

Cerebral Vasoreactivity in Parkinson's Disease: A Cross-Sectional Pilot Study in a Hispanic Cohort

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Abstract

Background: Abnormalities in cerebral vasomotor reactivity (CVR) in patients with idiopathic Parkinson's disease (IPD) have not been well determined; nonetheless, a vascular mechanism may be involved in some patients with this neurodegenerative disorder. The objective of this study was to compare CVR in IPD patients and subjects without Parkinson's disease.

Methods: A cross-sectional pilot study was conducted including Hispanic IPD patients and a control group. CVR in the middle cerebral arteries (MCA) was measured by transcranial Doppler ultrasonography (TCD) at rest and after inhalation of 7% CO₂. A comparison of CVR in the MCA of both groups was performed.

Results: 27 IPD Hispanic patients with a recent brain MRI were evaluated. The CVR showed a significant difference between the two groups (p=0.044). The CVR in 70% of the IPD patients was low in comparison to control subjects.

Conclusion: IPD patients are prone to exhibit diminished CVR in comparison with control group. Further studies may demonstrate this tendency and its implication in disease severity.

Keywords: Cerebral vasoreactivity; Parkinson's disease; Transcranial Doppler ultrasonography

Abbreviations: AD: Alzheimer Disease; BMI: Body Mass Index; BOLD: Blood Oxygen Level Dependent; CBF: Cerebral Blood Flow; CO₂: Carbon Dioxide; CVR: Cerebral Vasomotor Reactivity; DFV: Diastolic Flow Velocity; DM2: Diabetes Mellitus Type 2; fMRI: Functional Magnetic Resonance Imaging; H&Y: Hohen and Yahr Scale; HTN: Hypertension; IPD: Idiopathic Parkinson's Disease; LED: Levodopa Equivalence Dose; MCA: Middle Cerebral Arteries; MFV: Mean Flow Velocity; MMSE: Folstein's Mini-Mental Examination; MoCA: Montreal cognitive assessment; MRI: Magnetic resonance imaging; PET: Positron emission Tomography; SFV: Systolic Flow Velocity; SPECT: Single Photon Emission Computed Tomography; TCD: Transcranial Doppler Ultrasonography

Introduction

Idiopathic Parkinson's disease (IPD) is a progressive neurodegenerative disorder frequently associated with orthostatic hypotension and syncope with different underlying mechanisms. In IPD, the vagal nuclei are primarily affected and various neurocardiological and neurocirculatory abnormalities result from the degeneration of both central and peripheral autonomic centers, with this suggesting that autonomic insufficiency is a common and possible early, non-motor feature of IPD [1,2]. Recently, there has been considerable interest in the disturbance of the neurovascular unit function and its role in neurodegeneration. This neurovascular unit is a complex, metabolically active system of endothelial cells and glial cells in close proximity to a neuron, involved in the regulation of the cerebral autoregulatory capacity, which is the brain's ability to maintain a constant cerebral blood flow (CBF) despite changes in cerebral vasculature [3]. These effects are mediated by changes in diameters of cerebral arterioles and therefore, this phenomenon is described as the cerebral vasomotor reactivity (CVR). Various stimuli used to evaluate vascular function and CVR including hypercapnia, induced by apnea

or inhalation of CO₂ or by the administration of acetazolamide, all of which produce cerebral vasodilation, have been previously described [4], and its effects can be estimated directly by neuroimaging methods (e.g. single photon emission computed tomography (SPECT), positron emission tomography (PET), functional magnetic resonance imaging (fMRI) or indirectly through the measurement of blood flow velocity in major cerebral arteries by transcranial Doppler Ultrasonography (TCD), which allows a dynamically evaluation with high temporal resolution.

There is evidence suggesting that CVR might be impaired in neurodegenerative diseases. Although the contribution of CVR impairment to the pathogenesis of neurodegenerative diseases is not certain, it might be suspected that a reduced cerebrovascular reserve is an additional deteriorating factor in disease progression. In Alzheimer disease (AD), most studies with age-matched control groups reported a significant impairment of CVR, and studies reporting normal CVR in AD often did not make direct comparisons with age-matched control groups and/or were underpowered [5].

Lately, this issue has been addressed in a few studies with IPD patients, however, due to contradictory results; the alteration in CVR remains unclear.

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The objective of this study was to evaluate CVR by TCD in middle cerebral arteries (MCA) in IPD patients and matched control group at rest and after inhalation of CO₂.

Patients and Methods

A cross-sectional pilot study was conducted on Hispanic patients with IPD. A neurologist expert in movement disorders made the clinical diagnosis using the United Kingdom Brain Clinical criteria as modified by Douglas [6]. All IPD patients were attended at the Neurology and Neurosurgery Institute, Centro Medico Zambrano-Hellion of the Tecnológico de Monterrey between June and September 2014.

The clinical records of 120 Hispanic IPD patients were evaluated and 30 patients were recruited, those who consented to measurement of CVR, with a recent brain MRI available (performed less than 3 months before) and without exclusion criteria: clinical or radiological features suggesting secondary or atypical Parkinsonism, those with significant stenotic changes (more than 70%) of the extracranial carotid arteries based on a carotid Doppler assessment, or when it was not possible to obtain any transtemporal window.

Age, gender, body mass index (BMI), MMSE and MoCA results and comorbidities matched individuals without IPD, recruited from a cohort of adult patients with cardiovascular risk factors without a family history of neurodegenerative disease of the Neurology Department at the UANL University Hospital, conformed the control group.

All patients were assessed in "on" state of Parkinson's disease during a two and a half hour session. The clinical data recorded included time since diagnosis, disease severity using the Hohen and Yahr scale (H&Y), cognitive status using Folstein's Mini-Mental Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), since a recent study found that the MoCA is an adequate brief and well-validated screening tool for mild cognitive impairment in IPD and Dementia associated to IPD validated against patients with normal cognition and healthy controls [7]. Additionally, the levodopa equivalence dose (LED) adjusted by body weight (milligrams per kg) was determined, in levodopa equivalency units, for each anti-parkinsonian drug through conversion factors as proposed by Cervantes-Arriaga [8].

CBF was measured at baseline in both MCA using TCD (Sono Site, Titanm, Bothell WA, USA). Control subjects and IPD patients remained at rest in the semi-Fowler's position for ten minutes while vital signs were taken. Systolic and diastolic CBF velocities and mean flow velocity (MFV) were measured in MCA at rest and after a 5 min exposure to 7% CO₂ through a face mask. The CVR was defined using the formula: $CVR (\%) = (MFV_{\text{post-hypercapnia}} - MFV_{\text{at rest}}) \times 100 / MFV_{\text{at rest}}$. A CVR above 5% of the value at rest was considered positive [9].

CBF and CVR measures were taken from the right MCA for convenience in subjects with a carotid stenosis of 50% or less with hemodynamic repercussion determined by carotid Doppler ultrasound or when it was not possible to obtain the transtemporal window. The Institutional Ethics Committee reviewed and approved the study design. Written informed consent was obtained from all patients before inclusion.

Statistical analyses were performed using SPSS version V.21 for McIntosh. Frequency, median, interquartile range, means and standard deviations were used for descriptive analyses. Comparative analyses between TCD measures pre and post hypercapnia test were performed using Wilcoxon Test in both groups. CVR and demographic and clinical

characteristics were performed using the chi-square test for nominal variables, and the Mann-Whitney U test for continuous variables. Results with a p<0.05 were considered significant.

Results

Among the 30 IPD patients recruited, three were excluded due to a poor acoustic transtemporal window, leaving 27 patients for analysis. Twenty-one were men (78%) and 6 were women (22%). Mean age was 68 ± 10.02 years and mean time since diagnosis was 5.2 ± 4.7 years. IPD patients were compared with a matched control group that included 27 subjects as shown in Table 1.

A Wilcoxon signed-rank test determined that after a hypercapnic stimulus there was a statistically significant increase in medians of all TCD parameters in the control group but not within the IPD group (Table 2). The measured change was more significant in relation to MFV. A comparative analysis of the IPD group and control group showed a statistically significant difference in percentage differences of MFV

Variables	IPD group (n=27)	Control group (n=27)	p-value
Gender n (%)			
Men	21 (78)	20 (74)	0.500
Women	6 (22)	7 (26)	
Age (years)	68 ± 10.2	69 ± 7.2	
Men	68 ± 10.4	70 ± 7.2	0.822
Women	67 ± 9.9	69 ± 7.2	
Education (years)	14.2 ± 5.7	13.2 ± 9.5	0.719
BMI (kg/m ²)	28.5 ± 4.62	29.1 ± 4.5	0.775
Smoking n (%)	18(66)	16(59)	0.779
DM2 n (%)	4 (15)	7 (26)	0.250
HTN n (%)	13 (48)	14 (52)	0.500
Dyslipidemia n (%)	10 (37)	6 (22)	0.186
MMSE	27.1 ± 4.1	25.6 ± 3.7	0.735
SFV Pre-exposure	62.6 ± 15.4	56.7 ± 20.8	0.354
DFV Pre-exposure	23.3 ± 7.0	24.1 ± 10.7	0.993
MFV Pre-exposure	34.5 ± 9.7	35.0 ± 13.7	0.904
SFV% difference	5.7 ± 22.7	10.4 ± 19.8	0.229
DFV% difference	11.3 ± 22.3	13.9 ± 20.2	0.609
MFV% difference	6.0 ± 23.2	11.4 ± 16.7	0.044

SFV: Systolic Flow Velocity; DFV: Diastolic Flow Velocity; MFV: Mean Flow Velocity
Continuous variables are expressed in means ± SD. Groups were compared using Mann-Whitney U test for continuous variables and Fisher Exact Test for nominal variables. Statistic significance: p<0.05

Table 1: Demographic characteristics of IPD patients and control subjects. Comparative analysis of CVR amongst groups.

Groups	TCD parameters	Baseline	After CO ₂ test	p-value
IPD patients	SFV	62 ± 22	66 ± 22	0.602
	DFV	22 ± 12	28 ± 11	0.053
	MFV	37 ± 17	35 ± 15	0.553
Control subjects	SFV	57 ± 39	63 ± 36	0.007
	DFV	23 ± 16	25 ± 19.6	0.002
	MFV	34.7 ± 25.8	37 ± 24	0.001

MCA: Middle Cerebral Artery; TCD: Transcranial Doppler Ultrasonography; SFV: Systolic Flow Velocity; DFV: Diastolic Flow Velocity; MFV: Mean Flow Velocity
Continuous variables expressed in median+IQR. Wilcoxon Test was used for continuous variables. Statistic significance: p<0.05

Table 2: Results of TCD in the MCA in IPD and control groups.

Variable	CVR ≤ 5% (n=19)	CVR>5% (n=8)	p-value
Age (years)	66.3 ± 9.5	71.3 ± 11.9	0.180
Gender, n (%)			
Men	13 (68)	8 (100)	0.092
Women	6 (32)	0	
BMI (kg/m ²)	28.4 ± 4.2	28.8 ± 5.7	0.858
Smoking, n (%)	12(63)	6(75)	0.676
DM2, n (%)	4 (21)	0	0.221
HTN, n (%)	11 (58)	2 (25)	0.127
Dyslipidemia, n (%)	5 (27)	5 (63)	0.091
Years since diagnosis	5.8 ± 4.2	8.25 ± 5.8	0.360
Levodopa treatment, n (%)	16 (84)	8 (100)	0.331
Dopaminergic agonist treatment, n (%)	14 (74)	6 (75)	0.668
Weight-adjusted LED (mg/kg)	13.2 ± 9.7	18.7 ± 12.7	0.217
Hoehn & Yahr stage	2.5 (1.3-3.5)	1.8 (1.4-2.6)	0.696
MMSE	26.6 ± 4.6	28.6 ± 1.8	0.449
MoCA	23.3 ± 6.1	25.9 ± 3.6	0.515

CVR: Cerebral Vasoreactivity. IPD: Idiopathic Parkinson's Disease

Continuous variables expressed in means ± SD. Hoehn & Yahr stage is reported in median and IQR. Fisher Exact Test was used for nominal variables; Mann-Whitney U was used for continuous variables. Statistic significance: p<0.05

Table 3: Analysis of CVR and clinical characteristics in IPD patients.

in the MCA, with an expected lower increase in CBF in IPD patients after the hypercapnic stimulus (Table 1). There were no adverse events during or after exposure to CO₂. Only 30 % of IPD patients showed a change >5% in cerebral MFV; whereas 70% presented increases below 5%, no change at all, or showed a decrease in MFV. No statistically significant difference was found through a comparative analysis of IPD patients with CVR>5% and those with CVR<5% with respect to age, gender, comorbidities and clinical severity (Table 3).

Discussion

In recent years, a variety of studies have used TCD to estimate CVR in chronic diseases such as in cerebral microangiopathy, migraine, carotid occlusion, and other neurological disorders. Few have estimated CVR in IPD. Most of these reports have used acetazolamide and the apnea test [9]. Some authors have established that a normal CVR is about 6.19% (SD 3.67) [10], although variations exist depending on the methodology used to evaluate CVR. In the present study, we used inhalation of 7% CO₂ and TCD ultrasound. IPD patients showed a high prevalence of abnormal CVR (70%); whereas the CVR based on the percentage change from the top MFV normal 5%, 30% of IPD patients and 60% of controls showed CVR>5%, with a sample group of 27 subjects and a type I error of 5%, post hoc power analysis was 83%.

Similar to our study, Zamani [10] evaluated CVR in 44 IPD patients using the carbon dioxide test and detected an abnormal CVR in 34% of Parkinson patients using a cutoff point of an increase of 5% in CBF velocity in the right MCA after exposure to a hypercapnic stimulus, despite age and gender, disease duration, and type of treatment. However, impaired CVR was not associated with the presence of orthostatic hypotension in this study. Although we did not assess the presence of orthostatic hypotension in our IPD population, it could be interesting to see if the high prevalence of abnormal CVR we found is associated with this clinical manifestation since impaired cerebral autoregulatory capacity has been considered to be caused by neurogenic deficiency, normally mediated through the autonomic system, suggesting a degeneration of intracranial sympathetic innervation [9]. On this regard, a more recent study was also not able to find statistically

significant differences in CVR between groups of IPD patients with and without orthostatic hypotension, but there was a difference compared with healthy individuals against above mentioned groups [11].

In contrast, Hanby et al. did not find impairment in vasomotor reactivity measured by TCD between IPD patients and healthy individuals; however, their study was conducted under hypocapnic conditions. These results may be explained due to physiological adaptations of vascular beds in diseased states where resting perfusion and vasoconstriction are typically found to be preserved, while vasodilatation reserve is not [12].

Authors have recently postulated that the alteration of CVR in IPD patients might be caused by effects of levodopa treatment. Bouhaddi [13] demonstrated a slight alteration in autonomic cardiovascular control in Parkinson's disease and presented evidence suggesting that treatment with levodopa could aggravate autonomic control dysfunction. Nevertheless, in the present study, no relationship was found between CVR and levodopa treatment, as also suggested by Vokatch [14] who indicate that an alteration in CVR is independent of dopaminergic treatment. Similarly, a recent study by Krainik using fMRI to assess CVR after a hypercapnic stimulus in 20 IPD patients, demonstrated that levodopa administration has no influence on CVR [15].

The present study has several limitations including a small patient sample, operator dependent ultrasonography, and that TCD estimates one global parameter of CBF evaluating only the proximal portion of intracranial arteries. However, the hypercapnic test represents a non-invasive and accessible functional assessment where results are feasible to be reproduced in a larger number of IPD patients. Also, it was notable that there was a high prevalence of men in this study, a situation that can affect the representativeness of our findings in other IPD populations.

Our findings of altered CVR in IPD subjects are relevant due this mechanism could contribute to exacerbate their clinical condition, and may constitute a potential line of research for the development of new drugs.

Conclusion

Patients with IPD exhibit a decrease in CVR compared with control group under a hypercapnic stimuli measured by TCD, indicating that cerebral hemodynamic alterations may be present in IPD. Further studies with a larger number of patients are needed to determine if this tendency prevails and its implication in disease severity and outcome.

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