Original Article

Spectrum of Cardiovascular Autonomic Dysfunction and 24-hour Blood Pressure Variability in Idiopathic Parkinson's Disease

Ivy Sebastian, Mahesh P. Kate[1], Himani Khatter, Bharat Singh, Jeyaraj D. Pandian

Department of Neurology, Christian Medical College and Hospital, Ludhiana, Punjab, India, [1]Division of Neurology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Abstract

Background: Uncertainty prevails regarding the patterns of autonomic dysfunction in patients with idiopathic Parkinson's disease (IPD). This study was undertaken with the aim of assessing the complete spectrum of cardiovascular autonomic function tests (CAFTs) and blood pressure variability patterns in IPD patients while comparing the same with age-matched controls. **Methods:** Patients with IPD presenting to the Christian Medical College and Hospital from December 2016 to November 2018 along with age-matched controls were prospectively evaluated using CAFTs. The IPD patients also underwent ambulatory blood pressure (BP) monitoring (ABPM), and the diurnal systolic BP differences were used to classify into dippers (10-20%), non-dippers (0–10%), reverse dippers (<0%), and extreme dippers (>20%). **Results:** Autonomic dysfunction (AD) was prevalent in 41 (68.3%) IPD patients even in early disease (median (inter-quartile range) symptom duration 2 (1–4) years, mean Hoehn and Yahr (H&Y) stage 2 (1.5–2.8). Both sympathetic and parasympathetic parameters were impaired among IPD patients when compared to healthy controls. (E: I ratio 1.17 ± 0.12 vs 1.26 ± 0.14 ($P < 0.001$), Valsalva ratio (VR) 1.33 ± 0.27 vs 1.55 ± 0.25 ($P < 0.001$), PRT_{100} 9.6 ± 8.0 vs 3.1 ± 1.8 ($P < 0.001$), tilt-up SBP_{Avg} change 8.8 (4.2–13.8) vs 1.8 (−2.9–6.1) ($P < 0.001$), tilt-up HR_{Avg} change 4.8 (2.2–8.2) vs 1.9 (−0.7–5.1) ($P < 0.001$). BP variability was demonstrated in 47 (79.7%) of IPD patients, with reverse dipping pattern in 28 (47.5%) seen more frequently in this cohort. **Conclusions:** Timely detection of AD may be helpful not only in recognizing IPD in its pre-motor stages but also in optimizing management for this population of patients. BP variability and abnormal dipping patterns on ABPM can be a potential marker of dysautonomia.

Keywords: Ambulatory blood pressure monitoring, autonomic dysfunction, cardiovascular autonomic function tests, dysautonomia, idiopathic Parkinson's disease

Introduction

Idiopathic Parkinson's disease (IPD) is a heterogeneous disease with both motor and non-motor symptoms. Autonomic dysfunction (AD), although common, is a frequently under-diagnosed non-motor feature associated with poor quality of life and increased mortality among IPD patients. Until recently, AD has been considered a feature of advanced disease; however, new evidence supports its occurrence even early into the disease.[1,2] Moreover, uncertainty still prevails with regards to its prevalence, phenotypic correlations, association with severity and duration of disease, and racial variations, if any.

The cardiovascular autonomic function test (CAFT) is a non-invasive battery of tests, which forms the cornerstone for the assessment of autonomic functions. Whereas heart rate response to deep breathing (HRDB) assesses the parasympathetic component of the autonomic nervous system, blood pressure (BP) response to Valsalva maneuver (VM) and the head-up tilt (HUT) test provide information about the sympathetic component.[3] Recently, the BP recovery time (PRT 50 and PRT 100) from VM has been validated as a reliable marker of adrenergic function.[4] Blood pressure variability (BPV) is another manifestation of dysautonomia[5] that has been reported in IPD and can be assessed objectively using ambulatory blood pressure monitoring (ABPM). It has been acknowledged as an extremely useful test to diagnose diurnal BP variations and assess the circadian BP patterns over a prolonged time frame.[6]

Not many studies have objectively assessed cardiovascular autonomic functions in conjunction with ABPM in patients with IPD, and different studies have produced conflicting results. This study was undertaken with the aim of assessing

Address for correspondence: Dr. Jeyaraj D. Pandian, Professor and Principal, Department of Neurology, Christian Medical College and Hospital, Ludhiana - 141 008, Punjab, India.
E-mail: jeyarajpandian@hotmail.com

Submitted: 28-Mar-2022 **Revised:** 15-Jun-2022 **Accepted:** 20-Jun-2022
Published: 26-Jul-2022

DOI: 10.4103/aian.aian_289_22

the spectrum of cardiovascular autonomic functions and BPV patterns in IPD patients while comparing the same with age-matched controls.

Methods

The study was approved by the institutional research and ethics committees of Christian Medical College and Hospital, Ludhiana. Cardiovascular autonomic functions were prospectively evaluated in a cohort of consecutively consenting IPD patients presenting to the outpatient and inpatient clinics of the Department of Neurology, from December 2016 to November 2018. The controls were taken from the autonomic lab normative dataset developed by the department during the same time. Informed written consent was obtained from all of the participants of the study. The approval for the study was obtained from the institutional review board of Christian Medical College and Hospital, Ludhiana.

Diagnosis for IPD was confirmed by the UK Parkinson's Disease Society Brain Bank Clinical diagnostic criteria,[7] and patients were further classified according to stage and severity using modified H&Y scoring[8] and modified Unified Parkinson's Disease Rating Scale (MDS-UPDRS), respectively.[9] IPD patients were also screened and graded according to symptoms for orthostatic hypotension (OH) using a validated questionnaire.[10] [Supplementary material] Patients with diabetes or other comorbidities with associated autonomic symptoms, uncooperative patients with encephalopathy and dementia, patients with cerebrovascular disease, and any atypical features affecting the diagnostic certainty of IPD were excluded.

Autonomic tests

Both patients and age-matched controls underwent the CAFT using the WR Medical Electronics Co: Stillwater, MN, USA. The CAFT was conducted by a single assessor (senior technologist) who was blinded to the clinical data. IPD patients also underwent 24-hour ABPM using an OSCAR-2 (version) ABPM apparatus. ABPM was not performed in the control arm due to feasibility issues. AD was objectively diagnosed on the basis of the presence of either/or of any of the following[10]:

- A lack of heart rate (HR) response to DB
- Absent late phase 2 and phase 4 responses
- Systolic BP (SBP) fall of ≥20 mm Hg on tilt-up.

HR response to deep breathing test

The participant was made to lie supine for 3 minutes, while a baseline HR and BP was recorded; thereafter, the participant breathed maximally at a rate of 6 breaths per minute (inspiratory and expiratory cycles of 5 s each), establishing a smooth maximal inspiratory and expiratory rhythm. Eight cycles were recorded and repeated after a rest period of 5 minutes, followed by 3 minutes of normal breathing again. The average HRDB difference (maximum–minimum) of the five largest consecutive responses was derived.

HR and BP response to VM

The BP response to VM, generally classified into four phases, is dependent on the competency of the baroreflex pathways and can be frequently attenuated in patients with IPD.[11] The participant while recumbent was asked to maintain a column of mercury at 40 mm Hg for 15s via a bugle with an air leak to ensure open glottis. A recording was considered acceptable if the following were fulfilled: Expiratory pressure at least 30 mm Hg for 10 s, reproducible VM BP curve, and absence of a flat top BP curve. Three readings were taken for each patient, and the largest data from a satisfactory expiratory pressure was accepted. A delayed or absent late phase II or phase IV response signifies sympathetic dysfunction, lacking counter-regulation of falling pressures. The VR was derived from the maximum HR divided by the lowest HR following the VM. PRT is a reliable indicator of baroreflex adrenergic impairment and has been used as an additional indicator of the presence and severity of adrenergic failure. The PRT was calculated for SBP, mean arterial pressure (MAP), and diastolic BP (DBP) curves as described[4] for two time intervals of the maneuver: (1) time taken for recovery of BP from the lowest phase III amplitude to complete return to baseline (PRT 100) and (2) time interval from the lowest amplitude of phase III to 50% return to the baseline (PRT 50).

BP responses to the head upright tilt

The tilt study was conducted for a total duration of 30 minutes. The baseline SBP, MAP, DBP, and HR were recorded with the participant lying flat for 10 minutes, after which the patient was tilted up for 10 minutes to 80 degrees of head-up tilting, followed by another 10 minutes in the supine position. Clinical symptoms and HR and BP changes were recorded continuously from the fingertip using the Finapress during tilt-up. The systolic fall and HR increment at 1, 3, 5, 8, and 10 minutes of tilt-up were documented.

24-hour ambulatory BP monitoring

The second phase of the study involved 24- hour BP monitoring which was performed only on the IPD patients. A BP cuff tied on the arm of the patient measured continuous 24-hour BP records. The apparatus was calibrated to record daytime (6 am–10 pm) BP at 15-minute intervals and night-time (10 pm–6 am) at 30-minute intervals. Diurnal BP variability defined as the standard deviation (SD) from the mean BP at 24 hours was measured. A deviation of more than 15 mm Hg was considered significant. Patients were classified into extreme dippers, dippers, non-dippers, and reverse dippers based on the night-to-day SBP ratio using American Heart Association's calculation as follows.[12]

Sample size

A convenience sampling method was used to calculate the sample size of the study. All of the IPD patients who visited our hospital from December 2016 to November 2018 were recruited for the study. The sample size for Parkinson's patients was calculated using the prevalence for OH in IPD patients.[13] The minimum reported prevalence for OH in Parkinson's disease was noted at

a minimum of 22%, and a sample size of $n = 60$ minimum was calculated at type 1 error = 0.05 and margin of error = 0.1. The controls were taken from the autonomic lab normative dataset developed by the department during the same time.[14] Out of 254 controls, 113 age- and gender-matched healthy participants' data was selected and compared with the data of 70 IPD patients. The total sample size of our study was $n = 173$.

Statistical analysis

The data was analyzed using SPSS, version 21.0. Armonk, NY: IBM Corp. The significance level was set at $P < 0.05$. The Kolmogorov Smirnov test was used to check the normality of data. Chi-square was used to compare the categorical variables between groups. The independent t-test or Mann Whitney U test was used to compare the CAFT parameters between the groups. Pearson's correlation coefficient or Spearman's correlation coefficient was used to correlate CAFT parameters with baseline characteristics.

Results

A total of 70 patients visiting the neurology outpatient clinic met the inclusion criteria for IPD and were classified as cases, whereas 113 healthy participants with no comorbidities were recruited into the control arm of the study. 10 patients from the case arm were excluded later for various reasons. After exclusion, 60 cases and 113 controls were allocated to undergo CAFT. In addition, the 60 cases were also allocated to undergo 24-hour ABPM; however, 1 developed petechial rashes and could not continue with the procedure [Figure 1].

The mean (± SD) age was comparable in cases (60 ± 9.2 years) and in controls (58 ± 11.1 years, $P = 0.323$). Both groups were age- and gender-matched. Among the IPD patients, the median [inter-quartile range (IQR)] duration of symptoms was 2 (1–4) years, the mean H&Y stage was 2 (1.5–2.8), and the mean UPDRS was 34 (15–42). Ten (16.3%) patients were dopaminergic drug-naive, and 27 (45.0%) patients had clinical symptoms of OH [Table 1].

Cardiovascular autonomic function tests

The heart rate difference and E: I ratio were impaired in cases compared to controls $P < 0.001$ [Table 2].

The changes in the BP during the VM were not normally distributed and were expressed as medians. Table 1 shows that VRs (1.33 ± 0.27 vs 1.55 ± 0.25, $P < 0.001$) were impaired in cases as compared to controls. The PRT (PRT 50 and PRT 100) was also markedly increased in cases as compared to controls. A significant difference was noted in the amplitude of BP in different phases of VM in cases vs controls [Table 3].

In the HUT test, the fall in SBP at different intervals of time was higher in cases as compared to controls. The concomitant increments in heart rate followed a similar trend [Figure 2].

A high prevalence of AD 41 (68.3%) was found in IPD patients, with the majority of patients 31 (51.7%) having SBP fall in the tilt-up test [Figure 3].

Table 1: Baseline and clinical characteristics of IPD patients

Demographics	Values
Age (years) Mean±SD	60±9.2
Gender *n* (%)	
Male	39 (65.0)
Female	21 (35.0)
Diabetes	10 (16.7)
Hypertension	17 (28.3)
Dopaminergic medications	50 (83.3)
Orthostatic grading	
0	33 (55.0)
1	21 (35.0)
2	6 (10.0)
Duration of symptoms Median (IQR)	2 (1-4)
UPDRS	34 (15-42)
H&Y	2 (1.5-2.8)

SD: Standard deviation. IQR: Inter-quartile range. UPDRS: Unified Parkinson's disease rating scale. H&Y: Hoehn and Yahr scale

Table 2: Comparison of HRDB, VR, and pressure recovery time in cases vs controls

	Case (n=60) Mean±SD	Control (n=113) Mean±SD	*P*
HRDB			
Maximum heart rate	84.2±10.7	81.1±9.7	0.080
Minimum heart rate	73.3±10.3	65.4±9.9	<0.001
Heart rate difference	11.1±6.1	16.1±7.8	<0.001
E:I ratio	1.17±0.12	1.26±0.14	<0.001
VM			
VR	1.33±0.27	1.55±0.25	<0.001
PRT_{100}	9.6±8.0	3.1±1.8	<0.001
PRT_{50}	4.7±4.3	1.5±0.8	<0.001

HRDB: Heart rate response to deep breathing. E: I ratio: expiratory: inspiratory ratio. PRT: Pressure recovery time

Both parasympathetic markers HRDB and the E: I ratio showed a negative correlation with all parameters. There was a moderate correlation with age, H&Y, and UPDRS, implying that an increase in age, stage (H&Y), or severity (UPDRS) results in an increase in parasympathetic dysfunction. Similar results were noted with VR, implying a decrease in VR with the progression of age, stage, or severity of disease. Disease duration, however, had only a weak correlation with parasympathetic function [Table 4].

Progression in age was associated with increased sympathetic dysfunction in IPD patients, as evidenced by a moderate positive correlation seen with PRT 100 and PRT 50 with age. No correlation was seen with other parameters [Table 4]. Neither SBP fall nor HR increment in the HUT test showed any significant correlation with any of the demographic parameters in IPD patients.

Of the total 60 patients, 28 (45.9%) patients were clinically symptomatic for OH. Symptomatic patients had more impaired

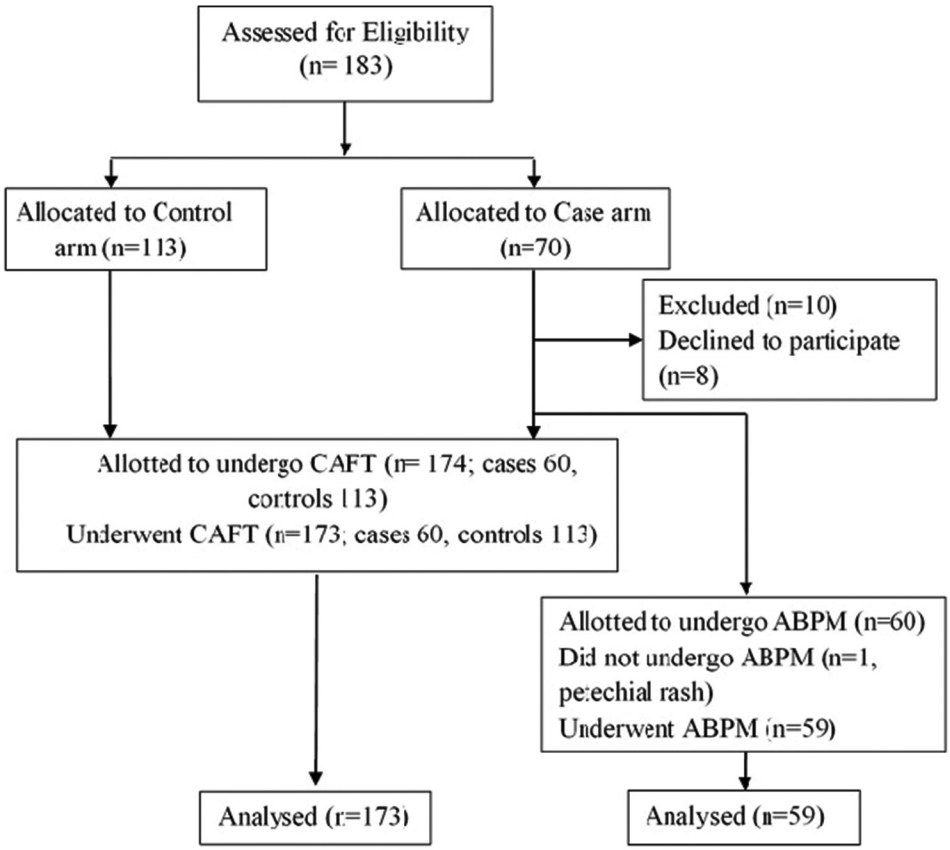

Figure 1: Consort figure

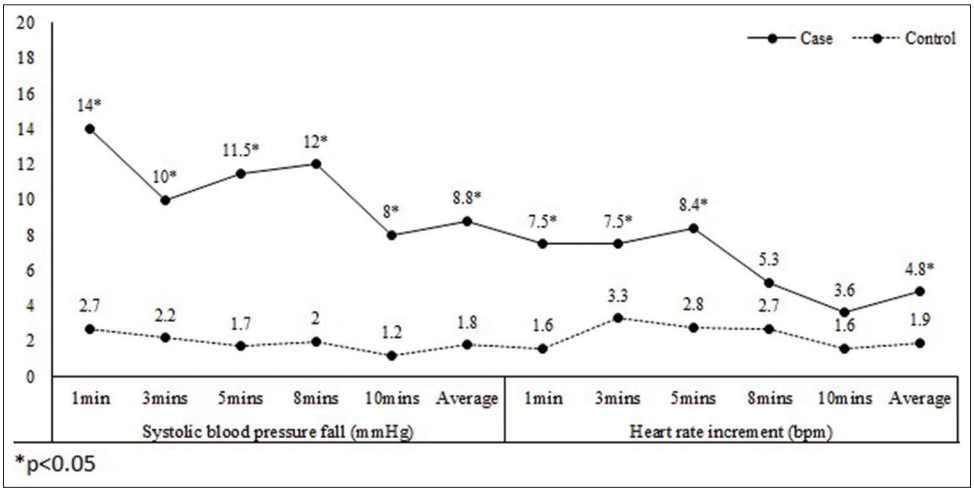

Figure 2: Comparison of SBP fall and heart rate increment in cases vs controls for HUT

autonomic parameters with lower HRDB, more prolonged PRTs, higher SBP falls, and lesser HR increments, compared to clinically asymptomatic patients [Figure 4].

Ten patients in the cohort were dopaminergic drug-naive; however, no correlation was found between intake of dopaminergic drugs and autonomic parameters.

Ambulatory BP monitoring

Baseline ABPM DATA

The average daytime mean was 131.4 ± 17.1 mm Hg (SBP) and 79.29 ± 10.2 mm Hg (DBP), whereas the average night-time mean was 128.19 ± 15.85 mm Hg (SBP) and 75.50 ± 9.16 mm Hg. Overall, BPV was seen in 47 (79.7%)

Table 3: Comparison of amplitude of BP in different phases of VM in cases vs controls

	Case (n=60) Median (IQR)	Control (n=113) Median (IQR)	P
Phase 1 (mm Hg)			
ΔSBP	10.7 (8.2-16.5)	17 (11.7-23.5)	<0.001
ΔMAP	13.3 (6.7-16.8)	15.3 (9.0-22.2)	0.066
ΔDBP	10.7 (6.4-19.0)	13.3 (7.2-19.5)	0.418
Early phase 1 (mm Hg)			
ΔSBP	−29 (−38.5-(−18.5))	−17 (−25.2-(−11.3))	<0.001
ΔMAP	−12 (−17.3-(−5.9))	−5 (−10-(−0.9))	<0.001
ΔDBP	−0.9 (−5.2-4.2)	−1.3 (−4-5.3)	0.997
Late Phase 2 (mm Hg)			
ΔSBP	4.5 (2-9.8)	14.3 (8.3-20.2)	<0.001
ΔMAP	3.3 (1-8)	11.3 (7-17.5)	<0.001
ΔDBP	2.3 (0.9-6)	10 (6.2-14.7)	<0.001
Phase 3 (mm Hg)			
ΔSBP	−20.5 (−29-(−12.9)	−30.3 (−40.5-(−24.5))	<0.001
ΔMAP	−16.4 (−25.6-(−10.8))	−14 (−24.2-(12.4))	0.062
ΔDBP	15.2 (−24.8-(−7.5))	−11 (−22-11)	0.042
Phase 4 (mm Hg)			
ΔSBP	1.7 (−5.2-12.5)	21 (13.3-31.2)	<0.001
ΔMAP	2.7 (−1.7-10.2)	15 (9.7-21.5)	<0.001
ΔDBP	2 (−1.7-6)	10 (5.2-14.7)	<0.001

SBP: Systolic blood pressure. DBP: Diastolic blood pressure. MAP: Mean arterial pressure

Table 4: Correlation of CAFT parameters with age, disease staging, and severity of IPD

CAFT parameters (n=60)	Age	Duration of Disease	Severity (UPDRS)	Staging (H&Y)
Heart rate difference (bpm)	−0.358*	−0.082	−0.550*	−0.594*
E/I ratio	−0.323*	−0.074	−0.508*	−0.582*
VR	−0.414*	0.009	−0.385*	−0.430*
SBP late phase2	−0.086	0.007	−0.044	0.037
SBP phase4	−0.156*	0.153	−0.057	−0.024
PRT_{100}	0.337*	−0.080	0.121	0.148
PRT_{50}	0.326*	−0.099	0.123	0.133
SBP fall (mmHg)	0.002	−0.073	0.024	−0.127
HR increment (bpm)	−0.202	−0.220	−0.098	−0.230

*P<0.05. VR: Valsalva ratio. E: I ratio: expiratory: inspiratory ratio. PRT: Pressure recovery time

of patients. The variability, although not statistically significant, was more during the daytime compared to night-time, (coefficient of variation: 0.14 ± 0.04 vs 0.13 ± 0.07 in SBP, P = 0.280 and 0.21 ± 0.08 vs 0.18 ± 0.09 in DBP, P = 0.069). Also both day- and night-time variability in DBP was more compared to SBP. There was no association between BPV and age, duration, staging, or severity of disease in patients with IPD. No association was noted with gender difference, use of dopaminergic drugs, or presence of clinically symptomatic OH also.

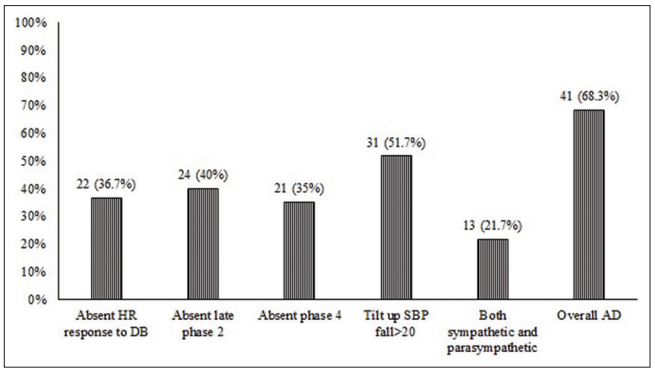

Figure 3: Prevalence of AD among IPD patients

Among the circadian BP patterns, the reverse dipping pattern in 28 (47.5%) was more frequently seen in this cohort of IPD patients, compared to other patterns such as non-dippers 18 (30.5%), dippers 8 (13.6%), and extreme dippers 5 (8.5%) [Figure 5].

Discussion

In this study, AD is observed to be prevalent in two-thirds of IPD patients even in the early disease. Both sympathetic and parasympathetic parameters were impaired among IPD patients compared to healthy controls. Within the IPD cohort, all measures of parasympathetic function showed progressive impairment with an increase in age, stage, and severity of disease. BP recovery time also showed age-dependent prolongation. The duration of disease and use of dopaminergic drugs had no influence on autonomic parameters. BPV and abnormal dipping patterns on ABPM can be a potential marker of dysautonomia.

Varying rates of dysautonomia ranging from 14% to 80% have been reported in earlier studies.[13,15] The high prevalence of AD in our study is perhaps due to the comprehensive autonomic assessment which included HRDB, BP response to VM, and HUT testing along with ABPM, unlike previous studies which used limited parameters. Furthermore, our cohort of patients was younger, with lesser duration and lower severity of disease. The UK tracking Parkinson's study[16] also reported AD in early IPD (mean disease duration: 1.3 ± 0.9 years), but it included older patients.

The association of dysautonomia with age, H&Y staging, and severity of disease in IPD is previously known.[17,18] In our study, although parasympathetic function (HRDB, VR) showed progressive impairment with increasing age, stage, and disease severity, no correlation was noted with sympathetic dysfunction (SBP fall or HR increment on tilt-up). This was in concordance with observations noted by researchers from Korea.[17] However, PRT, which is another measure of sympathetic function, did show a direct association with age.

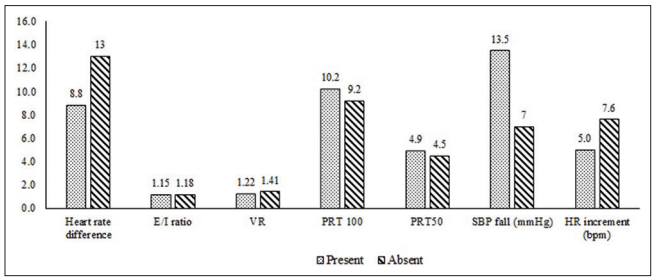

Figure 4: Association of CAFT parameters with clinically symptomatic OH

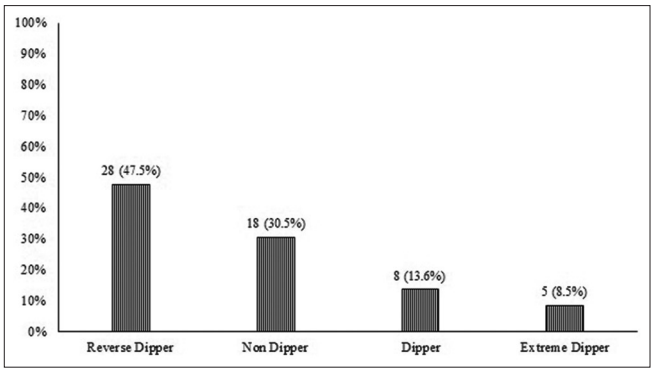

Figure 5: Distribution of circadian rhythm patterns in IPD patients

To a large extent, AD has been considered as a late feature of IPD. Studies have also reported an association of longer disease duration with more severe autonomic impairment.[19,20] However, recent data proposes that both sympathetic and parasympathetic dysfunction can occur early in the disease course of IPD and even among clinically asymptomatic patients.[21,22] This was in concordance with our study, where no significant association was noted between the autonomic parameters and disease duration. The presence of AD even in the earlier stages of Parkinson's disease finds explanation in the "central" Braak theory[23] which postulates the spread of Lewy body pathology via the olfactory bulb and vagus nerve to the substantia nigra and central nervous system.

The effect of dopaminergic drugs on cardiovascular autonomic functions is yet another domain which has been assessed in many studies but with conflicting results.[19,24] We found no influence of chronic dopaminergic treatment on autonomic function in our cohort; however, in the presence of dysautonomia, appropriate monitoring of dopaminergic drugs is recommended.

BP variability was found to be present in a large proportion (72.9%) of IPD patients, with an increase in daytime compared to night-time variations. This was in conformity with a 24-hour ABPM study from Japan[25] which reported increased BPV in IPD patients compared to controls. Similar findings were seen in another small study from Brazil,[26] where high BPV with increased daytime BP variations were reported in IPD patients. Impaired baroreflex activity, inappropriate sympathetic tone, and a high residual sympathetic surge on lying supine[27,28] are proposed mechanisms postulated to contribute toward supine hypertension and alterations in circadian rhythms. The reverse dipping pattern constituted the highest proportion of 28 (47.5%) in this cohort. A similar high prevalence of reverse dippers [86 (32.5%)] was reported by Milazzo *et al*.,[29] who even proposed the reverse dipping pattern as a potential marker of cardiovascular dysautonomia in IPD patients.

AD holds severe implications among IPD patients with a resultant increase in cardiovascular and small-vessel ischemic disease and subsequent morbidity and poor quality of life.[30] Timely detection of AD is crucial and can help in recognizing IPD in its early pre-motor stages. This research work assesses the complete set of cardiovascular autonomic parameters in detail in conjunction with ABPM using an internationally accepted methodology. Comparing the findings with a large control group adds to the strengths of this study. In addition, BP recovery time from VM, a relatively new index of adrenergic activity which had not been well studied in IPD patients previously is established as a marker of sympathetic activity.

The limitation of this study includes the small sample size. Although we excluded patients having comorbidities such as diabetes and hypertension with associated autonomic symptoms, not all patients with comorbidities were excluded which may have affected the results; however, in patients of this age category, multiple comorbidities are common and difficult to exclude. We did, however, sub-analyze between the sub-groups of patients with no comorbidities and controls also and found similar results for all autonomic parameters. As most of our IPD patients were recruited from the outpatient clinics during the daytime, CAFT assessment during off-time was not feasible. This may have affected some of the findings. Another limitation of the study is that we did not establish a pathological diagnosis of IPD, and some of these patients may evolve into Parkinson plus syndromes over the course of years. This, however, would require a long-term prospective follow-up.

Conclusion

Cardiovascular AD is common in IPD and occurs even in patients with early disease. Autonomic function progressively worsens with progression in age, stage, and severity of disease. BPV and abnormal dipping patterns on ABPM can be a potential marker of dysautonomia in IPD patients. A high index of suspicion should be maintained while evaluating for AD in IPD patients, and screening with both CAFTs and ABPM in IPD patients even early into the disease is warranted.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request**.**

Ethics approval

The approval for the study was obtained from the institutional review board of Christian Medical College and Hospital, Ludhiana.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Part of the manuscript was supported by the Indian Council of Medical Research

Conflicts of interest

There are no conflicts of interest.

References

1. Abbott RD, Petrovitch H, White LR, Koeppe RA, Scott PJ, Frey KA, *et al*. Frequency of bowel movements and the future risk of Parkinson's disease. Neurology 2001;57:456-62.
2. Müller ML, Albin RL, Kotagal V, Koeppe RA, Scott PJ, Frey KA, *et al*. Thalamic cholinergic innervation and postural sensory integration function in Parkinson's disease. Brain 2013;136:3282-9.
3. Low PA. Assessment: Clinical and autonomic testing report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology 1996;46:873-80.
4. Vogel ER, Sandroni P, Low PA. Blood pressure recovery from Valsalva maneuver in patients with autonomic failure. Neurology 2005;65:1533-7.
5. Portaluppi F, Tiseo R, Smolensky MH, Hermida RC, Ayala DE, Fabbian F. Circadian rhythms and cardiovascular health. Sleep Med Rev 2012;16:151-66.
6. Stuebner E, Vichayanrat E, Low D, Mathias CJ, Isenmann S, Haensch CA. Twenty-four hour non-invasive ambulatory blood pressure and heart rate monitoring in Parkinson's disease. Front Neurol 2013;4:49. doi: 10.3389/fneur. 2013.00049.
7. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-4.
8. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, *et al*. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: Status and recommendations the Movement Disorder Society Task Force on rating scales for Parkinson's disease. Mov Disord 2004;19:1020-8.
9. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, *et al*. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord 2008;23:2129-70.
10. Low PA, Suarez GA, Benarroch EE. Clinical autonomic disorders: Classification and clinical evaluation. In: Low PA, editor. Clinical Autonomic Disorders. 2nd ed. Philadelphia: Lipincott-Raven Publishers; 1997. p. 3-13.
11. Looga R. The Valsalva manoeuvre—cardiovascular effects and performance technique: A critical review. Respir Physiol Neurobiol 2005;147:39-49.
12. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring: Unique aspects of blood pressure during sleep. Hypertension 2007;49:1235-41.
13. Velseboer DC, de Haan RJ, Wieling W, Goldstein DS, de Bie RM. Prevalence of orthostatic hypotension in Parkinson's disease: A systematic review and meta-analysis. Parkinsonism Relat Disord 2011;17:724-9.
14. Singh S, Jaison V, Khatter H, Adya S, Singh B, Pandian JD. Establishment of normative data for autonomic function tests in Indian population. Ann Ind Acad Neurol 2022. doi: 10.4103/aian.aian_579_21.
15. Merola A, Romagnolo A, Rosso M, Suri R, Berndt Z, Maule S, *et al*. Autonomic dysfunction in Parkinson's disease: A prospective cohort study. Mov Disord 2018;33:391-7.
16. Malek N, Lawton MA, Grosset KA, Bajaj N, Barker RA, Burn DJ, *et al*. Autonomic dysfunction in early Parkinson's disease: Results from the United Kingdom tracking Parkinson's study. Mov Disord Clin Pract 2017;4:509-16.
17. Kim JB, Kim BJ, Koh SB, Park KW. Autonomic dysfunction according to disease progression in Parkinson's disease. Parkinsonism Relat Disord 2014;20:303-7.
18. Korchounov A, Kessler KR, Yakhno NN, Damulin IV, Schipper HI. Determinants of autonomic dysfunction in idiopathic Parkinson's disease. J Neurol 2005;252:1530-6.
19. Mehagnoul-Schipper DJ, Boerman RH, Hoefnagels WH, Jansen RW. Effect of levodopa on orthostatic and postprandial hypotension in elderly Parkinsonian patients. J Gerontol A Biol Sci Med Sci 2001;56:749-55.
20. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. Mov Disord 2008;23:837-44.
21. Kim JS, Lee SH, Oh YS, Park JW, An JY, Park SK, *et al*. Cardiovascular autonomic dysfunction in mild and advanced Parkinson's disease. J Mov Disord 2016;9:97-103.
22. Oh YS, Kim JS, Chung YA, You IeR, Yang DW, Chung SW, *et al*. Orthostatic hypotension, non-dipping and striatal dopamine in Parkinson disease. Neurol Sci 2013;34:557-60.
23. Rietdijk CD, Perez-Pardo P, Garssen J, van Wezel RJ, Kraneveld AD. Exploring Braak's hypothesis of Parkinson's disease. Front Neurol 2017;8:37. doi: 10.3389/fneur. 2017.00037.
24. Lee HM, Koh SB. Many faces of Parkinson's disease: Non-motor symptoms of Parkinson's disease. J Mov Disord 2015;8:92-7.
25. Tsukamoto T, Kitano Y, Kuno S. Blood pressure fluctuation and hypertension in patients with Parkinson's disease. Brain Behav 2013;3:710-4.
26. Kanegusuku H, Silva-Batista C, Peçanha T, Silva-Junior N, Queiroz A, Costa L, *et al*. Patients with Parkinson disease present high ambulatory blood pressure variability. Clin Physiol Funct Imaging 2017;37:530-5.
27. Shannon JR, Jordan J, Diedrich A, Pohar B, Black BK, Robertson D, *et al*. Sympathetically mediated hypertension in autonomic failure. Circulation 2000;101:2710-5.
28. Plaschke M, Trenkwalder P, Dahlheim H, Lechner C, Trenkwalder C. Twenty-four-hour blood pressure profile and blood pressure responses to head-up tilt tests in Parkinson's disease and multiple system atrophy. J Hypertens 1998;16:1433-41.
29. Milazzo V, Di Stefano C, Vallelonga F, Sobrero G, Zibetti M, Romagnolo A, *et al*. Reverse blood pressure dipping as marker of dysautonomia in Parkinson disease. Parkinsonism Relat Disord 2018;56:82-7.
30. Martinez-Martin P, Pecurariu CF, Odin P, van Hilten JJ, Antonini A, Rojo-Abuin JM, *et al*. Gender-related differences in the burden of non-motor symptoms in Parkinson's disease. J Neurol 2012;259:1639-47.

Supplementary Material

SYMPTOMS OF ORTHOSTATIC INTOLERANCE

Lightheadedness (dizziness)

Weakness or tiredness

Cognitive (thinking /concentrating)

Blurred vision

Tremulousness

Vertigo

Pallor

Anxiety

Tachycardia or palpitations

Clammy feeling

Nausea

GRADING OF ORTHOSTATIC INTOLERANCE BY SYMPTOMS

Grade 0

Normal orthostatic tolerance

Grade I

i. Orthostatic symptoms are infrequent, or only under conditions of increased orthostatic stress(prolonged standing, meals, exertion, heat stress)
ii. Able to stand >15min on most occasions
iii. Typically has unrestricted activities of daily living

Grade II

i. Orthostatic symptoms are frequent, developing at least once a week. Orthostatic symptoms commonly develop with orthostatic stress
ii. Able to stand >5min on most occasions
iii. Some limitation in activities of daily living is typical

Grade III

i. Orthostatic symptoms develop on most occasions and are regularly unmasked by orthostatic stress
ii. Able to stand >1min on most occasions
iii. Marked limitation in activities of daily living is typical

Grade IV

i. Orthostatic symptoms are consistently present
ii. Able to stand <1min on most occasions
iii. Seriously incapacitated, being bed or wheelchair bound because of orthostatic intolerance
iv. Syncope/ presyncope are common if the patient attempts to stand