Cognition and Visit-to-Visit Variability of Blood Pressure and Heart Rate in De Novo Patients with Parkinson's Disease

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ABSTRACT

Objective  We sought to identify whether the characteristics of long-term visit-to-visit blood pressure (BP) and heart rate (HR) are related to baseline cognitive profiles in Parkinson's disease (PD).

Methods  We selected drug-naïve PD patients who visited our hospital at least 10 times with a baseline assessment of the Seoul neuropsychological battery. BP and HR were measured at each visit, and the variability of the systolic BP/diastolic BP (DBP) and HR was derived from the parameters of serial 10 office visits. Mild cognitive impairment (MCI) in PD patients was determined according to the proposed criteria with a cut-off value of z-score ≤ -2.

Results  Forty-seven patients with PD (mean follow-up duration = 22.3 months) were enrolled in the study. Compared with non-MCI PD patients, MCI PD patients revealed a significant increase in HR and/or variability in DBP.

Conclusion  This exploratory study showed that baseline cognition in drug-naïve PD patients might be related to the visit-to-visit variability of DBP and/or HR.

Key Words  Parkinson's disease; blood pressure; heart rate; variability; cognition.

Non-motor symptoms, including cognitive and cardiovascular dysfunction, are commonly observed, even in the early stages of Parkinson's disease (PD). Mild cognitive impairment (MCI) was documented to range from 14.8% to 36% at the time of PD diagnosis.¹,² Cognitive function declines as PD progresses; therefore, up to 83% of PD patients can develop dementia in the late stage of the disease.³ Cardiovascular autonomic dysfunction has been widely observed in the early stage of PD. Functional studies with metaiodobenzylguanide (MIBG) myocardial scintigraphy not only showed the reduced uptake of MIBG⁴ but also demonstrated the diagnostic usefulness of PD even in the early stage.³ Moreover, Goldstein⁵ reported that 60% of early PD patients had significant orthostatic hypotension.

Previous studies have not yielded consistent results with respect to the association between cognitive impairment and blood pressure (BP): some showed that hypertension was highly related to cognitive dysfunction,⁷ whereas others reported that low BP or antihypertensive therapy was associated with worse cognitive function.⁸,⁹ In contrast, there has been increasing evidence to support the idea that cognitive dysfunction might be related to the variability of BP or heart rate (HR). Orthostatic hypotension was more frequently observed in cognitively impaired people,¹⁰ and abnormal nocturnal BP fluctuations were found in elderly patients with MCI.¹¹ Moreover, MCI subjects exhibited abnormal findings in BP as well as HR variability, which suggested that cardiovascular autonomic dysfunction is
associated with MCI. Nevertheless, the relationship between cognitive decline and cardiovascular autonomic dysfunction remains to be further elucidated, especially in patients with PD, although Kim et al. showed that cognitive dysfunction was related to cardiovascular abnormalities, including orthostatic hypotension and supine hypertension, in the early stage of PD.

Recently, the visit-to-visit variability of BP in the real office setting has turned out to be reproducible within individuals over time and independent of any association with mean BP. Increased visit-to-visit variability in systolic BP (SBP) was regarded as a new independent predictor in the elderly at high risk of stroke. In the general population, Muntner et al. exhibited that visit-to-visit variability in SBP was related to all-cause mortality. Additionally, visit-to-visit BP variability was associated with not only cognitive decline in patients with Alzheimer’s dementia but also an increased risk of dementia in the elderly. However, to our knowledge, there has been no report on the visit-to-visit variability of BP and/or HR in PD populations. Thus, we aimed to investigate whether the visit-to-visit variability of BP or HR is related to non-motor symptoms, including cognitive impairment, especially in de novo patients with PD.

MATERIALS & METHODS

Subjects
We retrospectively selected forty-seven de novo patients with PD by reviewing medical records at the Parkinson’s Disease Centre in Korea University Guro Hospital from January 2009 to March 2011. The inclusion criteria were as follows: 1) patients were diagnosed with de novo PD according to the UK brain bank criteria; 2) 3-T MRI scanning, including axial fluid attenuated inversion recovery images, and a full battery of neuropsychological tests were conducted in the same subject; 3) we excluded patients with dementia or moderate to severe ischemic or other structural lesions, based on the review of their brain MRI images; 4) all patients had visited our clinic at least 10 times; and 5) the existence of non-motor symptoms including rapid eye movement sleep behavior disorder (RBD)-like symptoms and subjective hyposmia was analyzed. The present study was approved by the Institutional Review Board of the Korea University Guro Hospital (KUGH IRB #14236).

Neuropsychological assessment and PD-MCI
The neuropsychological tests were administered in a constant protocol. The Seoul neuropsychological battery (SNSB) was performed on all patients with PD. The Korean version of the Mini-Mental Status Examination and the Geriatric Depression Scale was assessed in the same session. Because normative data of the SNSB from healthy Korean subjects were available, age-, gender-, and education-matched percentiles were obtained from the raw score of each test and thereby converted into z-scores. According to the task force guidelines from the movement disorder society, each test of the SNSB was categorized into five cognitive domains: attention and working memory, executive function, language, memory, and visuospatial function (Supplementary Table 1 in the online-only Data Supplement). MCI in patients with PD was defined according to the recommended Movement Disorder Society task force criteria. Impaired cognition in each test was determined with a cut-off value of 2 standard deviation (SD) below the appropriate norms. The subtypes were classified as follows: single-domain PD-MCI (amnestic or non-amnestic type) was derived from impairments on two tests within one single domain, with the other unimpaired, and multiple-domain PD-MCI was defined by abnormalities on at least one test in two or more domains. Because only one test was available in the SNSB for language and visuospatial function, abnormality on one test within such a domain was considered the fulfillment of a single-domain MCI pattern in the present study.

BP and HR measurements and visit-to-visit variability
Clinic BP and HR were measured in the sitting position after resting for approximately 5 to 10 minutes using a validated automatic oscillometric device (Model FT-500R, JAWON Medical Co. Ltd., Daejeon, Korea) at each visit. Overall, 10 values of BP and HR were obtained in 10 serial consecutive visits. The mean, maximum, and minimum values were calculated from the measured parameters, including SBP, diastolic BP (DBP), and HR. For the visit-to-visit variability, both the SD and coefficient of variation (CV) were assessed. CV was derived from
the ratio of SD to the mean (CV = SD / mean × 100%).

**Statistical analyses**

Group comparisons for non-MCI vs. MCI were conducted using Student’s t-test for continuous variables and Fisher’s exact test for categorical data, respectively. Analysis of covariance (ANCOVA) was performed using Bonferroni correction for visit-to-visit BP and HR parameters between PD with and without MCI. To predict MCI in de novo PD patients, logistic regression analysis was conducted. Because univariate analysis showed only one significant variable, multivariate analysis could not be performed. Correlation studies between cognitive tests and variability of BP and HR were analyzed using Pearson’s correlation coefficient. A p value < 0.05 was defined as statistically significant. Each statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

**RESULTS**

**Cognitive profiles of MCI in de novo patients with PD**

Based on neuropsychological data described in Supplementary Table 1 (in the online-only Data Supplement), subtype classification was performed in the study population. The cognitive profiles of patients were distributed as shown in Figure 1: 45% (21 of 47 patients) with normal cognition, 28% (13 of 47) with non-amnestic single-domain MCI, 19% (9 of 47) with multiple-domain MCI, and 8% (4 of 47) with amnestic single-domain MCI.

**Clinical characteristics between non-MCI and MCI in de novo PD**

Baseline examinations included age, gender, duration of education, parkinsonism motor symptoms, disease duration at the first and last visits, daily equivalent dose of levodopa at the last visit, body weight, height, current smoking status, and past medical history (diabetes mellitus, hypertension, previous stroke, coronary disease, other heart disease, and chronic kidney disease). Table 1 summarizes the results of those characteristics in the comparison between the non-MCI and MCI groups. Only the level of education revealed a tendency of having shorter durations of education in PD MCI compared with...
PD non-MCI (mean 6.7 years vs. mean 9.1 years, \( p = 0.082 \)). The rest of the clinical characteristics did not show any differences between the groups.

Visit-to-visit BP and HR parameters between non-MCI and MCI in de novo PD

For the profiles of visit-to-visit SBP, DBP, and HR, the comparisons between the non-MCI and MCI group are shown in Table 2. The primary parameters of SBP, DBP, and HR including mean, maximum, and minimum values were not different between the groups. The visit-to-visit variability of DBP and HR is shown in Table 3, Figure 2, and Supplementary Table 3 (in the online-only Data Supplement). ANCOVA in Table 3 exhibited not only a higher variability of visit-to-visit DBP (\( p = 0.042 \)) but also a tendency of visit-to-visit HR variability (\( p = 0.078 \)). As shown in Figure 2, PD MCI patients revealed a tendency of higher variability of visit-to-visit DBP, compared with non-MCI patients (SD values of 7.6 ± 2.7 mm Hg vs. 6.4 ± 1.4 mm Hg, \( p = 0.057 \); CV values of 11.1 ± 4.0% vs. 9.4 ± 2.2%, \( p = 0.080 \), respectively). Moreover, the visit-to-visit HR variability was greater in patients with PD MCI (SD = 8.7 ± 4.2 mm Hg; CV = 11.1 ± 5.9%, respectively) than in those with PD non-MCI (SD = 6.4 ± 2.5 mm Hg, \( p = 0.027 \); CV = 8.0 ± 3.0%, \( p = 0.020 \), respectively). However, there was no difference in the visit-to-visit SBP variability between both of them.

In addition, univariate logistic regression analysis was performed to predict MCI in de novo PD. As shown in Table 4, we found that visit-to-visit HR variability showed a significant risk factor for having MCI in de novo patients with PD.

Additionally, because anti-hypertensive medication could affect the variability of BP or HR, we compared the hypertensive and non-hypertensive PD groups, as shown in Supplementary Table 3 (in the online-only Data Supplement). The BP and HR parameters, including variability, were not different between the groups.

Correlations of cognitive test and visit-to-visit variability of BP or HR

We conducted correlation analyses for each cognitive test of the SNSB and each variability parameter in Supplementary Table 2 (in the online-only Data Supplement). The visit-to-visit SBP or HR variability did not show any correlation with cognitive tests. However, the visit-to-visit DBP variability was connected with memory function. Specifically, the visit-to-visit DBP variability was strongly associated with verbal memory: one test displayed a significant negative correlation (\( r = -0.389, p = 0.007 \)), and the other two tests revealed a tendency for a negative correlation (\( r = -0.283, p = 0.054 \); \( r = -0.273, p = 0.063 \), respectively). In addition, one test of the visual memory domain resulted in a negative correlation with visit-to-visit DBP variability (\( r = -0.316, p = 0.030 \)).

Table 2. Visit-to-visit blood pressure and HR parameters in de novo PD patients with and without MCI

<table>
<thead>
<tr>
<th></th>
<th>Non-MCI (n = 21)</th>
<th>MCI (n = 26)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>126.5 ± 13.4</td>
<td>124.6 ± 10.0</td>
<td>0.592</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>68.5 ± 8.1</td>
<td>68.3 ± 4.9</td>
<td>0.944</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>80.4 ± 12.3</td>
<td>79.2 ± 8.2</td>
<td>0.726</td>
</tr>
<tr>
<td><strong>Maximum values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>143.8 ± 14.4</td>
<td>142.0 ± 12.6</td>
<td>0.655</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>78.6 ± 8.5</td>
<td>80.7 ± 8.1</td>
<td>0.380</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>91.9 ± 14.2</td>
<td>94.1 ± 9.8</td>
<td>0.541</td>
</tr>
<tr>
<td><strong>Minimum values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>110.4 ± 16.1</td>
<td>106.0 ± 10.3</td>
<td>0.287</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>58.8 ± 8.0</td>
<td>56.6 ± 7.0</td>
<td>0.301</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>70.5 ± 10.6</td>
<td>65.4 ± 13.7</td>
<td>0.153</td>
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<tr>
<td><strong>SD values</strong></td>
<td></td>
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<td></td>
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<tr>
<td>SBP (mm Hg)</td>
<td>10.7 ± 4.0</td>
<td>11.8 ± 3.7</td>
<td>0.304</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>6.4 ± 1.4</td>
<td>7.6 ± 2.7</td>
<td>0.057</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>6.4 ± 2.5</td>
<td>8.7 ± 4.2</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>CV values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (%)</td>
<td>8.6 ± 3.4</td>
<td>9.5 ± 2.8</td>
<td>0.333</td>
</tr>
<tr>
<td>DBP (%)</td>
<td>9.4 ± 2.2</td>
<td>11.1 ± 4.0</td>
<td>0.080</td>
</tr>
<tr>
<td>HR (%)</td>
<td>8.0 ± 3.0</td>
<td>11.1 ± 5.9</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. PD: Parkinson’s disease, MCI: mild cognitive impairment, SD: standard deviation, CV: coefficient of variation, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate.

Table 3. ANCOVA for visit-to-visit blood pressure and HR parameters in de novo PD patients with and without MCI

<table>
<thead>
<tr>
<th></th>
<th>PD non-MCI (n = 21)</th>
<th>PD MCI (n = 26)</th>
<th>ANCOVA p value</th>
<th>Bonferroni-corrected p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>126.5 ± 13.4</td>
<td>124.6 ± 10.0</td>
<td>0.356</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>68.5 ± 8.1</td>
<td>68.3 ± 4.9</td>
<td>0.613</td>
<td>NS</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>80.4 ± 12.3</td>
<td>79.2 ± 8.2</td>
<td>0.675</td>
<td>NS</td>
</tr>
<tr>
<td><strong>CV values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (%)</td>
<td>8.6 ± 3.4</td>
<td>9.5 ± 2.8</td>
<td>0.054</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (%)</td>
<td>9.4 ± 2.2</td>
<td>11.1 ± 4.0</td>
<td>0.007</td>
<td>0.042</td>
</tr>
<tr>
<td>HR (%)</td>
<td>8.0 ± 3.0</td>
<td>11.1 ± 5.9</td>
<td>0.013</td>
<td>0.078</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation. Data are adjusted for age, gender, UP-DRS-motor, Depression Scale, MMSE, and levodopa equivalent daily dose. PD: Parkinson’s disease, MCI: mild cognitive impairment, ANCOVA: analysis of covariance, CV: coefficient of variation, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, NS: not significant, UPDRS: Unified Parkinson’s Disease Rating Scale, MMSE: Mini-Mental Status Examination.
Visit-to-visit BP and HR parameters based on RBD-like symptoms or subjective hyposmia

Approximately 28% (13 of 47) and 43% (20 of 47) of the patients reported subjective hyposmia. In Supplementary Table 4 (in the online-only Data Supplement), although the visit-to-visit variability of SBP and DBP showed no difference in subjective hyposmia, visit-to-visit HR variability was significantly increased in the presence of subjective hyposmia. In Supplementary Table 5 (in the online-only Data Supplement), none of the parameters of visit-to-visit variability of BP or HR were dependent on RBD-like symptoms.

DISCUSSION

To our knowledge, this is the first study to demonstrate the relationship between cognition and the visit-to-visit variability of BP and HR in de novo PD patients. The current study showed that MCI was 55% (26 of 47 patients) in drug-naïve PD patients (Figure 1). This high prevalence of MCI in newly diagnosed PD might have been derived from the following: 1) at the beginning of enrollment of de novo PD patients, a total of 54 patients revealed no or minimal structural lesions in brain MRI. Howev-
er, seven patients without MCI were excluded because they were all lost to follow-up before 10 serial office visits. In contrast, all PD patients with MCI and 10 serial visits were included. Thus, the prevalence of MCI in the current study was approximately 48% (26 of the 54 de novo patients). 2) Our Korean cohort revealed a female preponderance, which might affect the prevalence of MCI. In general, the PD population showed a male preponderance. One Korean study with an early PD population revealed a female preponderance in both the MCI and dementia subgroups. However, our point of view remains uncertain and thus should not be generalized.

We found that clinical characteristics, including age, gender, and level of education, did not affect the cognitive impairment in patients with de novo PD (Table 1), although only PD with MCI showed a tendency ($p = 0.082$) of longer duration of education compared with PD without MCI. Disease severity, including total motor score and Hoehn and Yahr stage, depression score, comorbidities, and last PD medications, were not significantly different between the two groups. Moreover, our results showed that the BP or HR parameters, including variability, were not dependent on the usage of antihypertensive agents (Supplementary Table 3 in the online-only Data Supplement). Collectively, our results suggested that we could not predict the existence of MCI in early PD patients according to baseline clinical features.

PD MCI showed significant differences in the visit-to-visit variability of HR and DBP, compared with PD non-MCI. However, the SBP variability was not different between the groups. Consistent with the literature, our findings showed that cardiovascular fluctuation was associated with cognitive impairment, even in the early stage of PD. According to neuropathological studies, α-synuclein aggregates were accompanied by neuronal cell loss in the sympathetic ganglia, indicating that cardiac sympathetic degeneration could lead to visit-to-visit variability in both BP and HR in PD. However, the mechanism of how visit-to-visit variability in BP or HR influence cognitive dysfunction remains unknown, especially in de novo patients with PD. As previously described, the BP variability might predict cognitive deterioration in the elderly or patients with Alzheimer's dementia. Two review articles reported that increased BP variability is related with vascular brain injury, including stroke or asymptomatic brain lesions. Recently, Nagai and Kario proposed the following hypothesis: arterial remodeling induced by high visit-to-visit BP variability might deregulate cerebral circulation and reduce cerebral blood flow; therefore, subsequent silent brain injury could influence cognitive impairment or deterioration. These previous studies demonstrated that cognitive dysfunction was associated with the visit-to-visit variability of SBP rather than that of DBP, while we found that cognitive impairment in PD population was related to DBP and HR variability, apart from SBP variability. Therefore, our results suggested that the pathophysiologic mechanism of BP or HR variability in PD might differ from that in stroke or Alzheimer’s disease.

We correlated each cognitive test with the visit-to-visit variability of SBP, DBP, and HR in Supplementary Table 2 (in the online-only Data Supplement). The DBP variability in PD subjects not only showed a significant association with recognition memory in verbal as well as visual tests but also revealed a negative correlation with verbal and visual recall memory. One group reported that both SBP and DBP variability showed associations with several cognitive deficits, including immediate and delayed memory function, in the elderly. Interestingly, the study revealed that hippocampal atrophy was related to the increased visit-to-visit variability in SBP as well as DBP. Thus, there is a possibility that the BP variability might be associated with the volume of the hippocampus.

In addition, we analyzed whether other non-motor symptoms, including RBD-like symptoms and subjective hyposmia, could affect visit-to-visit BP or HR, respectively. Neither RBD-like symptoms nor subjective hyposmia was related to MCI in patients with PD (data not shown). HR variability was associated with subjective hyposmia but not with RBD-like symptoms (Supplementary Table 1 and 5 in the online-only Data Supplement). Oka et al. previously revealed that olfactory dysfunction might be related to cardiovascular dysfunction in PD. Taken together, our results suggest that a common neurodegenerative pathway or network might be involved in both olfactory and cardiovascular systems in PD.

The present study had several potential shortcomings. First, our study was a retrospectively designed study with a relatively small sample number,
and the baseline neuropsychological assessment and BP/HR variability showed some associations in our study population. However, they could be separate manifestations of the neurodegenerative progression of PD, and our results should be interpreted with caution. Second, although we tried to minimize the effect of vascular burden in the brain by only including patients with no or mild ischemic lesions on their MRI scans, we did not investigate the relationship between vascular lesions and cognitive impairment in the current study. Therefore, we could not rule out the possibility that vascular lesions might affect cognitive impairment in patients with PD. It remains unknown whether subtle ischemic changes could affect our observations. Third, we could not adequately control unknown confounding factors, including visit time. Conversely, this indirectly reflects real clinical settings in the treatment of PD. Fourth, other non-motor symptoms, including RBD-like symptoms and subjective hyposmia, were not checked by using objective assessment tools.

In conclusion, we showed that the visit-to-visit DBP and HR variability might be related to cognitive dysfunction in de novo PD patients. Additionally, the visit-to-visit HR variability was associated with subjective hyposmia, regardless of cognitive impairment. The current study suggests that clinicians should pay more attention to the office BP and HR of patients with PD in clinical practice. Because this study is a preliminary study, well-designed studies with large sample sizes will be required to uncover the detailed relationship between non-motor symptoms, including cognitive dysfunction and cardiovascular variability, in patients with PD.

Supplementary Materials
The online-only Data Supplement is available with this article at http://dx.doi.org/10.14802/jmd.16012.

Conflicts of Interest
The authors have no financial conflicts of interest.

REFERENCES
Hypertension 2011;57:160-166.