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Original Research Article

DIAGNOSTIC ACCURACY OF SHORT-TERM HEART RATE VARIABILITY AGAINST EWING'S BATTERY OF TESTS, AND ITS RELATIONSHIP WITH THE COMPOSITE AUTONOMIC SYMPTOM SCORE 31, FOR CARDIOVASCULAR AUTONOMIC DYSFUNCTION IN PATIENTS WITH PARKINSON'S DISEASE

Rajani Bala Jasrotia[1], Saptarshi Chakraborty[2], Abdul Qavi[3], Arvind Kanchan[4], Dinkar Kulashreshtha[5], Arshi Ansari[6]

[1]Professor (junior grade) and HOD, Department of Physiology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
[2]3rd year MBBS Student, Dr. Ram Manohar Lohia Institute of Medical Sciences Lucknow, Uttar Pradesh, India
[3]Associate Professor, Department of Neurology Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
[4]Associate Professor, Department of Physiology, AIIMS Raebareli, Uttar Pradesh, India
[5]Professor, Department of Neurology, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India
[6]Assistant Professor, Department of Community Medicine, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

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Corresponding Author:
Dr. Abdul Qavi,
Associate Professor, Department of Neurology Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.
Email: drqavi2008@gmail.com

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ABSTRACT

Background: Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by motor and certain non-motor symptoms, including autonomic dysfunction, which is associated with poor quality of life. This study evaluated the diagnostic accuracy of resting short-term heart rate variability (HRV) against the heart-rate tests of Ewing's battery, and examined how the Composite Autonomic Symptom Score 31 (COMPASS-31) relates to HRV and to Ewing's tests in patients with PD.

Materials and Methods: This cross-sectional study was carried out over 6 months (patient assessment over 2 months, under an ICMR Short-Term Studentship) in the Departments of Physiology and Neurology of a tertiary care teaching hospital in an urban setting of north India. Fifty patients with PD completed the COMPASS-31 questionnaire, a 5-minute resting HRV recording and Ewing's battery of cardiovascular reflex tests. Associations were assessed with Spearman's correlation. Using each Ewing heart-rate test as the reference standard, the diagnostic accuracy of HRV indices (LF, HF, LF/HF ratio, total power) was assessed by ROC analysis. Sensitivity, specificity, predictive values, likelihood ratios and area under the curve (AUC) are reported with 95% confidence intervals (CI).

Results: Of the 50 patients (mean age 60.5 ± 9.86 years; 66% male), Ewing's battery was abnormal for the HR(VM) ratio in 40 (80%), HR(DB) in 28 (56%), the HR(DB) ratio in 27 (54%) and the 30:15 ratio in 25 (50%). The mean COMPASS-31 total score was 11.92 ± 8.79 and was not significantly correlated with any HRV index or Ewing test parameter ($|\rho| \leq 0.15$). Against the individual Ewing heart-rate tests, HRV indices showed poor-to-fair discrimination (AUC 0.513–0.708; the 95% CI included 0.5 in 12 of 16 comparisons). Total power had the highest AUC, against the Valsalva ratio (0.708, 95% CI 0.544–0.872). The LF/HF ratio was the only index with balanced sensitivity and specificity (against the HR(DB) ratio: 0.67 [0.48–0.81] and 0.65 [0.45–0.81]).

Conclusion: Resting short-term HRV agreed only poorly to fairly with the heart-rate tests of Ewing's battery in PD, and its apparent accuracy depended strongly on the cut-off used. The LF/HF ratio was the most balanced index.

COMPASS-31 scores were unrelated to both HRV and Ewing's tests, so symptom burden cannot substitute for objective testing. Neither tool can replace Ewing's battery. Whether combining COMPASS-31 with HRV improves the detection of cardiovascular autonomic neuropathy needs to be tested prospectively.
Keywords: Parkinson's disease, autonomic dysfunction, Composite Autonomic Symptom Score 31, heart rate variability, Ewing's battery of tests, cardiovascular autonomic neuropathy, diagnostic accuracy.

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder attributed to dysfunction of dopaminergic neurons in the basal ganglia. Bradykinesia, rigidity, tremor and postural instability are the four classic motor symptoms of PD.[1] In addition to these motor symptoms, several non-motor impairments such as cognitive impairment, sleep disturbances, olfactory abnormalities, anxiety, depression and autonomic dysfunction are frequently noted in patients with PD.[2,3]

Autonomic dysfunction is one of the prominent non-motor features of PD, increasing morbidity and interfering with quality of life.[4] Frequently observed debilitating symptoms of autonomic dysfunction in PD include orthostatic hypotension (OH); gastrointestinal problems such as delayed gastric emptying, constipation and dysphagia; genito-urinary complaints such as nocturia, urgency, urinary frequency, decreased libido and sexual dysfunction; and thermoregulatory dysfunction, such as altered sensitivity to temperature and abnormal sweating.[2] Furthermore, PD may sometimes be associated with early autonomic failure.[5,6] Many symptoms of autonomic dysfunction can be improved by lifestyle modification and a few additional medications. Therefore, early diagnosis and intervention for autonomic dysfunction is important for a better quality of life.

The clinical assessment tools for autonomic disturbances were first designed in diabetic patients by Ewing et al.[7] These tests were later performed in patients having or suspected of having cardiovascular autonomic neuropathy (CAN) and are popularly known as Ewing's battery of tests.[8] Despite the widespread use of these tests, there is still debate about the diagnostic criteria and staging of CAN.[9] Moreover, the battery takes time, requires patient cooperation (for example, a sustained Valsalva manoeuvre and handgrip) and trained staff, which limits its use in busy outpatient clinics.

The Composite Autonomic Symptom Score 31 (COMPASS-31) is a questionnaire-based, subjective scale that assesses autonomic symptoms across multiple domains. Several studies support the use of COMPASS-31 to evaluate autonomic dysfunction in outpatient settings.[10] However, its diagnostic accuracy remains uncertain because it relies on patients' recall of symptoms.

Heart rate variability (HRV) is an objective tool for assessing the autonomic nervous system. Time-domain and frequency-domain HRV indices quantify sympathetic and parasympathetic modulation of heart rate and their balance. Frequency-domain indices are commonly obtained by fast Fourier transformation of the RR-interval series derived from electrocardiographic recordings.[11]

Resting HRV and COMPASS-31 are both quick to obtain, and either could help to identify which patients with PD need full Ewing's testing. Before they can be combined, however, it must be known how each relates to the reference standard. The primary objective of this study was therefore to estimate the diagnostic accuracy of resting short-term HRV indices against the heart-rate tests of Ewing's battery in patients with PD. The secondary objective was to examine the association of the COMPASS-31 score with HRV indices and with Ewing's test parameters.

MATERIALS AND METHODS

Study design, setting and participants

This prospective cross-sectional study was carried out in the Departments of Physiology and Neurology, Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, a tertiary care teaching hospital in an urban setting. Data collection started after approval from the institutional ethics committee (1 August 2022; IEC No. 44/22). Written informed consent was obtained from every participant. The study was conducted under the Indian Council of Medical Research Short-Term Studentship (ICMR-STS) programme. Patients were recruited and assessed over 2 months, and the total study period, including data analysis, was 6 months. A total of fifty patients with Parkinson's disease aged 40–80 years were enrolled. The diagnostic accuracy analysis is reported in accordance with the STARD 2015 guidelines.[12]

Inclusion criteria

All willing patients with Parkinson's disease diagnosed according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria were enrolled.[13]

Exclusion criteria

- History suggestive of vascular parkinsonism, atypical parkinsonism or drug-induced parkinsonism.
- Comorbidities such as diabetes, hypertension, obesity, coronary artery disease or stroke; repeated head injury.
- Positive family history of Parkinson's disease.

- Use of alpha-blockers, beta-blockers or other drugs that may affect autonomic function tests.

Reference standard: Ewing's battery of tests

The following five tests were performed in all patients:

- Heart rate response to deep breathing [HR(DB): maximum minus minimum heart rate; HR(DB) ratio: maximum/minimum heart rate]
- Heart rate response to the Valsalva manoeuvre [HR(VM) ratio]
- Heart rate response to standing [HR(S), 30:15 ratio]
- Blood pressure (BP) response to sustained handgrip
- Blood pressure response to standing

For the diagnostic accuracy analysis, each heart-rate test was classified as abnormal using the following cut-offs, based on the reference values of Ewing and Clarke:[14] HR(DB) ≤ 10 beats per minute; HR(DB) ratio ≤ 1.07; HR(VM) ratio ≤ 1.20; and 30:15 ratio ≤ 1.00. Orthostatic hypotension was defined as a fall of ≥ 20 mmHg in systolic or ≥ 10 mmHg in diastolic blood pressure within 3 minutes of active standing.

COMPASS-31

The COMPASS-31 questionnaire was administered to all patients by the same investigator. It consists of 31 items in six domains: orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor. Raw domain scores were multiplied by their published weighting factors, giving weighted domain maxima of 40, 5, 15, 25, 10 and 5 respectively.[15] The total score is the sum of the weighted domain scores, ranging from 0 to 100, with higher scores indicating greater autonomic dysfunction.

Index test: heart rate variability

HRV was recorded from ECG lead II for 5 minutes at a sampling rate of 500 samples per second using a four-channel physiograph (AD Instruments South Asia (India) Pvt Ltd, New Delhi, India). All recordings were done at a fixed time of day (4:00 PM) to avoid diurnal variation. HRV was analysed using LabChart Pro v8.1.8 software with the HRV module v2.0.3. The frequency-domain analysis used fast Fourier transformation with the standard frequency bands,[16] very low frequency (VLF, ≤ 0.04 Hz), low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.40 Hz). The frequency-domain indices were LF power, HF power, total power and the LF/HF ratio, expressed in absolute units (ms^2) and normalised units (nu). The time-domain indices were SDNN (standard deviation of normal-to-normal RR intervals), RMSSD (root mean square of successive RR-interval differences) and pNN50 (percentage of successive RR intervals differing by more than 50 ms). The Poincaré plot indices SD1 and SD2 were also recorded. For the 2 × 2 analysis, each of LF, HF, the LF/HF ratio and total power was classified as abnormal at state the cut-off used for each index and its source.

Statistical methods: Data were recorded in MS-Excel and analysed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Normality was assessed with the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation and categorical variables as number (%). Student's t-test was used for normally distributed data and the Mann–Whitney U test for non-normally distributed data. Associations of the COMPASS-31 total score and HRV indices with Ewing's test parameters were assessed with Spearman's rank correlation.

Diagnostic accuracy: Each Ewing heart-rate test (HR(DB), HR(DB) ratio, HR(VM) ratio and 30:15 ratio) served in turn as the reference standard, and each HRV index (LF, HF, LF/HF ratio and total power) as the index test. A receiver operating characteristic (ROC) curve was constructed for each continuous HRV index, and its area under the curve (AUC) was calculated with a 95% confidence interval (CI) by the Hanley–McNeil method.[17] From the 2 × 2 table of the dichotomised HRV index against the Ewing test, we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR−). Ninety-five percent CIs were calculated by the Wilson score method for proportions,[18] and by the log method for likelihood ratios.[19] A p value < 0.05 was considered statistically significant.

RESULTS

Participant characteristics: A total of 50 patients with PD were included, with a mean age of 60.5 ± 9.86 years; 33 (66%) were male. [Table 1] shows that BMI was 23.15 ± 3.18 kg/m^2 and the total COMPASS-31 score was 11.92 ± 8.79. On Ewing's battery of tests, systolic and diastolic BP rose from baseline during handgrip and fell on sudden standing; HR(DB) was 22.89 ± 26.01 beats per minute and the HR(VM) ratio was 1.42 ± 0.86. Table 1 also shows the frequency-domain and time-domain HRV parameters.

Abnormal results on Ewing's heart-rate tests and HRV indices: Of the four heart-rate tests, the HR(VM) ratio was abnormal most often (40 patients, 80%), followed by HR(DB) (28, 56%), the HR(DB) ratio (27, 54%) and the 30:15 ratio (25, 50%) [Table 2]. At the cut-offs used, the dichotomised HRV indices classified 4 (8%) patients as abnormal on LF, 45 (90%) on HF, 26 (52%) on the LF/HF ratio and 44 (88%) on total power.

COMPASS-31 and its correlation with HRV and Ewing's battery: The mean COMPASS-31 total score was 11.92 ± 8.79 on a scale of 0–100. Spearman's rank correlations between the COMPASS-31 score, HRV indices and Ewing's battery parameters are shown in [Table 3]; statistically significant correlations ($p < 0.05$) are marked with an asterisk. The COMPASS-31 total score was not significantly correlated with any HRV

index, resting cardiovascular parameter or Ewing test parameter (ρ ranged from −0.152 to 0.130).

There was a significant positive correlation between the LF/HF ratio and the diastolic BP during handgrip and during standing. Diastolic BP during handgrip was also significantly positively correlated with RMSSD and SD1. Systolic BP during handgrip was significantly positively correlated with SD1 and SD2 and negatively correlated with SDNN. Total power was significantly positively correlated with HR(DB) and the HR(DB) ratio and negatively correlated with HR(HGD).

Diagnostic accuracy of HRV indices against Ewing's heart-rate tests: Against HR(DB) ≤ 10 bpm [Table 4, Figure 1], AUCs ranged from 0.528 to 0.628 and every 95% CI included 0.5. Because of the very different proportions classified as abnormal, LF had high specificity but very low sensitivity (0.91 [0.72–0.97] and 0.07 [0.02–0.23]), whereas HF and total power had high sensitivity but very low specificity (0.89 [0.73–0.96] and 0.09 [0.03–0.28]; 0.86 [0.69–0.94] and 0.09 [0.03–0.28]). The LF/HF ratio was the most balanced (sensitivity 0.61 [0.42–0.76], specificity 0.59 [0.39–0.77], AUC 0.599 [0.441–0.757]).

Against the HR(DB) ratio [Table 5, Figure 2], the LF/HF ratio gave the best balance of sensitivity and specificity (0.67 [0.48–0.81] and 0.65 [0.45–0.81]; LR+ 1.92 [1.03–3.56]; AUC 0.659 [0.508–0.810]). Total power had the highest AUC (0.683 [0.536–0.830]), but at the cut-off used its specificity was only 0.09 (0.02–0.27).

Against the HR(VM) ratio ≤ 1.20 [Table 6, Figure 3], AUCs ranged from 0.513 to 0.708. Total power performed best (AUC 0.708 [0.544–0.872]). At the cut-offs used, all likelihood ratios were close to 1 (LR+ 0.75–1.05). Because 80% of patients were abnormal on this test, the PPVs were high (0.75–0.81) and the NPVs low (0.17–0.21).

Against HR(S) ≤ 1.00 [Table 7, Figure 4], AUCs ranged from 0.528 to 0.660. HF and total power had high sensitivity (0.96 [0.80–0.99] and 0.92 [0.75–0.98]) but low specificity (0.16 [0.06–0.35] for both). The LF/HF ratio was inversely related to an abnormal 30:15 ratio (LR+ 0.53 [0.29–0.95]); its AUC of 0.660 reflects this reversed direction.

Overall, the 95% CI of the AUC included 0.5 in 12 of the 16 comparisons. Only four AUCs had a lower confidence limit above 0.5: total power against the HR(DB) ratio (0.683) and the HR(VM) ratio (0.708), and the LF/HF ratio against the HR(DB) ratio (0.659) and HR(S) (0.660, inverse).

Table 1: Descriptive statistics of the study participants (n = 50)

Variable	Mean ± SD
Socio-demographic	
Gender	Male: 33 (66%) Female: 17 (34%)
Age (years)	60.5 ± 9.86
Anthropometry	
Height (cm)	159.44 ± 9.70
Weight (kg)	58.98 ± 10.37
Body mass index (kg/m²)	23.15 ± 3.18
Autonomic symptoms	
COMPASS-31 total score (0–100)	11.92 ± 8.79
Resting cardiovascular	
Heart rate (beats/min)	81.62 ± 15.06
Systolic BP (mmHg)	124.24 ± 20.30
Diastolic BP (mmHg)	77.66 ± 12.29
Ewing's battery of tests	
Systolic BP, handgrip (mmHg)	132.14 ± 18.94
Diastolic BP, handgrip (mmHg)	86.10 ± 10.37
Systolic BP, standing (mmHg)	123.68 ± 20.39
Diastolic BP, standing (mmHg)	75.52 ± 11.37
HR(DB): max − min heart rate (beats/min)	22.89 ± 26.01
HR(DB) ratio: max/min heart rate	1.34 ± 0.42
HR(S): 30:15 ratio	1.05 ± 0.20
HR(VM) ratio	1.42 ± 0.86
Heart rate variability: frequency domain	
VLF (nu)	42.28 ± 23.85
VLF (ms²)	279.22 ± 282.87
LF (nu)	23.71 ± 10.94
LF (ms²)	199.75 ± 224.45
HF (nu)	29.99 ± 22.08
HF (ms²)	464.84 ± 824.32
LF/HF ratio	3.37 ± 10.55
Total power (ms²)	1021.02 ± 1198.59
Heart rate variability: time domain and Poincaré	
pNN50 (%)	7.93 ± 16.05
RMSSD (ms)	32.73 ± 32.26
SD1 (ms)	23.17 ± 22.84
SD2 (ms)	36.27 ± 18.07
SDNN (ms)	31.61 ± 18.69

Values are mean ± SD or n (%). Mean values rounded to two decimals. BP, blood pressure; HR(DB), heart rate response to deep breathing; HR(S), heart rate response to standing; HR(VM), heart rate response to the Valsalva manoeuvre; VLF, very low frequency; LF, low frequency; HF, high frequency; nu, normalised units; pNN50, percentage of successive RR intervals differing by > 50 ms; RMSSD, root mean square of successive RR-interval differences; SD1/SD2, Poincaré plot standard deviations; SDNN, standard deviation of normal-to-normal RR intervals.

Table 2: Number of patients with an abnormal result on each Ewing heart-rate test and each dichotomised HRV index (n = 50)

Test	Cut-off for abnormal	Abnormal, n (%)
Ewing's battery: heart-rate tests (reference standards)		
HR(DB): max − min heart rate	≤ 10 bpm	28 (56.0)
HR(DB) ratio	≤ 1.07	27 (54.0)
HR(VM) ratio	≤ 1.20	40 (80.0)
HR(S): 30:15 ratio	≤ 1.00	25 (50.0)
HRV indices (index tests)		
LF	cut-off	4 (8.0)
HF	cut-off	45 (90.0)
LF/HF ratio	cut-off	26 (52.0)
Total power	cut-off	44 (88.0)

Counts are taken from the 2 × 2 tables underlying Tables 4–7. HR(DB), HR(VM), HR(S): heart rate response to deep breathing, Valsalva manoeuvre and standing.

Table 3: Spearman rank correlation of COMPASS-31 score, resting cardiovascular parameters and HRV indices with Ewing's battery of tests

Spearman ρ	COMPASS-31 total	HR (DB)	HR (DB) ratio	HR (HGD)	HR (S)	HR (VM) ratio	SBP (HGD)	SBP (S)	DBP (HGD)	DBP (S)
DBP	-0.035	0.06	0.00	0.26	0.04	0.03	0.48	0.58	0.80	0.76
HR	0.130	-0.20	-0.35	0.95	-0.34	-0.16	-0.27*	-0.15	0.09	0.13
SBP	-0.015	0.12	0.11	-0.12	0.10	-0.03	0.86	0.86	0.71	0.60
HF (nu)	-0.024	0.15	0.13	-0.09	0.02	-0.30	-0.09	-0.05	-0.18	-0.18
HF (ms²)	-0.031	0.26	0.28	-0.35	0.10	-0.10	-0.09	-0.08	-0.20	-0.18
LF (nu)	0.002	0.02	0.07	-0.18	0.18	0.09	-0.03	-0.09	0.08	0.02
LF/HF	-0.028	-0.05	-0.03	0.02	-0.05	0.25	0.10	0.07	0.27*	0.27*
LF (ms²)	0.008	0.28*	0.34*	-0.50*	0.18	0.15	-0.07	-0.07	-0.12	-0.12
pNN50	-0.152	0.37*	0.39*	-0.38*	0.25	0.05	0.03	0.06	-0.21	-0.15
RMSSD	-0.085	0.25	0.24	-0.27*	0.20	-0.06	-0.07	0.00	-0.27*	-0.24
SD1	-0.085	0.25	0.25*	-0.27*	0.20	-0.06	-0.07*	0.007	-0.27*	-0.23*
SD2	0.088	0.35*	0.36*	-0.36*	0.26	0.23	-0.08*	-0.06	-0.21	-0.17
SDNN	0.056	0.31*	0.31*	-0.30*	0.20	0.16	-0.08*	-0.04	-0.25	-0.21
Total power	0.027	0.33*	0.36*	-0.44*	0.15	0.13	-0.04	-0.03	-0.16	-0.13
VLF (nu)	0.041	-0.19	-0.17	0.08	-0.07	0.28	0.07	0.03	0.13	0.15
VLF (ms²)	0.003	0.23	0.29*	-0.48*	0.20	0.29	0.008	0.01	-0.10	-0.05

DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate; HGD, handgrip dynamometer; S, standing; DB, deep breathing; VM, Valsalva manoeuvre; other abbreviations as in Table 1. * $p < 0.05$; $p < 0.01$.

Table 4: Diagnostic accuracy of HRV indices against an abnormal heart-rate response to deep breathing [HR(DB) ≤ 10 bpm]

Reference: 28 abnormal / 22 normal	LF	HF	LF/HF	Total power
2 × 2: TP / FN / FP / TN	2 / 26 / 2 / 20	25 / 3 / 20 / 2	17 / 11 / 9 / 13	24 / 4 / 20 / 2
Sensitivity	0.07 (0.02–0.23)	0.89 (0.73–0.96)	0.61 (0.42–0.76)	0.86 (0.69–0.94)
Specificity	0.91 (0.72–0.97)	0.09 (0.03–0.28)	0.59 (0.39–0.77)	0.09 (0.03–0.28)
PPV	0.50 (0.15–0.85)	0.56 (0.41–0.69)	0.65 (0.46–0.81)	0.55 (0.40–0.68)
NPV	0.43 (0.30–0.58)	0.40 (0.12–0.77)	0.54 (0.35–0.72)	0.33 (0.10–0.70)
LR+	0.79 (0.12–5.14)	0.98 (0.82–1.18)	1.48 (0.83–2.66)	0.94 (0.77–1.15)
LR−	1.02 (0.86–1.21)	1.18 (0.22–6.45)	0.66 (0.37–1.18)	1.57 (0.32–7.81)
AUC	0.549 (0.388–0.710)	0.528 (0.366–0.690)	0.599 (0.441–0.757)	0.628 (0.473–0.783)

Values are estimates (95% CI). Reference standard: the Ewing test; index test: the dichotomised HRV index (cut-offs in Table 2). Proportions: Wilson score CI; likelihood ratios: log method; AUC (from the continuous HRV index): Hanley–McNeil CI. The AUC of the LF/HF ratio was corrected from 0.5487 to 0.599, in agreement with Figure 1A. TP, true positive; FN, false negative; FP, false positive; TN, true negative; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; AUC, area under the ROC curve.

Table 5: Diagnostic accuracy of HRV indices against an abnormal HR(DB) ratio

Reference: 27 abnormal / 23 normal	LF	HF	LF/HF	Total power
2 × 2: TP / FN / FP / TN	2 / 25 / 2 / 21	24 / 3 / 21 / 2	18 / 9 / 8 / 15	23 / 4 / 21 / 2
Sensitivity	0.07 (0.02–0.23)	0.89 (0.72–0.96)	0.67 (0.48–0.81)	0.85 (0.68–0.94)
Specificity	0.91 (0.73–0.98)	0.09 (0.02–0.27)	0.65 (0.45–0.81)	0.09 (0.02–0.27)
PPV	0.50 (0.15–0.85)	0.53 (0.39–0.67)	0.69 (0.50–0.83)	0.52 (0.38–0.66)
NPV	0.46 (0.32–0.60)	0.40 (0.12–0.77)	0.63 (0.43–0.79)	0.33 (0.10–0.70)
LR+	0.85 (0.13–5.58)	0.97 (0.81–1.17)	1.92 (1.03–3.56)	0.93 (0.76–1.14)
LR−	1.01 (0.86–1.20)	1.28 (0.23–7.00)	0.51 (0.28–0.94)	1.70 (0.34–8.47)
AUC	0.554 (0.393–0.715)	0.514 (0.352–0.676)	0.659 (0.508–0.810)	0.683 (0.536–0.830)

Values are estimates (95% CI). Reference standard: the Ewing test; index test: the dichotomised HRV index (cut-offs in Table 2). Proportions: Wilson score CI; likelihood ratios: log method; AUC (from the continuous HRV index): Hanley–McNeil CI. TP, true positive; FN, false negative; FP, false positive; TN, true negative; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; AUC, area under the ROC curve.

Table 6: Diagnostic accuracy of HRV indices against an abnormal heart-rate response to the Valsalva manoeuvre [HR(VM) ratio ≤ 1.20]

Reference: 40 abnormal / 10 normal	LF	HF	LF/HF	Total power
2 × 2: TP / FN / FP / TN	3 / 37 / 1 / 9	36 / 4 / 9 / 1	21 / 19 / 5 / 5	35 / 5 / 9 / 1
Sensitivity	0.07 (0.03–0.20)	0.90 (0.77–0.96)	0.53 (0.37–0.67)	0.88 (0.74–0.95)
Specificity	0.90 (0.60–0.98)	0.10 (0.02–0.40)	0.50 (0.24–0.76)	0.10 (0.02–0.40)
PPV	0.75 (0.30–0.95)	0.80 (0.66–0.89)	0.81 (0.62–0.91)	0.80 (0.65–0.89)
NPV	0.20 (0.11–0.33)	0.20 (0.04–0.62)	0.21 (0.09–0.40)	0.17 (0.03–0.56)
LR+	0.75 (0.09–6.47)	1.00 (0.79–1.26)	1.05 (0.53–2.09)	0.97 (0.77–1.23)
LR−	1.03 (0.82–1.29)	1.00 (0.13–8.00)	0.95 (0.47–1.91)	1.25 (0.16–9.54)
AUC	0.600 (0.411–0.789)	0.608 (0.420–0.796)	0.513 (0.312–0.714)	0.708 (0.544–0.872)

Values are estimates (95% CI). Reference standard: the Ewing test; index test: the dichotomised HRV index (cut-offs in Table 2). Proportions: Wilson score CI; likelihood ratios: log method; AUC (from the continuous HRV index): Hanley–McNeil CI. TP, true positive; FN, false negative; FP, false positive; TN, true negative; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; AUC, area under the ROC curve.

Table 7: Diagnostic accuracy of HRV indices against an abnormal heart-rate response to standing [HR(S) 30:15 ratio ≤ 1.00]

Reference: 25 abnormal / 25 normal	LF	HF	LF/HF	Total power
2 × 2: TP / FN / FP / TN	3 / 22 / 1 / 24	24 / 1 / 21 / 4	9 / 16 / 17 / 8	23 / 2 / 21 / 4
Sensitivity	0.12 (0.04–0.30)	0.96 (0.80–0.99)	0.36 (0.20–0.55)	0.92 (0.75–0.98)
Specificity	0.96 (0.80–0.99)	0.16 (0.06–0.35)	0.32 (0.17–0.52)	0.16 (0.06–0.35)
PPV	0.75 (0.30–0.95)	0.53 (0.39–0.67)	0.35 (0.19–0.54)	0.52 (0.38–0.66)
NPV	0.52 (0.38–0.66)	0.80 (0.38–0.96)	0.33 (0.18–0.53)	0.67 (0.30–0.90)
LR+	3.00 (0.33–26.92)	1.14 (0.95–1.38)	0.53 (0.29–0.95)	1.10 (0.89–1.35)
LR−	0.92 (0.78–1.08)	0.25 (0.03–2.08)	2.00 (1.05–3.80)	0.50 (0.10–2.49)
AUC	0.630 (0.475–0.785)	0.574 (0.415–0.733)	0.660 (0.509–0.811)	0.528 (0.367–0.689)

Values are estimates (95% CI). Reference standard: the Ewing test; index test: the dichotomised HRV index (cut-offs in Table 2). Proportions: Wilson score CI; likelihood ratios: log method; AUC (from the continuous HRV index): Hanley–McNeil CI. For the LF/HF ratio the association was inverse (LR+ < 1), and the ROC analysis used the reversed direction. TP, true positive; FN, false negative; FP, false positive; TN, true negative; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; AUC, area under the ROC curve.

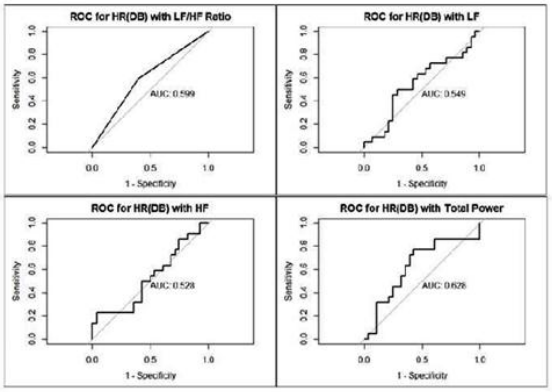


Figure 1 (A–D): ROC curves of HRV indices [(A) LF/HF ratio, (B) LF, (C) HF, (D) total power] against an abnormal HR(DB) response (≤ 10 bpm).

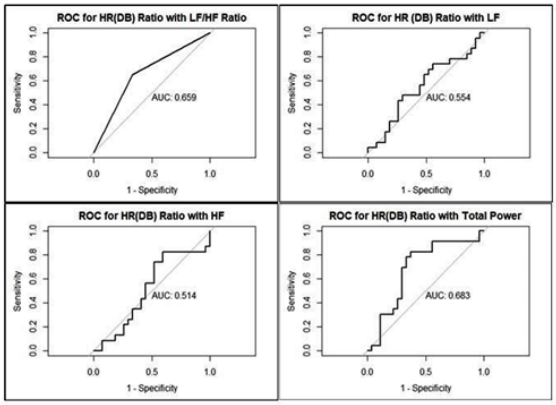


Figure 2 (A–D): ROC curves of HRV indices [(A) LF/HF ratio, (B) LF, (C) HF, (D) total power] against an abnormal HR(DB) ratio.

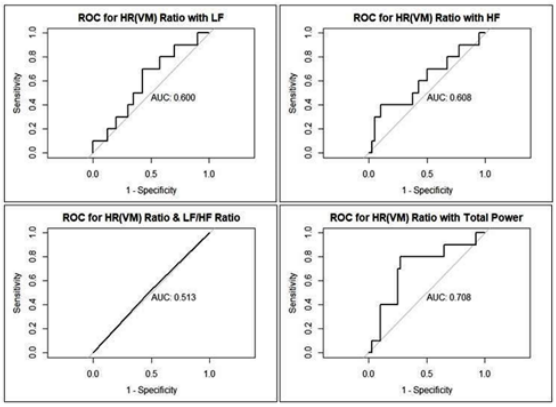


Figure 3 (A–D): ROC curves of HRV indices [(A) LF, (B) HF, (C) LF/HF ratio, (D) total power] against an abnormal HR(VM) ratio (≤ 1.20).

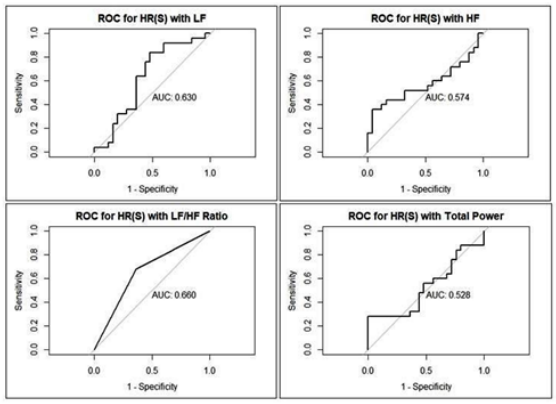


Figure 4 (A–D): ROC curves of HRV indices [(A) LF, (B) HF, (C) LF/HF ratio, (D) total power] against an abnormal HR(S) 30:15 ratio (≤ 1.00).

DISCUSSION

Autonomic dysfunction has recently become an important area of research in PD. The present study assessed how well resting short-term HRV agrees with the heart-rate tests of Ewing's battery in patients with PD, and how the COMPASS-31 symptom score relates to both.

Principal findings. Three findings stand out. First, abnormal cardiovagal reflexes were common: half to four-fifths of patients were abnormal on each heart-rate test. Second, resting HRV indices agreed only poorly to fairly with these tests (AUC 0.51–0.71), and their apparent accuracy depended heavily on the cut-off. Third, the COMPASS-31 score was not correlated with any HRV or Ewing parameter. This suggests that the questionnaire, which reflects multi-domain symptom burden, and the objective cardiovascular tests capture different aspects of autonomic dysfunction.

With increasing life expectancy, the worldwide prevalence of Parkinson's disease is also growing, making it the second most common neurodegenerative disorder in the world.[20] Apart from the classical motor features, several non-motor impairments, especially autonomic dysfunction, are characteristic of the disease. These autonomic abnormalities play a vital role in PD pathophysiology.[21]

A common pathological hallmark of PD is the presence of Lewy bodies. These are abnormal aggregates of alpha-synuclein protein, widely distributed in the CNS, that disrupt the central components of the reflex arcs involved in autonomic regulation.[22] Human studies and animal models of PD provide quantitative evidence of damage to brainstem parasympathetic neurons, including the vagus nerve.[22] Kaufmann et al. (2004) reported the clinical and post-mortem neuropathological findings in a patient with PD who first sought treatment for isolated autonomic failure, and suggested that neurodegeneration in PD may begin outside the CNS in autonomic postganglionic neurons.[5]

Heart rate variability is a non-invasive, low-cost and easy method of assessing cardiac autonomic control. HRV-derived estimates of cardiac parasympathetic activity are reduced in patients with PD.[23] For the sympathetic branch, orthostatic hypotension is often used as a clinical indicator. In the model proposed by Braak and colleagues, the PD process begins in the lower brainstem in the dorsal motor nucleus of the vagus nerve and ascends to the cerebral cortex, so the severity of symptoms depends on how far the disease has progressed.[24] Although most HRV indices primarily reflect vagal function, the LF component together with the LF/HF ratio is considered a marker of sympathetic modulation, and a decreased LF and LF/HF ratio at rest has been found in patients with PD compared with controls.[23]

Timely diagnosis of CAN helps to avoid many complications. In clinical practice, the five non-invasive cardiovascular reflex tests proposed by Ewing and Clarke remain the cornerstone of diagnosis because of their good sensitivity, specificity and reproducibility. Of the five tests, the heart-rate responses to deep breathing, the Valsalva manoeuvre and standing (30:15 ratio) mainly assess parasympathetic function,[25] and the remaining two assess sympathetic function.

HRV against Ewing's heart-rate tests: The modest agreement between resting HRV and Ewing's heart-rate tests is physiologically expected. Resting HRV

measures tonic autonomic modulation, whereas Ewing's tests measure the reflex response to a provocation. The two are related but not interchangeable. The significant correlations of total power, SDNN, SD2 and pNN50 with HR(DB) and the HR(DB) ratio [Table 3] support a shared cardiovagal basis. The 2 × 2 results also show that the cut-off chosen for each HRV index largely determines its apparent accuracy. The LF cut-off labelled only 8% of patients abnormal, giving high specificity but almost no sensitivity. The HF and total-power cut-offs labelled about 90% abnormal, giving the opposite pattern. In both cases the likelihood ratios were close to 1. Only the LF/HF ratio achieved a balanced trade-off, with a positive likelihood ratio of almost 2 against the HR(DB) ratio. Total power had the highest AUC as a continuous measure (0.708 against the Valsalva ratio). This suggests that a cut-off derived specifically for PD might improve its performance. Cut-offs for resting HRV in PD should therefore be derived and validated against a reference standard rather than taken from general normative data.

Respiration has a major effect on heart rate.[26] Heart rate increases during inspiration and decreases during expiration (respiratory sinus arrhythmia). Measurements made at a predefined deep-breathing rate allow HRV analysis to reflect vagal tone rather than differences in respiration.[27] The vagus nerve, the longest autonomic nerve, is affected early in autonomic neuropathy. Because it accounts for more than 75% of parasympathetic outflow, its involvement causes widespread derangement, including abnormal heart-rate-dependent Ewing tests.[25] There is evidence that more advanced PD leads to a progressive reduction in parasympathetically modulated HRV parameters (HF, total power), consistent with increasing damage to the vagus nerve over the course of the disease.[28,29]

COMPASS-31: COMPASS-31, proposed by Sletten et al., quantifies autonomic symptoms across six domains.[15] The mean total score in our cohort was low (11.92 of a possible 100), and the score was not correlated with any objective measure. Several factors may explain this. Autonomic dysfunction in PD presents with a wide range of symptoms, including orthostatic hypotension, constipation, urinary dysfunction, sexual dysfunction, excessive sweating, seborrhoea and hypersalivation.[30-32] Many of these symptoms are common and non-specific in older people. In a review, Palma and Kaufmann (2014) noted that autonomic symptoms are often absent in early PD, which limits their sensitivity. Specificity is also limited: constipation affects about 30% of older people, compared with a PD prevalence of about 1–2%, and autonomic symptoms often arise from comorbidities or medications.[3] In addition, Ewing's battery assesses only cardiovascular autonomic function, whereas COMPASS-31 also covers secretomotor, gastrointestinal, bladder and pupillomotor function. Kim et al. found COMPASS-31 useful as a screening tool in patients with parkinsonism.[10] Our results suggest that, in PD, it should complement rather than replace objective cardiovascular testing. Whether adding COMPASS-31 to HRV improves the detection of CAN could not be tested in this study and requires a prospective analysis at the patient level.

Limitations: This study has several limitations. First, the sample size (n = 50) was small and was not based on a formal sample-size calculation for diagnostic accuracy, so the confidence intervals are wide. Second, the combined diagnostic performance of COMPASS-31 and HRV could not be evaluated, because patient-level data for COMPASS-31 domain scores and for the overall CAN classification (no, early or definite CAN) were not available for analysis. For the same reason, the domain-wise COMPASS-31 results and the number of patients in each CAN category are not reported. Third, the HRV cut-offs were not derived from ROC analysis in this sample, which partly explains the unbalanced sensitivity and specificity of some indices. Fourth, each Ewing heart-rate test was used separately as the reference standard; Ewing's battery assesses only cardiovascular autonomic function. Fifth, because the study was cross-sectional, progression of autonomic dysfunction could not be assessed. Sixth, we did not enrol control subjects. Finally, disease stage (Hoehn and Yahr), disease duration and the timing of dopaminergic medication were not analysed, and these may influence both symptoms and HRV. A prospective study with a pre-specified combined analysis of COMPASS-31 and HRV against the full Ewing classification is needed.

CONCLUSION

Ewing's battery, the gold standard for CAN, is cumbersome and time-consuming and cannot easily be performed in every patient with PD in outpatient settings, so simpler tools are needed. In this study, resting short-term HRV agreed only poorly to fairly with the heart-rate tests of Ewing's battery. Its apparent accuracy depended strongly on the cut-off, and the LF/HF ratio was the most balanced index. COMPASS-31 scores were unrelated to both HRV and Ewing's test results. On the present evidence, neither resting HRV nor COMPASS-31 can replace Ewing's battery for diagnosing cardiovascular autonomic dysfunction in PD. A combined approach, using PD-specific HRV cut-offs, deserves evaluation in a larger prospective study.

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