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Original Article

Evaluation of Cardiac Autonomic Functions in Older Parkinson's Disease Patients: a Cross-Sectional Study

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ABSTRACT: In Parkinson's disease (PD), non-motor symptoms may occur such as autonomic dysfunction. We aimed to evaluate both parasympathetic and sympathetic cardiovascular autonomic dysfunction in older PD cases. 84 PD cases and 58 controls, for a total of 142, participated in the study. Parasympathetic tests were performed using electrocardiography. Sympathetic tests were assessed by blood pressure measurement and 24-hour ambulatory blood pressure measurement. The prevalence of orthostatic hypotension in PD patients was 40.5% in PD patients and 24.1% in the control group (p> 0.05). The prevalence of postprandial hypotension was 47.9% in the PD group and 27.5% in the controls (p <0.05). The prevalence of impairment in heart rate response to deep breathing was 26.2% in the PD group and 6.9% in the control group (p <0.05). The prevalence of postprandial hypotension in PD with orthostatic hypotension was 94% and 16% in PD patients without orthostatic hypotension (p <0.05). The prevalence of impairment in heart rate response to deep breathing was 52.9% in PD patients with orthostatic hypotension and 8% in PD cases without orthostatic hypotension (p<0.05). The prevalence of impairment in heart rate response to postural change was 41% in PD cases with orthostatic hypotension and 12% in PD cases without orthostatic hypotension (p <0.05). Although there are tests for assessing cardiovascular autonomic function that are more reliable, they are more complicated, and evaluation of orthostatic hypotension by blood pressure measurement and cardiac autonomic tests by electrocardiography are recommended since these tests are cheap and easy.

Key words: autonomic functions, cardiovascular, older, Parkinson's disease

Parkinson's disease (PD) is the most common movement disorder with essential tremor and the most common neurodegenerative disease after Alzheimer's disease [1, 2]. Progressive loss of dopaminergic neurons in substantia nigra and Lewy body formation are the main pathologies in PD. However, the pathology of PD is not just limited to substantia nigra, but many parts of the central nervous system are affected. As a result, besides motor symptoms of PD, various non-motor symptoms can be seen in PD and some of these symptoms are due to autonomic neuropathy[3]. Physicians mostly concentrate on motor symptoms and neglect the diagnosis and treatment of non-motor symptoms. Non-motor symptoms contribute to the severity of PD and adversely affect the quality of life [4, 5].

Cardiovascular autonomic nervous system disorders are part of autonomic neuropathy in PD. Both sympathetic and parasympathetic parts of the cardiovascular autonomic nervous system are affected in PD [6-8]. Orthostatic hypotension (OH), postprandial hypotension (PPH), non-dipping and supine hypertension (SHT) are the clinical consequences of cardiovascular autonomic dysfunction in PD [9-11].

Cardiovascular autonomic nervous system function can be evaluated by non-invasive methods. While office blood pressure measurements and twenty-four hour

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ambulatory blood pressure measurement monitoring (ABPM) can be used for evaluating sympathetic cardiovascular autonomic nervous system function, parasympathetic cardiovascular autonomic nervous system can be evaluated by assessing heart rate responses to various stimuli. In particular, ABPM gives more detailed information about blood pressure changes and that is why its utilization is increasing in clinical practice [12].

To the best of our knowledge, there are not enough studies evaluating both sympathetic and parasympathetic cardiovascular autonomic nervous system function in the literature. In this study, we aimed to evaluate the sympathetic cardiovascular autonomic nervous system by OH, PPH, non-dipping status, and SHT and the parasympathetic cardiovascular nervous system by heart rate responses to deep breathing, Valsalva maneuver and standing up in older PD patients and age-sex matched controls.

MATERIALS AND METHODS

Study Protocol

This was a cross-sectional study consisting of 84 individuals diagnosed with PD and 58 controls over 65 years old who were admitted to the outpatient clinics of the geriatric medicine and neurology departments of Ankara University School of Medicine. Inclusion criteria for the study were being diagnosed with PD and having no co-morbidity or only hypertension. Individuals with primary or secondary autonomic neuropathies, OH due to dehydration, other causes of Parkinsonism, dementia, atrial fibrillation or other arrhythmias affecting electrocardiography interpretation were excluded. Demographic data, medications and duration of PD were recorded. Physical examination of study participants was performed by both a neurologist and a geriatrician. Diagnosis of PD was re-evaluated according to the United Kingdom PD Society clinical diagnostic criteria. Anti-hypertensive and anti-Parkinson medications were not withheld before procedures due to ethical considerations.

Evaluation of the Cardiovascular Autonomic Sympathetic Nervous System

Cardiovascular sympathetic autonomic nervous system function was evaluated by OH, PPH and non-dipping status.

Orthostatic hypotension

OH was evaluated by measuring blood pressure in an office setting. An OMRON™ (Model M2) digital blood pressure measuring device was used for office measurements. Before evaluation, participants rested for 15 minutes in the supine position. After the participant stood up, blood pressure was measured every minute for three minutes. OH was defined as a 20 mmHg decrease in systolic blood pressure or a 10 mmHg decrease in diastolic blood pressure in three minutes after standing.

Postprandial hypotension

Twenty-four hour ABPM was used for detecting PPH. A *Mobilograph 24h ABP-CONTROL* device was used for 24 hour ABPM. Blood pressure was measured every 15 minutes from 09.00 to 22.00 and every 30 minutes from 22.00 to 09.00. Participants were asked to record their meal times, sleep and wake-up times. Postprandial systolic blood pressure drop was calculated according to the following formula: Average preprandial systolic blood pressure - average postprandial systolic blood pressure. Average preprandial systolic blood pressure was the mean of systolic blood pressure measurements during two hours before meal. Average postprandial systolic blood pressure was the mean of systolic blood pressure measurements during two hours after meal. PPH was diagnosed when average postprandial systolic blood pressure drop was 20 mmHg or more.

Non-dipping status and supine hypertension

Non-dipping status and SHT were also investigated by ABPM. Mean systolic blood pressure (MSP) and mean diastolic blood pressure (DBP) were calculated from ABPM measurements. A participant was defined as a non-dipper when the decrease in mean SBP or DBP at night was less than 10% of the mean SBP or DBP in daytime. SHT was diagnosed when systolic blood pressure was ≥140 mmHg and/or diastolic blood pressure was ≥90 mmHg. Blood pressure measurements recorded while participants were sleeping were used to diagnose SHT.

Evaluation of cardiovascular parasympathetic autonomic Nervous system

Cardiovascular parasympathetic autonomic nervous system function was evaluated by heart rate responses to standing up, Valsalva maneuver and deep breathing. Three-lead electrocardiography was used for monitoring heart rate responses. Participants rested for 10 minutes before each test.

Heart rate response to standing up (30:15 ratio)

Electrocardiography recording was started while participants were lying down. After that, participants

stood up and remained in this position for two minutes. Standing time was marked on the electrocardiography tape. R-R intervals at the 15th and 30th beats were measured. Division of the R-R interval at beat 30 by R-R interval at beat 15 gives the 30:15 ratio. 30:15 ratio< 1.04 was accepted as abnormal.

Heart rate response during valsalva maneuver (valsalva ratio)

The participants exhaled into a sphingometer with a mouthpiece at an expiratory pressure of 40 mmHg for 15 seconds. The Valsalva maneuver was repeated three times. Participants rested for five minutes between each maneuver. The mean of three test results was calculated. The ratio between the longest R-R interval in the 30 second period at the end of the maneuver and the shortest R-R interval in the 15 second period at the beginning of the maneuver gives the Valsalva ratio. The mean of three maneuvers was calculated. Participants rested five minutes between three maneuvers. Valsalva ratio< 1.21 was considered abnormal.

Heart rate response to deep breathing (E:I ratio)

Deep breathing (six cycles per minute) was performed. The ratio of expiration/inspiration (E:I ratio) was calculated by dividing the longest R-R interval during expiration by the shortest R-R interval during inspiration. E:I ratio lower than 1.15 was considered abnormal.

Statistical Analysis

SPSS version 16.0 (Statistical Package for Social Sciences) program was used for statistical analysis. Descriptive statistics were given as percentages and mean ± standard deviation (SD). Independent numeric variables were compared using Independent T test and Mann-Whitney U test. Chi squared test was used for evaluating differences of categorical variables in groups. P< 0.05 was accepted as statistically significant.

Informed consent was obtained from all participants. This study was approved by the ethical committee of the Ankara University School of Medicine.

RESULTS

There were 84 participants in the PD group and 58 participants in the control group. Clinical and demographic data of study participants are given in Table 1.

Table 1. Clinical and Demographic Variables of Study Participants

Variables	PD[1] group (n=84)	Control group (n=58)	P value
Age (years) (mean ± SD)	73 ±7.9	72.6 ±4.8	NS[2]
Gender (female/male) (%)	54.8%/45.2%	55.2%/44.8%	NS
Hypertension (%)	52.3%	89.7%	NS
Anti-hypertensive medications (%)	52.3%	86.2%	NS

[1]Parkinson's disease, [2]Not significant

Both groups were similar in terms of age and gender. In the control group (89.7%), the prevalence of hypertension was significantly higher than the PD group (52.3%) (p=0.03). Anti-hypertensive drug use in the control group (86.2%) was significantly higher than in the PD group (52.3%) (p=0.01).

Results of cardiovascular autonomic tests of both groups are given in table 2. Despite the high prevalence of OH in the PD group (40.5%) compared to controls (24.1%), the difference was not statistically significant (p=0.19). While the prevalence of PPH was 47.6% in the PD group, PPH was seen in 27.5% of controls and this difference was statistically significant (p=0.032). There was no difference between the two groups for SHT and non-dipper status. Among parasympathetic autonomic tests, the prevalence of abnormal E:I ratio was significantly different between the two groups (PD group (26.2%) vs. control group (6.9%), p=0.04).

Table 2. Cardiovascular Autonomic Tests in PD and Control Groups

CV[1] autonomic tests	PD[2] group (n=84)	Control group (n=58)	P value
OH[3] (%)	40.5%	24.1%	NS[6]
SHT[4] (%)	23.8%	22.8%	NS
PPH[5] (%)	47.6%	27.5%	0.032
Non-dipper status (%)	38.1%	37.5%	NS
Valsalva ratio<1.21 (%)	20.9%	15.3%	NS
E:I ratio<1.15 (%)	26.2%	6.9%	0.04
30:15 ratio≤1.04 (%)	23.8%	18.9%	NS

[1]Cardiovascular, [2]Parkinson's disease, [3]Orthostatic hypotension, [4]Supine hypertension, [5]Postprandial hypotension, [6]Not significant

Patients in the PD group were divided into two separate groups according to whether PD patients had OH or not. Clinical and demographic data of PD patients with and without OH are shown in table 3. Disease duration in PD patients with OH (82.7±60.7 months) was significantly higher than in PD patients without OH (38.5±46 months) ($p<0.01$). There was no difference between the two groups for age, gender, HT prevalence, anti-hypertensive and anti-Parkinson medications.

The results of cardiovascular autonomic tests of PD patients with and without OH are shown in Table 4. The prevalence of PPH in PD patients with OH (94%) was significantly higher than the prevalence of PPH in PD patients without OH (16%) ($p<0.001$). The prevalence of pathologic E:I ratio in PDpatients with OH (52.9%) was significantly higher than in patients without OH (8%) ($p=0.02$). The prevalence of pathologic 30:15 ratio was significantly higher in PD patients with OH (41%) compared to PD patients without OH (12%) ($p=0.031$). The prevalence of SHT, non-dipper status and pathologic Valsalva ratio were similar between PDpatients with OH and PD patients without OH.

Table 3. Clinical and Demographic Variables of PD Patients with and without OH

Variables	PD[1] with OH[2] (n=34)	PD without OH (n=50)	P value
Age (years) (mean±SD)	71.3±8.8	74.2±7.1	NS[5]
PD duration (months) (mean±SD)	82.7±60.7	38.5±46	<0.01
Gender (female/male) (%)	58.8%/41.2%	52%/48%	NS
Hypertension	47.1%	56%	NS
Anti-hypertensive medications (%)	47.1%	56%	NS
L-dopa[3] (%)	82.4%	76%	NS
DA[4] (%)	29.4%	20%	NS
Selegline (%)	23.5%	32%	NS
Amantadine (%)	5.9%	4%	NS

[1]Parkinson's disease, [2]Orthostatic hypotension, [3]Levodopa, [4]Dopamine agonists, [5]Not significant

Table 4. Cardiovascular Autonomic Tests of PD Patients with and without OH

CV[1] autonomic tests	PD[2] with OH[3] (n=34)	PD without OH (n=50)	P value
SHT[4] (%)	35.3%	24%	NS[6]
PPH[5] (%)	94%	16%	<0.001
Non-dipper status (%)	52.9%	28%	NS
Valsalva ratio<1.21 (%)	29.4%	16%	NS
E:I ratio<1.15 (%)	52.9%	8%	0.02
30:15 ratio<1.04 (%)	41%	12%	0.031

[1]Cardiovascular, [2]Parkinson's disease, [3]Orthostatic hypotension, [4]Supine hypertension, [5]Postprandial hypotension, [6]Not significant

DISCUSSION

PD is a movement disorder characterized by the degeneration of neurons in the nigrostriatal pathways and pathological formation of Lewy body. In recent years, many non-motor symptoms have been reported in a majority of PD cases in addition to motor symptoms [13]. Dysfunction of the cardiovascular autonomic system is one of the non-motor symptoms. In this study, we evaluated both sympathetic and parasympathetic parts of the cardiovascular autonomic nervous system in PD patients by comparing to controls with similar age and gender.

Lewy bodies invade autonomic centers, the dorsal motor nucleus of the glossopharygeal and vagal nerves, the gastrointestinal submucosal plexus and the post ganglionic sympathetic nervous system according to Braak staging [14]. These changes may underlie the pathophysiology of autonomic dysfunction in PD.

OH is the most common CV sympathetic autonomic dysfunction in PD. Prevalence of OH in PD varies between 30% and 58% [15-19]. The prevalence of OH in PD in our study was similar to the literature. Orthostatic hypotension is also frequently seen in the elderly population. The prevalence of OH in people 65 years old and older varies between 5% and 30% [20]. In our study, the prevalence of OH was 24.1% in the control group. This value, although within the limits specified in the literature, was high. This might be due to the high prevalence of HT and anti-hypertensive medications in the control group. In an observational study, an increase in the prevalence of OH was parallel to the increase in the number of drugs that cause OH [21]. In addition, the prevalence of OH was associated with uncontrolled hypertension and the number of anti-hypertensive medications in a cross-sectional study [20].

OH in individuals with PD is related to age, disease duration and disease severity [15,22,23]. Although no significant difference was found between the ages of PD cases with OH and without OH, there was a significant relationship between OH and disease duration in our study. However, we did assess PD severity. Drugs used in treatment of PD have been associated with OH [24-26]. However, there have also been studies indicating that there is no such relationship [27]. Decreased post ganglionic sympathetic innervation, neurodegeneration in the dorsal vagus nerve and central lesions in the upper brainstem affecting baroreflex function can be causes of OH in PD [28].

PPH is more common than OH in older people [29]. PPH was found to be related to age, residing in a nursing home, hypertension and other cardiovascular diseases [30-32]. PPH is also common in PD. Mehagnoul-Schipper et al. reported that PPH was seen in 82% of older individuals with PD [27]. It was found to be 61% in another study [33]. The severity of PD is associated with PPH [27]. Non-dipping and SHT was seen in PD with OH. The prevalence of non-dipping in PD patients with OH varies between 48% and 92.3% [9,11,34-36]. SHT was detected in 100% of PD patients with OH [10]. SHT was more common in PD patients with OH compared to PD patients without OH in the study of Goldstein et al. [37]. There was no statistically significant difference between controls and PD group for the prevalence of non-dipping and SHT in our study. There was also no statistically significant difference between PD patients with and without OH for the prevalence of non-dipping and SHT. The mechanisms of non-dipping and SHT in individuals with OH are not well known. Plasma epinephrine levels were found to be low in individuals with SHT. Excessive sensitivity of noradrenergic receptors due to general and cardiac sympathetic denervation and impairment of cardiovagal gain (parasympathetic part of baroreflex mechanism) were blamed for the development of SHT. In addition, arterial stiffness related to essential HT and endothelial damage are the other factors that are blamed.

SHT might be independent of sympathetic activity [38, 39]. Supine hypertension was related to target organ damage in individuals with OH [40].

While the prevalence of pathologic E:I ratio and pathologic 30:15 ratio was statistically different between PD patients with and without OH, the prevalence of impaired Valsalva ratio was similar between PD patients with OH and PD patients without OH in our study. Heart rate responses to various physiological maneuvers were used for testing parasympathetic cardiovascular function in this study. Parasympathetic cardiovascular dysfunction was evaluated in PD in different studies. While some of the cardiovascular tests were found to be impaired in some of these studies, all of them were impaired in others [7, 41-44]. Cardiovascular parasympathetic dysfunction was found to be related to disease severity [7]. Especially the Valsalva maneuver is difficult to perform for older people. Heart rate response to deep breathing might be the optimal method for older people [45].

Our study has some limitations. Firstly, the cross-sectional design of the study limited the evaluation of causality. We did not assess disease severity. Ambulatory blood measurements can also be affected by many factors, such as prolonged lying position, warm environment, and micturition [28]. Not ceasing anti-Parkinson medications might be another limitation of our study. However, little or no difference between individuals taking medications and individuals not taking medications was reported in previous studies [44, 46].

Cardiovascular autonomic dysfunction has high importance in PD because it causes impairment in activities of daily living, an increase in falls, syncope and sudden death [25, 47-49]. There is also an increase in all cause mortality [50]. Several studies have shown that non-motor symptoms may occur before motor symptoms develop in PD [51]. Proper cardiovascular autonomic function evaluation can be important in detecting PD at earlier stages [28]. OH was the most common presentation of the cardiovascular autonomic dysfunction in PD and it is easy to evaluate in office settings. Early diagnosis and treatment of OH can induce improvement in quality of life [52]. Considering OH may be a consequence of anti-parkinson treatment, anti-parkinson drugs should be reviewed. In addition, if OH is detected, the probability of other cardiovascular autonomic dysfunction manifestations such as PPH and SHT is high. Especially SHT is associated with target organ damage and cardiovascular events [53]. Management of SHT can decrease cardiovascular mortality in PD patients. Cardiovascular autonomic dysfunction in older PD patients should not be overlooked. Although there are cardiovascular tests that are more reliable for assessing autonomic dysfunction, they are more complicated, and measuring blood pressure for OH and performing cardiac autonomic tests by electrocardiography may be suggested since they are cheap and can be performed in outpatient settings. Ambulatory blood measurement can also be performed if possible.

Conflict of interest

There is no competing interest for the writers of this paper.

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