

Age-related changes of blood pressure and heart rate in patients with Parkinson's disease: Is there any effect of antiparkinsonian drugs?

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Abstract

Background

Many investigators have confirmed that orthostatic hypotension is more frequent in PD patients with longer disease duration and in those with higher scores on the disability scale. This study evaluated yearly changes of systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) in patients with Parkinson's disease (PD).

Methods

Data were collected for the last 16 years from medical records of 32 PD patients. Age-related changes in each group were analyzed by year using mean values of SBP, DBP, and HR obtained at their bi-monthly visits.

Results

In all PD patients, there was a gradual decrease in SBP with longer disease duration, and mean SBP significantly decreased from Year 7 to 11 compared to the mean values for Year 1 ($p < 0.001$ or $p < 0.01$). Regarding the effect of antiparkinsonian drugs, similar changes in SBP (levodopa and dopamine agonists combined therapy: -0.56 mmHg/year, levodopa monotherapy: -1.10 mmHg/year, $p < 0.01$ or $p < 0.05$) and DBP (levodopa and dopamine agonists combined therapy: -0.04 mmHg/year, levodopa monotherapy: -0.30 mmHg/year) were observed with longer disease duration. There were no significant changes in HR in both groups. No significant correlations between the increased change in levodopa-equivalent daily dose (LEDD) from Year 1 to Year 11 and SBP, DBP, or HR were found.

Conclusions

This is the first study to report age-related changes of BP and HR in individual patients with PD for over 10 years without an association with antiparkinsonian drug use or increases in LEDD.

Introduction

Various degrees of cardiovascular autonomic dysfunction have been reported in patients with Parkinson's disease (PD) [1–3]. While it has been reported that some autonomic symptoms such as constipation and urinary urgency were observed either in the early stages of PD or before diagnosis when motor symptoms begin to appear [3, 4], many investigators have confirmed that orthostatic hypotension (OH) and OH-related symptoms are more frequent in PD patients with longer disease duration and in those with higher scores on the disability scale [1, 3, 5]. Moreover, prospective studies

have shown that the frequency of OH apparent on head-up tilt tests or the severity of OH symptom scores gradually increased with longer PD duration [1–3, 6].

In our previous study, we confirmed similar findings by recording muscle sympathetic nerve activity that regulates blood pressure (BP) [7]. Moreover, we investigated age-related changes of BP in individual patients with idiopathic PD and those with neurological disorders other than PD for more than 10 years [8]. The results showed that systolic BP (SBP) in the PD group underwent a significant decrease with increasing age, whereas there were no significant changes in diastolic BP (DBP). In contrast, both SBP and DBP increased significantly with increasing age in the non-PD group. There were no significant age-related changes in heart rate (HR) in either group.

Many investigators have reported that antiparkinsonian drugs such as levodopa, dopamine agonists, and monoamine oxidase inhibitors may influence various autonomic functions, including resting BP, orthostatic changes in BP, and diurnal variation in BP [9, 10]. Because the association between age-related changes in BP and the effects of antiparkinsonian drugs could not be examined in detail in our previous report due to the word count limitation, the present study evaluated whether antiparkinsonian drugs influence age-related changes of BP and HR in patients with PD.

Methods

Subjects and clinical data

We reviewed the medical records of 32 patients (14 men and 18 women) with PD. These patients made bi-monthly outpatient clinic visits to the Department of Neurology at the University of Yamanashi Hospital between January 2009 and December 2025. Mean age was 68.1 ± 11.9 years (range: 51–88 years) and mean body mass index was 23.5 ± 3.3 kg/m² (range: 16.4–30.2 kg/m²). Mean disease duration was 13.9 ± 3.1 years (range: 11–26 years) as of December 2025. We used the Unified Parkinson's Disease Rating Scale as a measure of patient disability during the study period. The mean rating was 31.4 ± 21.0 (range: 8–91) in Year 1 and 64.2 ± 32.2 (range: 22–132) in Year 11 (Table 1).

We selected patients with idiopathic PD who met the following criteria: a diagnosis confirmed by at least 3 years of clinical observation, good response to levodopa treatment, and absence of demonstrable atrophy of the brainstem or cerebellum on magnetic resonance imaging. All patients were diagnosed with clinically definite PD using the British Brain Bank criteria [11].

Autonomic symptoms were present in 26 of the 32 patients during Year 11: constipation (n = 26), urinary urgency (n = 13), limb coldness (n = 9), orthostatic dizziness (n = 8), and sweating dysfunction (n = 6). Although seven patients with PD had OH, defined as a reduction in SBP at least 20 mmHg or in DBP at least 10 mmHg within three minutes of standing, no patients had severe manifestations of autonomic failure such as frequent syncope due to OH. The levodopa-equivalent daily dose (LEDD) ranged from 200 to 1358 mg, with a mean of 604.2 ± 262.8 mg. Twenty-two patients received both levodopa and dopamine agonists, and 10 patients received levodopa only (Table 1).

No patients had co-morbidities such as hypertension, cardiovascular disease, or cerebrovascular disease. We excluded patients who were taking other drugs that might affect the autonomic nervous system, including antihypertensive agents, muscle relaxants, vasodilators, or antidepressants. Patients with body weight fluctuations of over 5 kg were also excluded. The study protocol was approved by the institutional review board of the University of Yamanashi, and written informed consent was obtained from all participants.

Measurements

We confirmed that all patients were examined at rest and in a sitting position by an automated sphygmomanometer to measure SBP, DBP, and HR. The mean values of SBP, DBP, and HR obtained at the bi-monthly visits were calculated for each year. These data were considered the yearly quantitative values for each individual patient for 10 years or more. Age-related changes in each group were evaluated statistically. Age-related changes in SBP, DBP, and HR in patients taking only levodopa and in those taking both levodopa and dopamine agonists were measured, and the correlations between the increased change in LEDD from Year 1 to Year 11 and each of SBP, DBP, and HR were also evaluated.

Statistical analysis

Results are expressed as the mean $\pm$ SD. Student's paired t-test was used to evaluate differences in the results. Spearman's rank correlation coefficient was used to assess the relationships between age or LEDD and SBP, DBP, and HR. For all analyses, $p < 0.05$ was considered to indicate statistical significance.

Results

In all PD patients, there was a gradual decrease in SBP with longer disease duration (-0.67 mmHg/year), and the mean SBP significantly decreased from Year 7 to Year 11 compared to the mean value in Year 1 (Fig. 1, $p < 0.001$ or $p < 0.01$). A gradual decrease in DBP was also observed (Fig. 1, -0.09 mmHg/year), but this was not significant. There were no significant changes in HR. Regarding the effect of antiparkinsonian drugs, similar changes in SBP (Fig. 2A, levodopa and dopamine agonists combined therapy: -0.56 mmHg/year, levodopa monotherapy: -1.10 mmHg/year, $p < 0.01$ or $p < 0.05$) and DBP (Fig. 2B, levodopa and dopamine agonists combined therapy: -0.04 mmHg/year, levodopa monotherapy: -0.30 mmHg/year) were observed with longer disease duration. There were no significant changes in HR in both groups. Significant correlations between the increased change in LEDD from Year 1 to Year 11 and SBP ($\rho = -0.047$), DBP ($\rho = -0.1409$), or HR ($\rho = -0.067$) were not found. Regarding other antiparkinsonian drugs, a statistical analysis could not be conducted because of the small sample size.

Discussion

In this study, we investigated age-related changes of BP and HR in individual patients with idiopathic PD over a period of more than 10 years. The results showed that SBP decreased significantly, whereas there

were no significant changes in DBP. In healthy subjects, SBP and DBP generally tend to increase with age, according to retrospective and prospective studies [12, 13]. Antiparkinsonian drugs such as levodopa and dopamine agonists were previously reported to have various effects on BP in PD patients [10, 14]. In the present study, however, these drugs showed no influence on BP and HR, since similar changes observed in patients taking levodopa only and in those taking both levodopa and dopamine agonists. In addition, no significant correlations were found between the increased change in LEDD and SBP, DBP, or HR.

Many investigations regarding the influence of antiparkinsonian drugs on BP have been reported previously [3, 10, 14, 15]. Regarding BP changes immediately after the administration of levodopa, among 490 PD inpatients who underwent a levodopa challenge test, the incidence of OH using a supine-to-standing test was 33.1% before levodopa intake and 50.8% within 3 hours after drug intake, and PD patients who had a better response to levodopa showed a greater decline in SBP after levodopa intake [16]. Another levodopa challenge test revealed that SBP dropped significantly after levodopa intake in patients with late-stage PD, especially when patients were in their best ON condition compared to the OFF condition [17]. In 52 patients with early-stage PD, the prevalence of OH using a standardized standing test was 11.5% in the OFF state and 13.5% in the best ON state, and 73.1% of patients experienced levodopa-induced hypotension during the levodopa challenge test [18]. Introduction of levodopa treatment reduced BP and plasma norepinephrine levels in patients with newly diagnosed PD, and similar changes were found in patients with long-term-treated PD after short-term interruption of antiparkinsonian drugs [19].

Regarding the effect of chronic levodopa treatment, in PD patients who underwent levodopa treatment for 5 to 20 years without hypotension at the seated position, mean arterial pressure dropped significantly after the administration of levodopa tablets for up to 100 min, and the blood concentration of levodopa was inversely correlated with mean arterial pressure [20]. In contrast, in a placebo-controlled study of orally inhaled levodopa for early morning OFF periods in PD, there was no significant difference between the inhaled levodopa and placebo groups in the prevalence of OH using a supine-to-standing test, although the time to ON shortened significantly in the inhaled levodopa group compared to the placebo group [21]. It was also reported that six months' levodopa treatment improved the decline in SBP after tilting compared with that before treatment in patients with de novo PD [14].

Regarding dopamine receptor agonists, which are often administered to patients with PD, various effects on resting BP and orthostatic changes in BP have been reported [10, 22]. Bromocriptine, a dopamine receptor agonist, increased the decline in SBP after tilting compared with that before treatment in untreated PD patients [14]. Among three dopamine agonists, including pergolide, pramipexole, and ropinirole, 34% of patients met the criteria for OH by BP measurements in the supine and standing positions 2 hours after oral administration of each test dose [23]. In healthy subjects, it has been reported that plasma norepinephrine levels and BP were significantly reduced after oral administration of bromocriptine [24]. Furthermore, in a meta-analysis of three or more randomized controlled trials, dopamine agonists were significantly associated with an increased risk of OH compared with placebo

[10]. In contrast, rotigotine was reported not to influence cardiovascular autonomic function, unlike other dopamine receptor agonists [25]. Oka et al. reported that rotigotine improved abnormal BP fluctuations using 24-hour BP monitoring over 2 years [26].

In summary, most previous studies have reported lower resting BP and significantly higher frequency of OH in patients with PD compared with healthy subjects immediately after the administration of levodopa; however, it remains unclear whether chronic levodopa treatment affects BP. In contrast, dopamine receptor agonists were reported to cause a greater decline in SBP during tilting and increase the frequency of OH. Nevertheless, yearly changes in resting BP after administration of levodopa and/or dopamine agonists have not previously been reported. This is the first study to report age-related changes of BP and HR in individual patients with PD for over 10 years without an association with antiparkinsonian drug use or increases in LEDD.

Conclusion

In this study, we investigated age-related changes of BP and HR in individual patients with idiopathic PD for more than 10 years. The results showed that SBP decreased significantly, whereas there were no significant changes in DBP. Antiparkinsonian drugs such as levodopa and dopamine agonists have been reported to have some effects on BP in patients with PD. However, these drugs did not influence BP and HR in the present study, because we observed similar changes in patients taking levodopa only and in those taking both levodopa and dopamine agonists, and found no significant correlations between the increased change in LEDD and SBP, DBP, and HR. Regarding other antiparkinsonian drugs such as monoamine oxidase B inhibitors, future investigations in larger populations are warranted. Clinicians should be more aware of age-related changes of BP in PD patients, in addition to acute BP decreases due to levodopa, dopamine agonists, or other antiparkinsonian drugs, in order to avoid repeated reductions in cerebral blood flow that may lead to gradual worsening of cognitive impairment associated with abnormal BP changes, such as orthostatic or postprandial hypotension [27]. Even in the early stages of PD, assessment and management of BP abnormalities should be conducted in daily clinical practice.

Abbreviations

PD; Parkinson's disease

BP; blood pressure

SBP; systolic blood pressure

DBP; diastolic blood pressure

HR; heart rate

OH; orthostatic hypotension

LEDD; levodopa-equivalent daily dose

Declarations

Author contributions Kazumasa Shindo: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation. Akira Mugikura and Shota Nakamura: Writing – review and editing, Formal analysis. Tatsuya Saito and Yuto Morishima: Writing – review and editing, Project administration. Takanori Hata and Yuki Nakamura: Writing – original draft, Methodology, Supervision. Yosuke Taruno and Yuji Ueno: Supervision, Funding acquisition, Formal analysis.

Ethical compliance statement This study was approved by the institutional review board of the University of Yamanashi (number: 2266). All participants provided informed written consent.

Conflict of interest The authors have no conflicts of interest to disclose.

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Table 1

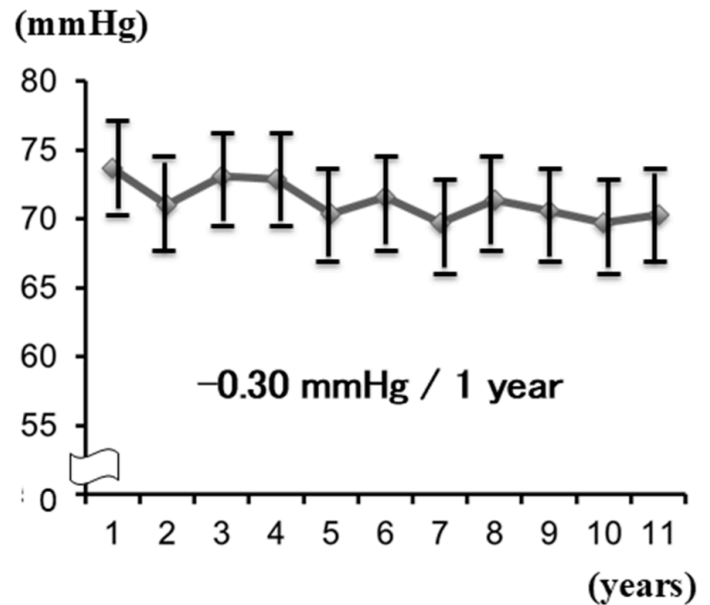
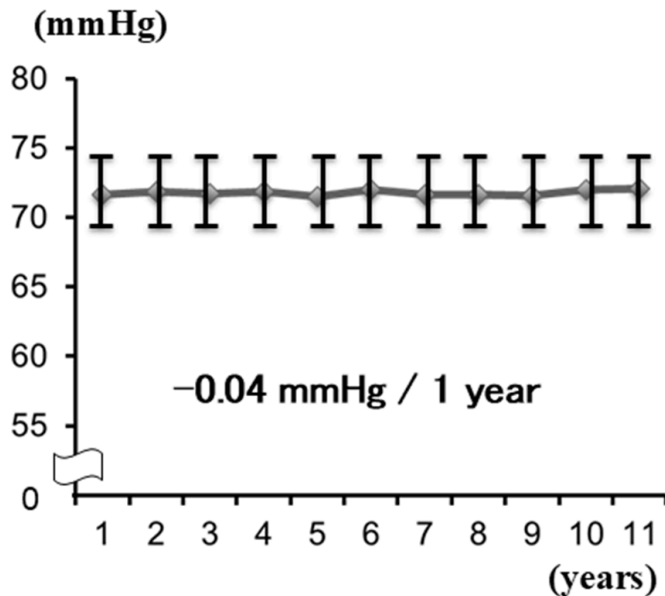
Table 1 is available in the Supplementary Files section.

Figures

Diastolic Blood Pressure

LD+DA combined therapy (n=22)

LD monotherapy (n=10)



DA, dopamine agonist

LD, levodopa

Disease duration

Figure 1

Age-related changes of systolic blood pressure and diastolic blood pressure in all patients with Parkinson's disease. There was a gradual decrease in systolic blood pressure with longer disease duration, and the mean systolic blood pressure decreased significantly from Year 7 to Year 11 compared with the mean value in Year 1. A gradual decrease in diastolic blood pressure was observed, but this was not significant.

*** * : p<0.01**

LD monotherapy (n=10)

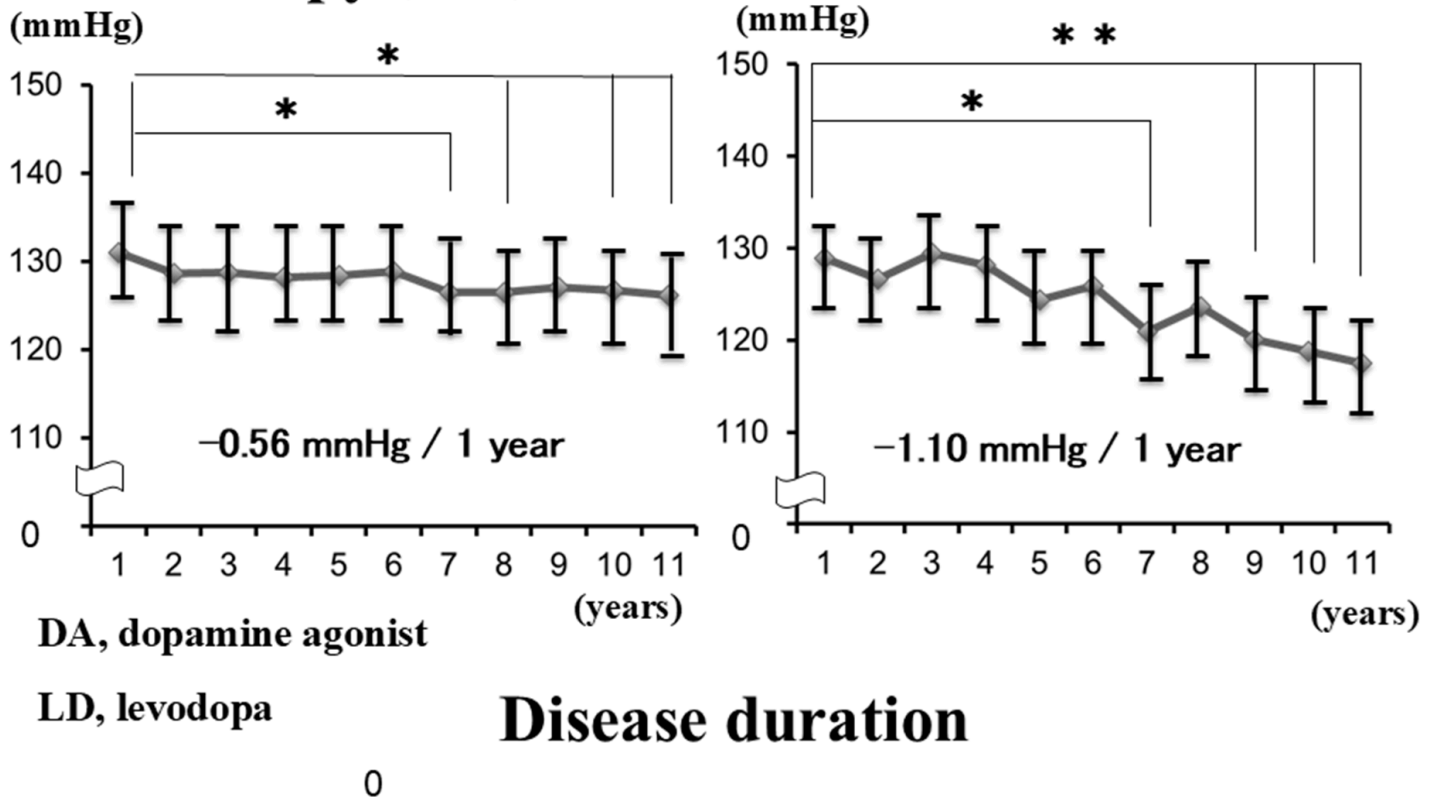


Figure 2

Age-related changes of systolic blood pressure (A) and diastolic blood pressure (B) in patients with PD receiving combination therapy with levodopa and a dopamine agonist and in those receiving levodopa monotherapy. In both groups, there was a gradual decrease in systolic blood pressure with longer disease duration. A slight decrease in diastolic blood pressure was observed.

Supplementary Files

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- Table1CAR1stvers..docx