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SHORT COMMUNICATION

# Is cerebral vasomotor reactivity impaired in Parkinson disease?

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**Abstract**
*Purpose* The ability of a blood vessel to change diameter in response to a change in carbon dioxide concentration is often referred to as vasomotor reactivity. This study aimed to determine whether vasomotor reactivity is impaired in patients with idiopathic Parkinson's Disease in comparison to healthy controls.
*Methods* Transcranial Doppler was used to measure cerebral blood flow velocity in the middle cerebral arteries at baseline and under hypocapnic conditions in 40 patients with idiopathic Parkinson's disease and 50 healthy controls.
*Results/Conclusions* Vasomotor reactivity, assessed under hypocapnic conditions, is not impaired in patients with idiopathic Parkinson's Disease in comparison to healthy controls.

**Keywords** Dopamine · Hypocapnia · Idiopathic Parkinson's disease · Transcranial Doppler · Vasomotor reactivity

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## Introduction

Vasomotor reactivity (VMR) is the ability of cerebral blood flow (CBF) to change in response to changes in arterial partial pressure of $CO_2$ [1]. Hypocapnia induces cerebral vasoconstriction, while hypercapnia induces cerebral vasodilatation. Such changes in the diameter of cerebral blood vessel diameter are largely determined by extracellular pH [2], but the autonomic nervous system has also been implicated [3]. Autonomic dysfunction has been reported in up to 58% of patients with idiopathic Parkinson's disease (IPD) [4].

Dynamic cerebral autoregulation (dCA) refers to how spontaneous fluctuations in arterial blood pressure (ABP) can be measured alongside beat-to-beat measurement of CBF velocity (CBFV). Parameters that assess the integrity of dCA include cerebrovascular resistance (CVR), critical closing pressure (CrCP), resistance area product (RAP) [5] and autoregulatory index (ARI) [6]. Under hypocapnic conditions, dCA has been shown to improve in healthy subjects [7, 8].

The aim of the current study was to address three questions: (1) Is VMR impaired in patients with IPD in comparison to age-matched healthy controls (HC)? (2) Under hypocapnic conditions, do measures of dCA, namely

CVR, CrCP, RAP and ARI, show significant increases of the same magnitude in both HC and IPD patients? (3) Does medication status (ON vs. OFF) affect either VMR or dCA measures under hypocapnic conditions?

## Methods

Patients with IPD were recruited from specialist clinics within the University Hospitals of Leicester NHS trust, and by direct invitation facilitated by Parkinson's disease UK. All had received a diagnosis of IPD according to the UK PD Brain Bank criteria [9] from a specialist physician. Age-matched HC were recruited from the local area or from spouses of patients with IPD. Exclusion criteria were diabetes mellitus, dementia, peripheral neuropathy, ischaemic heart disease and cerebrovascular disease. IPD patients with a dependence on anti-parkinsonian medications for a safe swallow (ensuring no risk of aspiration during their OFF scan) or previously treated with deep brain stimulation were also excluded.

Baseline demographics were collected from all participants including Hoehn and Yahr stage [10] and Unified Parkinson's Disease Rating Scale (UPDRS) scores [11].

All measurements were undertaken in a cardiovascular laboratory, free from distraction and of controlled temperature (20–24 °C). Participants were asked to refrain from consuming large meals, caffeine and alcohol, from smoking cigarettes and from participating in strenuous exercise for 4 h prior to measurements. HC underwent the Transcranial Doppler (TCD) scan once, while patients with IPD undertook the assessments twice, when ON and OFF dopaminergic medication, respectively. Patients were asked to abstain from their PD medications for either 12 or 24 h depending on the preparation.

Participants lay supine on a couch. Heart rate (HR), ABP and end-tidal $CO_2$ ($ETCO_2$) were continuously monitored with the use of a 3-lead echocardiography (ECG) system (Finometer®; Finapres Medical Systems, Amsterdam, The Netherlands), and nasal capnography (Capnocheck Plus oximeter; Smiths Medical, Ashford, UK), respectively. Bilateral insonation of the middle cerebral artery (MCA) was performed using TCD (Viasys Companion III; Viasys Healthcare, Becton Dickinson & Co, Franklin Lakes, NJ) with a 2-MHz probe.

The respiratory manouevre consisted of 60 s of rest, followed by 90 s of the participant breathing through their nose in time with an electronic metronome which gradually increased in frequency during the first 30 s to achieve a respiratory rate of 25 breaths per minute that was subsequently maintained for a further 60 s and finally by 120 s of rest. During the recording the internal plethysmography servo-adjust of the Finometer® was switched off, and a manual ABP calibration was taken at the commencement of the recording by a brachial sphygmomanometer (OMRON 705IT; Omron Corp., Kyoto, Japan). Data were edited using in-house customized software. The ABP signal was calibrated at the start of each recording. The R–R interval was automatically marked using the ECG trace. Mean ABP [(mean arterial pressure (MAP)] and CBFV were calculated for each cardiac cycle, and $ETCO_2$ was synchronized to the end of each cardiac cycle. CVR, CrCP and RAP for each cardiac cycle were calculated using the first harmonic method [5]. Beat-to-beat data were then spline interpolated and re-sampled at five samples per second to create time-series with a uniform time base. An auto-regressive moving average technique [8] was then used to model the dynamic relationship between MAP and CBFV leading to time-varying estimates of ARI, as described previously [7]. Changes in $ETCO_2$ following hyperventilation were marked by visual inspection. Values of population coherent averages and standard deviations were obtained for each variable at each time sample, synchronized by the beginning of the hyperventilation manouevre.

Paired and un-paired *t* tests were used to compare baseline peripheral and central haemodynamics between groups. The effects of hyperventilation on peripheral (HR, MAP) and cerebral haemodynamic parameters (CBFV, CVR, CrCP, RAP, ARI) within each group (IPD ON, IPD OFF, HC) were measured as the difference in their mean values obtained during a 12-s period during hyperventilation and an 18-s period within the 60 s of rest prior to the onset of hyperventilation by paired *t* tests. The 18-s period within the 60 s of rest was used to calculate all baseline peripheral and central haemodynamics.

IPD is a disease of laterality; therefore all cerebral haemodynamic data were calculated for both onset and other brain hemispheres in each medication state. For HC, cerebral haemodynamic data were calculated for the left and right hemispheres. When no significant difference was found on paired *t* tests between the values obtained for the sides, the mean value was taken and used in subsequent analyses.

VMR was calculated for each participant group (IPD ON, IPD OFF, HC) both in terms of absolute differences, namely,

$$\text{VMR (cm/mmHg s)} = (CBFV_H - CBFV_B)/(ETCO_{2\,H} - ETCO_{2\,B}),$$

and relative differences,

$$\text{VMR (\%/mmHg)} = (CBFV_H - CBFV_B/CBFV_B)/(ETCO_{2\,H} - ETCO_{2\,B}),$$

where B is baseline and H is hyperventilation state.

Statistical significance was set at $p < 0.05$. Bonferroni corrections were applied to multiple comparisons. Values obtained were presented as the mean with the standard

deviation (SD) or as the median with the interquartile range (IQR).

## Results

A total of 40 IPD patients and 50 HC were recruited to the study and completed the full protocol. The two groups were well matched with respect to baseline demographics [Electronic Supplementary Material (ESM) Table 1]. The mean disease duration of IPD was 7.5 (SD 17.3) years, and the median HY score was 1.5 (IQR 1–2.5; range 0–3). Median levodopa equivalent daily dose was 545 mg (IQR 300–760; range 150–1315). IPD ON patients had a median total UPDRS score of 34 (IQR 24–40; range 12–61). IPD patients off medication (IPD OFF) had significantly higher motor (Part III) UPDRS scores than those on medications (IPD ON) (20.5 vs. 14; $p < 0.0001$, respectively).

Baseline peripheral and central haemodynamic parameters did not differ between any of the three groups (Table 1).

Hyperventilation significantly increased the HR and reduced $ETCO_2$ in all three groups. Only in the HC did hyperventilation cause a significant reduction in the mean MAP [90.4 (SD 11.4) vs. 89.0 (SD 10.9); $p = 0.02$]. In terms of absolute differences between the three groups, the only significant difference was found between the IPD ON group and HC, where the mean reduction in $ETCO_2$ was significantly greater in the HC than in the IPD ON patients [8.02 (SD 3.3) vs. 6.33 (SD 3.0) mmHg; $p = 0.01$] (Fig. 1).

The only significant difference in cerebral haemodynamics between hemispheres was that of ARI values in IPD ON patients under hypocapnic conditions. The onset hemisphere was found to have a significantly higher mean ARI value than the other hemisphere [5.49 (SD 1.61) vs. 4.95 (SD 1.76); $p < 0.025$]. No significant differences between hemispheres in all other cerebral haemodynamic parameters (CBFV, CVR, CrCP, RAP) within each of the three groups were seen, under either normocapnic or hypocapnic conditions. Consequently, mean hemisphere values were taken to be representative of all cerebral haemodynamic parameters in each of the three groups when comparing baseline to hyperventilation values, except for IPD ON patients where ARI values between baseline and hyperventilation were compared within the individual hemispheres.

Effects of hyperventilation on cerebral haemodynamic parameters were the same in all three groups. Hyperventilation resulted in a significant reduction in CBFV ($p < 0.0001$) but significant increases in CVR ($p < 0.0001$), CrCP ($p < 0.0001$), RAP ($p < 0.0001$) and ARI ($p < 0.001$) (Fig. 1; ESM Table 2).

VMR was not significantly different between the three groups. Comparisons between the IPD ON and HC groups [1.17 (SD 1.11) vs. 1.50 (SD 0.78) cm/mmHg s; $p = 0.12$) and between the IPD OFF and HC groups [1.35 (SD 1.21) vs. 1.50 (SD 0.78) cm/mmHg s; $p = 0.52$) were not significant. Again, dopaminergic status was not found to have a significant effect [1.17 (SD 1.11) vs. 1.35 (SD 1.21) cm/mmHg s; $p = 0.48$]. Calculation of the mean percentage change in CBFV (cm/s) per mmHg change in $ETCO_2$ between baseline and hyperventilation in each of the three groups was also not found to be significant [IPD ON vs. HC: 2.5 (SD 2.6) vs. 2.9 (SD 1.0)%/mmHg, $p = 0.159$; IPD OFF vs. HC: 2.8 (SD 3.0) vs. 2.9 (SD 1.0)%/mmHg, $p = 0.442$; IPD ON vs. IPD OFF: 2.5 (SD 2.6) vs. 2.8 (SD 3.0)%/mmHg, $p = 0.640$).

**Table 1** Summary of baseline peripheral haemodynamic and central haemodynamic parameters of the study population according to patient/control status and medication status

| Haemodynamic parameters | IPD ON ($n$ = 40 patients)[a] | IPD OFF ($n$ = 40 patients)[a] | HC ($n$ = 50 controls) | $p$ value |
|---|---|---|---|---|
| Heart rate (bpm) | 61.9 (7.8) | 63.5 (8.9) | 62.4 (9.9) | >0.01 |
| Mean arterial pressure (mmHg) | 93.6 (13.7) | 95.3 (13.2) | 90.4 (11.4) | >0.01 |
| Systolic blood pressure (mmHg) | 129.1 (18.0) | 133.3 (16.8) | 137.6 (19.2) | >0.01 |
| Diastolic blood pressure (mmHg) | 74.3 (8.4) | 77.4 (8.0) | 77.3 (9.1) | >0.01 |
| End-tidal $CO_2$ (mmHg) | 36.4 (4.1) | 36.8 (4.4) | 37.5 (3.8) | >0.01 |
| Cerebral blood flow velocity (cm/s) | 46.8 (10.1) | 48.8 (12.3) | 49.79 (12.7) | >0.01 |

Data in table are presented as mean with the standard deviation in parenthesis

HC, Healthy controls

[a] The same patients were in the idiopathic Parkinson's disease (IPD) ON group and IPD OFF group. IPD ON patients were those with IPD on dopaminergic medication at time of scan; IPD OFF patients were those IPD patients who were off dopaminergic medication at time of scan

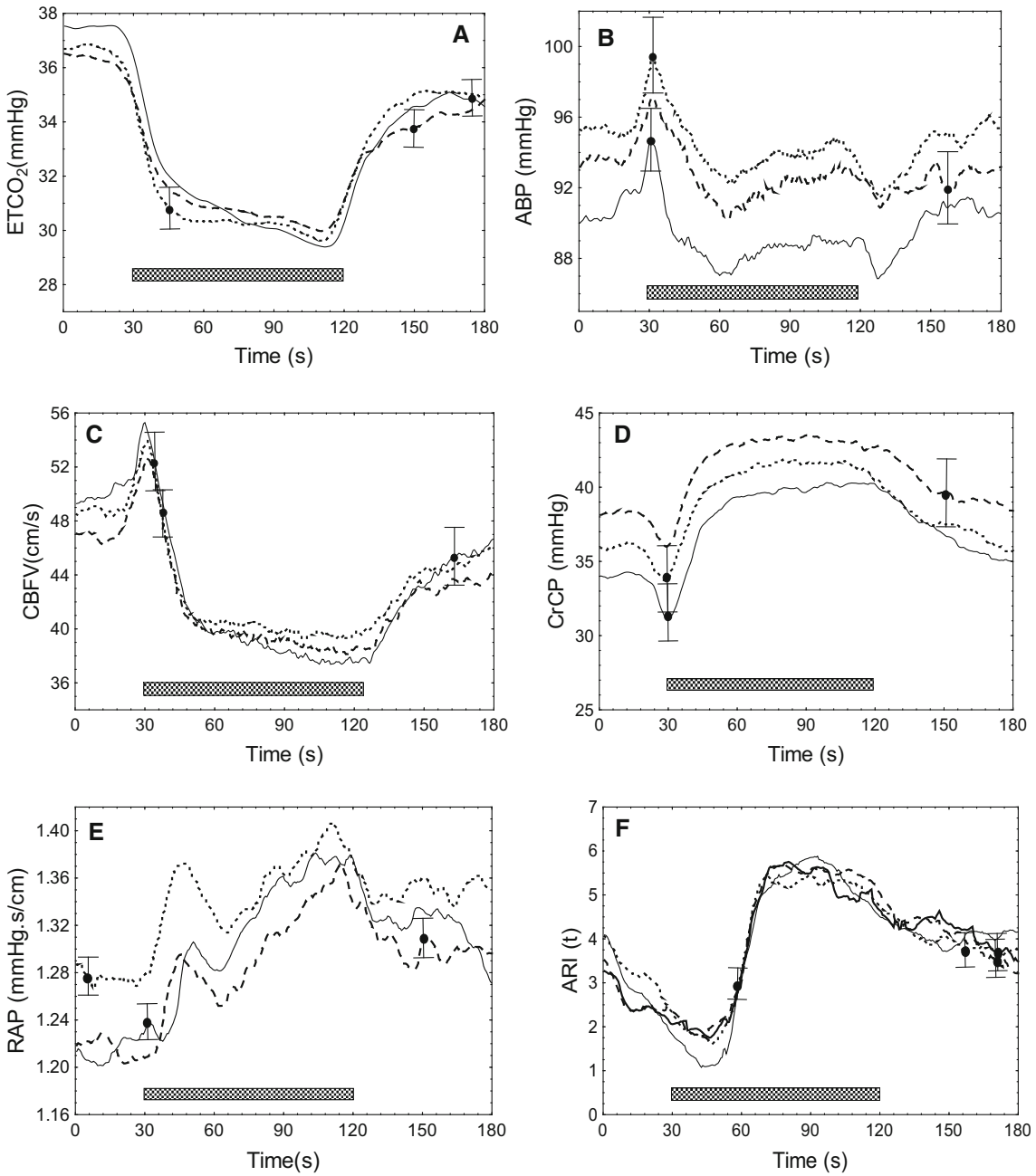


**Fig. 1** Effects of hyperventilation on end-tidal $CO_2$ (*ETCO*$_2$), arterial blood pressure (*ABP*), cerebral blood flow velocity (*CBFV*) and measures of dynamic cerebral autoregulation [critical closing pressure (*CrCP*), resistance area product (*RAP*), autoregulatory index (*ARI*)]. **a–f** Changes in $ETCO_2$ (**a**), ABP (**b**), CBFV (**c**), CrCP (**d**), RAP (**e**) and ARI (**f**) during the hyperventilation manouevre in patients with idiopathic Parkinson's disease while on medication (IPD ON) and off medication (IPD OFF) at time of scan, and in healthy controls (HC). For clarity only the largest ± 1 standard error is represented at the point of occurrence for each comparison group: *dashed line* IPD ON, *dotted line* IPD OFF, *continuous line* HC. *Horizontal bar* Duration of hyperventilation

## Discussion

The results of this study demonstrate that dCA and measures of VMR, assessed under hypocapnic conditions, do not significantly differ between HC and patients with IPD, irrespective of medication status.

To date there have been five studies investigating VMR in IPD [12–16]. Of these five studies, only one study found IPD participants to have impaired VMR in comparison to age-matched HC [16], two studies failed to include a comparative HC group [14, 15], while the latest studies using novel magnetic resonance imaging techniques

reported findings in agreement with those of our study [12, 13]. Importantly, these latter studies boasted larger participant numbers and more definite measures of monitoring $ETCO_2$ levels.

To allow more in-depth interpretation of our results, we also studied the temporal patterns of CrCP, RAP and ARI, as shown in Fig. 1. With the onset of hypocapnia (Fig. 1a), ABP shows a marked peak in all three groups, which is transmitted to CBFV (Fig. 1c). This marked change in ABP is likely to result from sympathetic stimulation caused by the stress of breathing in time with the metronome. The delayed peak in RAP (Fig. 1e) is likely to represent the myogenic response to the ABP peak and, together with the rise in CrCP, causes the rapid decrease of CBFV (Fig. 1c). Of considerable interest, the rise in ARI with hypocapnia (Fig. 1f) is delayed by approximately 30 s. One possible explanation is that dCA is initially depressed by the sympathetic stimulation associated with the alert reaction of hyperventilation [8]. After 60 s, the relatively small surge in ABP is manifest as a much steeper rise in RAP, possibly due to the much increased effectiveness of dCA, as indicated by the higher values of ARI in Fig. 1f. This secondary rise in RAP explains the continuing reduction in CBFV (Fig. 1c), since CrCP remains relatively constant during this phase (Fig. 1d). Although none of these cerebrovascular parameters showed significant differences due to IPD or dopamine, it is important to take into account the complex interactions induced by hypocapnia in future studies to allow a better understanding of the contribution of different co-variates.

A limitation of our study is not assessing VMR under hypercapnic conditions, which would enable assessment of both the vasomotor range and vasodilatation reserve in patients with IPD and HC. Due to physiological adaptations of vascular beds, in diseased states resting perfusion and vasoconstriction are typically found to be preserved states while vasodilatation reserve is not. However, in conclusion, our study reports that VMR, when assessed under hypocapnic conditions, in patients with IPD, irrespective of medication status, is not impaired in comparison to that of HC. Future studies should also determine the effects of hypercapnia on VMR in patients with IPD in comparison to HC.

#### Compliance with ethical standards

**Ethical approval** The study was obtained from the Northampton Research Ethics Committee, UK (reference 11/EM/0369).

**Informed consent** All participants were over 18 years of age and gave written informed consent.

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