Cardiovagal Baroreflex Sensitivity in Parkinson's Disease and Multiple-System Atrophy

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Background and Purpose   Parkinson's disease (PD) and multiple-system atrophy of the parkinsonian type (MSA-P) are progressive neurodegenerative disorders that in addition to dysfunction of the motor system also present with features of dysautonomia, frequently manifesting as orthostatic hypotension (OH). The pathophysiology of OH has been proposed to differ between these two disorders. This study investigated the spontaneous and cardiovagal baroreflex sensitivity (BRS) in Parkinson's disease patients with orthostatic hypotension (PD_{OH}) and multiple system atrophy of Parkinsonian type with orthostatic hypotension in an attempt to differentiate the two disorders.

Methods   Two methods were used for determining the BRS: a spontaneous method (spontaneous BRS) and the reflexive baroreflex gain (cardiovagal BRS) from phases II and IV of the Valsalva maneuver (VM) in PD_{OH} and MSA-P_{OH}.

Results   The spontaneous BRS (5.04±0.66 ms/mm Hg vs. 4.78±0.64 ms/mm Hg, p=0.54) and the cardiovagal BRS from phase II of the VM (0.96±0.75 ms/mm Hg vs. 1.34±1.51 ms/mm Hg, p=0.76) did not differ between PD_{OH} and MSA-P_{OH}, but the cardiovagal BRS from phase IV of the VM (0.03±0.07 ms/mm Hg vs. 2.86±2.39 ms/mm Hg, p=0.004) was significantly lower in PD_{OH}.

Conclusions   The cardiovagal BRS from phase IV of the VM has potential for differentiating PD_{OH} and MSA-P_{OH}, indicating a difference in the pathophysiological mechanisms underlying the autonomic dysfunction in the two disorders.

Key Words   baroreflex sensitivity, valsalva maneuver, Parkinson's disease, multiple system atrophy.

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INTRODUCTION

Parkinson's disease (PD) and multiple-system atrophy of the parkinsonian type (MSA-P) are two progressive neurodegenerative disorders that in addition to similar motor symptoms also present with symptoms of dysautonomia. Among the various symptoms of autonomic dysfunction, orthostatic hypotension (OH) is a common presentation in both of these disorders.[1-3] It has been suggested that despite their autonomic symptoms being similar, the underlying pathophysiological mechanisms are different.[4,5] Several studies have examined the baroreflex sensitivity (BRS) as a measure of autonomic function in PD and multiple-system atrophy (MSA). Some studies have shown BRS to be similarly low in PD and MSA.[5-7] while others have shown it to be significantly smaller in MSA.[8]

These previous studies are subject to a few important caveats. Some of them assessed the BRS using a spontaneous method while others used a reflexive method, with no compari-

son being performed between the two. It is well documented that MSA-C patients (MSA of the cerebellar type) and MSA-P patients show differences in both the severity and onset of OH[9] and it is noteworthy that several studies combined these patients in their analyses.[7,8] It has also been demonstrated that BRS is lower in Parkinson's disease patients with orthostatic hypotension (PD_{OH}) than in those without OH[5,10] and that a lower BRS is correlated with a higher score on the Hoehn and Yahr scale of severity.[8] BRS has also been shown to differ between males and females.[11,12] However, the groups included in all of the previous studies were heterogeneous in nature and the confounding factors were not taken into consideration.

In the present study we assessed the BRS as a spontaneous response (spontaneous BRS) and as a cardiovagal reflexive response (cardiovagal BRS) using the Valsalva maneuver (VM) in male PD_{OH} patients with a score on the Hoehn and Yahr scale of 1−3 and in male patients with multiple-system atrophy of the parkinsonian type ($MSA-P_{OH}$) both the groups having OH, taking care to maintain homogeneity in the groups. We also examined the sympathetic and parasympathetic modulation of the heart and the vasculature by measuring the heart rate variability (HRV) and the blood pressure variability (BPV).

METHODS

Patients with PD diagnosed using the United Kingdom Brain Bank criteria[13] and with MSA-P diagnosed using the Second Consensus Criteria 2008[14] were recruited from the Neurology Outpatient Department of the All India Institute of Medical Sciences (AIIMS), New Delhi, India. Patients with cerebrovascular and/or cardiovascular diseases and PD patients with scores on the Hoehn and Yahr scale of 4 or 5 were excluded from the study. The recruited patients were queried in interviews for the presence of symptoms of OH, which resulted in 16 PD patients and 22 MSA-P patients being selected and then tested for the confirmation of OH using a head-up tilt test in the Autonomic and Vascular Function Laboratory of the Department of Physiology, AIIMS (Table 1).

The study was conducted from April 2012 to November. Subjects were included in the study only after they had provided written consents. All subjects were asked to refrain from exercise and from consuming alcohol, caffeine, and nicotine for at least 4 hours prior to the tests.

Protocol

Three-lead electrocardiography (ECG) was used to measure the heart rate and the interbeat interval. The beat-to-beat blood pressure was measured by finger photoplethysmography (Finometer® model 2, Finapress Medical Systems, Amsterdam, the Netherlands). After 15 min of rest, ECG lead II and beat-to-beat blood pressure recordings were made for 5 min in the supine posture. The data were used to assess BRS as well as for power spectral analysis. After a 2-min rest in the sitting position, the subjects were asked to perform the VM at an expiratory pressure of 40 mm Hg for 15 s. Simultaneous ECG and beat-to-beat blood pressure recordings were then made.

Spontaneous BRS

The spontaneous BRS was computed from continuous interbeat interval recordings of the ECG and beat-to-beat changes in blood pressure using Nevrokard software. The BRS was quantified using the sequence method that is based on computer-based identification of spontaneously occurring sequences of three or more consecutive beats characterized by either a progressive rise in blood pressure and lengthening of the R-R interval or by a progressive decrease in blood pressure and shortening of the R-R interval. The criteria used for identifying the sequences were an R-R interval variation of greater than 5 ms, BP changes greater than 0.5 mm Hg, sequences longer than three beats, and a sequence correlation coefficient greater than 0.85.[15]

Cardiovagal BRS

Analyses were performed during phases II and IV of the VM. Systolic blood pressure values were linearly regressed against the corresponding R-R intervals on a beat-to-beat basis. The

Table 1. Demographic data

Subjects	*n*	Gender	Age (years)	Duration of the disease (years)	NIDDM	Hypertension	Levodopa	Fludrocortisone
PD+OH	11	Males	53±6	1.3±0.48	N/A	N/A	10	0
PD no OH	5	Males	52±5	1.4±0.54	N/A	N/A	5	0
MSA-P+OH	14	Males	52±5	1.5±0.51	N/A	N/A	13	7
MSA-P no OH	8	Males	51±4	1.37±0.51	N/A	N/A	7	0

Only male patients without the history of any co-morbid conditions were chosen for the procedure. Special care was taken to rule out patients of MSA-C and PD patients with severity of IV and V on the Hoehn and Yahr scale.
NIDDM: non insulin dependent diabetes mellitus, MSA-P: multiple-system atrophy of the parkinsonian type, OH: orthostatic hypotension, PD: Parkinson's disease.

cardiovagal BRS was quantified from the slope of the relationship between the cardiac interbeat interval and the systolic blood pressure during phase II of the VM.[7] In phase IV, the cardiovagal BRS was quantified from the point at which the R-R interval began to lengthen and continued to the point of maximum elevation of the systolic blood pressure. The slope of the relationship between the R-R interval and the systolic blood pressure was used as a measure of cardiovagal BRS if the correlation coefficient exceeded 0.80.[16]

Spectral analysis of heart rate variability and blood pressure variability

Short-term HRV was quantified from 5-min ECG recordings using a recommended method[17] implemented in Nevrokard HRV software (version 6.2.0, Slovenia). Briefly, consecutive R-R intervals were obtained from ECG recordings followed by quantification of HRV in the time domain and analysis in the spectral (frequency) domain. Time-domain measures included the standard deviation of all normal R-R intervals, the root-mean-square standard deviation, the difference between adjacent R-R intervals of more than 50 ms, and the percentage difference between two consecutive R-R intervals of more than 50 ms. Frequency domain measures were obtained using Fast Fourier Transform technique to quantify power in 2 bands i.e. low frequency (LF) 0.04−0.15 Hz, and high frequency (HF) 0.15−0.40 Hz followed by calculation of LF/HF ratio. Total power was estimated with the sum of the frequencies.[17]

Short-term BPV was computed in the time and frequency domains using methods in Nevrokard software similar to those used for HRV.

RESULTS

Spontaneous baroreflex sensitivity

The BRS obtained by the spontaneous method was found to be similar in PD and MSA-P patients. The BRS systolic blood pressure was 5.04±0.66 ms/mm Hg in PD and 4.78±0.64 ms/mm Hg in MSA-P (p=0.54) (Fig. 1A); the corresponding values for the BRS mean blood pressure were 7.40±1.14 ms/mm Hg vs. 7.23±0.71 ms/mm Hg (p=0.89).

Cardiovagal baroreflex sensitivity

Data obtained in phases II and IV of the VM were assessed. Only 6 out of 16 PD and 8 out of 22 MSA-P patients were able to perform the maneuver in accordance with the protocol. The baroreflex-cardiovagal gain in phase II of the VM did not differ significantly between PD and MSA-P (0.96±0.75 ms/

Table 2. Patients of PD_{OH} and MSA-P_{OH} did not differ in the time domain parameters of heart rate variability and time domain as well as frequency domain parameters of blood pressure variability

Parameters	PD_{OH}	MSA-P_{OH}	p
HRV			
SDNN (ms)	24.58±4.40	20.09±2.43	0.34
RMSSD (ms)	14.56±2.42	18.21±3.35	0.42
BPV			
SDNN (mm Hg)	7.52±0.97	5.89±0.58	0.14
RMSSD (mm Hg)	4.40±0.79	4.19±0.63	0.84
Log LF (mm²/Hz)	1.13±0.20	1.02±0.15	0.67
Log HF (mm²/Hz)	1.17±0.14	1.19±0.14	0.91
LF/HF	2.01±1.89	1.34±1.06	0.59

BPV: blood pressure variability, HF: high frequency, HRV: heart rate variability, LF: low frequency, MSA-P_{OH}: multiple-system atrophy of the Parkinsonian type with orthostatic hypotension, PD_{OH}: Parkinson's disease patients with orthostatic hypotension, RMSSD: square root of the mean squared differences of successive NN intervals, SDNN: Standard Deviation of the NN interval.
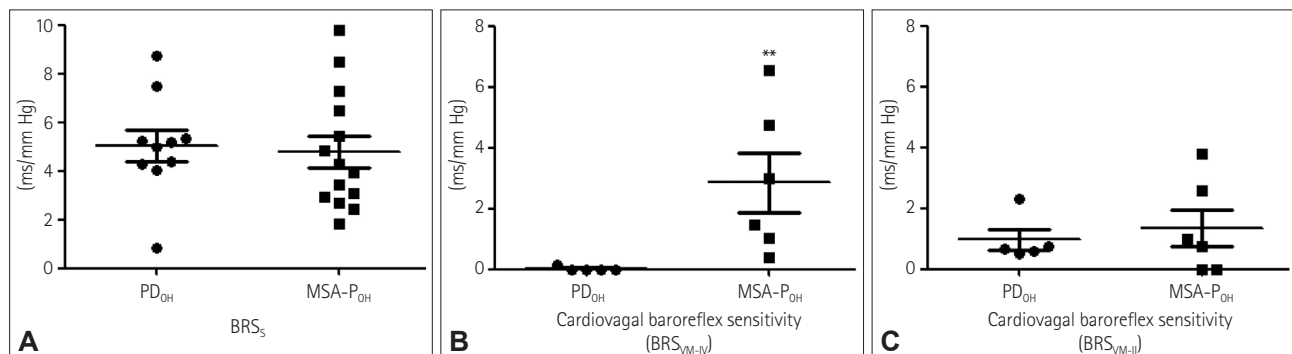

Fig. 1. BRS_S in PD_{OH} and MSA-P_{OH} (5.04±0.66 ms/mm Hg vs. 4.78±0.64 ms/mm Hg; p value=0.54) was not different in the two disorders (A) but BRS_{VM-PIV} from phase IV of VM in PD_{OH} was significantly lesser than MSA-P_{OH} (0.03±0.07 ms/mm Hg vs. 2.86±2.39 ms/mm Hg; p value=0.004) (B) even though the BRS_{VM-PII} from phase II of VM was not different in PD_{OH} and MSA-P_{OH} (0.96±0.75 ms/mm Hg vs. 1.34±1.51 ms/mm Hg; p value=0.76) (C). BRS_S: spontaneous baroreflex sensitivity, BRS_{VM-PII}: baroreflex sensitivity from phase II of Valsalva, BRS_{VM-PIV}: baroreflex sensitivity from phase IV of Valsalva, MSA-P_{OH}: multiple-system atrophy of the Parkinsonian type with orthostatic hypotension, PD_{OH}: Parkinson's disease patients with orthostatic hypotension.

mm Hg vs. 1.34±1.51 ms/mm Hg, *p*=0.76) (Fig. 1C). However, the BRS in phase IV was lower in PD patients than in MSA-P patients (0.03±0.07 ms/mm Hg vs. 2.86±2.39 ms/mm Hg, *p*=0.004) (Fig. 1B).

Power spectral analysis

Heart rate variability
The LF/HF ratio was significantly higher in PD_{OH} patients than in $MSA-P_{OH}$ patients (2.36±1.06 vs. 1.77±1.97, *p*=0.05) (Fig. 2). LF and HF indices of the HRV did not differ between PD_{OH} and $MSA-P_{OH}$ (1.78±0.21 ms^2 vs. 1.67±0.14 ms^2, *p*=0.66; and 1.45±0.18 ms^2 vs. 1.64±0.17 ms^2, *p*=0.47; respectively) (Table 2).

Blood pressure variability
Spectral analysis of the blood pressure showed that the LF power was significantly higher in PD_{OH} patients than in $MSA-P_{OH}$ patients (1.65±0.13 mm Hg vs. 1.0±0.12 mm Hg, *p*=0.0013). The LF power of the R-R interval was similar in the two groups. The HF power of the blood pressure and the R-R interval did not differ significantly between PD_{OH} and $MSA-P_{OH}$ (Table 2).

DISCUSSION

The spontaneous BRS did not differ significantly between the PD_{OH} and $MSA-P_{OH}$ patients in this study. However, the BRS quantified as the reflexive cardiovagal responsiveness (cardiovagal BRS) in phase IV of the VM was significantly lower in PD_{OH} patients than in $MSA-P_{OH}$ patients.

To the best of our knowledge this is the first report of the spontaneous BRS being similarly low in PD_{OH} and $MSA-P_{OH}$. Friedrich et al.[8] reported that BRS was lower in MSA than in PD. That study grouped the PD patients together irrespective of the disease severity and the presence or absence of OH,

and found an inverse correlation between the spontaneous BRS and disease severity. This is further supported by Barbic et al.[10] finding that BRS was lower in PD_{OH} patients than in PD patients without OH. The results of our study differed from those of Friedrich et al.[8] because we had excluded confounding factors by recruiting a group of PD patients who were homogeneous with respect to the severity of the disease and the presence of OH. The presence of OH and the similarity of the disease severity in the PD patients could explain why the spontaneous BRS was similar in the PD and MSA-P patients in our study.

Our findings for the cardiovagal BRS in phase II of the VM are consistent with Goldstein et al.[5] finding no difference between PD_{OH} and $MSA-P_{OH}$ patients. However, we found that the cardiovagal BRS in phase IV of the VM was lower in PD_{OH} than in $MSA-P_{OH}$. One strength of the present study is that the cardiovagal BRS in phase IV of the VM has not been reported previously for either PD_{OH} or $MSA-P_{OH}$ patients. During phase IV, the blood pressure increases due to the sudden increase in the venous return, resulting in a decrease in the heart rate induced by activation of the vagal component of autonomic control. This differs from the cardiac response in phase II, which is primarily due to parasympathetic withdrawal in the early phase and activation of the sympathetic component in the late phase.[18] Our study showed that the cardiovagal BRS in phase IV is lower in PD_{OH} than in $MSA-P_{OH}$. This could be due to either a compromised sympathetic response in $MSA-P_{OH}$ patients or poor parasympathetic activity in PD_{OH} patients. This finding is related to a recent report of α-synuclein deposition in the dorsal motor nucleus of the vagus occurring earlier in PD than in MSA-P.[19,20] In contrast, sympathetic denervation has been shown to be present in both PD and MSA-P.[21,22]

The HRV showed a significantly higher LF/HF ratio in PD_{OH} patients than in $MSA-P_{OH}$ patients. This may reflect either hyperactivity of the sympathetic system or hypoactivity of the
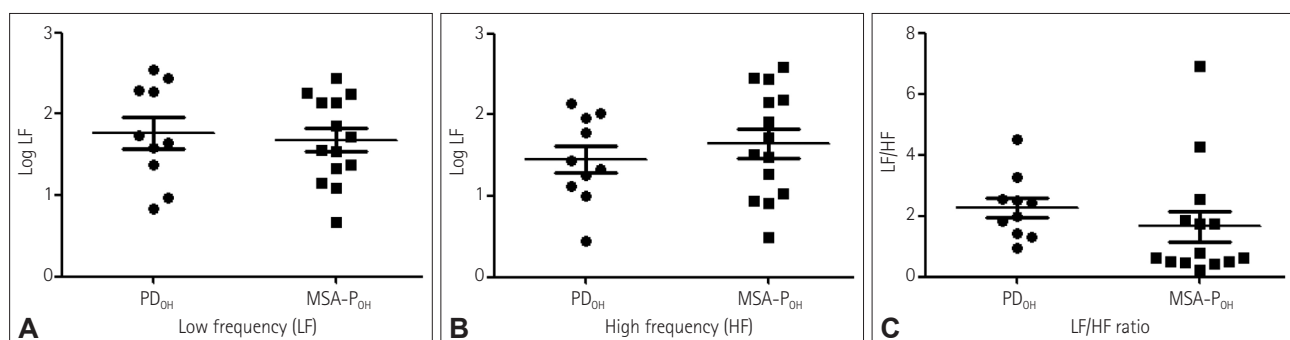

Fig. 2. LF and HF indices of the heart rate variability in PD_{OH} and $MSA-P_{OH}$ are not different between the two disorders (1.78±0.21 ms^2 vs. 1.67±0.14 ms^2; *p* value=0.66 and 1.45±0.18 ms^2 vs. 1.64±0.17 ms^2; *p* value=0.47 respectively) (A and B) and the LF/HF ratio shows a higher trend in PD_{OH} as compared to $MSA-P_{OH}$ (2.36±1.06 vs. 1.77±1.97; *p* value=0.05) (C). HF: high frequency, HRV: heart rate variability, LF: low frequency, $MSA-P_{OH}$: multiple-system atrophy of the parkinsonian type, PD_{OH}: Parkinson's disease patients with orthostatic hypotension.

parasympathetic system in PD_{OH} patients. However, the LF and HF values did not differ between the two diseases, which makes it difficult to comment on the sympathetic and parasympathetic components of the autonomic tone. The lower component of the systolic blood pressure in $MSA-P_{OH}$ patients compared to PD_{OH} patients predicts a comparatively poor sympathetic response in the former. These results are similar to those obtained by Friederich et al.,[8] and they probably explain the low LF/HF ratio obtained during HRV in $MSA-P_{OH}$ patients.

The similarly low spontaneous BRS indicates a compromised baroreflex activity in resting conditions in both patient groups. The significantly lower cardiovagal BRS and significantly higher LF/HF ratio from HRV are indicative of severe sympathovagal imbalance in the PH_{OH} patients. The LF and HF values did not differ between PD_{OH} and $MSA-P_{OH}$, and hence no difference in the sympathetic or parasympathetic activity of the autonomic nervous system in resting conditions is indicated. However, the reflexive parasympathetic reactivity as obtained from the low cardiovagal BRS in phase IV of the VM in PD_{OH} is found to be compromised relative to $MSA-P_{OH}$. It is possible that the significantly lower cardiovagal BRS in PD_{OH} relative to $MSA-P_{OH}$ is due to hyperactivity of the sympathetic system in $MSA-P_{OH}$, but in that case the cardiovagal BRS in phase II also should have been significantly higher in $MSA-P_{OH}$. Hence it can be postulated that the parasympathetic reactivity is compromised more in PD_{OH} than in $MSA-P_{OH}$.

The main limitation of the study was that relatively small proportions of the PD and MSA-P patients were able to perform the VM in accordance with the standard protocol. This is understandable since these patients have poor motor control. However, these findings open up the opportunity for further investigations in larger populations with certain modifications. A previous study used a lower pressure (30 mm Hg) and shorter duration (12 s) for the VM,[7] and such modifications may allow more patients to perform the maneuver. However, we could not lower the limits for the increase in pressure during the VM since this could have influenced the results obtained.

Conclusion
In conclusion, our data indicate that the cardiovagal BRS is compromised more in PD_{OH} patients than in $MSA-P_{OH}$ patients. The cardiovagal BRS in phase IV of the VM is potentially useful for differentiating between PD_{OH} and $MSA-P_{OH}$.

Conflicts of Interest
The authors have no financial conflicts of interest.

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