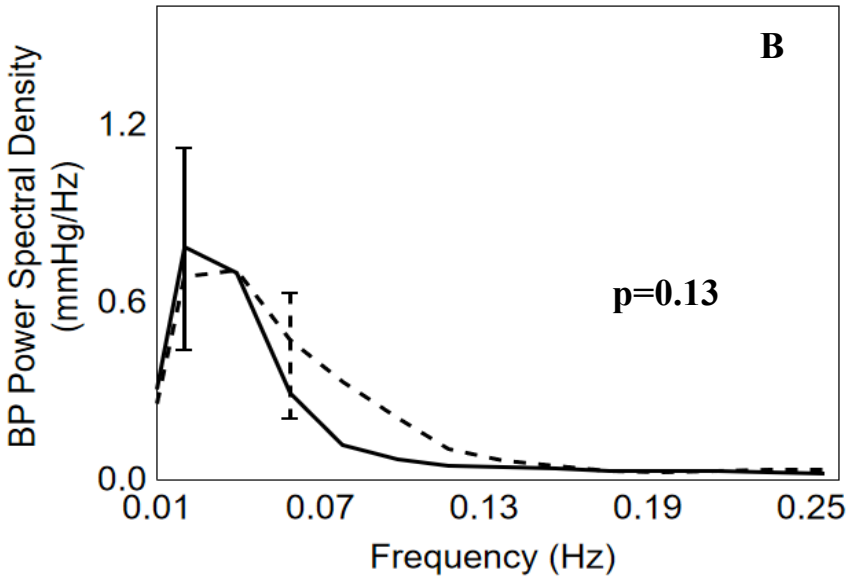



**Figure 7.13** BP variability expressed as spectral power in the 0.01 to 0.25 Hz frequency band. The baseline recording (continuous line) versus rapid head positioning (RHP) paradigm (dotted line) in control subjects is shown. Visit 1 (A), and Visit 2 (B) are shown. For clarity, only the largest ± 1 SE error bar is represented at the point of occurrence. P values correspond to Fisher's cumulative P calculation for the difference in spectral power between baseline and RHP recordings.


A
BP Power Spectral Density (mmHg/Hz)
1.2
0.6
0.0
0.01
0.07
0.13
0.19
0.25
Frequency (Hz)
p=0.24


B
BP Power Spectral Density (mmHg/Hz)
1.2
0.6
0.0
0.01
0.07
0.13
0.19
0.25
Frequency (Hz)
p=0.13

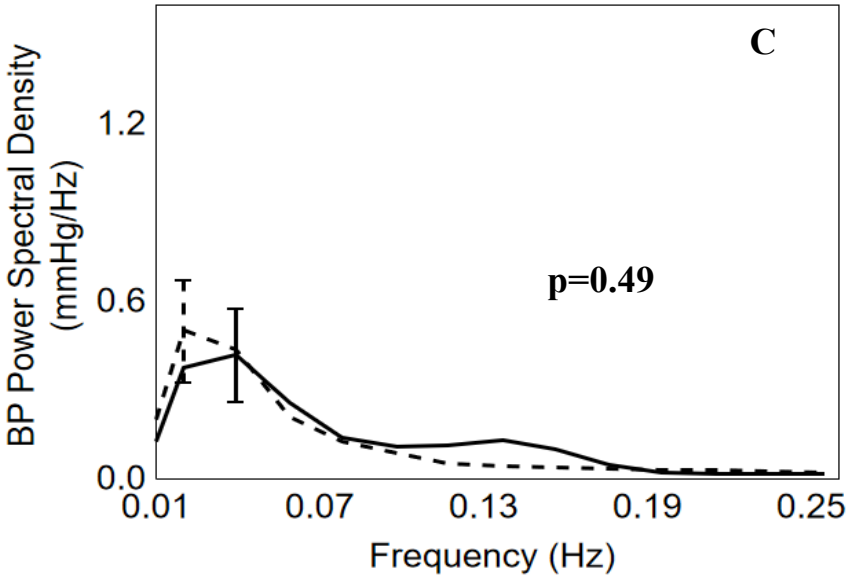

C
BP Power Spectral Density (mmHg/Hz)
1.2
0.6
0.0
0.01
0.07
0.13
0.19
0.25
Frequency (Hz)
p=0.49

**Figure 7.14** BP variability expressed as spectral power in the 0.01 to 0.25 Hz frequency band. The baseline recording (continuous line) versus rapid head positioning (RHP) paradigm (dotted line) in AIS participants is shown. Visit 1 (A), Visit 2 (B), and Visit 3 (C) are shown. For clarity, only the largest ± 1 SE error bar is represented at the point of occurrence. P values correspond to Fisher's cumulative P calculation for the difference in spectral power between baseline and RHP recordings.

## 7.4 Discussion

### 7.4.1 Main Findings

The author is not aware of any previous physiological or clinical studies in which RHP has been used to induce increases in BPV to overcome potential concerns about the limited SNR of spontaneous BP fluctuations, in which insufficient variability could lead to unreliable estimates of dCA (376).

Using repeated recordings in both control and AIS participants, this study investigated the three main hypotheses outlined above in this chapter. First, continuous measurements of BP and CBV are feasible during RHP, and such testing was well tolerated by both control subjects and patients with mild AIS. Second, RHP led to significant increases in BPV in control subjects but not in AIS patients, either acutely or at follow-up visits (Figures 7.13 and 7.14). This is a highly significant finding, likely to have impact well beyond the immediate objectives of this study as discussed below. Though control subjects were younger than AIS patients (Chapter 6, Table 6.1), the effect of RHP on BPV was still highly significant when only controls aged > 68 years old were included in the analysis. This result suggests that the lack of BPV increase from RHP in AIS patients cannot simply be explained by their older age compared to control subjects. Finally, RHP did not improve the discrimination between controls and AIS participants, based on the ARI. Contrary to our expectations, ARI did not show consistent differences between controls and AIS patients at rest, and this pattern persisted with RHP.

Similarly to Chapters 5 and 6, in the absence of other similar investigations, comparisons were made with related studies, such as changes in posture induced by HUT. A broad concordance with the temporal pattern of BP, HR, and $ETCO_2$ was observed during RHP (667, 668, 713). It is also interesting to observe that non-significant changes in either AH

or NAH CrCP in AIS patients in baseline and RHP recordings were seen at all visits, when compared to control subjects. However, when compare to controls, the increase in baseline AH and NAH RAP previously observed in AIS baseline recording was attenuated in the RHP paradigm. This is contrast to the results in Chapter 6 and the study previously carried out by Robertson et al.(685). As the present study was focused on AIS patients, the underlying pathophysiological mechanisms would be different when compared to the healthy ageing or an isolated hypertensive group. Furthermore, the effect of GHP and RHP and the duration of the measurement and subsequent analysis could also have an impact of the results, and therefore, it may not be sensible to carry out direct comparison between these two head positioning paradigms. However, it is certainly important to note that both CrCP and RAP were directly related to changes in BP and CBF; the underlying high BP and reduced CBV observed in AIS patients may influence the cerebrovascular response through altered central regulation, something that certainly warrants further investigation in future studies.

As mentioned in Chapter 5, Section 5.4.3, it is generally agreed that reduced ICP occurs when the head position is changed from the supine to sitting position, thereby avoiding hypertension-related reperfusion damage (714). Changes in other parameters, such as arterial $PaCO_2$ and BP, can also have significant impact on ICP and therefore, cerebral haemodynamics (715). Several studies have suggested that hydrostatic effects in the intra- and extracranial venous system, together with the ability of the internal jugular vein to collapse in response to upright posture, govern the variation of ICP in response to different body postures (714, 716). Previous literature has also proposed the vertebral plexus as an alternative venous outflow tract when the internal jugular vein is collapsed (715, 717). A systematic review and meta-analysis was carried out recently to look at the relationship between CA and ICP and found that there was a clear propensity of CA

impairment in TBI with increased ICP (718). It will be interesting to see whether similar observations occur in AIS patients who have disturbed CA. Although the investigation of the interaction between all these parameters when assessing CA in response to RHP changes is of merit, the feasibility of such assessments in most patient populations and healthy subjects may be considerably limited.

### 7.4.2 Physiological Methods to Increase BPV

As mentioned in Chapter 1, Section 1.3.4, posture changes, thigh cuff deflation , rhythmic hand grip , $CO_2$ inhalation, breath holding and hyperventilation (376) are some of the techniques that have been used to instigate greater BPV in dCA studies in AIS. However, such techniques may be difficult to perform in acute clinical settings (including HASU) and could add significant burden to patients who are medically unstable or cognitively impaired (AIS patients). Although only a small number of participants were recruited, a significant effort was made to include a variety of AIS patients with different subtypes, in particular, patients with POCS who often suffer dizziness and vertigo-like symptoms. Importantly, the percentage of recordings that needed to be rejected was similar to those studies reported in the literature using spontaneous BP fluctuations (375) and other physiological changes (719), thus suggesting that RHP is a feasible, robust technique that can be easily performed in acute medical settings.

### 7.4.3 Effect of RHP on BPV

It is generally agreed that reduced BP is observed when posture changes from supine to sitting up and vice versa (668). Therefore, the author postulated that by changing the head position frequently (RHP), this should result in a greater BPV than maintenance of a stationary posture (i.e., supine) at rest. In this chapter, the author demonstrated that RHP did result in a BPV increase when compared with baseline recordings in controls, but this

was not observed in AIS patients at any of the three visits. This observation could be explained by the pre-existing BPV already present in AIS patients (Figure 7.14) (159, 171), thus being insensitive to further stimulation. However, alternative explanations should also be discussed, considering that, at Visit 3, AIS patients had similar BPV to controls, but still failed to show increases attributable to RHP (Figure 7.14). Therefore, it is possible that other alterations resulting from IS are negating the potential effects of RHP in these patients, a finding that deserves further investigation. Although various dCA measurements, such as posture change (720) and thigh-cuff deflation (721), have demonstrated a greater BPV in healthy individuals, there is limited information regarding whether these techniques also exhibit greater BPV in disease settings, particularly in conditions that are known to already demonstrate significant BPV. Compared with healthy controls, Korpelainen et al. (722) demonstrated a significantly suppressed HR response to 90° HUT at acute (median: 7 days after stroke symptom onset), 1 month, and 6 months in AIS patients, although no significant change in the BP response was demonstrated. Zawadka-Kunikowska and colleagues (723) examined 17 patients with MCA AIS and showed significantly higher resting values of high frequency systolic BPV. They have also reported a significantly lower increase in post-tilt changes in SBP and in total peripheral vascular resistance when compared with controls. Therefore, an assertion that a paradigm may enhance BPV should only be made when it can be successfully demonstrated in both healthy and disease settings (376).

### 7.4.4 Use of BPV to assess CA

Although the underlying pathophysiological mechanisms responsible for increased BPV following AIS are not fully understood, it is generally agreed that beat-to-beat BPV is a composite measure of multiple physiological processes. Various suggestions have been identified to explain BPV after AIS, including location, infarct volume (724), presence of

proximal occlusion, extension of collaterals (725), carotid artery intima-media thickness (726), impaired baroreceptor sensitivity (168, 727) and vasomotor activity (728) leading to autonomic nervous system impairment, arterial stiffness (729), inflammation (730) and/or endothelial dysfunction (731). An extensive literature has demonstrated high BPV at hyperacute, acute, and subacute stages (up to 10 days of symptom onset) of AIS (159, 171), although information regarding BPV at more chronic stages in AIS (e.g., up to 3 months of IS symptom onset) is sparse. The literature supports this study chapter hypothesis that profound BPV is already demonstrated in AIS and could explain why RHP is therefore not able to increase BPV further in this population. Should this be the case, the author can possibly argue that other manoeuvres would also be unlikely to induce further increased BPV, ultimately suggesting that, in conditions that are known to have significant BPV, spontaneous BP fluctuation measurement could already produce a satisfactory BP SNR for dCA assessment.

ROC has been used to assess dCA in a wide variety of clinical settings. Previous studies have demonstrated that a ROC curve for ARI predicts TBI mortality (732) and secondary complications (708). In addition, Castro and colleagues (432) demonstrated that ROC curves of ARI in early IS could predict infarct volume and neurological recovery. The results in this study chapter are in contrast to Katsogridakis et al. (721), who demonstrated that increased BPV could improve CA impairment detection using ROC curves. This latter study was carried out in healthy controls and used random compressions and release of thigh cuffs to induce BPV, using hypercapnia as a surrogate of depressed dCA. The elevated BPV observed in AIS could be due to different underlying pathophysiological mechanisms, which could account for differences between studies. The non-significant differences demonstrated between AIS and controls at baseline in this study, precluded the potential of RHP to improve detection of dCA impairment. On the other hand, if ARI

differences between two groups were enhanced by RHP, this would point towards the potential clinical usefulness in such technique. However, it is important to note that non-significant ARI differences were observed between controls and AIS at baseline reading. This might suggest that AIS patients with a mild stroke (as evidenced by low median NIHSS), would not exhibit differences in any circumstances, and any worsening of dCA during RHP could be regarded as false-positives. Future studies should consider with participants whose ARI is significantly impaired when compared to controls, and observe whether RHP could enhance the detection of dCA impairment in such a cohort. It is also important to consider other disease populations (e.g. TBI) that are not known to have increased BPV to assess their responsiveness to RHP and whether this would improve sensitivity and specificity of dCA indices to detect disturbances in dCA.

### 7.4.5 Study Limitations

Apart from the study limitations already mentioned in Chapters 5 and 6, there are a number of limitations specifically applicable here. Firstly, the literature suggests that BPV could be an important prognostic factor of AIS; specifically greater systolic BPV, measured during the acute phase of the IS, is associated with a poorer functional outcome (159, 171). The initial hypothesis of this study was that RHP could enhance BPV in AIS, and therefore, there is a concern that this could present a potential risk to these patients. However, the measurement was only carried out for a short period of time (5 min), and no significant increase in BPV was demonstrated in AIS with RHP. Secondly, an alternative study design could be a 5-min resting (baseline) period immediately followed by the intervention (RHP). Instead, a separate 5-min lying flat recording, to outline the baseline physiology was carried out first, thereafter, a 2-min resting period followed by the RHP paradigm and then a further 2-min resting period, which gave an opportunity to recalibrate the Finometer® MIDI device (Physiocal) and thus minimising the risk of BP

drift and data rejection as a result. Finally, the use of TFA has assumed stationarity, both at baseline and during RHP. It may be beneficial to use an analytic model that could provide time-varying estimates of dCA to establish whether there are time-related changes and whether differences between controls and AIS patients are apparent over time.

## 7.5 Conclusions

This study chapter used RHP to enhance BPV to improve BP SNR and reliability of dCA. This small, pilot study provided evidence that RHP is a safe and practical technique to increase BPV; the author believes that it required minimal participant co-operation and was well accepted by both healthy individuals and AIS patients. RHP demonstrated increased BPV in controls but not in AIS patients, and this is likely because BPV at rest in AIS was already elevated; an important observation that warrants further investigation, as it could broaden our understanding of BP control in AIS. In the author's opinion, RHP could be considered a feasible alternative for assessing dCA, mainly in conditions of very reduced BPV as would be the case of patients under medications, such as anti-epileptics and certain classes of antihypertensives (e.g. calcium channel blocker) that are known to reduce BPV, or in conditions where BPV is compromised by autonomic nervous system disturbance (e.g. Parkinson's disease).

# Chapter 8: Cerebral Haemodynamic in Stroke Thrombolysis (CHiST) Study

Compared to pressor therapy, IVT is a widely used pharmacology reperfusion strategy which could rapidly restore CBF to ischaemic, but potentially, viable tissue, the so called penumbra. However, despite careful patient selection, successful recanalisation in IVT is only achieved in approximately 50% of cases. Understanding changes in dCA, during and following successful recanalisation in AIS patients who receive IVT, may inform the management of common physiological perturbations, including blood pressure, in turn reducing the risk of reperfusion injury, and therefore improvement in the functional outcome. This study chapter will focus on assessing CA and haemodynamic parameters changes in those AIS patients who received IVT.

## 8.1 Introduction

IVT is approved for medical reperfusion therapy in AIS, within 4.5 hours of stroke symptom onset (130, 733). Despite significant recent increases in thrombolysis rates (734, 735), improvement in selecting eligible participants, and availability of expertise and associated technologies, successful recanalisation of occluded intracranial arteries with IVT is achieved in only approximately 50% of AIS patients (513). Studies have suggested that without careful patient selection, angiographic recanalisation may not be associated with meaningful improvements in clinical outcomes (736, 737). Importantly, thrombolysis is associated with risk of reperfusion injury, such as post-ischaemic oedema and/or sICH.

Age, degree of initial neurological deficit, timing of reperfusion therapy, size of baseline infarct, location of occlusion, and presence of persistent or re-occlusion and haemorrhagic

transformation (738-740) are some of the factors which could predict the chance of success in recanalisation, and therefore, stroke outcome. Limited evidence is available on systemic arterial BP, an important factor which has significant impact on the penumbral lesion size, and its association with neurological recovery. Moreover, little information is available on whether optimal personalised BP could be one of the strategies to reduce complications of reperfusion, and therefore improve clinical outcome. SBP has been demonstrated as an important predictor of sICH (741) and the recently published Enhanced Control of Hypertension and Thrombolysis Stroke (ENCHANTED) trial reported that intensive BP lowering was associated with reduced rates of any ICH but without benefit on 90-day functional outcomes (554). Impairment in CA, in association with increases in BPV, means that large fluctuations in BP may lead to changes in CBF outside the CA plateau capacity and result in hyperaemic or ischaemic injury (2, 169). As mentioned in previous chapters, although extensive literature suggests CA impairment is observed during various stages of the disease (353, 373, 435), there is limited knowledge regarding the natural history and prognostic significance of impaired CA in patients who receive IVT treatment, and few studies have investigated the temporal relationship of CA during and immediately after IVT treatment in AIS patients. Therefore, the aim of this study was to investigate the feasibility of assessing CA, and associated systemic and cerebral haemodynamic parameters, in AIS patients during and immediately after IVT, and for up to 3 months of AIS symptom onset, so providing evidence to inform individualised BP management decisions in the future.

## 8.2 Methods

### 8.2.1 Research Participants

The study was carried out in accordance with the Declaration of Helsinki (2000) and was approved by the Nottingham Research Ethics Committee 1, UK (Reference: 15/EM/0485). Clinical Trial.gov unique identifier number: NCT 02928926.

Fifteen AIS patients were recruited from UHL, Leicester, UK. AIS patients were transferred by Rapid Ambulance Protocol to a dedicated HASU. Patients who met the criteria for thrombolytic therapy with IVT (335) were invited to participate in the study. AIS patients who were deemed not eligible for IVT, had premorbid mRS (693) greater than 3, or co-morbidity with anticipated life expectancy less than 3 months, or currently participating in another investigational drug trial, were excluded from the study.

As for the research participants from Chapter 6 and 7, clinical stroke subtype, stroke severity, and pre-morbid functional dependence were assessed using the OCSP classification (69), NIHSS (694), and mRS, respectively. Participants' handedness was determined by the Edinburgh Inventory (663). All routine aspects of the management of AIS patients with respect to investigation, hyperacute and acute management, and rehabilitation were continued according to both national and local hospital guidelines (742). Non-contrast CT imaging was carried out pre- and 24 hours post-IVT treatment. BP measurements according to the standard thrombolysis protocol, were recorded throughout the immediate 24-hour period following the initiation of IVT therapy, i.e. every 15 minutes for 2 hours, then every 30 minutes for 6 hours, and subsequently hourly for 16 hours. All AIS patients received pharmacological treatment, including antithrombotic, anticoagulant, antihypertensive and statin therapy according to local hospital protocols.

All participants or personal consultees provided informed consent in writing, and were aware of the right to withdraw from the study at any point in time without prejudice.

### 8.2.2 Measurements

Recordings were performed as described in Chapter 4, Section 4.4. Efforts were made to ensure all AIS assessments were carried out at a similar time of day at all visits. The study was carried out either in the HASU (Visit 1.1 – 1.4) or dedicated research laboratory (Visit 2 onwards), which was at a controlled temperature (20-24°C) with minimal external distraction. All participants were in the lying flat (0°) head position.

Once the MCAs had been identified and the ultrasound probes were secured in place, four 5-min measurements were recorded during (Visit 1.1 and 1.2), immediately prior to completion (Visit 1.3), and immediately after the completion (Visit 1.4) of IVT. Subsequent assessments were undertaken at approximately 24 hours (Visit 2, acute), 2 weeks (Visit 3, sub-acute) and 3 months (Visit 4, chronic) post stroke symptom onset.

### 8.2.3 Data Analysis

Data analysis was performed as described in Chapter 4, Section 4.5. As described in Chapter 5, section 5.2.3, TFA was adopted with parameter settings recommended by the CARNet (357) to estimate the CBV response to a hypothetical step change in BP. Each of the 10 template CBV step responses proposed by Tiecks et al. (356) was compared with the estimated CBV step response and the ARI value corresponding to the best fit, assessed by the minimum mean square error, was adopted for each of the 5-min recordings. In addition, estimates of coherence, phase, and gain were averaged for the VLF (0.02 – 0.07 Hz), LF (0.07 – 0.20 Hz), and HF (0.20 – 0.50 Hz) ranges (357).

#### 8.2.4 Statistical Analysis

Data were assessed for normality using the Shapiro-Wilk test. All normality distributed data are presented as mean ± SD, and continuous skewed data as median [interquartile range]. Mean values of haemodynamic parameters were calculated from each of the 5-min recordings. Two-way repeated measures ANOVA was undertaken to assess the effects of time (Intra-visit: Visit 1.1 to 1.4 and Inter-visit: Visit 1.4 to 4) and AH vs. NAH. The Tukey post hoc test was used to perform individual comparisons when ANOVA showed significant effects. A significance level of $p<0.05$ was adopted for all results.

As for Chapters 5, 6, and 7, a formal sample size calculation was not possible for the study. We adapted Brodie and colleagues' approach (375) in which a sample of 11 AIS patients will allow the detection of a difference in the ARI of 2 units with 80% power at the 5% significance level.

All statistical analyses were performed using TIBCO Statistica, version 13.0 (Statistica, Dell).

## 8.3 Results

#### 8.3.1 Baseline Data

Fifteen participants (7 female) were recruited, though suitable transtemporal windows could not be found in four participants (2 female) who were removed from the study. Therefore, a total of 11 AIS patients of mean age 68 years (range 42 to 80) were included in the analysis and completed the hyperacute, acute, sub-acute, and chronic visits at 132 ± 38 mins, 23.9 ± 2.6 hrs, 18.1 ± 7.0 days, and 89.6 ± 4.2 days after stroke onset, respectively. According to the OCSP classification, there were three total and six partial anterior circulation, one posterior circulation, and one lacunar stroke. None of the patients

were stroke mimics. According to the Edinburgh Handedness inventory (663), 10 participants were right-handed and one participant was left-handed. Mean baseline NIHSS and median pre-admission mRS scores at the first visit were 8.2 ± 3.8 and 0 [0-1], respectively. No patients underwent MT or received antihypertensive medication during IVT. Participant characteristics are further summarised in Table 8.1.

| | |
|---|---|
| **Participants (n)** | **11** |
| **Age (years)** | **68.0 ± 11.6** |
| **Sex (female), n (%)** | **5 (45.4)** |
| **Handedness (right), n (%)** | **10 (90.9)** |
| **Body mass index (BMI) $kg.m^{-2}$** | **27.1 ± 4.5** |
| **Smoker, n (%)** | |
| **Yes** | **2 (18.2)** |
| **Ex** | **4 (36.4)** |
| **Never** | **5 (45.5)** |
| **Past medical history, n (%)** | |
| **Hypertension** | **4 (36.4)** |
| **Hypercholesterolaemia** | **2 (18.2)** |
| **Diabetes** | **2 (18.2)** |
| **Ischaemic Heart Disease** | **2 (18.2)** |
| **Ipsilateral ICA stenosis, n (%)** | **1 (9.1)** |
| **Bilateral ICA stenosis, n (%)** | **1 (9.1)** |
| **NIHSS admission** | **8.2 ± 3.8** |
| **Post thrombolysis** | **5.2 ± 3.9** |
| **Visit 2** | **3.0 ± 2.9** |
| **Visit 3** | **0 [0-2]** |
| **Visit 4** | **1 [0-4]** |
| **mRS pre admission** | **0 [0-1]** |
| **Visit 2** | **1 [1-2]** |
| **Visit 3** | **1 [0-1]** |
| **Visit 4** | **2 [1-2]** |

**Table 8.1** Demographic characteristics of AIS participants receiving IVT.

Data are mean (SD), median [IQR], or n (%). AIS, acute ischaemic stroke; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale, mRS, modified Rankin score.

### 8.3.2 Temporal Pattern of Systemic Haemodynamic and $ETCO_2$ Responses

Systemic haemodynamic and other parameters averaged over 5-min are given in Table 8.2 for each visit. MAP decreased over four visits (Visit 1.1: 110.7 ± 16.3 to Visit 4: 94.0 ± 9.4 mmHg), although significant reduction was only observed during IVT (p=0.044, Table 8.2 and Figure 8.1A). Significant reduction in HR was observed post IVT (Visit 1.4: 81.2 ± 15.7 to Visit 4: 62.8 ± 14.9 bpm; p<0.005; Table 8.2 and Figure 8.1B). Hypocapnia was observed during the hyperacute phase of AIS and $ETCO_2$ did not show significant changes during or immediately after IVT infusion, or within the first 24 hours of stroke onset. However, significant increments were observed in subsequent visits (Visit 3: 35.5 ± 2.5 and Visit 4: 36.5 ± 1.7 mmHg; p=0.028; Table 8.2 and Figure 8.1C).

### 8.3.3 Temporal Pattern of Cerebral Haemodynamic Responses

Cerebral haemodynamic parameters averaged over 5-min are also given in Table 8.2 for each visit. CBV did not change across four visits, and there were no differences between hemispheres either (Table 8.2, Figure 8.2A). Though NAH CBV was numerically higher, compared to AH CBV across all four visits, differences did not reach statistical significance (Table 8.2 and Figure 8.2A). There were no significant changes with respect to AH CBV values during and immediately after IVT or across subsequent visits (Table 8.2 and Figure 8.2A). There were also no changes with respect to NAH CBV values during and immediately after IVT or across subsequent visits (Table 8.2 and Figure 8.2A). A non-significant rise in CrCP was demonstrated in both the AH and NAH, immediately after the completion of IVT, followed by a significant reduction over subsequent visits (AH Visit 1.4: 55.2 ± 12.9 to Visit 4: 43.3 ± 8.3 mmHg; p=0.02 and NAH Visit 1.4: 60.1 ± 12.6 to Visit 4: 40.9 ± 8.6 mmHg; p<0.05, Table 8.2, Figure 8.2B). No differences between hemispheric values were observed across all four visits. RAP did not change

across four visits, and there were no differences between hemispheres (Table 8.2, Figure 8.2C).

### 8.3.4 Temporal Pattern of Coherence, Gain, and Phase Responses

Averaged 5-min assessment values of coherence, gain, and phase at different frequency intervals (VLF, LF, and HF) are given in Tables 8.3, 8.4 and 8.5, respectively. There were no differences in overall temporal pattern for coherence and gain across all four visits, in VLF (Coherence: Figure 8.3A and Gain: Figure 8.4A), LF (Coherence: Figure 8.3B and Gain: Figure 8.4B) and HF (Coherence: Figure 8.3C and Gain: Figure 8.4C), nor were there any inter-hemispheric differences (Tables 8.3, 8.4, and 8.5; Figures 8.3 and 8.4). However, a reduction in phase (AH) at LF occurred during IVT (Visit 1.1: 0.89 ± 0.42 to Visit 1.4: 0.63 ± 0.26 radians; p=0.021), such reduction continued post IVT, and was followed by an increment at 3 months post stroke symptom onset (Visit 4: 0.70 ± 0.31 radians; p=0.048) (Table 8.5 and Figure 8.5B).

### 8.3.5 Temporal Pattern of ARI Responses

Overall, there were no changes in ARI values during IVT, across all visits, nor between AH and NAH (Table 8.6 and Figure 8.6).

Figure 8.7 shows individual AIS patients' ARI at each visit. There was no obvious trend demonstrated in terms of ARI values between AH (Figure 8.7A) and NAH (Figure 8.7B) across all visits.

### 8.3.6 Subgroup Analysis

Of the 11 AIS participants, two participants had negative CT imaging 24 hours post IVT treatment. Despite the low sensitivity of the CT imaging in detecting small ischaemic infarcts, we performed a subgroup analysis with removal of these two participants (n=9).

The only significant difference observed, in comparison with the entire group, was that the reduction in phase (AH at LF) during IVT became non-significant (p=0.33). There were no differences in terms of other systemic and cerebral haemodynamic parameters during, immediately after IVT, and up to 90 days post stroke symptom onset.

| Parameters | Visit 1.1 n = 11 | Visit 1.2 n = 11 | Visit 1.3 n = 10 | Visit 1.4 n = 11 | Visit 2 n = 11 | Visit 3 n = 8 | Visit 4 n = 7 | P value (Intra-visit effect Visit 1.1-1.4) | P value (Inter-visit effect Visit 1.4-4) | P value (Hemispheric effect, Visit 1.1-1.4) | P value (Hemispheric effect, Visit 1.4-4) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BP (mmHg) | 110.7±16.3 | 103.7±15.6 | 101.1±17.1* | 102.6±16.3 | 99.1±8.3 | 97.3±7.0 | 94.0±9.4 | **0.044** | 0.13 | NA | NA |
| Heart Rate (bpm) | 78.2±14.9 | 78.8±15.5 | 79.2±15.5 | 81.2±15.7 | 72.4±15.5† | 66.6±17.1† | 62.8±14.9†‡ | 0.12 | **<0.005** | NA | NA |
| End-Tidal $CO_2$ (mmHg) | 31.9±3.9 | 32.7±4.4 | 31.2±4.9 | 31.4±4.9 | 32.6±4.3 | 35.5±2.5 | 36.5±1.7† | 0.39 | **0.028** | NA | NA |
| CBV AH ($cm.s^{-1}$) | 35.5±10.9 | 35.9±9.7 | 36.5±9.1 | 35.3±7.1 | 37.9±7.0 | 35.6± 8.9 | 39.9±9.4 | 0.99 | 0.29 | 0.58 | 0.089 |
| CBV NAH ($cm.s^{-1}$) | 41.1±13.1 | 38.6±11.6 | 37.9±11.4 | 38.7±11.6 | 41.2±13.2 | 42.1±7.4 | 43.2±8.4 | 0.15 | 0.64 | | |
| CrCP AH (mmHg) | 53.0±18.6 | 52.9±11.4 | 52.3±12.8 | 55.2±12.9 | 48.0±10.9 | 45.1±10.9 | 43.3±8.3† | 0.69 | **0.02** | 0.24 | 0.08 |
| CrCP NAH (mmHg) | 54.8±15.1 | 49.1±8.8 | 51.5±4.5 | 60.1±12.6 | 48.2±10.0† | 45.0±6.9† | 40.9±8.6† | 0.12 | **<0.005** | | |
| RAP AH ($mmHg.s.cm^{-1}$) | 1.50±0.71 | 1.37±0.64 | 1.30±0.53 | 1.32±0.46 | 1.25±0.43 | 1.55±0.58 | 1.35±0.61 | 0.27 | 0.38 | 0.26 | 0.29 |
| RAP NAH ($mmHg.s.cm^{-1}$) | 1.56±0.75 | 1.34±0.47 | 1.35±0.44 | 1.31±0.41 | 1.30±0.50 | 1.29±0.29 | 1.20±0.31 | 0.40 | 0.92 | | |

**Table 8.2** Systemic and cerebral haemodynamic parameters in AIS participants receiving IVT.

Data are mean ± SD. P-values from two-way ANOVA for effects of during and immediately post-IVT (Intra-visit: Visit 1.1 to Visit 1.4) and subsequent visits (Inter-visit: Visit 1.4 to Visit 4) (Visit effect) and for the effects of hemisphere (AH vs. NAH). AIS, acute ischaemic stroke; BP, blood pressure; bpm, beats per minutes; CBV, cerebral blood velocity; CrCP, critical closing pressure; RAP, resistance area product; AH, affected hemisphere; IVT, intravenous thrombolysis NAH, non-affected hemisphere. Visit 1.1 and Visit 1.2 refer to during IVT, Visit 1.3 refers to immediately prior to end of IVT, and Visit 1.4 refers to immediately after the end of IVT. Visit 2, Visit 3 and Visit 4 refer to approximately 24 hours, 2 weeks, and 3 months post stroke symptom onset, respectively. * Tukey post hoc compared to Visit 1.1, † Tukey post hoc compared to Visit 1.4 and ‡ Tukey post hoc compared to Visit 2, all $p < 0.05$

| Parameters | Visit 1.1 n = 11 | Visit 1.2 n = 11 | Visit 1.3 n = 10 | Visit 1.4 n = 11 | Visit 2 n = 11 | Visit 3 n = 8 | Visit 4 n = 7 | P value (Intra-visit effect, Visit 1.1-1.4) | P value (Inter-visit effect, Visit 1.4-4) | P value (Hemispheric value, Visit 1.1-1.4) | P value (Hemispheric value, Visit 1.4-4) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Coherence VLF, AH | 0.46±0.13 | 0.33±0.21 | 0.48±0.14 | 0.37±0.16 | 0.51±0.21 | 0.51±0.21 | 0.61±0.12 | 0.18 | 0.065 | 0.17 | 0.47 |
| Coherence VLF, NAH | 0.45±0.16 | 0.42±0.17 | 0.36±0.17 | 0.38±0.16 | 0.50±0.15 | 0.43±0.21 | 0.60±0.13 | 0.41 | 0.057 | | |
| Coherence LF, AH | 0.47±0.20 | 0.40±0.21 | 0.45±0.25 | 0.46±0.17 | 0.50±0.23 | 0.54±0.26 | 0.63±0.27 | 0.80 | 0.057 | 0.82 | 0.17 |
| Coherence LF, NAH | 0.58±0.20 | 0.51±0.28 | 0.57±0.19 | 0.56±0.19 | 0.56±0.22 | 0.67±0.20 | 0.69±0.27 | 0.93 | 0.15 | | |
| Coherence HF, AH | 0.52±0.19 | 0.49±0.26 | 0.56±0.28 | 0.52±0.15 | 0.63±0.22 | 0.60±0.25 | 0.66±0.27 | 0.65 | 0.43 | 0.91 | 0.23 |
| Coherence HF, NAH | 0.57±0.27 | 0.56±0.25 | 0.61±0.26 | 0.60±0.24 | 0.71±0.18 | 0.70±0.22 | 0.75±0.27 | 0.90 | 0.40 | | |

**Table 8.3** Coherence in various frequencies (VLF, LF, HF) in AIS participants receiving IVT.

Data are mean ± SD. P-values from two-way ANOVA for effects of during and immediately post-IVT (Intra-visit: Visit 1.1 to Visit 1.4) and subsequent visits (Inter-visit: Visit 1.4 to Visit 4) (Visit effect) and for the effects of hemisphere (AH vs. NAH). AH, affected hemisphere; AIS, acute ischaemic stroke; HF, high frequency; IVT, intravenous thrombolysis; LF, low frequency; NAH, non-affected hemisphere; VLF, very low frequency. Visit 1.1 and Visit 1.2 refer to during IVT, Visit 1.3 refers to immediately prior to end of IVT, and Visit 1.4 refers to immediately after the end of IVT. Visit 2, Visit 3, and Visit 4 refer to approximately 24 hours, 2 weeks, and 3 months post stroke symptom onset, respectively.

| Parameters | Visit 1.1 n = 11 | Visit 1.2 n = 11 | Visit 1.3 n = 10 | Visit 1.4 n = 11 | Visit 2 n = 11 | Visit 3 n = 8 | Visit 4 n = 7 | P value (Intra-visit effect, Visit 1.1-1.4) | P value (Inter-visit effect, Visit 1.4-4) | P value (Hemispheric effect, Visit 1.1-1.4) | P value (Hemispheric effect, Visit 1.4-4) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gain VLF, AH (cm $s^{-1}$ $mmHg^{-1}$) | 0.40±0.22 | 0.53±0.36 | 0.52±0.31 | 0.51±0.35 | 0.65±0.44 | 0.76±0.52 | 0.68±0.46 | 0.34 | 0.11 | 0.29 | 0.29 |
| Gain VLF, NAH (cm $s^{-1}$ $mmHg^{-1}$) | 0.56±0.23 | 0.51±0.30 | 0.55±0.33 | 0.79±0.39 | 0.53±0.20 | 0.64±0.34 | 0.66±0.38 | 0.73 | 0.41 | | |
| Gain LF, AH (cm $s^{-1}$ $mmHg^{-1}$) | 0.53±0.33 | 0.67±0.62 | 0.78±0.67 | 0.73±0.52 | 0.82±0.45 | 0.81±0.52 | 0.92±0.56 | 0.28 | 0.24 | 0.49 | 0.13 |
| Gain LF, NAH (cm $s^{-1}$ $mmHg^{-1}$) | 0.73±0.42 | 0.66±0.32 | 0.77±0.32 | 0.81±0.38 | 0.76±0.26 | 0.73±0.22 | 0.82±0.22 | 0.54 | 0.89 | | |
| Gain HF, AH (cm $s^{-1}$ $mmHg^{-1}$) | 0.66±0.35 | 0.90±0.73 | 0.94±0.47 | 1.04±0.82 | 0.99±0.37 | 0.85±0.37 | 0.99±0.49 | 0.13 | 0.54 | 0.46 | 0.70 |
| Gain HF, NAH (cm $s^{-1}$ $mmHg^{-1}$) | 0.82±0.54 | 0.83±0.50 | 1.00±0.56 | 0.85±0.26 | 0.85±0.45 | 1.04±0.31 | 1.07±0.43 | 0.69 | 0.40 | | |

**Table 8.4** Gain in various frequencies (VLF, LF, HF) in AIS participants receiving IVT.

Data are mean ± SD. P-values from two-way ANOVA for effects of during and immediately post-IVT (Intra-visit: Visit 1.1 to Visit 1.4) and subsequent visit (Inter-visit: Visit 1.4 to Visit 4) (Visit effect) and for the effects of hemisphere (AH vs. NAH). AH, affected hemisphere; AIS, acute ischaemic stroke; HF, high frequency; IVT, intravenous thrombolysis; LF, low frequency; NAH, non-affected hemisphere; VLF, very low frequency. Visit 1.1 and Visit 1.2 refer to during IVT, Visit 1.3 refers to immediately prior to end of IVT, and Visit 1.4 refers to immediately after the end of IVT. Visit 2, Visit 3, and Visit 4 refer to approximately 24 hours, 2 weeks, and 3 months post stroke symptom onset, respectively.

| Parameters | Visit 1.1 n=11 | Visit 1.2 n=11 | Visit 1.3 n=10 | Visit 1.4 n=11 | Visit 2 n=11 | Visit 3 n=8 | Visit 4 n=7 | P value (Intra-visit effect, Visit 1.1-1.4) | P value (Inter-visit effect, Visit 1.4-4) | P value (Hemispheric effect, Visit 1.1-1.4) | P value (Hemispheric effect, Visit 1.4-4) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Phase VLF, AH (Radians) | 0.69±0.43 | 0.50±0.29 | 0.49±0.33 | 0.48±0.41 | 0.59±0.38 | 0.77±0.40 | 0.79±0.34 | 0.53 | 0.18 | 0.53 | 0.81 |
| Phase VLF, NAH (Radians) | 0.83±0.34 | 0.70±0.22 | 0.81±0.27 | 0.71±0.32 | 0.74±0.42 | 0.83±0.38 | 0.76±0.24 | 0.70 | 0.85 | | |
| Phase LF, AH (Radians) | 0.89±0.42 | 0.60±0.42* | 0.65±0.40 | 0.63±0.26* | 0.54±0.22 | 0.44±0.28 | 0.70±0.31§ | **0.021** | **0.048** | 0.24 | 0.87 |
| Phase LF, NAH (Radians) | 0.72±0.21 | 0.68±0.36 | 0.68±0.27 | 0.72±0.40 | 0.51±0.11 | 0.46±0.22 | 0.44±0.21 | 0.97 | 0.065 | | |
| Phase HF, AH (Radians) | 0.047±0.26 | -0.061±0.23 | 0.051±0.21 | 0.086±0.18 | 0.045±0.086 | 0.088±0.14 | 0.047±0.15 | 0.38 | 0.80 | 0.52 | 0.58 |
| Phase HF, NAH (Radians) | 0.012±0.11 | -0.031±0.20 | -0.074±0.22 | 0.094±0.13 | 0.069±0.088 | 0.066±0.062 | 0.11±0.18 | 0.10 | 0.81 | | |

**Table 8.5** Phase in various frequencies (VLF, LF, HF) in AIS participants receiving IVT.

Data are mean ± SD. P-values from two-way ANOVA for effects of during and immediately post-IVT (Intra-visit: Visit 1.1 to Visit 1.4) and subsequent visit (Inter-visit: Visit 1.4 to Visit 4) (Visit effect) and for the effects of hemisphere (AH vs. NAH). AH, affected hemisphere; AIS, acute ischaemic stroke; HF, high frequency; IVT, intravenous thrombolysis; LF, low frequency; NAH, non-affected hemisphere; VLF, very low frequency. Visit 1.1 and Visit 1.2 refer to during IVT, Visit 1.3 refers to immediately prior to end of IVT, and Visit 1.4 refers to immediately after the end of IVT. Visit 2, Visit 3, and Visit 4 refer to approximately 24 hours, 2 weeks, and 3 months post stroke symptom onset, respectively. * Tukey post hoc compared to Visit 1.1, § Tukey post hoc compared to Visit 3, all $p < 0.05$.

| Parameters | Visit 1.1 | Visit 1.2 | Visit 1.3 | Visit 1.4 | Visit 2 | Visit 3 | Visit 4 | P value (Intra-visit effect, Visit 1.1-1.4) | P value (Inter-visit effect, Visit 1.4-4) | P value (Hemispheric effect, Visit 1.1-1.4) | P value (Hemispheric effect, Visit 1.4-4) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ARI, AH | 5.45±2.65 | 5.10±3.15 | 4.23±2.65 | 4.88±1.69 | 4.91±1.79 | 4.95±1.36 | 4.96±1.46 | 0.99 | 0.89 | 0.17 | 0.68 |
| ARI, NAH | 5.71±1.64 | 5.19±2.48 | 6.16±1.63 | 5.72±1.87 | 5.22±1.26 | 5.34±1.01 | 5.23±1.79 | 0.59 | 0.30 | | |

**Table 8.6** ARI in AIS participants receiving IVT.

Data are mean ± SD. P-values from two-way ANOVA for effects of during and immediately post-IVT (Intra-visit: Visit 1.1 to Visit 1.4) and subsequent visit (Inter-visit: Visit 1.4 to Visit 4) (Visit effect) and for the effects of hemisphere (AH vs. NAH). AH, affected hemisphere; AIS, acute ischaemic stroke; ARI, autoregulation index; IVT, intravenous thrombolysis; NAH, non-affected hemisphere. Visit 1.1 and Visit 1.2 refer to during IVT, Visit 1.3 refers to immediately prior to end of IVT, and Visit 1.4 refers to immediately after the end of IVT. Visit 2, Visit 3, and Visit 4 refer to approximately 24 hours, 2 weeks, and 3 months post stroke symptom onset, respectively.

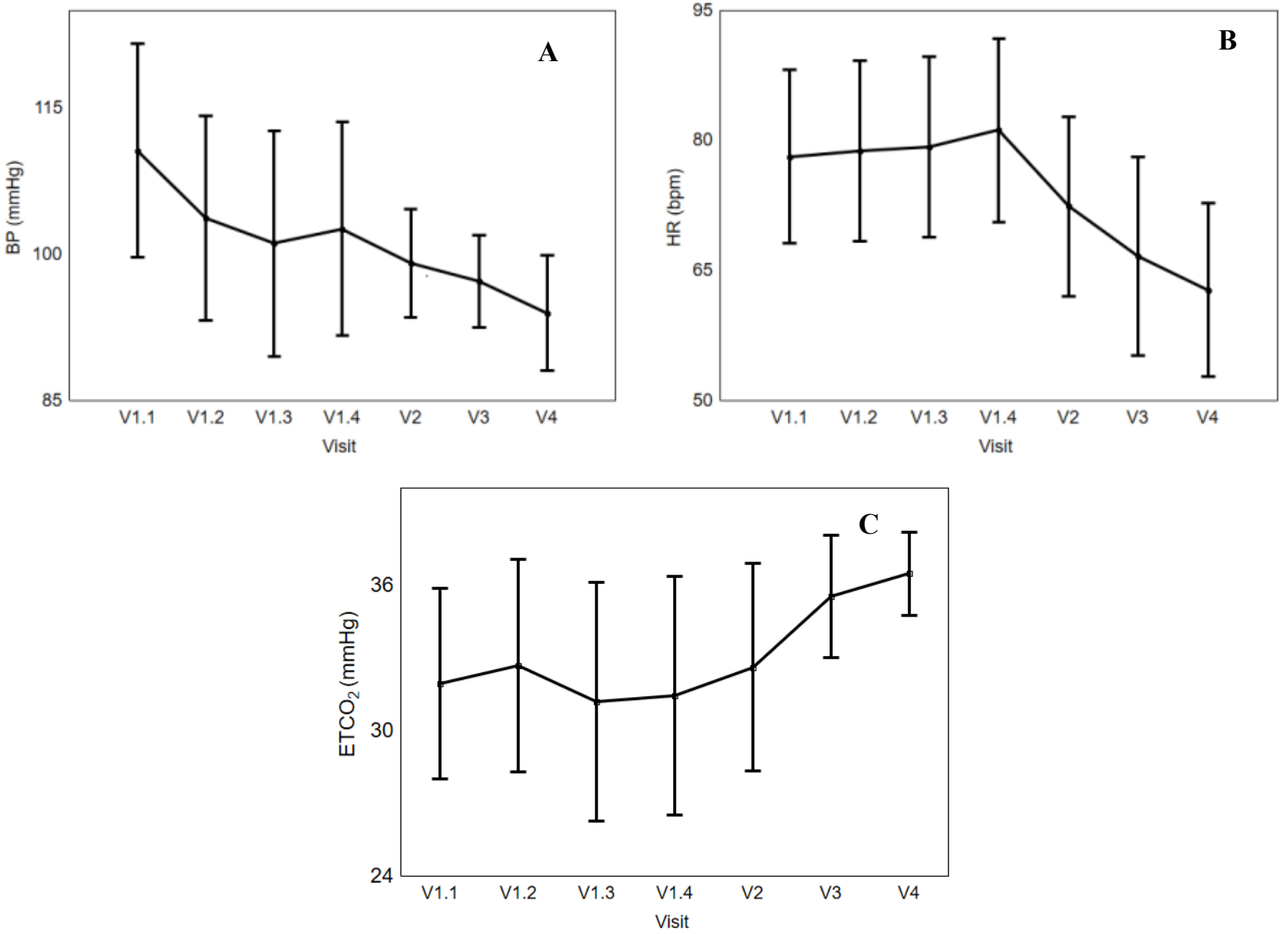

A
BP (mmHg)
115
100
85
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit
B
HR (bpm)
95
80
65
50
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit
C
ETCO2 (mmHg)
36
30
24
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit

**Figure 8.1** Effects of visit on the changes in BP (A), HR (B), and $ETCO_2$ (C). Vertical bar denotes 95% confidence interval. V1.1 and V1.2 refer to during IVT, V1.3 refers to immediately prior to end of IVT, and V1.4 refers to immediately after the end of IVT. V2, V3 and V4 refer to approximately 24 hours, 2 weeks and 3 months post stroke symptom onset, respectively.

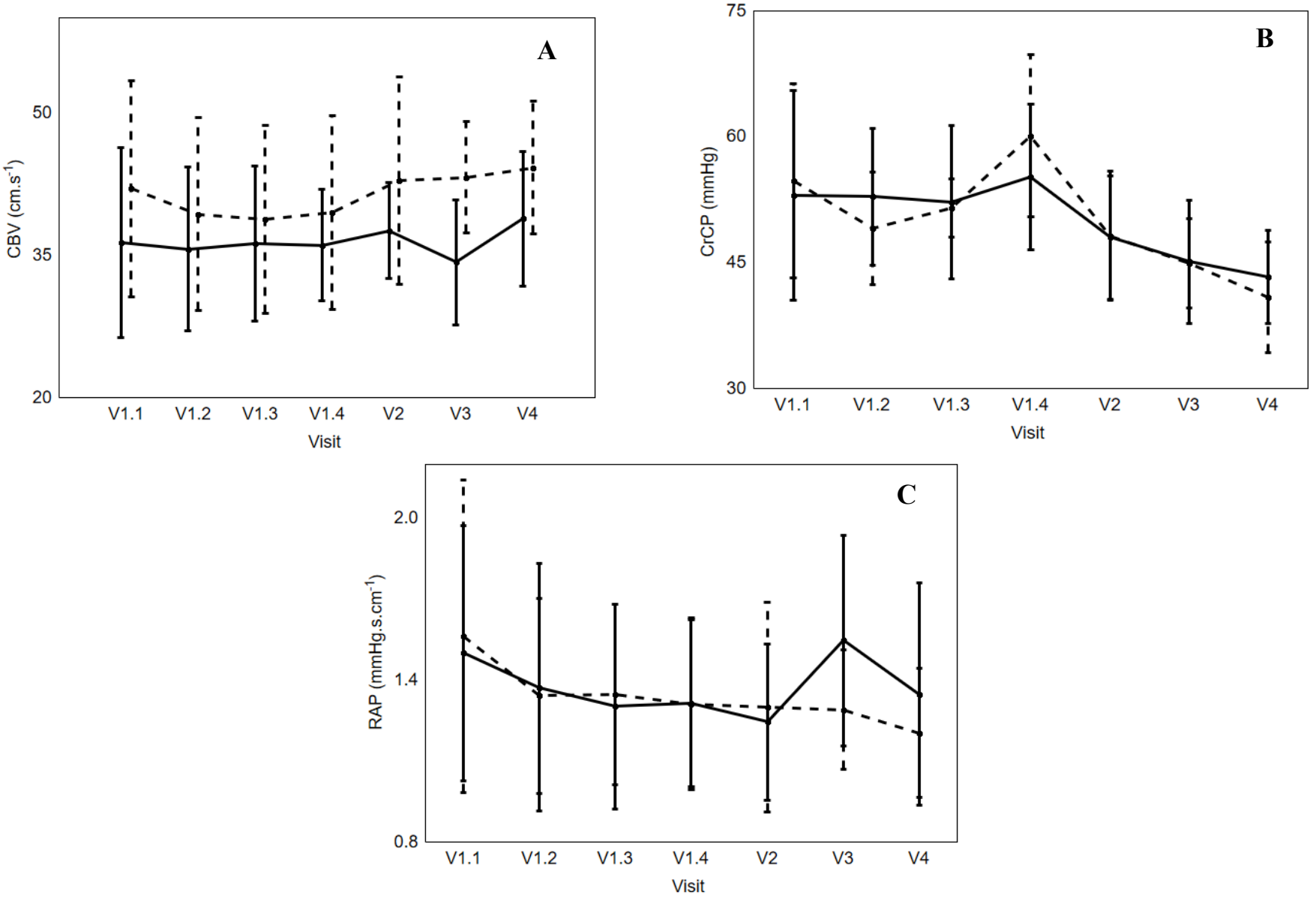
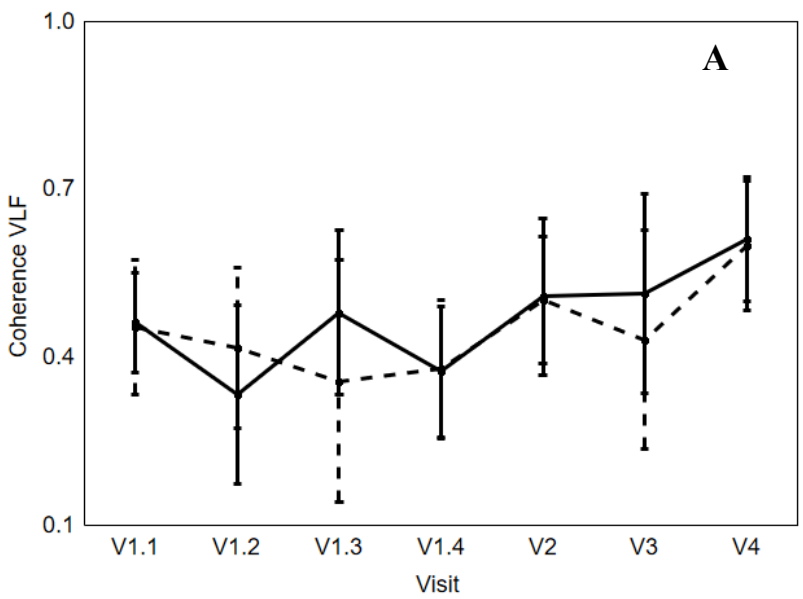
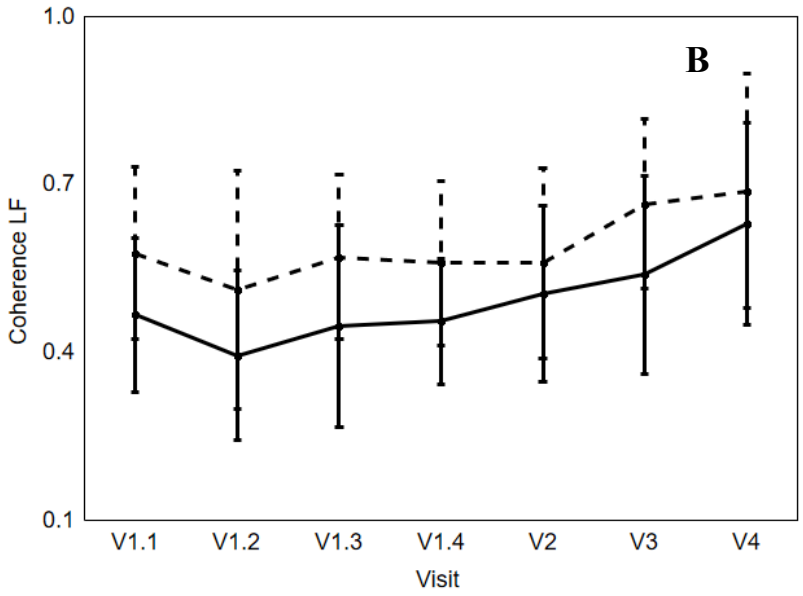

A
CBV (cm.s-1)
50
35
20
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit
B
CrCP (mmHg)
75
60
45
30
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit
C
RAP (mmHg.s.cm-1)
2.0
1.4
0.8
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit

**Figure 8.2** Effects of visit on the changes in CBV (A), CrCP (B), and RAP (C). Affected hemisphere (continuous line) versus non-affected hemisphere (dotted line). Vertical bar denotes 95% confidence interval. V1.1 and V1.2 refer to during IVT, V1.3 refers to immediately prior to end of IVT, and V1.4 refers to immediately after the end of IVT. V2, V3 and V4 refer to approximately 24 hours, 2 weeks and 3 months post stroke symptom onset, respectively.


A
1.0
0.7
0.4
0.1
Coherence VLF
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit


B
1.0
0.7
0.4
0.1
Coherence LF
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit

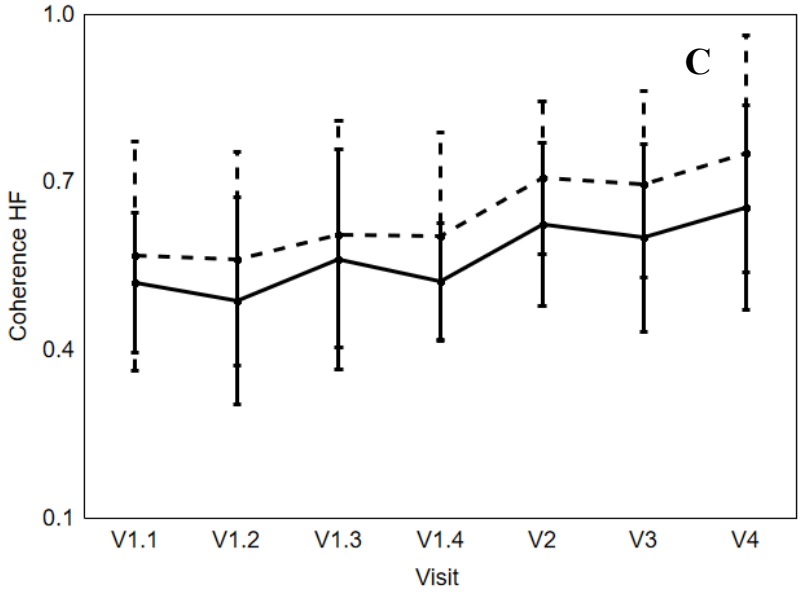

C
1.0
0.7
0.4
0.1
Coherence HF
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit

**Figure 8.3** Effects of visit on the changes in Coherence (A, B and C). Very low frequency (A) versus low frequency (B) versus high frequency (C). Affected hemisphere (continuous line) versus non-affected hemisphere (dotted line). Vertical bar denotes 95% confidence interval. V1.1 and V1.2 refer to during IVT. V1.3 refers to immediately prior to end of IVT, and V1.4 refers to immediately after the end of IVT. V2, V3, and V4 refer to approximately 24 hours, 2 weeks, and 3 months post stroke symptom onset, respectively.

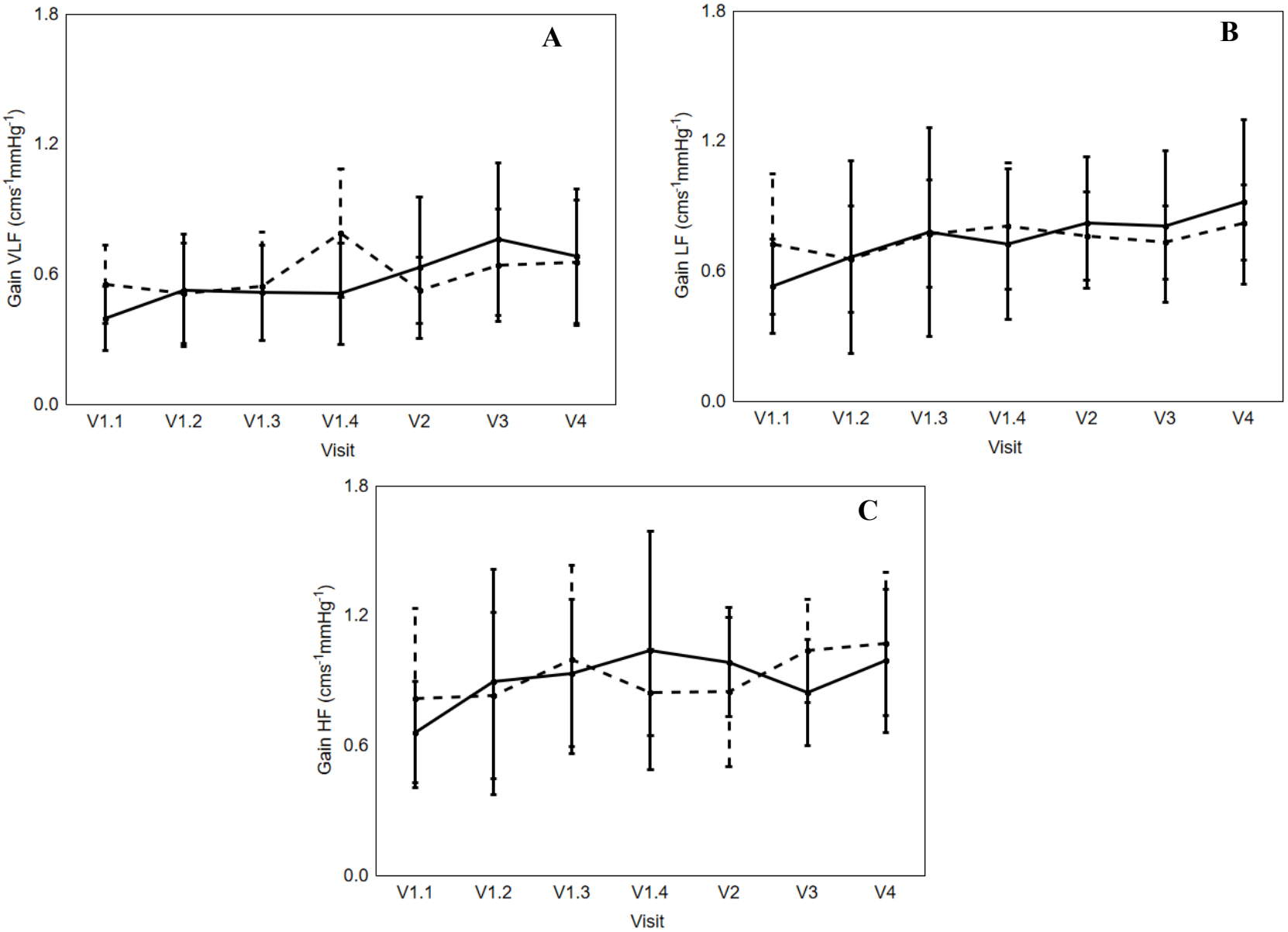

A
B
C
Gain VLF (cms-1mmHg-1)
Gain LF (cms-1mmHg-1)
Gain HF (cms-1mmHg-1)
1.8
1.2
0.6
0.0
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit

**Figure 8.4** Effects of visit on the changes in Gain (A, B and C). Very low frequency (A) versus low frequency (B) versus high frequency (C). Affected hemisphere (continuous line) versus non-affected hemisphere (dotted line). Vertical bar denotes 95% confidence interval. V1.1 and V1.2 refer to during IVT. V1.3 refers to immediately prior to end of IVT, and V1.4 refers to immediately after the end of IVT. V2, V3, and V4 refer to approximately 24 hours, 2 weeks, and 3 months post stroke symptom onset, respectively.

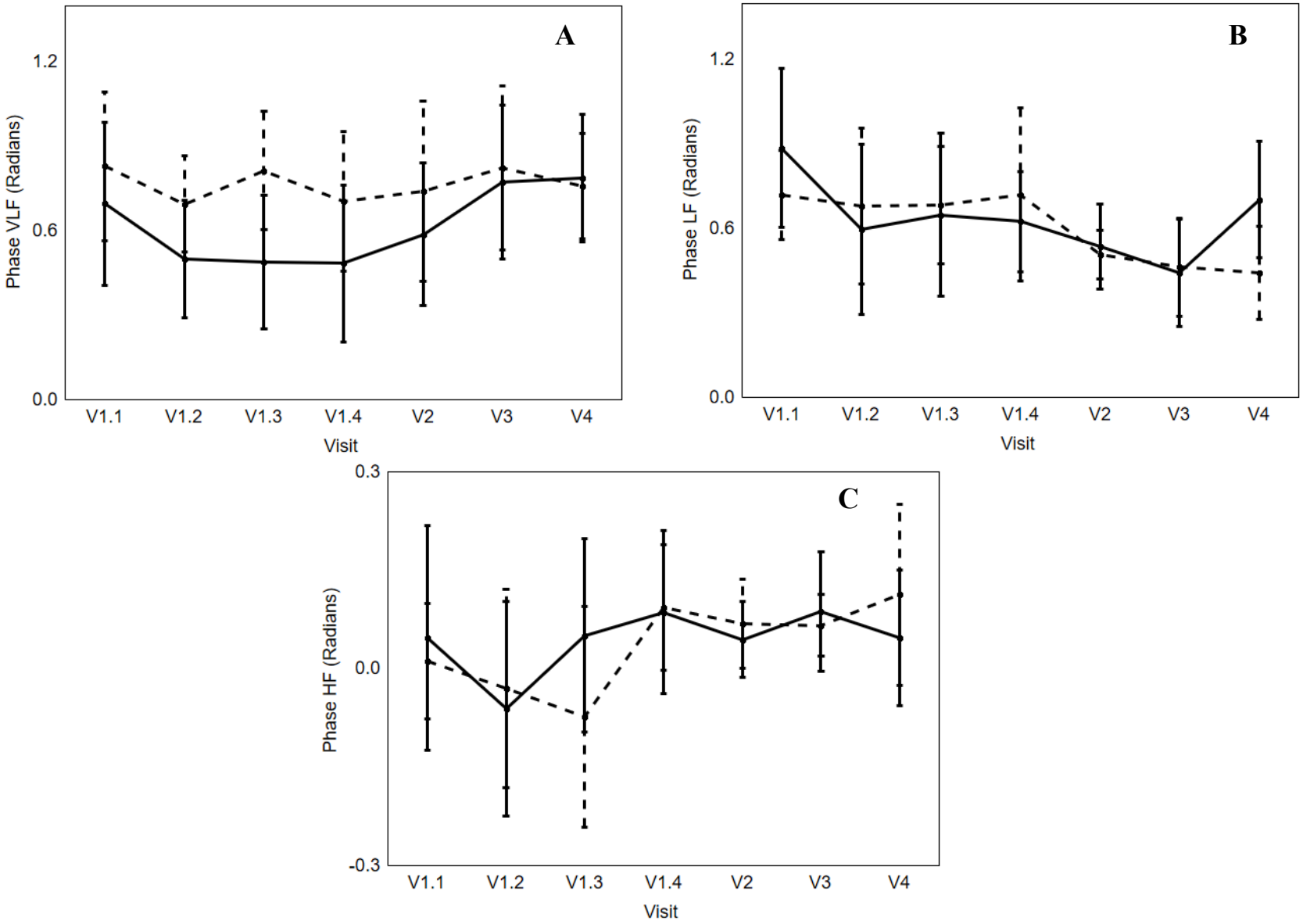

A
Phase VLF (Radians)
1.2
0.6
0.0
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit
B
Phase LF (Radians)
1.2
0.6
0.0
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit
C
Phase HF (Radians)
0.3
0.0
-0.3
V1.1
V1.2
V1.3
V1.4
V2
V3
V4
Visit

**Figure 8.5** Effects of visit on the changes in Phase (A, B and C). Very low frequency (A) versus low frequency (B) versus high frequency (C). Affected hemisphere (continuous line) versus non-affected hemisphere (dotted line). Vertical bar denotes 95% confidence interval. V1.1 and V1.2 refer to during IVT. V1.3 refers to immediately prior to end of IVT, and V1.4 refers to immediately after the end of IVT. V2, V3, and V4 refer to approximately 24 hours, 2 weeks, and 3 months post stroke symptom onset, respectively.

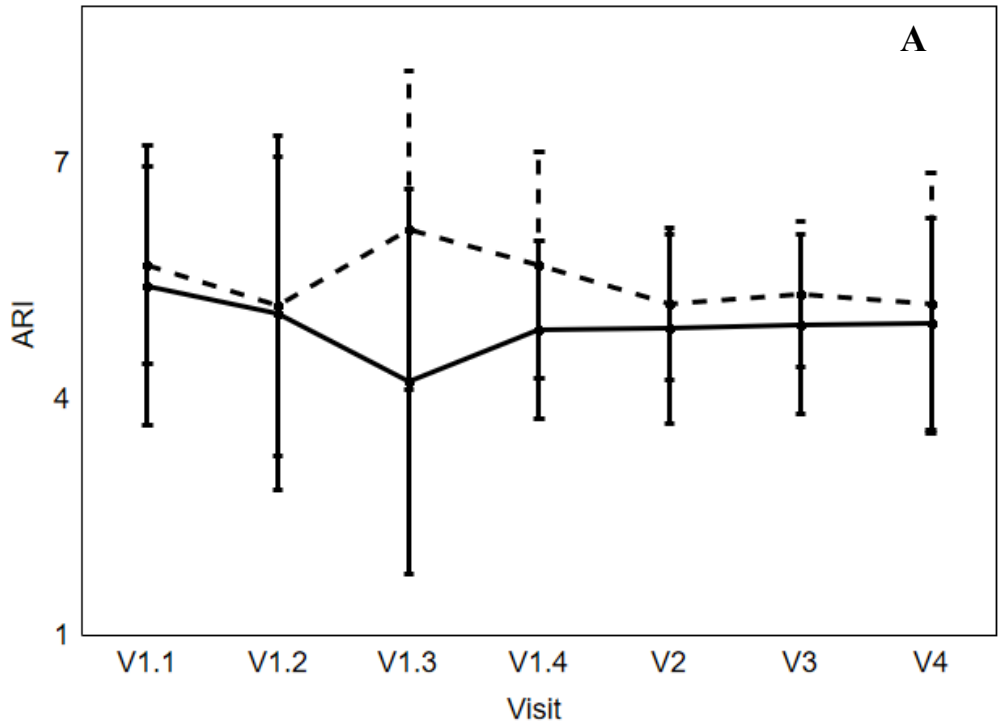



**Figure 8.6** Effects of visit on the changes in ARI (A). Affected hemisphere (continuous line) versus non-affected hemisphere (dotted line). Vertical bar denotes 95% confidence interval. V1.1 and V1.2 refer to during IVT. V1.3 refers to immediately prior to end of IVT, and V1.4 refers to immediately after the end of IVT. V2, V3, and V4 refer to approxiamtely 24 hours, 2 weeks, and 3 months post stroke symptom onset, respectively.

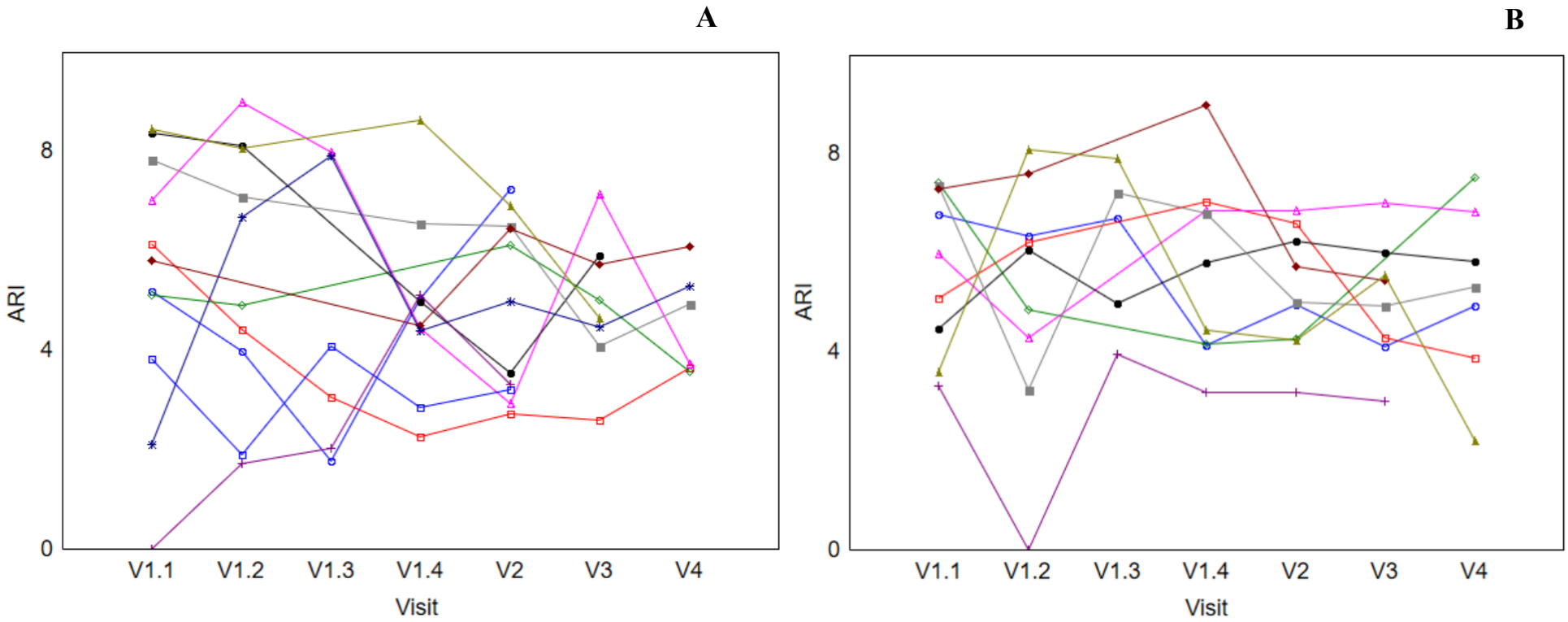



**Figure 8.7** Individual subjects' ARI values at each visit. AH ARI (A) versus NAH ARI (B). V1.1 and V1.2 refer to during IVT. V1.3 refers to immediately prior to end of IVT, and V1.4 refers to after the end of IVT. V2, V3 and V4 refer to approximately 24 hours, 2 weeks and 3 months post stroke symptom onset, respectively.

## 8.4 Discussion

### 8.4.1 Main Findings

This longitudinal study assessed serial TCD and other physiological measurements in CA, with associated systemic and cerebral haemodynamic parameters, during and after IVT administration, up to 3 months of post stroke symptom onset. As previous reports suggest CA changes in AIS patients tend to occur within days and weeks post stroke symptom onset (404, 427), the author chose to carry out 3 months follow up to correlate any CA changes with neurological recovery and functional outcome.

The study demonstrated a gradual reduction in BP and HR across visits, which is in broad agreement with other literature (427, 437, 539, 743). It is important to note that a significant BP reduction occurred during IVT, rather than during subsequent visits, highlighting the importance of having BP closely monitored during this critical period, though the author is also aware such an observation could be due to clinical (i.e. HASU) environmental reasons. Similar to Chapter 6 and 7, when compared to healthy controls (744), a profound hypocapnia was observed during and immediately after completion of IVT, and up to 24 hours after stroke onset, with significant increment in subsequent visits. These later increments coincided with a reduction in BP, HR and CrCP. Interestingly, vasodilatation, and increases in CBF, sympathetic activity, BP, and HR are usually demonstrated post normalisation of the hypocapnia (744, 745). Therefore, the reduction observed in BP, could be due to other reasons such as recovery from pain and discomfort secondary to AIS event, changes in neuro-endocrine hormones (746), transient autonomic nervous system imbalance (747), baroreceptor sensitivity (168), or Cushing's reflex (748).

### 8.4.2 Cerebral Haemodynamics changes following IVT

Similar to Chapter 6, there were no significant differences in both AH and NAH CBV changes during and immediately after IVT, and at subsequent follow-up visits. Reinhard et al. undertook a TCD study of the MCA in AIS patients, with a significant proportion of patients receiving IVT therapy (42%). This study reported a significant increment in both AH and NAH CBV, approximately 7 days post stroke symptom onset. Interestingly, it was associated with a reduction in phase, suggesting worsening of dCA within first week of onset (430). Of note, Akopov et al. found a wide range of serial CBV results in AIS patients, and suggested that this may be caused by the degree of intra-cranial arterial stenosis, occlusion and recanalisation (749). Interestingly, despite improvement in both stroke severity (NIHSS) and functional outcome (mRS) at 3 months in this study chapter AIS cohort, there were not any significant changes in respect of CBV between both hemispheres and over time. This is in conjunction with the recent study carried out by Salinet et al. who looked at more than 50 ischaemic stroke patients and carried out the assessment up to 31 hours post stroke symptom onset. Their study demonstrated that for participants who have mild (median NIHSS =2) and moderate (median NIHSS = 9) severity of stroke disease, there were no significant differences between AH and NAH CBV (422). The AIS participants in this study chapter had an admission mean NIHSS of 8.2, and this may explain why no significant differences between AH and NAH CBV were observed. However, in the absence of angiographic data, it is difficult to determine whether there was no occlusion at presentation and no recanalisation at follow-up, or alternatively complete MCA occlusion without successful recanalisation. Future studies should therefore include angiography to assess the degree of occlusion, recanalisation and response of treatment.

Previous studies reported that CrCP was inversely associated with $PaCO_2$ (411, 744, 750, 751). Grune and colleagues carried out a study on 10 patients who underwent general anesthesia and reported that hypocapnia led to an increment in CrCP (751). In this study, the concurrent increment of $ETCO_2$ and further exacerbation by BP reduction observed over the course of the disease, suggests that these parameters are likely to be inter-related. On the other hand, we did not demonstrate any significant changes in AH or NAH RAP either during or immediately after the completion of IVT, nor were there significant changes in AH or NAH RAP over subsequent follow-up visits. Unlike CrCP, the relationship between RAP and $ETCO_2$ is not clear. Some studies have not found an association between RAP and $ETCO_2$ (411, 752), whilst others have reported a negative correlation between RAP and $ETCO_2$ (744, 753). Future studies should consider investigating the regulatory mechanism between these factors.

Though it is known that dCA is effective in the VLF and LF regions, the author has also reported values in the HF band as recommended by the CARNet white paper (357). No differences in frequency or terms of temporal patterns were observed in coherence and gain in both AH and NAH at different frequency bands and visits. The reduction of LF phase observed in AH, during the early phase of IVT, indicates worsening of dCA may happen during this crucial stage of treatment. Although the subgroup analysis did not show a similar result, it may suggest that the two patients removed were not mimics and were in fact contributing to the observed reduction in phase during IVT. Subsequent alterations in dCA, following IVT, might have been obscured by the relatively wide scattering of phase shift values, reflecting limitations in statistical power, as discussed below.

Although the ARI dropped from 5.45 ± 2.65 (Visit 1.1) to 4.23 ± 2.65 (Visit 1.3), the author did not test the significance of this difference as the F-test for the intra-visit ANOVA was non-significant (Table 8.6, p=0.17). Importantly, there were only a small number of AIS patients (n=3) with impaired dCA in this study, as indicated by ARI<4 (409) at Visit 1.1. Figures 8.7A and B display the ARI values of AIS patients across all visits and it can be seen that such participants behave differently during the course of the disease. As the sample size of the study cohort is relatively small, it is difficult to draw any meaningful conclusions, especially as the study was designed to detect a change of ARI of 2 units. Further investigations should consider recruiting a larger number of patients, with higher NIHSS scores in order to assess any relationships between changes of such parameters in AIS patients, in particular to those who present secondary reperfusion injury or poorer functional outcome.

### 8.4.3 Study Limitations

Firstly, due to the study design and to avoid any delays in IVT administration, the author could not perform TCD measurement on AIS patients prior to thrombolysis treatment. Therefore, critical information regarding cerebral haemodynamic status prior to IVT therapy is lost, though initial assessments were performed within 20 minutes of commencing IVT. Secondly, angiographic imaging was not available. Assumption was made that successful reperfusion would allow presence of the MCA TCD signal, and non-recanalised participants, who are important and account for a significant proportion of AIS patients who receive IVT, were therefore not able to be included in the study, though the author also aware some of the stroke subtypes, such as LACS or POCS could have detectable MCA signals regardless of the recanalisation status. Given that patients had improved in NIHSS and mRS scores in the follow up visits, the author could possibly argue satisfactory recanalisation did occur. Future studies should consider using

alternative imaging modalities (e.g. CTA) in order to investigate this important, and yet often overlooked cohort. However, the key aim of this study was to investigate whether using TCD in AIS patients during IVT could provide useful information regarding dCA status AIS patients, in particular when multimodal imaging (CTA) is not routinely available. Thirdly, similar to Chapters 5 to 7, this study chapter also had a relatively small sample size with significant heterogeneity in stroke subtype. As a result, the positive and negative results observed in this study could be due to Type I and II error, respectively. Furthermore, an admission mean NIHSS of 8.2, indicated that the majority of AIS patients tended to have mild/ moderate stroke disease. Moreover, a median mRS of 2 indicated that the majority of the participants had a benign disease course with a satisfactory recovery at 3 months post symptom onset. Therefore, it would be beneficial for future studies to recruit a larger cohort, with higher NIHSS scores, in order to provide a better insight on the time course and changes in CA in AIS patients deemed suitable to receive IVT and their associated functional outcome. Fourthly, same as previous study chapters, TCD was used to measure CBV, as a surrogate of CBF, under the assumption that the insonated vessel diameter remains constant (338). Since TCD can only reflect CBV in the MCA or another large intra-cranial vessel, it can only provide global hemispheric values. Therefore, should CA impairment occur in a more localised, smaller infarct area or collaterals in the penumbra, TCD may be insensitive to provide information of such focal changes. Finally, with increasing use of MT with and without co-commitment IVT in AIS patients, it would be useful to carry out similar studies, to investigate how CA changes pre- and post-MT in AIS.

## 8.5 Conclusion

This study chapter has provided evidence of the feasibility of using TCD to assess dynamic CA in AIS patients during IVT, and up to 3 months following stroke. A reduction

in LF phase values in AH suggests that impairment of dCA could occur during IVT, and may warrant closer monitoring at such a critical stage. Though the evidence is limited, the author believes that functional CA status could be considered as part of routine clinical care, as it may provide valuable additional information about guidance of antihypertensive treatment and response to IVT or other interventions. The prolonged time course of CA evolution changes in AIS warrant further investigations, with a larger cohort and a wider range of stroke severity, as expressed by the NIHSS, and including other multi-modal imaging, such as cerebral angiography, to allow better patient risk stratification and assessment of outcome following IVT.

# Chapter 9: Thesis Conclusion

## 9.1 Introduction

There is no doubt that, the human brain is the most complex organ created by biological evolution and, despite decades of research, little is known on how the brain adapts and functions, making it such a fascinating field to explore. One thing for sure is the human brain has capacity for recovery after acute, severe insult (e.g. IS), and studies suggest cerebral haemodynamics could be one of the important underlying mechanisms responsible for initiating the regenerative event that lasts for several weeks, if not months (754). However, surprisingly, little is known on the impact of AIS perfusion strategies on cerebral haemodynamics, including how they optimise systemic and cerebrovascular physiology post injury, and therefore, impact on neuronal recovery post stroke.

Before assessing how AIS patients respond to perfusion strategies, it is necessary to understand firstly the CA regulation in healthy controls during different perfusion regimens. It would be unethical for control participants to receive IVT without a valid reason, therefore, this thesis sought to study healthy control responses to head positioning changes to determine both normal physiological changes, as well as reproducibility. This concluding chapter will summarise the author's findings, and the future clinical implications and research.

## 9.2 Main Findings of the thesis

***What is the existing evidence for using pressor agents in acute ischaemic stroke?*** (Chapter 3)

The results suggested that the use of pressor agents, as induced hypertension (IH) therapy, is feasible, relatively safe and effective in a selected group of AIS patients, though the current evidence is spare. High quality, prospective, randomised trials and improving reporting standards are required in order to minimise bias and provide further randomised evidence. Importantly, pre-morbid BP status, co-morbidity, stroke subtype and severity, can all affect BP thresholds among patients. Therefore, careful patient selection is crucial to optimise the recovery and IH could be considered as an adjunct in the situation where IVT/IAT/MT were not available/feasible or in a situation where failed recanalisation occurs post endovascular treatment. The systematic review findings highlighted the differences between individual patients and the importance in considering personalised stroke management plans.

***What is the effect of Gradual Head Positioning changes on cerebrovascular physiology in healthy older subjects (controls)?*** (Chapter 5)

The results suggested that static changes in key haemodynamic parameters (BP, CBV, CrCP) were observed in GHP, with reproducible results on repeated visits. Importantly, dCA, as expressed by the ARI index, and other haemodynamic parameters (HR, $ETCO_2$ and RAP) were not affected by a change from 0° to 30° head position in this healthy older group. The author has demonstrated the validity of using GHP paradigm in assessing cerebral haemodynamics, and therefore supports the use of such a paradigm in the assessment of AIS patients.

***What is the effect of Gradual Head Positioning changes on cerebrovascular physiology in AIS patients, when compared to controls?*** (Chapter 6)

The results suggested that AIS patients behaved differently when compared to controls in response to GHP. Both AIS and controls demonstrated a reduction in BP and CrCP,

without significant changes in HR and $ETCO_2$ during the 5-min SIT head position. Of note, reduction in ARI, but not CBV (AH and NAH) was observed during changes in head positioning in mildly affected, and well recovered AIS patients, arguing mobilisation could be safe in such a cohort.. These findings indicate that monitoring of CA parameters could provide important information regarding optimal head positioning and timing of rehabilitation in stroke patients.

***Could Rapid Head Positioning act as a new dynamic cerebral autoregulation paradigm in AIS and controls?*** (Chapter 7)

The results demonstrate RHP is a safe and well-tolerated technique by both controls and AIS patients. RHP resulted in increases of BPV in controls, but not in AIS patients, over 90 days post stroke symptom onset. This important finding highlights that significant BPV is likely to be already present in AIS and therefore, insensitive to RHP. RHP did not improve detection of impaired CA in AIS; further work is needed to understand the different responses observed.

***Does GHP or RHP act as a better paradigm in assessing dCA (Chapters 6 and 7)?***

The ideal technique for dCA assessment in AIS patients should provide considerable variability in BP but without the need for patient co-operation. The author proposed RHP could produce greater BPV, and therefore SNR, when compared to GHP (spontaneous BP fluctuation). However, this was not observed in the RHP paradigm when assessing AIS. Reduction in ARI, but not CBV was observed in the sitting up (>30°) head positioning in AIS in the GHP paradigm, but no significant differences were seen in other key systemic and cerebral haemodynamic parameters AIS patients in response to RHP. Due to the small sample size, it is difficult to conclude whether GHP is superior to RHP in assessing dCA, or vice versa. However, in the author's opinion, RHP could be

considered as a feasible alternative for assessing dCA in situations where BPV is compromised.

***Do cerebral haemodynamics, and associated parameters, change in AIS patients who receive IVT? (Chapter 8)***

The results of this work demonstrate the feasibility of using TCD to assess dCA in AIS patients during and after IVT, and up to approximately 90 days post stroke symptom onset. A  BP reduction was observed during IVT, highlighting the importance of closely monitoring BP during this critical period. Reductions in AH phase at low frequency were observed during thrombolysis and at subsequent visits. No changes were observed in CBV, coherence, gain and importantly, ARI during the follow up period. IVT in AIS patients induced changes in AH phase, but not other key haemodynamic parameters and ARI. Further investigation of CA is warranted in a larger AIS cohort to inform its potential role in individualised management plans.

***Comparison between AIS patients subject to non-pharmacological (head positioning changes, GHP) (Chapter 6) vs. pharmacological (IVT) perfusion therapy (Chapter 8)***

The author has carried out a comparison between these groups (both at lying flat (0°) head position), hoping to identify any similarities or differences, with a view to furthering the understanding of the natural history of AIS patients.

*Comparison between systemic haemodynamic parameters*

Both GHP and IVT group demonstrated a gradual BP reduction over the course of the disease, baseline HR was slightly lower in the GHP than the IVT group, and gradual HR reduction was noted in the IVT, but not in the GHP. On the other hand, hypocapnia was

observed in both IVT and GHP groups, though correction of hypocapnia was only observed in IVT, over the course of the disease.

*Comparison between cerebral haemodynamic parameters*

Similar baseline and inter-hemispheric (AH and NAH) CBV values were noted in both GHP and IVT groups, apart from a mild increased in AH CBV in visit 2 compared to visit 1 in the GHP group, there were no significant changes over the course of the disease. However, in CrCP and RAP, significant differences in terms of baseline and inter-hemisphere values were noted. Baseline CrCP was significantly lower in GHP when compared to the IVT group, but vice versa in RAP. Reduction of CrCP (AH and NAH) was noted in IVT, but not GHP over the course of the disease, whereas significant reduction of RAP (AH and NAH) was noted in GHP, but not IVT over approximately 90 days post stroke symptom onset.

In terms of ARI, both GHP and IVT demonstrated similar results: reduction in ARI (AH and NAH) was noted approximately 24 hours to 5 days post stroke symptom onset.

As mentioned above, the GHP and IVT participants were different AIS cohorts, with different demographics, stroke subtypes and severity. It is therefore difficult to carry out a direct comparison between these two groups. However, generally speaking, a gradual reduction in BP, hypocapnia and a reduction in ARI during subacute phase of the disease seems to be commonly observed in these two groups, suggesting this is a natural phenomenon of longitudinal changes in AIS disease. Both the GHP and IVT groups did not demonstrate any inter-hemispheric difference between CBV and ARI, which is consistent with the recent work carried out by Salinet et al. (422) and Xiong et al. (428). The inconsistent observation in CrCP and RAP definitely warrants further investigation;

ideally with larger cohorts and frequent follow up to provide better understanding about the natural history of cerebral haemodynamics after AIS.

## 9.3 Study Limitation and Future Work

The majority of the AIS patients studied in this research thesis had mild to moderate stroke, as evidenced by a median admission NIHSS of 5 (Chapters 6 and 7) and mean admission of NIHSS of 8.2 (Chapter 8). The small sample sizes and heterogeneity in stroke subtypes could mean that the positive and negative results we observed could be due to Type I and Type II error, respectively. Future studies should therefore consider recruiting larger cohorts, with high NIHSS scores. Secondly, although TCD provides excellent temporal resolution in assessing CA, without multimodal imaging (CT Angiography), it is difficult to provide definitive statements regarding patients' recanalisation status, and therefore, future studies should consider utilising such imaging modalities in the dCA investigation. Finally, the author has used TFA in assessing CA status, with the assumption of stationarity, and linear correlation between input (BP) and output (CBV). Given the dynamic manner of CA, future studies should consider using non-stationary or multi-variate mathematical models if possible.

To conclude, this thesis has furthered our understanding of how CA, and associated parameters, respond in AIS patients who undergo various perfusion regimes. AIS patients not only behave differently to controls, but there is heterogeneity of responses among patients themselves. Even participants with the same age, sex, stroke subtype and severity, may react differently according to the perfusion therapy deployed. This strengthens the argument that we need to consider a shift from "generalised" to "individualised" stroke management care. With careful patient selection, a combination of interventions (e.g. a patient with failed recanalisation post IVT might benefit from the lying flat head positioning and short term use of pressor therapy) may help to optimise post stroke recovery. Cerebral haemodynamics, and associated parameters, may help to inform these strategies, although the knowledge on how such crucial CA information may

translate into current clinical practice is still lacking. Future studies should consider recruiting larger, more heterogeneous, cohorts with higher NIHSS scores. Finally, future work should consider combining TCD assessment with multi-modal imaging in order to provide accurate recanalisation and reperfusion status.

.

# Appendix 1: Systematic Review Search Strategy

1) Stroke
2) Cerebr* vascular disease
3) Cerebr* isch*
4) Brain isch*
5) Cerebr* infarct*
6) Brain infarct*
7) 1 or 2 or 3 or 4 or 5 or 6
8) Induc* Hypertension
9) Induc* BP
10) Induc* Blood Pressure
11) Elevat* Blood Pressure
12) Elevat* BP
13) Rais* Blood Pressure
14) Rais* BP
15) Increas* Blood Pressure
16) Increas* BP
17) 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18) Pressor
19) Inotrop*
20) Vasoactive
21) Vasoconstrictor
22) Vasopressor
23) Catecholamine
24) Dobutamine
25) Orciprenaline
26) Dopamine
27) Adrenaline
28) Noradrenaline
29) Epinephrine
30) Norepinephrine
31) Vasopressin
32) Argipressin

33) Desmopressin

34) Lypressin

35) Felypressin

36) Ornipressin

37) Telipressin

38) Glypressin

39) Phenylephrine

40) Isoproperenol

41) Methylene Blue

42) 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 ‘;

43) 7 and 17 and 42

# Appendix 2: The Effects of Head Positioning on Beat-to-beat Cerebral Haemodynamics: A Comparison between Acute Ischaemic Stroke Patients and Controls Subjects (Chapter 5, 6 and 7)

## (Approvals and Information Sheet)

**Appendix 2.1** Ethical Approval Letter Dated 5th October 2015

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Gwasanaeth Moeseg Ymchwil
Research Ethics Service

Ariennir gan Lywodraeth Cymru
Funded by Welsh Government

**Wales Research Ethics Committee 1**
**Sixth Floor, Churchill House**
**17 Churchill Way**
**Cardiff CF10 2TW**

**Telephone: 029 2037 6823**

**E-mail: jagit.sidhu@wales.nhs.uk**
**Website: www.hra.nhs.uk**

05 October 2015

Professor Thompson G Robinson
Professor of Stroke Medicine /Honorary Consultant Physician
University of Leicester/ University Hospitals of Leicester NHS Trust
Department of Cardiovascular Sciences
Room 224, Robert Kilpatrick Clinical Sciences Building
PO BOX 65, University of Leicester, Leicester, United Kingdom
LE2 7LX

Dear Professor Robinson

| | |
|---|---|
| **Study title:** | **The effects of head positioning on beat-to-beat cerebral haemodynamics: a comparison between acute stroke patients and healthy control subjects** |
| **REC reference:** | **15/WA/0328** |
| **Protocol number:** | **UNOLE 0538** |
| **IRAS project ID:** | **183480** |

Thank you for your letter of 28th September 2015, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair, Dr K. Craig.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Jagjit Sidhu, jagit.sidhu@wales.nhs.uk.

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation [as revised], subject to the conditions specified below.

**Mental Capacity Act 2005**

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

**Conditions of the favourable opinion**

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.*

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of approvals from host organisations*

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**Ethical review of research sites**

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| Copies of advertisement materials for research participants [Research Participant Poster (Tracked Version) ] | 2 | 10 September 2015 |
| Copies of advertisement materials for research participants [Research Participant Poster (Clean Version) ] | 2 | 10 September 2015 |
| Covering letter on headed paper [Covering Letter ] | | 24 August 2015 |
| Covering letter on headed paper [Covering Letter ] | | 28 September 2015 |
| GP/consultant information sheets or letters [GP Information Leaflet (Patient) Tracked Version ] | 3 | 10 September 2015 |
| GP/consultant information sheets or letters [GP Information Leaflet (Patient) Clean Version] | 3 | 10 September 2015 |
| GP/consultant information sheets or letters [GP Information Leaflet (Volunteer) Tracked Version ] | 3 | 10 September 2015 |
| GP/consultant information sheets or letters [GP Information Leaflet (Volunteer) Clean Version ] | 3 | 10 September 2015 |
| IRAS Checklist XML [Checklist_25082015] | | 25 August 2015 |
| IRAS Checklist XML [Checklist_01102015] | | 01 October 2015 |
| Other [Dr Amit Mistri (Academic Supervisor) CV] | | 03 August 2015 |
| Other [Dr Victoria Haunton (Academic Supervisor) CV] | | 03 August 2015 |
| Other [REC Response letter ] | | 22 September 2015 |
| Other [MD Protocol (Clean Version) ] | 0.4 | 10 September 2015 |
| Other [University of Leicester Clinical Trials Insurance ] | | 03 August 2015 |
| Other [University of Leicester Professional Indemnity Insurance ] | | 03 August 2015 |
| Participant consent form [Personal Consultee Declaration Form (Tracked Version) ] | 1 | 10 September 2015 |
| Participant consent form [Personal Consultee Declaration Form (Clean Version) ] | 1 | 10 September 2015 |
| Participant consent form [Participant Consent Form (Patient) Tracked Version ] | 3 | 10 September 2015 |
| Participant consent form [Participant Consent Form (Patient) Clean Version ] | 3 | 10 September 2015 |

| | | |
|---|---|---|
| Participant consent form [Participant Consent Form (Volunteer) Tracked Version ] | 3 | 10 September 2015 |
| Participant consent form [Participant Consent Form (Volunteer) Clean Version ] | 3 | 10 September 2015 |
| Participant information sheet (PIS) [Personal Consultee Information Leaflet (Tracked Version) ] | 1 | 10 September 2015 |
| Participant information sheet (PIS) [Personal Consultee Information Leaflet (Clean Version)] | 1 | 10 September 2015 |
| Participant information sheet (PIS) [Patient Information Leaflet (Tracked Version) ] | 3 | 10 September 2015 |
| Participant information sheet (PIS) [Patient Information Leaflet (Clean Version)] | 3 | 10 September 2015 |
| Participant information sheet (PIS) [Volunteer Information Leaflet (Tracked Version)] | 3 | 10 September 2015 |
| Participant information sheet (PIS) [Volunteer Information Leaflet (Clean Version) ] | 3 | 10 September 2015 |
| Research protocol or project proposal [MD Protocol (Tracked Version) ] | 0.4 | 10 September 2015 |
| Summary CV for Chief Investigator (CI) [Professor Thompson G Robinson CV] | | 11 August 2015 |
| Summary CV for student [Dr Man Yee Lam CV] | | 11 July 2015 |
| Summary CV for supervisor (student research) [Professor Ronney Panerai CV] | | 14 August 2015 |

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

Notifying substantial amendments
Adding new sites and investigators
Notification of serious breaches of the protocol
Progress and safety reports
Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

**User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

**HRA Training**

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

| 15/WA/0328 | **Please quote this number on all correspondence** |
|---|---|

With the Committee's best wishes for the success of this project.

Yours sincerely

p.p.
**Dr K J Craig**
**Chair**

Email:jagit.sidhu@wales.nhs.uk

*Enclosures:* "After ethical review – guidance for researchers" *[SL-AR2]*

*Copy to:* Mrs Wendy Gamble - wg4@le.ac.uk
Ms Carolyn Maloney, Research and Development Manager, Research and Development Office - carolyn.maloney@uhl-tr.nhs.uk
Dr Man Yee Lam - ml376@le.ac.uk

**Appendix 2.2** Ethical Approval Letter 2 Re-issued on 20th April 2016

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Gwasanaeth Moeseg Ymchwil
Research Ethics Service

Ariennir gan Lywodraeth Cymru
Funded by Welsh Government

**Wales Research Ethics Committee 1**
**Castlebridge 4**
**15-19 Cowbridge Road East**
**Cardiff**
**CF11 9AB**

**Telephone: 02920 785738**
**E-mail: jagit.sidhu@wales.nhs.uk**
**Website : www.hra.nhs.uk**

20 April 2016

Professor Thompson G Robinson
Professor of Stroke Medicine /Honorary Consultant Physician
University of Leicester/ University Hospitals of Leicester NHS Trust
Department of Cardiovascular Sciences
Room 224, Robert Kilpatrick Clinical Sciences Building
PO BOX 65, University of Leicester
Leicester, United Kingdom
**LE2 7LX**

Dear Professor Robinson

| | |
|---|---|
| **Study title:** | **The effects of head positioning on beat-to-beat cerebral haemodynamics: a comparison between acute stroke patients and healthy control subjects** |
| **REC reference:** | **15/WA/0328** |
| **Protocol number:** | **UNOLE 0538** |
| **Amendment number:** | **0.5** |
| **Amendment date:** | **10 February 2016** |
| **IRAS project ID:** | **183480** |

The above amendment was reviewed at the meeting of the Sub-Committee held on the 12 April 2016.

**Ethical opinion**

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

In reaching that decision the Committee was of the view that the last paragraph on page 3 of the participant information sheet was difficult to understand. It was noted that whilst the rest of the information had been made more personal by referring to the reader as *"you"* this section referred to *"patients"*.

The Committee was grateful to receive an updated version of the information sheet in the term *"patients"* had been changed to a reference to *"you"*.

The Committee also noted that the section advised that "*patients can have a swallow screen.....*" and members were unclear if this meant that that this was optional or if it meant that it would be done if necessary based on the patients' medical history?

The Committee was also grateful for the confirmation that the swallowing screen was a routine assessment for all the patients who were admitted with a Stroke. As a result the sentence in question within the information sheet had been revised to read "*During the 24 hours of allocated head position, you will have a swallow screen and/or swallow assessment as a standard Hospital protocol".*

The Committee agreed that the issues they had raised had been satisfactorily addressed and the updated version of the participant information sheet (patient) has been listed in the following list of documents.

Please ensure that the associated consent form is also updated to reflect the change in version number and date of the patient information sheet.

**Approved documents**

The documents reviewed and approved at the meeting were:

| Document | Version | Date |
|---|---|---|
| Covering letter on headed paper | | 01 March 2016 |
| Notice of Substantial Amendment (non-CTIMP) | 0.5 | 10 February 2016 |
| Other [Personal Consultee Declaration Form (Clean)] | 2 | 10 February 2016 |
| Other [Personal Consultee Declaration Form (Tracked)] | 2 | 10 February 2016 |
| Other [Personal Consultee Information Leaflet (Clean)] | 2 | 10 February 2016 |
| Other [Personal Consultee Information Leaflet (Tracked)] | 2 | 10 February 2016 |
| Participant consent form [(Clean)] | 4 | 10 February 2016 |
| Participant consent form [(Tracked)] | 4 | 10 February 2016 |
| Participant information sheet (PIS) [(Clean)] | 5 | 10 April 2016 |
| Participant information sheet (PIS) [(Tracked)] | 5 | 10 April 2016 |
| Research protocol or project proposal [(Clean)] | 0.5 | 10 February 2016 |
| Research protocol or project proposal [(Tracked)] | 0.5 | 10 February 2016 |

**Membership of the Committee**

The members of the Committee who took part in the review are listed on the attached sheet.

**R&D approval**

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

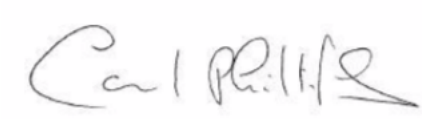
**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

**15/WA/0328: Please quote this number on all correspondence**

Yours sincerely



p.p
**Dr K J Craig**
**Chair**

E-mail: jagit.sidhu@wales.nhs.uk

Enclosures: List of names and professions of members who took part in the review

Copy to: Ms Carolyn Maloney, Research and Development Manager, Research and Development Office – carolyn.maloney@uhl-tr.nhs.uk

Mrs Wendy Gamble – wg4@le.ac.uk

**Wales REC 1**

**Attendance at Sub-Committee of the REC meeting on 12 April 2016**

**Committee Members:**

| Name | Profession | Present | Notes |
|---|---|---|---|
| Dr K J Craig | Nurse - Chair | Yes | |
| Sir D Walters | Alternate Vice Chair and Lay Member | Yes | |

**Appendix 2.3** R and D Approval Dated 13th November 2015

RESEARCH & INNOVATION

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH & INNOVATION

**Director:** **Professor Nigel Brunskill**
**Assistant Director:** **Dr David Hetmanski**
**Head of Research Operations:** **Carolyn Maloney**

Direct Dial: (0116) 258 8351
Fax No: (0116) 258 4226

Research & Innovation Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

13/11/2015

Professor Thompson G Robinson
Leicester Royal Infirmary
Department of Cardiovascular Sciences
Room 224, Robert Kilpatrick Clinical Sciences Building
PO BOX 65,
LE2 7LX

Dear Professor Thompson G Robinson

**Ref:** **UHL 11457**
**Title:** **The effects of head positioning on beat-to-beat cerebral haemodynamics: a comparison between acute stroke patients and healthy control subjects**
**Project Status:** **Project Approved**
**End Date:** **31/03/2017**

**Date of Valid Application: 11/11/2015**
**Days remaining to recruit first patient: 68 Days**

I am pleased to confirm that with effect from the date of this letter, the above study has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust. The research must be conducted in line with the Protocol and fulfil any contractual obligations agreed between UHL & the Sponsor. If you identify any issues during the course of your research that are likely to affect these obligations you must contact the R&D Office.

In order for the UHL Trust to comply with targets set by the Department of Health through the 'Plan for Growth', there is an expectation that the first patient will be recruited within 70 days of receipt of a Valid Application. The date that a Valid application was received is detailed above, along with the days remaining to recruit your first patient. **It is essential that you notify the UHL Data Management Team as soon as you have recruited your first patient to the study either by email to RIData@uhl-tr.nhs.uk or by phone 0116 258 4573.**

If we have not heard from you within the specified time period we will contact you not only to collect the data, but also to record any issues that may have arisen to prevent you from achieving this target. It is essential that you get in touch with us if there is likely to be a problem in achieving this target so that we can discuss potential solutions. The Trust is contractually obliged to meet the 70 day target and if an adequate reason acceptable to the NIHR has not

Version 17. 09/06/2015

been submitted to explain the issues preventing the recruitment of your first participant, the Trust will be financially penalised.

In addition, we are required to publish the Title, REC Reference number, local target recruitment and actual recruitment as well as 70 days data for this study on a quarterly basis on the UHL public accessed website.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

| Document Name | Version | Date |
|---|---|---|
| REC Favourable Opinion | Study Approval | 05/10/2015 |
| Participant Poster | V2 | 10/09/2015 |
| GP Information Leaflet: Patient | V3 | 10/09/2015 |
| GP Information Leaflet: Volunteer | V3 | 10/09/2015 |
| Protocol | 0.4 | 10/09/2015 |
| Personal Consultee Declaration Form | V1 | 10/09/2015 |
| Participant Consent Form: Patient | V3 | 10/09/2015 |
| Participant Consent Form: Volunteer | V3 | 10/09/2015 |
| Personal Consultee Information Leaflet | V1 | 10/09/2015 |
| Patient Information Leaflet | V3 | 10/09/2015 |
| Volunteer Information Leaflet | V3 | 10/09/2015 |

***Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.***

Undertaking research in the NHS comes with a range of regulatory responsibilities. Please ensure that you and your research team are familiar with, and understand the roles and responsibilities both collectively and individually.

Documents listing the roles and responsibilities for all individuals involved in research can be found on the R&I pages of the Public Website. It is important that you familiarise yourself with the Standard Operating Procedures, Policies and all other relevant documents which can be located by visiting www.leicestershospitals.nhs.uk/aboutus/education-and-research

The R&I Office is keen to support and facilitate research where ever possible. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office. Our contact details are provided on the attached sheet.

We wish you every success with your research.

Yours sincerely

Carolyn Maloney
**Head of Research Operations**

Encs: .R&I Office Contact Information

**Appendix 2.4** Sponsor Approval Letter Dated 17th November 2015

UNIVERSITY OF LEICESTER

**College of Medicine, Biological Sciences & Psychology**
**University of Leicester**
**Research Governance Office**
**Academic Department, Ground Floor**
**Leicester General Hospital**
**Gwendolen Road**
**Leicester, LE5 4PW**
**Email: uolsponsor@le.ac.uk**
**Tel: 0116 258 4099/258 4867**

17 November 2015

Professor Thompson G Robinson
Department of Cardiovascular Sciences
Room 224, Robert Kilpatrick Clinical Sciences Building
LE2 7LX

Dear Professor Thompson G Robinson

**Study:** **UNOLE 0538**
**Title:** **The effects of head positioning on beat-to-beat cerebral Haemodynamics: a comparison between acute stroke patients and healthy control subjects**
**Study Status:** **Approved**
**End Date:** **31/03/2017**

I am pleased to advise you that following confirmation of a Favourable Opinion from an Ethics Committee, NHS Trust R&D Approval and where relevant regulatory authority agreements have been received, the University are able to confirm sponsorship for the above research.

Please note you are required to notify the Sponsor and provide copies of:

- Changes in personnel to the Study
- Changes to the end date
- All substantial amendments and provisional and favourable opinions
- All minor amendments
- All serious adverse events (SAEs) and SUSARS
- Annual progress reports
- Annual MHRA (DSUR) safety reports (if applicable)
- End of study declaration form
- Notifications of significant breaches of Good Clinical Practices (GCP)or Protocol

**Please copy the Sponsor into all correspondence and emails by using uolsponsor@le.ac.uk.**

I would like to wish you well with your study and if you require further information or guidance please do not hesitate to contact me.

Yours sincerely

pp

**Mrs Wendy Gamble**
**Research Governance Manager**

**Appendix 2.5** Participant Information Leaflet (Volunteer) Version 3 Dated 10 September 2015



University Hospitals of Leicester NHS
NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT INFORMATION LEAFLET (VOLUNTEER)**

**The Effect of Head Positioning on Beat-to-Beat Cerebral Haemodynamics: a comparison between Acute Stroke Patients and Healthy Control Subjects**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

This is a small research study, which will involve two separate measurements of your blood pressure and blood vessels of the brain. The two measurements will be carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. The two measurements will be spaced over a time period of one week.

This study is being carried by Dr Man Yee LAM as part of a postgraduate educational qualification (MD) with the University of Leicester. The study is being supervised by senior staff from the University of Leicester including Professor Thompson Robinson (Professor of Stroke Medicine), Professor Ronney Panerai (Professor of Physiological Measurement), Dr Amit Mistri, Honorary Senior Lecturer and Dr Victoria Haunton, NIHR Clinical Lecturer. They are all helping to support the research at the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust.

If you decide to take part, you will be asked to sign the Participant Consent form (Volunteer). By signing it, you are telling us that you:

- Understand what you have read;
- Consent to take part in the research study and consent to have the tests that are described
- Consent to the use of your personal and health information as described.

**1. What is the purpose of the study?**

Blood flow to the brain has to be carefully controlled, otherwise there is a risk of too much or too little blood reaching the brain, both of which may be associated with risk and damage. The ability of the brain to control its blood supply is called autoregulation and it may range from no control to perfect control. Certain things affect brain blood flow (autoregulation) including changes in breathing rates and movement. Following acute ischaemic stroke (i.e. a type of stroke due to the blockage of an artery by an embolus or blood clot), blood flow following

the ischaemic event will be significantly reduced and can result death of the brain tissue (core area). This could lead to significant disability or even death of a stroke patient.

However, there is a "penumbral" region surrounding the core area where partial blood flow is maintained. This penumbral region is supplied by collateral circulation, a system of small, normally closed arteries start connecting and carrying blood to part of the brain when the brain artery is blocked. As a result these arteries can serve as alternate routes of blood supply. To improve the blood flow to the collateral circulation and therefore penumbra is considered as one of the important mechanisms to improve blood flow to the brain and therefore, a stroke patients' outcome. At present, we do not know whether we can improve the blood flow into these areas simply by adjusting the head position (i.e. lying flat or sitting up).

We can measure brain blood flow (autoregulation) non-invasively using ultrasound, which detects changes in blood flow in the main brain arteries called the middle cerebral arteries. This research will use these non-invasive measurements of ultrasound to examine brain blood flow changes in different head position (i.e. lying flat and sitting up). This will be done in both healthy volunteers and in patients who have suffered an acute stroke. This knowledge will help doctors to have a better understanding of how head position affects the brain blood flow control in acute stroke patients.

**2. Why have I been chosen?**

Measurements in brain blood flow, in different head positions, will be compared between patients with acute ischaemic stroke disease and volunteers of the same age, sex and blood pressure without stroke disease. You are being invited to participate in this study as a healthy volunteer.

**3. Do I have to take part?**

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You are very welcome to ask questions at any stage of the study. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

**4. What will happen to me if I take part?**

If you agree to join this study, you will have two study tests, which will be approximately 1 week apart. We will arrange for you to come into the hospital for approximately 1 hour. When you come into the hospital, you will be required to discuss this information sheet and sign a consent form. You will then be asked to lie quietly on a bed whilst a small cuff is attached to the fingers of one hand to measure your blood pressure, 3 stickers to your chest to monitor your heart rate, and a small mask over your nose to measure the waste gas from your breathing. You will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against both sides of your head. The head-frame is made of plastic material and able to adjust according to the head size (see figure 1 and 2). Both the head-frame and ultrasound probe will exert a slight pressure on the head. However, this is not painful and is used routinely in many medical units to monitor blood flow to the brain.

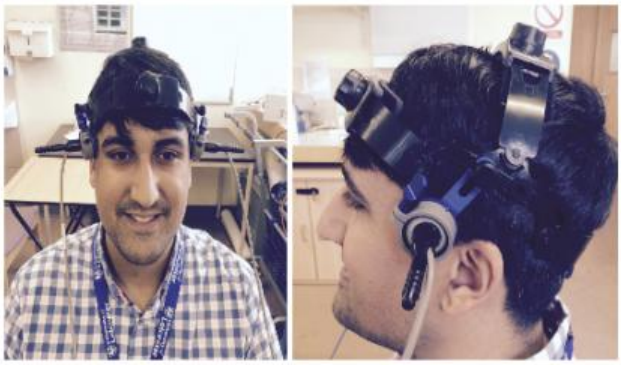


Figure 1 and 2, Head-frame with ultrasound probes

After the readings have stabilised, a recording will be made when you are lying flat, lasting 2 minutes. This will be followed by another recording when your head position slowly changes from lying flat to sitting up position over 30 seconds. We will then take another 5-minute recording while you are in sitting up position, thereafter, you will change from sitting up back to lying flat position over 30 seconds, another 2-minute recording will be carried out while you are in the lying flat position. The same sequence will be repeated twice.

Afterwards, you will lie flat for another couple of minutes to ensure the reading have stabilised again, afterwards, your head position will change from lying flat to sitting up then back to lying flat in 15 seconds. This movement will be repeated approximately four times in 1 minute.

Overall, the whole assessment will last approximately 1 hour.

The second assessment will require you to come back to the hospital approximately one week after the first assessment, when the same set of measurements will be recorded again.

**5. What treatments will be used?**

No specific treatments are given as part of this small study.

**6. What are the possible disadvantages and risks of taking part?**

The blood pressure cuff applies only a gentle pressure to your fingers to enable a blood pressure recording to be made every heartbeat. This may cause a slight tingling in your fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care. The head-frame and ultrasound probes will exert a slight pressure against your head. However, this is not painful, and again is routinely used in many units to monitor blood flow to the brain.

**7. What are the possible benefits of taking part?**

You should not expect to receive any personal benefit from taking part in this study. The study procedures are not diagnostic, and you will not routinely receive the test results. However, it is hoped that this study will help us all to learn more about the stroke disease.

Occasionally, during research studies, incidental abnormalities are found in healthy volunteers. For example, we may find an irregular heart beat or high blood pressure, or another medical condition that the volunteer is not aware of. Should this happen to you, we would tell you what we had found and then notify and liaise with your

general practitioner. Some of these medical conditions, including very high blood pressure, would mean you would not able to further participate in the study.

**8. What if I withdraw from this research study?**

As mentioned previously, if you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

If you decide to withdraw from the study, please notify a member of the research team. This notice will allow the research supervisor to further discuss any health risks or special requirements linked with withdrawing.

If you decide to leave the study, the researchers would like to keep the health information and the data about you that has been collected. This is to help them make sure that the results of the research can be assessed properly. If you do not want them to do this, you must tell them before you join the research study.

**9. Will travel expenses be paid?**

Yes, you will not be out of pocket if you decide to take part in this study. Travel costs to and from the hospital for the study will be reimbursed.

**10. What if something goes wrong?**

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of the study, the normal National Health Service complaints procedures should be available to you.

**11. Will my taking part be kept confidential?**

The blood pressure and blood flow data recorded during the study will be stored on a computer for subsequent analysis. However, you will not be identified by name, and only the researcher will know that the information is related to you. Any information collected during the study will be treated with the usual degree of confidentiality under the Data Protection Act and will not be passed to anyone else without your express permission. Your identity will not be revealed in any publication or presentation of the results from this study. However, with your permission, your own doctor (your GP) will be notified you have participated in the above study and if any health problems are identified that need further tests or treatment.

**12. Who is organising and funding the research?**

This research is coordinated by Professor Robinson and Professor Panerai from the University of Leicester.

**13. How will I find out the results of the research?**

At the end of the study, you will be sent a written letter, in plain English, with a summary of our study findings and conclusions. This can either be posted or emailed to you, depending on your preference.

**14. Whom can I contact?**

**For further information or appointments:**

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the principal research on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam

Role: Clinical Research Fellow of Stroke Medicine

Telephone: 0116 258 7257

Email: ml376@le.ac.uk

**For complaints:**

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Patient Information and Liaison Service (PILS)

Address: The Firs, C/O Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

Free phone line: 08081 788 337

Facsimile: 0116 258 8661

Email: pils@uhl-tr.nhs.uk

Once again, thank you for taking the time to read this information leaflet and for considering taking part in this study.

**Appendix 2.6** Participant Information Leaflet (Patient) Version 5 Dated 10 April 2016



University Hospitals of Leicester NHS
NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT INFORMATION LEAFLET (PATIENT)**

**The Effect of Head Positioning on Beat-to-Beat Cerebral Haemodynamics: a comparison between Acute Stroke Patients and Healthy Control Subjects**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

This is a small research study, which will involve three separate measurements of your blood pressure and blood vessels of the brain. The three measurements will be carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. The first two measurements will take place while you are still an in-patient under the care of the University Hospitals of Leicester NHS Trust Stroke Service, the final measurements will take place approximately 3 months after the stroke onset.

This study is being carried by Dr Man Yee LAM as part of a postgraduate educational qualification (MD) with the University of Leicester. The study is being supervised by senior staff from the University of Leicester including Professor Thompson Robinson (Professor of Stroke Medicine), Professor Ronney Panerai (Professor of Physiological Measurement), Dr Amit Mistri, Honorary Senior Lecturer and Dr Victoria Haunton, NIHR Clinical Lecturer. They are all helping to support the research at the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust.

**1. What is the purpose of the study?**

Blood flow to the brain has to be carefully controlled, otherwise there is a risk of too much or too little blood reaching the brain, both of which may be associated with risk and damage. The ability of the brain to control its blood supply is called autoregulation and it may range from no control to perfect control. Certain things affect brain blood flow (autoregulation) including changes in breathing rates and movement. Following acute ischaemic stroke (i.e. a type of stroke due to the blockage of an artery by an embolus or blood clot), blood flow following the ischaemic event will be significantly reduced and can result in death of the brain tissue (core area). This could lead to significant disability or even death of a stroke patient.

However, there is a "penumbral" region surrounding the core area where partial blood flow is maintained. This penumbral region is supplied by collateral circulation, a system of small, normally closed arteries that start

connecting and carrying blood to part of the brain where the brain artery is blocked. As a result these arteries can serve as alternate routes of blood supply. To improve the blood flow to the collateral circulation and therefore penumbra is considered as one of the important mechanisms to improve blood flow to the brain, and therefore a stroke patients' outcome. At present, we do not know whether we can improve the blood flow into these areas simply by adjusting the head position (i.e. lying flat or sitting up).

We can measure brain blood flow (autoregulation) non-invasively using ultrasound, which detects changes in blood flow in the main brain arteries called the middle cerebral arteries. This research will use these non-invasive measurements of ultrasound to examine brain blood flow changes in different head position (i.e. lying flat and sitting up). This will be done in both healthy volunteers and in patients who have suffered an acute stroke. This knowledge will help doctors to have a better understanding of how the head position affects the brain blood flow control in acute stroke patients.

**2. Why have I been chosen?**

Measurements of brain blood flow, in different head positions, will be compared between patients with acute ischaemic stroke disease and volunteers of the same age, sex and blood pressure without stroke disease. You are being invited to participate in this study as you have had an acute ischaemic stroke.

**3. Do I have to take part?**

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information leaflet to keep and be asked to sign a consent form (patient). You are very welcome to ask questions at any stage of the study. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

**4. What will happen to me if I take part?**

If you agree to join this study, you will have three study tests on three separate days. You will be randomly allocated (like the toss of a coin) to:

1) Transient head position change from 'lying flat' to 'sitting up' position (the whole process will take place approximately one hour), or

2) Persistent lying flat head position in the first 24 hours of hospital admission, or

3) Persistent sitting up head position in the first 24 hours of hospital admission.

**For all patients:**

We will arrange for you to come into the hospital for approximately 1 hour. When you come into the hospital, you will be required to discuss this information leaflet and sign a consent form. You will then be asked to lie quietly on a bed whilst a small cuff is attached to the fingers of one hand to measure your blood pressure, 3 stickers to your chest to monitor your heart rate, and a small mask over your nose to measure the waste gas from your breathing. You will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against both sides of your head. The head-frame is made of plastic material and able to adjust according to head size (see figure). Both the head-frame and ultrasound probe will exert a slight pressure on the head. However, this is not painful and is used routinely in many medical units to monitor blood flow to the brain.

Figure: Head-frame and ultrasound probes

**For patients randomised to transient head position change:**

After the readings have stabilised, a recording will be made when you are lying flat, lasting 2 minutes. This will be followed by another recording when your head position slowly changes from lying flat to sitting up position over 30 seconds. We will then take another 5-minute recording while you are in sitting up position, thereafter, you will change from a sitting up back to lying flat position over 30 seconds, another 2-minute recording will be carried out while you are in lying flat position. The same sequence will be repeated twice.

Afterwards, you will lie flat for another two minutes to ensure the reading have stabilised again. Afterwards, your head position will change from lying flat to sitting up then back to lying flat in 15 seconds. This movement will be repeated approximately four times during a 1 minute period.

Overall, the whole assessment will take approximately 1 hour.

For the second and third assessments, you will be asked to discuss the progress of stroke disease (i.e. any recurrent stroke events), new medical events, medication changes or intervention carried out during this period of time. We will then carry out the same set of measurement as before.

**For patients randomised to persistent head position (for the first 24 hours of hospital admission):**

The first assessment will carried out soon after your allocated head position is noted. After the readings have stabilised, a recording will be made in your allocated head position, lasting 5 minutes. This will be followed by another 5 minutes recording when the arm will be flexed and extended at the elbow on one side of the body, then followed by another 5 minutes recording when breathing a slightly higher than normal, but safe, concentration of waste gas (5% carbon dioxide). Overall, the whole assessment will take approximately 45 minutes.

During the 24 hours of allocated head position, you will have a swallow screen and/or swallow assessment as a standard hospital protocol, and be allocated to any type of feeding according to the local hospital protocols. If you have been allocated to lying flat position, you are allowed to sit up for a short period of time (less than 30 minutes) on no more than 3 occasions during the 24-hour period for period for feeding and toileting. If you are allocated to sitting up head position, in exceptional circumstances, i.e. to perform imaging, you can be nursed with your head lowered. You are allowed to have 'lying flat' head position for a short period of time (less than 30

minutes) on no more than 3 occasions during the 24-hour period for feeding and toileting. However, if you cannot tolerate a persistent 'lying flat' or 'sitting up' head position, you will not be invited to participate in the study.

For the second and third assessments, you will be asked to discuss the progress of stroke disease (i.e. any recurrent stroke events), new medical events, medication changes or intervention carried out during this period of time. We will then carry out the same set of measurement as before.

**5. What treatments will be used?**

No specific treatments are given as part of this small study.

**6. What are the possible disadvantages and risks of taking part?**

The blood pressure cuff applies only a gentle pressure to your fingers to enable a blood pressure recording to be made every heartbeat. This may cause a slight tingling in your fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care. The head-frame and ultrasound probes will exert a slight pressure against your head. However, this is not painful, and again is routinely used in many units to monitor blood flow to the brain.

For the manoeuvre to breathe in 5% carbon dioxide (waste gas), a face mask will be placed covering the nose and mouth, some people find this uncomfortable, but there are no side effects of the carbon dioxide as the concentration being used for the purpose of this study is very low.

**7. What are the possible benefits of taking part?**

You should not expect to receive any personal benefit from taking part in this study. The study procedures are not diagnostic, and you will not routinely receive the test results. However, it is hoped that this study will help us all to learn more about the stroke disease.

**8. What if I withdraw from this research study?**

As mentioned previously, if you decide to take part in the study you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. Furthermore, the research team can also decide to withdraw you from the study if they believe it is in your best interest, i.e. progression of the stroke disease which requires discontinuation of the study.

If you decide to withdraw from the study, please notify a member of the research team. This notice will allow the research supervisor to further discuss any health risks or special requirements linked with withdrawing.

If you decide to leave the study, the researchers would like to keep the health information and the data about you that has been collected. This is to help them make sure that the results of the research can be assessed properly. If you do not want them to do this, you must tell them before your join the research study.

In the extremely unfortunate and unusual circumstance that you become more unwell and lose the ability to decide whether you should continue to participate in this research study, the research team would not invite you to continue participate in this research study. However, the research team would still like to keep the health information and the data about you that has been collected so far for the final analysis. If you do not want them to do this, you must also tell them before you join the research study.

**9. Will travel expenses be paid?**

Yes, you will not be out of pocket if you decide to take part in this study. Travel costs to and from the hospital for the study will be reimbursed.

**10. What if something goes wrong?**

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of the study, the normal National Health Service complaints procedures should be available to you.

**11. Will my taking part be kept confidential?**

The blood pressure and blood flow data recorded during the study will be stored on a computer for subsequent analysis. However, you will not be identified by name, and only the researcher will know that the information is related to you. Any information collected during the study will be treated with the usual degree of confidentiality under the Data Protection Act and will not be passed to anyone else without your express permission. Your identity will not be revealed in any publication or presentation of the results from this study. However, with your permission, your own doctor (your GP) will be notified you have participated in the above study and if any health problems are identified that need further tests or treatment.

**12. Who is organising and funding the research?**

This research is coordinated by Professor Robinson and Professor Panerai from the University of Leicester.

**13. How will I find out the results of the research?**

At the end of the study, you will be sent a written letter, in plain English, with a summary of our study findings and conclusions. This can either be posted or emailed to you, depending on your preference.

**14. Whom can I contact?**

**For further information or appointments:**

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the principal research on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam

Role: Clinical Research Fellow of Stroke Medicine

Telephone: 0116 258 7257

Email: ml376@le.ac.uk

**For complaints:**

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Patient Information and Liaison Service (PILS)

Address: The Firs, C/O Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

Free phone line: 08081 788 337

Facsimile: 0116 258 8661

Email: pils@uhl-tr.nhs.uk

Once again, thank you for taking the time to read this information sheet and for considering taking part in this study.

**Appendix 2.7** Personal Consultee Information Leaflet Version 2 Dated 10 February 2016



University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PERSONAL CONSULTEE INFORMATION LEAFLET**

**The Effect of Head Positioning on Beat-to-Beat Cerebral Haemodynamics: a comparison between Acute Stroke Patients and Healthy Control Subjects**

Your friend/relative is being invited to take part in a research study. However, due to the nature of the illness, he/she is unable to decide for himself/herself whether to participate in the research study at the moment. To help decide if he/she should join the study, we would like to ask your opinion whether or not he/she would want to be involved. We would ask you to set aside your own views and consider his/her interests and what you feel would be his/her wishes and feelings. Any advanced directive that he/she may have made and that you are aware of should take precedence.

Before you decide whether to take on the personal consultee role, it is important for you to understand 1) what is a personal consultee 2) the personal consultee's role and responsibility and 3) why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. The following information leaflet is the same as would have been provided to your friend/relative.

Thank you for reading this.

**1. What is a personal consultee?**

It is fairly common for patients who suffer acute stroke to lose the ability to make decisions for themselves (i.e. they lack capacity), this could be due to difficulty in communication, reduced consciousness level (alertness) or confusion. In order to involve patients who lack of capacity in research, under legislation (the Mental Capacity Act 2005), the research team must seek advice from the patient's personal consultee.

A personal consultee is someone who knows the patient and has a role in caring for the patient or is interested in the patient's welfare. A personal consultee is someone whom the patient who lacks of capacity would trust with important decisions about their welfare. He/she should be someone who can advise the researcher about the wishes and feelings of the patient who lacks of capacity in relation to the project and whether they would want to join the research study. A personal consultee is usually someone with a close personal relationship with the patient, for example, next of kin, spouse, partner or friend.

**2. What is the role and the responsibility of a personal consultee?**

A personal consultee must themselves have the ability to make a decision at the time and be prepared to be consulted by the research team about the possible involvement of the patient who lacks capacity. They should be able to advise the research team whether the patient who lacks capacity should take part in the project. For example, the personal consultee should consider whether the person who lacks capacity would be content to take part or whether doing so might upset them. The personal consultee must also give their opinion on what the past and present wishes and feelings of the patient who lacks capacity would have been about taking part in the research study. The personal consultee must set aside any views they may have about the research and consider only the views and interests of the patient who lacks capacity.

It is also important to remember that the personal consultee gives advice but is not being asked to consent on behalf of the patient who lacks capacity. The responsibility to decide whether the patient should be entered into the research lies ultimately with the researcher. However, we always respect the personal consultee's view and if the personal consultee objects to the inclusion of the patient in this research study, his/her view will be respected and the patient will not be enrolled in the study.

If you are unsure about taking the role of the personal consultee you may seek independent advice. We will understand if you do not want to take on this responsibility.

**3. Why this research study is being done?**

This is a small research study, which will involve three separate measurements of blood pressure and blood vessels of the brain. The three measurements will be carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. The first measurement will take place while your friend/relative is still an in-patient under the care of the University Hospitals of Leicester NHS Trust Stroke service, the second measurement will take place approximately 72 hours after the stroke onset and the final measurement will take place approximately 3 months after the stroke onset.

This study is being carried by Dr Man Yee LAM as part of a postgraduate educational qualification (MD) with the University of Leicester. The study is being supervised by senior staff from the University of Leicester including Professor Thompson Robinson (Professor of Stroke Medicine), Professor Ronney Panerai (Professor of Physiological Measurement), Dr Amit Mistri, Honorary Senior Lecturer and Dr Victoria Haunton, NIHR Clinical Lecturer. They are all helping to support the research at the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust.

**4. What is the purpose of the study?**

Blood flow to the brain has to be carefully controlled, otherwise there is a risk of too much or too little blood reaching the brain, both of which may be associated with risk and damage. The ability of the brain to control its blood supply is called autoregulation and it can be ranged from no control to perfect control. Certain things affect brain blood flow (autoregulation) including changes in breathing rates and movement. In the acute ischaemic stroke (i.e. a type of stroke due to the blockage of an artery by an embolus or blood clot), blood flow following the ischaemic event will be significantly reduced and subsequently it could result in brain tissue (core area) death. This could lead to significant disability or even death of a stroke patient.

However, there is a "penumbral" region surrounding the core area where partial blood flow is maintained. This penumbral region is supplied by a collateral circulation, a system of small, normally closed arteries start

connecting and carrying blood to part of the brain when the brain artery is blocked. As a result these arteries can serve as alternate routes of blood supply. To improve the blood flow to the collateral circulation and therefore penumbral region is considered as one of the important mechanisms to improve blood flow to the brain and therefore, a stroke patients' outcome. At present, we do not know whether we can improve the blood flow into these areas simply by adjusting the head position (i.e. lying flat or sitting up).

We can measure brain blood flow (autoregulation) non-invasively using ultrasound, which detects changes in blood flow in the main brain arteries called the middle cerebral arteries. This research will use these non-invasive measurements of ultrasound to examine brain blood flow changes in different head positions (i.e. lying flat and sitting up). This will be done in both healthy volunteers and in patients who suffered acute stroke. This knowledge will help doctors to have better understanding on how the head position affects the brain blood flow control in acute stroke patients.

**5. Why has your friend/relative been chosen?**

Measurements in brain blood flow, in different head positions, will be compared between patients with acute ischaemic stroke disease and volunteers of the same age, sex and blood pressure without stroke disease. Your friend/relative is being invited to participate in this study as he/she has suffered an acute ischaemic stroke.

**6. Does he/she has to take part?**

It is up to you to decide whether or not he/she should take part. If you decide your relative/friend would have no objection to taking part we will ask you to read and sign the Personal Consultee Declaration form. We will then give both you and your friend/relative a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or you think your relative/friend should be withdrawn. Even if you have decided for your friend/relative would have no objection to take part in the study, you are still free to request he/she to withdrawn from the study at anytime, and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care he/she receives.

**7. What will happen to me if your friend/relative takes part?**

If you agree for your friend/relative to join this study, he/she will have three study tests on three separate days. He/she will be randomly allocated (like the toss of a coin) to:

1) Transient head position transition from 'lying flat' to 'sitting up' position (the whole process will take place approximately one hour), or

2) Persistent 'lying flat' head position in the first 24 hours of hospital admission, or

3) Persistent 'sitting up' head position in the first 24 hours of hospital admission.

**For all patients:**

We will arrange for you and your friend/relative to come into the hospital for approximately 1 hour. When both of you arrive the hospital, you will be required to discuss this information leaflet and sign the Personal Consultee Declaration Form. He/she will then be asked to lie quietly on a bed whilst a small cuff is attached to the fingers of one hand to measure the blood pressure, 3 stickers to the chest to monitor heart rate, and a small mask over the nose to measure the waste gas from breathing. He/she will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against both sides of the head. The head-frame is made of plastic material and able to adjust according to head size (see figure). Both the head-frame and

ultrasound probe will exert a slight pressure on to head. However, this is not painful and is used routinely in many medical units to monitor blood flow to the brain.

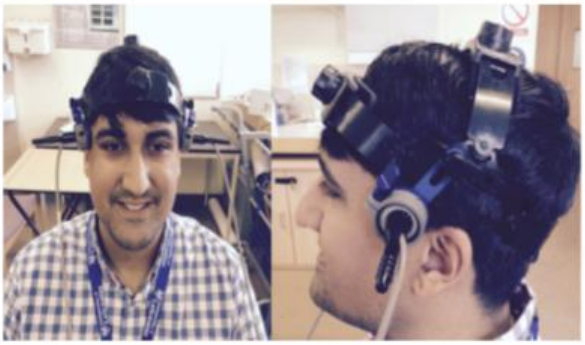


Figure: Head-frame and ultrasound probes

**For patients randomised to transient head position transition:**

After the readings have stabilised, a recording will be made when your friend/relative is lying flat, lasting 2 minutes. This will be followed by another recording when his/her head position slowly changes from a lying flat to sitting up position over 30 seconds. We will then take another 5-minute recording while he/she is in sitting up position, thereafter, he/she will change from a sitting up back to lying flat position over 30 seconds, another 2-minute recording will be carried out while he/she is in the lying flat position. The same sequence will be repeated twice.

Afterwards, your friend/relative will lie flat for another two minutes to ensure the readings have stabilised again, afterwards, his/her head position will change from lying flat to sitting up then back to lying flat in 15 seconds. This movement will be repeated approximately four times in 1 minute.

Overall, the whole assessment will last approximately 1 hour.

For the second (72 hours post stroke onset) and third assessment (3 months post stroke onset), you will be asked to discuss the progress of stroke disease (i.e. any recurrent stroke events), new medical events, medication changes or interventions carried out during this period of time on behalf of your friend/relative. You will be asked again to read the information leaflet and sign the Personal Consultee Declaration Form. We will then carry out the same set of measurements as before.

**For patients randomised to persistent head position (for the first 24 hours of hospital admission):**

The first assessment will carried out soon after your friend/relative's allocated head position is noted. After the readings have stabilised, a recording will be made in your friend/ relative's allocated head position, lasting 5 minutes. This will be followed by another 5 minutes recording when the arm will be flexed and extended at the elbow on one side of the body, then followed by another 5 minutes recording when breathing a slightly higher

than normal, but safe, concentration of waste gas (5% carbon dioxide). Overall, the whole assessment will take approximately 45 minutes.

During the 24 hours of allocated head position, your friend/relative can have a swallow screen and/or swallow assessment, and be allocated to any type of feeding according to the local hospital protocols. If your friend/relative have been allocated to lying flat position, they are allowed to sit up for a short period of time (less than 30 minutes) on no more than 3 occasions during the 24- hour period for period for feeding and toileting. If your friend/relative is allocated to sitting up head position, in exceptional circumstances, i.e. to perform imaging, they can be nursed with their head lowered. They are allowed to have 'lying flat' head position for a short period of time (less than 30 minutes) on no more than 3 occasions during the 24-hour period for feeding and toileting. However, if your friend/relative cannot tolerate a persistent 'lying flat' or 'sitting up' head position, they will not be invited to participate in the study.

For the second and third assessments, you will be asked to discuss the progress of stroke disease (i.e. any recurrent stroke events), new medical events, medication changes or intervention carried out during this period of time on behalf of your friend/relative. You will be asked to read the information leaflet and sign the Personal Consultee Declaration Form. We will then carry out the same set of measurement as before.

**8. What treatments will be used?**

No specific treatments are given as part of this small study.

**9. What are the possible disadvantages and risks of taking part?**

The blood pressure cuff applies only a gentle pressure to fingers to enable a blood pressure recording to be made every heartbeat. This may cause a slight tingling in fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care. The head-frame and ultrasound probes will exert a slight pressure against the head. However, this is not painful, and again is routinely used in many units to monitor blood flow to the brain.

For the manoeuvre to breathe in 5% carbon dioxide (waste gas), a face mask will be placed covering the nose and mouth, some people find this uncomfortable, but there are no side effects of the carbon dioxide as the concentration being used for the purpose of this study is very low.

**10. What are the possible benefits of taking part?**

Both you and your friend/relative should not expect to receive any personal benefit from taking part in this study. The study procedures are not diagnostic, neither you nor your friend/relative will routinely receive the test results. However, it is hoped that this study will help us all to learn more about the stroke disease.

**11. What happen if I withdraw my friend/relative from the study?**

Even if you have decided your friend/relative would have no objection to take part in the study, you are still free to request to withdraw him/her from the study at any time, without giving a reason or affecting the care he/she receives. Furthermore, the research team can also decide to withdraw your friend/relative from the study if they believe it is in his/her best interest, i.e. progression of the stroke disease which requires discontinuation of the study.

If you decide to withdraw your friend/relative from the study, please notify a member of the research team. This notice will allow the research supervisor to further discuss any health risks or special requirements linked with withdrawing.

If you decide for your friend/relative to leave the study, the researchers would like to keep the health information and data about your friend/relative that has been collected so far. This is to help them make sure that the results of the research can be assessed properly. If you do not want them to do this, you must tell them before your friend/relative joins the research study.

**12. What happen if I withdraw myself as the Personal Consultee?**

Even if you have decided to take on the role of Personal Consultee, you are still free to withdraw yourself from this role at any time, without giving a reason or affecting the care your friend/relative receives. Should this situation occur we would kindly ask you to nominate someone else to take on the role of Personal Consultee. However, if you feel that no one can take on the role, we will not invite your friend/relative to continue to participate in the study. Should this situation occur, the researchers would also like to keep the health information and data about your friend/relative that has been collected so far. If you do not want them to do this, you must also tell them before your friend/relative joins the research study.

**13. What happen if my friend/relative regains the ability to make decisions for themselves (capacity) during the study period?**

If your friend/relative regains capacity during the study period, he/she would need to give us full informed written consent themselves in order to continue to participate in the study. We will explain the details of the research study to your friend/relative and provide a Participant (patient) information leaflet as well. The research team will answer any questions that your friend/ relative has concerning the study and he/she will also have the opportunity to ask questions of the research team, his/her GP or other independent parties to decide whether he/she would like to continue to participate in the study.

If your friend/relative does not wish to remain in the study, he/she will be withdrawn from the study. Unless your friend/relative agrees for the research team to retain and analysis any health information and data collected so far, all of these will also be destroyed.

**14. Will travel expenses be paid?**

Yes, both yourself and your friend/relative will not be out of pocket if you decide your friend/relative has no objection to taking part in this study. Travel costs to and from the hospital for the study will be reimbursed.

**15. What if something goes wrong?**

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of the study, the normal National Health Service complaints procedures should be available to you.

**16. Will my taking part be kept confidential?**

The blood pressure and blood flow data recorded during the study will be stored on a computer for subsequent analysis. However, your friend/relative will not be identified by name, and only the researcher will know that the

information is related to your friend/relative. Any information collected during the study will be treated with the usual degree of confidentiality under the Data Protection Act and will not be passed to anyone else without your express permission. Your friend/relative's identity will not be revealed in any publication or presentation of the results from this study. However, with your permission, your friend/relative's own doctor (GP) will be notified he/she has participated in the above study and if any health problems are identified that need further tests or treatment.

**17. Who is organising and funding the research?**

This research is coordinated by Professor Robinson and Professor Panerai from the University of Leicester.

**18. How will I find out the results of the research?**

At the end of the study, you and your friend/relative will be sent a written letter, in plain English, with a summary of our study findings and conclusions. This can either be posted or emailed to you and your friend/relative, depending on your preference.

**19. Whom can I contact?**

**For further information or appointments:**

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the Principal Investigator on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam

Role: Clinical Research Fellow of Stroke Medicine

Telephone: 0116 258 7257

Email: ml376@le.ac.uk

**For complaints:**

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Patient Information and Liaison Service (PILS)

Address: The Firs, C/O Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

Free phone line: 08081 788 337

Facsimile: 0116 258 8661

Email: pils@uhl-tr.nhs.uk

Once again, thank you for taking the time to read this information leaflet.

**Appendix 2.8** Participant Consent Form (Volunteer) Version 3 Dated 10th September 2015

University Hospitals of Leicester NHS
NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT CONSENT FORM (VOLUNTEER)**

**The Effects of Head Positioning on Beat-to-Beat Cerebral Haemodynamics: a comparison between Acute Stroke Patients and Healthy Control Subjects**

**Researcher Name: Dr** _____ **Please initial**

**Patient Study ID Number:** _____

| | |
|---|---|
| I confirm that I have read and understand the Information Leaflet (Version 3, dated 10th September 2015) for the above study, and have had the opportunity to ask questions and have had these answered satisfactorily. | ☐ |
| I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected. | ☐ |
| I understand that relevant sections of my medical notes and/or data collected during the study, may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. I give permission for these individuals to have access to my records. | ☐ |
| I understand that if I decide to withdraw prior to the completion of the study, the researcher would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |
| I understand that my GP will be informed about my participation in this study, and by signing this consent form I am granting permission for this. | ☐ |
| I agree to take part in the above study. | ☐ |

Participant Name:_____ Date:_____ Signature: _____

Witness Name: _____ Date:_____ Signature: _____

Researcher: _____ Date:_____ Signature: _____

(File: 1 for participant, 1 for researcher) Version 3, 10th September, 2015

**Appendix 2.9** Participant Consent Form (Patient) Version 4 Dated 10th February 2016

University Hospitals of Leicester NHS
NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT CONSENT FORM (PATIENT)**

**The Effects of Head Positioning on Beat-to-Beat Cerebral Haemodynamics: a comparison between Acute Stroke Patients and Healthy Control Subjects**

**Researcher Name: Dr** _____ **Please initial**

**Patient Study ID Number:** _____

| | |
|---|---|
| I confirm that I have read and understand the Information Leaflet (Version 4, Dated 10th February, 2016) for the above study, and have had the opportunity to ask questions and have had these answered satisfactorily. | ☐ |
| I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected. | ☐ |
| I understand I will be contacted by the research team via telephone approximately 3 months after my stroke onset, to collect information regarding my stroke recovery and any other health-related issues. | ☐ |
| I understand that if I decide to withdraw prior to the completion of the study, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |
| I understand that my GP will be informed about my participation in this study, and by signing this consent form I am granting permission for this. | ☐ |
| I understand that in the unusual circumstance that I became unwell and lose the ability to decide whether I should continue to participate in the research study, the research team would withdraw me from the study. However, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |

I understand that relevant sections of my medical notes and/or data collected during the study, may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. I give permission for these individuals to have access to my records. ☐

I agree to take part in the above study. ☐

Participant Name:_____ Date:_____ Signature: _____

Witness Name: _____ Date:_____ Signature: _____

Researcher: _____ Date:_____ Signature: _____

(File: 1 for patient, 1 for researcher, 1 for hospital notes)

Version 4, 10th February 2016

**Appendix 2.10** Personal Consultee Declaration Form Version 2 Dated 10th February 2016

University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PERSONAL CONSULTEE DECLARATION FORM**

**The Effects of Head Positioning on Beat-to-Beat Cerebral Haemodynamics: a comparison between Acute Stroke Patients and Healthy Control Subjects**

**Researcher Name: Dr** _____ **Please initial**

**Patient Study ID Number:** _____

| | |
|---|---|
| I (name of Personal Consultee) have been consulted about (name of potential Participant)'s participation in this research study. I confirm that I have read and understand the Personal Consultee Information Leaflet (Version 2, Dated 10th February 2016) for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily. | ☐ |
| I understand that I can refuse to act as a Personal Consultee at anytime, by signing this form I am agreeing to act as a Personal Consultee. | ☐ |
| I understand that (name of potential participant)'s participation is voluntary and that I am free to withdraw him/her any time, without giving a reason, without any medical care or legal rights being affected. | ☐ |
| In my opinion (name of potential participant) would have no objection to taking part in the above study . | ☐ |
| I agree to (name of potential participant)'s GP or other care professional being informed of his/her participation of the study. | ☐ |
| I understand that if I decide to withdraw (name of potential participant) prior to the completion of the study, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am in agreement with this. | ☐ |

I understand that in the unusual circumstance that I became unwell and lose the ability to decide whether (name of potential participant) should continue to participate in the research study, the research team would withdraw (name of participant) from the study. However, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am in agreement with this. ☐

I understand that relevant sections of his/her medical notes and/or data collected during the study, may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. ☐

Personal Consultee Name: _____ Date:_____ Signature:_____

Relationship to participant: _____

Researcher: _____ Date:_____ Signature: _____

(File: 1 for patient, 1 for Personal Consultee, 1 for researcher site file, 1 for hospital notes)

Version 2, 10th February 2016

**Appendix 2.11** GP Information Leaflet (Volunteer) Version 3 Dated 10th September 2015

University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**GP INFORMATION LEAFLET (Volunteer)**

**The Effects of Head Positioning on Beat-to-Beat Cerebral Haemodynamics: a comparison between Acute Stroke Patients and Healthy Control Subjects**
**REC: 15/WA/0328**

Dear Dr GP

**Re:**
**Name**
**DOB:**
**Address:**

Your patient above has been recruited as a healthy control to the above study, which is being carried out by researchers at the University of Leicester. The study involves measurement of beat to beat blood pressure and heart rate, along with measurement of cerebral blood flow velocity using Transcranial Doppler.

As part of this study, your patient will be required to attend 2 assessments which are approximately one week apart. They have been counselled regarding this.

Participation in the above study is entirely voluntary.

If you have any further questions regarding this trial, please contact us on the details below.

Yours Faithfully,

Dr Man Yee LAM BSc MBBS MRCP(UK)
Honorary Clinical Research Fellow/Honorary Specialist Registrar of Stroke Medicine

Telephone 0300 303 1573 (Extension 7257)

On behalf of Professor T G Robinson BMedSci, MBBS, MD, FRCP
Professor of Stroke Medicine/Honorary Consultant Physician

**Appendix 2.12** GP Information Leaflet (Patient) Version 3 Dated 10th September 2015

University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**GP INFORMATION LEAFLET (Patient)**

**The Effects of Head Positioning on Beat-to-Beat Cerebral Haemodynamics: a comparison between Acute Stroke Patients and Healthy Control Subjects**
**REC: 15/WA/0328**

Dear Dr GP

**Re:**
**Name**
**DOB**
**Address:**

Your patient above has been recruited to the above study, which is being carried out by researchers at the University of Leicester. The study involves measurement of beat to beat blood pressure and heart rate, along with measurement of cerebral blood flow velocity using Transcranial Doppler.

As part of this study, patient will be required to participate for up to 3 months post stroke symptom onset, during which up to a total of 3 assessments will be made. They have been fully counselled regarding this.

Participation in the above study is entirely voluntary.

If you have any further questions regarding this trial, please contact us on the details below.

Yours Faithfully,

Dr Man Yee LAM BSc MBBS MRCP(UK)
Honorary Clinical Research Fellow/Honorary Specialist Registrar of Stroke Medicine

Telephone 0300 303 1573 (Extension 7257)

On behalf of Professor T G Robinson BMedSci, MBBS, MD, FRCP
Professor of Stroke Medicine/Honorary Consultant Physician

**Appendix 2.13** Research Participant Poster Version 2 Dated 10th September 2015

# Research Participants Needed!

We are looking at how to maximise brain blood flow in Stroke patients by changing head position. But first we need to establish a baseline – how healthy adults perform on the same test.

**We need volunteers to take the test. It involves non-invasive measurements of your blood pressure and brain blood vessels.**

**Who?** Aged 18 or above , do **NOT** practice yoga regularly (i.e. more than once weekly)

***Where?*** Cardiovascular Research Laboratory, Windsor Building, Leicester Royal Infirmary

**How long will it take?** You will have two study tests, approximately 1 week apart, each study will take approximately 1 hour.

**How will my data be used?** Your data will be anonymised. A written letter regarding a summary of the study findings will be sent to you when the study is completed.

**If you are aged 18 or above**, do **NOT practice yoga regularly and interested in the study:**

Contact Dr Manda LAM, Clinical Research Fellow in Stroke Medicine

ml376@le.ac.uk

Tel: 0116 258 7257

University of Leicester

University Hospitals of Leicester NHS NHS Trust

Research Participant Poster Version 2 Dated 10 September 2015

# Appendix 3: Cerebral Haemodynamic in Stroke Thrombolysis (CHiST) Study (Chapter 8)

# (Approvals and Information Sheet)

**Appendix 3.1** Ethical Approval Letter Dated 23rd December 2015

NHS
Health Research Authority
East Midlands - Nottingham 1 Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839269

23 December 2015

Professor Thompson G Robinson
Professor of Stroke Medicine/Honorary Consultant Physician
University of Leicester/University Hospitals of Leicester NHS Trust
Department of Cardiovascular Sciences
Room 224, Robert Kilpatrick Clinical Sciences Building
PO BOX 65, University of Leicester, Leicester, United Kingdom
Leicester Royal Infirmary, PO Box 65
Leicester
LE2 7LX

Dear Professor Robinson

| | |
|---|---|
| **Study title:** | **Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study** |
| **REC reference:** | **15/EM/0485** |
| **Protocol number:** | **UNOLE 0542** |
| **IRAS project ID:** | **186865** |

Thank you for your letter of 18 December 2015, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Rachel Nelson;

NRESCommittee.EastMidlands-Nottingham1@nhs.net

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above

research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

**Mental Capacity Act 2005**

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

**Conditions of the favourable opinion**

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).*

*Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.*

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of management permissions from host organisations*

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**Ethical review of research sites**

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| Covering letter on headed paper [Covering Letter ] | | 10 October 2015 |
| Covering letter on headed paper [Covering Letter ] | | 12 December 2015 |
| Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor - Indemnity for the study ] | | 07 September 2015 |
| GP/consultant information sheets or letters [GP Information leaflet ] | 2 | 25 August 2015 |
| IRAS Checklist XML [Checklist_14102015] | | 14 October 2015 |
| Other [Dr Amit Mistri CV ] | | 03 August 2015 |
| Other [Dr Victoria Haunton CV] | | 03 August 2015 |
| Other [University of Leicester clincal Trials Insurance ] | | 03 August 2015 |
| Other [University of Leicester Professional Indemnity Insurance ] | | 03 August 2015 |
| Other [REC Response Letter ] | | 28 November 2015 |
| Participant consent form [Participant Consent Form (Non-rtPA Treated Patient) ] | 2 | 25 August 2015 |
| Participant consent form [Participant Consent Form (rtPA-Treated Patient) Short Version ] | 2 | 25 August 2015 |
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| REC Application Form [REC_Form_14102015] | | 14 October 2015 |
| Research protocol or project proposal [MD Protocol ] | 0.2 | 25 August 2015 |
| Research protocol or project proposal [MD Protocol ] | 0.3 | 28 November 2015 |
| Summary CV for Chief Investigator (CI) [Professor Robinson CV] | | 11 August 2015 |
| Summary CV for student [Dr Man Yee Lam CV] | | 11 July 2015 |

| | | |
|---|---|---|
| Summary CV for supervisor (student research) [Professor Panerai CV] | | 14 August 2015 |

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

**User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

**HRA Training**

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

| | |
|---|---|
| **15/EM/0485** | **Please quote this number on all correspondence** |

With the Committee's best wishes for the success of this project.

Yours sincerely

P.P

**Appendix 3.2** Ethical Approval Letter 2 Re-issued on 3rd March 2016

Re-Issue to correct version numbers 03.03.2016 TA

NHS
Health Research Authority
East Midlands - Nottingham 1 Research Ethics Committee
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839269

23 December 2015

Professor Thompson G Robinson
Professor of Stroke Medicine/Honorary Consultant Physician
University of Leicester/University Hospitals of Leicester NHS Trust
Department of Cardiovascular Sciences
Room 224, Robert Kilpatrick Clinical Sciences Building
PO BOX 65, University of Leicester, Leicester, United Kingdom
Leicester Royal Infirmary, PO Box 65
Leicester
LE2 7LX

Dear Professor Robinson

| | |
|---|---|
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| **REC reference:** | **15/EM/0485** |
| **Protocol number:** | **UNOLE 0542** |
| **IRAS project ID:** | **186865** |

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NRESCommittee.EastMidlands-Nottingham1@nhs.net

**Confirmation of ethical opinion**

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above

Re-Issue to correct version numbers 03.03.2016 TA

research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

**Mental Capacity Act 2005**

I confirm that the committee has approved this research project for the purposes of the Mental Capacity Act 2005. The committee is satisfied that the requirements of section 31 of the Act will be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

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*Sponsors are not required to notify the Committee of management permissions from host organisations*

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To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

Re-Issue to correct version numbers 03.03.2016 TA

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**Ethical review of research sites**

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**Approved documents**

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| Covering letter on headed paper [Covering Letter ] | | 12 December 2015 |
| Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Sponsor - Indemnity for the study ] | | 07 September 2015 |
| GP/consultant information sheets or letters [GP Information leaflet ] | 2 | 25 August 2015 |
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| Summary CV for supervisor (student research) [Professor Panerai CV] | | 14 August 2015 |

**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Re-Issue to correct version numbers 03.03.2016 TA

**User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

**HRA Training**

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

| **15/EM/0485** | **Please quote this number on all correspondence** |
|---|---|

With the Committee's best wishes for the success of this project.

Yours sincerely

P.P

**Dr Carl Edwards Chair**

Email:NRESCommittee.EastMidlands-Nottingham1@nhs.net

*Enclosures:* "After ethical review – guidance for researchers"

*Copy to:* *Mrs Wendy Gamble*
*Ms Carolyn Maloney , Research and Development Manager, Research and Development Office*

**Appendix 3.3** R and D Approval Dated 6th April 2016

Fw: CHIST - EDGE ID 52232

**Sent:** 06 April 2016 11:59
**To:** Lam Man Yee - Specialist Registrar
**Cc:** Hill Jayne - Research Governance Lead; Mistri Amit - Consultant In Stroke Medicine
**Subject:** CHIST - EDGE ID 52232

Dear Manda

I am pleased to confirm that with effect from the date of this email, the above study has Trust Research & Innovation authorisation to commence at University Hospitals of Leicester NHS Trust. The research must be conducted in line with the Protocol and fulfil any contractual obligations agreed. If you identify any issues during the course of your research that are likely to affect these obligations you must contact the R&I Office as soon as possible.

In order for the UHL Trust to comply with targets set by the Department of Health through the 'Plan for Growth', there is an expectation that the first participant will be recruited within 70 days of receipt of a Valid Application. The date that a Valid application was received was **23rd March 2016.** You therefore have **86 days** remaining to recruit your first participant. **It is essential that you notify the UHL Data Management Team as soon as you have recruited your first participant to the study, and ensure that the date is recorded on the EDGE Database by your local EDGE User. The UHL Data Management team can be contacted on RIData@uhl-tr.nhs.uk or by phone 0116 258 4573.**

If we have not heard from you within the specified time period we will contact you not only to collect the data, but also to record any issues that may have arisen to prevent you from achieving this target. It is essential that you get in touch with us if there is likely to be a problem in achieving this target so that we can discuss potential solutions. The Trust is contractually obliged to meet the 70 day target and if an adequate reason acceptable to the NIHR has not been submitted to explain the issues preventing the recruitment of your first participant, the Trust will be financially penalised. In addition, we are required to publish the Title, REC Reference number, local target recruitment and actual recruitment as well as 70 days data for this study on a quarterly basis on the UHL public accessed website.

Undertaking research in the NHS comes with a range of regulatory responsibilities. Please ensure that you and your research team are familiar with, and understand the roles and responsibilities both collectively and individually.

Documents listing the roles and responsibilities for all individuals involved in research can be found on the R&I pages of the Public Website. It is important that you familiarise yourself with the Standard Operating Procedures, Policies and all other relevant documents which can be located by visiting http://www.leicestersresearch.nhs.uk/standard-operating-procedures/

The R&I Office is keen to support and facilitate research where ever possible. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office. Our contact details are provided on the attached sheet.

**Please note that a letter confirming authorisation will not be sent. Please retain a copy of this email in your site file.**

We wish you every success with your research.

With Best Wishes
Carolyn
Mrs. Carolyn Maloney
Head of Research Operations

0116 258 4109 (LGH) Mon, Tues & Fri
07903 877501 (Mobile) Weds & Thurs
LRI Base Weds / GGH Base Thurs.

RESEARCH & INNOVATION

**Appendix 3.4** Sponsor Approval Dated 7th April 2016

UNIVERSITY OF LEICESTER

**Research & Enterprise Division**
**University of Leicester**
**Research Governance Office**
**Academic Department, Ground Floor**
**Leicester General Hospital**
**Gwendolen Road**
**Leicester, LE5 4PW**
**Email: uolsponsor@le.ac.uk**
**Tel: 0116 258 4099/258 4867**

7 April 2016

Professor Robinson
Department of Cardiovascular Sciences,
Robert Kilpatrick Clinical Sciences Building,
Leicester Royal Infirmary
LE2 7LX

Dear Professor Robinson

**Study:** 0542
**Title:** Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study
**Study Status:** Approved
**End Date:** 01/10/2017
**Site:** University Hospitals of Leicester NHS Trust

I am pleased to advise you that following confirmation of a Favourable Opinion from an Ethics Committee, NHS Trust R&D Approval and where relevant regulatory authority agreements have been received, the University are able to confirm sponsorship for the above research.

Please note you are required to notify the Sponsor and provide copies of:

- Changes in personnel to the Study
- Changes to the end date
- All substantial amendments and provisional and favourable opinions
- All minor amendments
- All serious adverse events (SAEs) and SUSARS
- Annual progress reports
- Annual MHRA (DSUR) safety reports (if applicable)
- End of study declaration form
- Notifications of significant breaches of Good Clinical Practices (GCP)or Protocol

**Please copy the Sponsor into all correspondence and emails by using uolsponsor@le.ac.uk.**

Please note it is essential that you notify the us as soon as you have recruited your first patient to the study.

I would like to wish you well with your study and if you require further information or guidance please do not hesitate to contact me.

Yours sincerely

**Mrs Wendy Gamble**
**Research Governance Manager**

**Appendix 3.5** Participant Information Leaflet (rtPA-Treated Patient) short Version 3 Dated 28th November 2015



University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square, Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257), Fax: 0116 252 5847

**PARTICIPANT INFORMATION LEAFLET (rtPA-TREATED PATIENT) (Short Version)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**

**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

You have had an ischaemic stroke (a stroke caused by blockage of an artery by an embolus or blood clot) that needs urgent care. You will get all the usual emergency care for Stroke that we provide at this hospital, in particular, you will receive a 'clot-dissolving drug' called rtPA (The decision to give rtPA will be made by your treating doctor). As well as this, we would like to invite you to take part in a research study which involves measurements of your blood pressure and blood vessels of the brain and neck. The first measurement will be carried out whilst you are receiving the rtPA, at the hospital bedside in the Hyperacute Stroke Unit, ward 25, Level 3, Windsor Building, Leicester Royal Infirmary. The subsequent measurements being carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, Leicester Royal Infirmary. There will be a medical doctor with you whilst you are in the Cardiovascular Research Laboratory.

We will need to collect some information about your medical condition, we would also like to measure the brain blood flow **Non-invasively** using ultrasound. You will be asked to lie on the bed whilst a small cuff is attached to the finger of one hand to measure blood pressure, 3 stickers to your chest to monitor your heart rate, and a small mask over your nose to measure the waste gas from your breathing. You will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against to both side of your head. We would like to measure your brain blood flow whilst you are receiving the rtPA infusion and when the rtPA infusion is finished.
If you have decided to take part in the study, you are still free to request to withdraw from the study, without giving a reason or affecting of care you receive.

If you would like to know more about the study now, then we will tell you. But otherwise we will tell you more about it later.

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the Principal Investigator (Professor Tom Robinson) on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam; role: Clinical Research Fellow of Stroke Medicine

Address: Room 228, Level 2, Robert Kilpatrick Clinical Science Building, Leicester Royal Infirmary, Leicester, LE1 5WW

Telephone: 0116 258 7257;Email: ml376@le.ac.uk

(File: 1 for patient, 1 for researcher, 1 for hospital notes)

Version 3, 28th November 2015

**Appendix 3.6** Participant Information Leaflet (rtPA-Treated Patient) Full Version 3 Dated 28th November 2015



University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT INFORMATION LEAFLET (rtPA-TREATED PATIENT)**
**(Full VERSION)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**

**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. This Participant Information Leaflet outlines the research study and explains what procedures are involved. We hope this will help you decide if you want to take part in the research study.

Thank you for reading this.

This is a small research study, which will involve five separate measurements of your blood pressure and blood vessels of the brain and neck. The first measurement will be carried out at the hospital bedside in the Hyperacute Stroke Unit, Ward 25, Level 3, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust. The subsequent four measurements will be carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. The first three measurements will take place while you are still an in-patient under the care of the University Hospitals of Leicester NHS Trust Stroke Service (during the clot-dissolving recombinant tissue plasminogen activator (rtPA) treatment, 24 hours and 72 hours after the stroke onset), the 4th measurement will take place after approximately 7 days and the final measurements will take place approximately 3 months after the stroke onset. There will be a medical doctor with you whilst you are in the Cardiovascular Research Laboratory.

This study is being carried by Dr Man Yee LAM as part of a postgraduate educational qualification (MD) with the University of Leicester. The study is being supervised by senior staff from the University of Leicester including Professor Thompson Robinson (Professor of Stroke Medicine), and Professor Ronney Panerai (Professor of Physiological Measurement. They are all helping to support the research at the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust.

**1. What is the purpose of the study?**

Blood flow to the brain has to be carefully controlled, otherwise there is a risk of too much or too little blood reaching the brain, both of which may be associated with risk and damage. The ability of the brain to control its blood supply is called autoregulation and it can range from no to perfect control. Certain things affect brain blood flow (autoregulation) including changes in breathing rates and movement. In acute ischaemic stroke (i.e. a type of stroke due to the blockage of an artery by an embolus or blood clot), blood flow following the ischaemic event will be significantly reduced and can result in death of the brain tissue (core area). This could lead to significant disability or even death of a stroke patient.

However, there is a "penumbral" region surrounding the core area where partial blood flow is maintained. This penumbral region is supplied by a collateral circulation, a system of small, normally closed arteries start connecting and carrying blood to part of the brain where the brain artery is blocked. As a result these arteries can serve as alternate routes of blood supply. To improve the blood flow to the collateral circulation and therefore penumbra is considered one of the important mechanisms to improve blood flow to the brain, and therefore a stroke patients' outcome.

At presence, we do not know if there is any relationship between the degree of the impairment in the brain blood flow (autoregulation) and blood pressure changes after the acute ischaemic stroke event.

We can measure brain blood flow (autoregulation) non-invasively using ultrasound, which detects changes in blood flow in the main brain arteries called the middle cerebral arteries. This research will use these non-invasive measurements of ultrasound to examine brain and neck blood flow whilst you are receiving the rtPA treatment, and at 24 hours, 72 hours, 7 days and 3 months post stroke onset. This knowledge will help doctors to have a better understanding of how to manage blood pressure in acute ischaemic stroke patients.

**2. Why have I been chosen?**

Measurements of brain blood flow will be compared between 'clot-dissolving' rtPA-treated patients with acute ischaemic stroke disease and acute ischaemic stroke patients of the same age, sex and blood pressure without rtPA treatment. You are being invited to participate in this study because: (a) you have had an acute ischaemic stroke; and (b) you are eligible to receive the 'clot-dissolving' drug rtPA (the decision to give rtPA will be made by your treating doctor).

**3. Do I have to take part?**

It is up to you to decide whether or not to take part. However, you will be asked to decide quickly as the rtPA treatment needs to be started as soon as possible. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form (rtPA-Treated Patient). You are very welcome to ask questions at any stage of the study. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

If you decide to participate in the study, you will be asked to sign the Patient Consent form (rtPA-Treated Patient). By signing it, you are telling us that you:

- Understand what you have read;
- Consent to take part in the research study;
- Consent to have the measurements that are described;
- Consent to the use of your personal and health information as described;

**4. What will happen to me if I take part?**

If you agree to join this study, you will have five study tests on five separate days. The first three measurements will be carried out whilst you are still an in-patient, and for the last 2 measurements, we will arrange for you to come into the hospital for approximately 1 hour. You will then be asked to lie quietly on a bed whilst a small cuff is attached to the finger of one hand to measure blood pressure, 3 stickers to your chest to monitor your heart rate, and a small mask over your nose to measure the waste gas from your breathing. You will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against both sides of your head. The head-frame is made of plastic material and able to adjust according to head size (see figure). Both the head-frame and ultrasound probe will exert a slight pressure on the head. However, this is not painful and is used routinely in many medical units to monitor blood flow to the brain.

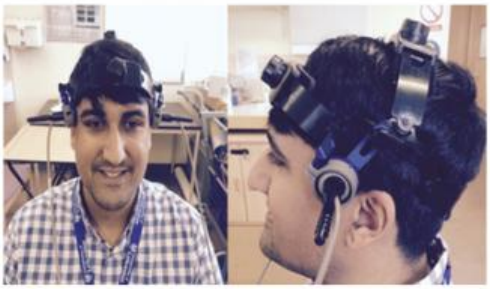

Figure: Head-frame and ultrasound probes

For the first measurement, after the readings have stabilised, a 15-minute recording will be carried out while you are receiving the rtPA infusion, this will be followed by another 5-minute recording when the rtPA infusion is finished. Afterwards, we will remove one of the ultrasound probes which is attached to your head onto your neck. Thereafter, another 20-minute recording will be carried out while the ultrasound probes are attached to both the head and the neck. Overall, the whole assessment will take approximately 1 hour.

**Day 1**

- Measurements (as described above) will be carried out whilst you are receiving and after the commencement of rtPA infusion.

**Day 2, 4 and 7**

- Measurements (as described above) will be carried out on Day 2, 4 and 7.
- On Day 4, you will be assessed for your level of consciousness and degree of neurological impairment.
- On Day 7 or the day of you discharge from the hospital (if you are discharged before Day 7), you will be assessed for your degree of independence in everyday activities, so called 'activities of daily living'.

**Day 90**

- Measurements (as described above) will be carried out on Day 90.
- You will be assessed again on your ability to perform activities of daily living and you will be asked about your quality of life, use of health services, medication changes or intervention carried out during this period of time.

**5. What treatments will be used?**

No specific treatments are given as part of this small study.

**6. What are the possible disadvantages and risks of taking part?**

The blood pressure cuff applies only a gentle pressure to your fingers to enable a blood pressure recording to be made every heartbeat. This may cause a slight tingling in your fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care. The head-frame and ultrasound probes will exert a slight pressure against your head. However, this is not painful, and again is routinely used in many units to monitor blood flow to the brain.

**7. What are the possible benefits of taking part?**

You should not expect to receive any personal benefit from taking part in this study. The study procedures are not diagnostic, and you will not routinely receive the test results. However, it is hoped that this study will help us all to learn more about the stroke disease.

**8. What if I withdraw from this research study?**

Even if you have decided to take part in the study, you are still free to request to withdraw from the study at anytime, without giving a reason or affecting the care you receive. Furthermore, the research team can also decide to withdraw you from the study if they believe it is in your best interest, i.e. progression of the stroke disease which requires discontinuation of the study or loss of the capacity during the study period.

If you decide to withdraw from the study, please notify a member of the research team. This notice will allow the research supervisor to further discuss any health risks or special requirements linked with withdrawing.

If you decide to leave the study, the researchers would like to keep the health information about you that has been collected. This is to help them make sure that the results of the research can be assessed properly. If you do not want them to do this, you must tell them before you join the research study.

In the extremely unfortunate and unusual circumstance that you become more unwell and lose the ability to decide whether you should continue to participate in this research study, the research team would not invite you to continue participate in this research study. However, the research team would still like to keep the health information and the data about you that has been collected so far for the final analysis. If you do not want them to do this, you must also tell them before you join the research study.

**9. Will travel expenses be paid?**

Yes, you will not be out of pocket if you decide to take part in this study. Travel costs to and from the hospital for the study will be reimbursed.

**10. What if something goes wrong?**

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of the study, here are the details of the National Health Service complaints procedures:

Patient Information and Liaison Service (PILS)

Address: The Firs, C/O Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

Free phone line: 08081 788 337

Facsimile: 0116 258 8661

Email: pils@uhl-tr.nhs.uk

**11. Will my taking part be kept confidential?**

The blood pressure and blood flow data recorded during the study will be stored on a computer for subsequent analysis. However, you will not be identified by name, and only the researcher will know that the information is related to you. Any information collected during the study will be treated with the usual degree of confidentiality under the Data Protection Act and will not be passed to anyone else without your express permission. Your identity will not be revealed in any publication or presentation of the results from this study. However, with your permission, your own doctor (your GP) will be notified you have been participated in the above study and if any health problems are identified that need further tests or treatment.

The relevant sections of your medical notes and/or data collected during the study, may also be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, for monitoring and audit purposes.

**12. Who is organising and funding the research?**

This research is coordinated by Professor Robinson and Professor Panerai from the University of Leicester.

**13. How will I find out the results of the research?**

At the end of the study, you will be sent a written letter, in plain English, summary of our study findings and conclusions. This can either be posted or emailed to you, depending on your preference.

**14. Whom can I contact?**

**For further information or appointments:**

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the Principal Investigator (Professor Tom Robinson) on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam;

Role: Clinical Research Fellow of Stroke Medicine

Address: Room 228, Level 2, Robert Kilpatrick Clinical Science Building, Leicester Royal Infirmary, LE12 5WW, UK

Telephone: 0116 258 7257;

Email: ml376@le.ac.uk

Once again, thank you for taking the time to read this information sheet and for considering taking part in this study.

**Appendix 3.7** Participant Information Leaflet (rtPA-Treated Patient Who Regains Capacity) Version 1 Dated 28th November 2015



University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT INFORMATION LEAFLET (rtPA-TREATED PATIENT WHO REGAINS CAPACITY)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**

**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

While you were very unwell, your friend/relative agreed for you to participate in the above research study. We are pleased you are feeling better now and therefore, we would like you to consider whether you would like to continue to participate in this research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. This Participant Information Leaflet outlines the research study and explains what procedures are involved. We hope this will help you decide if you want to continue take part in the research study.

Thank you for reading this.

This is a small research study, which will involve five separate measurements of your blood pressure and blood vessels of the brain and neck. The first measurement will be carried out at the hospital bedside in the Hyperacute Stroke Unit, Ward 25, Level 3, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust. The subsequent four measurements will be carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. The first three measurements will take place while you are still an in-patient under the care of the University Hospitals of Leicester NHS Trust Stroke Service (during the clot-dissolving recombinant tissue plasminogen activator (rtPA) treatment, 24 hours and 72 hours after the stroke onset), the 4th measurement will take place after approximately 7 days and the final measurements will take place approximately 3 months after the stroke onset. There will be a medical doctor with you whilst you are in the Cardiovascular Research laboratory.

This study is being carried by Dr Man Yee LAM as part of a postgraduate educational qualification (MD) with the University of Leicester. The study is being supervised by senior staff from the University of Leicester including Professor Thompson Robinson (Professor of Stroke Medicine) and Professor Ronney Panerai (Professor of Physiological Measurement). They are all helping to support the research at the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust.

**1. What is the purpose of the study?**

Blood flow to the brain has to be carefully controlled, otherwise there is a risk of too much or too little blood reaching the brain, both of which may be associated with risk and damage. The ability of the brain to control its blood supply is called autoregulation and it can range from no to perfect control. Certain things affect brain blood flow (autoregulation) including changes in breathing rates and movement. In acute ischaemic stroke (i.e. a type of stroke due to the blockage of an artery by an embolus or blood clot), blood flow following the ischaemic event will be significantly reduced and can result in death of the brain tissue (core area). This could lead to significant disability or even death of a stroke patient.

However, there is a "penumbral" region surrounding the core area where partial blood flow is maintained. This penumbral region is supplied by a collateral circulation, a system of small, normally closed arteries start connecting and carrying blood to part of the brain where the brain artery is blocked. As a result these arteries can serve as alternate routes of blood supply. To improve the blood flow to the collateral circulation and therefore penumbra is considered one of the important mechanisms to improve blood flow to the brain, and therefore a stroke patients' outcome.

At presence, we do not know if there is any relationship between the degree of the impairment in the brain blood flow (autoregulation) and blood pressure changes after the acute ischaemic stroke event.

We can measure brain blood flow (autoregulation) non-invasively using ultrasound, which detects changes in blood flow in the main brain arteries called the middle cerebral arteries. This research will use these non-invasive measurements of ultrasound to examine brain and neck blood flow whilst you are receiving the rtPA treatment, and at 24 hours, 72 hours, 7 days and 3 months post stroke onset. This knowledge will help doctors to have a better understanding of how to manage blood pressure in acute ischaemic stroke patients.

**2. Why have I been chosen?**

Measurements of brain blood flow will be compared between 'clot-dissolving' rtPA-treated patients with acute ischaemic stroke disease and acute ischaemic stroke patients of the same age, sex and blood pressure without rtPA treatment. You are being invited to participate in this study because: (a) you have had an acute ischaemic stroke; and (b) you are eligible to receive the 'clot-dissolving' drug rtPA (the decision to give rtPA will be made by your treating doctor).

**3. Do I have to take part?**

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form (rtPA-Treated Patient Who Regains Capacity). You are very welcome to ask questions at any stage of the study. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

If you decide to participate in the study, you will be asked to sign the Patient Consent form (rtPA-Treated Patient Who Regains Capacity). By signing it, you are telling us that you:

- Understand what you have read;
- Consent to take part in the research study;
- Consent to have the measurements that are described;
- Consent to the use of your personal and health information as described;

**4. What will happen to me if I take part?**

If you agree to join this study, you will have five study tests on five separate days. The first three measurements will be carried out whilst you are still an in-patient, and for the last 2 measurements, we will arrange for you to come into the hospital for approximately 1 hour. You will then be asked to lie quietly on a bed whilst a small cuff is attached to the finger of one hand to measure blood pressure, 3 stickers to your chest to monitor your heart rate, and a small mask over your nose to measure the waste gas from your breathing. You will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against both sides of your head. The head-frame is made of plastic material and able to adjust according to head size (see figure). Both the head-frame and ultrasound probe will exert a slight pressure on the head. However, this is not painful and is used routinely in many medical units to monitor blood flow to the brain.

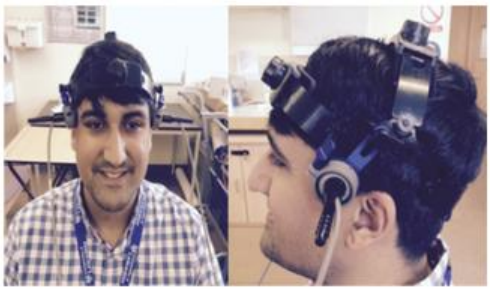

Figure: Head-frame and ultrasound probes

For the first measurement, after the readings have stabilised, a 15-minute recording will be carried out while you are receiving the rtPA infusion, this will be followed by another 5-minute recording when the rtPA infusion is finished. Afterwards, we will remove one of the ultrasound probes which is attached to your head onto your neck. Thereafter, another 20-minute recording will be carried out while the ultrasound probes are attached to both the head and the neck. Overall, the whole assessment will take approximately 1 hour.

**Day 1**

- Measurements (as described above) will be carried out whilst you are receiving and after the commencement of rtPA infusion.

**Day 2, 4 and 7**

- Measurements (as described above) will be carried out on Day 2, 4 and 7.
- On Day 4, you will be assessed for your level of consciousness and degree of neurological impairment.
- On Day 7 or the day of you discharge from the hospital (if you are discharged before Day 7), you will be assessed for your degree of independence in everyday activities, so called 'activities of daily living'.

**Day 90**

- Measurements (as described above) will be carried out on Day 90.
- You will be assessed again on your ability to perform activities of daily living and you will be asked about your quality of life, use of health services, medication changes or intervention carried out during this period of time.

**5. What treatments will be used?**

No specific treatments are given as part of this small study.

**6. What are the possible disadvantages and risks of taking part?**

The blood pressure cuff applies only a gentle pressure to your fingers to enable a blood pressure recording to be made every heartbeat. This may cause a slight tingling in your fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care. The head-frame and ultrasound probes will exert a slight pressure against your head. However, this is not painful, and again is routinely used in many units to monitor blood flow to the brain.

**7. What are the possible benefits of taking part?**

You should not expect to receive any personal benefit from taking part in this study. The study procedures are not diagnostic, and you will not routinely receive the test results. However, it is hoped that this study will help us all to learn more about the stroke disease.

**8. What if I withdraw from this research study?**

Even if you have decided to take part in the study, you are still free to request to withdraw from the study at anytime, without giving a reason or affecting the care you receive. Furthermore, the research team can also decide to withdraw you from the study if they believe it is in your best interest, i.e. progression of the stroke disease which requires discontinuation of the study or loss of the capacity during the study period.

If you decide to withdraw from the study, please notify a member of the research team. This notice will allow the research supervisor to further discuss any health risks or special requirements linked with withdrawing.

If you decide to leave the study, we would like to keep the health information about you that has been collected. This is to help them make sure that the results of the research can be assessed properly. If you do not want them to do this, please let us know.

**9. Will travel expenses be paid?**

Yes, you will not be out of pocket if you decide to take part in this study. Travel costs to and from the hospital for the study will be reimbursed.

**10. What if something goes wrong?**

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of the study, here are the details of the National Health Service complaints procedures:

Patient Information and Liaison Service (PILS)

Address: The Firs, C/O Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

Free phone line: 08081 788 337

Facsimile: 0116 258 8661

Email: pils@uhl-tr.nhs.uk

**11. Will my taking part be kept confidential?**

The blood pressure and blood flow data recorded during the study will be stored on a computer for subsequent analysis. However, you will not be identified by name, and only the researcher will know that the information is related to you. Any information collected during the study will be treated with the usual degree of confidentiality under the Data Protection Act and will not be passed to anyone else without your express permission. Your identity will not be revealed in any publication or presentation of the results from this study. However, with your permission, your own doctor (your GP) will be notified you have been participated in the above study and if any health problems are identified that need further tests or treatment.

The relevant sections of your medical notes and/or data collected during the study, may also be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, for monitoring and audit purposes.

**12. Who is organising and funding the research?**

This research is coordinated by Professor Robinson and Professor Panerai from the University of Leicester.

**13. How will I find out the results of the research?**

At the end of the study, you will be sent a written letter, in plain English, summary of our study findings and conclusions. This can either be posted or emailed to you, depending on your preference.

**14. Whom can I contact?**

**For further information or appointments:**

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the Principal Investigator (Professor Tom Robinson) on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam;

Role: Clinical Research Fellow of Stroke Medicine

Address: Room 228, Level 2, Robert Kilpatrick Clinical Science Building, Leicester Royal Infirmary, LE12 5WW, UK

Telephone: 0116 258 7257;

Email: ml376@le.ac.uk

Once again, thank you for taking the time to read this information sheet and for considering taking part in this study.

**Appendix 3.8** Participant Information Leaflet (Non-rtPA treated Patient) Version 3 Dated 28th November 2015



University Hospitals of Leicester NHS
NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT INFORMATION LEAFLET (NON-rtPA TREATED PATIENT)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**

**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. This Participant Information Leaflet outlines the research study and explains what procedures are involved. We hope that this will help you decide if you want to take part in the research study.

Thank you for reading this.

This is a small research study, which will involve five separate measurements of your blood pressure and blood vessels of the brain and neck. The first measurement will be carried out at the hospital bedside in the Hyperacute Stroke Unit, Ward 25, Level 3, Windsor Building, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust. The subsequent four measurements will be carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. The first three measurements will take place while you are still an in-patient under the care of the University Hospitals of Leicester NHS Trust Stroke Service (within 6 hours, at 24 hours and 72 hours after the stroke onset), the 4th measurement will take place after approximately 7 days and the final measurements will take place approximately 3 months after the stroke onset. There will be a medical doctor with you whilst you are in the Cardiovascular Research Laboratory.

This study is being carried by Dr Man Yee LAM as part of a postgraduate educational qualification (MD) with the University of Leicester. The study is being supervised by senior staff from the University of Leicester including Professor Thompson Robinson (Professor of Stroke Medicine) and Professor Ronney Panerai (Professor of Physiological Measurement). They are all helping to support the research at the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust.

**1. What is the purpose of the study?**

Blood flow to the brain has to be carefully controlled, otherwise there is a risk of too much or too little blood reaching the brain, both of which may be associated with risk and damage. The ability of the brain to control its blood supply is called autoregulation and it can range from no control to perfect control. Certain things affect brain blood flow (autoregulation) including changes in breathing rates and movement. In acute ischaemic stroke (i.e. a type of stroke due to the blockage of an artery by an embolus or blood clot), blood flow following the

ischaemic event will be significantly reduced and can result in death of the brain tissue (core area). This could lead to significant disability or even death of a stroke patient.

However, there is a "penumbral" region surrounding the core area where partial blood flow is maintained. This penumbral region is supplied by a collateral circulation, a system of small, normally closed arteries start connecting and carrying blood to part of the brain where the brain artery is blocked. As a result these arteries can serve as alternate routes of blood supply. To improve the blood flow to the collateral circulation and therefore penumbra is considered one of the important mechanisms to improve blood flow to the brain, and therefore a stroke patients' outcome.

At presence, we do not know if there is any relationship between the degree of the impairment in the brain blood flow (autoregulation) and blood pressure changes after the acute ischaemic stroke event.

We can measure brain blood flow (autoregulation) non-invasively using ultrasound, which detects changes in blood flow in the main brain arteries called the middle cerebral arteries. This research will use these non-invasive measurements of ultrasound to examine your brain and neck blood flow within 6 hours, at 24 hours, 72 hours, 7 days and 3 months post stroke onset. This knowledge will help doctors to have a better understanding of how to manage blood pressure in acute ischaemic stroke patients.

**2. Why have I been chosen?**

Measurements of brain blood flow will be compared between 'clot-dissolving' rtPA-treated patients with acute ischaemic stroke disease and acute ischaemic stroke patients of the same age, sex and blood pressure without rtPA treatment. You are being invited to participate in this study because: (a) you have had an acute ischaemic stroke and (b) you are not eligible to receive 'clot-dissolving' rtPA treatment (the doctor treating you will have explained why you are not eligible to receive rtPA treatment).

**3. Do I have to take part?**

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a Consent Form (Non-rtPA Treated Patient). You are very welcome to ask questions at any stage of the study. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

If you decide to participate in the study, you will be asked to sign the Consent Form (Non-rtPA Treated Patient). By signing it, you are telling us that you:

- Understand what you have read;
- Consent to take part in the research study;
- Consent to have the measurements that are described;
- Consent to the use of your personal and health information as described.

**4. What will happen to me if I take part?**

If you agree to join this study, you will have five study tests on five separate days. The first three measurements will be carried out whilst you are still an in-patient, and for the last 2 measurements, we will arrange for you to come into the hospital for approximately 1 hour. You will then be asked to lie quietly on a bed whilst a small cuff

is attached to the finger of one hand to measure your blood pressure, 3 stickers to your chest to monitor your heart rate, and a small mask over your nose to measure the waste gas from your breathing. You will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against both sides of your head. The head-frame is made of plastic material and able to adjust according to head size (see figure). Both the head-frame and ultrasound probe will exert a slight pressure on the head. However, this is not painful and is used routinely in many medical units to monitor blood flow to the brain.

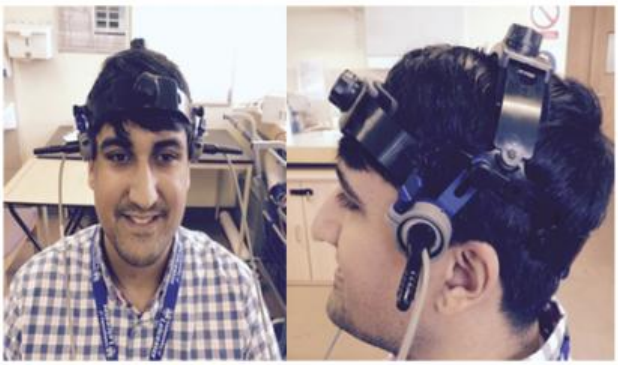

Figure: Head-frame and ultrasound probes

After the readings have stabilised, a 20-minute recording will be carried out within 6 hours of your stroke onset. Afterwards, we will remove one of the ultrasound probes which is attached to your head onto your neck. Thereafter, another 20-minute recording will be carried out while the ultrasound probes will be attached to both the head and the neck. Overall, the whole assessment will take approximately 1 hour.

**Day 1**

- Measurements (as described above) will be carried out within 6 hours of stroke onset.

**Day 2, 4 and 7**

- Measurements (as described above) will be carried out on Day 2, 4 and 7.
- On Day 4, you will be assessed the level of consciousness and degree of neurological impairment.
- On Day 7 or the day of you discharge from the hospital (if you are discharged before Day 7), you will be assessed for your degree of independence in everyday activities, so called 'activities of daily living'.

**Day 90**

- Measurements (as described above) will be carried out on Day 90.
- You will be assessed again on your ability to perform activities of daily living and you will be asked about your quality of life, use of health services, medication changes or intervention carried out during this period of time.

**5. What treatments will be used?**

No specific treatments are given as part of this small study.

**6. What are the possible disadvantages and risks of taking part?**

The blood pressure cuff applies only a gentle pressure to your fingers to enable a blood pressure recording to be made every heartbeat. This may cause a slight tingling in your fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care. The head-frame and ultrasound probes will exert a slight pressure against your head. However, this is not painful, and again is routinely used in many units to monitor blood flow to the brain.

**7. What are the possible benefits of taking part?**

You should not expect to receive any personal benefit from taking part in this study. The study procedures are not diagnostic, and you will not routinely receive the test results. However, it is hoped that this study will help us all to learn more about the stroke disease.

**8. What if I withdraw from this research study?**

Even if you have decided to take part in the study, you are still free to request to withdraw from the study at anytime, without giving a reason or affecting the care you receive. Furthermore, the research team can also decide to withdraw you from the study if they believe it is your best interest, i.e. progression of the stroke disease which requires discontinuation of the study or loss of the capacity during the study period.

If you decide to withdraw from the study, please notify a member of the research team. This notice will allow the research supervisor to further discuss any health risks or special requirements linked with withdrawing.

If you decide to leave the study, the researchers would like to keep the health information about you that has been collected. This is to help them make sure that the results of the research can be assessed properly. If you do not want them to do this, you must tell them before you join the research study.

In the extremely unfortunate and unusual circumstance that you become more unwell and lose the ability to decide whether you should continue to participate in this research study, the research team would not invite you to continue participate in this research study. However, the research team would still like to keep the health information and the data about you that has been collected so far for the final analysis. If you do not want them to do this, you must also tell them before you join the research study.

**9. Will travel expenses be paid?**

Yes, you will not be out of pocket if you decide to take part in this study. Travel costs to and from the hospital for the study will be reimbursed.

**10. What if something goes wrong?**

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of the study, here are the details of the National Health Service complaints procedures:

Patient Information and Liaison Service (PILS)

Address: The Firs, C/O Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

Free phone line: 08081 788 337

Facsimile: 0116 258 8661

Email: pils@uhl-tr.nhs.uk

**11. Will my taking part be kept confidential?**

The blood pressure and blood flow data recorded during the study will be stored on a computer for subsequent analysis. However, you will not be identified by name, and only the researcher will know that the information is related to you. Any information collected during the study will be treated with the usual degree of confidentiality under the Data Protection Act and will not be passed to anyone else without your express permission. Your identity will not be revealed in any publication or presentation of the results from this study. However, with your permission, your own doctor (your GP) will be notified you have been participated in the above study and if any health problems are identified that need further tests or treatment.

The relevant sections of your medical notes and/or data collected during the study, may also be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, for monitoring and audit purposes.

**12. Who is organising and funding the research?**

This research is coordinated by Professor Robinson and Professor Panerai from the University of Leicester.

**13. How will I find out the results of the research?**

At the end of the study, you will be sent a written letter, in plain English, with a summary of our study findings and conclusions. This can either be posted or emailed to you, depending on your preference.

**14. Whom can I contact?**

**For further information or appointments:**

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the Principal Investigator (Professor Tom Robinson) on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam;

Role: Clinical Research Fellow of Stroke Medicine

Address: Room 228, Level 2, Robert Kilpatrick Clinical Science Building, Leicester Royal Infirmary, Leicester, LE1 5WW, UK

Telephone: 0116 258 7257;

Email: ml376@le.ac.uk

Once again, thank you for taking the time to read this information sheet and for considering taking part in this study.

**Appendix 3.9** Participant Information Leaflet (Non-rtPA treated Patient Who Regains Capacity) Version 1 Dated 28th November 2015



University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT INFORMATION LEAFLET (NON-rtPA TREATED PATIENT Who Regains Capacity)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**

**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

While you were very unwell, your friend/relative agreed for you to participate in the above research study. We are pleased you are feeling better now and therefore, we would like you to consider whether you would like to continue to participate in this research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. This Participant Information Leaflet outlines the research study and explains what procedures are involved. We hope that this will help you decide if you want to continue to take part in the research study.

Thank you for reading this.

This is a small research study, which will involve five separate measurements of your blood pressure and blood vessels of the brain and neck. The first measurement will be carried out at the hospital bedside in the Hyperacute Stroke Unit, Ward 25, Level 3, Windsor Building, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust. The subsequent four measurements will be carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. The first three measurements will take place while you are still an in-patient under the care of the University Hospitals of Leicester NHS Trust Stroke Service (within 6 hours, at 24 hours and 72 hours after the stroke onset), the 4th measurement will take place after approximately 7 days and the final measurements will take place approximately 3 months after the stroke onset. There will be a medical doctor with you whilst you are in the Cardiovascular Research Laboratory.

This study is being carried by Dr Man Yee LAM as part of a postgraduate educational qualification (MD) with the University of Leicester. The study is being supervised by senior staff from the University of Leicester including Professor Thompson Robinson (Professor of Stroke Medicine) and Professor Ronney Panerai (Professor of Physiological Measurement). They are all helping to support the research at the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust.

**1. What is the purpose of the study?**

Blood flow to the brain has to be carefully controlled, otherwise there is a risk of too much or too little blood reaching the brain, both of which may be associated with risk and damage. The ability of the brain to control its blood supply is called autoregulation and it can range from no control to perfect control. Certain things affect

brain blood flow (autoregulation) including changes in breathing rates and movement. In acute ischaemic stroke (i.e. a type of stroke due to the blockage of an artery by an embolus or blood clot), blood flow following the ischaemic event will be significantly reduced and can result in death of the brain tissue (core area). This could lead to significant disability or even death of a stroke patient.

However, there is a "penumbral" region surrounding the core area where partial blood flow is maintained. This penumbral region is supplied by a collateral circulation, a system of small, normally closed arteries start connecting and carrying blood to part of the brain where the brain artery is blocked. As a result these arteries can serve as alternate routes of blood supply. To improve the blood flow to the collateral circulation and therefore penumbra is considered one of the important mechanisms to improve blood flow to the brain, and therefore a stroke patients' outcome.

At presence, we do not know if there is any relationship between the degree of the impairment in the brain blood flow (autoregulation) and blood pressure changes after the acute ischaemic stroke event.

We can measure brain blood flow (autoregulation) non-invasively using ultrasound, which detects changes in blood flow in the main brain arteries called the middle cerebral arteries. This research will use these non-invasive measurements of ultrasound to examine your brain and neck blood flow within 6 hours, at 24 hours, 72 hours, 7 days and 3 months post stroke onset. This knowledge will help doctors to have a better understanding of how to manage blood pressure in acute ischaemic stroke patients.

**2. Why have I been chosen?**

Measurements of brain blood flow will be compared between 'clot-dissolving' rtPA-treated patients with acute ischaemic stroke disease and acute ischaemic stroke patients of the same age, sex and blood pressure without rtPA treatment. You are being invited to participate in this study because: (a) you have had an acute ischaemic stroke and (b) you are not eligible to receive 'clot-dissolving' rtPA treatment (the doctor treating you will have explained why you are not eligible to receive rtPA treatment).

**3. Do I have to take part?**

It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a Consent Form (Non-rtPA Treated Patient Who Regains Capacity). You are very welcome to ask questions at any stage of the study. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

If you decide to participate in the study, you will be asked to sign the Consent Form (Non-rtPA Treated Patient Who Regains Capacity). By signing it, you are telling us that you:

- Understand what you have read;
- Consent to take part in the research study;
- Consent to have the measurements that are described;
- Consent to the use of your personal and health information as described.

**4. What will happen to me if I take part?**

If you agree to join this study, you will have five study tests on five separate days. The first three measurements will be carried out whilst you are still an in-patient, and for the last 2 measurements, we will arrange for you to come into the hospital for approximately 1 hour. You will then be asked to lie quietly on a bed whilst a small cuff is attached to the finger of one hand to measure your blood pressure, 3 stickers to your chest to monitor your heart rate, and a small mask over your nose to measure the waste gas from your breathing. You will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against both sides of your head. The head-frame is made of plastic material and able to adjust according to head size (see figure). Both the head-frame and ultrasound probe will exert a slight pressure on the head. However, this is not painful and is used routinely in many medical units to monitor blood flow to the brain.

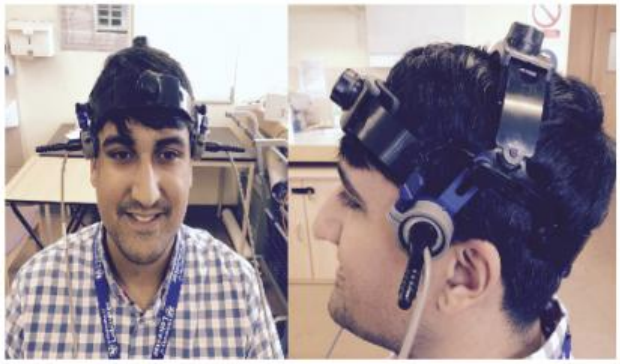

Figure: Head-frame and ultrasound probes

After the readings have stabilised, a 20-minute recording will be carried out within 6 hours of your stroke onset. Afterwards, we will remove one of the ultrasound probes which is attached to your head onto your neck. Thereafter, another 20-minute recording will be carried out while the ultrasound probes will be attached to both the head and the neck. Overall, the whole assessment will take approximately 1 hour.

**Day 1**

- Measurements (as described above) will be carried out within 6 hours of stroke onset.

**Day 2, 4 and 7**

- Measurements (as described above) will be carried out on Day 2, 4 and 7.
- On Day 4, you will be assessed the level of consciousness and degree of neurological impairment.
- On Day 7 or the day of you discharge from the hospital (if you are discharged before Day 7), you will be assessed for your degree of independence in everyday activities, so called 'activities of daily living'.

**Day 90**

- Measurements (as described above) will be carried out on Day 90.

- You will be assessed again on your ability to perform activities of daily living and you will be asked about your quality of life, use of health services, medication changes or intervention carried out during this period of time.

**5. What treatments will be used?**

No specific treatments are given as part of this small study.

**6. What are the possible disadvantages and risks of taking part?**

The blood pressure cuff applies only a gentle pressure to your fingers to enable a blood pressure recording to be made every heartbeat. This may cause a slight tingling in your fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care. The head-frame and ultrasound probes will exert a slight pressure against your head. However, this is not painful, and again is routinely used in many units to monitor blood flow to the brain.

**7. What are the possible benefits of taking part?**

You should not expect to receive any personal benefit from taking part in this study. The study procedures are not diagnostic, and you will not routinely receive the test results. However, it is hoped that this study will help us all to learn more about the stroke disease.

**8. What if I withdraw from this research study?**

Even if you have decided to take part in the study, you are still free to request to withdraw from the study at anytime, without giving a reason or affecting the care you receive. Furthermore, the research team can also decide to withdraw you from the study if they believe it is your best interest, i.e. progression of the stroke disease which requires discontinuation of the study or loss of the capacity during the study period.

If you decide to withdraw from the study, please notify a member of the research team. This notice will allow the research supervisor to further discuss any health risks or special requirements linked with withdrawing.

If you decide to leave the study, the researchers would like to keep the health information about you that has been collected. This is to help them make sure that the results of the research can be assessed properly. If you do not want them to do this, you must tell them before you join the research study.

**9. Will travel expenses be paid?**

Yes, you will not be out of pocket if you decide to take part in this study. Travel costs to and from the hospital for the study will be reimbursed.

**10. What if something goes wrong?**

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of the study, here are the details of the National Health Service complaints procedures:

Patient Information and Liaison Service (PILS)

Address: The Firs, C/O Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

Free phone line: 08081 788 337

Facsimile: 0116 258 8661

Email: pils@uhl-tr.nhs.uk

**11. Will my taking part be kept confidential?**

The blood pressure and blood flow data recorded during the study will be stored on a computer for subsequent analysis. However, you will not be identified by name, and only the researcher will know that the information is related to you. Any information collected during the study will be treated with the usual degree of confidentiality under the Data Protection Act and will not be passed to anyone else without your express permission. Your identity will not be revealed in any publication or presentation of the results from this study. However, with your permission, your own doctor (your GP) will be notified you have been participated in the above study and if any health problems are identified that need further tests or treatment.

The relevant sections of your medical notes and/or data collected during the study, may also be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, for monitoring and audit purposes.

**12. Who is organising and funding the research?**

This research is coordinated by Professor Robinson and Professor Panerai from the University of Leicester.

**13. How will I find out the results of the research?**

At the end of the study, you will be sent a written letter, in plain English, with a summary of our study findings and conclusions. This can either be posted or emailed to you, depending on your preference.

**14. Whom can I contact?**

**For further information or appointments:**

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the Principal Investigator (Professor Tom Robinson) on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam;

Role: Clinical Research Fellow of Stroke Medicine

Address: Room 228, Level 2, Robert Kilpatrick Clinical Science Building, Leicester Royal Infirmary, Leicester, LE1 5WW, UK

Telephone: 0116 258 7257;

Email: ml376@le.ac.uk

Once again, thank you for taking the time to read this information sheet and for considering taking part in this study.

**Appendix 3.10** Personal Consultee Leaflet (rtPA-Treated Patient) Short Version 2 Dated 28th November 2015



University Hospitals of Leicester NHS
NHS Trust

In Leicester Royal Infirmary
Infirmary Square, Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257), Fax: 0116 252 5847

**PERSONAL CONSULTEE INFORMATION LEAFLET (rtPA-TREATED PATIENT) (Short Version)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**

**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

Your friend/relative has had an ischaemic stroke (a stroke caused by blockage of an artery by an embolus or blood clot) that needs urgent care. He/she will get all the usual emergency care for Stroke that we provide at this hospital, in particular, he/she will receive a 'clot-dissolving drug' called rtPA (The decision to give rtPA will be made by his/her treating doctor). As well as this, we would like to invite him/her to take part in a research study which involves measurements of the blood pressure and blood vessels of the brain and neck. The first measurement will be carried out whilst he/she is receiving the rtPA, at the hospital bedside in the Hyperacute Stroke Unit, ward 25, Level 3, Windsor Building, Leicester Royal Infirmary. The subsequent measurements being carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, Leicester Royal Infirmary. There will be a medical doctor with him/her whilst he/she is in the Cardiovascular Research Laboratory.

However, due to the nature of the illness, he/she is unable to decide for himself/herself whether to participate in the research study at the moment. To help decide if he/she should join the study, we would like to ask your opinion whether or not he/she would want to be involved. We would ask you to set aside your own views and consider his/her interests and what you feel would be his/her wishes and feelings. Any advanced directive that he/she may have made and that you are aware of should take precedence.

It is also important to remember that the personal consultee give advice but is not being asked to consent on behalf of the patient who lacks capacity. The responsibility to decide whether the patient should entered into the research lies ultimately with the researcher. However, we always respect the personal consultee's view and if the personal consultee object to the inclusion of the patient in this research study, the patient will not be enrolled in the study.

We will need to collect some information about his/her medical condition, we would also like to measure the brain blood-flow **Non-invasively** using ultrasound. He/she will be asked to lie on the bed whilst a small cuff is attached to the finger of one hand to measure blood pressure, 3 stickers to his/her chest to monitor the heart rate, and a small mask over his/her nose to measure the waste gas from the breathing. Your friend/relative will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against to both side of his/her head. We would like to measure the blood flow whilst he/she is receiving the rtPA infusion and when the rtPA infusion is finished.

Even if you have decided for your friend/relative would have no objection to take part in the study, you are still free to request him/her to withdraw from the study, without giving a reason or affecting the standard of care he/she receives. However, the researchers would like to keep the health information about your friend/relative that has been collected. This is to help them make sure that

the results of the research can be assessed properly. If you do not want them to do this, you must tell them before your friend/relative joins the research study.

If you would like to know more about the study now, then we will tell you. But otherwise we will tell you more about it later.

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the Principal Investigator (Professor Tom Robinson) on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam; role: Clinical Research Fellow of Stroke Medicine

Address: Room 228, Level 2, Robert Kilpatrick Clinical Science Building, Leicester Royal Infirmary, Leicester, LE1 5WW

Telephone: 0116 258 7257;

Email: ml376@le.ac.uk

**For complaints:**

If you have any complaints about any aspect of the project, the way it is being conducted, then you may contact:

Patient Information and Liaison Service (PILS)

Address: The Firs, C/O Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

Free phone line: 08081 788 337

Facsimile: 0116 258 8661

Email: pils@uhl-tr.nhs.uk

Once again, thank you for taking the time to read this information leaflet.

**Appendix 3.11** Personal Consultee Information Leaflet (rtPA-Treated Patient) Full Version 2 Dated 28th November 2015



University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PERSONAL CONSULTEE INFORMATION LEAFLET (rtPA-TREATED PATIENT)**
**(Full Version)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**

**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

Your friend/relative is being invited to take part in a research study. However, due to the nature of the illness, he/she is unable to decide for himself/herself whether to participate in the research study at the moment. To help decide if he/she should join the study, we would like to ask your opinion whether or not he/she would want to be involved. We would ask you to set aside your own views and consider his/her interests and what you feel would be his/her wishes and feelings. Any advanced directive that he/she may have made and that you are aware of should take precedence.

Before you decide on whether to take on the personal consultee role, it is important for you to understand 1) what is a personal consultee 2) the personal consultee's role and responsibility and 3) why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish your friend/relative to take part. This personal consultee information leaflet outlines the research study and explains what procedures are involved. We hope that this will help you decide if you would like your friend/relative to take part in the research study, though you can refuse to act as a Personal Consultee. The following information leaflet is the same as would have been provided to your friend/relative.

Thank you for reading this.

**1. What is a personal consultee?**

It is fairly common for patients who suffer acute stroke to lose the ability to make decisions for themselves (i.e. they lack capacity), this could be due to difficulty in communication, reduced consciousness level (alertness) or confusion. In order to involve patients who lack of capacity in research, under legislation (the Mental Capacity Act 2005), the research team must seek advice from the patient's personal consultee.

A personal consultee is someone who knows the patient and has a role in caring for the patient or is interested in the patient's welfare. A personal consultee is someone whom the patient who lacks of capacity would trust with important decisions about their welfare. He/she should be someone who can advise the researcher about the wishes and feelings of the patient who lacks of capacity in relation to the project and whether they would want to join the research study. A personal consultee is usually someone with a close personal relationship with the patient, for example, next of kin, spouse, partner or friend.

**2. What is the role and the responsibility of a personal consultee?**

A personal consultee must themselves have the ability to make a decision at the time and be prepared to be consulted by the research team about the possible involvement of the patient who lacks capacity. They should be able to advise the research team whether the patient who lacks capacity should take part in the project. For example, the personal consultee should consider whether the person who lacks capacity would be content to take part or whether doing so might upset them. The personal consultee must also give their opinion on what the past and present wishes and feelings of the patient who lacks capacity would have been about taking part in the research study. The personal consultee must set aside any views they may have about the research and consider only the views and interests of the patient who lacks capacity.

It is also important to remember that the personal consultee gives advice but is not being asked to consent on behalf of the patient who lacks capacity. The responsibility to decide whether the patient should be entered into the research lies ultimately with the researcher. However, we always respect the personal consultee's view and if the personal consultee objects to the inclusion of the patient in this research study, his/her view will be respected and the patient will not be enrolled in the study.

If you are unsure about taking the role of the personal consultee you may seek independent advice. We will understand if you do not want to take on this responsibility.

**3. Why this research study is being done?**

This is a small research study, which will involve five separate measurements of blood pressure and blood vessels of the brain and neck. The first measurement will be carried out at the hospital bedside in the Hyperacute Stroke Unit, Ward 25, Level 3, University Hospitals of Leicester NHS Trust. The subsequent four measurements will be carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. The first three measurements will take place while your friend/relative is still an in-patient under the care of the University Hospitals of Leicester NHS Trust Stroke service (during the clot-dissolving recombinant tissue plasminogen activator (rtPA) treatment, 24 hours and 72 hours after the stroke onset), the 4th measurement will take place after approximately 7 days and the final measurement will take place approximately 3 months after the stroke onset. There will be medical doctor with your friend/relative whilst he/she is in the Cardiovascular Research Laboratory.

This study is being carried by Dr Man Yee LAM as part of a postgraduate educational qualification (MD) with the University of Leicester. The study is being supervised by senior staff from the University of Leicester including Professor Thompson Robinson (Professor of Stroke Medicine) and

Professor Ronney Panerai (Professor of Physiological Measurement). They are all helping to support the research at the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust.

**4. What is the purpose of the study?**

Blood flow to the brain has to be carefully controlled, otherwise there is a risk of too much or too little blood reaching the brain, both of which may be associated with risk and damage. The ability of the brain to control its blood supply is called autoregulation and it can range from no to perfect control. Certain things affect brain blood flow (autoregulation) including changes in breathing rates and movement. In acute ischaemic stroke (i.e. a type of stroke due to the blockage of an artery by an embolus or blood clot), blood flow following the ischaemic event will be significantly reduced and can result in death of the brain tissue (core area). This could lead to significant disability or even death of a stroke patient.

However, there is a "penumbral" region surrounding the core area where partial blood flow is maintained. This penumbral region is supplied by a collateral circulation, a system of small, normally closed arteries start connecting and carrying blood to part of the brain when the brain artery is blocked. As a result these arteries can serve as alternate routes of blood supply. To improve the blood flow to the collateral circulation and therefore penumbral region is considered one of the important mechanisms to improve blood flow to the brain and therefore, a stroke patients' outcome.

At presence, we do not know if there is any relationship between the degree of the impairment in the brain blood flow (autoregulation) and blood pressure changes after the acute ischaemic stroke event.

We can measure brain blood flow (autoregulation) non-invasively using ultrasound, which detects changes in blood flow in the main brain arteries called the middle cerebral arteries. This research will use these non-invasive measurements of ultrasound to examine brain and neck blood flow changes whilst your friend/relative is receiving rtPA treatment, and at 24 hours, 72 hours, 7 days and 3 months post stroke onset. This knowledge will help doctors to have a better understanding of how to manage blood pressure in acute ischaemic stroke patients.

**5. Why has your friend/relative been chosen?**

Measurements in brain blood flow will be compared between 'clot-dissolving' rtPA-treated patients with acute ischaemic stroke disease and acute ischaemic stroke patients of the same age, sex and blood pressure without rtPA treatment. Your friend/relative is being invited to participate in this study because: (a) he/she has had an acute ischaemic stroke; and (b) he/she is eligible to receive the 'clot-dissolving' drug rtPA (the decision to give rtPA will be made by his/her treating doctor).

**6. Does he/she has to take part?**

It is up to you to decide whether or not he/she should take part. If you decide your friend/relative would have no objection to taking part we will ask you to read and sign the Personal Consultee Declaration Form (rtPA-Treated Patient). We will then give both you and your friend/ relative a copy

to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or you think your relative/friend should be withdrawn. Even if you have decided for your friend/relative would have no objection to take part in the study, you are still free to request him/her to withdraw from the study at anytime, and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care he/she receives.

**7. What will happen to me if your friend/relative takes part?**

If you believe your friend/relative would have no objection to join this study, he/she will have five study tests on five separate days. The first three measurements will be carried out whilst your friend/relative is still an in-patient, and for the last 2 measurements, we will arrange for you and your friend/relative to come into the hospital for approximately 1 hour. He/she will then be asked to lie quietly on a bed whilst a small cuff is attached to the finger of one hand to measure blood pressure, 3 stickers to the chest to monitor heart rate, and a small mask over the nose to measure the waste gas from breathing. He/she will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against both sides of the head. The head-frame is made of plastic material and able to adjust according to head size (see figure). Both the head-frame and ultrasound probe will exert a slight pressure on to head. However, this is not painful and is used routinely in many medical units to monitor blood flow to the brain.

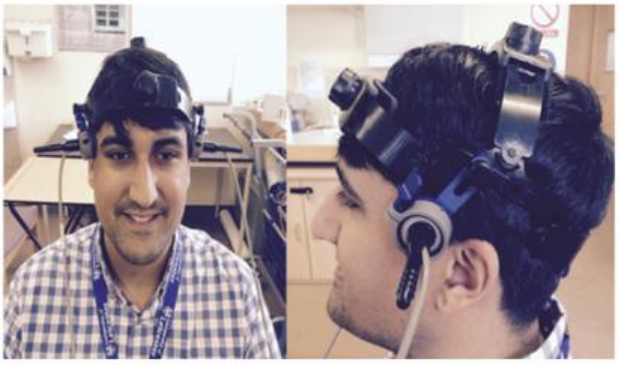

Figure: Head-frame and ultrasound probes

After the readings have stabilised, a 15-minute recording will be carried out while he/she is receiving the rtPA infusion, this will be followed by another 5-minute recording when the rtPA infusion is finished. Afterwards, we will remove one of the ultrasound probes which is attached to your friend/relative's head onto their neck. Thereafter, another 20-minute recording will be carried out while the ultrasound probes are attached to both the head and the neck. Overall, the whole assessment will take approximately 1 hour.

**Day 1**

- Measurements (as described above) will be carried out whilst your friend/relative is receiving and after the commencement of rtPA infusion.

**Day 2, 4 and 7**

- Measurements (as described above) will be carried out on Day 2, 4 and 7.
- On Day 4, your friend/relative will be assessed for his/her level of consciousness and degree of neurological impairment.
- On Day 7 or the day of your friend/relative's discharge from the hospital (if he/she is discharged before Day 7), he/she will be assessed for his/her degree of independence in everyday activities, so called 'activities of daily living'.

**Day 90**

- Measurements (as described above) will be carried out on Day 90.
- Your relative/friend will be assessed again on his/her ability to perform activities of daily living and he/she will be asked about their quality of life and use of health services.
- You will be asked to discuss the progress of stroke disease (i.e. any recurrent stroke events), new medical events, medication changes or intervention carried out during this period of time on behalf of your friend/relative. You will asked again to read the information leaflet and sign the Personal Consultee Declaration Form. We will then carry out the same set of measurements as before.

**8. What treatments will be used?**

No specific treatments are given as part of this small study.

**9. What are the possible disadvantages and risks of taking part?**

The blood pressure cuff applies only a gentle pressure to fingers to enable a blood pressure recording to be made every heartbeat. This may cause a slight tingling in fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care. The head-frame and ultrasound probes will exert a slight pressure against the head. However, this is not painful, and again is routinely used in many units to monitor blood flow to the brain.

**10. What are the possible benefits of taking part?**

Both you and your friend/relative should not expect to receive any personal benefit from taking part in this study. The study procedures are not diagnostic, neither you nor your friend/relative will

routinely receive the test results. However, it is hoped that this study will help us all to learn more about the stroke disease.

**11. What if I withdraw my friend/relative from the study?**

Even if you have decided for your friend/relative behalf to take part in the study, you are still free to request him/her to withdraw from the study at anytime, without giving a reason or affecting the care he/she receives. Furthermore, the research team can also decide to withdraw your friend/relative from the study if they believe it is in his/her best interest, i.e. progression of the stroke disease which requires discontinuation of the study or fluctuation of the capacity.

If you decide to withdraw your friend/relative from the study, please notify a member of the research team. This notice will allow the research supervisor to further discuss any health risks or special requirements linked with withdrawing.

If you decided for your friend/relative to leave the study, the researchers would like to keep the health information about your friend/relative that has been collected. This is to help them make sure that the results of the research can be assessed properly. If you do not want them to do this, you must tell them before your friend/relative joins the research study.

**12. What happen if I withdraw myself as the Personal Consultee?**

Even if you have decided to take on the role of Personal Consultee, you are still free to withdraw yourself from this role at any time, without giving a reason or affecting the care your friend/relative receives. Should this situation occur we would kindly ask you to nominate someone else to take on the role of Personal Consultee. However, if you feel that no one can take on the role, we will not invite your friend/relative to continue to participate in the study. Should this situation occur, the researchers would also like to keep the health information and data about your friend/relative that has been collected so far. If you do not want them to do this, you must also tell them before your friend/relative joins the research study.

**13. What happen if my friend/relative regains the ability to make decisions for themselves (capacity) during the study period?**

If your friend/relative regains capacity during the study period, he/she would need to give us full informed written consent themselves in order to continue to participate in the study. We will explain the details of the research study to your friend/relative and provide a Participant (rtPA-Treated Patient Who Regains Capacity) information leaflet as well. The research team will answer any questions that your friend/relative has concerning the study and he/she will also have the opportunity to ask questions of the research team, his/her GP or other independent parties to decide whether he/she would like to continue to participate in the study.

If your friend/relative does not wish to remain in the study, he/she will be withdrawn from the study. Unless your friend/relative agrees for the research team to retain and analysis any health information and data collected so far, all of these will also be destroyed.

**15. Will travel expenses be paid?**

Yes, both yourself and your friend/relative will not be out of pocket if you decide that your friend/relative has no objection to taking part in this study. Travel costs to and from the hospital for the study will be reimbursed.

**16. What if something goes wrong?**

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you or your friend/relative have been approached or treated during the course of the study, here are the details of the National Health Service complaints procedures:

Patient Information and Liaison Service (PILS)

Address: The Firs, C/O Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

Free phone line: 08081 788 337

Facsimile: 0116 258 8661

Email: pils@uhl-tr.nhs.uk

**17. Will my taking part be kept confidential?**

The blood pressure and blood flow data recorded during the study will be stored on a computer for subsequent analysis. However, your friend/relative will not be identified by name, and only the researcher will know that the information is related to your friend/relative. Any information collected during the study will be treated with the usual degree of confidentiality under the Data Protection Act and will not be passed to anyone else without your express permission. Your friend/relative's identity will not be revealed in any publication or presentation of the results from this study. However, with your permission, your friend/relative's own doctor (GP) will be notified he/she has been participated in the above study and if any health problems are identified that need further tests or treatment.

The relevant sections of your friend/relative's medical notes and/or data collected during the study, may also be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, for monitoring and audit purposes.

**18. Who is organising and funding the research?**

This research is coordinated by Professor Robinson and Professor Panerai from the University of Leicester.

**19. How will I find out the results of the research?**

At the end of the study, you and your friend/relative will be sent a written letter, in plain English, with a summary of our study findings and conclusions. This can either be posted or emailed to you and your friend/relative, depending on your preference.

**20. Whom can I contact?**

**For further information or appointments:**

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the Principal Investigator (Professor Tom Robinson) on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam;

Role: Clinical Research Fellow of Stroke Medicine

Address: Room 228, Level 2, Robert Kilpatrick Clinical Science Building, Leicester Royal Infirmary, Leicester, LE1 5WW, UK

Telephone: 0116 258 7257;

Email: ml376@le.ac.uk

Once again, thank you for taking the time to read this information sheet.

**Appendix 3.12** Personal Consultee Information Leaflet (Non-rtPA Treated Patient) Version 2 Dated 28th November 2015



University Hospitals of Leicester NHS
NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PERSONAL CONSULTEE INFORMATION LEAFLET (NON-rtPA TREATED PATIENT)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**

**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

Your friend/relative is being invited to take part in a research study. However, due to the nature of the illness, he/she is unable to decide for himself/herself whether to participate in the research study at the moment. To help decide if he/she should join the study, we would like to ask your opinion whether or not he/she would want to be involved. We would ask you to set aside your own views and consider his/her interests and what you feel would be his/her wishes and feelings. Any advanced directive that he/she may have made and that you are aware of should take precedence.

Before you decide whether to take on the personal consultee role, it is important for you to understand 1) what is a personal consultee 2) the personal consultee's role and responsibility and 3) why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. The following information leaflet is the same as would have been provided to your friend/relative.

Thank you for reading this.

**1) What is a personal consultee?**

It is fairly common for patients who suffer acute stroke to lose the ability to make decisions for themselves (i.e. they lack capacity), this could be due to difficulty in communication, reduced consciousness level (alertness) or confusion. In order to involve patients who, lack of capacity in research, under legislation (the Mental Capacity Act 2005), the research team must seek advice from the patient's personal consultee.

A personal consultee is someone who knows the patient and has a role in caring for the patient or is interested in the patient's welfare. A personal consultee is someone whom the patient who lacks of capacity would trust with important decisions about their welfare. He/she should be someone who can advise the researcher about the wishes and feelings of the patient who lacks of capacity in relation to the project and whether they would want to join the research study. A personal consultee is usually someone with a close personal relationship with the patient, for example, next of kin, spouse, partner or friend.

**2. What is the role and the responsibility of a personal consultee?**

A personal consultee must themselves have the ability to make a decision at the time and be prepared to be consulted by the research team about the possible involvement of the patient who lacks capacity. They should be able to advise the research team whether the patient who lacks capacity should take part in the project. For example, the personal consultee should consider whether the person who lacks capacity would be content to take part or whether doing so might upset them. The personal consultee must also give their opinion on what the past and present wishes and feelings of the patient who lacks capacity would have been about taking part in the research study. The personal consultee must set aside any views they may have about the research and consider only the views and interests of the patient who lacks capacity.

It is also important to remember that the personal consultee gives advice but is not being asked to consent on behalf of the patient who lacks capacity. The responsibility to decide whether the patient should be entered into the research lies ultimately with the researcher. However, we always respect the personal consultee's view and if the personal consultee objects to the inclusion of the patient in this research study, his/her view will be respected and the patient will not be enrolled in the study.

If you are unsure about taking the role of the personal consultee you may seek independent advice. We will understand if you do not want to take on this responsibility.

**3. Why this research study is being done?**

This is a small research study, which will involve five separate measurements of blood pressure and blood vessels of the brain and neck. The first measurement will be carried out at the hospital bedside in the Hyperacute Stroke Unit, ward 25, Level 3, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust. The subsequent four measurements will be carried out in the Cardiovascular Research Laboratory, Level 5, Windsor Building, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom. The first three measurements will take place while your friend/relative is still an in-patient under the care of the University Hospitals of Leicester NHS Trust Stroke service (within 6 hours, at 24 hours and 72 hours after the stroke onset), the 4$^{th}$ measurement will take place after approximately 7 days and the final measurement will take place approximately 3 months after the stroke onset. There will be a medical doctor whilst he/she is in the Cardiovascular Research Laboratory.

This study is being carried by Dr Man Yee LAM as part of a postgraduate educational qualification (MD) with the University of Leicester. The study is being supervised by senior staff from the University of Leicester including Professor Thompson Robinson (Professor of Stroke Medicine), and Professor Ronney Panerai (Professor of Physiological Measurement). They are all helping to support the research at the Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust.

**4. What is the purpose of the study?**

Blood flow to the brain has to be carefully controlled, otherwise there is a risk of too much or too little blood reaching the brain, both of which may be associated with risk and damage. The ability of the brain to control its blood supply is called autoregulation and it can range from no to perfect

control. Certain things affect brain blood flow (autoregulation) including changes in breathing rates and movement. In acute ischaemic stroke (i.e. a type of stroke due to the blockage of an artery by an embolus or blood clot), blood flow following the ischaemic event will be significantly reduced and can result in death of the brain tissue (core area). This could lead to significant disability or even death of a stroke patient.

However, there is a "penumbral" region surrounding the core area where partial blood flow is maintained. This penumbral region is supplied by a collateral circulation, a system of small, normally closed arteries start connecting and carrying blood to part of the brain when the brain artery is blocked. As a result these arteries can serve as alternate routes of blood supply. To improve the blood flow to the collateral circulation and therefore penumbral region is considered one of the important mechanisms to improve blood flow to the brain and therefore, a stroke patients' outcome.

At presence, we do not know if there is any relationship between the degree of the impairment in the brain blood flow (autoregulation)and blood pressure changes after the acute ischaemic stroke event.

We can measure brain blood flow (autoregulation) non-invasively using ultrasound, which detects changes in blood flow in the main brain arteries called the middle cerebral arteries. This research will use these non-invasive measurements of ultrasound to examine your friend/relative's brain and neck blood flow changes within 6 hours, at 24 hours, 72 hours, 7 days and 3 months post stroke onset. This knowledge will help doctors to have a better understanding of how to manage blood pressure in acute ischaemic stroke patients.

**5. Why has your friend/relative been chosen?**

Measurements in brain blood flow will be compared between 'clot-dissolving' rtPA-treated patients with acute ischaemic stroke disease and acute ischaemic stroke patients of the same age, sex and blood pressure without rtPA treatment. Your friend/relative is being invited to participate in this study because: (a) he/she has had an acute ischaemic stroke; and (b) he/she is not eligible to receive 'clot-dissolving' rtPA treatment (the doctor treating your friend/relative will have explained why he/she is not eligible to receive rtPA treatment).

**6. Does he/she has to take part?**

It is up to you to decide whether or not he/she should take part. If you decide your relative/friend would have no objection to taking part we will ask you to read and sign the Personal Consultee Declaration Form (Non-rtPA Treated Patient). We will then give both you and your friend/relative a copy to keep. We will keep you fully informed during the study so you can let us know if you have any concerns or you think your relative/friend should be withdrawn. Even if you have decided for your friend/relative would have no objection to take part in the study, you are still free to request him/her to withdraw from the study at anytime, and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care he/she receives.

**7. What will happen to me if your friend/relative takes part?**

If you believe your friend/relative would have no objection to join this study, he/she will have five study tests on five separate days. The first three measurements will be carried out whilst your friend/relative is still an in-patient, and for the last 2 measurements, we will arrange for you and your friend/relative to come into the hospital for approximately 1 hour. He/she will then be asked to lie quietly on a bed whilst a small cuff is attached to the finger of one hand to measure blood pressure, 3 stickers to the chest to monitor heart rate, and a small mask over the nose to measure the waste gas from breathing. He/she will be asked to wear a head-frame, which will hold the small ultrasound probes that are used to measure blood flow against both sides of the head. The head-frame is made of plastic material and able to adjust according to head size (see figure). Both the head-frame and ultrasound probe will exert a slight pressure on to head. However, this is not painful and is used routinely in many medical units to monitor blood flow to the brain.

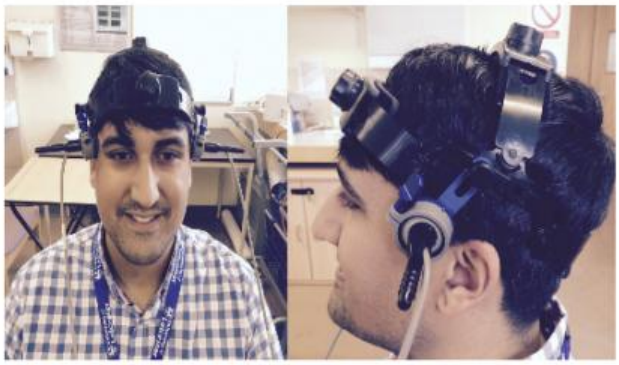

Figure: Head-frame and ultrasound probes

After the readings have stabilised, a 20-minute recording will be carried out within 6 hours of your friend/relative's stroke onset. Afterwards, we will remove one of the ultrasound probes which is attached to his/her head into the neck, thereafter, another 20-minute recording will be carried out while the ultrasound probes are attached to both the head and the neck. Overall, the whole assessment will take approximately 1 hour.

**Day 1**

- Measurements (as described above) will be carried out within 6 hours of stroke onset.

**Day 2, 4 and 7**

- Measurements (as described above) will be carried out on Day 2, 4 and 7.
- On Day 4, your friend/relative will be assessed for his/her level of consciousness and degree of neurological impairment.

- On Day 7 or the day of your friend/relative's discharge from the hospital (if he/she is discharged before Day 7), he/she will be assessed for his/her degree of independence in everyday activities, so called 'activities of daily living'.

**Day 90**

- Measurements (as described above) will be carried out on Day 90.
- Your relative/friend will be assessed again on his/her ability to perform activities of daily living and he/she will be asked about their quality of life and use of health services.
- You will be asked to discuss the progress of stroke disease (i.e. any recurrent stroke events), new medical events, medication changes or intervention carried out during this period of time on behalf of your friend/relative. You will be asked again to read the information leaflet and sign the Personal Consultee Declaration Form. We will then carry out the same set of measurements as before.

**8. What treatments will be used?**

No specific treatments are given as part of this small study.

**9. What are the possible disadvantages and risks of taking part?**

The blood pressure cuff applies only a gentle pressure to fingers to enable a blood pressure recording to be made every heartbeat. This may cause a slight tingling in fingers, but this should not be painful or cause any harm. Indeed, this type of blood pressure monitoring is often used routinely, e.g. in patients under general anaesthetic or in intensive care. The head-frame and ultrasound probes will exert a slight pressure against the head. However, this is not painful, and again is routinely used in many units to monitor blood flow to the brain.

**10. What are the possible benefits of taking part?**

Both you and your friend/relative should not expect to receive any personal benefit from taking part in this study. The study procedures are not diagnostic, neither you nor your friend/relative will routinely receive the test results. However, it is hoped that this study will help us all to learn more about the stroke disease.

**11. What happen if I withdraw my friend/relative from the study?**

Even if you have decided for your friend/relative would have no objection to take part in the study, you are still free to request him/her to withdraw from the study at any time, without giving a reason or affecting the care he/she receives. Furthermore, the research team can also decide to withdraw your friend/relative from the study if they believe it is in his/her best interest, i.e. progression of the stroke disease which requires discontinuation of the study or fluctuation of the capacity.

If you decide to withdraw your friend/relative from the study, please notify a member of the research team. This notice will allow the research supervisor to further discuss any health risks or special requirements linked with withdrawing.

If you decide for your friend/relative to leave the study, the researchers would like to keep the health information about your friend/relative that has been collected. This is to help them make sure that the results of the research can be assessed properly. If you do not want them to do this, you must tell them before your friend/relative joins the research study.

**12. What happen if I withdraw myself as the Personal Consultee?**

Even if you have decided to take on the role of Personal Consultee, you are still free to withdraw yourself from this role at any time, without giving a reason or affecting the care your friend/relative receives. Should this situation occur we would kindly ask you to nominate someone else to take on the role of Personal Consultee. However, if you feel that no one can take on the role, we will not invite your friend/relative to continue to participate in the study. Should this situation occur, the researchers would also like to keep the health information and data about your friend/relative that has been collected so far. If you do not want them to do this, you must also tell them before your friend/relative joins the research study.

**13. What happen if my friend/relative regains the ability to make decisions for themselves (capacity) during the study period?**

If your friend/relative regains capacity during the study period, he/she would need to give us full informed written consent themselves in order to continue to participate in the study. We will explain the details of the research study to your friend/relative and provide a Participant (Non-rtPA Treated Patient who regain capacity) information leaflet as well. The research team will answer any questions that your friend/relative has concerning the study and he/she will also have the opportunity to ask questions of the research team, his/her GP or other independent parties to decide whether he/she would like to continue to participate in the study.

If your friend/relative does not wish to remain in the study, he/she will be withdrawn from the study. Unless your friend/relative agrees for the research team to retain and analysis any health information and data collected so far, all of these will also be destroyed.

**14. Will travel expenses be paid?**

Yes, both yourself and your friend/relative will not be out of pocket if you decide that your friend/relative has no objection to taking part in this study. Travel costs to and from the hospital for the study will be reimbursed.

**15. What if something goes wrong?**

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the National Health Service, i.e. compensation is only available if negligence occurs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you or your friend/relative have been approached or treated during the course of the study, here are the details of the National Health Service complaints procedures:

Patient Information and Liaison Service (PILS)

Address: The Firs, C/O Glenfield Hospital, Groby Road, Leicester, LE3 9QP, UK

Free phone line: 08081 788 337

Facsimile: 0116 258 8661

Email: pils@uhl-tr.nhs.uk

**16. Will my taking part be kept confidential?**

The blood pressure and blood flow data recorded during the study will be stored on a computer for subsequent analysis. However, your friend/relative will not be identified by name, and only the researcher will know that the information is related to your friend/relative. Any information collected during the study will be treated with the usual degree of confidentiality under the Data Protection Act and will not be passed to anyone else without your express permission. Your friend/relative's identity will not be revealed in any publication or presentation of the results from this study. However, with your permission, your friend/relative's own doctor (GP) will be notified he/she has been participated in the above study and if any health problems are identified that need further tests or treatment.

The relevant sections of your friend/relative's medical notes and/or data collected during the study, may also be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, for monitoring and audit purposes.

**17. Who is organising and funding the research?**

This research is coordinated by Professor Robinson and Professor Panerai from the University of Leicester.

**18. How will I find out the results of the research?**

At the end of the study, you and your friend/relative will be sent a written letter, in plain English, with a summary of our study findings and conclusions. This can either be posted or emailed to you and your friend/relative, depending on your preference.

**19. Whom can I contact?**

**For further information or appointments:**

If you have any concerns or other questions about the study, or the way it has been carried out, you should contact the Principal Investigator (Professor Tom Robinson) on 0116 252 3182 or any of the following people:

Name: Dr Man Yee Lam

Role: Clinical Research Fellow of Stroke Medicine

Address: Room 228, level 2, Robert Kilpatrick Clinical Science Building, Leicester Royal Infirmary, Leicester, LE1 5WW, UK

Telephone: 0116 258 7257;

Email: ml376@le.ac.uk

**Once again, thank you for taking the time to read this information sheet.**

**Appendix 3.13** Participant Consent Form (rtPA-Treated Patient) Short Version 3 Dated 28th November 2015

University Hospitals of Leicester NHS
NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT CONSENT FORM (rtPA-TREATED PATIENT)**
**Short Version**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**
**Principal Investigator: Professor Tom Robinson**
**Reseracher: Dr Man Yee Lam**

**Researcher Name: Dr** _____ **Please initial**

**Patient Study ID Number:** _____

| | |
|---|---|
| I confirm that I have read and understand the Participant Information Leaflet (rtPA-Treated Patient) Short Version 3, dated 28 November, 2015 for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily. | ☐ |
| I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected. | ☐ |
| I understand that if I decide to withdraw prior to the completion of the study, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |
| I agree to take part in the above study. | ☐ |

Participant Name:_____ Date:_____ Signature: _____

Witness Name: _____ Date:_____ Signature: _____

Researcher: _____ Date:_____ Signature: _____

(File: 1 for patient, 1 for researcher, 1 for hospital notes)

Version 3, 28th November 2015

**Appendix 3.14** Participant Consent Form (rtPA-Treated Patient) Full Version 3 Dated 28th November 2015

University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT CONSENT FORM (rtPA-TREATED PATIENT)**
**Full Version**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**
**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

**Researcher Name: Dr** _____ **Please initial**

**Patient Study ID Number:** _____

| | |
|---|---|
| I confirm that I have read and understand the Participant Information Leaflet (rtPA-Treated Patient) Full Version 3, dated 25 November, 2015 for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily. | ☐ |
| I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected. | ☐ |
| I understand that my GP will be informed about my participation in this study, and by signing this consent form I am granting permission for this. | ☐ |
| I understand that if I decide to withdraw prior to the completion of the study, research team would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |
| I understand that in the unusual circumstance that I became unwell and lose the ability to decide whether I should continue to participate in the research study, the research team would withdraw me from the study. However, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |

I understand that relevant sections of my medical notes and/or data collected during the study, may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. I give permission for these individuals to have access to my records. ☐

I agree to take part in the above study. ☐

Participant Name:_____ Date:_____ Signature: _____

Witness Name: _____ Date:_____ Signature: _____

Researcher: _____ Date: _____ Signature: _____

(File: 1 for patient, 1 for researcher, 1 for hospital notes)

Version 3, 28th November 2015

**Appendix 3.15** Participant Consent Form (rtPA-Treated Patient Who Regains Capacity) Full Version 1 Dated 28th November 2015

University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT CONSENT FORM (rtPA-TREATED PATIENT WHO REGAINS CAPACITY)**
**Full Version**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**
**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

**Researcher Name: Dr** _____ **Please initial**

**Patient Study ID Number:** _____

| | |
|---|---|
| I confirm that I have read and understand the Participant Information Leaflet (rtPA-Treated Patient Who Regains Capacity) Version 1, dated 25 November, 2015 for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily. | ☐ |
| I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected. | ☐ |
| I understand that my GP will be informed about my participation in this study, and by signing this consent form I am granting permission for this. | ☐ |
| I understand that if I decide to withdraw prior to the completion of the study, research team would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |
| I understand that in the unusual circumstance that I became unwell and lose the ability to decide whether I should continue to participate in the research study, the research team would withdraw me from the study. However, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |

I understand that relevant sections of my medical notes and/or data collected during the study, may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. I give permission for these individuals to have access to my records. ☐

I agree to take part in the above study. ☐

Participant Name:_____ Date:_____ Signature: _____

Witness Name: _____ Date:_____ Signature: _____

Researcher: _____ Date: _____ Signature: _____

(File: 1 for patient, 1 for researcher, 1 for hospital notes)

Version 1, 28th November 2015

**Appendix 3.16** Participant Consent Form (Non-rtPA Treated Patient) Version 3 Dated 28th November 2015

University Hospitals of Leicester NHS
NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT CONSENT FORM (NON-rtPA TREATED PATIENT)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**
**Principal Investigator: Professor Tom Robinson**
**Researcher : Dr Man Yee Lam**

**Researcher Name: Dr _____** **Please initial**

**Patient Study ID Number: _____**

| | |
|---|---|
| I confirm that I have read and understand the Participant Information Leaflet (Non-rtPA Treated Patient) Version 3, dated 28 November, 2015 for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily. | ☐ |
| I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected. | ☐ |
| I understand that my GP will be informed about my participation in this study, and by signing this consent form I am granting permission for this. | ☐ |
| I understand that if I decide to withdraw prior to the completion of the study, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |
| I understand that in the unusual circumstance that I became unwell and lose the ability to decide whether I should continue to participate in the research study, the research team would withdraw me from the study. However, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |

I understand that relevant sections of my medical notes and/or data collected during the study, may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. I give permission for these individuals to have access to my records. ☐

I agree to take part in the above study. ☐

Participant Name:_____ Date:_____ Signature: _____

Witness Name: _____ Date:_____ Signature: _____

Researcher: _____ Date:_____ Signature: _____

(File: 1 for patient, 1 for researcher, 1 for hospital notes)

Version 3, 28th November 2015

**Appendix 3.17** Participant Consent Form (Non-rtPA Treated Patient Who Regains Capacity) Version 1 Dated 28th November 2015

University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PARTICIPANT CONSENT FORM (NON-rtPA TREATED PATIENT WHO REGAINS CAPACITY)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**
**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

**Researcher Name: Dr** _____ **Please initial**

**Patient Study ID Number:** _____

| | |
|---|---|
| I confirm that I have read and understand the Participant Information Leaflet (Non-rtPA Treated Patient Who Regains Capacity) Version 1, dated 28 November 2015 for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily. | ☐ |
| I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected. | ☐ |
| I understand that my GP will be informed about my participation in this study, and by signing this consent form I am granting permission for this. | ☐ |
| I understand that if I decide to withdraw prior to the completion of the study, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am granting permission for this. | ☐ |
| I understand that relevant sections of my medical notes and/or data collected during the study, may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. I give permission for these individuals to have access to my records. | ☐ |
| I agree to take part in the above study. | ☐ |

Participant Name:_____ Date:_____ Signature: _____

Witness Name: _____ Date:_____ Signature: _____

Researcher: _____ Date:_____ Signature: _____

(File: 1 for patient, 1 for researcher, 1 for hospital notes)

Version 1, 28th November 2015

**Appendix 3.18** Personal Consultee Declaration Form (rtPA-Treated Patient) Short Version 2 Dated 28th November 2015

University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PERSONAL CONSULTEE DECLARAION FORM (rtPA-TREATED PATIENT)**
**SHORT VERSION**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**
**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

**Researcher Name: Dr** _____ **Please initial**

**Patient Study ID Number:** _____

| | |
|---|---|
| I (name of Personal Consultee) have been consulted about (name of potential participant)'s participation in this research study. I confirm that I have read and understand the Personal Consultee Information Leaflet (rtPA-treated Patient) Short Version 2, dated 28 November, 2015 for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily. | ☐ |
| I understand that I can refuse to act as a Personal Consultee at anytime, by signing this form I am agreeing to act as a Personal Consultee. | ☐ |
| I understand that (name of potential participant)'s participation is voluntary and that I am free to withdraw him/her any time, without giving a reason, without any medical care or legal rights being affected. | ☐ |
| I understand if I decide to withdraw (name of potential participant) prior to the completion of the study, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am in agreement with this. | ☐ |
| In my opinion (name of potential participant) would have no objection to taking part in the above study. | ☐ |

Personal Consultee Name:_____ Date:_____

Signature: _____ Relationship to Participant: _____

Researcher: _____ Date:_____ Signature: _____

(File: 1 for patient, 1 for Personal Consultee, 1 for researcher site file, 1 for hospital notes)

Version 2, 28th November, 2015

**Appendix 3.19** Personal Consultee Declaration Form (rtPA-Treated Patient) Full Version 2 Dated 28th November 2015

University Hospitals of Leicester NHS
NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PERSONAL CONSULTEE DECLATATION FORM (rtPA-TREATED PATIENT)**
**Full VERSION**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**
**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

**Researcher Name: Dr _____** **Please initial**

**Patient Study ID Number: _____**

| | |
|---|---|
| I (name of Personal Consultee) have been consulted about (name of potential participant)'s participation in this research study. I confirm that I have read and understand the Personal Consultee Information Leaflet (rtPA-Treated Patient) Full version 2, dated 28th November, 2015 for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily. | |
| I understand that I can refuse to act as a Personal Consultee anytime, by signing this form I am agreeing to act as a Personal Consultee. | |
| I understand that (name of potential participant)'s participation is voluntary and that I am free to withdraw him/her any time, without giving a reason, without any medical care or legal rights being affected. | |
| In my opinion (name of potential participant) would have no objection to taking part in the above study. | |
| I agree to (name of potential participant)'s GP or other healthcare professional being informed of his/her participation of the study. | |
| I understand that if I decide to withdraw (name of potential participant) prior to the completion of the study, the research team would like to keep all the health information and data that has been collected so far for the final | |

analysis and I am in agreement with this.

I understand that in the unusual circumstance that I became unwell and lose the ability to decide whether (name of potential participant) should continue to participate in the research study, the research team would withdraw (name of participant) from the study. However, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am in agreement with this. ☐

I understand that relevant sections of his/her medical notes and/or data collected during the study, may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. ☐

Personal Consultee Name: _____ Date:_____

Signature: _____ Relationship to Participant: _____

Researcher: _____ Date:_____ Signature: _____

(File: 1 for patient, 1 for Personal Consultee , 1 for researcher site file, 1 for hospital notes)

Version 2, 28th November, 2015

**Appendix 3.20** Personal Consultee Declaration Form (Non-rtPA Treated Patient) Version 2 Dated 28th November 2015

University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester, LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**PERSONAL CONSULTEE DECLARATION FORM (NON-rtPA TREATED PATIENT)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**
**Principal Investigator: Professor Tom Robinson**
**Researcher: Dr Man Yee Lam**

**Researcher Name: Dr _____** **Please initial**

**Patient Study ID Number: _____**

| | |
|---|---|
| I (name of Personal Consultee) have been consulted about (name of potential participant)'s participation in this research study. I confirm that I have read and understand the Personal Consultee Information Leaflet (NON-rtPA Treated Patient) Version 2, dated 28th November 2015 for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily. | |
| I understand that I can refuse to act as a Personal Consultee anytime, by signing this form, I am agreeing to act as a Personal Consultee. | |
| I understand that (name of potential Participant)'s participation is voluntary and that I am free to withdraw him/her any time, without giving a reason, without any medical care or legal rights being affected. | |
| In my opinion (name of potential participant) would have no objection to taking part in the above study. | |
| I agree to (name of potential participant)'s GP or other care professional being informed of his/her participation of the study. | |
| I understand that if I decide to withdraw (name of potential participant) prior to the completion of the study, the research team would like to keep all the health information and data that has been collected so far for the final analysis and | |

I am in agreement with this.

I understand that in the unusual circumstance that I became unwell and lose the ability to decide whether (name of potential participant) should continue to participate in the research study, the research team would like to keep all the health information and data that has been collected so far for the final analysis and I am in agreement with this. ☐

I understand that relevant sections of his/her medical notes and/or data collected during the study, may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities, where it is relevant to taking part in this research. ☐

Personal Consultee Name: _____ Date:_____

Signature: _____ Relationship to participant: _____

Researcher: _____ Date:_____ Signature: _____

(File: 1 for patient, 1 for personal Consultee, 1 for researcher site file, 1 for hospital notes)

Version 2, 28th November, 2015

**Appendix 3.21** GP Information Leaflet (Patient) Version 2 Dated 25th August 2015

University Hospitals of Leicester NHS
NHS Trust

Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 (Ext 7257)
Fax: 0116 252 5847

**GP INFORMATION LEAFLET (Patient)**

**Cerebral Haemodynamics in Stroke Thrombolysis (CHiST) Study**
**REC Number**

Dear Dr GP

**Re:**
**Name**
**dob**
**Address:**

Your patient above has been recruited to the above study, which is being carried out by researchers at the University of Leicester. The study involves measurement of beat to beat blood pressure and heart rate, along with measurement of cerebral blood flow velocity using Transcranial Doppler.

As part of this study, patient will be required to participate for up to 3 months post stroke symptom onset, during which up to a total of 5 assessments will be made. They have been fully counselled regarding this.

Participation in the above study is entirely voluntary.

If you have any further questions regarding this trial, please contact us on the details below.

Yours Faithfully,

Dr Man Yee LAM BSc MBBS MRCP(UK)
Honorary Clinical Research Fellow/Honorary Specialist Registrar of Stroke Medicine

Telephone 0300 303 1573 (Extension 7257)

On behalf of Professor T G Robinson BMedSci, MBBS, MD, FRCP
Professor of Stroke Medicine/Honorary Consultant Physician

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