



Prognostic Value of Cerebrovascular Reactivity in Patients with Parkinson's Disease

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Abstract

Introduction: Parkinson's disease (PD) is one of the most common movement disorders. Some studies have reported cerebral hemodynamic abnormalities in patients with Parkinson's disease. This study aimed to measure cerebrovascular reactivity in patients with Parkinson's disease and to examine its relationship with the Unified Parkinson's Disease Rating Scale scores.

Methods: In this case-control study was conducted on 36 patients with Parkinson's disease and 36 age- and gender-matched healthy individuals as the control group in 2022. Sampling was performed with the convenience method. Transcranial Doppler was performed to measure the mean flow velocity of the middle cerebral artery at rest and after the apnea test. The Unified Parkinson's Disease Rating Scale was administered to patients, and the results were statistically analyzed.

Results: The Breath-Holding Index (BHI) was 1.02 ± 0.19 and 0.714 ± 0.14 in the control and patient groups, respectively, indicating a statistically significant difference ($P < 0.001$). Also, BHI showed a statistically significant relationship with all questionnaire items and the questionnaire's total score.

Conclusion: Cerebrovascular reactivity decreased in patients with PD, and this decrease was correlated with clinical findings.

Keywords: Parkinson's disease, Cerebrovascular reactivity, Unified Parkinson's disease rating scale

Introduction

As the second leading neurodegenerative disorder, Parkinson's disease (PD) affects 1–2% of the elderly population. It is characterized by the progressive degeneration of dopamine-secreting neurons in the substantia nigra, leading to the disease's hallmark motor symptoms, including rhythmic shaking, limb rigidity, and delayed initiation of movement (1). With an estimated 200 Parkinson's cases per 100,000 residents, Iran ranks among countries with relatively elevated prevalence rates (2). The clinical presentation of PD encompasses multiple motor impairments and non-motor disturbances (3). Tremor, bradykinesia, limited range of motion, muscle stiffness, and imbalance are among the most commonly observed motor dysfunctions in patients. In most cases, these symptoms start unilaterally and appear on the opposite side in a few years (4). Beyond the classical motor impairments, PD is associated with an extensive array of non-motor complications, including cognitive decline, fatigue, affective disorders, and sleep disturbances, including

insomnia. Non-motor symptoms often precede the onset of motor impairments and can have a profound impact on patients' overall quality of life, highlighting the complex nature of PD's underlying mechanisms. (5). Early diagnosis of PD relies on recognizing a spectrum of motor dysfunctions and non-motor complications, with non-motor symptoms often emerging before the motor signs. This combination is crucial for identifying the disease at an earlier stage. (6). The Unified Parkinson's Disease Rating Scale (UPDRS) is widely recognized as the standard clinical instrument for monitoring the clinical deterioration of PD. This scale consists of 1) assessment of aspects related to cognition, mood regulation, and behavioral expression, 2) patient-reported activities of daily living (ADL), 3) motor examination conducted by a clinician, 4) evaluation of therapy-induced complications, 5) clinical scale introduced by Hoehn and Yahr to categorize the advancement of Parkinson's symptoms, and 6) the Schwab and England ADL Scale, which evaluates the level of functional independence (7,8).



Cerebrovascular reactivity (CVR) describes the ability of the brain vasculature to modulate its caliber in response to changes in CO₂ concentration. Changes in CO₂ concentration cause corresponding alterations in the flow velocity of the middle cerebral artery (MCA), reflecting adjustments in arterial diameter (9). Although prior investigations have hinted at disruptions in cerebrovascular reactivity (CVR) across various neurodegenerative conditions—including Parkinson's disease—the precise contribution of these vascular changes to disease mechanisms remains elusive (10,11). Recent findings suggest a link between CVR and overall disease severity in PD, yet the specific clinical domains most affected by this vascular parameter have not been systematically explored (12,13,14). This study pioneers a targeted analysis of CVR in relation to the core components of the Unified Parkinson's Disease Rating Scale (UPDRS), offering a novel perspective on how cerebral hemodynamic responsiveness may intersect with distinct symptom profiles in PD.

Methods

This case-control study involved 36 patients diagnosed with Parkinson's disease (PD) alongside 36 healthy control participants matched for age and sex in 2022. Sampling was performed with the convenience method. The diagnosis of PD was established by a neurologist using the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria, providing a standardized, clinically validated method for participant inclusion. (15). Patients were excluded if they had other significant medical conditions (e.g., asthma), a history of medication use unrelated to PD, narcotic use or drug addiction, current or past smoking, or clinical/radiological features suggestive of secondary or atypical Parkinsonism (16). Healthy volunteers from the community were selected and matched to the patient group by age and sex. The case and control groups underwent an ultrasound at the Ultrasound Department of Shafa Hospital in Kerman using a DWL duplex ultrasound machine (model: Multi-Dop X Digital), and cerebrovascular reactivity was calculated for each patient. Cerebrovascular reactivity was calculated based on the breath-holding test. During the procedure, initial blood flow velocity (V1) was measured within the M1 portion of the middle cerebral artery. Subsequently, participants were asked to perform a breath-hold maneuver without deep inhalation, with 't' denoting the apnea duration in seconds. Subsequently, the flow velocity at the conclusion of the apnea phase (V2) was recorded.

BHI (Breath Holding Index) was computed using the formula shown below:

$$\text{BHI} = \frac{V_2 - V_1}{V_1 \times t} \times 100$$

A trained assistant performed the sonography under the

supervision of a neurologist before the patient received the morning dose of the drug in the ON phase of the disease (17, 18). Patients with severe extracranial vessel stenosis (ECAS) were excluded from the study based on sonography, as were patients with a poor temporal window (16).

A trained neurologist measured the UPDRS score. The scores for the four questionnaire sections (cognitive and emotional status, patient-reported daily functional capacity, clinician-rated motor performance, and therapy-related complications) were evaluated. Quantitative scoring (0–4) is used for the initial three sections, while the fourth section has a binary format (8). The levodopa equivalent dose was calculated for the patient group (19).

All subjects provided informed consent, and the investigation was conducted with approval from the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1398.209). SPSS software (version 20) was used to conduct descriptive statistical analyses using independent *t*-tests and Pearson's correlation coefficient. Results with *P*-values less than 0.05 were deemed significant.

Results

The study enrolled 36 individuals with a confirmed diagnosis of PD and 36 healthy controls. Among individuals diagnosed with PD, there were equal numbers of females and males (18 each, 50%), whereas the control group consisted of 19 males (52.8%) and 17 females (47.2%). The control group had a mean age of 64.5 ± 11.45 years (range: 47–81), while the patient group had a mean age of 64.10 ± 10.44 years (range: 46–82). No significant differences were found between the groups regarding age (*P*=0.98) or gender distribution (*P*=0.814). Cerebrovascular reactivity was measured using the Breath Holding Index (BHI), which was notably lower in the PD patients (0.714 ± 0.14) than in healthy controls (1.02 ± 0.19), suggesting a reduced vasodilatory response among those with Parkinson's disease (*P*<0.001) (Table 1). Pearson's correlation analysis demonstrated a statistically significant association between the BHI score and all individual sections, as well as the questionnaire's overall score. The BHI score demonstrated a statistically significant correlation with all subscales and the total UPDRS score, indicating that higher UPDRS scores are associated with lower BHI values (see Table 2). In the patient group, BHI values for males and females were 0.88 ± 0.23 and 0.85 ± 0.23, respectively, with no significant gender difference (*P*=0.506). Both Pearson and Spearman correlation tests indicated that, among the non-motor symptoms, only orthostatic hypotension (OH) was significantly correlated with the BHI score (*P*=0.012; see Table 3). There was no statistically significant relationship between disease duration and cerebrovascular reactivity (CVR).

Statistical Annotations

- **Statistical test used:** *The parametric correlation index (r) as defined by Pearson*

Table 1. Demographic and clinical profile comparison between PD patients and healthy controls

		PD group	Control	P-value
		N (%)	N (%)	
Sex	17 (47.2%)	18 (50%)	Female	0.814
	19 (52.8%)	18 (50%)	Male	
Mean ± standard deviation				
Age (year)		64.5 ± 11.45	64.44 ± 10.44	0.98
BHI		0.714 ± 0.14	0.02 ± 0.191	(P<0.001)

Table 2. Correlation between BHI and UPDRS scores in PD Group¹

Domains		BHI	Part I	Part II	Part III	Part IV	UPDRS
BHI	Correlation coefficient	1	0.413–	–0.44	0.359–	–0.552	–0.573
	P-value		0.012	0.007	0.032	0.001 >	($P < 0.001$)
Part I	Correlation coefficient	0.413–	1	0.420	0.518	0.504	0.693
	P-value	0.012		0.011	0.001	0.002	($P < 0.001$)
Part II	Correlation coefficient	–0.44	0.420	1	0.415	0.359	0.738
	P-value	0.007	0.011		0.012	0.031	($P < 0.001$)
Part III	Correlation coefficient	0.359–	0.518	0.415	1	0.647	0.847
	P-value	0.032	0.001	0.012		<0.001	($P < 0.001$)
Part IV	Correlation coefficient	–0.552	0.504	0.359	0.647	1	0.805
	P-value	0.001 >	0.002	0.031	<0.001		($P < 0.001$)
UPDRS	Correlation coefficient	–0.573	0.693	0.738	0.847	0.805	1
	P-value	0.001 >	<0.001	<0.001	<0.001	<0.001	

¹UPDRS: Unified Parkinson's Disease Rating Scale

BHI: Brain Health Index

Table 3. Correlation between BHI and clinical parameters in the PD Group

Different clinical parameters	Index	BH	OH	Age	Age of onset of disease	PD duration	Levodopa dose
BH	Correlation coefficient	1	–0.412	–0.2210.195	–0.153	–0.071	–0.172
	P-value		0.012		0.372	0.671	0.316
OH	Correlation coefficient	–0.4120.012	1	0.45	0.332	0.54	0.029
	P-value			<0.001	0.048	0.001	0.868
Age	Correlation coefficient	–0.2210.195	0.45	1	0.973	0.121	–0.346
	P-value		<0.001		<0.001	0.483	0.039
Age of onset of disease	Correlation coefficient	–0.153	0.332	0.973	1	–0.468	0.005
	P-value	0.372	0.045	<0.001		0.004	0.978
PD duration	Correlation coefficient	–0.071	0.029	–0.346	–0.468	1	0.238
	P-value	0.671	0.868	0.039	0.004		0.162
Levodopa dose	Correlation coefficient	–0.172	0.54	0.121	0.005	0.238	1
	P-value	0.316	0.001	0.483	0.978	0.162	

- **Significance level:** *P*-values below 0.05 were interpreted as statistically significant
- **Bolded values** (if presented in publication) typically indicate statistically significant correlations.
- **Pearson's correlation coefficient (*r*):** The Pearson correlation coefficient (*r*) was employed to determine linear correlations.

Significance Level (OR Threshold for Statistical Significance)

- *P*-values below 0.05 were interpreted as statistically significant.
- Significant correlations include:
 - **BH vs. OH:** $r = -0.412$, $P = 0.012$
 - **OH vs. Age:** $r = 0.450$, $P < 0.001$
 - **OH vs. Age of onset:** $r = 0.332$, $P = 0.045$

- **OH vs. Levodopa dose:** $r = 0.540$, $P = 0.001$
- **Age vs. Age of onset:** $r = 0.973$, $P < 0.001$
- **Age vs. PD Duration:** $r = -0.346$, $P = 0.039$
- Age of onset vs. PD Duration:** $r = -0.468$, $P = 0.004$

Discussion

The objective of this study was to assess cerebrovascular reactivity in individuals diagnosed with PD and explore its relationship with different sections of the UPDRS. CVR was found to be impaired in the PD group compared to neurologically healthy participants. The findings align with previous research, such as the cross-sectional study by Camargo et al., which reported abnormal Breath Holding Index (BHI) scores in 54.5% of their 22 PD patients (18). In another cross-sectional study on patients with PD in Iran, 34.1% of the studied

subjects showed abnormal cerebrovascular reactivity (20). Another case-control study showed that 70% of the patients studied had CVR abnormalities (16). At the same time, studies have reported results inconsistent with those of the present study. The study by Pelizzari et al. indicated that the difference in CVR between patients and controls was not statistically meaningful (14). Hanby et al. also did not report any CVR abnormality in patients with PD compared with others during the apnea test (21). In another study, CVR was evaluated using acetazolamide, and no abnormalities were observed (22). Differences in the target population and technical differences may lead to different results.

Data from the present study indicated that the Breath Holding Index (BHI) score was significantly correlated with all major sections of the questionnaire and with the overall total score. Notably, this study is the first to examine the association between cerebrovascular reactivity (CVR) and all questionnaire components. Earlier research by Pelizzari et al., based on a case-control study, identified a specific association between cerebrovascular reactivity (CVR) and motor symptom severity, suggesting its potential utility as a diagnostic or prognostic biomarker (14). Rubino et al. also reported that CVR abnormality is related to cognitive impairment (23). According to the present data, CVR dysfunction is not restricted to isolated symptoms, as individuals with PD are susceptible to a wide range of clinical presentations. The CVR abnormalities reported in this study, along with those documented in previous research, underscore the involvement of cerebral microvasculature in Parkinson's disease. Although the exact impact of vascular factors on disease progression is not fully understood, current evidence suggests a multifactorial mechanism. Contributing elements may include elevated levels of vascular endothelial growth factor (VEGF) and interleukin-1 β (IL-1 β) in the basal nuclei (24), as well as pathological degeneration affecting both peripheral and central neural structures—such as the brainstem, cerebral cortex, spinal cord, and autonomic ganglia (25). These homeodynamic disorders have also been confirmed by other methods. For example, arterial spin labeling sequences performed with MRI indicate reduced cortical cerebral blood flow and increased arterial transit time in patients with PD (26). In this study, only orthostatic hypotension showed a statistically significant association with BHI, consistent with other studies. In a case-control study by Camargo et al. involving 24 PD patients with and without orthostatic hypotension, BHI was significantly impaired in the orthostatic hypotension group; this clinical finding is an indicator of cerebral hemodynamic disorders (18). In another study by Zamani et al., CVR disorder was reported to be strongly associated with orthostatic hypotension (10). It appears that greater sympathetic system

degeneration occurs in Parkinsonian patients with orthostatic hypotension (27). Some studies show that levodopa increases the risk of orthostatic hypotension (27). However, this study had some limitations. One limitation is that the CVR was evaluated solely through the apnea test; using other techniques would help us achieve better results and strengthen the conclusion. Another limitation is that, in this study, it was assumed that levodopa consumption does not affect the CVR.

Conclusion

This study revealed a significant reduction in cerebrovascular reactivity (CVR), as measured by the Breath Holding Index (BHI), in patients with Parkinson's disease (PD) compared with healthy individuals. CVR decline is significant and consistently linked to important clinical aspects, including symptom severity and duration, and patients' functional independence. The observed negative correlation between BHI and UPDRS scores indicates that CVR could serve as a valuable non-invasive biomarker for monitoring disease progression and symptom severity in PD. These findings highlight the relevance of assessing cerebral hemodynamics during clinical evaluations of PD and support the need for future longitudinal research to determine its potential prognostic role.

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Authors' Contribution

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Competing Interests

The authors declare that they have no conflicts of interest.

Ethical Approval

All subjects provided informed consent, and the investigation was conducted with approval from the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.AH.REC.1398.209).

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References

1. Weihofen A, Liu Y, Arndt JW, Huy C, Quan C, Smith BA, et al. Development of an aggregate-selective, human-derived α -synuclein antibody BIIB054 that ameliorates disease phenotypes in Parkinson's disease models. *Neurobiol Dis*

- 2019;124:276-88. doi:[10.1016/j.nbd.2018.10.016](https://doi.org/10.1016/j.nbd.2018.10.016)
2. Fereshtehnejad SM, Shafieesabet M, Rahmani A, Delbari A, Lökk J. Medium-to-high prevalence of screening-detected parkinsonism in the urban area of Tehran, Iran: data from a community-based door-to-door study. *Neuropsychiatr Dis Treat* 2015;11:321-32. doi:[10.2147/ndt.S77391](https://doi.org/10.2147/ndt.S77391)
3. Ho CY, Troncoso JC, Knox D, Stark W, Eberhart CG. Beta-amyloid, phospho-tau and alpha-synuclein deposits similar to those in the brain are not identified in the eyes of Alzheimer's and Parkinson's disease patients. *Brain Pathol* 2014;24(1):25-32. doi:[10.1111/bpa.12070](https://doi.org/10.1111/bpa.12070)
4. Sveinbjornsdottir S. The clinical symptoms of Parkinson's disease. *J Neurochem* 2016;139 Suppl 1:318-24. doi:[10.1111/jnc.13691](https://doi.org/10.1111/jnc.13691)
5. Crowley EK, Nolan YM, Sullivan AM. Exercise as a therapeutic intervention for motor and non-motor symptoms in Parkinson's disease: evidence from rodent models. *Prog Neurobiol* 2019;172:2-22. doi:[10.1016/j.pneurobio.2018.11.003](https://doi.org/10.1016/j.pneurobio.2018.11.003)
6. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord* 2015;30(12):1600-11. doi:[10.1002/mds.26431](https://doi.org/10.1002/mds.26431)
7. Keezer MR, Wolfson C, Postuma RB. Age, gender, comorbidity, and the MDS-UPDRS: results from a population-based study. *Neuroepidemiology* 2016;46(3):222-7. doi:[10.1159/000444021](https://doi.org/10.1159/000444021)
8. 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(15):2129-70. doi:[10.1002/mds.22340](https://doi.org/10.1002/mds.22340)
9. Herrera CR, Beltrami GC, Avelar WM, Lima FO, Li LM. Cerebral vasomotor reactivity assessment using transcranial Doppler and MRI with apnea test. *Braz J Med Biol Res* 2016;49(11):e5437. doi:[10.1590/1414-431x20165437](https://doi.org/10.1590/1414-431x20165437)
10. Alwatban M, Murman DL, Bashford G. Cerebrovascular Reactivity Impairment in Preclinical Alzheimer's Disease. *J Neuroimaging* 2019;29(4):493-8. doi:[10.1111/jon.12606](https://doi.org/10.1111/jon.12606)
11. Sur S, Lin Z, Li Y, Yasar S, Rosenberg P, Moghekar A, et al. Association of cerebrovascular reactivity and Alzheimer pathologic markers with cognitive performance. *Neurology* 2020;95(8):e962-72. doi:[10.1212/wnl.00000000000010133](https://doi.org/10.1212/wnl.00000000000010133)
12. Smoliński Ł, Członkowska A. Cerebral vasomotor reactivity in neurodegenerative diseases. *Neurol Neurochir Pol* 2016;50(6):455-62. doi:[10.1016/j.pjnns.2016.07.011](https://doi.org/10.1016/j.pjnns.2016.07.011)
13. Li H, Shao X, Jia J, Wang B, Wang J, Liu K, et al. A multi-modal study on cerebrovascular dysfunction in cognitive decline of de novo Parkinson's disease. *Neuroimage Clin* 2025;48:103836. doi:[10.1016/j.nicl.2025.103836](https://doi.org/10.1016/j.nicl.2025.103836)
14. Pelizzari L, Laganà MM, Rossetto F, Bergsland N, Galli M, Baselli G, et al. Cerebral blood flow and cerebrovascular reactivity correlate with severity of motor symptoms in Parkinson's disease. *Ther Adv Neurol Disord* 2019;12:1756286419838354. doi:[10.1177/1756286419838354](https://doi.org/10.1177/1756286419838354)
15. Marsili L, Rizzo G, Colosimo C. Diagnostic criteria for Parkinson's disease: from James Parkinson to the concept of prodromal disease. *Front Neurol* 2018;9:156. doi:[10.3389/fneur.2018.00156](https://doi.org/10.3389/fneur.2018.00156)
16. Ojeda AE, Martinez HR, Rivera FG, Garza JE, Medina HC, Davila SS. Cerebral vasoreactivity in Parkinson's disease: a cross-sectional pilot study in a Hispanic cohort. *J Alzheimers Dis Parkinsonism* 2017;7(3):336. doi:[10.4172/2161-0460.1000336](https://doi.org/10.4172/2161-0460.1000336)
17. Hamzeee-Moghadam A, Iranmanesh F, Arabpour-Fathabadi A, Mohammadi F. Cerebrovascular reactivity and carotid intima-media thickness in opium dependents: a case-control study. *Addict Health* 2018;10(2):131-6. doi:[10.22122/ahj.v10i2.555](https://doi.org/10.22122/ahj.v10i2.555)
18. Camargo CH, Martins EA, Lange MC, Hoffmann HA, Luciano JJ, Young Blood MR, et al. Abnormal cerebrovascular reactivity in patients with Parkinson's disease. *Parkinsons Dis* 2015;2015:523041. doi:[10.1155/2015/523041](https://doi.org/10.1155/2015/523041)
19. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010;25(15):2649-53. doi:[10.1002/mds.23429](https://doi.org/10.1002/mds.23429)
20. Zamani B, Mehrabani M, Fereshtehnejad SM, Rohani M. Evaluation of cerebral vasomotor reactivity in Parkinson's disease: is there any association with orthostatic hypotension? *Clin Neurol Neurosurg* 2011;113(5):368-72. doi:[10.1016/j.clineuro.2010.12.014](https://doi.org/10.1016/j.clineuro.2010.12.014)
21. Hanby MF, Panerai RB, Robinson TG, Haunton VJ. Is cerebral vasomotor reactivity impaired in Parkinson disease? *Clin Auton Res* 2017;27(2):107-11. doi:[10.1007/s10286-017-0406-x](https://doi.org/10.1007/s10286-017-0406-x)
22. Gurevich T, Gur AY, Bornstein NM, Giladi N, Korczyn AD. Cerebral vasomotor reactivity in Parkinson's disease, multiple system atrophy and pure autonomic failure. *J Neurol Sci* 2006;243(1-2):57-60. doi:[10.1016/j.jns.2005.11.028](https://doi.org/10.1016/j.jns.2005.11.028)
23. Rubino A, Romeo T, Di Battista ME, Valente M, Papi C, Giacomini P, et al. Cognitive impairment in Parkinson disease is associated with reduced cerebrovascular reactivity. *Parkinsonism Relat Disord* 2016;22:e59. doi:[10.1016/j.parkreldis.2015.10.126](https://doi.org/10.1016/j.parkreldis.2015.10.126)
24. Muñoz A, Garrido-Gil P, Dominguez-Mejide A, Labandeira-Garcia JL. Angiotensin type 1 receptor blockage reduces L-DOPA-induced dyskinesia in the 6-OHDA model of Parkinson's disease. Involvement of vascular endothelial growth factor and interleukin-1β. *Exp Neurol* 2014;261:720-32. doi:[10.1016/j.expneurol.2014.08.019](https://doi.org/10.1016/j.expneurol.2014.08.019)
25. Braak H, Rüb U, Gai WP, Del Tredici K. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J Neural Transm (Vienna)* 2003;110(5):517-36. doi:[10.1007/s00702-002-0808-2](https://doi.org/10.1007/s00702-002-0808-2)
26. Al-Bachari S, Parkes LM, Vidyasagar R, Hanby MF, Tharakan V, Leroi I, et al. Arterial spin labelling reveals prolonged arterial arrival time in idiopathic Parkinson's disease. *Neuroimage Clin* 2014;6:1-8. doi:[10.1016/j.nicl.2014.07.014](https://doi.org/10.1016/j.nicl.2014.07.014)
27. Bouhaddi M, Vuillier F, Fortrat JO, Cappelle S, Henriët MT, Rumbach L, et al. Impaired cardiovascular autonomic control in newly and long-term-treated patients with Parkinson's disease: involvement of L-DOPA therapy. *Auton Neurosci* 2004;116(1-2):30-8. doi:[10.1016/j.autneu.2004.06.009](https://doi.org/10.1016/j.autneu.2004.06.009)