IS DYNAMIC CEREBRAL AUTOREGULATION IMPAIRED IN IDIOPATHIC PARKINSON’S DISEASE?

Thesis submitted for the degree of

Doctor of Medicine (MD)

at the University of Leicester

by

Victoria Joanna Haunton

Department of Cardiovascular Sciences

University of Leicester

October 2013
ABSTRACT

Title: Is dynamic cerebral autoregulation impaired in idiopathic Parkinson’s disease?

Author: Victoria Joanna Haunton

Background:
Cerebral autoregulation (CA) refers to the ability of the brain to maintain a relatively constant cerebral blood flow (CBF) in response to significant changes in cerebral perfusion pressure. CA is governed by several key mechanisms, which can be described as neurogenic, myogenic and metabolic. Idiopathic Parkinson’s disease (PD) is a common neurodegenerative disease with a significant autonomic component, and it has been hypothesised that CA in PD may therefore be impaired. However, to date, the literature on this subject has been limited in its scope, of uneven quality and has yielded conflicted findings.

Objective:
This Thesis aimed to determine if dynamic CA is impaired in patients with idiopathic PD, compared to healthy control subjects, and if dynamic CA varies between the ‘on’ and ‘off’ states of PD.

Methods:
CA was assessed by means of continuous non-invasive monitoring of arterial blood pressure (BP) and velocities in the middle cerebral arteries bilaterally using transcranial Doppler ultrasound. A cohort of patients with idiopathic Parkinson’s disease were studied in both their clinically ‘on’ and ‘off’ states, and their data were compared to that obtained from age- and sex-matched healthy controls. In addition to assessing the CA response to spontaneous fluctuations in BP, a variety of paradigms were used to induce changes in mean cerebral blood flow velocity and BP, including passive arm movement and hyperventilation.

Results:
This study has demonstrated that CA responses to spontaneous fluctuations in BP do not differ significantly between the on and off states of PD, but do differ significantly between PD patients and healthy controls, ultimately suggesting that CA is altered, but not necessarily impaired, in idiopathic PD. CBF velocity responses to passive arm movement and hyperventilation did not differ significantly between the on and off states of PD, or between PD patients and healthy controls.
ACKNOWLEDGEMENTS

I wish to express my deepest gratitude to Professors Thompson Robinson and Ronney Panerai for their time, encouragement and skilful supervision of my work; they are outstanding supervisors who set the bar extremely high for others. I am especially grateful to Tom for his mentorship and to Ronney for his infectious enthusiasm and endless patience. (Ronney is owed an additional ‘thank you’ for kindly and quietly overlooking my choice of English Literature over Physics at A Level in the late 1990s).

A sincere ‘thank you’ is also owed to Dr Nelson Lo for his clinical supervision and support with the study; his interest and ideas have been warmly received and his advice highly valued. The timely support of Dr Suzanne Dawson and Dr Nainal Shah will always be remembered, and was very much appreciated.

My grateful thanks are given to the Leicester Grant-In-Aid fund for supporting my MD work with a research grant, and to Parkinson’s UK for their help with recruiting patients to the study. I would also like to acknowledge Dr Guanmei Luo and Dr Martha Hanby for their assistance with data collection; both were a pleasure to work with.

My time spent in research was very much enhanced by the strong friendship of all those working in the Departments of Ageing and Stroke Medicine and Medical Physics at the University of Leicester. I am extremely grateful for their support and for making me feel so included. My fellow doctoral students Angela Salinet and Nazia Saeed deserve a special mention and thank you for their help and guidance.

Thank you to my wonderful family for your continual support and for your belief in me. Your love and pride are both overwhelming and sustaining. Thank you to my incredible husband Tom, the completion of this work would not have been possible without your unconditional and unwavering love, support and encouragement.

Finally, I owe a huge debt of gratitude to all the patients who took part in the study. It has been a privilege and a pleasure to meet every one of you; I have been truly humbled by your spirit, your selflessness, and your willingness to support any research into this unforgiving disease.
Dedicated to my family.

Especially Granny B, who has always believed in the power of education.
CONTRIBUTORSHIP

The design, organisation and administration of this study were performed by the author with the advice and guidance of Professors Thompson Robinson and Ronney Panerai, University of Leicester.

The recruitment and study of all subjects was undertaken by the author with the assistance of Dr Guanmei Luo and Dr Martha Hanby.

The data analysis software was written and developed by Professor Ronney Panerai and the Medical Physics Group, Department of Cardiovascular Sciences, University of Leicester, and had already been in use for several years at the time of the research. All data analysis was performed by the author using this software, with the author taking care to ensure that she had a good working knowledge of both the software and the physical and technical principles involved. Professor Panerai periodically reviewed the quality of both the obtained data, and the subsequent analyses, providing advice and support where needed.

All statistical analyses were performed by the author.

Professors Robinson and Panerai provided constructive guidance on the structure, and the content, of the Thesis at all stages of its creation. I confirm that unless otherwise acknowledged or referenced all original work contained within this Thesis is my own.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title Page</td>
<td>-</td>
</tr>
<tr>
<td>Abstract</td>
<td>I</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>II</td>
</tr>
<tr>
<td>Dedication</td>
<td>III</td>
</tr>
<tr>
<td>Contributorship</td>
<td>IV</td>
</tr>
<tr>
<td>Table of Contents</td>
<td>V</td>
</tr>
<tr>
<td>List of Tables</td>
<td>XIII</td>
</tr>
<tr>
<td>List of Figures</td>
<td>XVI</td>
</tr>
<tr>
<td>List of Abbreviations</td>
<td>XVIII</td>
</tr>
</tbody>
</table>

## 1 Introduction

1.2 PARKINSON’S DISEASE

1.2.1 Definition

1.2.2 Epidemiology and Aetiology

1.2.3 Pathology

- Neuronal loss
- Neurotransmitter depletion
- Lewy bodies
- Other pathological features

1.2.4 Clinical Features

- Motor features
- Non-motor features
2 Systematic Review of the Literature

2.1 BACKGROUND

2.2 MATERIALS AND METHODS

2.3 RESULTS

2.3.1 Study quality

2.3.2 Study characteristics

2.3.3 Measurement techniques and CA inputs

2.3.4 Modelling techniques

2.3.5 Cerebral haemodynamic responses

2.4 DISCUSSION

2.5 SUMMARY

3 Research Methods

3.1 METHODS

3.2 ETHICAL APPROVAL

3.3 RESEARCH METHODS

3.3.1 Subjects

3.3.2 Recruitment

3.3.3 Research Protocol

Hoehn and Yahr Scale

Unified Parkinson’s Disease Rating Scale
4 Dynamic Cerebral Autoregulation Indices in the ‘On’ and ‘Off’ States of PD

4.1 INTRODUCTION

4.2 METHODS

4.2.1 Protocol

4.2.2 Data Analysis

4.2.3 Statistics

4.3 RESULTS

4.3.1 Baseline Demographics

4.3.2 Anti-Parkinsonian Medication

4.3.3 Baseline Peripheral Haemodynamic Data

4.3.4 MCBFV, CrCP and RAP Data

4.3.5 Frequency Domain Parameters

4.3.6 ARI Values

4.3.7 The Influence of Disease Stage

4.3.8 The Influence of Orthostatic Hypotension

4.4 DISCUSSION
6.2.3 Statistics

6.3 RESULTS

6.3.1 Baseline Demographics

6.3.2 Baseline Peripheral Haemodynamic Data

6.3.3 Baseline MCBFV Values

6.3.4 Baseline dCA Indices

6.3.5 Peripheral Haemodynamic Response to Hyperventilation

6.3.6 CBFV Response to Hypocapnia

6.3.7 Intra-Manoeuvre dCA Indices

6.4 DISCUSSION

6.5 LIMITATIONS

6.6 SUMMARY

7 The Natural History of Cerebral Autoregulation in Idiopathic Parkinson’s Disease

7.1 INTRODUCTION

7.2 METHODS

7.2.1 Protocol

7.2.2 Data Analysis

7.2.3 Statistics

7.3 RESULTS

7.3.1 Baseline Demographics

7.3.2 Baseline Peripheral Haemodynamic Data

7.3.3 Mean Cerebral Blood Flow Velocity
<table>
<thead>
<tr>
<th>11</th>
<th>Unified Parkinson’s Disease Rating Scale</th>
<th>195</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Parkinson’s Disease Non-Motor Symptom Questionnaire</td>
<td>199</td>
</tr>
<tr>
<td>13</td>
<td>Summary of patient recruitment and inclusion in data analyses</td>
<td>200</td>
</tr>
<tr>
<td>14</td>
<td>Publications and presentations arising from this Thesis</td>
<td>201</td>
</tr>
</tbody>
</table>
LIST OF TABLES

1.1 The non-motor symptoms of Parkinson’s Disease .......................... 11
1.2 UK Parkinson’s Disease Society Brain Bank Criteria for the Diagnosis of PD .................. 13
2.1 Overview of studies included in the systematic review ................. 39
2.2 Checklist for study quality ........................................................ 40
2.3 Scores for quality assessment detailed by individual study .......... 41
2.4 Patient age and disease duration detailed by study .................. 44
2.5 Mean CBFV detailed by vessel and by study ............................. 48
3.1 Depth and flow direction of the major intracranial vessels when assessed using TCD .................................................. 61
3.2 Mean velocities of the major intracranial vessels denoted by age .................................................. 61
3.3 Abstinence period by medication type for ‘off’ measurements ........ 64
4.1 Baseline characteristics of participants ..................................... 75
4.2 Baseline demographics of PD patients ..................................... 76
4.3 Anti-Parkinsonian medications of study participants ................. 76
4.4 Baseline peripheral haemodynamic data of study participants .... 76
4.5 Baseline values of MBFV, CrCP and RAP for healthy controls and PD patients, detailed by side and by clinical state .................. 79
4.6 Baseline values of MBFV, CrCP and RAP for PD patients detailed by hemisphere of disease onset, and by clinical state .......... 79
4.7 MCBFV denoted by ages of participants .................................. 80
4.8 Mean frequency domain parameters for healthy controls and PD patients, detailed by frequency range ........................................ 81
4.9 Tukey’s post-hoc analysis of frequency domain parameters ........ 84
4.10 ARI values for PD patients in each clinical state and healthy controls 85
4.11 Post-hoc analysis of ARI values obtained for PD patients in each clinical state and healthy controls. 85
4.12 Median ARI values detailed for PD patients by disease stage 88
4.13 Post-hoc analysis of ARI values for PD patients at different disease stages 88
4.14 Median ARI values detailed for PD patients with and without a history of OH 89
4.15 Post-hoc analysis of ARI values for PD patients with and without a history of OH 89

5.1 Baseline demographics of PD patients and healthy controls in the NVC study 103
5.2 PD specific baseline data for patients in the NVC study 103
5.3 Baseline peripheral haemodynamic data for PD patients and healthy controls in the NVC study 104
5.4 Baseline values of MCBFV in cm/s, detailed by right and left sides for healthy controls, and by disease onset hemisphere for PD patients 105

6.1 Baseline demographics of PD patients and healthy controls in the VMR study 122
6.2 PD specific baseline data for patients in the VMR study 122
6.3 Baseline peripheral haemodynamic data for PD patients and healthy controls in the VMR study 123
6.4 Baseline values of MCBFV in cm/s, detailed by right and left sides for healthy controls, and by disease onset hemisphere for PD patients 124
6.5 Baseline dCA indices for subjects in the VMR study 124
6.6 dCA indices for subjects in the VMR study obtained at timepoint 1 127
6.7 dCA indices for subjects in the VMR study obtained at timepoint 2 127
7.1 Baseline demographics of patients enrolled into the natural history study 140
7.2 Medication regimes at each time point for patients in the natural history study 141
7.3 H&Y stage, NMS-Quest and UPDRS scores for patients in the natural history study, detailed by patient, clinical state and visit 142
7.4 Longitudinal peripheral haemodynamic data, detailed by patient, clinical state and visit 143
7.5 Longitudinal values of MCBFV, detailed by patient, clinical state and visit 144
7.6 Longitudinal ARI values detailed by patient, clinical state and visit 145
LIST OF FIGURES

1.1 Simplified basal ganglia motor circuit 6
1.2 The relationship between cerebral perfusion pressure and cerebral blood flow when regulated by an intact autoregulation mechanism 20
1.3 The acoustic windows of the skull used for TCD 25
1.4 Tiecks’ cerebral autoregulation curves 31
3.1 Typical data recording as viewed in the MS-DOS editing software 66
3.2 Plethysmography waveform drift 67
3.3 Spike artefact 67
3.4 Noisy, poor quality signal 67
3.5 Poor quality, unreliable, ECG trace 68
4.1 Acceptable impulse response 72
4.2 Unacceptable impulse response 72
4.3 Mean coherence function for PD patients and healthy controls 82
4.4 Mean transfer function amplitude (gain) frequency response 82
4.5 Mean transfer function phase frequency response 83
5.1 CBFV responses to passive arm movement of healthy controls 106
5.2 CBFV responses to passive arm movement of PD patients in the on state 107
5.3 CBFV responses to passive arm movement of PD patients in the off state 107
5.4 CBFV responses to passive arm movement of PD patients in the on and off states 108
5.5 CBFV responses to passive arm movement of healthy controls and PD patients in the on state 108
5.6 CBFV responses to passive arm movement of healthy controls and PD patients in the off state
5.7 CBFV responses to passive arm movement of healthy controls and PD patients in both states.
5.8 BP response of subjects during the motor paradigm
5.9 HR response of subjects during the motor paradigm
6.1 Hyperventilation induced change in EtCO₂, shown for each subject group
6.2 Hyperventilation induced change in HR, shown for each subject group.
6.3 Hyperventilation induced change in ABP, shown for each subject group
6.4 Hyperventilation induced change in MCBFVs, healthy controls
6.5 Hyperventilation induced change in MCBFVs, PD patients ON
6.6 Hyperventilation induced change in MCBFVs, PD patients OFF
6.7 Hyperventilation induced change in MCBFVs, PD patients ON and OFF
6.8 Hyperventilation induced change in MCBFVs, all subjects
7.1 Longitudinal ARI values for patient 1, by on and off states
7.2 Longitudinal ARI values for patient 2, by on and off states
7.3 Longitudinal ARI values for patient 3, by on and off states
7.4 Longitudinal ARI values for all patients, by on and off states
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP</td>
<td>arterial blood pressure</td>
</tr>
<tr>
<td>ACZ</td>
<td>acetazolamide</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ARI</td>
<td>autoregulatory index</td>
</tr>
<tr>
<td>BH</td>
<td>breath hold</td>
</tr>
<tr>
<td>BHI</td>
<td>breath hold index</td>
</tr>
<tr>
<td>BOLD-fMRI</td>
<td>blood oxygenation level-dependent functional MRI</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>bpm</td>
<td>beats per minute</td>
</tr>
<tr>
<td>CA</td>
<td>cerebral autoregulation</td>
</tr>
<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
</tr>
<tr>
<td>CBFV</td>
<td>cerebral blood flow velocity</td>
</tr>
<tr>
<td>CO₂</td>
<td>carbon dioxide</td>
</tr>
<tr>
<td>CPP</td>
<td>cerebral perfusion pressure</td>
</tr>
<tr>
<td>CPT</td>
<td>cold pressor test</td>
</tr>
<tr>
<td>CR</td>
<td>cerebrovascular reactivity</td>
</tr>
<tr>
<td>CrCP</td>
<td>critical closing pressure</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CVR</td>
<td>cerebrovascular resistance</td>
</tr>
<tr>
<td>CVRi</td>
<td>cerebrovascular resistance index</td>
</tr>
<tr>
<td>DA</td>
<td>dopamine agonist</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>dCA</td>
<td>dynamic cerebral autoregulation</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EHI</td>
<td>Edinburgh handedness inventory</td>
</tr>
</tbody>
</table>
EtCO\textsubscript{2}  end-tidal carbon dioxide
f-MRI  functional magnetic resonance imaging
f-TCD  functional transcranial Doppler
FFT  fast Fourier transform
H&Y  Hoehn and Yahr
HC  healthy controls
HF  high frequency
HR  heart rate
HUT  head up tilt
IQR  inter-quartile range
LF  low frequency
MAP  mean arterial pressure
MCA  middle cerebral artery
MCBFV  mean cerebral blood flow velocity
MF  middle frequency
mmHg  millimetre of mercury
MRI  magnetic resonance imaging
MSA  multi system atrophy
NIRS  near infra-red spectroscopy
NVC  neurovascular coupling
O\textsubscript{2}  oxygen
OH  orthostatic hypotension
PaCO\textsubscript{2}  partial pressure of carbon dioxide
PAF  primary autonomic failure
PCA  posterior cerebral artery
PCBFV  peak cerebral blood flow velocity
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PI</td>
<td>pulsatility index</td>
</tr>
<tr>
<td>PSP</td>
<td>progressive supranuclear palsy</td>
</tr>
<tr>
<td>RAP</td>
<td>resistance area product</td>
</tr>
<tr>
<td>RR</td>
<td>respiratory rate</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SPECT</td>
<td>single-photon emission computed tomography</td>
</tr>
<tr>
<td>STN-DBS</td>
<td>subthalamic nucleus deep brain stimulation</td>
</tr>
<tr>
<td>TCD</td>
<td>transcranial Doppler ultrasound</td>
</tr>
<tr>
<td>TFA</td>
<td>Transfer Function Analysis</td>
</tr>
<tr>
<td>UPDRS</td>
<td>Unified Parkinson’s Disease Rating Scale</td>
</tr>
<tr>
<td>VA</td>
<td>vertebral artery</td>
</tr>
<tr>
<td>VEP</td>
<td>visual evoked paradigm</td>
</tr>
<tr>
<td>VMR</td>
<td>vasomotor reactivity</td>
</tr>
</tbody>
</table>
CHAPTER 1 INTRODUCTION

“The disease, respecting which the present inquiry is made, is of a nature highly afflictive”.

James Parkinson, 1817

1.1 INTRODUCTION

This introductory chapter will provide an overview of both idiopathic Parkinson’s disease (PD) and of cerebral autoregulation (CA), with particular consideration to the epidemiology, pathology, clinical features and treatments for the former, and definitions, mechanisms, and methods of measurement of the latter. The chapter concludes with the Thesis hypotheses and aims.

1.2 PARKINSON’S DISEASE

1.2.1 Definition

PD is defined as a chronic neurodegenerative disorder characterised clinically by bradykinesia, rigidity, tremor and postural instability, and pathologically by a severe loss of dopaminergic neurons in the pars compacta of the substantia nigra and the presence of abnormal protein aggregates called Lewy bodies. Although there are several historical and literary references to the condition, it was first described in detail in the medical literature by the English surgeon James Parkinson in his seminal “Essay on the Shaking Palsy” in 1817\(^1\). However, the condition did not receive its eponymous title until 1884 when it was named “maladie de Parkinson” by the French neurologist Jean-Martin Charcot.\(^2\)
1.2.2 Epidemiology and Aetiology

PD is the second commonest neurodegenerative disease in the UK, after Alzheimer’s dementia. It is estimated to affect 100-180 per 100,000 of the population with an annual incidence of 4-20/100,000. The prevalence rises steeply with age, from 0.6% of the population aged 65-69 years to 3.5% of those aged 85-89 years. The median age of onset of the disease is 60 years, with a lifetime risk of developing the condition of 1.5%. Although there is evidence that men are approximately 1.5 times more likely than women to develop PD, it is important to note that this difference is not consistent between studies, and might be restricted to people older than 70 years of age in western populations.

The aetiology of PD remains poorly understood, although the disease is likely to arise from a complex interplay of genetic and environmental factors. After increasing age, a family history of PD remains the biggest risk factor for developing the condition, although it should be noted that inherited forms of the disease account for a small proportion of all cases. Nonetheless, at present there is robust evidence linking 7 genes to hereditary PD: alpha-synuclein, DJ-1, LRRK2, Parkin, PINK1, ATP13A2 and GBA. Less conclusive evidence implicates other possible genes in PD, including NURR1, synphilin-1 and UCH-L1.

With respect to environmental factors, never smokers are twice as likely to develop PD, and a low caffeine intake confers a 25% additional risk of developing the condition. Additionally, associations have been reported between PD and rural living, middle-age obesity, and lack of exercise.
Exposure to various infectious agents has been postulated as a potential cause for PD, but serological analysis does not support the notion of a specific infection being any more common in cases of PD.\textsuperscript{24} Interestingly however, high levels of serum urate (an anti-oxidant) and a clinical diagnosis of gout may be protective from PD and be associated with a better prognosis.\textsuperscript{25,26} Recent evidence also suggests that hypercholesterolaemia or treatment with the cholesterol lowering drug simvastatin may also reduce the risk of PD.\textsuperscript{27,28}

### 1.2.3 Pathology

At present, the cellular mechanisms of Parkinson’s disease are not well understood, although oxidative stress, mitochondrial dysfunction, glutamate excitotoxicity and apoptosis have all been implicated.\textsuperscript{29} Nonetheless, although the mechanisms are not well understood, there are three pathological hallmarks of Parkinson’s disease:

1) Neuronal loss
2) Neurotransmitter depletion
3) Presence of Lewy bodies

**Neuronal loss**

Neuronal loss in PD is widespread, affecting the locus coeruleus, the thalamus, the hypothalamus, nucleus basalis of Meynert, the ventral tegmental dorsal nuclei of the vagus, raphe nuclei, limbic cortex, cerebral neocortex and the autonomic nervous
system (including sympathetic and parasympathetic ganglia and the myenteric plexus in the gut). Importantly though, the striatum (comprising caudate nucleus and putamen) is unaffected.\textsuperscript{30, 31}

However, the key neuronal loss occurs in the substantia nigra (SN).\textsuperscript{32} The SN, together with the striatum, globus pallidus, nucleus accumbens and the subthalamic nucleus, forms the basal ganglia, which is the area of the brain implicated in motor preparation, timing, action gating, action selection, reward-based learning, exploratory and goal-orientated behaviours, working memory, fatigue and apathy.\textsuperscript{33}

The SN is divided into the pars reticulata and the pars compacta, and it is the pars compacta which is predominantly affected in PD. The pars compacta can be further subdivided into ventral and dorsal tiers. Cell loss in PD preferentially affects the ventral tier,\textsuperscript{34} which is in contrast to normal ageing where the dorsal tier is mainly affected.\textsuperscript{35}

**Neurotransmitter depletion**

The pars compacta is the principal source of dopaminergic neurones, and cell loss in this area therefore leads to a profound loss of the neurotransmitter dopamine. Dopamine is synthesised from the amino acid tyrosine, which is converted to L-3, 4-dihydroxyphenylalanine (L-dopa) by the enzyme tyrosine hydroxylase. Dopamine is stored in vesicles and released by a calcium dependent mechanism. After release, dopamine is removed from the synaptic cleft by an active reuptake mechanism, following which it is once again available for vesicular storage. Dopamine is
metabolised enzymatically by both intracellular monoamine oxidase (principally MAO-B) and extracellular catechol-o-methyl transferase (COMT). Loss of dopamine causes disruption to the motor circuit of the basal ganglia, although clinical symptoms may not emerge until as much as 80% of dopamine has been lost.

The motor circuit of the basal ganglia is complicated; several subcircuits which interact in a complex manner are still poorly understood. However, a simple model is that the globus pallidus interna (GPI), together with the SN pars reticulata, has an inhibitory output to the ventrolateral thalamus, which in turn has an excitatory output to the motor cortex. The GPI receives input from the putamen via two pathways – direct and indirect. The direct pathway runs monosynaptically from putamen to GPI, and its effects are inhibitory. The indirect pathway is excitatory and runs from the putamen to the GPI via the globus pallidus externa and subthalamic nucleus. Dopamine stimulates the direct pathway by acting on D1 receptors, and inhibits the indirect pathway by acting on D2 receptors. In PD, loss of dopamine therefore leads to understimulation of the direct pathway and underinhibition of the indirect pathway, resulting in an increased inhibitory output from the GPI to the ventrolateral thalamus and diminished output from the ventrolateral thalamus to the motor cortex. This circuit is represented diagrammatically in figure 1.1.
Although the principal loss is of dopaminergic neurones, it is important to note that serotonergic, noradrenergic and cholinergic ascending pathways also degenerate in PD.\textsuperscript{37}

\textbf{Lewy bodies}

Lewy bodies are abnormal aggregates of protein, named after the German pathologist Frederic Lewy. They are found in all areas of neuronal degeneration in PD and are
composed of three layers, namely a densely staining central core, less densely staining larger outer body and pale, poorly staining, surrounding halo.\textsuperscript{30} Lewy bodies contain phosphorylated neurofilaments, proteases, tubulin, microtubulin-associated protein, α-synuclein and ubiquitin.\textsuperscript{38,39} Although there has been a great deal of research dedicated to understanding the Lewy body, its precise role in the pathophysiology of PD remains unknown. Importantly, although PD is the only condition in which Lewy bodies are invariably found, Lewy bodies can also be found in other conditions including Alzheimer’s dementia, panthone kinase associated neurodegeneration, multi system atrophy, progressive supranuclear palsy, and the Parkinsonian dementia complex of Guam, suggesting that they may be a common end-product of neuronal degeneration.\textsuperscript{40}

\textbf{Other pathological features}

Another cellular inclusion, known as the ‘pale body’ is frequently found in PD. Like Lewy bodies, they also stain positively for ubiquitin and neurofilament proteins but unlike Lewy bodies, they are only found in PD.\textsuperscript{41}

Dopaminergic neurons within the pars compacta are heavily pigmented with neuromelanin. Degeneration of these neurons therefore leads to a loss of neuromelanin, giving rise to pallor of the SN at post-mortem.\textsuperscript{42}

Levels of copper and iron have been shown to be increased in the SN in PD, but this is likely to be a secondary phenomenon, rather than a primary cause of the disease.\textsuperscript{43}
1.2.4 Clinical Features

The clinical features of PD are wide-ranging and can be classified as being either ‘motor’ or ‘non-motor’.

Motor features

James Parkinson described the disease as being one of “involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace”.

Although Parkinson neglected to mention hypertonia, this definition established PD as a ‘motor’ disorder and tremor, bradykinesia, rigidity and postural instability are the most recognised features of the condition today.

Tremor

Tremor is defined as an involuntary rhythmic oscillatory movement of a body part resulting from repetitive muscle contractions. Tremor is the presenting symptom in 40-70% of cases of PD, and between 68% and 100% of PD patients will have rest tremor during the course of their illness. In PD, the tremor is typically a rest tremor, which starts in one hand, then progresses to the ipsilateral leg, later spreading contralaterally. However, tremor of the lips, jaw, chin and tongue can also occur, particularly in older patients. The tremor occurs at a frequency of 4-6Hz, and is described as ‘pill-rolling’ as it has a rotatory component. It is often made worse by
anxiety and, whilst it is difficult to treat, patients with tremor predominant disease
tend to have a less aggressive disease course and better prognosis.44

**Bradykinesia**

Bradykinesia is a slowness of initiating movement and sustaining repetitive
movements, with progressive reduction in speed and amplitude. It manifests clinically
as loss of arm swing when walking, hypomimia (loss of facial expression), increasingly
small handwriting, a shuffling short-steppage gait, freezing of gait or start hesitation,
impairment of dexterity, difficulty turning over in bed and generally marked slowing
down.

**Rigidity**

Rigidity is an involuntary increase in muscle tone (hypertonia), which can affect all
muscle groups. In PD, hypertonia is categorised as ‘lead-pipe’ rather than ‘clasp-knife’.
It can also be described as ‘cogwheeling’, occurring because of superimposed tremor.

**Postural Instability**

This is a late feature of the disease, but manifests as poor balance, unsteadiness and
falls.
Other motor features

Other motor features of PD which may occur include speech disorders (particularly hypophonia and palilalia), dysphagia, dystonia and the presence of frontal lobe reflexes.

Non-motor features

In addition to describing the motor phenomena of the disease, James Parkinson also made some other key observations about the condition. In particular, he remarked that “the bowels which had been all along torpid now, in most cases, demand stimulating medicines of very considerable power”, “the sleep becomes much disturbed”, “food is difficultly swallowed and the saliva fails of being directed to the back part of the fauces” and “at the last, constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release”. These observations are now recognised as descriptions of some of the non-motor features of PD. The non-motor features, which are summarised in table 1.1, are wide-ranging, often present prior to diagnosis and impact significantly on patients’ morbidity, quality of life and mortality. Importantly, many of the non-motor symptoms are autonomic in origin. Orthostatic hypotension (OH) in particular affects up to 40% of patients with PD and, in addition to being a potential cause of falls and subsequent injuries, is also felt to be an independent risk factor for cognitive decline and increased mortality and morbidity. Whilst not fully understood, the mechanisms underlying OH in PD seem to involve various neurocardiological and neurocirculatory abnormalities resulting
from degeneration of both central and peripheral autonomic centres.\textsuperscript{46,50-51} Dopaminergic medications used to treat the disease are also implicated in OH,\textsuperscript{52} although it is unclear whether symptomatic OH is due to medications alone or whether these drugs mainly act as precipitating or aggravating factors. As patients with de novo, untreated, PD already demonstrate autonomic dysfunction, the latter hypothesis is currently favoured.\textsuperscript{53}

<table>
<thead>
<tr>
<th>Neuropsychiatric symptoms</th>
<th>Sleep disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression, apathy, anxiety</td>
<td>Restless legs and periodic limb movements</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>Rapid eye movement (REM) sleep behaviour disorder</td>
</tr>
<tr>
<td>Attention deficit</td>
<td>Non-REM-sleep related movement disorders</td>
</tr>
<tr>
<td>Hallucinations, illusions, delusions</td>
<td>Excessive daytime somnolence</td>
</tr>
<tr>
<td>Obsessional / repetitive behaviours</td>
<td>Vivid dreaming</td>
</tr>
<tr>
<td>Dementia</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Confusion /delirium</td>
<td>Sleep disordered breathing</td>
</tr>
<tr>
<td>Panic attacks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal symptoms</th>
<th>Autonomic symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sialorrhoea</td>
<td>Bladder disturbances</td>
</tr>
<tr>
<td>Ageusia</td>
<td>Sweating</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Reflux</td>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>Constipation</td>
<td>Xerostomia</td>
</tr>
<tr>
<td>Incomplete voiding of bowel</td>
<td></td>
</tr>
<tr>
<td>Faecal incontinence</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Sensory symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Pain</td>
</tr>
<tr>
<td>Diplopia</td>
<td>Paraesthesia</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>Olfactory disturbance / anosmia</td>
</tr>
<tr>
<td>Seborrhoea</td>
<td></td>
</tr>
<tr>
<td>Weight loss / gain</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.1: The non-motor symptoms of PD. (Adapted from original reference)\textsuperscript{45}
1.2.5 Diagnosis

**Clinical evaluation**

The National Institute for Health and Clinical Excellence recommend that the diagnosis of PD should be made by a specialist, reviewed regularly and reconsidered if atypical clinical features develop.\(^5^4\) The diagnosis is predominantly made clinically, using the UK Parkinson’s Disease Society Brain Bank Clinical Criteria,\(^5^5\) listed in table 1.2. In specialist hands, the Brain Bank criteria have been shown to demonstrate adequate sensitivity and specificity in comparison with post-mortem findings, with the accuracy of diagnosis using the Brain Bank criteria increasing as the condition progresses.\(^5^5\)
## Step 1: Diagnosis of a Parkinsonian Syndrome

- Bradykinesia and at least one of the following:
  - Muscular rigidity
  - Rest tremor (4-6Hz)
  - Postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction

## Step 2: Exclusion criteria for Parkinson’s disease

- History of:
  - Repeated strokes
  - Repeated head injury
  - Antipsychotic or dopamine-deleting drugs
  - Definite encephalitis or oculogyric crises on no drug treatment
  - More than one affected relative
  - Sustained remission
  - Negative response to large doses of levodopa (if malabsorption excluded)
  - Strictly unilateral features after three years
  - Other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski sign, early severe dementia with disturbances of language, memory or praxis
  - Exposure to neurotoxin
  - Presence of cerebral tumour or communicating hydrocephalus on neuroimaging

## Step 3: Supportive criteria for Parkinson’s disease

- Three or more required for diagnosis of definite Parkinson’s disease:
  - Unilateral onset
  - Rest tremor present
  - Progressive disorder
  - Persistent asymmetry affecting the side of onset most
  - Excellent response to levodopa
  - Severe levodopa-induced chorea
  - Levodopa response for over five years
  - Clinical course of over 10 years

---

**Table 1.2:** UK Parkinson’s Disease Society Brain Bank Criteria for the Diagnosis of PD
(Reproduced from original reference)
Imaging

Whilst the diagnosis of PD is made on clinical grounds alone in the majority of patients, brain imaging may be helpful in selected cases. Functional imaging with Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) can be used to evaluate striatal dopamine terminal function although, importantly, it will not differentiate idiopathic PD from basal ganglia ischaemia or Parkinson’s plus syndromes such as multi system atrophy, Lewy body dementia and progressive supranuclear palsy.

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) show normal nigral structure in PD, but can exclude disease mimics such as normal pressure hydrocephalus and cerebrovascular disease.

Transcranial ultrasonography has recently emerged as a potential imaging modality in PD. The SN appears hyperechogenic when viewed with ultrasound in 90% of patients with PD, possibly as a result of increased iron deposition. Several studies have suggested that the larger the echogenic area of the SN, the earlier the onset of PD and the slower the progression of the disease. However, hyperechogenicity of the SN is not unique to PD, and is also seen in spinocerebellar ataxias, dementia with Lewy bodies and 10% of the healthy population. At present therefore, the technique is still under evaluation and is only used for research purposes.56
1.2.6 Treatment

**Drug therapies**

There is longstanding controversy about both the timing of drug treatments and the class of drug therapies which should be used in patients with PD. The drug therapies which are effective in the treatment of PD fall into several categories, namely:

1) **Drugs that replace dopamine**
   - a. Levodopa plus decarboxylase inhibitor (e.g. Madopar®/Sinemet®)

2) **Drugs that prevent dopamine breakdown**
   - a. Monoamine Oxidase B Inhibitors (e.g. Rasagiline, Selegiline)
   - b. Catechol O-Methyl Transferase (COMT) inhibitors (Entacapone, Tolcapone)

3) **Drugs that stimulate dopamine release**
   - a. Amantidine

4) **Antimuscarinic drugs** (reduce the relative central cholinergic excess that occurs as a result of dopamine deficiency)
   - a. Orphenadrine, Procyclidine, and Trihexyphenidyl

5) **Drugs that mimic the action of dopamine**
   - a. Dopamine agonists (e.g. Ropinirole, Pramipexole, Rotigotine®)
   - b. Apomorphine
   - c. Bromocriptine, Pergolide and Lisuride

6) **Acetylcholine antagonists** (rarely used now)
   - a. Benztropine
At present, there is no evidence for any neuroprotective or disease modifying therapy and NICE therefore recommend commencing either levodopa, a dopamine agonist or a monoamine oxidase inhibitor only once motor symptoms interfere with everyday life. NICE state that all three drug classes are effective and suitable for use as first line therapy.\textsuperscript{54} Certainly, there is evidence from randomised controlled trials to support their efficacy. However, it is not clear which class of drug to choose in any individual patient situation. The recently completed and presented, although notably yet to formally publish, PD MED trial\textsuperscript{57} was designed to try and resolve this uncertainty. PD MED was a large, "real-life" trial that aimed to determine which class of drug provides the most effective control, with the fewest side-effects, for both early and later PD. The main outcome measure was the patient-rated PDQ-39\textsuperscript{58} quality of life scale. The trialists concluded that patient-rated quality of life was slightly better in patients receiving levodopa than levodopa-sparing therapies, but that these improvements needed to be balanced against increased motor complications. MAO-B inhibitors appeared more effective than dopamine agonists as levodopa-sparing therapy. The trialists therefore suggest that all patients should have levodopa as their initial therapy, with the dose steadily titrated as the disease progresses to a maximum of 600mg/day. When patients begin to experience wearing-off, a MAO-B inhibitor should be added. Selegiline should be tried first as it is less expensive, but switched to Rasagiline if it is not tolerated. With disease progression dopamine agonists and COMT inhibitors can be added. Beyond this, amantadine may be used as an antidyskinesia agent and subcutaneous apomorphine may be used to treat patients with significant, severe wearing-off periods.
Other therapies and interventions

In addition to drug treatments, there is also a surgical option in the treatment of PD, known as Deep Brain Stimulation. Improved understanding of the neural mechanism of PD showed that the subthalamic nucleus (STN) is overactive. This led to the development of bilateral subthalamic stimulation surgery to ‘switch off’ this nucleus. The NICE guidelines recommend STN stimulation for patients with motor complications refractory to best medical treatment, who are biologically fit with no clinically significant active comorbidities and who are levodopa responsive.

Regardless of other treatments, all patients benefit from regular specialist review and the input of a Parkinson’s nurse specialist. Physiotherapy, speech and language therapy and occupational therapy may also all be helpful, despite a paucity of clinical trials in these areas.

1.2.7 Prognosis

There is no evidence to suggest that the rate of progression of PD is affected by age of onset. The mean duration of the disease from diagnosis to death is 15 years, with a mortality ratio of 2 to 1.59

1.2.8 Parkinson’s Disease and Cerebral Autoregulation

As our knowledge of Parkinson’s disease has advanced, it has come to be seen as a multi-system disorder and not simply a motor condition. The non-motor symptoms in
particular can have a profound impact on patients’ quality of life, and many of these result from disturbances in the autonomic nervous system. In recent times there has been significant research into cardiovascular dysfunction in PD, in an attempt to understand the OH which so frequently accompanies the disease. However, there has been surprisingly little work on cerebrovascular dysfunction in PD; specifically there is a paucity of research evaluating cerebral haemodynamics and cerebral autoregulation (Chapter 2).

1.3 CEREBRAL AUTOREGULATION

1.3.1 Cerebral Blood Flow

Adequate cerebral blood flow (CBF) is essential for brain survival and function. Cerebral metabolism is almost entirely dependent on oxidative mechanisms, particularly the metabolism of glucose into ATP, and the brain has a very limited capacity for anaerobic function. Adequacy and constancy of cerebral blood flow are therefore vital in ensuring both a steady supply of oxygen, glucose and other nutrients, and the removal of waste products of metabolism. Cerebral blood flow is dependent on cerebral perfusion pressure (CPP), which is the difference between the mean arterial blood pressure (MAP) and the mean cerebral venous pressure. The latter is difficult to measure directly, but approximates to the more easily measured intracranial pressure (ICP).

\[ CPP = MAP - ICP \]  

Eq. 1.1
MAP can be estimated as equal to: diastolic BP + 1/3 pulse pressure. MAP in healthy adults is approximately 90mmHg. ICP is much lower and is usually less than 13mmHg.

Given the dependence of CPP on MAP, the brain requires a protective homeostatic mechanism to ensure adequate and constant CBF, despite changes to MAP.

1.3.2 Definition of Cerebral Autoregulation

Cerebral autoregulation (CA) refers to the ability of the brain to maintain a relatively constant cerebral blood flow (CBF) in response to significant changes in cerebral perfusion pressure. Thus, in response to an increase or decrease in cerebral perfusion pressure, there is a vasodilatation or vasoconstriction of cerebral vessels. This variable resistance to flow occurs mainly in the cerebral arteriolar bed; the major cerebral arteries are essentially conductive rather than compliant. That cerebral autoregulation occurs at the level of the smallest arterioles is corroborated both theoretically by Poiseuille’s Law which states that flow is proportional to the fourth power of the cylinder’s radius, and experimentally in studies by Itoh et al\textsuperscript{60}, Kuga et al\textsuperscript{61} and Kontos et al\textsuperscript{62}. The classic concept of CA whereby, under normal physiological conditions, cerebral blood flow (CBF) is around 50ml/100g/min and this is maintained across a wide range of blood pressures (MAP of 60-160mmHg), was first described by Lassen in 1959\textsuperscript{63} and is illustrated schematically in figure 1.2.
Figure 1.2: The relationship between cerebral perfusion pressure and cerebral blood flow when regulated by an intact autoregulation mechanism (Reproduced from original reference)

CA is usually described as being static, reflecting the integrity of such mechanisms over time, or dynamic, occurring in response to sudden fluctuations in perfusion pressure.

1.3.3 MECHANISMS

Cerebral autoregulation is accomplished through the complex interplay of a variety of mechanisms which can be classified as myogenic, chemical and metabolic, and neurogenic.
Myogenic

Smooth muscle cells of the cerebral vasculature in the arteriolar bed are responsive to changes in transmural pressure. Such changes in pressure alter the resting tone of the cerebral vasculature, producing vasoconstriction or vasodilatation. Although the exact mechanism by which this occurs is not known, it has been postulated that smooth muscle stretch may be linked to calcium. In response to perfusion pressure increasing, the smooth muscle membrane depolarizes leading to a calcium influx via voltage-gated calcium channels which causes vasoconstriction and an increase in vascular resistance, with the reverse occurring with decreased perfusion pressure.\textsuperscript{65,66}

Chemical and metabolic

Cerebral metabolism is a critical factor in the control of CBF. In conditions leading to increased metabolism, oxygen levels decrease locally and levels of metabolites in the arterial endothelium (such as nitric oxide, CO\textsubscript{2}, hydrogen ions, calcium, lactate and adenosine) rise, leading to localized and restricted CBF increase through vasodilatation.\textsuperscript{67,68} Although myogenic reactivity and basal tone are intrinsic to vascular smooth muscle, the ambient level of tone is modulated by endothelial synthesis and the release of both vasoconstricting and vasodilating substances. Nitric oxide (NO) is continuously produced by the endothelium and it is thought to be the most important chemical for maintenance of resting cerebrovascular tone.

Variations in arterial PaCO\textsubscript{2} exert a profound influence on CBF. Hypercapnia causes cerebrovasodilatation, whereas hypocapnia produces marked intracerebral
vasoconstriction. The arteriolar response which follows changes in PaCO\textsubscript{2} is believed to be mediated by pH variations in the extracellular fluid surrounding resistance vessels in the brain. At PaCO\textsubscript{2} levels within the normal range, CBF changes by approximately 3 – 4% for every 1% change in PaCO\textsubscript{2}. Accurate measurements of PCO\textsubscript{2} are therefore essential for proper evaluation of CBF levels.

**Dopamine**

The effects of dopamine on cerebral blood flow and autoregulatory responses are currently not well understood. Histopathological animal studies have demonstrated that dopaminergic neurons contact cerebral microvessels and that perivascular application of dopamine results in significant vasoconstriction, although the mechanism by which this occurs is, at present, unknown. However, translating in-vitro studies to in-vivo studies has proved difficult. One study, using intravenous dopamine in sheep, suggests that, whilst dopamine directly increases MAP and therefore CPP, it has no additional independent effects on autoregulation or cerebrovascular mechanics. However, another study by Hahn et al, which aimed to elucidate the effect of dopamine on cerebral vasculature by studying cerebral perfusion (laser-Doppler flux) and oxygenation (near-infrared spectroscopy) in 12 anaesthetised piglets subjected to both dopamine infusion and non-pharmacologically (intra-aortic balloon pump) induced hypertension, found that whilst dopamine increases CPP by its direct vasoconstrictor action and increase in MAP, it does not result in an increase in cerebral intravascular oxygenation. This raises the possibility that dopamine increases the cerebral metabolic rate of oxygen concurrently with CBF. Importantly, studies using
intravenous dopamine are difficult to interpret as, within normal physiological conditions, dopamine does not cross the blood brain barrier. The effect of dopamine on cerebral haemodynamics can therefore only be studied in states of altered blood brain barrier permeability or modified physiology (e.g. systemic hypertension).

**Neurogenic**

The role of neurogenic mechanisms in the control of CA is uncertain and controversial. Nonetheless, the autonomic nervous system is thought to be involved and anatomic studies have shown an extensive nerve supply to the extra- and intracranial vessels. It is believed that parasympathetic stimulation leads to cerebral vasodilatation and sympathethic innervations plays a modulating role during acute hypertensive episodes resulting in vasoconstriction of the cerebral vasculature. More recently, the locus coeruleus, nucleus basalis and raphe nucleus have been implicated as a source of innervation of cerebral microvasculature although it is not clear whether neurons here directly contact the microvessels or if the signal is transduced through astrocytic foot processes.

1.3.4 Methods of Cerebral Autoregulation Measurement

To assess CA, BP, PaCO₂ (and ideally HR) should be continuously measured simultaneously with CBF. BP can be recorded invasively via an arterial line, or non-invasively using a device such as the Finapres® (see section 3.3.3). In the case of CBF, whilst this can be measured directly, it is difficult and necessitates the use of either
indicator dilution techniques such as $^{133}$Xenon or NO injection which take several minutes to yield a single value and require steady-state conditions, or electromagnetic flowmetry which requires cannulation of major extra-cranial arteries such as the internal carotid artery, and there are few situations in which this would be considered acceptable. MRI, near infra-red spectroscopy (NIRS), Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT) all allow for the non-invasive measurement of CBF, but it is really Transcranial Doppler Ultrasonography (TCD) which has revolutionised our ability to study CA. TCD is simple to use, relatively low-cost and enables the non-invasive measurement of CBF velocity (CBFV), which is a reliable and practical surrogate for direct CBF measurement. In TCD, instantaneous flow velocities are recorded in real-time within the main intracranial vessels, typically the middle cerebral artery (MCA). As there is theoretically no significant change of the cross sectional area of the MCA during autoregulatory action (as the autoregulatory action occurs at the level of the small arterioles) it can be assumed that CBF is directly proportional to cerebral blood flow velocity (CBFV). This has been confirmed in several key studies performed on patients undergoing carotid endarterectomy. In these studies, CBF and CBFV were simultaneously recorded, using electromagnetic flowmetry or $^{133}$Xenon and TCD respectively, and compared. In both cases, it was found that TCD provided comparable information to that obtained with direct measurement.

TCD is simply the application of standard Doppler ultrasonography through the skull. Although the skull is usually too thick to penetrate with ultrasound, there are a number of acoustic windows (figure 1.3) where there is a natural foramina, or where the bone is sufficiently thin for ultrasound energy to penetrate. These are known as
the transtemporal, submandibular, transorbital and transforaminal (suboccipital) windows. Although these acoustic windows permit TCD examination, it is still necessary to use very low transmitted frequencies of ultrasound as attenuation increases with frequency. TCD examinations are therefore typically performed with 2MHz probes.

The Doppler effect (or Doppler shift), named after the Austrian physicist Christian Doppler, is the change in the frequency of sound, light, or other waves as the source and observer move toward (or away from) each other. In TCD, the Doppler probe generates an ultrasound beam which is reflected by red blood cells in a large vessel with a frequency shift that is directly proportional to the velocity of the scattering

Figure 1.3 The acoustic windows of the skull used for TCD (Reproduced from original reference)
The frequency shift between transmitted ultrasound and reflected ultrasound allows calculation of the CBFV through the equation:

\[ \nu = \frac{c(f_t - f_r)}{2f_t \cos \theta} \]

where \( \nu \) is blood flow velocity, \( c \) is the speed of sound in blood, \( f_t \) and \( f_r \) are transmitted and received ultrasound respectively and \( \theta \) is the insonation angle between the ultrasound beam and the blood vessel direction at the depth of insonation. In most situations, assumption can be made that the insonation angle is zero. In the presence of laminar flow, the velocity distribution will be approximately parabolic. Consequently, the reflected Doppler frequency shift will comprise a distribution of frequencies, rather than a single value. The most common approach to extract meaningful velocity information from the distribution of frequencies is to apply the fast Fourier transform (FFT) to short segments (typically \( \Delta t = 5 \text{ms} \)) of the raw Doppler shifted signal. The FFT is an algorithm which converts time to frequency and vice versa and thus, by applying it to the Doppler signal, it is possible to obtain the spectral distribution of power at each frequency. From this distribution, either the maximum frequency (i.e. maximum velocity), or its intensity-weighted mean are extracted to represent the mean velocity for the time interval \( \Delta t \). The velocity distribution, and the maximum velocity envelope are normally displayed by most TCD devices as a colour coded sonogram, which can often be recorded from the device as an analog output signal.

Historically, dynamic cerebral autoregulation (dCA) has been measured using induced changes in arterial blood pressure, and hence cerebral perfusion pressure, while measuring the rate at which CBF or CBFV returns to baseline. Methods used to induce
changes in BP (known as CA challenges, or inputs) have included bilateral thigh cuff inflation to suprasystolic blood pressure and their simultaneous release, lower body negative pressure, postural changes, the valsalva manoeuvre and the cold pressor stimulus (placing a hand in ice water). However, more recently it has been shown that dCA can also be reliably assessed using spontaneous fluctuations in arterial blood pressure occurring naturally at rest. Blood pressure oscillations ranging from 0.02 to 0.4Hz occur in humans throughout the day and night without externally triggered BP manipulations and independent of daily life stimuli. Panerai et al. demonstrated a good correlation between the ARI derived from an induced BP fall with thigh cuffs and spontaneous fluctuations in BP, and Brodie et al. demonstrated excellent absolute and relative reliability of spontaneous fluctuations in BP and subsequent change in CBFV in calculating the ARI. This method is therefore particularly advantageous in assessing patients in whom a sudden drop in blood pressure may be undesirable, including patients with PD. It is important to note that, at present, there is conflicting evidence as to whether patients with PD have similar or fewer spontaneous fluctuations in BP than the general population; one study of 37 PD patients and 37 healthy controls found reduced BP variability in the PD group, but another study comparing cardiovascular parameters in four groups (19 young healthy controls aged 20-30 years, 28 healthy older controls aged 67-83 years, 25 individuals with extrapyramidal slowing not meeting the criteria for PD aged 59-91 years, and 25 patients with PD aged 61-84 years) found no significant differences in BP variability across the four groups.

In addition to using spontaneous fluctuations in BP, the efficiency of the dCA response can also be evaluated by studying CBF responses to cerebral activation, a concept
known as ‘neurovascular coupling’. Although the exact mechanisms of neurovascular coupling continue to be explored and evaluated, it is thought that cerebral activation triggers a haemodynamic response involving neurons, astrocytes, vascular cells and local metabolites.\textsuperscript{96,97} Cerebral activation can be achieved through various cognitive activities such as reading,\textsuperscript{98} writing\textsuperscript{99} and speaking,\textsuperscript{100} by visual stimulation,\textsuperscript{101} and/or by sensorimotor tasks.\textsuperscript{102,103} Cognitive tasks generally induce significant increases in global CBF due to the involvement of a large number of cortical areas, whereas sensorimotor paradigms increase regional CBF with the changes mostly lateralized to the irrigating artery in the opposite side to the sensorimotor action.

The efficiency of the dCA response can also be reliably assessed by looking at CBF responses to hypercapnia and hypocapnia, using hypo- and hyperventilation respectively.\textsuperscript{104} This concept is known as assessing vasomotor (or CO\textsubscript{2}) reactivity. Importantly, it appears that local brain metabolic changes in CO\textsubscript{2} have a minimal role in the CBF response to brain activation, suggesting that neurovascular coupling and vasomotor reactivity are mediated by different regulatory mechanisms.\textsuperscript{105,106}

The use of spontaneous fluctuations in BP, brain activation paradigms and hypo- and/or hyper-capnia are now therefore all accepted as practical alternatives to induced step changes of blood pressure in the assessment of CA.

### 1.3.5 Analysis of Cerebral Autoregulation

After a change in BP, whether spontaneous or induced, the relationship between CBF and BP has to be quantified in order to assess dCA and this can be done in either the
frequency domain, or in the time domain. Both these methods approach the relationship between BP and CBF as if it is linear. Although more complex mathematical models have been developed that allow for non-linearity they are, at present, awaiting further evaluation and validation.107

**Frequency domain**

The most widely used, validated, modelling technique in the analysis of the relationship between CBFV and BP in the frequency domain is transfer function analysis (TFA). TFA makes it possible to examine the transfer of BP fluctuations to CBF as a measure of CA. It quantifies the extent to which the input signal, BP, is reflected in the output signal, CBFV, and was first proposed by Giller.108 Welch’s method and FFT are used to decompose the input and output signals into sine waves of various frequencies, and variations of a particular frequency in the input signal are transformed to signals of the same frequency in the output signal.108-110 The parameter which tests the linearity between the input and output signals at each frequency is called the coherence, with values of coherence ranging between zero and one. Values of coherence approaching one indicate a perfect linear relationship between input and output (i.e. CBFV and BP). If coherence is zero, it suggests a non-linear relationship between input and output, but may also reflect a poor signal-to-noise ratio.111 Although there is currently no consensus on the threshold at which good coherence is assumed, many studies have adopted a coherence of ≥ 0.5 to accept the relationship as significant.109,111
TFA also allows for the calculation of two further parameters useful in exploring the relationship between BP and CBFV, and thus dCA, and these are phase and gain. Phase is equivalent to the shift in radians from 0 to $2\pi$ (or degrees from 0° to 360°) that would be required to align input (BP) with output (CBFV) at a given frequency, and so gives an indication of the relative timing of the two signals. The magnitude of the phase response may be an indicator of the integrity of the autoregulatory response; phase is positive in intact CA (CBFV recovers faster than changes in BP) and it tends to zero in impaired CA when CBFV tends to follow BP, during steady-state conditions.\(^{109,112}\) Gain is the ratio of the amplitude of the output signal to the input signal, and so indicates the magnitude of change in CBFV that is due to a change in BP. Although gain alone is not a reliable measure of CA, an increase in gain suggests that CA is impaired, whereas a low gain indicates an efficient CA.\(^{108,113}\)

**Time domain**

The time domain approach is used to extract information about the CA mechanism from the analysis of mean BP, CBFV, HR and EtCO\(_2\) with respect to time. Historically, dCA has been assessed using induced changes in BP while the rate of return (RoR) to baseline of CBFV is measured.\(^{69}\) Tiecks et al\(^{114}\) derived a set of equations and curves based on the CBFV response to a sudden fall in BP induced by thigh cuff deflation. These equations and curves allow for the calculation of an autoregulatory index (ARI) from 0 to 9, where 0 represents absence of autoregulation i.e. CBF dependent on CPP, (a ‘pressure-passive relationship’) and 9 represents best measurable autoregulation.
These curves are shown in Figure 1.4. 'Normal' autoregulation is represented by an ARI of 5±1.

![Figure 1.4 Responses of cerebral autoregulation model to a step change in BP (Reproduced from original reference)](image)

It has subsequently been shown that spontaneous fluctuations in BP can also be used to calculate the ARI in the time domain. From inverse Fourier transform of the gain and phase, calculated in the frequency domain, it is possible to estimate the CBFV response to spontaneous fluctuations in BP, termed 'impulse response'. This impulse response is then used to calculate the CBFV step response, from which the ARI can subsequently be estimated. This is done by comparison of the calculated step response with Tiecks' model curves and selecting the 'best-fit' 0-9. The least square error or the correlation coefficient may be used as measures of fitting, with a correlation coefficient >0.7 suggesting an acceptable level of agreement between the actual step response and the predicted curve.
Other parameters obtainable in the time domain may also provide useful information regarding the integrity of dCA, including critical closing pressure (CrCP) and resistance area product (RAP). CrCP is expressed in mmHg and is defined as the arterial pressure below which small vessels collapse and forward blood flow becomes zero, which in the cerebral circulation is equivalent to the sum of ICP and the contributions of vascular smooth muscle tone.\textsuperscript{115} RAP is expressed in mmHg.s/cm and is an index of cerebrovascular resistance, which is equal to the total cerebrovascular resistance x cross-sectional area of the vessel.\textsuperscript{116} It is determined as the inverse of the linear regression slope between instantaneous CBFV and ABP relationship for each cardiac cycle.\textsuperscript{90,116}

Other methods have been used to quantify dynamic cerebral autoregulation in the time domain, including calculation of cerebrovascular resistance (CVR) and the cerebrovascular resistance index (CVRI), calculation of the pulsatility index (PI) and calculation of the correlation coefficient (Mx). Cerebrovascular resistance refers to the resistance of the small cerebral vessels distal to the site of insonation, and is felt to be the regulator between the input (BP) and output (CBFV) signals. According to Ohm’s law, it is defined as mean BP/mean CBF. As TCD measures CBFV and not CBF, studies using TCD to study CVR must divide the mean BP by mean CBFV, thus calculating the CVRI. However, these calculations all assume entirely linear flow through a uniform conductor down a pressure gradient, and this does not necessarily apply to biological systems making it difficult to interpret their clinical validity. Despite this, CVR and CVRI are widely used and reported in studies of autoregulatory function. The PI, sometimes called Gosling’s PI\textsuperscript{117} is also sometimes used to reflect CVR, and is defined as the difference between systolic and diastolic extremes of CBFV divided by the mean
CBFV. However, PI is not a reliable parameter for assessing dCA, as a quantitative relationship with CVRi only exists in stable, steady-state conditions. The Mx was first described by Czosynka et al in studies of patients with head injury, and is determined by calculating Pearson’s correlation coefficients between consecutive samples of averaged CPP and flow velocity for three minute periods. Lang et al subsequently showed that this index is valid if BP is used instead of CPP in these patients, obviating the need for invasive measures of ICP. However, the technique has yet to be validated outside the context of head injury, haemorrhagic stroke and carotid stenosis.

1.3.6. Factors Affecting Cerebral Autoregulation

A systematic review has shown that there is no evidence for an effect of ageing on dCA. However, it should be noted that the age range studied only included adults up to the age of 75, whether dCA is preserved at ages beyond this is, at present, unknown. Gender is thought to have an effect on CA, with female subjects displaying higher CO$_2$ reactivity and higher ARI values. Hypertension is known to affect CA, with a right shift in the autoregulatory curve meaning that the lowest MAP before symptoms of cerebral hypoperfusion appear is higher in people with hypertension than in normotensive persons.

CA is also known to be affected in various disease states, including head injury, carotid stenosis, ischaemic stroke and chronic diabetes mellitus. However, there are many disease states in which information regarding cerebral autoregulation
remains either untested or inconclusive, including idiopathic PD (see following chapter).

1.4 SUMMARY

Idiopathic PD is a common neurodegenerative disorder, characterised clinically by bradykinesia, rigidity, tremor and postural instability, and pathologically by a severe loss of dopaminergic neurons in the substantia nigra, and the presence of Lewy bodies. The clinical features are wide ranging, and include many autonomic phenomena. CA refers to the ability of the brain to maintain a relatively constant CBF in response to significant changes in cerebral perfusion pressure, and is governed by a host of mechanisms which can be classified as chemical and metabolic, myogenic and neurogenic. CA can be reliably assessed using spontaneous fluctuations in BP by utilising TCD and non-invasive BP monitoring, and data obtained can be analysed in time or frequency domains. The efficiency of the dCA response can also be evaluated by studying CBF responses to cerebral activation and changes in PaCO₂. CA is known to be impaired in various disease states, but there are many conditions in which information regarding cerebral autoregulation remains either untested or inconclusive.
1.5 STUDY HYPOTHESES

This Thesis will test the following hypotheses:

1) dCA is impaired in patients with idiopathic PD.
2) NVC and VMR are impaired in idiopathic PD.
3) Impairment in dCA is apparent in the early stages of idiopathic PD.
4) Dopaminergic medications further impair dCA.
5) Patients with OH are more likely to have impaired dCA.

1.6 AIMS OF THIS MD

This aims of this MD Thesis are as follows:

Primary

1) To determine if dCA is impaired in patients with idiopathic PD, compared to healthy control subjects.
2) To determine if NVC and VMR are impaired in patients with idiopathic PD, compared to healthy controls.

Secondary

1) To determine at what stage of the disease (if any) dCA is impaired in patients with idiopathic PD.
2) To determine whether any impairment in dCA in patients with idiopathic PD is caused by the disease itself or medications used to treat the disease.
“But of what nature that morbid change is.... is, at present, the subject of doubt and conjecture”

James Parkinson, 1817

2.1 BACKGROUND

In recent times there has been a great deal of interest in the non-motor symptoms of PD, many of which appear to be autonomic in origin. In an attempt to understand the OH which so frequently accompanies the disease, a number of studies have assessed cerebral haemodynamic function and cerebral autoregulation in patients with PD. However, to date, there has been very little synthesis of data. The aim of this review was to therefore systematically evaluate all TCD studies of human cerebral autoregulation in PD.

2.2 MATERIALS AND METHODS

A literature search in the bibliographic databases MEDLINE, EMBASE, CINAHL and Web of Science was undertaken by the Thesis author and an independent researcher (Angela SM Salinet MSc), using the following search strategy:

“Parkinson* AND cerebral autoregulation OR Transcranial Doppler Ultrasonography OR cerebral haemodynamics OR cerebral hemodynamics OR cerebrovascular circulation OR cerebral blood flow OR neurovascular coupling OR carbon dioxide”
Different MESH terms or subcategories available on the search database were truncated to increase the sensitivity of the search. The references and citation indices of selected articles were hand-searched for additional relevant studies. Included were published studies of human cerebral autoregulation using TCD in PD. Given the relative paucity of literature in this field, the review included all studies which evaluated changes in CBF in response to an autoregulatory stimulus, including studies of NVC and vasomotor reactivity. Eligibility was assessed by reading abstracts and, if necessary, whole articles. Case studies, abstracts, non-English language articles and studies that did not specify the type of Parkinsonism were excluded. Studies including patients with diseases other than PD without a separate analysis were also excluded. The following data were extracted: study design, inclusion and exclusion criteria, number of patients and controls, how the diagnosis of PD had been made or confirmed, the comorbidities of patients, disease duration, stage and severity, peripheral haemodynamic recording, CA challenges (inputs), autoregulation evaluation method (modelling), main conclusions and study limitations. Study quality was assessed by the Thesis author and the independent researcher using a checklist adapted from the Meta-analysis of Observational Studies in Epidemiology\textsuperscript{128} and other systematic reviews which have evaluated studies of CBF and CA.\textsuperscript{129,130}

2.3 RESULTS

A total of 2175 citations were identified. After dismissing duplicates, non-relevant topics and studies without a CA challenge or input, 19 abstracts remained. Five of these were excluded as they were found to be conference abstracts (4) or comments (1). A further study was excluded as patients with PD were grouped together with
patients with other neurological disorders without a separate analysis, leaving a total of 13 articles. These were supplemented with one more study found through a reference search. An overview of these studies is provided in table 2.1.

2.3.1 Study quality

There were no disagreements in the assessment of study quality between reviewers. The median score resulting from the quality checklist (table 2.2) was 11/15 (range 4-13) reflecting varied and incomplete reporting of key methodological criteria in the majority of studies. The individual scores for each study are detailed in table 2.3.
### Table 2.1: Overview of studies included in the systematic review

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Number of controls</th>
<th>Vessel imaged</th>
<th>Input method</th>
<th>Analytical method</th>
<th>Main results and conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angeli et al.</td>
<td>19</td>
<td>19</td>
<td>Rt. MCA</td>
<td>HUT (70°)</td>
<td>CVRi</td>
<td>No difference in MCBFV at rest between controls and PD patients. PD patients have a trend to higher PI during tilting, but no significant differences in CVRi with tilting. CA is preserved in PD patients without symptoms of orthostatic intolerance.</td>
</tr>
<tr>
<td>Azevedo et al.</td>
<td>20</td>
<td>20</td>
<td>Lt. PCA</td>
<td>VEP</td>
<td>Second-order differential equation model</td>
<td>PD patients showed no NVC changes in PCA territory compared to controls, and STN-DBS did not change blood flow regulatory parameters.</td>
</tr>
<tr>
<td>Gurevich et al.</td>
<td>9</td>
<td>None</td>
<td>Both MCAs and both VAs</td>
<td>ACZ</td>
<td>MCBFV</td>
<td>VMR varied between patients, but not significantly different to patients with MSA or PAF</td>
</tr>
<tr>
<td>Hamdy et al.</td>
<td>15</td>
<td>15</td>
<td>MCA(s) (unclear which)</td>
<td>BH</td>
<td>MCBFV</td>
<td>No difference in medicated/unmedicated PD patients MCBFVs with controls, but PD patients have a lower BHI than controls suggesting impaired vasoreactivity</td>
</tr>
<tr>
<td>Haubrich et al.</td>
<td>26</td>
<td>25</td>
<td>Lt. MCA</td>
<td>HUT (80°)</td>
<td>TFA</td>
<td>PD patients with OH have tilt-induced BP instability but the CA response to tilting is preserved. Gain and phase normal with tilting. Suggest OH occurs if BP falls below autoregulated range.</td>
</tr>
<tr>
<td>Mihci et al.</td>
<td>30</td>
<td>15</td>
<td>Both MCAs</td>
<td>HUT (90°)</td>
<td>CBFV</td>
<td>CBFV lower in PD patients than controls, but decreases follow a similar pattern with tilting. Abnormal CA response likely due to age rather than PD.</td>
</tr>
<tr>
<td>Niehaus et al.</td>
<td>15</td>
<td>15</td>
<td>Rt. MCA</td>
<td>HUT (70°)</td>
<td>MCBFV</td>
<td>Drop in MCBFV similar in PD patients and controls suggesting a normal autoregulatory mechanism</td>
</tr>
<tr>
<td>Rätspe et al.</td>
<td>7</td>
<td>7</td>
<td>Both MCAs</td>
<td>CPT</td>
<td>MCBFV</td>
<td>MCBFV similar in PD patients and controls, and in STN-DBS on/off states but percentage change of MCBFV to CPT higher in controls than in PD patients, and in STN-DBS on state. CR is impaired in patients with advanced PD, and improved by STN-DBS.</td>
</tr>
<tr>
<td>Rosengarten et al.</td>
<td>175</td>
<td>20</td>
<td>Both PCAs</td>
<td>VEP</td>
<td>Second-order differential equation model</td>
<td>Responses to VEP compared between 4 groups, patients with PD, patients with PD+dementia, patients with PD+dementia+acetylcholinesterase inhibitor therapy and healthy controls. Resting FV in all PD groups no different to healthy controls. No difference in NVC parameters (frequency and attenuation not statistically different, gain just slightly higher in controls).</td>
</tr>
<tr>
<td>Schwagen et al.</td>
<td>32</td>
<td>9</td>
<td>Both MCAs</td>
<td>VEP</td>
<td>MCBFV</td>
<td>No differences between the MCBFVs of controls and PD patients either at rest or during tilting. CA is preserved.</td>
</tr>
<tr>
<td>Treizi et al.</td>
<td>12</td>
<td>12</td>
<td>Both MCAs</td>
<td>VEP</td>
<td>MCBFV</td>
<td>Emotional paradigm produced different activation pattern to controls. Other neurovascular coupling paradigms no different. No differences in BHI between controls and PD patients.</td>
</tr>
<tr>
<td>Tsai et al.</td>
<td>49</td>
<td>49</td>
<td>Unilateral MCA (best signal)</td>
<td>CPT</td>
<td>MCBFV</td>
<td>Baseline values for control and PD subjects not statistically different Greater PI decrease, and lower percentage change of CVRi in PD group after CPT suggesting impaired CVR</td>
</tr>
<tr>
<td>Vokatch et al.</td>
<td>14</td>
<td>11</td>
<td>Unilateral MCA (best signal)</td>
<td>TCT</td>
<td>MCBFV</td>
<td>Flattened MCBFV curve with TCT in PD patients but no significant differences between PD patients and controls in terms of CVRi or PI. Evidence of impaired CA in PD patients, which is independent of dopaminergic treatment</td>
</tr>
<tr>
<td>Zamani et al.</td>
<td>44</td>
<td>None</td>
<td>MCA (unclear which)</td>
<td>CO₂</td>
<td>MCBFV</td>
<td>Impaired VMR observed in 15 patients, but was not associated with OH.</td>
</tr>
</tbody>
</table>

ACZ acetazolamide, BH breath hold, BHI breath hold index, CA cerebral autoregulation, CBFV cerebral blood flow velocity, CO₂ carbon dioxide, CPT cold pressor test, CR cerebrovascular reactivity, CVR cerebrovascular resistance, CVRi cerebrovascular resistance index, HUT head up tilt, MCA middle cerebral artery, MCBFV mean cerebral blood flow velocity, MSA multi system atrophy, OH orthostatic hypotension, PCA posterior cerebral artery, PAF primary autonomic failure, PCBFV peak cerebral blood flow velocity, PD Parkinson’s disease, PI pulsatility index, STN-DBS subthalamic nucleus deep brain stimulation, TFA transfer function analysis, VA vertebral artery, VEP visual evoked paradigm, VMR vasomotor reactivity.
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Study published in peer-reviewed journal</td>
</tr>
<tr>
<td>B</td>
<td>Aims/hypothesis of research is described in the introduction/methods</td>
</tr>
<tr>
<td>C</td>
<td>The population of the study is described (age, sex, co-morbidities)</td>
</tr>
<tr>
<td>D</td>
<td>Study has ethical approval AND informed consent taken from study participants</td>
</tr>
<tr>
<td>E</td>
<td>Sample size calculated before start of experiment</td>
</tr>
<tr>
<td>F</td>
<td>Inclusion and exclusion criteria are clearly described</td>
</tr>
<tr>
<td>G</td>
<td>Study protocol clearly described</td>
</tr>
<tr>
<td>H</td>
<td>Relationship between dependent and independent variable is tested for statistical significance</td>
</tr>
</tbody>
</table>
| I         | CBF measurements clearly presented and consistent  
|           | CBF(v) calculation is present |
| J         | Graph/table summarising results |
| K         | Study tested reliability and validity of used measurements or referred to other studies which established reliability and validity |
| L         | Strength of evidence for each main outcome was discussed |
| M         | Limitations of the study are presented and discussed |
| N         | Suggestions made for future research |
| O         | Authors’ conflicts of interest are declared |

**Table 2.2: Checklist for study quality**
<table>
<thead>
<tr>
<th>Study</th>
<th>Criterion</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
<th>L</th>
<th>M</th>
<th>N</th>
<th>O</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angeli et al. 131</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>11</td>
</tr>
<tr>
<td>Azevedo et al. 104</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>12</td>
</tr>
<tr>
<td>Gurevich et al. 132</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>10</td>
</tr>
<tr>
<td>Hamdy et al. 144</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>12</td>
</tr>
<tr>
<td>Haubrich et al. 154</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>11</td>
</tr>
<tr>
<td>Mihci et al. 125</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>11</td>
</tr>
<tr>
<td>Niehaus et al. 136</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>9</td>
</tr>
<tr>
<td>Rätsep et al. 147</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>10</td>
</tr>
<tr>
<td>Rosengarten et al. 138</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>12</td>
</tr>
<tr>
<td>Schwalen et al. 143</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>4</td>
</tr>
<tr>
<td>Troisi et al. 139</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>9</td>
</tr>
<tr>
<td>Tsai et al. 140</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>13</td>
</tr>
<tr>
<td>Vokatch et al. 141</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>12</td>
</tr>
<tr>
<td>Zamani et al. 142</td>
<td></td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 2.3: Scores for quality assessment detailed by individual study
2.3.2 Study characteristics

Study sample size varied from seven to 175 patients, and all but 2 studies included a control group. However, where control groups were included, these were notably not always of the same size as the PD group. None of the studies included a calculation or analysis of the sample size required to achieve statistical power. The ages of participants were detailed in all studies, and participant genders were listed in all but one study. Duration of disease was also generally well reported, only being missing in two studies. A summary of patient ages and disease duration by study is provided in table 2.4. Disease stage was only detailed in eight studies. Information on how the diagnosis of PD had been made or confirmed was missing in seven of the studies, where this information was provided the diagnosis was reported as being made clinically in all cases, with four studies using the UK brain bank criteria, two studies detailing their own criteria and one study using the Calne criteria. Inclusion and exclusion criteria were generally well documented, although the actual criteria varied significantly between the studies. Ten studies specifically excluded patients with carotid stenosis, eight excluded patients with cerebrovascular disease and seven excluded patients with diabetes. Patients with demonstrable OH were variably included; six studies specifically included patients with OH, whilst two studies specifically excluded these patients. In the remainder of the studies, it was unclear whether the studied population had any evidence of OH. There was marked inconsistency with respect to continuation or discontinuation of Parkinsonian medications. In six of the studies, anti-Parkinsonian medications
were continued as normal and the patients were studied in their clinically ‘on’ state. In two studies, it was stated that medications were withheld for 3 hours,\textsuperscript{132,142} whilst timing of medications in relation to measurement of CA was unclear in another two studies.\textsuperscript{135,143} One study examined patients in the unmedicated state,\textsuperscript{137} although the patients in this study were notably receiving STN-DBS and were studied in both the stimulation ‘on’ and ‘off’ states. Three studies attempted to assess CA in PD patients both ‘on’ and ‘off’ their medication. In one of these studies, 15 patients were studied first thing in the morning after administration of their medications as normal before levodopa was discontinued for 12 hours and the measurement repeated.\textsuperscript{133} However, it should be noted that whilst levodopa was discontinued, the patients other anti-Parkinsonian medications (including dopamine agonists) were continued as normal. In another study,\textsuperscript{140} 12 patients were again studied first thing in the morning after taking their morning medications as prescribed. Medications were then withheld in 7 of these patients for 48 hours before the CA measurements were repeated. In the final study,\textsuperscript{141} all 14 patients were studied both on their medications, and after their medications had been withheld for a period of 12 hours.
<table>
<thead>
<tr>
<th>Study</th>
<th>Age of patients in years Mean ± SD (range)</th>
<th>Disease duration in years or months Mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angeli et al.</td>
<td>64.8 ± 8.4</td>
<td>66.6 ± 48.8&quot;</td>
</tr>
<tr>
<td>Azevedo et al.</td>
<td>56 ± 9.1</td>
<td>Not recorded</td>
</tr>
<tr>
<td>Gurevich et al.</td>
<td>79.8 ± 4.3</td>
<td>7.3 ± 4.9</td>
</tr>
<tr>
<td>Hamdy et al.</td>
<td>63.73 ± 6.5</td>
<td>4.93 ± 1.7</td>
</tr>
<tr>
<td>Haubrich et al.</td>
<td>Asymptomatic OH group 73 ± 4</td>
<td>Asymptomatic OH group 6 ± 4</td>
</tr>
<tr>
<td></td>
<td>Symptomatic OH group 64 ± 9</td>
<td>Symptomatic OH group 7 ± 6</td>
</tr>
<tr>
<td>Mihci et al.</td>
<td>61 ± 8</td>
<td>62 ± 45&quot;</td>
</tr>
<tr>
<td>Niehaus et al.</td>
<td>58 ± 8</td>
<td>8 ± 3</td>
</tr>
<tr>
<td>Rätsep et al.</td>
<td>66.6 (62-71)</td>
<td>17.3 (10-26)</td>
</tr>
<tr>
<td>Rosengarten et al.</td>
<td>PD group 65 ± 9</td>
<td>PD group 7 ± 4</td>
</tr>
<tr>
<td></td>
<td>PD dementia group 72 ± 8</td>
<td>PD dementia group 8 ± 5</td>
</tr>
<tr>
<td></td>
<td>PD dementia+acetylcholinesterase inhibitor group 73 ± 6</td>
<td>PD dementia+acetylcholinesterase inhibitor group 10 ± 5</td>
</tr>
<tr>
<td>Schwalen et al.</td>
<td>66.8 ± 9.15</td>
<td>Not recorded</td>
</tr>
<tr>
<td>Troisi et al.</td>
<td>64.5 ± 7.8</td>
<td>7.3 ± 4.8</td>
</tr>
<tr>
<td>Tsai et al.</td>
<td>68.4 ± 9.6</td>
<td>5.4 (3-9)</td>
</tr>
<tr>
<td>Vokatch et al.</td>
<td>67.2 ± 15.2</td>
<td>8.2 ± 5.1</td>
</tr>
<tr>
<td>Zamani et al.</td>
<td>57.75 ± 11.39</td>
<td>75.27 ± 53.63&quot;</td>
</tr>
</tbody>
</table>

*Table 2.4: Patient age and disease duration detailed by study*
2.3.3 Measurement techniques and CA inputs

An overview of the measurement techniques is given in table 2.1. Importantly, one study\textsuperscript{140} used Transcranial colour-coded duplex sonography instead of conventional TCD. Twelve studies evaluated CBFV in the MCA\textsuperscript{131,132,133,134,135,136,137,139,140,141,142,143} and two\textsuperscript{101,138} (notably the studies using a visual evoked paradigm) in the PCA. Of the studies involving the MCA, TCD insonation was unilateral in five studies\textsuperscript{131,136,140,141,142} and bilateral in six studies.\textsuperscript{132,134,135,137,139,143} In one study, it was unclear whether insonation was bilateral or unilateral.\textsuperscript{133} Where insonation was unilateral, two of the studies stated that they had selected the side with the strongest signal\textsuperscript{140,141} but the reason for selection of a specific side was unclear in the remaining studies. Of the studies which involved evaluation of CBFV in the PCA, insonation was unilateral in one study\textsuperscript{101} and bilateral in another.\textsuperscript{138} Reporting of the depth of vessel insonation was present in eight of the fourteen studies.\textsuperscript{131,132,134,135,136,137,139,142} A variety of approaches (inputs) were used to instigate the CA response; head-up tilt was most commonly used (five studies\textsuperscript{131,134,135,136,143}), although the degree of tilt varied between studies from 70° to 90°. Other inputs used were acetazolamide,\textsuperscript{132} CO\textsubscript{2},\textsuperscript{142} breath holding,\textsuperscript{133} [30], the cold pressor test,\textsuperscript{137,140} visual evoked paradigms,\textsuperscript{101,138} and the thigh cuff release test.\textsuperscript{141} One study\textsuperscript{139} investigated cerebrovascular responses to multiple inputs including emotional tasks, cognitive paradigms, a motor task (sequential thumb to finger opposition) and breath holding. One study combined HUT with an analysis of CA based on spontaneous fluctuations in BP.\textsuperscript{134} In addition to the varying inputs between studies, there was also varying recording of peripheral haemodynamic parameters. Three studies did not make any recordings of BP or HR\textsuperscript{133,142,143} whilst just four studies made a continuous recording of BP and
One study recorded HR continuously, but BP at intervals of 1 minute. In the remaining studies, both HR and BP were recorded intermittently, at intervals which were either unknown or varied from every 20 seconds, to every 5 minutes. EtCO₂ was monitored in just four studies. Furthermore, with specific regards to the study protocol, room temperature was documented in eight of the studies, four studies specifically mentioned that they had asked patients to refrain from caffeine for a set period of time prior to the recording and six studies made the same statement with regards to large meals. However, just one study specifically commented on avoidance of alcohol and just two on the avoidance of smoking.

2.3.4 Modelling techniques

There was marked heterogeneity in the modelling techniques used to evaluate CA. Most studies simply calculated the mean or peak CBFV pre- and post-stimulus and reported this as a percentage change or used the values to calculate the cerebrovascular resistance index CVRᵢ or PI. Two studies reported a breath holding index (BHI), calculated by dividing the percentage increase in mean blood flow velocity (MFV) occurring during breath holding by seconds of breath holding. Two studies calculated CA indices using a second-order differential equation model and just one study used TFA to model CA.

2.3.5 Cerebral haemodynamic responses

Although the heterogeneity of the CA inputs and modelling techniques employed by the various studies makes direct comparison of the studies very difficult, it is possible
to draw some general conclusions. The majority of studies (ten,\textsuperscript{101,131,132,133,136,137,138,139,140,143}) reported that resting MBFV was not significantly different in PD patients when compared to healthy controls or to normal laboratory values. The values of MBFV provided by the studies are listed in table 2.5.
<table>
<thead>
<tr>
<th>VESSEL</th>
<th>STUDY</th>
<th>MBFV (cm/s)</th>
<th>HEALTHY CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angeli et al. 131</td>
<td>Not recorded</td>
<td>Not recorded</td>
</tr>
<tr>
<td></td>
<td>Gurevich et al. 132</td>
<td>71.1 ± 5.0</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td>Hamdy et al. 133</td>
<td>On medication 40.9 ± 7.1</td>
<td>45.67 ± 10.93</td>
</tr>
<tr>
<td></td>
<td>Haubrich et al. 134</td>
<td>Asymptomatic OH group 54.7 ± 2.0</td>
<td>56.5 ± 9.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic OH group 52.6 ± 8.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mihci et al. 135</td>
<td>46 ± 9</td>
<td>55 ± 10</td>
</tr>
<tr>
<td></td>
<td>Niehaus et al. 136</td>
<td>49.2 ± 17.5</td>
<td>51.7 ± 11.9</td>
</tr>
<tr>
<td></td>
<td>Rätsep et al. 137</td>
<td>Deep brain stimulation on 37.6 ± 10.7</td>
<td>36.9 ± 9.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deep brain stimulation off 41.0 ± 13.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schwalen et al. 138</td>
<td>51 ± 12</td>
<td>58 ± 12</td>
</tr>
<tr>
<td></td>
<td>Troisi et al. 139</td>
<td>Not recorded</td>
<td>Not recorded</td>
</tr>
<tr>
<td></td>
<td>Tsai et al. 140</td>
<td>54.78 ± 2.80</td>
<td>61.77 ± 2.35</td>
</tr>
<tr>
<td></td>
<td>Vokatch et al. 141</td>
<td>On medication 49.8 ± 14.6</td>
<td>62.3 ± 8.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After 12 hour medication withdrawal 53.7 ± 12.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zamani et al. 142</td>
<td>30.20 ± 9.6</td>
<td>Not available</td>
</tr>
<tr>
<td>PCA</td>
<td>Azevedo et al. 143</td>
<td>Pre deep brain stimulation surgery 47 ± 12</td>
<td>47 ± 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post deep brain stimulation surgery 47 ± 13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haubrich et al. 144</td>
<td>Asymptomatic OH group 34.6 ± 9.4</td>
<td>37.4 ± 9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic OH group 37.0 ± 7.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosengarten et al. 145</td>
<td>PD group 46 ± 10</td>
<td>48 ± 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD dementia group 45 ± 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PD dementia+acetylcholinesterase inhibitor group 47 ± 12</td>
<td></td>
</tr>
<tr>
<td>VA</td>
<td>Gurevich et al. 132</td>
<td>41.8 ± 4.1</td>
<td>Not available</td>
</tr>
</tbody>
</table>

**Table 2.5:** Mean CBFV detailed by vessel and by study
Of the remaining four studies, one study had not included a control group or defined normal values for resting MBFV,\textsuperscript{142} one study did not specifically comment on resting MBFV,\textsuperscript{141} one study found MBFV to be consistently lower in PD patients than in controls\textsuperscript{135} and the other found MBFV to be lower in PD patients with symptomatic OH, but not in those without.\textsuperscript{134} Seven studies concluded that cerebral autoregulation is preserved in PD,\textsuperscript{101,131,134,135,136,138,143} six concluded that CA is abnormal\textsuperscript{133,137,139,140,141,142} and the other study simply concluded that vasomotor reactivity is the same in patients with PD as it is in patients with primary autonomic failure and multi system atrophy.\textsuperscript{132} ‘Abnormal’ CA was generally determined by a statistically significant difference in CBFV values when compared to control populations. Of the three studies which assessed NVC, two (using a VEP) found neurovascular coupling responses to be no different to healthy controls,\textsuperscript{101,138} whilst the third found neurovascular coupling responses to be normal with motor and cognitive paradigms but abnormal with emotional stimulus.\textsuperscript{139} The five studies which used HUT as the input stimulus concluded that CA is preserved in patients with PD, whereas both studies using the cold pressor test concluded that CA is abnormal – although interestingly for different reasons, one finding a higher CVRi following the CPT,\textsuperscript{137} and one finding a lower CVRi.\textsuperscript{140} The study using the thigh cuff release test also concluded that CA is abnormal in PD patients,\textsuperscript{141} as did the two studies which examined vasomotor reactivity according to its true definition (i.e. cerebrovascular response to alterations in PaCO\textsubscript{2}).\textsuperscript{133,142} The effect of anti-Parkinsonian medications on cerebral haemodynamic responses, whilst only evaluated in three studies, was not found to be significant.
2.4 DISCUSSION

This review has yielded conflicting findings regarding CA in patients with PD, particularly as the studies here have all defined CA in different ways. The results of this review suggest that NVC is probably preserved in PD patients, whilst vasomotor reactivity is impaired. Furthermore, aggressive inputs leading to large fluctuations in BP (such as the cold pressor test, acetazolamide challenge and the thigh cuff release test) produce different autoregulatory responses than HUT. The reasons for this are, at present, unclear. There also appears to be some evidence suggesting that anti-Parkinsonian medications do not affect CA responses.

However, it is important to note that the literature supporting these conclusions is limited in its scope and of uneven quality. In particular, the relatively small sample sizes, small or absent control groups and the lack of consideration for statistical power makes it especially difficult to draw firm conclusions from these studies. It was reported in 2009 that at least 45 subjects are needed in a group to show a difference in the ARI of 1 unit, with 80% power at the 5% level, suggesting that all but two of the studies included in this review were underpowered. The marked heterogeneity in study methodology is a further concern. Despite good evidence that smoking, caffeine, alcohol, and large meals can affect cerebral haemodynamics these were given surprisingly little consideration. Of greater concern is the marked variation in monitoring of peripheral haemodynamic parameters, particularly BP and PaCO₂. As both static and dynamic definitions of CA refer to changes in CBF following a change in mean arterial BP, it follows that BP should be carefully, and continuously, recorded. Accurate measurements of PaCO₂ are also essential for proper evaluation of CBF levels and this can be done with infra-red capnography or mass spectroscopy.
The choice of CA input employed in these studies also warrants consideration. Although all inputs are valid, and have been used in other studies of CA, consideration should be given to the possibility of direct sympathetic activation resulting from different inputs.\textsuperscript{149} The tolerability of inputs should also be considered; patients with PD are generally older and there is evidence that manoeuvres such as the thigh cuff test are poorly tolerated in aged subjects.\textsuperscript{113}

With respect to modelling technique, it is important to note that the majority of the studies reported here drew their conclusions from simple comparison of the mean or peak CBFVs pre- and post-stimulus, or from calculations of CVRi or PI. Comparison of mean CBFVs is not statistically robust, and does not take into account the influence of time-delays and other co-variates of CA, such as cardiac output, HR and PaCO\textsubscript{2}.\textsuperscript{149} CVRi and PI are not the most robust estimates of CA and, as there are well documented, validated methods for quantification of CBFV responses and CA indices,\textsuperscript{107,149} these should ideally be used in preference to the modelling techniques reported by the majority of studies included in this review.

The issue of the influence of anti-Parkinsonian medications on CA was insufficiently addressed by the studies in this review. In total, just 21 patients were studied in both the medicated state and after a period of drug withdrawal. Importantly, drug withdrawal periods appeared arbitrary – no reference was given to medication pharmacokinetics or relevant pharmacology literature.

Further aspects for consideration include PD diagnosis and stage. Although the UK Brain Bank criteria applied by experts show 90% sensitivity and specificity, in early disease clinical diagnosis is less straightforward. PD diagnosis made in the community by non-experts is associated with a 25% error rate.\textsuperscript{150} In all studies involving PD
patients, care should therefore be taken to ensure that the diagnosis has been made by a specialist, and this should be reported. Consideration to disease stage is also important due to the progressive nature of the disease.

2.5 SUMMARY

The literature on CA in PD is limited in its scope and is of uneven quality. Overall, there is currently insufficient evidence to either confirm or refute the presence of abnormal CA in PD, although there is a suggestion that neurovascular coupling is probably preserved in PD patients, whilst vasomotor reactivity is likely to be impaired. Furthermore, there is some evidence that cerebral haemodynamic responses vary according to the autoregulatory stimulus used. There is also weak evidence suggesting that anti-Parkinsonian medications do not affect CA. Given the insufficiency of the evidence, there is a need for further work to provide clarity.
CHAPTER 3    RESEARCH METHODS

“Anatomical examination, the only sure foundation for pathological knowledge”

James Parkinson, 1817

3.1 METHODS

This chapter will detail the methods used to obtain the scientific data contained within this Thesis.

3.2 ETHICAL APPROVAL

Ethical approval for the study was obtained from the Northampton Research Ethics Committee, United Kingdom acting on behalf of the National Research Ethics Service (REC reference 11/EM/0369). Approval was also obtained from the Trust research and development department (R and D reference 11087). The research was performed in accordance with the principles of Good Clinical Practice\textsuperscript{151} and the Declaration of Helsinki of the World Medical Association.\textsuperscript{152} Management of all study data was in compliance with the Data Protection Act.\textsuperscript{153}

3.3 RESEARCH METHODS

3.3.1 Subjects

Patients with idiopathic PD who fulfilled the inclusion and exclusion criteria detailed below were recruited from both the specialist PD clinic at University Hospitals of
Leicester NHS Trust, and by direct invitation facilitated by Parkinson’s UK, the national PD support and research charity. Importantly, clinic-based recruitment was initially facilitated through the geriatric led PD service only; recruitment through the neurology led service did not occur until later because of their recruitment to competing trials and studies.

Inclusion criteria:

1) Aged > 18 years
2) Able to give informed consent
3) Diagnosis of idiopathic PD according to the UK PD Society Brain Bank Criteria*

Exclusion criteria:

1) Diabetes mellitus
2) Dementia
3) Peripheral neuropathy
4) Ischaemic heart disease
5) Cerebrovascular disease (history of stroke or TIA)
6) Deep brain stimulation*
7) Dependence on anti-Parkinsonian medications for safe swallow*

* Not applicable to healthy controls
3.3.2 Recruitment

In the outpatient clinic, once potentially suitable patients had been identified by the researcher, they were provided with an explanation of the nature of the research and a study information sheet (Appendix 3) to take away and read. A follow-up telephone call was then made to them in the following days and, if the patient remained keen to participate in the study, an appointment was made for them to attend the cardiovascular research laboratory at Leicester Royal Infirmary, where they underwent the research protocol detailed in the following section.

Those patients and participants recruited through Parkinson’s UK contacted the researcher directly, either by email or by telephone. After initial contact had been made, the participant was provided with both a formal letter of invitation (Appendix 4) and a study information sheet (Appendix 3). As before, if, after reading the study information sheet, they remained keen to participate, an appointment was made for them to attend the cardiovascular research laboratory at Leicester Royal Infirmary, where they underwent the research protocol detailed in the following section.

Healthy controls were recruited from departmental volunteers, patient relatives and friends, and by advertisement in the local Parkinson’s UK newsletters. Care was taken to ensure that the healthy controls were well matched to the patients in terms of age, gender and medical comorbidities. The majority of the healthy controls were therefore recruited after the patient group had been scanned. Healthy controls were provided with a volunteer specific information sheet (Appendix 5) which they were instructed to read carefully before deciding to take part.
3.3.3 Research Protocol

The research protocol was undertaken in a dedicated cardiovascular research laboratory at Leicester Royal Infirmary, which is of controlled temperature (20-24°C) and free from distraction. Prior to attending the research laboratory, each participant was asked to behave in a similar fashion, specifically avoiding large meals, caffeine, alcohol, cigarettes and strenuous exercise for at least four hours prior to each recording (all of which have been shown to potentially affect CBF and/or BP). Upon attending the research laboratory, the participant was again provided with an explanation of the nature and purpose of the research, and was given the opportunity to ask questions. Participants were then required to give their formal written consent to participate in the study by completing the appropriate consent form (Appendices 6 and 7).

In the case of patients with PD, a letter (Appendix 8) was sent to their General Practitioner to inform them of the patient’s participation in the study.

Once consent had been obtained, baseline data of participant age, sex, co-morbidities and medications were recorded, and handedness was determined for each participant using the Edinburgh Handedness Inventory (EHI), a well validated and widely used 10 point questionnaire used to assess laterality (Appendix 9). Participants were also questioned regarding the presence of symptoms of orthostatic hypotension. Standard questions were used which comprised:
1) “Do you ever feel light-headed shortly after standing up, or after you have been standing for a while?”

2) “Do you ever feel light-headed after eating large meals, or after a hot shower or bath?”

3) “If yes to the above, do the symptoms resolve when you sit or lie-down?”

For the participants with PD, additional data regarding disease stage (assessed using the Hoehn and Yahr Scale, Appendix 10), length of time since diagnosis, disease severity (assessed using the Unified Parkinson's Disease Rating Scale, Appendix 11) and non-motor symptom burden (assessed using the Non Motor Symptom Questionnaire, Appendix 12) was also recorded.

**Hoehn and Yahr Scale**

The Hoehn and Yahr scale is a rating scale which is commonly used for describing, in broad terms, how Parkinson’s symptoms progress and the relative level of disability. Among its advantages are that it is simple, easily applied and captures typical patterns of progressive motor impairment which can be applied whether or not patients are receiving dopaminergic therapy. The scale was originally published in 1967 in the Journal of Neurology and included stages 1 through 5, where stage 1 is the earliest stage of the disease and stage 5 the last. The scale was subsequently modified by the Movement Disorders Society in 2004 to include stages 1.5 and 2.5, which help to better describe the intermediate course of the disease. At stage 1, a patient would only have unilateral symptoms of PD. At stage 1.5, a patient would have unilateral
symptoms and axial involvement, and at stage 2 would have bilateral symptoms. Stages 2.5 and 3 describe bilateral symptoms with progressive impairment of balance. By stage 4 the patient is severely disabled by and at stage 5 bed- or wheelchair-ridden. Progression in Hoehn and Yahr stages has been found to correlate with deterioration in quality of life, and neuroimaging studies of dopaminergic loss. Please refer to Appendix 10 for more detail.

**Unified Parkinson’s Disease Rating Scale**

The Unified Parkinson’s Disease Rating Scale (UPDRS) was introduced in 1987 by a team of PD investigators as an overall assessment scale that would quantify both the signs and symptoms of PD, and is now the standard tool for measuring Parkinsonian signs and symptoms in both clinical practice and research. It was developed by combining various PD rating scales in use at the time, including the Webster and Columbia scales. The development of the UPDRS notably involved multiple trial versions, and the final published scale is officially known as UPDRS version 3.0. The UPDRS includes both a patient symptom questionnaire and objective scoring by a clinician (motor examination). The scale is divided into four parts. Parts one, two and four are the questionnaire based components and evaluate mentation and mood, activities of daily living and complications of dopaminergic therapy respectively. Part three comprises an assessment of motor function based on clinical examination. The UPDRS has been shown to have high internal consistency and excellent inter- and intra-rater reliability. Please refer to appendix 11 for further detail.
Non Motor Symptom Questionnaire (NMS Quest)\textsuperscript{45}

The Non Motor Symptom Questionnaire is a 30 point questionnaire which was developed by Chaudhuri and colleagues in 2006, in recognition that non motor symptoms are under-reported by patients, under-recognised by clinicians and under-represented in the UPDRS.\textsuperscript{167-171} The questionnaire is self-completed by patients, and lists 30 symptoms such as dribbling of saliva, feeling anxious, excessive sweating and constipation. The patient is asked to tick “Yes” or “No” next to each symptom depending on whether they have experienced the symptom in the last month. The questionnaire is designed to complement the UPDRS and, whilst it is an evaluation and not a discriminant tool, it is helpful in evaluating the burden of non-motor symptoms, which have been shown to correlate with disease progression and duration.\textsuperscript{45} Please refer to appendix 12 for more detail.

Having completed the relevant baseline assessments and questionnaires, the participant was asked to lie supine on a couch with their head supported on a pillow and their legs uncrossed. Upon doing so, the participant was connected to several key pieces of physiological monitoring equipment, namely a three lead ECG monitor (Graseby Cardiac Monitor 304), brachial sphygmomanometer (OMRON 705IT), beat-to-beat BP plethysmograph (Portapres® Model-2, Finapres Medical Systems; Amsterdam, The Netherlands or Finapres®, Ohmeda 2300; Louisville, CO, USA) and capnograph (Capnocheck Plus) via nasal cannulae (Salter Labs).
Beat-to-beat blood pressure monitoring

Finapres® and Portapres® are well validated, well tolerated, non-invasive devices which allow for continuous peripheral monitoring of arterial BP. Using the methodology outlined by Penaz they are able to continuously display the arterial pressure waveform. Both devices use a small, inflatable, cuff to apply a volume clamp to the finger. The total finger volume under an unloading cuff is determined by infra-red plethysmography and, despite the changing arterial pressure, this volume is maintained at a set level by modulating the cuff pressure using a high speed electropneumatic servo-system. The continuously changing cuff pressure is measured electronically, and the signal displayed is the arterial pressure. To ensure accuracy, the signal is automatically calibrated against pre-determined criteria (known as the servo-adjust function). For consistency in this study, the finger cuff of the Portapres® or Finapres® was placed on the middle finger of the non-dominant hand, with the arm supported at heart level. Hand-dominance was determined by the EHI. Where the EHI revealed the participant to be ambidextrous, dominance was established by using the hand used for writing.

Please note that Portapres® and Finapres® are interchangeable, simply being different machine models of the same technology. The Portapres® is a portable version of the plethysmography and the Finapres® is a larger, less portable machine. It was unfortunately necessary to switch to using the Finapres® approximately halfway through the study as the Portapres® broke. However, both machines were carefully calibrated by the medical physics department and it was felt that the potential for error resulting from the change in equipment was low.
Simultaneous insonation of the middle cerebral arteries (MCAs) was then performed using TCD (Viasys Companion III, Viasys Healthcare). A 2 MHz probe was placed onto each temporal window and the MCAs were identified according to their reported waveforms and characteristics, which are summarised in tables 3.1 and 3.2. The TCD probes were standardised as channel 1 for the right MCA and channel 2 for the left MCA.

<table>
<thead>
<tr>
<th>ARtery</th>
<th>DEPth (mm)</th>
<th>FLOW DIRECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle cerebral artery (MCA)</td>
<td>30-60</td>
<td>Towards probe</td>
</tr>
<tr>
<td>Anterior cerebral artery (ACA) (A1)</td>
<td>60-80</td>
<td>Away from probe</td>
</tr>
<tr>
<td>Posterior cerebral artery (PCA) (P1)</td>
<td>60-70</td>
<td>Towards probe</td>
</tr>
</tbody>
</table>

**Table 3.1:** Depth and flow direction of the major intracranial vessels when assessed using TCD

<table>
<thead>
<tr>
<th>ARtery</th>
<th>MEAN VELOCITY in cm/sec*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Middle cerebral artery (MCA)</td>
<td>73 (33-133)</td>
</tr>
<tr>
<td>Anterior cerebral artery (ACA)</td>
<td>53 (33-83)</td>
</tr>
<tr>
<td>Posterior cerebral artery (PCA)</td>
<td>49 (25-73)</td>
</tr>
</tbody>
</table>

**Table 3.2:** Mean velocities of the major intracranial vessels denoted by age
*Values given are mean (± 2 SD)

Once the MCA signals had been identified and optimised to provide the maximum velocity envelope, the ultrasound probes were secured in place using a customised headframe in preparation for recording.

Following a stabilisation period of ten minutes, four recordings were made. These comprised two, five minute, baseline recordings, a respiratory paradigm lasting 4 and a half minutes, and finally a motor paradigm lasting 4 minutes.
During each period of recording the plethysmograph servo-adjust was switched off, and a manual BP calibration was taken at the commencement of each recording. In between each recording, the servo-adjust was switched back on and an adequate time interval given to allow for stabilisation before making subsequent recordings.

The five minute baseline recordings simply required the participant to relax in silence, whilst lying supine and still on the couch. Participants were, however, instructed that they should keep their eyes open and remain awake.

The respiratory paradigm was designed to result in a period of hyperventilation with associated hypocapnia. The paradigm comprised a 60 second period of rest, followed by a 90 second period where they were asked to breathe in time with an electronic metronome. For the first 30 seconds of this period, participants gradually increased their respiratory rate to 25 breaths per minute, which they then sustained for a further 60 seconds. This recording then concluded with a two minute period of recovery during which the metronome was switched off and the participant was asked to relax and once again breathe normally. To optimise participants’ compliance with, and ability to perform, the respiratory paradigm participants were given the opportunity to listen to the metronome and have several practice attempts during the briefing phase of their visit to the cardiovascular sciences laboratory.

The motor paradigm began with a 90 second period of rest. Then, for one minute, participants were asked to relax while the researcher repetitively flexed and extended the upper limb at the elbow of the dominant arm, with an excursion range of ~ 90°. The movements were driven by an electronic metronome to ensure a constant
frequency of 1Hz. The paradigm was then concluded with a recovery period of a further 90 seconds, where the participant again relaxed in silence.

‘On’ and ‘off’ recordings

The participants with PD were required to undergo the above protocol on two separate occasions, no more than two weeks apart. On the first occasion, they attended in their clinical ‘on’ state having taken their anti-Parkinsonian medications as normal. On the second occasion, they were required to attend in their ‘off’ state having abstained from their anti-Parkinsonian medications for either 12 or 24 hours, depending on the preparation (Table 3.3). Withdrawal periods for the medications were determined by reviewing the product literature pertaining to pharmacokinetics. Both measurements for the ‘on’ and ‘off’ states were notably carried out at the same time of the day, which for all patients was between 09:30 and 11:30 in the morning. ‘On’ and ‘off’ states were assessed objectively using the motor component (part three) of the UPDRS.
<table>
<thead>
<tr>
<th>ANTI-PARKINSONIAN MEDICATION</th>
<th>PERIOD OF ABSTINENCE REQUIRED PRIOR TO ‘OFF MEASUREMENT’</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa (Co-careldopa and co-beneldopa as Sinemet®, Sinemet® Plus, Madopar®, Madopar® Dispersible)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Standard release dopamine agonists (Pramipexole, Ropinirole, Apomorphine)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Transdermal dopamine agonist (Rotigotine as Neupro®)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Catechol-0-methyltransferase inhibitors (Entacapone, Tolcapone, Stalevo®)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Antimuscarinic drugs (Procyclidine, Trihexyphenidyl, Orphenadrine)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Sustained release levodopa (Caramet® CR, Sinemet® CR, Half Sinemet® CR, Madopar® CR)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Sustained release dopamine agonists (Mirapexin® prolonged release, Ropinirole MR, Requip® XL)</td>
<td>24 hours</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors (Rasagiline, Selegiline)</td>
<td>24 hours</td>
</tr>
</tbody>
</table>

Table 3.3: Abstinence period by medication type for ‘off’ measurement in subjects with PD

Healthy volunteers were only required to attend the laboratory to undergo the research protocol on one occasion. Measurements were made at a time of day convenient to the participant.
Natural history measurements

In order to evaluate the natural history of CA responses, keen and consenting participants were enrolled into a natural history arm of the study, whereby they underwent repeat pairs of measurements every four months for one year (i.e. eight measurements in total).

3.4 DATA COLLECTION

The data collected as part of the protocol above (CBFV, EtCO₂, BP, ECG and metronome activity) were simultaneously recorded onto a computer hard drive by a physiological data acquisition system (PHYSIDAS, Department of Medical Physics, University Hospitals of Leicester NHS Trust) for subsequent off-line analysis. Each recorded file was anonymised but named using a coded sequence which allowed the researcher to identify both the subject and individual recordings.

3.5 DATA EDITING AND ANALYSIS

Data were edited using MS-DOS based software designed by the Medical Physics Group, Department of Cardiovascular Sciences, University of Leicester. A typical data recording as viewed in the editing software is shown in figure 3.1.
Using the software, ECG, EtCO₂, BP and stimulus markers were sampled at 500 samples/s. The BP signal was calibrated at the start of each recording. In the case of the Portapres®, its own calibration signal was used to calibrate arterial BP measurements, and this signal was then removed. For the Finapres®, a manual calibration was performed using the brachial BP measurements obtained during the research protocol with the brachial OMRON 705IT sphygmomanometer. After calibration, the BP waveform was inspected for drift (which can occur if the Servo has been off for some time or if the subject’s finger becomes cold, figure 3.2) and all signals were visually inspected to assess data quality, and to identify spike artefacts (figure 3.3) and noise. Narrow spikes were removed using linear interpolation. In cases of poor signal quality (figure 3.4), excessive artefact or noise, the data segment was excluded from analysis.
Figure 3.2: Plethysmography waveform drift

Figure 3.3: Spike artefact

Figure 3.4: Noisy, poor quality signal
Following CBFV spike removal a median filter was applied, followed by a low-pass Butterworth filter, with a cut-off frequency of 20Hz. The R-R interval was automatically marked using the ECG trace, and continuous HR plotted against time. The R-R interval was visually inspected to ensure correct marking and, in cases where the marking appeared unreliable (figure 3.5), the editing software permitted R-R marking from the plethysmograph trace. Ectopic beats caused spikes in the HR signal; these were identified by visual inspection of each and every QRS complex by the author, and were then manually removed by linear interpolation of the time periods at which they occurred.

![Figure 3.5: Poor quality, unreliable, ECG trace](image)

Mean BP, CBFV and systolic/diastolic values 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. The instantaneous relationship between BP and CBFV was used to estimate CrCP and RAP for each cardiac cycle using the first harmonic method. Beat-to-beat data were then spline interpolated and resampled at 5 samples/s seconds to create a uniform time base.
The subsequent analysis of the data for each study paradigm required varying software programmes, and different statistical considerations. These are therefore detailed individually in the following results chapters.
CHAPTER 4  DYNAMIC CEREBRAL AUTOREGULATION
INDICES IN THE ‘ON’ AND ‘OFF’ STATES OF PD

“By these repeated observations, he hoped that he had been led to a probable conjecture as to the nature of the malady”

James Parkinson, 1817

4.1 INTRODUCTION

A review of the literature (Chapter 2) has highlighted a paucity of TCD studies evaluating CA in patients with PD. In particular, there are very few studies which have used validated modelling techniques to assess CA; just one study\textsuperscript{134} has used spontaneous fluctuations in BP and TFA. Furthermore, CA in PD has never been reported in terms of an ARI, and the influence of anti-Parkinsonian medications on CA has, to date, been inadequately assessed. The aim of this study was to therefore use TCD and spontaneous fluctuations in BP to determine CA indices for patients with idiopathic PD in both their ‘on’ (medicated) and ‘off’ (unmedicated) states, and to compare these indices with those obtained for healthy controls.

4.2 METHODS

4.2.1 Protocol

Subjects were recruited to the study, and data collected, as described previously in Chapter 3. In this analysis, the two, five-minute, baseline TCD recordings made at each
visit immediately after the stabilisation period were used for the calculation of dCA indices.

4.2.2 Data Analysis

Raw data were edited using the method detailed in section 3.5. After calculation of mean BP, CBFV, systolic/diastolic values, EtCO₂, CrCP and RAP for each cardiac cycle, a FFT transform was applied to the data, thus transferring it from the time domain into the frequency domain. An averaging analysis programme was used to review individual files and then auto- and cross-power spectral densities were estimated using the Welch method. The complex transfer function of the BP-CBFV dynamic relationship was calculated by selecting arterial BP as the input variable and right, then left, CBFV as the output variable, yielding values of coherence, phase, gain and an impulse response. The CBFV step response was subsequently derived from inverse FFT (integration) of this impulse response, representing realisation of frequency parameters in the time domain. An ARI value was then assigned to each recording by matching the CBFV step response to one of the 10 model ARI curves proposed by Tiecks (Section 1.3.5) using the ‘best fit’ least squares method. The ‘best fit’ of the model curves was the one which most closely matched the rate of change, and return to baseline, of the CBFV observed in each recording.

At all stages of the analysis, data were carefully inspected and checked for quality. In the frequency domain, coherence was considered to be acceptable if it reached ≥0.5 at any frequencies <0.25Hz. Where coherence was lower than this, data was rejected.
and was not used for further calculations of CA indices. The impulse response was considered acceptable if a narrow central response was displayed at t=0 (figure 4.1). If large amplitude oscillations were present which competed with the amplitude of the central impulse peak this was an indication for data rejection (figure 4.2). Data were also rejected when there was poor model fitting between the CBFV step response and the Tiecks model curves (correlation coefficient <0.7), as this made it impossible to obtain reliable and accurate ARI values.

Figure 4.1: Acceptable impulse response

Figure 4.2: Unacceptable impulse response
4.2.3 Statistics

Data were collated in Microsoft Excel 2010 and analysed using Statistica version 8. Categorical data are presented as absolute numbers and percentages. Continuous data were plotted and assessed for normality using the Shapiro-Wilk test; normally distributed values are reported as mean (±standard deviation (SD), range) and non-normal data are presented as median (inter-quartile range (IQR), range). Values of CrCP and RAP were notably considered to be continuous. Values of ARI were also treated as continuous, having been interpolated at the time of the least-squares fitting.

Differences in categorical variables were assessed using Fisher’s exact test. For comparisons between ‘on’ and ‘off’ recordings in the patient group, as these were made on the same group of patients, where continuous values were normally distributed they were compared using the Student’s paired t-test, and where they were not normally distributed the Wilcoxon signed rank test was used. For comparisons involving a single value between patients and controls, an unpaired t-test was used for normally distributed data, and a Mann-Whitney test for non-normal data. For comparisons between healthy controls and PD patients in both their on and off states, one-way ANOVA was used for normal data and a Kruskal-Wallis test for non-normal data. For comparisons between baseline CBFV, RAP and CrCP values in both the on and off states and side of recording, a two-way ANOVA was used with clinical state (on and off) as the between factor, and side of recording (disease onset hemisphere, other hemisphere) as the within factor.
In all cases, where ANOVA or the Kruskall-Wallis test suggested statistical significance, appropriate post-hoc testing was performed to identify the significant relationship(s).

In all analyses, statistical significance was assumed when p<0.05.

4.3 RESULTS

4.3.1 Baseline Demographics

A total of 35 patients with idiopathic PD were recruited to the study and attended for TCD measurements. Eight patients were subsequently excluded because of inadequate transtemporal insonation windows. These subjects, three males and five females, did not differ significantly in terms of age, PD severity, BP or HR from the rest of the group. It was unfortunately necessary to exclude the data obtained from one further patient (female aged 75, disease duration 1.5 years) because of multiple ectopic beats which occurred during the recording. Additionally, one patient (male aged 59, disease duration 2.5 years) was, by his own choice, not receiving any treatment for his PD and was therefore only scanned once in his ‘off’ state. A second patient (female aged 66, disease duration two years) withdrew from the study after attending for her ‘on’ scan due to apprehension regarding the temporary cessation of medication required for the ‘off’ scan, meaning that she was only scanned once, in her ‘on’ state. These two patients were excluded from paired analyses, meaning 24 paired readings were available for evaluation in the patient group. Please refer to Appendix 13 for a pictorial summary of patient inclusion in this study.
28 volunteers were also recruited to the study, three of whom were subsequently excluded because of inadequate transtemporal insonation windows. These patients were notably all female, but did not otherwise differ significantly in terms of age, BP or HR from the rest of the volunteer group. It was unfortunately necessary to exclude data collected from two of the remaining volunteers because of poor signal quality and noise, leaving a total of 23 healthy controls.

The baseline characteristics of PD patients and healthy controls are detailed in 4.1. No significant differences were observed between the two groups in terms of age, gender or handedness. However, it should be noted that the p value for difference in age was approaching significance; participants in the healthy control group were slightly younger. It should also be noted that whilst just one healthy control was left-handed with the others all being right-handed, of the patients with PD, 21 were right-handed, three were left-handed and two were ambidextrous according to the EHI.

11 of the patients in the PD group reported symptoms of OH, identified using the questions outlined in section 3.3.3; the healthy controls were all free from OH.

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS</th>
<th>HEALTHY CONTROLS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>16 (62)</td>
<td>15 (65)</td>
<td>1.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.3 (±11.4, 42-85)</td>
<td>59.9 (±11.0, 42-82)</td>
<td>0.052</td>
</tr>
<tr>
<td>Right-handed</td>
<td>21 (81)</td>
<td>22 (96)</td>
<td>0.19</td>
</tr>
<tr>
<td>Presence of OH</td>
<td>11 (42)</td>
<td>0 (0)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Table 4.1: Baseline characteristics of participants

Data specific to the PD group are detailed in table 4.2. Of note, seven of the 26 patients with PD did not complete the NMS-Questionnaire, meaning the value given
reflects data obtained from 19 of the patients. The majority of the patients (23) were H&Y stages 1 to 2.5; only two patients were H&Y stage 3, and just one patient was H&Y stage 4.

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (years)</td>
<td></td>
<td>3 (2-5.5, 0.3-13)</td>
<td></td>
</tr>
<tr>
<td>H&amp;Y Stage</td>
<td></td>
<td>1.5 (1-2.5, 1-4)</td>
<td></td>
</tr>
<tr>
<td>NMS-Quest Score</td>
<td>10 (9-14, 6-21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS</td>
<td>35 (±13.2, 12-64)</td>
<td>43.8 (±13.6, 21-76)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

Table 4.2: Baseline demographics of PD patients

4.3.2 Anti-Parkinsonian Medications

Not unexpectedly, there was marked variation in the types, and doses of anti-Parkinsonian medications being taken by those who participated in the study.

A summary is provided in table 4.3.

<table>
<thead>
<tr>
<th>MEDICATION REGIME</th>
<th>NO. OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levodopa only</td>
<td>7</td>
</tr>
<tr>
<td>Dopamine agonist only</td>
<td>4</td>
</tr>
<tr>
<td>Levodopa + dopamine agonist</td>
<td>5</td>
</tr>
<tr>
<td>Levodopa and MAOB inhibitor</td>
<td>1</td>
</tr>
<tr>
<td>Levodopa and Trihexyphenidyl</td>
<td>1</td>
</tr>
<tr>
<td>Levodopa and dopamine agonist and MAOB inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Levodopa and dopamine agonist and COMT inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>Levodopa and MAOB inhibitor and COMT inhibitor</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4.3: Anti-Parkinsonian medications of study participants
Just four patients were not taking any form of levodopa, and these were the patients who were being treated with dopamine agonists alone. Two of these patients were taking a dopamine agonist in the form of a transdermal patch, whilst the other two were taking long acting oral dopamine agonists. Where taken, the median daily dose of levodopa was 300mg (200-450mg, 150-600mg).

### 4.3.3 Baseline Peripheral Haemodynamic Data

Baseline peripheral haemodynamic data are detailed in table 4.4. No significant differences were observed in HR, SBP, DBP or MAP between PD patients and healthy controls, or between PD patients in their on and off states. A statistically significant difference was, however, observed between the EtCO$_2$ levels of PD patients in their off state and that of healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>p value</th>
<th>HEALTHY CONTROLS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (bpm)</strong></td>
<td>61 (±8, 46-79)</td>
<td>63 (±10, 46-91)</td>
<td>0.20</td>
<td>62 (±11, 38-78)</td>
<td>1.16</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>90.0 (±14, 58-121)</td>
<td>90.0 (±11, 66-114)</td>
<td>0.90</td>
<td>92.6 (±10, 75-120)</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>131 (±20, 90-179)</td>
<td>131 (±16, 98-173)</td>
<td>0.91</td>
<td>131 (±17, 110-188)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td>71 (±13, 42-98)</td>
<td>71 (±10, 52-92)</td>
<td>0.99</td>
<td>73 (±9, 53-96)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>EtCO$_2$ (mmHg)</strong></td>
<td>37 (34-39, 24-44)</td>
<td>37* (35-40, 16-44)</td>
<td>0.78</td>
<td>40* (38-41, 20-45)</td>
<td>5.03</td>
</tr>
</tbody>
</table>

Table 4.4: Baseline peripheral haemodynamic data of study participants

*p<0.05, Tukey's post-hoc analysis for the comparison between PD patients (OFF) and healthy controls
4.3.4 MCBFV, CrCP and RAP Data

The baseline MCBFVs of the right MCA and left MCA for PD patients in both states, and for healthy controls are shown in table 4.5, together with the mean CrCP and RAP for each side. The values of MCBFV obtained for PD patients were notably very similar for both the right and left MCAs, and in both the on and off states. However, all values of MCBFV obtained for PD patients were significantly lower than those obtained for healthy controls. Values of CrCP and RAP, however, were not statistically significant between PD patients and healthy controls, or between PD patients in the on and off states.

As Parkinson’s disease is a condition with laterality (the onset is classically unilateral, with typically persistent asymmetry affecting the side of onset most), MBFVs, CrCPs and RAPs are also presented as HEMISPHERE\textsubscript{ONSET} and HEMISPHERE\textsubscript{OTHER} in table 4.6. Of note, there has been no previous research in this field which details CBFV and autoregulation data by hemisphere of dominance, or by side of disease onset.

Importantly, no significant differences were identified between the side of disease onset and the other side in either the on or off states. Given this, subsequent values of phase, gain, coherence and ARI for PD patients are given as an average of the two hemispheres.
<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>p value</th>
<th>HEALTHY CONTROLS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F value</td>
</tr>
<tr>
<td>MBFV Right MCA</td>
<td>43.8 (±8.5)*</td>
<td>44.0 (±8.5)*</td>
<td>0.95</td>
<td>49.7 (±13.6)*</td>
<td>6.16</td>
</tr>
<tr>
<td>(cm/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBFV Left MCA</td>
<td>43.8 (±8.5)*</td>
<td>44.3 (±7.7)*</td>
<td>0.84</td>
<td>49.7 (±10.2)*</td>
<td>9.15</td>
</tr>
<tr>
<td>(cm/s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCP Right MCA</td>
<td>33.1 (±15.3)</td>
<td>31.2 (±13.3)</td>
<td>0.39</td>
<td>31.6 (±13.4)</td>
<td>0.66</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCP Left MCA</td>
<td>32.2 (±15.5)</td>
<td>31.1 (±14.6)</td>
<td>0.68</td>
<td>30.7 (±11.4)</td>
<td>0.66</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAP Right MCA</td>
<td>1.34 (±0.38)</td>
<td>1.39 (±0.42)</td>
<td>0.44</td>
<td>1.28 (±0.32)</td>
<td>1.10</td>
</tr>
<tr>
<td>(mmHg.s/cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAP Left MCA</td>
<td>1.35 (±0.34)</td>
<td>1.36 (±0.39)</td>
<td>0.69</td>
<td>1.27 (±0.25)</td>
<td>1.19</td>
</tr>
<tr>
<td>(mmHg.s/cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.5:** Baseline values of MBFV, CrCP and RAP for healthy controls and PD patients, detailed by side and by clinical state.

Values given are mean (±SD)

<table>
<thead>
<tr>
<th></th>
<th>MBFV HEMISPHERE_ONSET (cm/s)</th>
<th>MBFV HEMISPHERE_OTHER (cm/s)</th>
<th>ANOVA</th>
<th>CrCP HEMISPHERE_ONSET (mmHg)</th>
<th>CrCP HEMISPHERE_OTHER (mmHg)</th>
<th>ANOVA</th>
<th>RAP HEMISPHERE_ONSET (mmHg.s/cm)</th>
<th>RAP HEMISPHERE_OTHER (mmHg.s/cm)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD PATIENTS ON</td>
<td>43.7 (±9.0)</td>
<td>43.9 (±8.0)</td>
<td>F = 0.032</td>
<td>32.3 (±15.4)</td>
<td>33.0 (±15.5)</td>
<td>F = 0.48</td>
<td>1.4 (±0.4)</td>
<td>2.4 (±5.2)</td>
<td>F = 1.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p = 0.99</td>
<td></td>
<td></td>
<td>p = 0.70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD PATIENTS OFF</td>
<td>44.2 (±8.3)</td>
<td>44.2 (±7.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.6:** Baseline values of MBFV, CrCP and RAP for PD patients detailed by hemisphere of disease onset, and by clinical state. Values given are mean (±SD)
Averaged values of MCBFV are also detailed by age of subjects in table 4.7, to allow for comparison with those reported in the literature.

<table>
<thead>
<tr>
<th>Age</th>
<th>PD PATIENTS (ON) (cm/s)</th>
<th>PD PATIENTS (OFF) (cm/s)</th>
<th>HEALTHY CONTROLS (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 40-60</td>
<td>50.9 (±8.4)</td>
<td>50.1 (±5.9)</td>
<td>52.1 (±11.5)</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>42.0 (±7.2)</td>
<td>42.3 (±7.4)</td>
<td>47.3 (±11.6)</td>
</tr>
</tbody>
</table>

*Table 4.7: MCBFV denoted by ages of participants. Values given are mean (±SD)*

### 4.3.5 Frequency Domain Parameters

Scrutiny of the data according to the quality criteria detailed in section 4.2.2 led to the exclusion of 24 recordings from healthy controls, 20 recordings from patients in the on state and 29 recordings from patients in the off state. These recordings were distributed at random between subjects, and between sides of recording (left and right). This left a total of 68 recordings for healthy controls, 76 recordings from PD patients in the on state, and 67 recordings from PD patients in the off state from which to obtain frequency domain data and ARI values.

The frequency domain parameters coherence, gain and phase, obtained for healthy controls and PD patients are detailed by frequency range in table 4.8, and are shown graphically as overall means in figures 4.3 to 4.5.
<table>
<thead>
<tr>
<th>Frequency Range</th>
<th>MEAN COHERENCE</th>
<th>MEAN GAIN (%/%)</th>
<th>MEAN PHASE (Radians)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LF range</td>
<td>MF range</td>
<td>HF range</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>0.57 (±0.12)</td>
<td>0.69 (±0.14)</td>
<td>0.62 (±0.15)</td>
</tr>
<tr>
<td>PD patients ON</td>
<td>0.47 (±0.16)</td>
<td>0.60 (±0.19)</td>
<td>0.74 (±0.17)</td>
</tr>
<tr>
<td>PD patients OFF</td>
<td>0.45 (±0.14)</td>
<td>0.58 (±0.17)</td>
<td>0.69 (±0.19)</td>
</tr>
</tbody>
</table>

ANOVA: F 12.72, p <0.001

Table 4.8: Mean frequency domain parameters for healthy controls and PD patients, detailed by frequency range

Values given are mean (±SD)
Figure 4.3: Mean coherence function for PD patients and healthy controls

Figure 4.4: Mean transfer function amplitude (gain) frequency response
With the notable exception of gain in the low frequency, and phase in the high frequency, ANOVA suggested statistically significant differences between PD patients and healthy controls for most frequency parameters, at the majority of frequency ranges. A post-hoc analysis was therefore conducted (table 4.9) which revealed several key findings. Firstly, no significant difference was seen for any frequency parameter at any range between PD patients in the on and off states. Secondly, whilst there are differences between PD patients and healthy controls, the difference appears to be most marked for comparisons involving healthy controls and PD patients in the off state. Importantly, the values of phase should be interpreted cautiously as negative results should theoretically not be possible, and have only occurred because of ‘wrap-around’. This is exhibited when the value of phase is greater than π radians, and the signal ‘wraps around’ the y-axis, and is therefore estimated as a negative value giving a false result.
<table>
<thead>
<tr>
<th>FREQUENCY DOMAIN PARAMETER</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COHERENCE</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Low Frequency</strong></td>
<td></td>
</tr>
<tr>
<td>PD patients ON and OFF</td>
<td>0.59</td>
</tr>
<tr>
<td>PD patients ON and healthy controls</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PD patients OFF and healthy controls</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Middle Frequency</strong></td>
<td></td>
</tr>
<tr>
<td>PD patients ON and OFF</td>
<td>0.47</td>
</tr>
<tr>
<td>PD patients ON and healthy controls</td>
<td>0.03</td>
</tr>
<tr>
<td>PD patients OFF and healthy controls</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>High Frequency</strong></td>
<td></td>
</tr>
<tr>
<td>PD patients ON and OFF</td>
<td>0.33</td>
</tr>
<tr>
<td>PD patients ON and healthy controls</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PD patients OFF and healthy controls</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>GAIN</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Middle Frequency</strong></td>
<td></td>
</tr>
<tr>
<td>PD patients ON and OFF</td>
<td>0.49</td>
</tr>
<tr>
<td>PD patients ON and healthy controls</td>
<td>0.08</td>
</tr>
<tr>
<td>PD patients OFF and healthy controls</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>High Frequency</strong></td>
<td></td>
</tr>
<tr>
<td>PD patients ON and OFF</td>
<td>0.84</td>
</tr>
<tr>
<td>PD patients ON and healthy controls</td>
<td>0.006</td>
</tr>
<tr>
<td>PD patients OFF and healthy controls</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PHASE</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Low Frequency</strong></td>
<td></td>
</tr>
<tr>
<td>PD patients ON and OFF</td>
<td>0.07</td>
</tr>
<tr>
<td>PD patients ON and healthy controls</td>
<td>0.81</td>
</tr>
<tr>
<td>PD patients OFF and healthy controls</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Middle Frequency</strong></td>
<td></td>
</tr>
<tr>
<td>PD patients ON and OFF</td>
<td>0.80</td>
</tr>
<tr>
<td>PD patients ON and healthy controls</td>
<td>0.002</td>
</tr>
<tr>
<td>PD patients OFF and healthy controls</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 4.9:** Tukey’s post-hoc analysis of frequency domain parameters
4.3.6 ARI Values

The ARI values, obtained using the ‘best fit’ least squares method of matching CBFV step responses to one of the 10 model ARI curves proposed by Tiecks (Section 1.3.5), are detailed for PD patients in each state and for healthy controls in table 4.10. Of note, the values obtained were not normally distributed in any group and are therefore listed as median (IQR, range). A Kruskall-Wallis test revealed statistically significant relationships, and the post-hoc analysis is detailed in table 4.11. Most notably, the values obtained for PD patients in each state were significantly different to those obtained for healthy controls with the result being most dramatic for PD patients in the off state (p = <0.0001). The difference in ARI values between the on and off states for PD patients was borderline significant.

<table>
<thead>
<tr>
<th></th>
<th>PD patients ON</th>
<th>PD patients OFF</th>
<th>HEALTHY CONTROLS</th>
<th>KRUSKALL-WALLIS TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARI</strong></td>
<td>5.1 (4.0-6.4, 2.6-8.0)</td>
<td>4.9 (3.2-5.8, 0-7.3)</td>
<td>6.0 (4.8-6.8, 3.2-7.6)</td>
<td>Chi-Square = 15.25881</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>df = 2 p = 0.005</td>
</tr>
</tbody>
</table>

Table 4.10: ARI values for PD patients in each clinical state and healthy controls

<table>
<thead>
<tr>
<th>ARI COMPARISON</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD patients ON and OFF</td>
<td>0.059*</td>
</tr>
<tr>
<td>PD patients ON and healthy controls</td>
<td>0.005*</td>
</tr>
<tr>
<td>PD patients OFF and healthy controls</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Table 4.11: Post-hoc analysis of ARI values obtained for PD patients in each clinical state and healthy controls. *Wilcoxon Signed Rank Test. *Mann-Whitney U Test
4.3.7 The Influence of Disease Stage

In order to evaluate whether patients with early stage, unilateral, disease (H&Y stages 0-1.5) have different ARI values to those with later stage, bilateral disease (H&Y stage ≥ 2), the PD cohort was divided into these groups, and comparisons made between both groups, in both clinical states and with healthy controls. Each group contained 13 subjects. Mean age of those in the early stage group was 65.3 (±10.5, 42-81), and in the later stage group was 67.5 (±12.3, 42-85), p = 0.59. The early stage group contained 7 males, and the later group contained 9 males, p = 0.69. Interestingly, statistical analysis revealed that there are no significant differences in ARI values between patients with early stage disease and those with later disease. However, significant differences were again seen for all PD patients when compared to healthy controls, irrespective of disease stage. These differences were once again most striking for comparisons made between healthy controls and PD patients in their off state. Median ARI values for the disease stage groups, with their respective IQRs and ranges are shown in table 4.12, with the subsequent post-hoc analysis detailed in table 4.13.

4.3.8 The Influence of Orthostatic Hypotension

In order to evaluate whether PD patients with a history of OH have lower ARI values than those without such a history, the cohort was divided into such groups and comparisons made between them, in both clinical states and with healthy controls. To be included in the OH cohort, patients needed to have responded affirmatively to the
questions asked in section 3.3.3. There were 11 subjects with OH, and 15 without. In the OH group, 3 of the patients were female, and in the non-OH group 7 were female, \( p = 0.43 \). Mean age of those in the OH group was 66.5 (±8.8, 53\-81) and in the non-OH group was 66.2 (±13.8, 42\-85), \( p = 0.96 \). Median ARI values for the orthostatic hypotension groups are shown in table 4.14.

There was no significant difference in ARI values between patients with and without a history of OH in the clinically on state, but there notably was in the clinical off state. With the exception of the comparison of PD patients without OH in their on state and healthy controls, statistically significant differences were seen for all comparisons between healthy controls and PD patients. The difference was once again most marked for patients in the off state, most dramatically in this analysis for those patients with a history of OH. The full post hoc analysis is detailed in table 4.15.
Table 4.12: Median ARI values detailed for PD patients by disease stage

<table>
<thead>
<tr>
<th>ARI COMPARISON</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD patients ON H&amp;Y stage 0-1.5 and PD patients ON H&amp;Y stage ≥2</td>
<td>0.81</td>
</tr>
<tr>
<td>PD patients OFF H&amp;Y stage 0-1.5 and PD patients OFF stage ≥2</td>
<td>0.68</td>
</tr>
<tr>
<td>PD patients ON H&amp;Y stage 0-1.5 and healthy controls</td>
<td>0.011</td>
</tr>
<tr>
<td>PD patients OFF H&amp;Y stage 0-1.5 and healthy controls</td>
<td>0.0001</td>
</tr>
<tr>
<td>PD patients ON H&amp;Y stage ≥2 and healthy controls</td>
<td>0.038</td>
</tr>
<tr>
<td>PD patients OFF H&amp;Y stage ≥2 and healthy controls</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 4.13: Post-hoc analysis of ARI values for PD patients at different disease stages
* Mann-Whitney U Test

Table 4.12: Median ARI values detailed for PD patients by disease stage

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS WITH H&amp;Y STAGE ≥2</th>
<th>PD PATIENTS WITH H&amp;Y STAGE 0-1.5</th>
<th>HEALTHY CONTROLS</th>
<th>KRUSKALL-WALLIS TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 13</td>
<td>n = 13</td>
<td>n = 23</td>
<td></td>
</tr>
<tr>
<td>ARI</td>
<td>5.5 (3.1-6.7, 2.6-7.5)</td>
<td>4.8 (2.9-5.9, 0.7-3)</td>
<td>4.9 (3.8-5.4, 2.0-7.1)</td>
<td>6.0 (4.8-6.8, 3.2-7.6)</td>
</tr>
<tr>
<td></td>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td></td>
<td>5.5 (3.1-6.7, 2.6-7.5)</td>
<td>4.8 (2.9-5.9, 0.7-3)</td>
<td>4.9 (3.8-5.4, 2.0-7.1)</td>
<td>6.0 (4.8-6.8, 3.2-7.6)</td>
</tr>
</tbody>
</table>

Chi-Square = 16.137
df = 4   p = 0.0028
<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS WITH OH</th>
<th>PD PATIENTS WITHOUT OH</th>
<th>HEALTHY CONTROLS</th>
<th>KRUSKAL-WALLIS TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 11</td>
<td>n = 15</td>
<td>n = 23</td>
<td></td>
</tr>
<tr>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
<td>OFF</td>
<td></td>
</tr>
<tr>
<td>ARI</td>
<td>4.8 (4.1-6.0, 2.6-7.4)</td>
<td>5.3 (3.8-6.8, 2.6-8.0)</td>
<td>5.2 (3.5-6.2, 0-7.3)</td>
<td>6.0 (4.8-6.8, 3.2-7.6)</td>
</tr>
<tr>
<td></td>
<td>4.1 (3.2-5.0, 0-6.6)</td>
<td>5.2 (3.5-6.2, 0-7.3)</td>
<td></td>
<td>df = 4 p = 0.0004</td>
</tr>
</tbody>
</table>

**Table 4.14:** Median ARI values detailed for PD patients with and without a history of OH

<table>
<thead>
<tr>
<th>ARI COMPARISON</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD patients ON with OH PD patients ON without OH</td>
<td>0.60</td>
</tr>
<tr>
<td>PD patients OFF with OH and PD patients OFF without OH</td>
<td>0.02</td>
</tr>
<tr>
<td>PD patients ON with OH and healthy controls</td>
<td>0.005</td>
</tr>
<tr>
<td>PD patients OFF with OH and healthy controls</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>PD patients ON without OH and healthy controls</td>
<td>0.06</td>
</tr>
<tr>
<td>PD patients OFF without OH and healthy controls</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Table 4.15:** Post-hoc analysis of ARI values for PD patients with and without a history of OH

* Mann-Whitney U Test
4.4 DISCUSSION

This is the first study which has reported CA in PD in terms of an ARI, and is only the second to have used spontaneous fluctuations in BP as an input stimulus for CA evaluation. It is also one of just very few studies to have assessed CA in both the on and off states of the disease. The data obtained appear to show several novel and key findings.

Firstly, whilst values of HR, MAP, SBP and DBP did not differ significantly between healthy controls and PD patients, the values of MCBFV obtained for Parkinsonian patients in this study were consistently and significantly lower than those obtained for healthy controls, regardless of whether patients were scanned in their on or off state. Importantly, whilst the values of MCBFV obtained for both PD patients and healthy controls in this study were notably lower than the mean reference values quoted in the literature, they were certainly well within the reported, and accepted, ranges.

That MCBFV is lower in patients with PD is largely in disagreement with the existing literature; the majority of previously published TCD studies in patients with PD have concluded that resting MCBFV is not significantly different between PD patients and healthy controls. Indeed, just two studies\textsuperscript{134,135} have reported a similar finding to that discovered here, and in one of those studies\textsuperscript{134} a difference in MCBFV was only observed in those patients with symptomatic OH. That resting MCBFV is lower in PD patients than in healthy controls may help to explain the high rates of symptomatic OH in PD patients, although precisely why MCBFV should be lower is unclear. Whilst age is known to decrease CBFV,\textsuperscript{181} the patients and healthy controls in this study were age-matched. Furthermore, it is important to reiterate that, in this study, it was only
values of MCBFV which were lower in PD patients; values of MAP and SBP were not, indicating that the finding cannot simply be explained by lower BP. Previous work has suggested that MCBFV in PD patients is not related to age, disease duration, gender or age at disease onset. However, there has been limited research in this field.

The isolated finding that PD patients in their off state had a lower EtCO$_2$ is a little surprising and difficult to explain; it is possible that due to heightened anxiety in their off states, patients were mildly hyperventilating, although importantly the mean values of EtCO$_2$ were the same at both their visits. Further scrutiny of individual patient data suggests that there was an outlying result, with a single patient having an extremely low EtCO$_2$ in his off state, presumed due to anxiety and hyperventilation. When his data are removed, statistical significance disappears, suggesting that, ultimately, this finding may simply be a spurious, and irrelevant, result.

The finding that values of MCBFV, CrCP and RAP do not differ by brain hemisphere (whether left or right, or by disease onset hemisphere and other hemisphere) is important, and provides yet more evidence for PD being a multi-system disorder. Certainly, the results would suggest that if it were only possible to obtain unilateral TCD data, then important conclusions could still be drawn.

The finding that values of CrCP and RAP do not differ significantly between PD patients and healthy controls is especially important, as it is strongly suggestive that the myogenic mechanisms of CA are not altered in PD. If the myogenic mechanisms are intact, then it is likely to be either the metabolic and/or the neurogenic mechanisms which are altered or impaired. Given that there is now emerging evidence that areas of the brain such as the raphe nucleus the locus coeruleus and nucleus basalis play an
important role in the neurogenic control of CA, areas known to degenerate in PD, it appears reasonable to hypothesise that it may well be the neurogenic mechanism which is altered in PD patients.

The dCA indices obtained in this study provide some of the most exciting data. There is a suggestion here that there is a trend for CA indices to be a little better in the on state of the disease than the off (although not statistically significantly so). The differences in values of phase at the LF particularly seem to suggest a very strong effect of the off state. However, it is the difference in CA indices between PD patients and healthy controls which is most striking, a difference which is most apparent when comparing healthy controls to PD patients in their off states. From the frequency domain parameters, we can see that coherence is generally higher in healthy controls, gain is lower (suggesting a poorer relationship between CBFV and BP in PD patients) and phase is higher in healthy controls than in PD patients. The ARI values obtained from fitting step responses to spontaneous fluctuations in BP with Tieck’s model curves represent the first time that CA in PD has been described in this way, and are perhaps the strongest indication that CA is different in patients with PD to healthy controls. That a lower ARI value was seen in PD patients in their off state compared to healthy controls, even in the presence of relative hypocapnia (a state known to improve CA) suggests that the observed results here are genuine.

The absence of a significant difference in CA indices between the on and off states of the disease is in strong agreement with all three previous studies which have attempted to evaluate CA in patients both on and off their medications.
The lack of a difference in ARI values between patients at different disease stages suggests that any alteration in CA is likely to appear early in the disease process and persist.

That ARI values vary between patients with and without a history of OH in their off states, and do not vary between PD patients without a history of OH in their on state and healthy controls has implications for using CA to better understand PD phenotype. Importantly, whilst it appears possible to state that CA is different in PD patients and healthy controls, it is perhaps not justified to state that CA is impaired in PD. However, the trend for ARI values to be higher in healthy controls, and for the values to be slightly better in the on state is exciting, and would lend support for the experimental evidence that dopamine plays a key role in the neurogenic regulation of the cerebral microcirculation.\textsuperscript{76,77,182}

4.5 LIMITATIONS

It is important to acknowledge several key limitations to this study. As stated in Chapter 1, the measurement of TCD assumes constant diameter of the insonated vessel. Whilst this assumption has been found to be valid in various studies,\textsuperscript{183,184} it remains possible that the larger cerebral vessels do, in fact, change diameter, and as such, any TCD data should be openly interpreted with this possibility in mind. Additionally, it is important to note that TCD is considered to be very operator dependent. Marked inter-operator differences have been described and error rates of as much as 15 - 30% have been reported.\textsuperscript{185} However, it is thought that the error rate
is reduced by continuous transcranial Doppler measurement techniques,\textsuperscript{186,187} and, interestingly, there is also evidence that intra-operator reproducibility is much better than inter-operator reproducibility, regardless of level of experience.\textsuperscript{188} In this study, all subjects were scanned by one operator (the author) who attended an intensive TCD training course, and who spent a significant period of time observing, and receiving training from, other experienced operators. Variation between recordings for PD patients obtained in the on and off states (notably obtained on separate days, up to two weeks apart) was limited as much as possible by carefully documenting TCD depth and power and ensuring that these were the same at each visit.

The sample size in this study warrants consideration. Whilst this is the largest study to date of CA in PD in both the on and off states, it was reported in 2009 that at least 45 subjects are needed in a group to show a difference in the ARI of 1 unit, with 80\% power at the 5\% level,\textsuperscript{93} suggesting that the study is ultimately underpowered. Reasons for the small sample size are multifold. Firstly, recruitment to the study was difficult; not only were patients understandably apprehensive about the need to temporarily stop their anti-Parkinsonian medications, but the stringent exclusion criteria also prevented a significant number of interested patients from taking part. In this regard, peripheral neuropathy was a surprisingly frequent problem, although there is recent, and increasing, evidence that patients with PD have a higher incidence of peripheral neuropathy.\textsuperscript{189-191} Secondly, the inability to obtain data from 11 subjects (eight PD patients and 3 healthy volunteers) because of poor temporal insonation windows was disappointing. However, this rate of window failure is in keeping with other studies which have demonstrated window failure rates of 5-37\%.\textsuperscript{192-194} Female gender and increasing age are felt to be the strongest predictors of window failure.\textsuperscript{195}
and notably eight of the subjects with window failure in this study were female. The need to reject data recordings during the frequency domain analysis was also disappointing, but vital in preserving data quality.

It is disappointing that seven of the patients did not complete the NMS-Quest. ‘Questionnaire fatigue’ by the participants was felt to be the main cause for this, particularly as the patients completed this questionnaire in their clinically off state. The data obtained from the NMS-Quest were of limited use and, were this study to be repeated, it is therefore likely that this questionnaire would be omitted from the protocol.

Whilst the study’s exclusion criteria were generally felt to be robust, it is important to note that subjects were not screened for carotid stenosis, a condition known to affect CA.\textsuperscript{125} The main reasons for this were that the researcher was not trained in carotid ultrasound, and that the study TCD machine could not be used to image carotid arteries for this purpose. It would therefore have been necessary for the participant to attend for a separate hospital appointment with another department. Ultimately, the study budget did not allow for this, although the research team also felt that multiple appointments and scans would have been quite onerous for participants. It is therefore possible that subjects included in this study had an unknown and asymptomatic carotid stenosis, with the potential to confound results. Were this study to be repeated, carotid stenosis would be made an exclusion criteria and screening for carotid stenosis would certainly be undertaken.

With regard to certainty of PD diagnosis, it should be noted that just four of the PD patients in this study had been investigated with functional imaging of striatal
dopamine terminal function at diagnosis, the rest all having been diagnosed clinically. However, all patients were under the care of either a geriatrician or a neurologist with a specialist interest in movement disorders, and all met the UK brain bank criteria for a diagnosis of idiopathic PD. Furthermore, the author, a geriatric trainee with a specialist interest in movement disorders, examined patients carefully during the study and did not observe any unusual features to support alternative diagnoses.

It is important to note that clinic-based recruitment of PD patients was initially facilitated through the geriatric service only, and that recruitment from the neurology service did not occur until later in the study. This may mean that a less representative sample of PD patients was obtained for the study. However, as recruitment was also facilitated through Parkinson’s UK, sample bias is ultimately felt to be unlikely.

With further regard to PD patients, the majority of patients were H&Y stage 1-2.5, with a lack of representation from patients at later H&Y stages. It is likely that the study design (the need to attend a hospital laboratory on two separate occasions, to be free from dementia and to be able to temporarily stop anti-Parkinsonian medications) led to the relative exclusion of patients at later disease stages as, by definition, these are patients who are frailer, more physically dependent and more likely to be suffering with dementia. Nonetheless, the lack of patients with late stage disease is an important consideration when interpreting the study’s results.

The marked heterogeneity in medication type, and dose, being taken by the patients in the PD group is another important point for consideration. It is possible that different anti-Parkinsonian medications produce different effects on CA, with the subsequent implication that PD patient’s on states are not comparable. At the present time there
has been no research evaluating the effects of different types of anti-Parkinsonian medications on cerebral autoregulation. However, it appears reasonable to hypothesise that drugs which replace dopamine may produce different effects to dopamine mimics or drugs which stimulate dopamine release, and that, in turn, dopaminergic medications may produce very different effects to non-dopaminergic anti-Parkinsonian drugs (e.g. antimuscarinics). Unfortunately, sample size was too small to allow for sub-group analysis to explore this further. However, it is important to consider that this situation very much reflects real-life practice where PD patients take a variety of different medications, at different doses and at different times of the day. Ultimately, the comparison here was between dopamine replete, and dopamine deficient, states.

As a final limitation, it should be stated that the author was not blinded when analysing data files, raising the possibility of bias. However, each data file was processed in the same way and was subjected to the same analysis software, with predetermined criteria for rejection or inclusion. Bias was ultimately felt to be unlikely.

4.6 SUMMARY

This study of dynamic CA in patients with PD, studied in both the on and off states and compared to healthy matched controls has demonstrated that patients with PD have lower resting MCBFVs than healthy controls, an effect which appears to be independent of clinical state, BP or MAP. Laterality does not appear to be a factor in the assessment of CA in PD; values of MBFV, RAP and CrCP are extremely similar
between brain hemispheres, suggesting once again that PD is a multi-system disorder. This study has also demonstrated that whilst dCA indices do not differ significantly between the on and off states of PD, indices are significantly different between PD patients and healthy controls, ultimately suggesting that CA is altered, but not necessarily impaired, in idiopathic PD.
CHAPTER 5 NEUROVASCULAR COUPLING IN IDIOPATHIC PARKINSON’S DISEASE

“The arms, the first parts manifesting disordered action, of course direct us”.

James Parkinson, 1817

5.1 INTRODUCTION

CBF is directly linked to cerebral activity, a concept known as ‘neurovascular coupling’ (NVC). Although the exact mechanisms of NVC continue to be explored and evaluated, it is thought that cerebral activation triggers a haemodynamic response involving neurons, astrocytes, vascular cells and local metabolites. The close spatial and temporal relationship between CBF and cerebral activity means that the CBF response to neural activation paradigms can be used as an index of neuronal activity and metabolism, providing further information about cerebral haemodynamics. Whilst cerebral activation can be achieved through various cognitive activities such as speaking, visual stimulation, and/or by sensorimotor tasks, given that PD is a movement disorder, it is perhaps the CBF response to motor activation which is of the most interest. Although there have been a number of PET and f-MRI studies evaluating CBF responses to cerebral activation in PD, there has been a relative paucity of TCD studies; just three in total, only one of which used a motor paradigm to induce cerebral activation. This study therefore aimed to use TCD to evaluate CBF responses to motor induced cerebral activation in a cohort of patients with PD, in both
their clinically on and off states, and in an age and sex matched cohort of healthy controls.

5.2 METHODS

5.2.1 Protocol

Subjects were recruited to the study, and data collected, as described previously in Chapter 3. In this analysis, the motor paradigm, which was the last of the TCD recordings made at each visit, was used for the evaluation of CBF responses. In brief, cerebral activation was induced by repetitive passive flexion and extension of the upper limb at the elbow of the dominant arm for one minute. The elbow excursion range was ~ 90° and the movements were driven by an electronic metronome to ensure a constant frequency of 1Hz. The paradigm was preceded, and concluded, by 90 second baseline periods of rest. Passive arm movement was selected as the motor activation task based on its previously reported reproducibility in healthy older volunteers.\textsuperscript{102} Whilst the use of an active movement paradigm was contemplated, it was felt that the responses of PD patients, particularly in their clinically off states, had the potential to be sufficiently variable to prevent meaningful comparisons.

5.2.2 Data Analysis

Raw data were edited using the method detailed in section 3.5. After the signals had been calculated with a uniform time-base, averages were performed for each variable
synchronised from the beginning of the paradigm. The beginning of the paradigm was identified by using the electrical signal from the metronome. Values were normalised in percent by their baseline values, and population coherent averages were obtained for each time sample value.

In order that the CBFV and BP responses to motor activation during the paradigm could be compared between groups, CBFV changes were further averaged for the specific period relating to passive movement and greatest change in CBFV (see figure 5.7). Once again, as PD is a condition with laterality, the CBFV data are detailed by disease onset hemisphere, and other hemisphere, rather than simply by right and left sides as for healthy controls.

Baseline values of MCBFV, HR, ABP and EtCO₂, were obtained from the 60 seconds preceding the motor paradigm.

5.2.3 Statistics

Data were collated in Microsoft Excel 2010 and analysed using Statistica version 8. Categorical data are presented as absolute numbers and percentages. Continuous data were plotted and assessed for normality using the Shapiro-Wilk test; normally distributed values are reported as mean (±standard deviation (SD)) and non-normal data are presented as median (inter-quartile range (IQR), range). Baseline demographic data between PD patients and healthy controls were compared using a Student’s t-test for independent samples and Fisher’s exact test for nominal data.
Baseline UPDRS scores for PD patients in their on and off states were compared using the Wilcoxon signed rank test.

ANOVA was used to compare baseline values of mean HR, ABP and EtCO₂ for PD patients in each clinical state and healthy controls. A two-way ANOVA was used to compare MCBFVs for each side of recording in both the on and off states; clinical state was used as the between factor, and side of recording (disease onset hemisphere, other hemisphere) as the within factor. ANOVA was also used to compare averaged CBFV, BP and HR values for the intra-manoeuvre time period. Post-hoc comparisons (Tukey’s test) were performed when appropriate. The significance level was set at p<0.05.

5.3 RESULTS

5.3.1 Baseline Demographics

A total of 35 patients with idiopathic PD were recruited to the study and attended for TCD measurements, eight of whom were subsequently excluded because of inadequate transtemporal insonation windows. In this analysis, it was unfortunately necessary to exclude the data obtained from three patients because of multiple ectopic beats which occurred during the recordings, and from one further patient because the motor paradigm resulted in significant artefact and noise in the recordings. Additionally, one patient (male aged 59, disease duration 2.5 years) was, by his own choice, not receiving any treatment for his PD and was therefore only scanned once in his ‘off’ state. A second patient (female aged 66, disease duration two
years) withdrew from the study after attending for her ‘on’ scan due to apprehension regarding the temporary cessation of medication required for the ‘off’ scan, meaning that she was only scanned once, in her ‘on’ state. These two patients were also excluded from paired analyses, meaning 21 paired (on and off) recordings were available for evaluation in the patient group. Please refer to Appendix 13 for a pictorial summary of patient inclusion in this study.

Again, as before, 28 volunteers were also recruited to the study, three of whom were subsequently excluded because of inadequate trans-temporal insonation windows. In this analysis, it was unfortunately necessary to exclude data collected from six of the remaining volunteers because of poor signal quality and noise, leaving data from 19 healthy controls.

The baseline characteristics of PD patients and healthy controls included in this study are detailed in tables 5.1 and 5.2. Importantly, there were no significant differences between the control group and PD group in terms of age or gender.

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS</th>
<th>HEALTHY CONTROLS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender n (%)</td>
<td>14 (66)</td>
<td>11 (58)</td>
<td>0.75</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (±11.3, 42-81)</td>
<td>60 (±11.1, 42-82)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Table 5.1: Baseline demographics of PD patients and healthy controls in the NVC study*

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (years)</td>
<td></td>
<td>3 (2-6, 0.3-13)</td>
<td></td>
</tr>
<tr>
<td>H&amp;Y Stage</td>
<td></td>
<td>1.5 (1-2.5, 1-4)</td>
<td></td>
</tr>
<tr>
<td>UPDRS</td>
<td>34 (25-42, 12-64)</td>
<td>42 (34-56, 21-76)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Table 5.2: PD specific baseline data for patients in the NVC study*
5.3.2 Baseline Peripheral Haemodynamic Data

Baseline peripheral haemodynamic data are reported in table 5.3. No significant differences were observed in values of HR, ABP or EtCO₂ between PD patients in either state, or between PD patients in either state and healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>HEALTHY CONTROLS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>59.2 (±7.6)</td>
<td>61.0 (±9.8)</td>
<td>62.4 (±11.9)</td>
<td>0.469</td>
</tr>
<tr>
<td>ABP (mmHg)</td>
<td>93.7 (±15.3)</td>
<td>92.2 (±11.0)</td>
<td>93.3 (±12.3)</td>
<td>0.062</td>
</tr>
<tr>
<td>EtCO₂ (mmHg)</td>
<td>36.1 (±5.3)</td>
<td>35.5 (±7.7)</td>
<td>37.7 (±5.4)</td>
<td>0.917</td>
</tr>
</tbody>
</table>

Table 5.3: Baseline peripheral haemodynamic data for PD patients and healthy controls in the NVC study. Values given are mean (±SD)

Baseline values of MCBFV are detailed in table 5.4. No significant difference was observed between the MCBFVs of the hemisphere of disease onset and the other hemisphere for PD patients, or between PD patients in their on and off states. Values of MCBFV were a little higher in healthy controls than in PD patients, but the difference was not statistically significant. Importantly, right and left measurements were obtained at the same time.
<table>
<thead>
<tr>
<th>PD PATIENTS ON</th>
<th>PD PATIENTS OFF</th>
<th>HEALTHY CONTROLS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset Hemisphere</td>
<td>Other Hemisphere</td>
<td>Onset Hemisphere</td>
<td>Other Hemisphere</td>
</tr>
<tr>
<td>45.2 (±9.23)</td>
<td>45.9 (±9.5)</td>
<td>44.7 (±9.5)</td>
<td>45.3 (±9.5)</td>
</tr>
</tbody>
</table>

**Table 5.4:** Baseline values of MCBFV in cm/s, detailed by right and left sides for healthy controls, and by disease onset hemisphere for PD patients. Values given are mean (±SD)

### 5.3.4 CBFV Responses

Passive arm movement resulted in an increase in MCBFV bilaterally in all subjects, with a steep bilateral increase occurring approximately five seconds after the beginning of the task which appeared to peak a further 15 seconds later. A small spike in CBFV was actually seen 30s before the commencement of the motor paradigm – this was likely caused by the researcher taking hold of the subjects’ hand in preparation for the paradigm, as this notably occurred at that time point. This spike in CBFV was most pronounced in the PD off group. The CBFV responses are best seen graphically, and are therefore shown in figures 5.1 – 5.7. Visually, the plots indicated that the magnitude of the increase in MCBFV was greatest in healthy controls, and lowest in PD patients in the on state; a 13% maximal increase in CBFV was seen in healthy controls, a 12% increase in PD patients in their off state and a 10% increase in PD patients in their on state. Furthermore, the plots also suggested that whilst healthy controls maintained the increase in CBFV for the duration of the exercise, CBFV in patients with PD showed a trend to decline, with an apparently faster return to baseline levels. Interestingly, this effect appeared more evident for PD patients in their on state.
However, ANOVA analysis revealed no statistically significant differences in the intra-manoeuvre CBFV responses of PD patients and healthy controls (ANOVA F = 0.76, p = 0.58). Furthermore, there were no statistically significant interhemispheric differences observed for healthy controls or for PD patients – the brain hemisphere of disease onset notably behaving remarkably similarly to the other hemisphere.

Figure 5.1: CBFV responses to passive arm movement of healthy controls
Figure 5.2: CBFV responses to passive arm movement of PD patients in the on state

Figure 5.3: CBFV responses to passive arm movement of PD patients in the off state
Figure 5.4: CBFV responses to passive arm movement of PD patients in the on and off states

Figure 5.5: CBFV responses to passive arm movement of healthy controls and PD patients in the on state
Figure 5.6: CBFV responses to passive arm movement of healthy controls and PD patients in the off state.

Figure 5.7: CBFV responses to passive arm movement of healthy controls and PD patients in both states. The solid grey bar indicates the period of passive arm movement, and the solid black bar indicates the time period where the CBFV responses were averaged for statistical analysis.
5.3.5 BP Response

The temporal BP response during the motor paradigm is shown in figure 5.8. Whilst ABP increased in all subjects during the paradigm, the magnitude of change was similar in all groups and statistical testing did not reveal any significant difference between BP responses of PD patients in either clinical state, and healthy controls (ANOVA F = 0.25, p = 0.78).

Figure 5.8: BP response of subjects during the motor paradigm

5.3.6 HR Response

As with the BP response, whilst HR appeared to increase intra-paradigm, there were no significant differences between the HR responses of PD patients and healthy controls (ANOVA F= 1.99, p = 0.15). These are shown for each group in figure 5.9.
5.4 DISCUSSION

This study has shown that CBFV, BP and HR responses to cerebral activation induced by a motor paradigm are not statistically different in patients with PD to those of healthy controls. The lack of an observed difference in CBFV responses in particular would appear to suggest that NVC is not impaired in idiopathic PD. This finding is notably in agreement with all three of the previously published studies which have assessed NVC in PD using TCD.\textsuperscript{101,138,139} However, when comparing the TCD studies of NVC, it is important to note that only one of these studies had used a motor paradigm to induce cerebral activation, the other two\textsuperscript{101,138} having used visual evoked paradigms to assess posterior cerebral artery CBFV responses. In one of these studies,\textsuperscript{138} the visual evoked paradigm consisted of a modified checkerboard test in which the participants focused on a spot in the centre of a 21” computer monitor whilst black and white, emotionally neutral, pictures were alternately flashed on the screen with

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.9.png}
\caption{HR response of subjects during the motor paradigm}
\end{figure}
their negatives to induce contrast-based visually evoked responses. The stimulation protocol consisted of 10 cycles, each with a resting phase of 20 seconds with eyes closed and a stimulation phase of 40 seconds. In the other study, the visual evoked paradigm again consisted of 10 cycles with a resting phase of 20 seconds with eyes closed and a stimulating phase of 40 seconds. However, the visual stimulation in this study came from silent reading of a hand-held paper news magazine. In both studies, changes between resting and stimulation phases were signalled acoustically using a tone.

Direct comparisons between this study and the visually evoked studies should therefore be made with a degree of caution, as the methods of neuro-activation are very different. The study which did use a motor paradigm, that of Troisi et al, used a sequential thumb-to-finger opposition task, performed with each hand simultaneously at a rate of two oppositions every three seconds. In their study of 12 PD patients and 12 healthy controls, they found that the group effects of mean values of flow velocity change associated with the paradigm were not significant. As in this study, they again found that motor activity increased ABP and HR slightly with respect to the rest condition, but that the size of the increase was comparable in controls and in PD patients.

Despite the negative studies so far, after a review of the wider literature, it appears reasonable to continue to hypothesise that NVC may indeed be altered or impaired in PD. Certainly, there is emerging evidence that disruption to the neurovascular unit can be found in other neurodegenerative diseases such as Alzheimer’s dementia. Furthermore, a 2011 study by Sorond et al demonstrated that NVC may be involved
in compensatory mechanisms responsible for preservation of gait speed in elderly people. In their study, 22 fast walkers (≥0.67m/s) and 20 slow walkers (<0.67m/s) had their NVC assessed by means of TCD and a cognitive task. The study demonstrated that NVC was attenuated in subjects with slow gait speed, and that intact NVC mechanisms were associated with fast gait speed, even in individuals with a high burden of white matter hyperintensities and small vessel cerebral vascular disease. This study is of particular interest when considering NVC in PD; it is possible that NVC may actually only be impaired in those with the postural instability gait disorder subtype of the disease (i.e. those prone to freezing and walking difficulties) and perhaps not in those with the tremor predominant subtype, who are generally much less bradykinetic.

Studies of CBF in PD which have been performed using motor paradigms and f-MRI and PET have predominantly been conducted to assess which areas of the brain are involved in movement, rather than to assess NVC per se. However, there are two studies which are notably relevant to this work. Firstly a study by Kraft et al,198 which used f-MRI to assess the effect of a single dose of levodopa on cortical and subcortical motor-circuit activation during bimanual grip force in PD patients. In this study, 12 right handed patients with PD, all at H&Y stages 1-2, were studied after a period of at least 12 hours without medication and a second time 1 hour after oral administration of levodopa. Blood-oxygenation-level-dependent (BOLD) f-MRI was measured whilst patients underwent two bimanual, and two unilateral, grip force movements with a defined amplitude and force. 12 healthy controls were also studied without
administration of levodopa. The authors found that grip force tasks activated a specific pattern of cortical and subcortical structures in all patients (namely the following components of the motor circuit: contralateral sensorimotor cortex, lateral pre-motor cortex, supplementary motor area proper, right cerebellar hemisphere in the right hand condition and left cerebellar hemisphere in the left hand condition, as well as the superior temporal gyrus and the inferior parietal lobule). However, BOLD-MRI responses were statistically different between PD patients in the off state and healthy controls, with lower BOLD values and less putaminal and thalamic responsiveness observed in the PD off group. Interestingly, this difference disappeared after the administration of levodopa, i.e. levodopa increases the BOLD responses of motor-circuits. Critically, this strongly suggests that NVC is affected by dopaminergic medications. The authors of this study concluded that further work evaluating NVC in the on and off states would be helpful.

The other relevant study, by Carbon et al, evaluated correlates of movement initiation and velocity in patients with PD using a longitudinal PET study, finding that as PD advances, motor performance is associated with the recruitment of brain regions normally involved in the execution of more complex tasks. This suggests that there is potential for compensation of NVC mechanisms and that different paradigms may be required to reveal subtle abnormalities or deficits.

The lack of a statistically significant difference in baseline MCBFVs of PD patients and healthy controls in this study is in conflict to the findings of the previous study reported in chapter 4. It should however be noted that the sample size in this study was smaller; findings may therefore be related to statistical power.
Whilst no statistically significant differences in CBF responses to passive arm movement were observed in this study, the subtle trend for the CBFVs of PD patients to decrease more rapidly than those of healthy controls is interesting. It is possible that with sustained movement, NVC responses in PD patients become less efficient or fail. Further work using different paradigms, and of different lengths, would be helpful in exploring this further. Given the findings outlined above of Sorond et al\textsuperscript{197} regarding NVC and gait speed, it would also be interesting to specifically investigate NVC in PD patients with the postural instability gait disorder subtype of the disease, and/or those with a significant history of PD related freezing.

5.5 LIMITATIONS

The specific limitations regarding the accuracy of TCD data, PD diagnosis, possibility of having included patients with carotid stenosis, and lack of author blinding which have been previously discussed in section 4.5 should again be observed.

Study sample size again warrants specific comment; the relatively small numbers of subjects in this study being likely to have limited statistical power. Indeed, a recent f-TCD study of the reproducibility of cerebral and peripheral haemodynamic responses to passive and motor imagery paradigms in older healthy volunteers\textsuperscript{102} suggests that 34 subjects are needed to detect a 3% change in CBFV of 3% in the contralateral side to passive movement. However, this is the largest TCD study to date of NVC in PD using a motor paradigm, making the findings noteworthy.
As stated above, given the finding that NVC is impaired in healthy older people with slow gait speed, it would be interesting and helpful to divide the PD patients into subgroups according to their disease phenotype (i.e. tremor predominant type vs. postural instability gait disorder type) in order to compare their responses. Unfortunately, sample size in this study was too small to permit such a sub-group analysis.

It is also possible that the use of a passive movement paradigm was not sufficient to effectively study NVC in PD and that an active paradigm (which should theoretically be more likely to recruit the basal ganglia) would have been more appropriate. As outlined in the introduction, there were concerns regarding the use of an active paradigm, particularly for PD patients in the off state, because of the potential for significant variability in responses and difficulty in comparing data. However, there has been some recent research in healthy older volunteers which has demonstrated that CBFV can be consistently and reproducibly increased not only by passive and active motor paradigms, but also by motor imagery paradigms - that is the patient simply ‘imagining’ flexing and extending their arm, whilst keeping it quite still.\textsuperscript{102} It is therefore possible that such an imagery paradigm could be used in PD patients, and indeed may be very helpful in overcoming inherent difficulties with motor induced neuro-activation. Of note, there have been no studies evaluating which paradigms are most appropriate to use when studying NVC in PD; further work in this area would be helpful. Certainly, a comparison of active, passive and imaginary paradigms in PD patients would be of significant interest.
The motor paradigm was notably only performed once, predominantly because this was undertaken as one part of a much longer overall protocol (described in detail in Chapter 3), and there were concerns regarding overall tolerability for subjects, particularly PD patients in their off states. Ideally, the paradigm would have been performed at least twice, to ensure reproducibility of results.

The spike in CBFV prior to the commencement of the passive movement, which likely resulted from the examiner taking hold of the subject’s hand in preparation for the manoeuvre, is another confounder; the plots suggest that following this spike, CBFVs had not returned to their original resting values before the commencement of the passive arm movement. However, as all subjects were treated identically during the protocol, the data is still comparable. Nonetheless, this finding is an important consideration for the design of any future studies and paradigms; stimulation of any kind prior to the onset of such a paradigm needs to be carefully avoided.

5.6 SUMMARY

The results of this study suggest that CBFV, HR and ABP responses to passive motor activation are not statistically different between the on and off states of PD, or between PD patients and healthy controls. However, it should be noted that there is a paucity of literature evaluating NVC in PD, and this study has highlighted several key areas in which further work appears warranted.
CHAPTER 6  
VASOMOTOR REACTIVITY IN IDIOPATHIC PARKINSON’S DISEASE

“A local afflux and determination of blood into the minute vessels”

James Parkinson, 1817

6.1  INTRODUCTION

CBF is strongly influenced by arterial partial pressure of CO₂ (PaCO₂), which also modulates the effectiveness of CA; CA being improved by hypocapnia and impaired by hypercapnia.⁶⁹,⁷⁰ It has been shown that CA can be reliably assessed by evaluating CBF responses to changes in PaCO₂, such as those induced by hypo- and hyperventilation respectively.¹⁰⁴ This concept is known as assessing vasomotor (or CO₂) reactivity. To date, there have been relatively few TCD studies of vasomotor reactivity (VMR) in PD. Furthermore, of the studies which have assessed VMR, all have used hypercapnia as a stimulus; none have used hypocapnia. This study therefore aimed to assess CBFV and CA responses to hypocapnia in both PD patients in their on and off states, and in a group of healthy controls.

6.2  METHODS

6.2.1  Protocol

Subjects were recruited to the study, and data collected, as described previously in Chapter 3. In this analysis the hyperventilation paradigm, which was the penultimate
TCD recording made at each visit, was used for the evaluation of CBFV and CA responses to hypocapnia. In brief, after a sixty second baseline period, participants were asked to breathe in time with an electronic metronome for 90 seconds. For the first 30 seconds of this period, the respiratory rate of participants was gradually increased to 25 breaths per minute, which they then sustained for a further 60 seconds. The electronic metronome was then switched off and the participant was asked to relax and once again breathe normally. Participants were notably given the opportunity to listen to the metronome and have several practice attempts during the briefing phase of their visit.

6.2.2 Data Analysis

Raw data were edited using the method detailed in section 3.5. In brief, mean BP, CBFV and systolic/diastolic values were calculated for each cardiac cycle, and linear interpolation was used to obtain estimates of EtCO₂ synchronised to the end of each cardiac cycle. The instantaneous relationship between BP and CBFV was used to estimate CrCP and RAP for each cardiac cycle using the first harmonic method. Beat-to-beat data were spline interpolated and resampled at 5 samples/s to create a uniform time base. An auto-aggressive moving average (ARMA) technique was then used to model the dynamic relationship between BP and CBFV for the data, leading to estimates of the dynamic ARI, as well as the unconstrained gain parameter (K') of Tiecks and Aaslid. To obtain time-varying rates of ARI and K', the sampling rate was reduced to 0.6s time intervals, and each calculation was performed for a 60s segment of data. New estimates of K' and ARI were obtained by shifting the 60s
window along the BP and CBFV signals every 0.6s. For estimation of ARI, CBFV template response curves were fitted to the first 6s of the CBFV step response. Time varying estimates are expressed as ARI(t) and K’(t). After the main inflection points in the EtCO₂ had been marked under visual inspection, values of population coherent averages were obtained for each variable at each time sample. To enable statistical comparisons, values were then normalised in percent by their baseline values.

Once again, as PD is a condition with laterality, the CBFV data are detailed by disease onset hemisphere, and other hemisphere, rather than simply by right and left sides as for healthy controls.

Baseline values of MCBFV, HR, ABP and EtCO₂ were obtained from a time point midway through the baseline period preceding the hyperventilation paradigm.

### 6.2.3 Statistics

Data were collated in Microsoft Excel 2010 and analysed using Statistica version 8. Categorical data are presented as absolute numbers and percentages. Continuous data were plotted and assessed for normality using the Shapiro-Wilk test; normally distributed values are reported as mean (±standard deviation (SD), range) or mean(±SD), and non-normal data are presented as median (inter-quartile range (IQR), range). Baseline demographic data between PD patients and healthy controls were compared using a Student’s t-test for independent samples and Fisher’s exact test for nominal data. Baseline UPDRS scores for PD patients in their on and off states were compared using the Wilcoxon signed rank test.
ANOVA was used to compare baseline values of mean HR, ABP and EtCO$_2$ for PD patients in each clinical state and healthy controls. A two-way ANOVA was used to compare MCBFVs for each side of recording in both the on and off states; clinical state was used as the between factor, and side of recording (left, right, disease onset hemisphere, other hemisphere) as the within factor. ANOVA was also used to compare averaged values of CBFV, EtCO$_2$, BP and HR, obtained from two specific intra-manoeuvre time points (Fig 6.8). Post-hoc comparisons (Tukey’s test) were performed when appropriate. Statistical significance was assumed when $p<0.05$.

6.3 RESULTS

6.3.1 Baseline Demographics

A total of 35 patients with idiopathic PD were recruited to the study and attended for TCD measurements, eight of whom were subsequently excluded because of inadequate transtemporal insonation windows. In this analysis, it was unfortunately necessary to exclude the data obtained from three patients because of multiple ectopic beats which occurred during the recordings, and from one further patient who struggled to complete the hyperventilation manoeuvre and had to stop halfway through the recording. Additionally, one patient (male aged 59, disease duration 2.5 years) was, by his own choice, not receiving any treatment for his PD and was therefore only scanned once in his ‘off’ state. A second patient (female aged 66, disease duration two years) withdrew from the study after attending for her ‘on’ scan due to apprehension regarding the temporary cessation of medication required for the
‘off’ scan, meaning that she was only scanned once, in her ‘on’ state. These two patients were also excluded from paired analyses, meaning 21 paired (on and off) recordings were available for evaluation in the patient group. Please refer to Appendix 13 for a pictorial summary of patient inclusion in this study.

28 volunteers were also recruited to the study, three of whom were subsequently excluded because of inadequate trans-temporal insonation windows. In this analysis, it was unfortunately necessary to exclude data collected from three of the remaining volunteers because of poor signal quality and noise, leaving data from 22 healthy controls.

The baseline characteristics of PD patients and healthy controls included in this study are detailed in tables 6.1 and 6.2. No differences were observed between the control group and PD group in terms of age or gender.

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS</th>
<th>HEALTHY CONTROLS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender n (%)</td>
<td>13 (62)</td>
<td>13 (59)</td>
<td>1.0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.9±11.1, 42-85</td>
<td>59.6±11.1, 42-82</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*Table 6.1:* Baseline demographics of PD patients and healthy controls in the VMR study

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (years)</td>
<td>3 (2-5.5, 0.3-13)</td>
<td>3 (2-5.5, 0.3-13)</td>
<td></td>
</tr>
<tr>
<td>H&amp;Y Stage</td>
<td>1.5 (1-2.5, 1-3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UPDRS</td>
<td>34 (24-37, 12-61)</td>
<td>41 (34-46, 21-76)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Table 6.2:* PD specific baseline data for patients in the VMR study
6.3.2 Baseline Peripheral Haemodynamic Data

Baseline peripheral haemodynamic data are reported in table 6.3. No significant differences were observed in values of HR, ABP or EtCO$_2$ between PD patients in either state, or between PD patients in either state and healthy controls.

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>HEALTHY CONTROLS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (bpm)</strong></td>
<td>62.0 (±8.9)</td>
<td>64.0 (±11.4)</td>
<td>63.3 (±10.5)</td>
<td>0.349</td>
</tr>
<tr>
<td><strong>ABP (mmHg)</strong></td>
<td>92.2 (±14.8)</td>
<td>95.3 (±13.8)</td>
<td>93.4 (±12.7)</td>
<td>0.269</td>
</tr>
<tr>
<td><strong>EtCO$_2$ (mmHg)</strong></td>
<td>36.6 (±4.0)</td>
<td>37.3 (±4.3)</td>
<td>38.3 (±4.9)</td>
<td>0.957</td>
</tr>
</tbody>
</table>

*Table 6.3:* Baseline peripheral haemodynamic data for PD patients and healthy controls in the VMR study. Values given are mean (±SD)

6.3.3 Baseline MCBFV Values

Baseline values of MCBFV are detailed in table 6.4. No significant difference was observed between the MCBFVs of the hemisphere of disease onset and the other hemisphere for PD patients, or between PD patients in their on and off states. Values of MCBFV were a little higher in the PD off state than in the on state, and were also higher in healthy controls than in PD patients. However, these differences were not statistically significant.
Table 6.4: Baseline values of MCBFV in cm/s, detailed by right and left sides for healthy controls, and by disease onset hemisphere for PD patients. Values given are mean (±SD)

<table>
<thead>
<tr>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>HEALTHY CONTROLS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset Hemisphere</td>
<td>Other Hemisphere</td>
<td>Onset Hemisphere</td>
</tr>
<tr>
<td></td>
<td>CrCP (mmHg)</td>
<td></td>
<td>CrCP (mmHg)</td>
</tr>
<tr>
<td>49.6</td>
<td>(±11.6)</td>
<td>49.6</td>
<td>(±9.9)</td>
</tr>
</tbody>
</table>

**6.3.4 Baseline dCA Indices**

Baseline dCA indices obtained from a specific time point mid-way through the baseline recording are detailed in table 6.5. No statistically significant differences were observed for any parameter between participant groups, clinical PD states or sides of recording. However, values of K'(t) appeared lower in the PD on state than in the off state, and lower than those seen in healthy controls.

<table>
<thead>
<tr>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>HEALTHY CONTROLS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset Hemisphere</td>
<td>Other Hemisphere</td>
<td>Onset Hemisphere</td>
</tr>
<tr>
<td></td>
<td>CrCP (mmHg)</td>
<td></td>
<td>CrCP (mmHg)</td>
</tr>
<tr>
<td>33.8</td>
<td>(±16.2)</td>
<td>34.9</td>
<td>(±15.2)</td>
</tr>
<tr>
<td>1.33</td>
<td>(±0.36)</td>
<td>1.32</td>
<td>(±0.33)</td>
</tr>
<tr>
<td>0.58</td>
<td>(±1.4)</td>
<td>0.35</td>
<td>(±0.48)</td>
</tr>
<tr>
<td>2.3</td>
<td>(±2.5)</td>
<td>2.5</td>
<td>(±2.7)</td>
</tr>
</tbody>
</table>

Table 6.5: Baseline dCA indices for subjects in the VMR study
6.3.5 Peripheral Haemodynamic Responses to Hyperventilation

As would be expected, the hyperventilation resulted in a significant decrease in EtCO$_2$ (figure 6.1), with the greatest change observed in healthy controls (change in EtCO$_2$ of 24%, compared to 18% in PD patients in their on state and 20% in PD patients in their off state).

Hyperventilation also resulted in an increase in HR and decrease in ABP (figures 6.2 and 6.3). These followed very similar patterns between the groups but were of different magnitudes. The percentage changes in HR between the groups, or clinical states, at time points 1 and 2, was not statistically significant (ANOVA F = 0.28, p = 0.75 and F = 0.21, p =0.81 respectively).

The percentage change in ABP was not statistically significant at time point 1, (ANOVA F = 1.23, p = 0.30), but a statistical difference was observed between PD patients in their on state and healthy controls at time point 2 (p = 0.02).

6.3.6 CBFV Responses to Hypocapnia

Hyperventilation resulted in a significant decrease in MCBFV bilaterally in all subjects, with a steep decrease occurring a few seconds after the initial drop in EtCO$_2$. Overall, there was excellent agreement between averages for the right and left MCAs in healthy controls and between disease onset hemispheres and other hemispheres in PD patients (figures 6.4-6.8).
No statistically significant differences were observed for percentage changes in CBFVs between the groups, or clinical states, at time points 1 and 2, (ANOVA $F = 0.28$, $p = 0.75$ and $F = 0.21$, $p = 0.81$ respectively).

### 6.3.7 Intra-Manoeuvre dCA Indices

dCA indices for time points 1 and 2 are detailed in tables 6.5 and 6.6 respectively. Values of $K'(t)$ are not reported as the values obtained appeared physiologically implausible (i.e. values obtained were $>1.0$ which, according to physical principles, should not be possible). This may have resulted from the sampling rate of 0.6s and 60s duration of the moving window for the ARMA technique being inadequate to enable accurate capture of this parameter, despite being the best temporal resolution available at present.

At timepoint 1, ARI values were significantly higher in healthy controls than in PD patients in the off state, with the effect significant between all sides of recording. A statistically significant difference was also observed between the values obtained for the ‘other’ hemisphere of PD patients in the on state, and the left MCA of healthy controls at this timepoint.

There were no statistically significant differences in values of CrCP and RAP at timepoint 1, and no statistically significant differences were observed for any dCA indices at timepoint 2.
<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>HEALTHY CONTROLS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset Hemisphere</td>
<td>Other Hemisphere</td>
<td>Onset Hemisphere</td>
<td>Other Hemisphere</td>
</tr>
<tr>
<td>CrCP (mmHg)</td>
<td>39.9 (±16.1)</td>
<td>39.3 (±17.0)</td>
<td>39.0 (±14.0)</td>
<td>40.5 (±14.8)</td>
</tr>
<tr>
<td>RAP (mmHg.s/cm)</td>
<td>1.40 (±0.37)</td>
<td>1.40 (±0.44)</td>
<td>1.41 (±0.39)</td>
<td>1.38 (±0.37)</td>
</tr>
<tr>
<td>ARI(t)</td>
<td>3.4 (±2.8)</td>
<td>2.9* (±2.7)</td>
<td>2.6* (±2.4)</td>
<td>2.5* (±2.7)</td>
</tr>
</tbody>
</table>

Table 6.6: dCA indices for subjects in the VMR study obtained at timepoint 1

*Significant relationships identified by Tukey’s post-hoc testing

<table>
<thead>
<tr>
<th></th>
<th>PD PATIENTS (ON)</th>
<th>PD PATIENTS (OFF)</th>
<th>HEALTHY CONTROLS</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset Hemisphere</td>
<td>Other Hemisphere</td>
<td>Onset Hemisphere</td>
<td>Other Hemisphere</td>
</tr>
<tr>
<td>CrCP (mmHg)</td>
<td>37.9 (±16.9)</td>
<td>38.6 (±16.9)</td>
<td>38.5 (±13.1)</td>
<td>39.3 (±13.8)</td>
</tr>
<tr>
<td>RAP (mmHg.s/cm)</td>
<td>1.5 (±0.38)</td>
<td>1.5 (±0.40)</td>
<td>1.46 (±0.38)</td>
<td>1.46 (±0.39)</td>
</tr>
<tr>
<td>ARI(t)</td>
<td>4.5 (±3.2)</td>
<td>5.0 (±3.2)</td>
<td>4.6 (±2.9)</td>
<td>4.5 (±2.9)</td>
</tr>
</tbody>
</table>

Table 6.7: dCA indices for subjects in the VMR study obtained at timepoint 2

ARI values notably showed a strong trend to increase from baseline to timepoint 2 in all groups.
Figure 6.1: Hyperventilation induced change in EtCO₂ shown for each subject group. Left plot depicts change in EtCO₂ by mmHg, and right plot depicts change in %.
Figure 6.2: Hyperventilation induced change in HR shown for each subject group. Left plot depicts change in HR by bpm, and right plot depicts change in %.
Figure 6.3: Hyperventilation induced change in ABP shown for each subject group. Left plot depicts change in ABP by mmHg, and right plot depicts change in %.
Figure 6.4: Hyperventilation induced change in MCBFVs, healthy controls

Figure 6.5: Hyperventilation induced change in MCBFVs, PD patients ON
Figure 6.6: Hyperventilation induced change in MCBFVs, PD patients OFF

Figure 6.7: Hyperventilation induced change in MCBFVs, PD patients ON and OFF
Figure 6.8: Hyperventilation induced change in MCBFVs, all subjects. The points marked 1 and 2 represent the time periods used to obtain values of ARI(t) and K'(t), and for ANOVA analysis of averaged values of CBFV, EtCO₂, BP and HR.

6.4 DISCUSSION

The key findings of this study are that CBFV responses to hyperventilation show excellent agreement between PD patients and healthy controls, and also between hemispheres in both healthy controls and patients with PD. Furthermore, CBFV responses to hyperventilation do not vary significantly between the on and off states of PD. ARI values for both healthy controls and patients with PD improve with hyperventilation, although the improvement appears to occur more rapidly in healthy controls than in PD patients.
The finding that CBFV responses to hyperventilation do not differ significantly between healthy controls and patients with PD is important, and suggests that VMR is intact in PD. However, as ARI values appeared to improve more rapidly in response to hyperventilation in healthy controls, it may be that there is some subtle slowing or impairment of the VMR mechanisms in PD. The lack of any observed laterality suggests that VMR does not, however, vary by hemisphere.

Extensive comparisons of these study findings with the literature are difficult; this is the first study to have examined CBFV responses to hyperventilation in patients with PD using TCD. However, there have been TCD studies which have used hypercapnia to study VMR and CBFV in PD, using breath-hold and CO₂ inhalation paradigms. These studies,¹³³,¹³⁹,¹⁴² which notably number just three, produced mixed findings and conclusions. Troisi et al¹³⁹ and Hamdy et al¹³³ both used a breath-hold paradigm in patients with PD. Both studies found that breath-hold increased CBFV, however Troisi et al found that the increase in CBFV was no different between healthy controls and patients with PD. This was in conflict to Hamdy et al who concluded that the difference between PD patients and healthy controls was significant, with higher MCBFVs achieved by healthy controls. It is worth noting that whilst Troisi et al calculated the difference in MCBFV as a percentage change, as in this study, Hamdy et al simply compared mean values of MCBFV, and that their control group notably had higher baseline resting values of MCBFV. Importantly, both studies found no differences in responses to changes in PaCO₂ between PD patients in the on and off states which would be in agreement with our findings, and also those of Krainik et al,²⁰¹ who studied cerebral vasoreactivity to hypercapnia using BOLD-fMRI in patients with PD before and after levodopa administration. In their study, 10 patients
underwent BOLD-fMRI imaging whilst receiving CO₂ inhalation, before and 60 minutes after a suprathreshold (120%) therapeutic levodopa dose. Hypercapnic stimulus increased whole-brain BOLD MRI signal, but no significant difference was seen globally or regionally between the on and off states.

In a further study using CO₂ inhalation, Zamani et al. evaluated the CBFV responses of PD patients to hypercapnia with TCD. In their study, they administered CO₂ to PD patients via an anaesthetic face mask, whilst recording bilateral MCBFVs in the MCAs. CO₂ was administered until an end-tidal concentration of 8% by volume in the exhaled air was achieved. After the hypercapnic plateau was reached, subjects were hyperventilated for 1-2 minutes. Values of peak, and mean, CBFV were then compared and a VMR index was determined by calculating the percentage difference in peak systolic flow velocity in the MCA at baseline and after the CO₂ test. They found an impaired VMR index in 15 of their 44 PD subjects. However, it is important to note that this study was not case controlled, and that their calculation of a VMR index has not been robustly evaluated.

Overall, there is very little evidence regarding vasomotor reactivity in Parkinson’s disease. Although the excellent agreement of results obtained in this study suggests that the findings are highly likely to be reproducible, further work will be needed for confirmation.
6.5 LIMITATIONS

The specific limitations regarding the accuracy of TCD data, PD diagnosis, possibility of having included patients with carotid stenosis, and lack of author blinding which have been previously discussed in section 4.5 should again be observed.

Allowing subjects to control their own hyperventilation manoeuvres inherently allows for greater inter-subject variability, compared with more controlled protocols based on end-tidal forcing. However, for reasons of feasibility (such protocols would require the participant to be intubated and ventilated), this was not possible.

The hyperventilation paradigm was notably only performed once, predominantly because this was undertaken as one part of a much longer overall protocol (described in detail in Chapter 3), and there were concerns regarding overall tolerability for subjects, particularly PD patients in their off states. Ideally, the paradigm would have been performed at least twice, to ensure reproducibility of results. However, the excellent agreement of responses seen in both the same group of subjects (PD patients in their on and off states), and in a different group altogether (healthy controls) suggests that the data are robust, and indicates significant reproducibility.

It would have been optimal to compare the hyperventilation response to a hypoventilation response, using either breath-hold or inhaled CO₂. However, again for reasons of overall protocol length and tolerability for subjects, this was not deemed practicable. Recent evidence has however suggested that VMR is actually much greater for hypercapnia than hypocapnia, and also that it could be physiologically a
different challenge altogether. A future study evaluating the CBFV responses of PD patients to hypercapnia would therefore be of interest.

Of note, subjects were not screened for respiratory pathology, and smoking status was not controlled for. However, anecdotally very few of the study participants were smokers (indeed, non-smoking status is a risk factor for PD), and no participant would have had a cigarette within four hours of attending the research laboratory because of stipulations within the study protocol. It is therefore felt that these limitations are unlikely to be of particular significance.

The 60s duration of the moving window for the ARMA technique, can be seen as a limitation of the best temporal resolution that can be achieved with this approach.

6.6 SUMMARY

The study has demonstrated that CBFV responses to hyperventilation show excellent agreement between PD patients and healthy controls, and between hemispheres in both healthy controls and patients with PD. Furthermore, CBFV responses to hyperventilation do not vary significantly between the on and off states of PD. This all suggests that VMR is likely to be intact in PD. However, whilst ARI values for both healthy controls and patients with PD improve with hyperventilation, the improvement appears to occur more rapidly in healthy controls than in PD patients, suggesting that there may be some subtle impairment or slowing in VMR. Overall, there has been a paucity of work in this area and for clarity, further work would be helpful.
CHAPTER 7  THE NATURAL HISTORY OF CEREBRAL AUTOREGULATION IN IDIOPATHIC PARKINSON’S DISEASE

“To connect the symptoms... requires a continuance of observation of the same case.....”

James Parkinson, 1817

7.1  INTRODUCTION

The natural history of CA in idiopathic PD has never before been studied, although it appears reasonable to hypothesise that, as PD is a progressive disease involving the autonomic nervous system, CA indices may deteriorate with time. The aim of this study was to therefore follow up a cohort of patients with PD over a 12 month period, monitoring the evolution of their ARI values.

7.2  METHODS

7.2.1  Protocol

Subjects were recruited to the study, and data collected, as described previously in Chapter 3. In this analysis, as in Chapter 4, the two, five-minute, baseline TCD recordings made at each visit immediately after the stabilisation period were used for the calculation of ARI values.
7.2.2 Data Analysis

Data were analysed as reported previously in sections 3.5 and 4.2.2, and were subject to the same rejection criteria. In this analysis, just one recording (the second baseline recording obtained from patient 2 at his 8 month ‘ON’ visit was rejected for being of poor quality, whilst at the frequency domain stage 14 files from an overall total of 46 were rejected. These files were all from patients 2 and 3, but were distributed randomly between visits and sides of recording. As the analyses in Chapters 4-6 revealed that values of MBFV do not differ significantly between hemisphere, these values, and those of ARI, were averaged to provide a mean value for each clinical state at each visit.

7.2.3 Statistics

Data were collated in Microsoft Excel 2010 and analysed using Statistica version 8. Longitudinal values of MCBFV and ARI were compared using repeated measures ANOVA, with clinical state as the between factor, and time period as the within factor. Statistical significance was set at the p <0.05 level.
7.3 RESULTS

7.3.1 Baseline Demographics

Three PD patients, notably all right handed males, consented to be enrolled into the natural history study; their baseline demographics are summarised in table 7.1.

<table>
<thead>
<tr>
<th></th>
<th>PATIENT 1</th>
<th>PATIENT 2</th>
<th>PATIENT 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at 1st visit (years)</td>
<td>42</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>Disease duration at 1st visit (years)</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Presence of OH</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Table 7.1:* Baseline demographics of patients enrolled into the natural history study

Details of the patients’ medication regimes at each stage of the study are shown in table 7.2. All three patients were notably taking a combination of levodopa and long acting dopamine agonist at the point of enrolment into the study, and all three patients continued on the same medication regime for the first eight months of the study period. However, by 12 months, the medication regimes for all three patients had changed; two of the patients (patients 1 and 2) having had the dose of their dopamine agonist increased, and the third (patient 3) having been commenced on an additional agent (Trihexyphenidyl).
Table 7.2: Medication regimes at each time point for patients in the natural history study

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications</strong></td>
<td>Sinemet 62.5mg TDS</td>
<td>Madopar 125mg QDS</td>
<td>Sinemet 125mg TDS</td>
</tr>
<tr>
<td><strong>at baseline</strong></td>
<td>Ropinorole XL 20mg OD</td>
<td>Ropinirole XL 16mg OD</td>
<td>Mirapexin 2.62mg OD</td>
</tr>
<tr>
<td><strong>at 4 months</strong></td>
<td>Sinemet 62.5mg TDS</td>
<td>Madopar 125mg QDS</td>
<td>Sinemet 125mg TDS</td>
</tr>
<tr>
<td></td>
<td>Ropinorole XL 20mg OD</td>
<td>Ropinirole XL 16mg OD</td>
<td>Mirapexin 2.62mg OD</td>
</tr>
<tr>
<td><strong>at 8 months</strong></td>
<td>Sinemet 62.5mg TDS</td>
<td>Madopar 125mg QDS</td>
<td>Sinemet 125mg TDS</td>
</tr>
<tr>
<td></td>
<td>Ropinorole XL 20mg OD</td>
<td>Ropinirole XL 16mg OD</td>
<td>Mirapexin 2.62mg OD</td>
</tr>
<tr>
<td><strong>at 12 months</strong></td>
<td>Sinemet 62.5mg TDS</td>
<td>Madopar 125mg QDS</td>
<td>Sinemet 125mg TDS</td>
</tr>
<tr>
<td></td>
<td>Ropinorole XL 24mg OD</td>
<td>Ropinirole XL 20mg OD</td>
<td>Mirapexin 2.62mg OD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trihexyphenidyl 1mg TDS</td>
</tr>
</tbody>
</table>

Hoehn and Yahr stage, UPDRS scores and NMS-Quest scores are detailed for each patient, at each time point, in table 7.3. Patient 1, the youngest, remained at the same H&Y stage throughout the 12 month follow up, whilst patients 2 and 3 progressed; patient 2’s disease notably becoming bilateral by the end of the study period.

A general progressive increase in UPDRS scores was observed for each patient, although some inter-visit variability was observed. This is not unusual; patients with Parkinson’s disease can experience significant daily, even hourly, fluctuations in their motor state, which is often related to medication timing. These motor fluctuations may therefore have resulted in different, objectively observed, UPDRS Part 3 scores at the different visits. It is also possible that some variation in scores resulted from differing, subjective, reporting of Parkinsonian symptoms by patients in Parts 1 and 2 of the UPDRS at each visit.
Unfortunately, NMS-Quest data was not collected for the patients at their first two visits, and is therefore only available for their final two visits.

<table>
<thead>
<tr>
<th></th>
<th>PATIENT 1</th>
<th>PATIENT 2</th>
<th>PATIENT 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H&amp;Y Stage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4 months</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>8 months</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>12 months</td>
<td>1</td>
<td>2</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>NMS-Quest Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
</tr>
<tr>
<td>4 months</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
</tr>
<tr>
<td>8 months</td>
<td>12</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>12 months</td>
<td>12</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td><strong>UPDRS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>ON 29</td>
<td>OFF 42</td>
<td>ON 24</td>
</tr>
<tr>
<td></td>
<td>OFF 42</td>
<td>OFF 32</td>
<td>OFF 25</td>
</tr>
<tr>
<td>4 months</td>
<td>ON 41</td>
<td>OFF 51</td>
<td>ON 22</td>
</tr>
<tr>
<td></td>
<td>OFF 51</td>
<td>OFF 36</td>
<td>OFF 31</td>
</tr>
<tr>
<td>8 months</td>
<td>ON 43</td>
<td>OFF 55</td>
<td>ON 20</td>
</tr>
<tr>
<td></td>
<td>OFF 55</td>
<td>OFF 44</td>
<td>OFF 39</td>
</tr>
<tr>
<td>12 months</td>
<td>ON 48</td>
<td>OFF 51</td>
<td>ON 39</td>
</tr>
<tr>
<td></td>
<td>OFF 51</td>
<td>OFF 53</td>
<td>OFF 40</td>
</tr>
</tbody>
</table>

Table 7.3: H&Y stage, NMS-Quest and UPDRS scores for patients in the natural history study, detailed by patient, clinical state and visit

### 7.3.2 Baseline Peripheral Haemodynamic Data

Baseline peripheral haemodynamic data of HR, MAP, SBP, DBP and EtCO₂ are shown for each patient, in each clinical state, at each time point in table 7.4.
<table>
<thead>
<tr>
<th></th>
<th>PATIENT 1</th>
<th></th>
<th>PATIENT 2</th>
<th></th>
<th>PATIENT 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td><strong>HR (bpm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>66 (±1.18)</td>
<td>60 (±2.53)</td>
<td>54 (±0.01)</td>
<td>52 (±0.18)</td>
<td>48 (±0.06)</td>
<td>46 (±0.21)</td>
</tr>
<tr>
<td>4 months</td>
<td>66 (±0.11)</td>
<td>66 (±0.87)</td>
<td>54 (±0.95)</td>
<td>59 (±1.17)</td>
<td>48 (±0.38)</td>
<td>48 (±0.13)</td>
</tr>
<tr>
<td>8 months</td>
<td>65 (±0.91)</td>
<td>69 (±0.58)</td>
<td>55 (±0.28)</td>
<td>60 (±0.28)</td>
<td>46 (±0.39)</td>
<td>47 (±0.04)</td>
</tr>
<tr>
<td>12 months</td>
<td>59 (±0.44)</td>
<td>67 (±2.64)</td>
<td>61 (±1.27)</td>
<td>59 (±0.13)</td>
<td>44 (±0.81)</td>
<td>50 (±0.50)</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>59 (±1.27)</td>
<td>67 (±0.37)</td>
<td>73 (±0.98)</td>
<td>87 (±0.20)</td>
<td>72 (±0.61)</td>
<td>76 (±2.21)</td>
</tr>
<tr>
<td>4 months</td>
<td>80 (±3.92)</td>
<td>74 (±5.48)</td>
<td>77 (±0.53)</td>
<td>90 (±2.78)</td>
<td>73 (±2.07)</td>
<td>85 (±9.30)</td>
</tr>
<tr>
<td>8 months</td>
<td>77 (±0.39)</td>
<td>83 (±2.36)</td>
<td>84 (±2.91)</td>
<td>84 (±1.70)</td>
<td>87 (±4.96)</td>
<td>83 (±1.08)</td>
</tr>
<tr>
<td>12 months</td>
<td>80 (±1.32)</td>
<td>81 (±7.00)</td>
<td>78 (±0.45)</td>
<td>89 (±2.48)</td>
<td>83 (±2.33)</td>
<td>88 (±3.45)</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>92 (±1.88)</td>
<td>99 (±2.35)</td>
<td>108 (±1.03)</td>
<td>136 (±1.20)</td>
<td>118 (±2.93)</td>
<td>119 (±6.10)</td>
</tr>
<tr>
<td>4 months</td>
<td>110 (±6.84)</td>
<td>103 (±7.49)</td>
<td>103 (±4.79)</td>
<td>122 (±0.35)</td>
<td>108 (±0.71)</td>
<td>126 (±16.14)</td>
</tr>
<tr>
<td>8 months</td>
<td>109 (±1.18)</td>
<td>114 (±8.06)</td>
<td>112 (±4.24)</td>
<td>116 (±1.33)</td>
<td>138 (±3.4)</td>
<td>113 (±2.84)</td>
</tr>
<tr>
<td>12 months</td>
<td>109 (±0.22)</td>
<td>114 (±7.74)</td>
<td>108 (±2.18)</td>
<td>124 (±2.04)</td>
<td>119 (±11.16)</td>
<td>126 (±6.69)</td>
</tr>
<tr>
<td><strong>DBP (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>43 (±1.46)</td>
<td>51 (±0.42)</td>
<td>59 (±1.07)</td>
<td>69 (±0.27)</td>
<td>55 (±0.18)</td>
<td>58 (±1.24)</td>
</tr>
<tr>
<td>4 months</td>
<td>65 (±2.36)</td>
<td>60 (±4.19)</td>
<td>67 (±2.12)</td>
<td>78 (±4.06)</td>
<td>62 (±2.62)</td>
<td>70 (±6.25)</td>
</tr>
<tr>
<td>8 months</td>
<td>61 (±0.04)</td>
<td>67 (±0.70)</td>
<td>74 (±1.80)</td>
<td>71 (±1.43)</td>
<td>75 (±1.67)</td>
<td>69 (±0.59)</td>
</tr>
<tr>
<td>12 months</td>
<td>64 (±2.09)</td>
<td>62 (±5.26)</td>
<td>65 (±0.03)</td>
<td>72 (±2.77)</td>
<td>69 (±1.37)</td>
<td>75 (±1.71)</td>
</tr>
<tr>
<td><strong>EtCO₂ (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>38 (±0.32)</td>
<td>38 (±0.16)</td>
<td>31 (±0.45)</td>
<td>35 (±0.57)</td>
<td>26 (±1.81)</td>
<td>34 (±5.26)</td>
</tr>
<tr>
<td>4 months</td>
<td>39 (±0.25)</td>
<td>37 (±0.13)</td>
<td>34 (±0.30)</td>
<td>34 (±0.52)</td>
<td>25 (±2.36)</td>
<td>32 (±2.28)</td>
</tr>
<tr>
<td>8 months</td>
<td>38 (±0.18)</td>
<td>38 (±0.58)</td>
<td>35 (±0.29)</td>
<td>29 (±2.47)</td>
<td>31 (±2.15)</td>
<td>37 (±1.27)</td>
</tr>
<tr>
<td>12 months</td>
<td>36 (±0.21)</td>
<td>35 (±0.59)</td>
<td>35 (±0.06)</td>
<td>33 (±0.84)</td>
<td>32 (±9.26)</td>
<td>33 (±8.14)</td>
</tr>
</tbody>
</table>

Table 7.4: Longitudinal peripheral haemodynamic data, detailed by patient, clinical state and visit
Values given are mean (±SD)
7.3.3 Mean Cerebral Blood Flow Velocity

The values of MCBFV obtained for each patient, in each state and at each time point are shown in table 7.5. As before, the values obtained are at the lower level of, but within, the reported reference range. Repeated measures ANOVA did not reveal any statistically significant relationship between the different time points for any of the patients.

<table>
<thead>
<tr>
<th></th>
<th>PATIENT 1</th>
<th>PATIENT 2</th>
<th>PATIENT 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ON (cm/s)</td>
<td>OFF (cm/s)</td>
<td>ON (cm/s)</td>
</tr>
<tr>
<td>Baseline</td>
<td>49.1 (±4.2)</td>
<td>51.4 (±0.6)</td>
<td>40.5 (±1.9)</td>
</tr>
<tr>
<td>4 months</td>
<td>50.1 (±1.6)</td>
<td>50.0 (±0.9)</td>
<td>36.8 (±2.9)</td>
</tr>
<tr>
<td>8 months</td>
<td>49.5 (±0.8)</td>
<td>47.2 (±3.1)</td>
<td>40.5 (±1.7)</td>
</tr>
<tr>
<td>12 months</td>
<td>49.4 (±0.2)</td>
<td>43.2 (±1.7)</td>
<td>38.0 (±3.8)</td>
</tr>
</tbody>
</table>

Table 7.5: Longitudinal values of MCBFV, detailed by patient, clinical state and visit. Values given are mean (±SD)

7.3.4 ARI Values

The ARI values obtained for each patient, in each state, and at each time point are detailed in table 7.6, and are also shown graphically in figures 7.1-7.4.

As with MCBFV values, repeated measures ANOVA did not reveal any statistically significant differences in ARI values. Furthermore, ARI values for each patient at varying time points appeared inconsistent between the on and off states, values occasionally improving in the off state, and occasionally worsening. However, when
values were plotted and considered by each clinical state for each patient, there appeared to be a general trend for ARI values to decrease or remain static for the first three visits, and then increase at the final visit. This trend was most obvious for patients 2 and 3 in their on states.

<table>
<thead>
<tr>
<th></th>
<th>PATIENT 1</th>
<th></th>
<th>PATIENT 2</th>
<th></th>
<th>PATIENT 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
<td>OFF</td>
<td>ON</td>
<td>OFF</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>3.5 (±0.49)</td>
<td>5.1 (±0.33)</td>
<td>6.7 (±0.27)</td>
<td>4.6 (±1.13)</td>
<td>5.3 (±0.95)</td>
<td>5.2 (±0.64)</td>
</tr>
<tr>
<td><strong>4 months</strong></td>
<td>3.1 (±0.40)</td>
<td>4.7 (±0.72)</td>
<td>6.1 (±0.28)</td>
<td>3.1 (±0.14)</td>
<td>2.7 (±1.05)</td>
<td>4.8 (±1.62)</td>
</tr>
<tr>
<td><strong>8 months</strong></td>
<td>4.3 (±0.57)</td>
<td>3.0 (±0.38)</td>
<td>1.6 (±1.16)</td>
<td>3.5 (±0.70)</td>
<td>2.8 (±0.59)</td>
<td>5.2 (±0.88)</td>
</tr>
<tr>
<td><strong>12 months</strong></td>
<td>4.6 (±0.60)</td>
<td>4.3 (±0.75)</td>
<td>4.8 (±0.89)</td>
<td>3.7 (±0.23)</td>
<td>6.3 (±0.72)</td>
<td>5.3 (±1.58)</td>
</tr>
</tbody>
</table>

**Table 7.6:** Longitudinal ARI values detailed by patient, clinical state and visit

Values give are mean (±SD)
Figure 7.1: Longitudinal ARI values for patient 1, by on and off states

Figure 7.2: Longitudinal ARI values for patient 2, by on and off states
Figure 7.3: Longitudinal ARI values for patient 3, by on and off states

Figure 7.4: Longitudinal ARI values for all patients, by on and off states
7.4 DISCUSSION

This study, whilst small, has raised a few points of interest. Firstly, there appears to be intra-subject variability in ARI at different time points. Whilst this has previously been demonstrated in subjects without PD,\textsuperscript{203} the possibility is raised here that variability in ARI may be related to clinical condition, especially as patients with PD are known to have a fluctuating clinical state. Of note, the magnitude of difference in patient’s UPDRS scores varied between visits at different time points, indicating some subtle variability in motor state.

Secondly, there is a suggestion here that ARI values deteriorate with time, but improve when dopaminergic therapies are increased. This finding would fit with the previous findings in Chapter 4 that ARI values display a trend, albeit not a statistically significant one, to be higher in the on state than the off state of Parkinson’s disease. As before, this finding would lend support for dopamine replacement potentially improving CA and thus for dopamine playing a key role in CA.

Interestingly, whilst the natural history of CA in PD patients has never before been reported, there has been a TCD study assessing serial resting MCBFV of PD patients who were taking levodopa.\textsuperscript{204} In this study, the authors hypothesise that, as levodopa is known to cause a rise in serum homocysteine levels, it may lead to alterations in cerebral haemodynamics via hyperhomocysteinaemia induced endothelial dysfunction, smooth muscle cell proliferation, and the associated increase in systemic vascular resistance. To test their hypothesis, the authors measured serum homocysteine levels and TCD parameters in the middle cerebral arteries of 17 patients with de novo PD and a mean age of 67.9(±8.6), before and after three months of
levodopa therapy. Importantly, they found no meaningful changes in MCBFV or PI at three months, despite significant elevations in serum homocysteine levels. Whilst it is likely that their follow up period was actually too short to allow for significant changes in haemodynamic parameters, it is interesting to note that they reported a resting MCBFV of 48.6(±7.7) cm.s\textsuperscript{-1} in their patients at baseline (pre-treatment), and a resting MCBFV of 48.4(±7.4) at follow up. Of note, these values are also towards the lower end of the reported reference range, suggesting once again that the lower MCBFV being observed in patients with PD is independent of dopaminergic medications.

7.5 LIMITATIONS

Clearly, the most important limitation to this study was sample size. It is difficult to identify anything other than very general trends with only three patients; statistical analysis is particularly difficult and unlikely to reveal significant relationships. The main reason for small sample size was an (understandable) reluctance of study participants to attend for repeated measurements in their off state, although many indicated that they would have been happy to attend for serial measurements in their on state. Nonetheless, despite the small sample size, as this is the first time longitudinal CA data has been obtained for patients with PD, it is important to have reported the findings, as they have the potential to inform future studies, and also provide some pilot/feasibility data.

Even allowing for the extremely small sample size, it is important to note that all three of the patients in this study were male. Furthermore, the patients included in this
study were again all in the relatively early stages of PD, and on similar medication regimes. Additionally, it is entirely plausible that the follow up period of one year was always going to be too short to demonstrate any relevant changes in CA. It would be more robust to follow up a much larger cohort, at varying disease stages and on differing medication regimes for a much longer period.

The usual limitations regarding the accuracy of TCD data, PD diagnosis, possibility of having included patients with carotid stenosis, and lack of author blinding should again be observed.

7.6 SUMMARY

This small study has not demonstrated any significant differences in ARI values of PD patients over the course of one year. However, a trend for ARI values to deteriorate with time, and improve when dopaminergic therapies are increased was observed. Low resting values of MCBFV in PD patients were once again demonstrated, although as with ARI values, these did not significantly alter over the course of twelve months. Some intra-subject variability in ARI at different time points was observed, although whether this was spurious or related to clinical/motor condition is, at present, uncertain.
CHAPTER 8  CONCLUSIONS

“He therefore considered it to be a duty to submit his opinions to the examination of others....”

James Parkinson, 1817

8.1 INTRODUCTION

In the last 20 years, it has been hypothesised that CA may be impaired in idiopathic PD as yet another sign of abnormal autonomic, or non-motor, function. This Thesis has aimed to explore CA in PD, with the objectives of determining whether CA is impaired in PD and, if impairment is present, whether this is caused by the disease itself, or by the medications used in its treatment. This concluding chapter will summarise the author’s findings, and their implications for future clinical practice and research.

8.2 MAIN FINDINGS OF THIS THESIS

Chapter 2 of this Thesis details the results of a systematic review of the literature relating to TCD studies of CA in PD. This revealed that, to date, there had been only limited work in this field. Furthermore, the work that had been undertaken had been limited in its scope, of uneven quality and had yielded conflicted findings. Certainly, there was insufficient evidence from the systematic review to either confirm or refute the presence of abnormal CA in PD, although there was a suggestion that neurovascular coupling is probably preserved in PD patients, whilst vasomotor reactivity is likely to be impaired. Furthermore, there was some evidence that cerebral haemodynamic responses vary according to the autoregulatory stimulus used,
indicating that a variety of paradigms should ideally be used to comprehensively evaluate CA in PD. The systematic review also suggested that anti-Parkinsonian medications do not affect CA, although on and off states had notably been studied inconsistently, and in a very small number of patients.

In chapter 4, spontaneous fluctuations in BP were used as an input stimulus for the assessment of CA in patients with PD in both their on and off states, and in healthy controls. This study found that patients with PD have significantly lower values of resting MCBFV when compared to healthy controls, an effect which appears to be independent of resting ABP. This finding may help to explain the high rates of OH which are observed in PD. ARI values were significantly lower in PD patients than in healthy controls, especially in the off state, suggesting that CA is almost certainly altered in PD. The trend for dCA indices to be better in the on state of PD than the off, whilst not statistically significant, was interesting and may help to confirm the hypothesis that dopamine plays a key role in the neurogenic regulation of cerebral blood flow. However, as ARI values were still significantly lower in PD patients in their medicated state than in healthy controls, it may be that this theory only applies to endogenous, and not synthetic, dopamine. The lack of any laterality observed in MCBFVs and dCA indices between the hemisphere of disease onset and the other hemisphere provides further evidence for PD being a multi-system disorder. Importantly, laterality of ARI had never before been assessed in PD. This lack of laterality has important implications for future studies, suggesting that valid results could be obtained from unilateral TCD assessment.
The study finding that ARI values vary between patients with and without a history of OH in their off states, and do not vary between PD patients without a history of OH in their on state and healthy controls has implications for using CA to better understand PD phenotype.

Chapter 5 evaluated the NVC mechanism in PD by using a passive arm movement paradigm. This study demonstrated that CBFV, HR and ABP responses to passive motor activation are not statistically different between the on and off states of PD, or between PD patients and healthy controls. Furthermore, responses once again did not show any tendency towards laterality, which is perhaps a surprise given that PD is a movement disorder of unilateral onset. However, it should be noted that there is a paucity of literature evaluating NVC in PD, and this study highlighted several key areas in which further work appears warranted.

Chapter 6, which evaluated CBFV responses to hyperventilation, similarly did not observe any difference between the on and off states of PD, or between PD patients and healthy controls. Indeed CBFV responses were extremely consistent between all subjects, in all states, suggesting that VMR is intact in PD. ARI values were improved by hyperventilation, which was the expected effect.

Chapter 7 was a small study assessing the natural history of CA in PD. Whilst too small to be statistically robust, there was a fascinating trend for ARI values to deteriorate with time, and to improve when new dopaminergic medication was commenced. This study was entirely novel, the natural history of CA in PD having never before been studied.
8.3 LIMITATIONS

The author acknowledges that there were limitations with this research, and these have been described in detail throughout the Thesis. However, several of these limitations warrant further consideration and comment here. The greatest limitation was, of course, the lack of statistical power. Recruitment to the study was challenging; before the involvement of Parkinson’s UK and the neurology led service patients were only being recruited from one geriatric clinic at University Hospitals of Leicester NHS Trust. The need to have support with, and different methods of, recruitment was certainly a learning point for the author. Recruitment was also limited by patients being reluctant to stop their anti-Parkinsonian medications, however temporarily, and this is another learning point for the author; greater involvement of patients at the protocol design phase would be extremely useful. The author has now joined a research support network, run by Parkinson’s UK and comprising both researchers and patients, in order to actively seek patient opinions on proposed research. Lastly with respect to sample size, the high TCD window failure rate observed also played a role here. Whilst it is not possible to control for, or predict, this, the author did learn to screen the participants for TCD windows before putting them through the rest of the protocol.

Whilst the inclusion and exclusion criteria for the study were initially felt to be robust, on reflection, the author would have wished to have excluded participants with carotid stenosis, and to have carefully controlled for this with carotid screening.

In each of the limitations sections throughout this Thesis, the author has described various measures which may enhance study quality, e.g. repetition of paradigms,
increase in paradigm length and trialling of different paradigms (e.g. active motor paradigms, hypercapnoeic paradigms). However, it is important to note that, in the pragmatic real-world, for reasons of tolerability, some of these may simply never be feasible or appropriate. In any study, the welfare of participants is the key priority.

8.4 FUTURE WORK

Importantly, this study has been continued by another researcher (Dr Martha Hanby, Academic Clinical Fellow in geriatric medicine). There has been a significant increase in recruitment to both the main study and to the natural history arm of the study, and there is now greater representation from patients at later disease stages. The author believes the significant increase in recruitment is largely due to the greater involvement of Parkinson’s UK and liaison with neurology led services, which was organised by the author. The study is predicted to achieve a statistically powered sample size by late Spring 2014. As many of the analyses in this Thesis were limited by statistical power, it is therefore hoped that it will be possible to confirm (or indeed refute) the key findings of this Thesis in the not too distant future.

With respect to future research, as there is a trend for ARI values to be higher in PD patients in their on state, it would be helpful to explore the effects of anti-Parkinsonian medications in more detail, comparing cohorts of PD patients taking different dopaminergic therapies (e.g. levodopa vs. dopamine agonist).

Given the finding that CA indices may show an association with OH in patients with PD, further work specifically evaluating disease phenotype would also be helpful. There is
emerging evidence that PD phenotype is related to disease course; tremor predominant patients appearing to have a better prognosis than those with the rigid akinetic type. Furthermore patients with a high burden of autonomic symptoms also appear to have a worse prognosis overall. It may be that CA assessment could be a useful tool in the evaluation of disease phenotype and/or have a role in disease prognostication.

The suggestion that the myogenic mechanism is preserved in PD (indicated by values of RAP and CrCP comparable to those of healthy controls) indicates that any impairment in CA is more likely to be due to dysfunction of the metabolic or neurogenic mechanisms. Degeneration of the neurogenic mechanism would appear logical. Subcomponents analysis to determine the contributions of the different mechanisms would therefore be extremely interesting.

Given the relative paucity of work evaluating NVC in PD, further studies here would also appear to be warranted and of interest. An exploration of the optimal paradigm to assess NVC in PD would be especially helpful. Additionally, it would be interesting to trial motor imaginary paradigms in PD patients, as has been done in healthy volunteers.

As already highlighted, an assessment of CBFV responses to hypercapnia may help to provide much needed clarity regarding VMR in PD.

It would be exciting to explore the trends seen in the in the natural history study; following up drug naïve patients from the point of diagnosis would be of particular interest.
As described previously, there is currently some early research studying iron deposition in the substantia nigra with standard transcranial ultrasound. This research is being undertaken in different centres, and the technique is being evaluated as a potential diagnostic tool in PD. It would be extremely interesting to combine a TCD protocol with one of these transcranial ultrasound protocols to see if a combined approach leads to a more comprehensive, or accurate, diagnostic assessment.

To conclude, this Thesis has made some important contributions to the understanding of CA in PD, and it is the author’s significant hope that work in this field will continue and grow.
REFERENCES

1 Parkinson J. Essay on the Shaking Palsy. London: Sherwood, Neely and Jones, 1817

2 Goetz CG. Excerpts from nine case presentations on general neurology delivered at the Salpetriere Hospital in 1887-8. In: Charcot JM (ed), The Tuesday lessons, New York: Raven Press, 1987


~ 158 ~


29 Marsden CD, Olanow CW. The causes of Parkinson’s disease are being unravelled and rational neuroprotective therapy is close to reality. *Ann Neurol* 1998; 44: S189-S196


33 Chakravarthy VS, Joseph D, Bapi RS. What do the basal ganglia do? A modelling perspective. *Biol Cybern* 2010; 103:237–253

35 Fearnley JM, Lees AJ. Ageing is not involved in the pathophysiology of Parkinson's disease. *Brain* 1991; 114: 2283-2301


40 Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease *J Neurol Neurosurg Psych* 1988; 51: 745-752


patients with early Parkinson’s disease: Results from PD MED EARLY. *Parkinsonism
relat disord* 2012; 18(Suppl 2):S32

measure of functioning and well-being for individuals with Parkinson’s disease. *Qual

PDRG-UK trial comparing three initial treatments in PD *Neurology* 2008; 71: 474–480

60 Itoh Y, Suzuki N. Control of brain capillary blood flow. *JCBMF* 2012; 32: 1167 - 76

61 Kuga N, Hirata T, Sakai I, et al. Rapid and local autoregulation of cerebrovascular blood

62 Kontos HA, Wei EP, Navari RM, et al. Responses of cerebral arteries and arterioles to

63 Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev* 1959;
39: 183-238

64 Aaslid R. Cerebral autoregulation and vasomotor reactivity. *Front Neurol Neurosci*
2006; 21: 216-228

65 Reading SA, Brayden JE. Central role of TRPM4 channels in cerebral blood flow

66 Bevan JA, Hwa JJ. Myogenic tone and cerebral vascular auto-regulation - the role of a

67 Kuschinsky W, Wahl M. Local chemical and neurogenic regulation of cerebral vascular-
resistance. *Physiol Rev* 1978; 58: 656-689

68 Raichle ME, Grubb RL, Mokhtar HG et al. Correlation between regional cerebral blood
flow and oxidative metabolism. *Arch Neuro* 1976; 33: 523-526

70 Paulson OB, Strandgaard S, Edvinson L. Cerebral autoregulation. *Cerebrovasc Brain Met Rev* 1990: 2; 161-192


75 Davis SM, Ackerman RH, Correia JA. Cerebral blood flow and cerebrovascular carbon dioxide reactivity in stroke-age normal controls. *Neurology* 1983; 33: 391-399


*J Neurosci* 2003; 23(27): 9254-9262


87 Evans DH, McDicken WN. Doppler Ultrasound: Physics, Instrumentation and signal processing. Chichester: John Wiley. 2000; 247


Salinet ASM, Robinson TG, Panerai RB. Reproducibility of cerebral and peripheral haemodynamic responses to active, passive and motor imagery paradigms in older healthy volunteers: A fTCD study. J Neurosci Meth. 2012; 206: 143-150


Claasen J, Zhang R. Cerebral autoregulation in Alzheimer’s disease. JCBFM 2011; 31: 1572-1577

Panerai RB. Cerebral autoregulation: From models to clinical applications. Cardiovascular engineering 2008; 8: 42-59


BIBLIOGRAPHY


Aaslid R. Cerebral autoregulation and vasomotor reactivity. In Baumgartner RW (ed.) Handbook on Neurovascular Ultrasound. Karger 2006; 216-228
16 November 2011

Professor Thompson G Robinson
Professor of Stroke Medicine/Honorary Consultant Physician
University of Leicester/University Hospitals of Leicester NHS Trust
Room 537, Robert Kilpatrick Clinical Sciences Building
Leicester Royal Infirmary, Infirmary Square
Leicester
LE1 5WW

Dear Professor Robinson

Study title: Is cerebral autoregulation impaired in idiopathic Parkinson’s Disease?
REC reference: 11/EM/0369

Thank you for your letter of 11 November 2011, 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.

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.

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 been notified of the outcome of 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. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

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

This Research Ethics Committee is an advisory committee to the East Midlands Strategic Health Authority.
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England.
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.

1. The Patient Consent Form should be updated in point 1 to reflect the new version and date of the updated Participant Information Sheet (Patients)

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).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Confirmation should also be provided to host organisations together with relevant documentation.

Approved documents

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

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advertisement</td>
<td>1</td>
<td>26 September 2011</td>
</tr>
<tr>
<td>Covering Letter</td>
<td></td>
<td>03 October 2011</td>
</tr>
<tr>
<td>Evidence of insurance or indemnity</td>
<td></td>
<td>16 August 2011</td>
</tr>
<tr>
<td>Investigator CV</td>
<td></td>
<td>29 September 2011</td>
</tr>
<tr>
<td>Other: CV for Ronney Panerai</td>
<td></td>
<td>03 October 2011</td>
</tr>
<tr>
<td>Other: CV for Amit Mistri</td>
<td></td>
<td>29 September 2011</td>
</tr>
<tr>
<td>Other: CV for Dr Victoria Haunton</td>
<td></td>
<td>28 September 2011</td>
</tr>
<tr>
<td>Other: GP Information Sheet (Volunteers)</td>
<td>1</td>
<td>23 September 2011</td>
</tr>
<tr>
<td>Other: GP Information Leaflet (Patients)</td>
<td>2</td>
<td>08 November 2011</td>
</tr>
<tr>
<td>Participant Consent Form: Patients</td>
<td>1</td>
<td>23 September 2011</td>
</tr>
<tr>
<td>Participant Consent Form: Volunteers</td>
<td>2</td>
<td>08 November 2011</td>
</tr>
<tr>
<td>Participant Information Sheet: Volunteers</td>
<td>2</td>
<td>08 November 2011</td>
</tr>
<tr>
<td>Participant Information Sheet: Patients</td>
<td>2</td>
<td>08 November 2011</td>
</tr>
<tr>
<td>Protocol</td>
<td>1.1</td>
<td>01 September 2011</td>
</tr>
<tr>
<td>REC application</td>
<td></td>
<td>03 October 2011</td>
</tr>
<tr>
<td>Response to Request for Further Information</td>
<td></td>
<td>11 November 2011</td>
</tr>
</tbody>
</table>
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 NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

11/EM/0369  Please quote this number on all correspondence

With the Committee’s best wishes for the success of this project

Yours sincerely

Mr Ken Willis
Chair

Email: lisa.gregory@nottspct.nhs.uk

Enclosures:  *After ethical review – guidance for researchers*

Copy to:  Dr Victoria Haunter  Graham Hewitt, University of Leicester  Mrs Carolyn Maloney
APPENDIX 2

R&D APPROVAL FOR THE STUDY

University Hospitals of Leicester NHS

DIRECTORATE OF RESEARCH & DEVELOPMENT
Director: Professor D Rowbotham
Assistant Director: Dr David Hetmanski
R&D Manager: Carolyn Maloney

Direct Dial: (0116) 258 6351
Fax No: (0116) 258 4226

06/12/2011

Prof Thompson G Robinson
University of Leicester/University of Hospitals of Leicester NHS Trust
Room 537, Robert Kilpatrick Clinical Sciences Building
Leicester Royal Infirmary, Infirmary Square
LEICESTER
LE1 5WW

Dear Prof Thompson G Robinson

Ref: UHL 11087
Title: Is cerebral autoregulation impaired in idiopathic Parkinson’s Disease?
Project Status: Project Approved
End Date: 31/08/2013

I am pleased to confirm that with effect from the date of this letter, the above study now has
Trust Research & Development permission to commence at University Hospitals of Leicester
NHS Trust.

All documents received by this office have been reviewed and form part of the approval. The
documents received and approved are as follows:

<table>
<thead>
<tr>
<th>Document Name</th>
<th>Version Number</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
<td>1.1</td>
<td>01/09/2011</td>
</tr>
<tr>
<td>Participant information Sheet: Patients</td>
<td>2</td>
<td>08/11/2011</td>
</tr>
<tr>
<td>Participant information Sheet: Volunteers</td>
<td>2</td>
<td>08/11/2011</td>
</tr>
<tr>
<td>Participant Consent Form: Volunteers</td>
<td>2</td>
<td>08/11/2011</td>
</tr>
<tr>
<td>Other: GP Information Leaflet (Patients)</td>
<td>2</td>
<td>08/11/2011</td>
</tr>
<tr>
<td>Other: GP Information Leaflet (Volunteers)</td>
<td>1</td>
<td>23/09/2011</td>
</tr>
<tr>
<td>Advertisement</td>
<td>1</td>
<td>26/09/2011</td>
</tr>
<tr>
<td>Participant Consent Form: Patients</td>
<td>2</td>
<td>24/11/2011</td>
</tr>
</tbody>
</table>

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.

Version 5, 20.04.10
We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities. Attached to this letter is a reminder of your responsibilities during the course of the research. Please ensure that you and the research team are familiar with and understand the roles and responsibilities both collectively and individually.

You are required to submit an annual progress report to the R&D Office and to the Research Ethics Committee. We will remind you when this is due.

The R&D Office is keen to support research, researchers and to facilitate approval. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office.

We wish you every success with your research.

Yours sincerely

Carolyn Maloney
R&D Manager

Encs: Researcher Information Sheet
APPENDIX 3
PATIENT INFORMATION SHEET

University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmery Square
Leicester
LE1 5WW
Tel: 0300 303 1573 x 7452
Fax: 0116 232 5847

PARTICIPANT INFORMATION LEAFLET (PATIENTS)

Allerations in Brain Blood Flow in Patients with Parkinson’s Disease
(Is cerebral autoregulation impaired in Idiopathic Parkinson’s Disease?)

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. The study is being carried by Dr Victoria Haunton 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 Romney Farley (Professor of Physiological Measurement) and Dr Amit Misri, Senior Lecturer. Dr Nelson Lo, Consultant Physician from University Hospitals of Leicester NHS Trust, is helping to support the research at Leicester General Hospital.

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 be scored from ‘0’ (no control) to ‘9’ (perfect control). Certain things affect brain blood flow (autoregulation) including changes in breathing rates and movement. However, at present, we do not know if this control of blood flow in the brain (autoregulation) is affected in patients with Parkinson’s disease and/or whether it is affected by the medicines used to treat Parkinson’s disease. 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 both at rest and during short periods of breathing manoeuvres and arm movements. This will be done in both healthy volunteers and in patients with Parkinson’s disease whilst on and off their medication. This knowledge will help doctors to better understand the changes in brain blood flow control in Parkinson’s disease.

2. Why have I been chosen?
Measurements in brain blood flow both at rest and during short periods of breathing manoeuvres and arm movements, will be compared between patients with Parkinson’s disease and volunteers of the same age, sex and blood pressure without Parkinson’s disease.

Patient Information Sheet Version 3, 23rd October 2012
You are being invited to participate in this study as you have Parkinson’s disease.

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 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 on two separate days. Each of these will involve attending the hospital for approximately 2 hours. On the first occasion, you will be asked to take your Parkinson’s medicines as normal on the day of the test. When you attend 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 probe that are used to measure blood flow against both sides of your head. After the readings have stabilised, 2 recordings will be made, each lasting 5 minutes. This will be followed by a 5 minute recording during which you are first asked to rest for 60 seconds and then breathe in time with a metronome (similar to that used by piano players) for 90 seconds before again resting for 2 minutes. After this, a final recording will be made where, after resting for 90 seconds, the researcher will bend your arm backwards and forwards at the elbow for 1 minute before you again rest for 90 seconds.

For the second study test, you will be asked to stop your Parkinson’s medicines for between 12 and 24 hours, depending on the type of medicine that you are on) before again attending the hospital for the same set of measurements as before.

For most patients, this will then be the end of their involvement in the study. However, we may ask a very small group of patients if they would be prepared to have these measurements repeated again every 4 months over the course of 1 year, in order to learn more about the natural history of brain blood flow in Parkinson’s disease. This would mean attending the hospital on 8 occasions rather than 2.

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 heart beat. 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 probe 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. Over-breathing (hyperventilation) may be associated with symptoms of numbness or tingling in the hands, feet and lips, and a feeling of lightheadedness.

For the second part of this study, you will be required to temporarily stop your Parkinson’s medications. This will be for between 12 and 24 hours depending on the type of your medicine.

Stopping your medicines is likely to make you feel slower and titfer and occasionally shaker than normal. In order to try and minimise the effect of this, the study measurement will take place first thing in the morning, so that these symptoms will mostly occur overnight. You will also be asked to bring your medications with you on the day of the second test so that you can take them as soon as the recordings have finished. If, after stopping your medicines you feel...
unwell before attending for the test, then you can, and should, take your medications but must notify the researcher that you have done so.

On the day of the study, you will be monitored closely by the researcher (who is a doctor with specialist training in Parkinson’s disease).

7. What are the possible benefits of taking part?
You should not expect to receive any personal benefit from taking part in this study and it is important that you know that 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 Parkinson’s disease.

8. 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.

9. 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 mechanisms should be available to you.

10. 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. With your permission, your own doctor (your GP) will be notified of your participation in the study.

11. Who is organising and funding the research?
This research is coordinated by Professor Robinson from the University of Leicester.

12. How will I find out the results of the research?
At the end of the study, you will be sent a summary, in plain English, of all of our study findings and conclusions. This can either be posted or emailed to you, depending on your preference.

13. What if I have any concerns?
If you have any concerns or other questions about this study, or the way it has been carried out, you should contact the investigator (Professor Robinson, Telephone 0116 2522182, Facsimile 0116 2525847, Email kae@le.ac.uk)
You may also contact the hospital complaints department (Freephone 08081 788337, Facsimile 0116 2585661, Email pcts.complaints.compliments@uht-tr.nhs.uk).

14. Who has reviewed the study?
The study has been reviewed by the Northampton Research Ethics Committee.

Once again, thank you for taking the time to read this information sheet and for considering taking part in this study.
APPENDIX 4

PATIENT LETTER OF INVITATION

University Hospitals of Leicester NHS
NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 x 7452
Fax: 0116 252 5847
ybh12@le.ac.uk

Dear Sir / Madam,

This is an invitation to take part in a Parkinson’s disease research study which is being run by the University of Leicester. The study has been approved by Parkinson’s UK, who have kindly contacted you on our behalf; none of your personal details have been given to us.

The research study is called “Is cerebral autoregulation impaired in idiopathic Parkinson’s disease?” and is looking at the blood flow to the brain in people with Parkinson’s disease. We hope to use the information from this research to understand how well the blood supply to the brain is controlled in people with Parkinson’s disease, and whether the blood flow to the brain is affected by Parkinson’s medicines. By studying this, we hope to understand more about both Parkinson’s disease and Parkinson’s medicines as a whole. The information from this study may also be helpful in explaining some of the symptoms which can occur in Parkinson’s disease, such as feeling dizzy when you stand up.

The study involves attending the Leicester Royal Infirmary on two separate occasions for an ultrasound scan of your brain. On the first occasion, we would ask you to attend having taken all of your Parkinson’s medicines as normal. On the second occasion we would ask you attend after temporarily stopping your medications for between 12 and 24 hours, depending on the type of medicines you take. Each test takes between 1 and 2 hours in total.

Participation in the study is entirely voluntary, and if you decide to take part you can change your mind at any time. However, before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. I have therefore included a detailed information sheet about the study with this letter, which I hope will provide you with all of this information. I would be very grateful if you could read the information sheet carefully. Take time to decide whether or not you wish to take part and discuss the study with your friends, relatives and your GP if you wish. If you have any queries, or if you would like more information, please get in touch and I will call you back.

We understand that some people might feel anxious about taking part in a research project but I would like to reassure you that the research team have a lot of experience of working with people with Parkinson’s disease, and will do everything we can to help and support you.

If after reading all the enclosed information you decide that you would like to be involved with the research study, then please simply get in touch using the details above.

Thank you very much for your time.

Yours Sincerely,

Dr Victoria Haunton BM, DGM, MRCP(UK)
Clinical Research Fellow, University of Leicester

Enc: Participant Information Leaflet (Patients), Version 3, 23rd October 2012

Trust Headquarters, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW
Tel: 0116 258 8000 Fax: 0116 258 4895 Website: www.uhnl.nhs.uk
Chairman Mr. Martin Hindle Chief Executive Mr. John Adler
Letter of Invitation (patients), Version 1, 23rd October 2012
APPENDIX 5
HEALTHY VOLUNTEER INFORMATION SHEET

University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 x 7452
Fax: 0116 252 5847

PARTICIPANT INFORMATION LEAFLET (VOLUNTEERS)

Alterations in Brain Blood Flow in Patients with Parkinson’s Disease
(Is cerebral autoregulation impaired in Idiopathic Parkinson’s Disease?)

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 a single 60 minute measurement of your blood
pressure and blood vessels. The study is being carried out by Dr Victoria Haughton 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 Ronnie Panerai (Professor of
Physiological Measurement) and Dr Amit Mistry, Senior Lecturer.

Dr Nelson Lo, Consultant Physician from University Hospitals of Leicester NHS Trust, is helping to support the research at
Leicester General Hospital.

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 be scored from
‘0′ (no control) to ‘9′ (perfect control). Certain things affect brain blood flow (autoregulation)
including changes in breathing rates and movement. However, at present, we do not know if
this control of blood flow in the brain (autoregulation) is affected in patients with Parkinson’s
disease and/or whether it is affected by the medicines used to treat Parkinson’s disease. 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 both at rest and during short periods of breathing manoeuvres and arm movements.

This will be done in both healthy volunteers and in patients with Parkinson’s disease whilst on
and off their medication. This knowledge will help doctors to better understand the changes in
brain blood flow control in Parkinson’s disease.

Trust Headquarters, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW
Tel: 0116 258 8000 Fax: 0116 258 4000 Website: www.uh-tr.nhs.uk
Chairman Mr. Martin Hindle Chief Executive Mr. John Adler

Volunteer Information Sheet Version 3, 23rd October 2012

~ 187 ~
2. Why have I been chosen?
Measurements in brain blood flow, both at rest and during short periods of breathing manoeuvres and arm movements, will be compared between patients with Parkinson’s disease and volunteers of the same age, sex and blood pressure without Parkinson’s 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 a single study test when we will arrange for you to come into the hospital for 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. After the readings have stabilised, 2 recordings will be made, each lasting 5 minutes. This will be followed by a 5 minute recording during which you are first asked to rest for 30 seconds and then breathe in time with a metronome (similar to that used by piano players) for 90 seconds before again resting for 2 minutes. After this, a final recording will be made where, after resting for 90 seconds, the researcher will bend your arm backwards and forwards at the elbow for 1 minute before you again rest for 90 seconds.

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 heart beat. 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. Over-breathing (hyperventilation) may be associated with symptoms of numbness or tingling in the hands, feet and lips, and a feeling of lightheadedness.

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 Parkinson’s disease.

8. 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.

Trust Headquarters, Leicester General Hospital, Gwendolen Road, Leicester, LE6 9PW
Tel: 0116 226 6000 Fax: 0116 226 4900 Website: www.ulct.nhs.uk
Chairman Mr Martin Hinde Chief Executive Mr John Adler
Volunteer Information Sheet Version 3, 23rd October 2012

~ 188 ~
9. 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 mechanisms should be available to you.
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, or Parkinson’s disease would mean that you would not be able to further participate in the study.

10. 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 if any health problems are identified that need further tests or treatment.

11. Who is organising and funding the research?
This research is coordinated by Professor Robinson from the University of Leicester.

12. How will I find out the results of the research?
At the end of the study, you will be sent a written summary, in plain English, of all of our study findings and conclusions. This can either be posted or emailed to you, depending on your preference.

13. What if I have any concerns?
If you have any concerns or other questions about this study, or the way it has been carried out, you should contact the investigator (Professor Robinson, Telephone 0116 252382, Facsimile 0116 2525847, Email tzr2@le.ac.uk). You may also contact the hospital complaints department (Freephone 0800 7888337, Facsimile 0116 258 8661, Email nls.complaints.compliments@uhl-tr.nhs.uk).

14. Who has reviewed the study?
The study has been reviewed by the Northampton Research Ethics Committee.

Once again, thank you for taking the time to read this information sheet and for considering taking part in this study.
APPENDIX 6

PATIENT CONSENT FORM

University Hospitals of Leicester NHS
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 x 7452
Fax: 0116 252 5847

PARTICIPANT CONSENT FORM (PATIENTS)
Brain Blood Flow Changes in Parkinson’s Disease
(Is Cerebral Autoregulation Impaired in Idiopathic Parkinson’s Disease?)

Researcher Name: ______________________

I confirm that I have read and understand the Information Sheet (Version 3, dated 23rd October 2012) for the above study, and have had the opportunity to ask questions.

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 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.

Please initial: ☐

Patient Name: ______________________ Date: ____________ Signature: ____________

Witness Name: ______________________ Date: ____________ Signature: ____________

Researcher: ______________________ Date: ____________ Signature: ____________

(File 1 for patient, 1 for researcher, 1 for hospital notes)

Version 3, 29th October 2012

Trust Headquarters, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW
Tel: 0116 258 8835 Fax: 0116 258 4836 Website: www.ubird.nhs.uk
Chairman Mr. Martin Hindle Chief Executive Mr. John Adler
APPENDIX 7

HEALTHY VOLUNTEER CONSENT FORM

University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 X 7452
Fax: 0116 252 5847

PARTICIPANT CONSENT FORM (VOLUNTEERS)
Brain Blood Flow Changes in Parkinson’s Disease
(Is Cerebral Autoregulation Impaired in Idiopathic Parkinson’s Disease?)

Researcher Name: Dr ____________________________

I confirm that I have read and understand the Information Sheet (Version 3, dated 23rd October 2012) for the above study, and have had the opportunity to ask questions.

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 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 participant, 1 for researcher)

Version 3, 29th October 2012
APPENDIX 8

GP INFORMATION SHEET

University Hospitals of Leicester NHS Trust
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW
Tel: 0300 303 1573 x 7452
Fax: 0116 252 5847

GP INFORMATION LEAFLET

Alterations in Brain Blood Flow in Patients with Parkinson’s Disease
(Is cerebral autoregulation impaired in Idiopathic Parkinson’s Disease?)
REC Number: 11/EM/0369

Dear

Re:

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, they will be required to stop their anti-Parkinsonian medications for between 12 to 24 hours. They have been fully counselled regarding this.

Participation in the above study is entirely voluntary.

If you have any further questions regarding this study, then please contact us on the details below.

Yours Faithfully,

Dr Victoria Hautton BM DGM MRCP(UK)
Clinical Research Fellow / Honorary Specialist Registrar

Telephone: 0300 303 1573 x 7452

On behalf of Professor T G Robinson BMedSc, MBBS, MD, FRCP
Professor of Stroke Medicine/Honorary Consultant Physician

Version 3, 23rd October 2012
APPENDIX 9

EDINBURGH HANDEDNESS INVENTORY

*Edinburgh Handedness Inventory*\(^1\)


Your Initials: _______________

Please indicate with a check (✔️) your preference in using your left or right hand in the following tasks.

Where the preference is so strong you would never use the other hand, unless absolutely forced to, put two checks (✔️ ✔️).

If you are indifferent, put one check in each column (✔️ | ✔️).

Some of the activities require both hands. In these cases, the part of the task or object for which hand preference is wanted is indicated in parentheses.

<table>
<thead>
<tr>
<th>Task / Object</th>
<th>Left Hand</th>
<th>Right Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Writing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Drawing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Throwing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Scissors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Toothbrush</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Knife (without fork)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Spoon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Broom (upper hand)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Striking a Match (match)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Opening a Box (lid)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total checks: LH = RH =

Cumulative Total CT = LH + RH =

Difference D = RH – LH =

Result R = (D / CT) \times 100 =

Interpretation:
- (Left Handed: R < -40)
- (Ambidextrous: -40 \leq R \leq +40)
- (Right Handed: R > +40)
APPENDIX 10

HOEHN AND YAHR STAGING OF PARKINSON’S DISEASE

Hoehn and Yahr Staging of Parkinson’s Disease

1 Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967; 17(5); 427-42

• Stage 0: No signs of disease.
• Stage 1: Unilateral symptoms only.
• Stage 1.5: Unilateral and axial involvement.
• Stage 2: Bilateral symptoms. No impairment of balance.
• Stage 2.5: Mild bilateral disease with recovery on pull test.
• Stage 3: Balance impairment. Mild to moderate disease. Physically independent
• Stage 4: Severe disability, but still able to walk or stand unassisted.
• Stage 5: Needing a wheelchair or bedridden unless assisted.
APPENDIX 11

UNIFIED PARKINSON’S DISEASE RATING SCALE (UPDRS)


I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression
0 = None.
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Marked excess of saliva with some drooling.
3 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrostomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

~ 195 ~
9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have startlesation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression.
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.
21. **Action or Postural Tremor of hands**
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. **Rigidity** (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. **Finger Taps** (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. **Hand Movements** (Patient opens and closes hands in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. **Rapid Alternating Movements of Hands** (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. **Leg Agility** (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. **Arising from Chair** (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. **Posture**
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. **Gait**
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. **Postural Stability** (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.
31. Body Bradykinesia and Hypokinesia
(Combining slowness, hesitancy, decreased arm swing, and poverty of movement.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias?
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia
0 = No
1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?
0 = No
1 = Yes

37. Are "off" periods unpredictable?
0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Any sleep disturbances, such as insomnia or hypersonolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?
0 = No
1 = Yes
APPENDIX 12

NON-MOTOR SYMPTOM QUESTIONNAIRE


PD NMS QUESTIONNAIRE

Name: ................................. Date: ...................... Age: ......................
Centre ID: ................................. Male ☐ Female ☐

NON-MOVEMENT PROBLEMS IN PARKINSON’S
The movement symptoms of Parkinson’s are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box ‘Yes’ if you have experienced it during the past month. The doctor or nurse may ask you some questions to help decide if you have not experienced the problem in the past month tick the ‘No’ box. You should answer ‘No’ even if you have had the problem in the past but not in the past month.

Have you experienced any of the following in the last month?

1. Dribbling of saliva during the daytime ☐ ☐
2. Loss or change in your ability to taste or smell ☐ ☐
3. Difficulty swallowing food or drink or problems with choking ☐ ☐
4. Vomiting or feelings of sickness (nausea) ☐ ☐
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces) ☐ ☐
6. Bowel (fecal) incontinence ☐ ☐
7. Feeling that your bowel-emptying is incomplete after having been to the toilet ☐ ☐
8. A sense of urgency to pass urine makes you rush to the toilet ☐ ☐
9. Getting up regularly at night to pass urine ☐ ☐
10. Unexplained pains (not due to known conditions such as arthritis) ☐ ☐
11. Unexplained change in weight (not due to change in diet) ☐ ☐
12. Problems remembering things that have happened recently or forgetting to do things ☐ ☐
13. Loss of interest in what is happening around you or doing things ☐ ☐
14. Seeing or hearing things that you know are told are not there ☐ ☐
15. Difficulty concentrating or staying focused ☐ ☐
16. Feeling sad, ‘low’ or ‘blue’ ☐ ☐
17. Feeling anxious, frightened or panicky ☐ ☐
18. Feeling less interested in sex or more interested in sex ☐ ☐
19. Finding it difficult to have sex when you try ☐ ☐
20. Feeling light headed, dizzy or weak standing from sitting or lying ☐ ☐
21. Falling ☐ ☐
22. Finding it difficult to stay awake during activities such as working, driving or eating ☐ ☐
23. Difficulty getting to sleep at night or staying asleep at night ☐ ☐
24. Intense, vivid dreams or frightening dreams ☐ ☐
25. Talking or moving about in your sleep as if you are ‘acting’ out a dream ☐ ☐
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move ... ☐ ☐
27. Swelling of your legs ☐ ☐
28. Excessive sweating ☐ ☐
29. Double vision ☐ ☐
30. Believing things are happening to you that other people say are not true ☐ ☐
APPENDIX 13

SUMMARY OF PATIENT RECRUITMENT AND SUBSEQUENT INCLUSION IN DATA ANALYSES

35 patients recruited

→ 8 patients excluded as no TCD windows

→ 27 patients

→ 2 patients excluded from all analyses as paired recordings not possible

→ 1 patient excluded from all analyses due to multiple ectopic beats

→ 24 patients

→ DATA ANALYSED FOR CHAPTER 4

→ 2 patients excluded as further ectopic beats

→ 22 patients

→ 1 patient (female aged 85) excluded as noise during motor paradigm recording

→ 1 patient (male aged 79) excluded as did not tolerate respiratory paradigm

→ 21 patients

DATA ANALYSED FOR CHAPTER 5

→ 21 patients

DATA ANALYSED FOR CHAPTER 6
APPENDIX 14

PUBLICATIONS AND PRESENTATIONS ARISING FROM THESIS

ABSTRACTS

Haunton V, Lo N, Panerai R, Robinson T. Cerebral autoregulation indices are not significantly different between the ‘on’ and ‘off’ states of idiopathic Parkinson’s disease. *Cerebrovasc Dis* 2013; 35(suppl 2): 19

POSTER PRESENTATIONS


ORAL PRESENTATIONS

“Cerebral autoregulation indices in the on and off states of Parkinson’s disease.” The 18th Meeting of the European Society of Neurosonology and Cerebral Haemodynamics, Porto, Portugal, 24th May 2013

PAPERS

Haunton V, Salinet ASM, Lo N, Panerai RB, Robinson TG
Cerebral autoregulation in idiopathic Parkinson’s disease: A systematic review of transcranial Doppler studies
*Submitted to Movement Disorders Feb 2014*