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ORIGINAL ARTICLE

A Comparative Study of Central Hemodynamics in Parkinson's Disease

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ABSTRACT

Objective To explore the central aortic pressure in patients with Parkinson's disease (PD).

Methods We investigated central arterial stiffness by measurement of the augmentation index (AIx) in PD patients. Patients were eligible for the study if they were *de novo* PD and 45 years of age or older. The patients' demographics, vascular risk factors, and neurologic examinations were collected at baseline. The AIx was measured by applanation tonometry.

Results A total of 147 subjects (77 in control and 70 in PD groups) were enrolled in the study. While there was no significant difference in peripheral systolic blood pressure (SBP), diastolic blood pressure (DBP), or mean arterial pressure between groups, peripheral pulse pressure (PP) was significantly lower in the PD group than in the control group ($p = 0.012$). Regarding central pressure, aortic DBP was significantly higher and PP was significantly lower in the PD group ($p = 0.001$, < 0.0001). Although there was no significant difference in the AIx between the groups, a trend toward a lower AIx was observed in the PD group (31.2% vs. 28.1%, $p = 0.074$).

Conclusion This study showed that peripheral and central PP was significantly lower in the PD group than in the control group. Our study suggests that PD patients may have a low risk of a cardiovascular event by reason of a lower PP.

Key Words Arterial stiffness; augmentation index; Parkinson's disease; pulse pressure.

Parkinson's disease (PD) is a complex bradykinetic disorder because of its progressive nature and heterogeneous clinical presentation.[1,2] Stroke and PD may be concurrent disorders, both of which affect individuals of advanced age. Individuals with PD who have high levels of disability due to stroke are most likely to experience poor-health-related quality of life,[1] and great attention has been given to the issue of the frequency of stroke in patients with PD.[2] Several studies have addressed this problem, but there is controversy over whether the prevalence of stroke in PD patients is lower than,[3] similar to,[4] or higher than the prevalence among the general population.[5]

Arterial walls also stiffen with age, but it is not exclusively normative. Aging, environmental, and genetic factors are responsible for structural and functional changes in the arterial wall, leading to decreased elasticity and increased stiffness. Arterial stiffness of the large, elastic conduit arteries is considered a risk marker of vascular aging, as well as a new biomarker of cardiovascular (CV) mortality, fatal and nonfatal coronary events, and symptomatic strokes.[6] Previous studies have demonstrated that arterial stiffness is associated with cognitive impairment, the presence of lacunar infarctions, white-matter hyperintensities, and cerebral microbleeds.[7]

In this study, we investigated central arterial stiffness by measurement of the augmentation index (AIx) in patients with PD. The AIx is a well-established index of aortic stiffness. Increased AIx measurements are associated with several vascular risk factors, including age, smoking, hypertension, diabetes mellitus, and dyslipidemia.[8] The aim of the present study was to explore the central aortic pressure in patients with PD.

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MATERIALS & METHODS

Patients

For the study, we enrolled all consecutive *de novo* PD patients over 45 years old, fulfilling the UK-PD Brain Bank criteria from the outpatient clinic, Department of Neurology, Sanggye Paik Hospital, Inje University. We excluded patients with atypical Parkinsonism.

Control subjects were patients presenting to the neurology outpatient clinic for headache and normal brain CT/MRI in the same period. All patients were evaluated according to the same protocol. The patients' demographics, vascular risk factors, and neurologic examinations were collected at baseline. All subjects signed an informed consent form, and this study was approved by the local Ethical Committee.

Pulse wave analysis

The methods of pulse wave analysis have been published previously.[9] In brief, the AIx was measured by applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia). Applanation tonometry was used to record the radial artery pressure waveform continuously, and the mean values of the two screens of pulse waves of good quality were used for analysis. On the basis of the collected data, an average radial pressure waveform was generated and a corresponding aortic pressure waveform and blood pressure (BP) were calculated by the validated transfer function (SphygmoCor version 7.1, AtCor Medical, Sydney, Australia). Only high-quality recordings, defined as having an in-device quality index of ≥ 80% and acceptable curves on visual inspection, were included in the analysis.

Statistical analysis

Data are expressed as the mean ± SD or numbers (%). The baseline characteristics of the two groups were compared using Student's t test for continuous variables and using a χ^2 test for categorical variables. The Mann-Whitney U test was used to compare the non-normally distributed data, and Student's *t*-test was used to compare normally distributed data. Simple and multivariate linear regression models were used to analyze the association of univariate significant variables. A two-sided *p*-value of < 0.05 was considered statistically significant. SAS version 4.2 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

RESULTS

Demographics and clinical information

A total of 147 subjects (77 in control and 70 in PD groups) were enrolled in the study. Demographic and baseline characteristic data for the patient and control groups are shown in Table 1. In the total study population, the mean age was 68.6 years, and 45.6% were women. Of the enrolled subjects, 47.6% had histories of hypertension, 21.8% of diabetes, 8.8% of dyslipidemia, and 17.7% of current smoking. The baseline characteristics were well balanced between the groups, and there were no statistically significant differences in these characteristics except random plasma glucose, low-density-lipoprotein cholesterol, and triglyceride levels. Whereas baseline triglyceride levels were significantly lower in the PD group ($p = 0.038$), random plasma glucose and low-density-lipoprotein cholesterol levels were higher in the PD group ($p = 0.039$, 0.010).

Hemodynamic indexes

Hemodynamic indexes of the enrolled subjects are shown in Table 2. Although there were no significant differences in peripheral systolic blood pressure (SBP), diastolic blood pressure (DBP), or mean arterial pressure between the groups, peripheral pulse pressure (PP) was significantly lower in the PD group than in the control group ($p = 0.012$). With regard to central pressure, aortic DBP was significantly higher and PP was significantly lower in the PD group ($p = 0.001$, < 0.0001). Although there was no significant difference in AIx measurements between the groups, a trend toward lower AIx measurements was observed in the PD group (31.2% vs. 28.1%, $p = 0.074$).

In all subjects, simple linear regression analysis revealed that peripheral and aortic PP were significantly associated with AIx measurements ($p = 0.005$, < 0.0001). Multiple linear regression analysis showed that aortic PP was significantly related to AIx measurements (β coefficient = 0.545, $p < 0.0001$). In the PD group, multiple linear regression analysis also demonstrated that only aortic PP was significantly associated with AIx measurements (β coefficient = 1.585, $p < 0.0001$).

Table 1. Baseline characteristics of the study population

	Total (*n* = 147)	Control (*n* = 77)	PD (*n* = 70)	*p*
Age (years)	68.6 ± 7.89	67.8 ± 7.83	69.4 ± 7.93	0.215
Female	67 (45.6)	33 (42.9)	34 (48.6)	0.487
Hypertension	70 (47.6)	39 (50.6)	34 (48.6)	0.801
Diabetes mellitus	32 (21.8)	16 (20.8)	16 (22.9)	0.760
Hypercholesterolemia	13 (8.8)	6 (7.8)	7 (10.0)	0.638
Current smoking	26 (17.7)	17 (22.1)	9 (12.9)	0.143
Random sugar (mg/dL)	118.3 ± 39.56	111.6 ± 25.78	125.8 ± 49.88	0.039*
Total cholesterol (mg/dL)	163.8 ± 39.26	168.2 ± 37.92	158.8 ± 40.43	0.149
LDL-cholesterol (mg/dL)	110.9 ± 40.47	102.7 ± 33.03	120.6 ± 46.11	0.010*
HDL-cholesterol (mg/dL)	47.3 ± 16.44	46.9 ± 11.32	47.7 ± 20.86	0.776
Triglyceride (mg/dL)	128.9 ± 59.97	138.4 ± 73.02	118.2 ± 38.58	0.038*

Data are the mean ± SD or numbers (%). *statistically significant. PD: Parkinson's disease, LDL: low-density lipoprotein, HDL: high-density lipoprotein.

Table 2. Hemodynamic indexes of the study population

	Total (*n* = 147)	Control (*n* = 77)	PD (*n* = 70)	*p*
Peripheral SBP (mm Hg)	133.8 ± 15.99	135.1 ± 16.19	132.4 ± 15.75	0.310
Peripheral DBP (mm Hg)	76.3 ± 9.87	74.8 ± 9.48	77.9 ± 10.09	0.053
Peripheral MAP (mm Hg)	96.7 ± 10.97	95.7 ± 9.97	97.3 ± 11.50	0.470
Peripheral PP (mm Hg)	57.7 ± 13.55	60.3 ± 14.70	54.79 ± 11.60	0.012*
Aortic SBP (mm Hg)	123.2 ± 16.03	124.3 ± 16.09	121.9 ± 15.98	0.366
Aortic DBP (mm Hg)	74.9 ± 11.19	71.9 ± 10.05	78.2 ± 11.53	0.001*
Aortic PP (mm Hg)	48.2 ± 13.07	52.4 ± 13.55	43.7 ± 10.96	< 0.0001*
AIx (%)	29.7 (10.58)	31.2 (10.38)	28.1 (10.63)	0.074
AIx@75 (%)	25.6 (9.41)	25.4 (9.36)	25.9 (9.53)	0.757

Data are the mean ± SD or numbers (%). *statistically significant. PD: Parkinson's disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, PP: pulse pressure, AIx: augmentation index, AIx@75: augmentation index correlated with heart rate 75 bpm.

DISCUSSION

According to previous reports, one study reported that the risk of stroke is lower in patients with PD than in normal controls,[3] whereas other studies[2] report a higher risk. Unfortunately, the question of whether the prevalence of stroke in patients with PD is higher than control is often noted but rarely studied from a central and peripheral hemodynamics aspect. Although we do not know the exact mechanism by which L-dopa affects BP control in patients with PD, L-dopa-derived dopamine may exert an inhibitory effect on adrenergic transmission, and the adrenergic neurotransmitters of the sympathetic nervous system are also involved in regulation of lipid and glucose turnover.[10] Based on that hypothesis, dopamine deficiency in PD could ameliorate ischemic damage and may provide additional protection from stroke. Dopamine depletion has also been found to lessen ischemic neuronal damage, and thus the deficiency of neurotransmitters implicated in excitotoxic cell death may have a role in our finding of decreased stroke risk in patients with PD.[2] In contrast, many patients with PD are prone to sedentary lifestyles based on physical impairments, and it is conceivable that the lack of sufficient regular physical activity is a risk factor in the development of atherosclerotic vascular disease.[11] L-dopa treatment may promote secondary hyperhomocysteinemia, which can induce atherosclerosis by impairing endothelial function and thereby promoting the development of CV disease and stroke.[2,10]

We have shown that the carotid intima-media thickness value is lower in patients with restless legs syndrome (RLS), suggesting that the progression of atherosclerosis is slow in RLS.[12] Dopaminergic dysfunction is a common underlying pathophysiology in both PD and RLS, and dopaminergic treatment is effective for both diseases. Considering the similar pathophysiological mechanisms of both diseases, a part of dopaminergic dysfunction may be related to the lower risk of atherosclerotic progression.[12]

In this study, we found that central hemodynamic results of patients with PD were different than those

of patients in the control group. Although there was no significant difference in the AIx measurements, both peripheral PP and central PP were significantly lower in the PD group than in the control group. High peripheral and central DBP may be the cause of a lower PP in patients with Parkinson's disease in our study. Although we could not give an exact explanation for the finding, we suggest that the higher age of the cases was the reason for the high DBPs.[13] This study found that diastolic pressure is higher in PD groups, which suggests that patients with PD are at risk for CV events, based on the association of higher DBP with CV risk.[14] Research regarding DBP has evolved considerably over the last several decades. Recently, there has been much debate about which increased diastolic value alone is more predictive of adverse CV outcomes in various patient populations.[15] Since the diastolic pressure in a population rises until the sixth decade and then subsequently declines with increasing age, an elevation in the diastolic pressure alone is less useful as an outcome predictor in older patients.[16]

Considering the relationship between PP and atherosclerotic vascular events,[17] the results suggest that the risk of CV events in patients with PD is lower than in controls. Higher PP is usually associated with a higher SBP and a lower DBP, and even healthy people with normal SBP levels may demonstrate a decline in DBP, leading to an increase in PP.[18] PP has been known to be an independent predictor of CV events, and it predicts atherosclerosis-related complications.[17] PP is also a major determinant of small-artery disease and is associated with the prevalence and severity of cerebral white-matter hyperintensities.[19]

Although increased central arterial stiffness is a well-recognized mechanism of higher PP, clear reasons for the excessive risk of stroke associated with higher PP are uncertain.[17] The central aortic pressure wave comprises a forward-traveling wave generated by left ventricular ejection and a late-arriving reflected wave from the periphery. As central aortic stiffness increases, the transmission velocity of both forward and reflected waves increases, causing the reflected wave to arrive earlier in the central aorta and to augment pulsatile load in the late systole phase. Those augmented pulsatile components of BP may be related to the increased risk of stroke in higher PP.[8]

Our study has several limitations. First, we did not include certain clinical factors such as PD stage, duration of PD, PD subtype and biomarkers of inflammation such as interleukin-6 and tumor necrosis factor-alpha, which may give more comprehensive information on the relationship between inflammation and vascular stiffness. For that reason, we cannot demonstrate whether those factors affected the central hemodynamic findings. Second, the number of study participants was not sufficient, and the study's sample size was not determined a priori. Third, only South Korean patients with PD were enrolled in the study, thereby limiting the findings' generalizability to other geographic regions. Last, we did not assess the relationship between the AIx and the use of anti-hypertensive drugs, lipid lowering agents that can influence arterial stiffness. Certain drugs, especially antihypertensive drugs, such as calcium channel blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors decrease arterial stiffness. These limitations should be considered when interpreting our data. Despite those limitations, we found that the central hemodynamics of patients with PD differed from those of normal controls. In conclusion, this study showed that peripheral PP and central PP were significantly lower in the PD group than in the control group. Our study suggests that patients with PD may have a lower risk of a CV event by reason of a lower PP. Further clinical studies are required to answer the question about frequency of stroke and other CV events in patients with PD and to establish whether treatment aimed at reducing PP would decrease the incidence of CV events.

Conflicts of Interest

The authors have no financial conflicts of interest.

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