CEREBROVASCULAR MECHANISMS OF IDIOPATHIC PARKINSON'S DISEASE; AN ARTERIAL SPIN LABELED PERFUSION MRI STUDY OF CEREBROVASCULAR DYSFUNCTION

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Target Audience: Clinicians with an interest in Parkinson's disease and MR researchers interested in the application of ASL in degenerative disease.
Purpose: Idiopathic Parkinson's disease (IPD) is the second most common neurodegenerative disorder, yet treatment remains symptomatic with a complete absence of disease modifying or neuroprotective agents. In addition there is significant heterogeneity of both motor and non motor clinical features within IPD; yet our understanding of phenotype specific pathophysiologies and subsequent management is lacking. Recent advances in our understanding of the neurodegenerative process have led to the emergence of the 'neurovascular model', which challenges the purely neurocentric model and implicates neurovascular mechanisms as key players in the neurodegenerative process (1). The central aim of this study is to determine whether Arterial Spin Labeling (ASL) measurements of cerebral haemodynamics, coupled with structural measures, can reveal cerebrovascular dysfunction in IPD and whether this is specific to certain IPD phenotypes.
Methods: 14 patients (mean age 65.1± 5.9) with IPD and 14 (mean age 64.6± 4.2) age and cardiovascular risk matched control subjects were scanned on a 3T Philips Achieva MRI scanner. During this visit an assessment of IPD phenotype was made using the unified Parkinson's disease rating scale (UPDRS).*Scan protocol*: A Look-Locker (LL) ASL sequence was used with STAR labeling and 4 readout times of 800, 1400, 2000, 2600 ms, TR: 3500 ms; 3.5 x3.5 x 6 mm voxels; 15 slices; FA: 40 deg; TE: 22 ms with vascular crusher. This was applied continuously during 5 mins of breathing room air followed by 6 mins hypercapnia, administered using a non-rebreathing circuit using the Fenn and Craig technique (2). End-tidal CO_2 ($ETCO_2$)and O_2 were continuously monitored using Powerlab (ADI Instruments, Colorado Springs, USA) and the CO_2 flow-rate was altered to ensure all subjects reached an increased end tidal level approximately 1% above their baseline $ETCO_2$. A FLAIR scan was also acquired and a white matter lesion score determined using the Wahlund rating scale (3). *Analysis*: ASL data were analysed using in-house MATLAB routines using a single blood compartment model (4) adapted for LL readout (5), to produce quantitative maps of cerebral blood flow (CBF) and arrival time (tA) during periods of air and hypercapnia. Whole brain BOLD signal was also extracted during these periods using the sum of the ASL images. Whole brain values for CBF, tA, CVR_BOLD (% BOLD change/ $\Delta ETCO_2$), CVR_CBF (% CBF change/ $\Delta ETCO_2$) and CVR_tA ($\Delta tA/ \Delta ETCO_2$) were calculated. Voxel-wise analysis was also performed using SPM8 to compare baseline CBF and tA maps between patients and controls.
Results: All 14 controls and 13 IPD participants successfully completed the scanning protocol. 2 controls and 2 further IPD participants have been excluded from the analysis of CVR as gas response was outside the expected limits (a change of 4-12 mmHg). After assessment of phenotype 5 patients fulfilled the postural instability and gait difficulty(PIGD) group, 6 the tremor dominant group and 2 were intermediate.

	Controls (n=14)	Patients (n=13)		PIGD (n=5)		Tremor (n=6)		
	Mean ± s.d.	Mean ± s.d.	p (vs. controls)	Mean ± s.d.	p (vs. controls)	Mean ± s.d.	p (vs. controls)	p (vs. PIGD)
Change in ETCO2 (mmHg)	6.6 ± 2.1	5.7±1.8	0.3	6.2±3.1	0.9	5.6±1.2	0.2	0.8
Baseline CBF (ml/min/100ml)	38.0 ± 9.3	35.3±5.8	0.5	38.2±8.5	0.9	35.9±5.7	0.7	0.8
Baseline tA (ms)	1335 ± 165	1532±138	0.005	1461±123	0.1	1640±121	0.0009	0.2
CVR_BOLD (%/ΔmmHg)	0.10 ± 0.03	0.13±0.05	0.09	0.08±0.05	0.1	0.15±0.05	0.1	0.05
CVR_CBF (%/ΔmmHg)	2.2 ± 2.9	4.0±2.9	0.2	1.4±0.5	0.4	5.7±2.9	0.05	0.03
CVR_tA (%/ΔmmHg)	-21.5 ± 7.1	-15.3±11.2	0.2	-16.8±4.8	0.2	-17.1±15.2	0.6	1.0
WM Lesions (score)	1.0±0.6	1.3±0.66	0.9	1.8±0.5	0.003	1.0±0.6	1.0	0.03

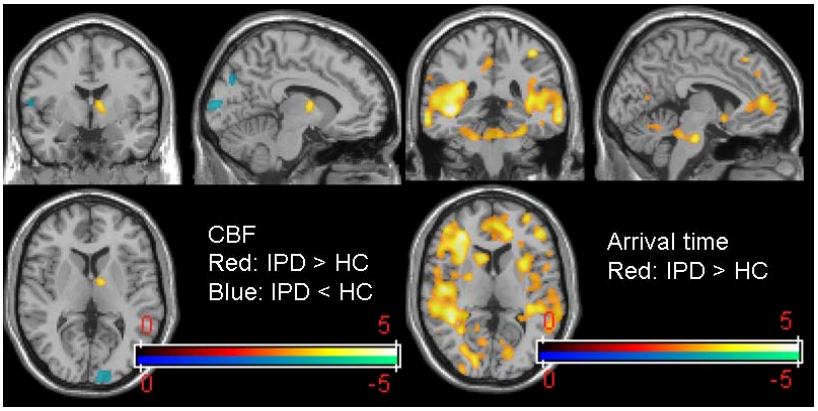

Fig. 1 T statistic maps obtained by comparison of absolute CBF values between patients and controls (on left) and arrival time (on right), thresholded to p<0.005 uncorrected and cluster size 10. Thus displaying positive and negative t values, representing increased and decreased CBF and tA respectively.

The results reveal a significant widespread increase in baseline- tA in the patient group (Table and Figure), which appears to be dominated by the tremor dominant group (Table). There were no significant differences in global baseline CBF but voxel-based analysis revealed focal regions of hyperperfusion in the thalamus of the IPD group compared to controls and areas of hypoperfusion in the posterior cortices. CVR_CBF was significantly higher in the tremor dominant group when compared to controls, with no differences between controls and PIGD group. The WML burden was significantly increased in the PIGD, but not the tremor group.

Discussion and Conclusion – In this study differences in cerebral haemodynamics have been demonstrated between patients and controls. Arrival time is significantly prolonged in the patient group, perhaps indicative of chronic vascular alterations in order to maintain CBF. Prolonged arrival time has been attributed to increased collateral circulation, chronic vasodilatation and/or increased tortuosity of vessels in other studies (6). CBF differences were much more localised, with posterior cortical hypoperfusion in the IPD brain in keeping with recent studies (7). Cerebrovascular reactivity results showed evidence of a differential response between the two IPD phenotypes. Overall the results suggest differences in CV dysfunction between groups with differing phenotypes, potentially reflecting differences in pathophysiology, but at this stage this is speculative and demands further study on the path to finding disease modifying and neuroprotective agents for this disabling disease.

· **References –**1) Grammas P et al. (2011). Expert Reviews in Molecular Medicine. 13; E19 2) Fenn WO and Craig WO (1963). J. appl. Physiol. 18, 1023-1024.3)Wahlund - Stroke 2001; 32:1318-22 4) Parkes LM, Tofts PS (2002). Magn Reson Med; 48(1):27-41.5) Parkes et al, ISMRM 2012 6) Liu Y et al (2012), Magnetic Resonance in Medicine 68:912–922 7) Fernandez-Seara et al.(2012).Neuroimage 59;2743-2750