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# HEART RATE VARIABILITY AND COMPOSITE AUTONOMIC SYMPTOM SCORE-31 QUESTIONNAIRE AS INDICATORS OF AUTONOMIC DYSFUNCTION IN PARKINSON'S DISEASE: A CROSS-SECTIONAL STUDY

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## ABSTRACT

**Background:** Parkinson's disease (PD) is the second most common neurodegenerative disorder. It is characterized by dopamine deficiency which leads to classical motor dysfunctions. In addition, Parkinson's disease may include several non-motor impairments, including autonomic and cardiovascular dysfunction. At present clinical diagnostic criteria for Parkinson's disease are exclusively based on motor symptoms and the treatment for Parkinson's disease mainly improves motor symptoms. Non motor symptoms, especially autonomic symptoms are still under recognized in clinical practice. The current study aimed to evaluate these autonomic functions by using Heart Rate Variability (HRV) and Composite Autonomic Symptom Score 31 questionnaire (COMPASS 31).

**Materials and Methods:** This cross-sectional study included 137 diagnosed cases of PD. The resting autonomic balance was assessed by HRV test which included frequency domain indices, time domain indices and nonlinear parameters. Non motor symptoms were assessed by using COMPASS 31 questionnaire which evaluated six domains namely orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor domains. The six domain scores sum to a total score of 0 to 100 with a higher score indicating more severe autonomic symptoms.

**Results:** The participants showed a sympathetic overdrive on assessing with HRV. Among the non-motor symptoms gastrointestinal symptoms were the most common symptoms (95.62%) in Parkinson's disease patients. Subsequently there was involvement of secretomotor (85.4%), bladder symptoms (71.53%), pupillomotor symptoms (52.55%), orthostatic intolerance symptoms (50.36%) and vasomotor symptoms (13.14%) on evaluating autonomic functions by COMPASS 31 questionnaire. A statistically significant correlation was observed between HF (ms2) and COMPASS 31 questionnaire ($p<0.05$).

**Conclusion:** The autonomic function tests can be used as a screening tool in outpatient department of Neurology. This could reduce the morbidity of Parkinson's disease patients as we employ these autonomic function tests as an early intervention for Parkinson's disease. COMPASS 31 questionnaire can be used in health care centres for early detection of neurodegenerative disorders like Parkinson's disease which could prevent the disease progression and aid in early treatment plan.

**Keywords:** Parkinson's disease, neurodegenerative disorder, autonomic function test, HRV, COMPASS 31 questionnaire.

## INTRODUCTION

Parkinson's disease (PD) is a complex progressive neurodegenerative disease, which generally present in later life with classic motor symptoms of bradykinesia, resting tremor, rigidity and postural instability.[1] It is 1.5 times more common in males as compared to females.[2] It is associated with death of dopaminergic neurons in substantia nigra pars compacta (SNpc) and noradrenergic neurons in locus coeruleus which leads to classic motor symptoms.[3,4] Not only dopaminergic neurons but also serotonergic neurons in the raphe nuclei, cholinergic neurons of the nucleus basalis of Meynert, norepinephrine neurons in the locus coeruleus, as well as neurons of the olfactory system and autonomic nervous system are all influenced by neuronal degeneration with inclusion body formation. This nondopaminergic pathology most likely leads to the development of the non-motor signs of PD.[5] which includes orthostatic intolerance, vasomotor symptoms, secretomotor symptoms, gastrointestinal system, urinary and pupillomotor symptoms.

There is no specific laboratory investigation or imaging technique to diagnose PD. Heart rate variability (HRV) provides a non-invasive index of neurocardiac function, reflecting the complex interplay between heart-brain interactions and dynamic non-linear processes within the autonomic nervous system (ANS).[6] Hence, it has emerged as a multifaceted parameter for evaluation of coordinated activity of interdependent regulatory systems operating on diverse time scales to facilitate organismic adaptation to environmental and psychological stressors.

On the other hand, another tool that has gathered interest in terms of predicting autonomic functions is the Composite Autonomic Symptom Score-31 (COMPASS 31). It is a self-rating questionnaire, evaluating six domains of autonomic function: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor domain.[7] While, the COMPASS 31 has already been reported as a useful tool for the evaluation of autonomic dysfunction in various neurologic diseases, however its role in Parkinson's patients has been limited, although it serves to be an efficient method, especially in countries like India, with less paying capacity and high financial burden of Parkinson's Disease. Hence, clinicians can use this questionnaire in the OPD to assess non motor symptoms of PD patients.

There are only a few population based studies evaluating autonomic function among PD patients in Indian population. Moreover the studies done so far have used only one or two parameters to evaluate autonomic functions in PD patients. COMPASS 31 was used by Sletten DM et al,[7] to evaluate autonomic dysfunction in Parkinson patients. HRV was the basis for assessing autonomic dysfunction in PD patients by Konstantin G. Heimrich et al,[8] and Zhichun Chen et al.[9] Hence the present study was aimed to evaluate the autonomic function in individuals with Parkinson's through HRV and COMPASS-31 questionnaire.

## MATERIAL AND METHODS

**Subjects**

The present study was an observational cross-sectional study carried out in Department of Physiology in collaboration with Department of Neurology, Dr. RMLIMS, Lucknow, after obtaining Institutional Ethical Committee approval (IEC No. 72/22).

After receiving informed written consent, 137 patients, both male and female in the age group of 50-80 years, with diagnosed Parkinson's disease using the diagnostic criteria of the UK Parkinson's Disease Society Brain Bank.[10] were enrolled in the study between September 2022 to February 2024. Patients were taken upto stage three of Hoehn and Yahr staging.[11]

Exclusion criteria included history of repeated strokes with stepwise progression of Parkinsonian features, history of repeated head injuries, history of definite encephalitis, oculgyric crises, neuroleptic treatment at onset of symptoms, more than one affected relative, sustained remission, strictly unilateral features after three years, supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, early severe dementia with disturbances of memory, language and praxis, positive Babinski sign, presence of cerebral tumor or communication hydrocephalus on imaging study, negative response to large doses of levodopa in absence of malabsorption, methylphenyl tetra hydro pyridine exposure.

**Procedures**

Body weight was measured on a calibrated weighing scale in kg. Standing height was measured by stadiometer in cm. BMI was calculated as person's weight in kilograms divided by the square of the person's height in metres (kg/m2).

Waist circumference and hip circumference was measured in cm. with a soft non stretchable measuring tape at the midpoint between the lowest rib margin and iliac crest and at the greater trochanters respectively. Heart rate (HR) was measured at baseline after giving 10 minutes of rest. Systolic and Diastolic blood pressure (SBP and DBP) was measured in the upper arm using a Digital fully automatic blood pressure monitor (OMRON HEM 7121J) with the subject lying comfortably in supine position.

Subjects were asked not to consume tea/coffee or any cardio-modulator substance at least 6 hours before the test and to remove any wrist or ankle jewellery before the test itself. HRV was recorded by ECG lead II for 5 minutes at a frequency of 500 samples per second by four channel Physiograph

(AD instruments South Asia (India) Pvt. Ltd., New Delhi, India.). HRV was analyzed by spectral analysis using software LABCHART PROV 8.1.8 with HRV module V.2.0.3. The frequency domain analysis was performed using fast Fourier transformation. Following frequency domain indices were considered: Low frequency (LF) power (ms2), High frequency (HF) power (ms2), Total power (ms2), LF/HF ratio. The following time-domain indices were considered: SDRR in ms (SD of successive RR interval differences), RMSSD in ms (root mean square of successive RR interval differences), pRR50 in percentage (% of successive RR intervals differing by more than 50 ms). Nonlinear parameters which were included: SD1 (ms) and SD2 (ms).

The COMPASS-31 questionnaire was administered to all PD patients. The questionnaire consisted of 31 questions involving six domains namely orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor. Scoring of COMPASS 31 questionnaire:

1. Simple yes or no questions were scored as 0 points for no and 1 point for yes.
2. Questions about a specific site of symptoms or symptoms under specific circumstances were scored as 0 if not present and as 1 if present for each site or circumstance.
3. All questions regarding the frequency of symptoms were scored as 0 points for rarely or never, 1 point for occasionally or sometimes, 2 points for frequently or "a lot of the time," and 3 points for almost always or constantly.
4. All questions regarding the severity of symptoms were scored as 1 point for mild, 2 points for moderate, and 3 points for severe.
5. When assessing the time course of a symptom, we scored 0 points for responses such as "gotten somewhat better," "gotten much better," "completely gone," and "I have not had any of these symptoms," 1 point for "stayed about the same," 2 points for "gotten somewhat worse," and 3 points for "gotten much worse."
6. The scores for changes in bodily functions depended on the individual question asked. For example, "I get full a lot more quickly than I used to when eating a meal" was scored 2 points and "I get full a lot less quickly than I used to" was scored 0 points, while the answer "I sweat much more than I used to" was given 1 point and "I sweat much less than I used to" was scored 2 points.

Final score was calculated as the sum of all subscales, varying from 0 to 100, higher scores signifying greater dysfunction.[7]

Statistical analysis

SPSS version 21 was used for statistical computation and analysis. Categorical variables were represented in numbers (frequency) and percentage, otherwise continuous variables were represented in Mean and Standard Deviation (SD). Student t test, Spearman's correlation test and ANOVA test were used to analyze the results. 95% of confidence interval (CI), considering p value <0.05 as statistically significant.

## RESULTS

Table 1 shows demographic information of the study population. Participants in the study had a mean age of 62.28±7.61 years. Majority of the patients were aged between 50 to 69 years (77.4%), while the remaining were aged 70-79 years. Study population consisted of 62% males and 38% females. Males outnumbered females by 1.63. [Table 1]

Table 2 shows HRV parameters of the study population. LF ranged from 1.61 to 817.7 ms2 (Mean 164.37±190) and 1.63 to 93.44 nu (Mean 49.71± 23.19). HF ranged from 1.205 to 767 ms2 (Mean 121.55± 157) and 6.98 to 91.75 nu (Mean 46.18± 20.15). LF/HF ranged from 0.02 to 13.30 (Mean 1.80±2.10). Total power ranged from 101.8 to 5625 ms2 (Mean 892.07± 1002). RMSSD ranged from 2.14 to 185.50ms (Mean 29.54± 31.87). pNN50 ranged from 0 to 80.72% (Mean 5.16 ±12.0). LF-low frequency; HF-high frequency; LF/HF-sympatho-vagal balance; T. power-total power; RMSSD- root mean square of successive RR interval differences; SDNN- SD of successive RR interval differences; pNN50- % of successive RR intervals differing by more than 50 ms. [Table 2]

Table 3 shows association of age with HRV parameters. p value shows level of significance. *p < 0.05 is statistically significant. A statistically significant association of age with time domain parameters of HRV was seen (SDNN 35.4±24.7; p=0.037 and SD2 41.8±27.1; p=0.020) in the age group 60-69 years. Age has a significant role to play in HRV estimates and HRV parameters are highly influenced by other factors such as anxiety and emotional stress. [Table 3]

Table 4 shows assessment of non motor symptoms using COMPASS 31 questionnaire. Gastrointestinal system was maximally involved in PD patients (95.62%) with a mean of 6.50±3.25. Least involved system was vasomotor (13.14%) with a mean of 0.34±0.92. [Table 4]

Table *5* shows a statistically significant positive correlation of COMPASS 31 and HF ($ms^2$) HRV parameter. *p<0.05 is statistically significant. [Table 5]

**Table 1: Demographic profile of the study population**

| Variables | No. of participants | n (%) |
|---|---|---|
| Gender | | |
| Females | 52 | 38% |
| Males | 85 | 62% |

| | | |
|---|---|---|
| Age in completed years | | |
| 50-59 | 54 | 39.4% |
| 60-69 | 52 | 38% |
| 70-79 | 31 | 22.6% |

**Table 2: HRV parameters of the study population**

| Parameters | Range | Mean±SD |
|---|---|---|
| **HRV Frequency Domain Measures** | | |
| LF (%) | 1.56 to 55.71 | 23.20±11.52 |
| LF ($ms^2$) | 1.61 to 817.7 | 164.37±190 |
| LF (nu) | 1.63 to 93.44 | 49.71±23.19 |
| HF (%) | 0.68 to 83.83 | 27.73±21.08 |
| HF ($ms^2$) | 1.205 to 767 | 121.55±157 |
| HF (nu) | 6.98 to 91.75 | 46.18±20.15 |
| VLF (%) | 1.54 to 3052.00 | 69.78±258.16 |
| VLF ($ms^2$) | 3.048 to 999.1 | 217.9±214.61 |
| LF/HF | 0.02 to 13.30 | 1.80±2.10 |
| HRV Time Domain Measures | | |
| T Power ($ms^2$) | 101.8 to 5625 | 892.07±1002 |
| RMSSD (ms) | 2.14 to 185.50 | 29.54±31.87 |
| SDNN (ms) | 5.02 to 127.30 | 30.01±20.97 |
| pNN50 (%) | 0.00 to 80.72 | 5.16±12.00 |
| HRV Non Linear Measure | | |
| SD1 (ms) | 1.51 to 131.30 | 20.73±22.56 |
| SD2 (ms) | 1.50 to 149.50 | 35.30±22.27 |

**Table 3: Association of Age with HRV parameters**

| HRV parameter | 50-59 years | 60-69 years | 70-79 years | ANOVA | |
|---|---|---|---|---|---|
| | Mean± SD | Mean± SD | Mean± SD | F | p |
| LF (%) | 24.2±10.2 | 23.6±12.8 | 20.53±11.09 | 1.110 | 0.332 |
| LF ($ms^2$) | 141.1±162.6 | 202.8±222.8 | 140.3±168.3 | 1.736 | 0.180 |
| LF (nu) | 52.0±21.5 | 47.4±23.5 | 49.3±25.9 | 0.509 | 0.601 |
| HF (%) | 25.7±19.6 | 29.6±20.9 | 27.8±24.01 | 0.443 | 0.642 |
| HF ($ms^2$) | 126.8±161.9 | 137.7±179.4 | 85.03±93.6 | 1.150 | 0.319 |
| HF (nu) | 43.5±19.0 | 49.1±20.3 | 45.9±21.7 | 1.033 | 0.358 |
| VLF | 46.6±22.8 | 103.1±417.5 | 53.9±41.4 | 0.706 | 0.495 |
| VLF ($ms^2$) | 193.0±190.7 | 232.8±200.6 | 236.3±272.4 | 0.599 | 0.550 |
| LF/HF | 1.76±1.53 | 1.7±2.2 | 2.02±2.62 | 0.225 | 0.798 |
| T Power ($ms^2$) | 712.3±875.8 | 1031.8±911.4 | 970.7±1299.3 | 1.479 | 0.231 |
| RMSSD (ms) | 23.8±24.4 | 34.6±36.0 | 30.9±35.1 | 1.567 | 0.212 |
| SDNN (ms) | 25.1±15.0 | 35.4±24.7 | 29.3±21.5 | 3.352 | 0.037* |
| pNN50 (%) | 4.68±12.35 | 7.75±14.37 | 1.6±2.6 | 2.635 | 0.075 |
| SD1 (ms) | 16.4±17.1 | 24.4±25.4 | 21.9±24.9 | 1.776 | 0.173 |
| SD2 (ms) | 30.12±15.54 | 41.8±27.1 | 33.2±21.0 | 4.013 | 0.020* |

**Table 4: Response of study population to different domains of COMPASS-31**

| COMPASS 31 domains | Number | % | Mean±SD |
|---|---|---|---|
| Orthostatic intolerance | 69 | 50.36% | 2.40±2.72 |
| Vasomotor | 18 | 13.14% | 0.34±0.92 |
| Secreto-motor | 117 | 85.4% | 2.82±1.87 |
| Gastrointestinal | 131 | 95.62% | 6.50±3.25 |
| Bladder symptoms | 98 | 71.53% | 1.81±1.44 |
| Pupillo-motor | 72 | 52.55% | 2.27±2.56 |
| Total Score | | | 16.13±8.19 |

**Table 5: Spearman's Correlation of COMPASS 31 with HRV parameters**

| HRV parameters | Correlation coefficient | P value |
|---|---|---|
| Total power | 0.004 | 0.964 |
| LF/HF | 0.063 | 0.467 |
| LF ($ms^2$) | 0.089 | 0.303 |
| LF (nu) | 0.036 | 0.679 |
| HF ($ms^2$) | 0.175 | 0.04* |
| HF (nu) | -0.061 | 0.481 |

## DISCUSSION

Majority of the patients in our study were aged between 50 to 69 years (77.4%). Similar age of patients with PD has been reported by Merola et al,[12] and Gerasimova-Meigal et al.[13] Middle aged population was more affected with PD, this may be due to age-related decline in dopaminergic activity.[14]

Male to female ratio in our study was 1.63:1 with 62% males and 38% females. Similar population distribution was seen in studies conducted by Gerasimova-Meigal et al,[13] and Cholerton et al.[15] Possible reasons for this increased risk of Parkinson's disease in men are neuroprotection by oestrogen, mitochondrial dysfunction, or X linkage of genetic risk factors.[16]

Our study showed a sympathetic overdrive in PD patients which was in accordance with study done by Haapaniemi et al.[17] A statistically significant association of age with time domain parameters of HRV (SDNN and SD2) was seen in our study in the age group 60-69 years. Age has a significant role to play in HRV estimates and HRV parameters are highly influenced by other factors such as anxiety and emotional stress.

Non motor symptoms in PD patients in our study were assessed by COMPASS 31 questionnaire which showed maximum involvement of gastrointestinal symptoms (95.62%). This finding is in accordance with the study done by Chen Z et al,[9] which stated that 88.9% of PD patients develop constipation prior to onset of motor symptoms. The gastrointestinal motility is controlled by the vagus nerve which gets degenerated in PD patients. Using high-resolution ultrasound, Pelz et al,[18] found that vagus nerve axons were considerably smaller in PD patients.

Secretomotor system in our study was affected in 85.4% of PD patients. As studied by Asahina et al,[19] in PD patients, sympathetic sudomotor and vasoconstrictive functions become impaired in parallel with a reduction in intraepidermal nerve fibre density and an increase in skin α-synuclein deposition. Therefore, skin neuropathy may be a potential cause of thermoregulatory dysfunction in PD.

71.53% PD patients in our study were found to have bladder symptoms like urinary incontinence. Bladder and urethra are controlled by noradrenergic sympathetic and cholinergic parasympathetic nerves. Urinary centres in the brain include the pontine storage centre, pontine micturition centre, hypothalamus, basal ganglia and frontal cortex. Multiple peripheral and central structures in this urinary controlling system are involved in PD; particularly, frontal lobe and basal ganglia dysfunction resulting in bladder overactivity.[20]

In our study pupillomotor system was found to be affected in 52.55% patients. Pupil diameter is controlled by both the parasympathetic and the sympathetic nerves. The parasympathetic nerve arises from neurons in the ciliary ganglion, which receives impulses from Edinger–Westphal nucleus in the midbrain. The sympathetic nerve originates from the superior cervical ganglion, which receives input from the ciliospinal centre in the spinal cord. Both Edinger–Westphal nucleus and the ciliospinal centre are regulated by the cortex, thalamus, hypothalamus, pretectum and several other nucleus in the brainstem. The superior cervical ganglion, ciliospinal centre and several of the higher control centres are impaired in PD which lead to pupillomotor dysfunctions.[20]

Orthostatic intolerance (OH) was seen in 50.36% of PD patients in our study. Transitioning from the supine to the standing posture reduces the amount of blood returning to the right heart from the peripheral organs, which in turn lowers cardiac output and blood pressure. When this decrease in the pressure is sensed by carotid sinus baroreceptor, the cardiovascular system experiences a decrease in parasympathetic activity and an increase in sympathetic activity which helps to maintain blood pressure towards normal on orthostatic position change. Blaho et al,[21] found that low baroreflex sensitivity is strongly associated with orthostatic hypotension in PD patients.

The least effected system in our study was vasomotor (13.14%). α-synuclein may affect the biosynthesis of melanin and neuromelanin (NM) by regulating activities of certain enzymes like tyrosinase, tyrosine hydroxylase, and peroxidase. In addition, α-synuclein may change the structure and biosynthesis of NM.[22]

**Limitations**

A large sample size and a case control study could be a better study design to implement the outcome of the study on Indian population. Prospective studies are required to validate the role of autonomic function test in neurodegenerative disorders. Exploring advancements in autonomic function tests may validate the study better.

## CONCLUSION

PD patients showed a sympathetic overdrive on assessing with HRV test. Gastrointestinal symptoms were the most common symptoms (95.62%) with vasomotor domain being least affected. A statistically significant positive correlation was observed between HF (ms2) and COMPASS 31 questionnaire ($p<0.05$). A statistically significant association of age with SDNN and SD2 parameters of HRV was observed.

These autonomic function tests can be used as a screening tool in outpatient department of Neurology. This could reduce the mortality of PD patients as we employ these autonomic function tests as an early intervention for Parkinson's disease. COMPASS 31 questionnaire can be used in health care centres for early detection of neurodegenerative disorders like Parkinson's disease which could prevent the disease progression and aid in early treatment plan.

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