Al-Rafidain J Med Sci. 2025;8(2):157-160.
DOI: https://doi.org/10.54133/ajms.v8i2.1875

Online ISSN (2789-3219)

Research Article

Assessment of Autonomic Function in Iraqi Patients with Parkinson's Disease

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Received: 15 March 2025; Revised: 18 May 2025; Accepted: 25 May 2025

Abstract

Background: Parkinson's disease (PD) is a neurodegenerative disorder that is second to Alzheimer's regarding its prevalence. It is characterized by motor and non-motor symptoms. The outcomes of the latter can be used to evaluate and depict prognoses of the quality of life in PD patients. ***Objectives***: To evaluate the autonomic function patterns in PD patients in three settings using electromyography (EMG). ***Methods***: The current study is a case-control study involving 40 PD patients and 40 healthy controls collected from Ghazi Al-Hariri Hospital (Baghdad, Iraq). R-R interval variability (RRIV) of each participant was estimated at rest (RRIVr), deep breath (RRIVdb), and Valsalva maneuver (RRIVv). ***Results***: The results showed a significant reduction in the RRIV values of PD patients compared to the control. The most significant reduction was observed in RRIVv value. Moreover, the values of RRIV were correlated positively in PD patients. Also, RRIVv has shown excellent sensitivity in the diagnosis of PD with 97% sensitivity and 90% specificity, which was better than RRIVr and RRIVdb. ***Conclusions***: Thus, using RRIVv settings can reflect a very sensitive tool in the assessment of autonomic function for the diagnosis and prognosis of PD that can overwhelm the other RRIV settings for better management of PD patients.

Keywords: Autonomic function, Parkinson's disease, RR-IV, Valsalva maneuver.

تقييم الوظيفة اللاإرادية لدى المرضى العراقيين المصابين بمرض باركنسون

الخلاصة

الخلفية: مرض باركنسون (PD) هو اضطراب تنكسي عصبي يأتي في المرتبة الثانية بعد مرض الزهايمر فيما يتعلق بانتشاره. يتميز بأعراض حركية وغير حركية. يمكن استخدام نتائج هذا الأخير لتقييم وتصوير تكهنات نوعية الحياة لدى مرضى باركنسون. **الأهداف**: تقييم أنماط الوظائف اللاإرادية لدى مرضى باركنسون في ثلاثة أماكن باستخدام تخطيط كهربية العضل (EMG). **الأساليب**: الدراسة الحالية هي دراسة حالة وشواهد شملت 40 مريضا بمرض باركنسون و 40 من الضابطين الأصحاء تم جمعها من مستشفى غازي الحريري (بغداد ، العراق). تم تقدير تقلب الفاصل الزمني R-R (RRIV) لكل مشارك في الراحة (RRIVr) ، والتنفس العميق (RRIVdb) ، ومناورة فالسالفا (RRIVv). **النتائج**: أظهرت النتائج انخفاضا معتدا به في قيم RRIV لمرضى باركنسون مقارنة بالمجموعة الضابطة. لوحظ أكبر انخفاض في قيمة RRIVv. علاوة على ذلك ، ارتبطت قيم RRIV بشكل إيجابي في مرضى باركنسون. أيضا ، أظهر RRIVv حساسية ممتازة في تشخيص مرض باركنسون بحساسية 97٪ وخصوصية 90٪ ، وهو ما كان أفضل من RRIVr و RRIVdb. **الاستنتاجات**: إن استخدام إعدادات RRIVv يمكن أن يعكس أداة حساسة للغاية في تقييم الوظيفة اللاإرادية لتشخيص وتشخيص مرض باركنسون والتي يمكن أن تطغى على إعدادات RRIV الأخرى من أجل إدارة أفضل لمرضى باركنسون.

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Article citation: Al-Janabi AA, Ameer AH. Assessment of Autonomic Function in Iraqi Patients with Parkinson's Disease. *Al-Rafidain J Med Sci*. 2025;8(2):157-160. doi: https://doi.org/10.54133/ajms.v8i2.1875

INTRODUCTION

Parkinson's disease is just after Alzheimer's disease as among the most common neurodegenerative disorders [1]. Current diagnostic criteria rely on the presence of bradykinesia as the main symptom, with the presence of one of two: rest tremor and rigidity or both [1]. The presentation usually is multifaceted with other non-motor symptoms like sleep disturbance and autonomic deregulation. Autonomic dysfunction in PD patients has been recognized frequently and has many manifestations that can affect the quality of patients' lives and their well-being [2]. The non-motor symptoms of autonomic dysfunction involve problems with gut motility (like constipation), cardiovascular dysregulation with orthostatic hypotension and tachycardia, urinary and sexual dysfunction, and problems in sweating and body temperature regulation [3]. In a large Chinese cohort study on the prevalence of autonomic dysfunction in Parkinson's disease, it was estimated that about 91.8 % of the participants have autonomic dysfunction [4]. Parkinson's disease results from the degeneration of the neurons in multiple areas of the brain with multiple functions, so that it is not only present with motor dysfunction [5]. The main pathology is the degeneration of the dopaminergic neuron in the substantia nigra pars compacta of the midbrain [6]. The pathology is characterized by the accumulation of Lewy bodies that are composed of the non-soluble aggregates of the protein alpha-synuclein [7]. The large variety in the presentation came from the fact that the pathological process can affect multiple neurons in the brain, meaning the involvement of the non-dopaminergic neurons [8]. It has been estimated

that Parkinson's affects about 6.1 million worldwide [9]. It showed increased prevalence with age; people over 65 showed prevalence of 1-1.5 % and reaching the age of 80, the prevalence showed an increment of 4-5% (Parkinson's Foundation). The increased prevalence of PD as well as the poor management of PD patients requires a sensitive tool for autonomic function assessment. Here, we have estimated three settings of RR-IV in PD patients as rest, deep breath, and Valsalva maneuver.

METHODS

Study design and setting

This is a case-control study that has been conducted in Ghazi Al-Hariri Surgical Teaching Hospital, which has an established connection with Baghdad Medical College. The study is designed to investigate the R-R interval variability test in PD patients at three different settings, including rest (RRIVr), deep breath (RRIVdb), and Valsalva maneuver (RRIVv), using EMG technology and comparing the results with normal individuals (control).

Sample selection

We have 40 patients with an established diagnosis of PD according to the international Parkinson's and Movement Disorders criteria. All of the patients are aged more than 40. All of the 40 subjects have been assessed clinically with history and neurological examination; we focused on the history on the symptoms of autonomic dysfunction. The control group consists of 40 subjects with normal history and neurological examination. They were matching with the PD-affected group.

Exclusion criteria

The study included only PD patients in the PD group and healthy subjects in the control group. People with Alzheimer's disease, multiple sclerosis, and other neurological disorders were excluded.

Outcomes measurements

The group with Parkinson's disease was first assessed for the non-motor symptoms. The two groups were then assessed with the aid of an EMG machine to measure the R-R interval variability test. We used one bracelet ground that attached to the left wrist and two surface electrodes that applied to the chest after identifying the apical pulse. The two groups were assessed in different states of the heart that affect the heart activity (heart rate). The first state was in the resting position, in which the participant was asked to lie on the bed with a 45-degree inclination and asked to breathe normally. In the second state, the participant was asked to take a deep breath of about 6 breaths for one minute. In the latter two states, we assessed the participants for 5 minutes (measuring about 5 times), and we measured the mean heart rate range, which iss the ratio (maximum-minimum/mean). In the last state, we assessed the participants with the aid of the Valsalva maneuver, in which the participants were asked to blow in a closed passage for about 15-20 seconds while the pressure was maintained between 30-40 mmHg, and then we measured the ratio of the maximum heart rate to the minimum (max./min.). It is also done 3-5 times; each trial is one minute with 20 seconds before starting the maneuver and 20 seconds after the start in a complete rest position.

Statistical analysis

The data collected were processed statistically using the Statistical Package for Social Sciences (SPSS) version 26.0 for mean comparison between groups in an independent t-test, considering significance at $p<0.05$. Moreover, the correlation between the three EMG settings was estimated by Pearson's correlation (r), while the diagnostic sensitivity was estimated by the receiver operating characteristic (ROC) test.

RESULTS

The differences in age between PD patients (60.43±6.73 years) and the control group were non-significant ($p>0.05$). PD patients have shown an average duration of 5.18±2.85 years, with significantly lower values of RRIVr (29.92±7.16), RRIVdb (53.40±12.51), and RRIVv (2.25±0.95) compared to control (39.98±5.07, 67.26±7.08, and 4.22±0.44 for RRIVr, RRIVdb, and RRIVv, respectively), as shown in Table 1.

Table 1: Characteristics of the subjects studied n=40 in each group)

Parameter	Control	PD patients	*p*-value
Age (year)	57.65±5.67	60.43±6.73	0.051
Duration (year)	---	5.18±2.85	---
RRIVr	39.98±5.07	29.92±7.16	<0.001
RRIVdb	67.26±7.08	53.40±12.51	<0.001
RRIVv	4.22±0.44	2.25±0.95	<0.001

Values are expressed as mean±SD.

The 40 PD patients have shown a spectrum of clinical features, including constipation (75%), postural hypotension (37.5%), dizziness (47.5%), dysphagia (25%), impotence (20%), sweating (35%), heat and cold intolerance (42.5%), and sphincter dysfunction (12.5%), as shown in Table 2.

Table 2: Clinical features of PD patients

Feature	Observed	Not-observed
Constipation	30(75)	10(25)
Postural hypotension	15(37.5)	25(62.5)
Dizziness	19(47.5)	21(52.5)
Dysphagia	10(25)	30(75)
Impotence	8 (20)	32(80)
Sweating	14(35)	26(65)
Heat and cold intolerance	17(42.5)	23(57.5)
Sphincter Dysfunction	5(12.5)	35(87.5)

Values are expressed as Number and percentage.

The 40 PD patients were divided into two groups according to their age, 17 of whom were ≥60 years and 23 patients were <60 years. The differences in the values of RRIVs in PD patients according to their age were non-significant ($p> 0.05$), as shown in Table 3. The 40 PD patients were divided into two groups according to the duration of the disease, 23 of whom

had had the disease for ≥5 years, while 17 patients had had the disease for <5 years.

Table 3: Comparison of RRIV values according to age in PD patients

Parameter	≥60 years n=17	<60 years n=23	*p*-value
RRIVr	28.82±7.73	30.74±6.78	0.419
RRIVdb	52.13±14.11	54.33±11.42	0.601
RRIVv	2.23±1.03	2.27±0.91	0.909

Values were expressed as mean±SD.

The differences in the values of RRIVs in PD patients according to the duration of the disease were non-significant ($p > 0.05$), as shown in Table 4.

Table 4: Comparison of RRIV values according to duration in PD patients

Parameter	≥5 years n=23	<5 years n=17	*p*-value
RRIVr	30.18±6.74	29.58±7.90	0.802
RRIVdb	54.48±12.02	51.93±13.37	0.538
RRIVv	2.30±0.90	2.18±1.04	0.698

Values were expressed as mean±SD.

In Table 5, the correlations between RRIV values have been listed in PD patients. RRIVr was correlated strongly and positively with RRIVdb (r=0.925, $p < 0.001$) and correlated strongly and positively with RRIVv (r= 0.847, $p < 0.001$). Also, RRIVdb and RRIVv were correlated positively and strongly (r= 0.932, $p < 0.001$) in PD patients.

Table 5: Correlation of RRIV values in PD patients

Parameter	RRIVr		RRIVdb		RRIVv	
	r	*p*	r	*p*	r	*p*
Age	0.029	0.860	0.024	0.883	0.021	0.900
Duration	0.007	0.967	0.141	0.387	0.131	0.422
RRIVr	-	-	0.925	<0.001	0.847	<0.001
RRIVdb	0.925	<0.001	-	-	0.932	<0.001
RRIVv	0.847	<0.001	0.932	<0.001	-	-

The sensitivity of using RRIV values as autonomic diagnostic materials for PD was investigated (Table 6).

Table 6: ROC analysis for analyzing diagnostic sensitivities of RRIVs in PD

Parameters	RRIVr	RRIVdb	RRIVv
AUC	0.864	0.834	0.954
SE	0.039	0.044	0.025
p-value	<0.001	<0.001	<0.001
Cut-off value	36.10	63.30	3.52
Sensitivity (%)	77.5	77.5	97.5
Specificity (%)	75	75	90

RRIVr has shown good sensitivity (AUC= 0.864) for diagnosing PD with a cut-off value of 36.10, at 77.5% sensitivity and 75% specificity. Moreover, RRIVdb has shown good sensitivity (AUC= 0.834) for diagnosing PD with a cut-off value of 63.30, at 77.5% sensitivity and 75% specificity. The most accurate indicator was RRIVv, where it exhibited excellent sensitivity (AUC= 0.954) for diagnosing PD with a cut-off value of 3.52 at 97.5% sensitivity and 90% specificity (Figure 1).

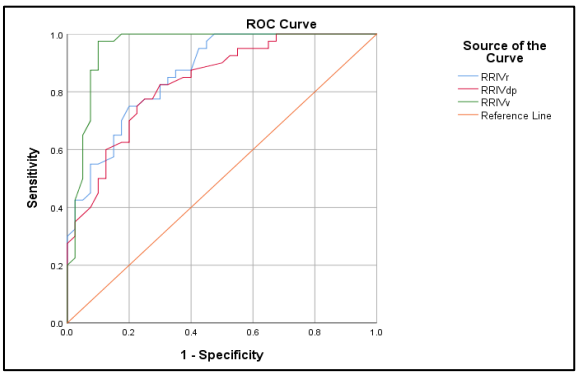

Figure 1: ROC curve of RRIVr (blue), RRIVdb (red), and RRIVv (green) in the diagnosis of PD.

DISCUSSION

The autonomic nervous system is in control of heart activity with both its divisions, the sympathetic and parasympathetic [10,11]. The sympathetic division originated from the thoracic and lumbar regions of the spinal cord, sending short fibers to the para-spinal sympathetic ganglia, which in turn send the adrenergic post-ganglionic sympathetic fibers to the heart and blood vessels. It has a positive chronotropic effect (increasing the heart rate) and a positive ionotropic effect (increases cardiac contractility) [12]. The parasympathetic supply of the heart is from the vagal nerve that acts on the muscarinic receptor M3 to cause a reduction in the heart rate and conduction velocity of the AV node [13,14]. In the state of Parkinson's disease, autonomic dysfunction is often seen and presents with what has been called non-motor symptoms [15]. The mechanism for the autonomic dysfunction of PD is largely understood in the study of cardiovascular symptoms. In which there is cardiovascular autonomic dysfunction (CAD) that can be attributed to a defective baroreflex mechanism and the degeneration of the noradrenergic neurons. Whether this degeneration is cardiac or extra-cardiac [16,17]. The baroreflex mechanism, which is activated by the baroreceptors in the wall of the carotid sinus, aortic arch, and great blood vessels, can increase the sympathetic drive on the heart and hence its effect through afferent fibers that act to activate the nucleus of the tractus solitarius (NTS) in the dorsomedial medulla, which in turn causes inhibition of the nucleus ambiguous that results in reduction of the vagal output effect on the heart. At the same time, it activates the sympathetic intermediolateral cells of the thoracic spine through its connection with the intermediolateral column and the rostral ventrolateral medulla. This baroreflex mechanism is disrupted in the case of Parkinson's dysautonomia [18]. In our study the participants of the two groups were tested for autonomic dysfunction by measuring the heart rate variability with an EMG machine to various stressors (three states). In the first stage (resting), the study showed that there is a significant difference in comparisons to the control group of participants (Table 5). In the second state, in which we used deep breath to assess the autonomic response, during the deep breath, the heart rate will increase to some extent in the normal participant, while the participant with

PD showed significant deviation from the normal response (Table 5). At last, the participants were assessed with the aid of the Valsalva maneuver, in which more stress to the heart was delivered due to the mechanism of the maneuver and provided more challenge to the baroreflex mechanism, and for those reasons, it showed a powerful significance difference between the two groups of participants.

Conclusions

This study implies that the R-RIV test is a reliable method in the assessment of autonomic function in patients with PD, especially in the setting of the Valsalva maneuver. Such findings will aid the early detection of autonomic dysfunction in PD patients and hence better management. However, large-scale studies are required to validate the results and exploit clinical application.

Conflict of interests

The authors declared no conflict of interest.

Funding source

The authors did not receive any source of funds.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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