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# Different Significances Exist between Steady-State Change of Cerebral Blood Flow and Its Dynamism Depending on the Effect of Drugs in Parkinson's Disease —A Serial Cerebral Blood Flow Single-Photon Emission Computed Tomography (SPECT) Study—

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**Objective**: Parkinson's disease (PD) is a common disorder of the cerebral extrapyramidal system. There remains no definite significance in the distribution of cerebral blood flow decrease in PD. We analyze both steady-state distribution of decrease in the cerebral blood flow and its dynamism induced by the anti-PD drugs.

**Methods**: We performed cerebral blood flow SPECT on 43 patients with PD 2 hours after administration of anti-PD drugs and examined correlation with the clinical features. Fourteen of these 43 patients simultaneously underwent SPECT during the trough state of drugs to assess changes in the distribution profile of blood flow decreases.

**Results**: The steady-state blood flow reduction could be categorized into three groups by visual assessment. The anterior dominant group showed good drug-reactivity, but disease progression and decline in drug-efficacy tended to be faster. The posterior dominant group showed comparatively slower progression. The patchy decrease group showed the poorest drug responsiveness and rapid progression. A lobe level regional quantitative analysis revealed drug-induced dynamic regain of decreased blood flow within the lentiform nucleus correlated with improvement in motor symptoms, whereas the depression in the frontal blood flow was enlarged.

**Conclusion**: Dynamic regain of the decreased blood flow within the lenticular nucleus reflects the drugs reactivity, then the decline in drug-efficacy might dependent upon its blood flow dynamism. On the contrary, the inverse dynamism of flow decrease within the frontal lobe may regulate its excessive non-specific blood flow, resulting in the smooth regulation of voluntary movements.

Key words: Parkinson's disease, cerebral perfusion, antiparkinson drugs, cerebral blood flow SPECT

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## INTRODUCTION

Parkinson's disease (PD) is a chronic progressive neurological disorder that causes motor symptoms of the extrapyramidal system manifesting as resting tremor, muscular rigidity, akinesia/bradykinesia, and postural instability, deriving from the degeneration and loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain[1]. Neural circuits of the basal ganglia, which are initiated by dopaminergic neurons, consist of both the direct pathway immediately through to the globus pallidus interna, and the indirect pathway through to the globus pallidus interna via the globus pallidus externa and the subthalamic nucleus. Both pathways control smooth voluntary movement, in coordination with the hyper-direct pathway of the glutaminergic system from the cerebral cortex[2]. In the patients, these dopaminergic transmissions from the midbrain was pathologically declined, causing dysfunction of the dopamine neural pathways in the basal ganglia. Thus, the first line of PD treatment is the oral administration of dopamine derivatives containing L-dopa, dopamine precursor, and other dopamine agonists. The appearance of the clinical effects of these anti-PD drugs is relatively rapid, time-course dependent and transient, in accordance with the drugs taken. Therefore we believe it would be more useful to elucidate the dynamic effect of anti-PD drugs on the brain in real time, which could allow for expanded practical usage including ascertaining the changes in cerebral function associated with the expression of various motor complications, determining the effect of several economizers, and identifying the impacts of new drugs in the future.

Single-photon emission computed tomography (SPECT) and positron-emission tomography (PET) are widely applied for functional imaging studies of the brains of PD patients, because they allow the objective assessment of lesion spreading from both a structural and functional perspective. Recent progress in these imaging techniques including dopamine transporter (DAT)-SPECT, has resulted in the improvement of diagnostic accuracy, facilitation of early diagnosis, and the determination of therapeutic effects. Nevertheless, cerebral blood flow SPECT is more commonly used because of its ability to allow an assessment of the activity throughout the whole brain. Unfortunately, previous studies applying cerebral blood flow SPECT on PD patients have reported inconsistent and controversial results in the decrease distribution patterns, and no definite pattern in cerebral blood flow changes in PD has been identified[3)4)]. Moreover, although there have been several studies investigating the relationship between the dynamic changes in cerebral blood flow by the L-dopa administration and clinical features[5)~7)], they have not reported in detail by using standardized scale to assess any changes.

In this study, we aimed to investigate both the steady-state distribution of decrease in the cerebral blood flow and dynamic changes brought about by anti-PD drugs using SPECT imaging study. We then analyzed correlation between their findings and the clinical features. In addition, we applied SPECT study to patients with the trough state of drugs, to analyze the change in the distribution profile of the regional blood flow decrease.

## MATERIALS AND METHODS

Forty three patients who met the Brain Bank clinical diagnosis standards[8], receiving administration of anti-PD drugs including L-dopa and dopamine agonists of immediate-release type (levodopa/carbidopa: 150～600 mg, levodopa/

benserazide: 300～750 mg, pramipexole: 0.5～1.5 mg, ropinirole: 3～9 mg, selegiline: 2.5～5.0 mg, pergolide: 750～1000 μg, entacapone: 300～500 mg, amantadine: 50～200 mg, trihexyphenidyl hydrochloride: 2～6 mg, droxidopa: 100～900 mg, zonisamide: 25 mg) were subjected to cerebral blood flow SPECT study conducted 2 hours after anti-PD drug administration. (Table 1; 21 men and 22 women; mean age: 73.1±8.0 years; mean disease duration: 8.5±6.7 years, mean Unified Parkinson's Disease Rating Scale [UPDRS] Part III score, which indicate the degree of motor symptoms, during Off-time: 16.0±9.0; and mean UPDRS Part III score during On-time: 12.5±8.3)

The SPECT system using this study was Infinia; GE healthcare Japan Co., Ltd. The tracer was $^{99m}$Tc-ethyl cysteinatedimer (ECD), which has little effect on the chronological changes in the intracerebral distribution. Each subject received a 600-MBq intravenous injection of $^{99m}$Tc-ECD. Then 9 minutes after the injection of $^{99m}$Tc-ECD, SPECT was performed. An image analysis was performed using voxel-based analysis stereotactic extraction estimation (vbSEE), which is a type of Voxel-Based Morphometry software (FUJIFILM RI Pharma Co., Ltd.). We analyzed the regional cerebral perfusion of the volumes-of-interest (VOI) based on anatomical regions[9]. According to this analysis, we calculated the percentage of decreased blood flow VOI coordinates within the target region (Decrease Extent [%]: number of decreased blood flow coordinates in the target region/number of all coordinates in the target region ×100), that allows for a higher sensitivity of detection for the reduced flow sites than a simple comparison of Z scores would do.

Fourteen of the 43 subjects (Table 1, No. 30～43; seven men and seven women; mean age: 73.4±7.2 years; mean disease duration: 8.0±5.4 years; mean UPDRS Part III score during pre-examination Off-time: 20.4±12.5; mean UPDRS Part III score after anti-PD drug administration during On-time; 16.5±11.7) visited hospital without taking medicine in the morning. Then, they were subjected to cerebral blood flow SPECT study, and analyze the regional perfusion during trough state of anti-PD drugs. Then we assessed the degree of improvement or expansion in the decreased blood flow distribution ratio by calculating the differences in the Decrease Extent in the regional blood perfusion of all VOIs before and after anti-PD drug administration (Degree of change in decreased blood flow: (Off–On) Decrease Extent [%]).

We performed Mini-Mental State Examination (MMSE) and Hasegawa's Dementia Scale for Revised (HDS-R) for all subjects. Both the scores of them caliculated 24 points or more, showing that none had the complication of definite dementia. In addition, we performed the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD)[10] for all subjects. MRI system using this study was MAGNETOM Avanto and Aera (Siemens). Based on the results of our analysis of VSRAD using vbSEE and the easy Z-score imaging system (eZIS)[11], we created difference images for the Z-score map, which allowed us to eliminate the influence of cerebral atrophy on the decreased blood flow.

Clinical symptoms of the subjects were assessed using the UPDRS Part III[12]. We quantitatively determined improvement rate of motor symptoms after administration of anti-PD drugs by calculating the difference between anti-PD drug pre-administration and post-administration values.

The statistical analysis was performed as

Table 1. The clinical profiles

| Case no. | Sex (male, female) | Age, y | Clinical type | Initial symptom | Disease duration, y | Off UPDRS Part III Score | On UPDRS Part III Score | Off–On UPDRS Part III Score | Types of decrease |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 70 | tremor | tremor | 4 | 14 | 6 | 8 | |
| 2 | F | 76 | tremor | tremor | 10 | 33 | 24 | 9 | |
| 3 | M | 71 | tremor | tremor | 4 | 11 | 8 | 3 | |
| 4 | F | 85 | tremor | tremor | 5 | 7 | 5 | 2 | |
| 5 | M | 86 | tremor | tremor | 5 | 13 | 7 | 6 | |
| 6 | F | 66 | tremor | tremor | 10 | 22 | 18 | 4 | anterior dominant |
| 7 | F | 81 | tremor | bradykinesia | 1 | 4 | 3 | 1 | |
| 8 | F | 77 | rigidity | bradykinesia | 3 | 15 | 9 | 6 | |
| 9 | M | 48 | rigidity | bradykinesia | 2 | 14 | 8 | 6 | |
| 10 | F | 87 | rigidity | bradykinesia | 4 | 15 | 6 | 9 | |
| 11 | M | 75 | rigidity | bradykinesia | 6 | 15 | 13 | 2 | |
| 12 | F | 79 | tremor | tremor | 10 | 19 | 17 | 2 | |
| 13 | F | 68 | tremor | tremor | 15 | 13 | 11 | 2 | |
| 14 | M | 72 | rigidity | bradykinesia | 28 | 15 | 12 | 3 | |
| 15 | M | 59 | rigidity | bradykinesia | 14 | 11 | 8 | 3 | |
| 16 | M | 70 | rigidity | bradykinesia | 28 | 21 | 12 | 9 | posterior dominant |
| 17 | F | 74 | rigidity | bradykinesia | 18 | 11 | 9 | 2 | |
| 18 | M | 73 | rigidity | bradykinesia | 10 | 9 | 7 | 2 | |
| 19 | M | 75 | rigidity | bradykinesia | 16 | 16 | 15 | 1 | |
| 20 | M | 70 | rigidity | bradykinesia | 10 | 13 | 12 | 1 | |
| 21 | F | 74 | tremor | tremor | 6 | 11 | 8 | 3 | |
| 22 | F | 65 | tremor | tremor | 6 | 7 | 5 | 2 | |
| 23 | F | 83 | tremor | tremor | 6 | 22 | 20 | 2 | |
| 24 | F | 63 | tremor | tremor | 4 | 10 | 9 | 1 | |
| 25 | M | 76 | rigidity | tremor | 19 | 15 | 14 | 1 | patchy |
| 26 | M | 83 | rigidity | bradykinesia | 2 | 6 | 4 | 2 | |
| 27 | F | 75 | rigidity | bradykinesia | 2 | 17 | 14 | 3 | |
| 28 | M | 73 | rigidity | bradykinesia | 6 | 13 | 12 | 1 | |
| 29 | M | 63 | rigidity | bradykinesia | 1 | 12 | 10 | 2 | |
| 30 | F | 68 | tremor | tremor | 5 | 15 | 10 | 5 | |
| 31 | F | 73 | tremor | tremor | 2 | 10 | 7 | 3 | anterior dominant |
| 32 | M | 71 | tremor | tremor | 5 | 10 | 8 | 2 | |
| 33 | F | 80 | tremor | tremor | 10 | 43 | 33 | 10 | |
| 34 | M | 59 | tremor | tremor | 15 | 12 | 5 | 7 | |
| 35 | M | 81 | tremor | tremor | 3 | 9 | 4 | 5 | posterior dominant |
| 36 | M | 71 | rigidity | tremor | 10 | 28 | 23 | 5 | |
| 37 | F | 73 | tremor | tremor | 3 | 20 | 13 | 7 | |
| 38 | F | 82 | tremor | tremor | 3 | 10 | 9 | 1 | |
| 39 | M | 73 | tremor | tremor | 2 | 3 | 3 | 0 | |
| 40 | F | 65 | rigidity | tremor | 12 | 21 | 19 | 2 | patchy |
| 41 | F | 69 | rigidity | bradykinesia | 13 | 44 | 40 | 4 | |
| 42 | M | 88 | rigidity | bradykinesia | 9 | 32 | 31 | 1 | |
| 43 | M | 75 | rigidity | bradykinesia | 20 | 29 | 26 | 3 | |

No. 1～29; SPECT examinations were conducted 2 hours after anti-PD drugs administraton. No. 30～42; SPECT examinations were conducted 2 hours after anti-PD drugs administration and during trough state.

follows: multiple comparison tests were performed using the Bonferroni method, comparisons between two corresponding groups were performed using the Wilcoxon signed-rank test, and the statistical software used was JMP (SAS Institute Inc.). We assessed correlations using the Spearman's rank order correlation coefficient ($\rho$). The level of significance was set at $P < 0.05$.

## RESULTS

### 1. Correlation between the visual classification of decreased brain blood flow distribution and the clinical features of PD patients

We observed steady-state distribution of decreased cerebral blood flow of the whole brain of 43 patients shown in the SPECT findings 2 hours after anti-PD drug administration. This allowed us to classify the subjects visually into three groups: (1) 16 subjects showed predominantly anterior decline; (2) 12 subjects exhibited predominantly posterior decline; and (3) 15 of the patients presented with patchy decline (Fig. 1a-c). In addition, based on the pre-administration SPECT findings for the 14 patients who underwent SPECT both before and after anti-PD drug administration, we found the same as the post-administration distributions without any inter-pattern shift.

The clinical features of the patients as classified into these three groups are presented in Table 2. There were no patients with psychosis. An analysis of the clinical types of PD indicate that a relatively high number of tremor type cases were in the predominantly decreased anterior blood flow group, whereas a large number of muscle rigidity cases were in the predominantly decreased posterior blood flow group and the patchy decreased group. Although there were no significant differences among the groups in terms of age at the SPECT examination, those in the predominantly anterior decreased group were the oldest age at onset, followed by those in the patchy decreased group and those in the predominantly posterior decreased group, and a significant difference was noted between the predominantly decreased anterior group and the predominant-

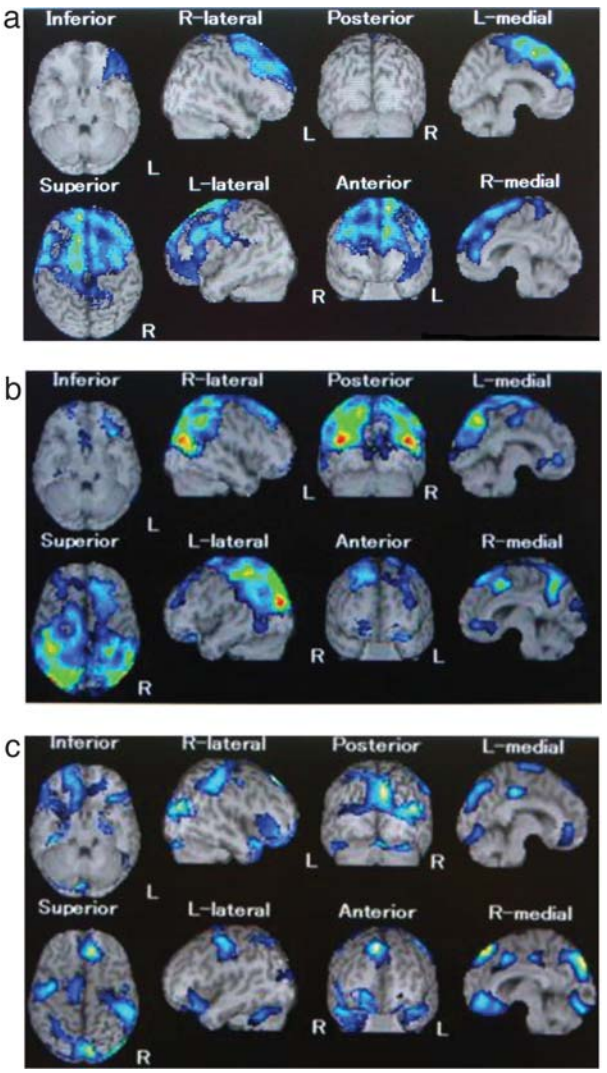


Figure 1. Representative cases of decreased regional cerebral blood flow distribution 2 hours after anti-PD drugs administration.
a: Predominantly anterior decreased blood flow distribution (Table 1: Patient No. 31). b: Predominantly posterior decreased blood flow distribution (Table 1: Patient No. 42). c: Patchy decreased distribution (Table 1: Patient No. 34).

Table 2. The clinical features of the patients as classified three groups

| | anterior dominant | posterior dominant | patchy |
|---|---|---|---|
| Sex (male, female) | 16 (5, 11) | 12 (9, 3) | 15 (7, 8) |
| Age, y | 74.8±9.4 | 70.9±6.4 | 73.2±7.2 |
| Clinical type | tremor 12<br>rigidity 4 | tremor 4<br>rigidity 8 | tremor 6<br>rigidity 9 |
| Age at onset, y | 69.9±9.6* | 56.7±10.2* | 65.8±8.9 |
| Disease duration, y | 4.9±2.6* | 14.2±7.1*# | 7.4±5.9# |
| Off UPDRS Part III Score | 15.7±9.5 | 14.5±4.8 | 17.5±10.6 |
| On UPDRS Part III Score | 10.9±7.6 | 11.3±5.1 | 15.2±10.1 |
| Off–On UPDRS Part III Score | 4.8±2.9S | 3.3±2.4# | 2.3±1.6S# |
| Off UPDRS Part III Score/Disease duration | 3.5±1.4* | 1.3±0.7*# | 3.6±3.0# |
| On UPDRS Part III Score/Disease duration | 2.3±0.9 | 0.9±0.6# | 3.0±2.4# |

*#S P＜0.05 (respectively)

Off UPDRS Part III Score; UPDRS Part III Score during trough state in the morning.
On UPDRS Part III Score; UPDRS Part III Score in steady state 2 hours after anti-PD drugs administration.
Off–On UPDRS Part III Score; Changes in the UPDRS Part III Score before and after anti-PD drugs administration.

ly decreased posterior group (predominantly decreased anterior group: 69.9±9.6 years old, predominantly decreased posterior group: 56.7 ±10.2 years old, P＜0.05). The analysis of the disease duration indicated that patients in the predominantly posterior decreased group had significantly longer disease duration than those in the other two groups (predominantly anterior decreased group: 4.9±2.6 years; predominantly posterior decreased group: 14.2±7.1 years; patchy decreased group: 7.4±5.9 years, the predominantly posterior decreased group to each of the other two comparison: P＜0.05 and P＜0.05, respectively).

Analysis of the relationship between the distribution patterns of decreased cerebral blood flow and the PD symptoms indicated that there were no significant differences among the three groups in terms of the UPDRS Part III scores of both On-time and Off-time. However, change in the UPDRS Part III scores before and after anti-PD drug administration [Off-time–On-time UPDRS Part III score] which represented the response to anti-PD drugs, revealed that the subjects in the patchy decreased group had significantly the worst scores among three groups (predominantly decreased anterior group: 4.8±2.9, predominantly decreased posterior group: 3.3±2.4, patchy decreased group: 2.3±1.6, patchy decreased group to each of the other two comparison: P＜0.05 and P＜0.05, respectively). With regard to the relationship between the types of SPECT findings and disease pathological progression of PD, we compared surrogate values among the groups, which calculated by dividing the UPDRS Part III score during Off-time by the disease duration of each patient. Then the predominantly posterior group was 1.3±0.7, which was significantly the lowest among three groups (predominantly anterior decreased group: 3.5±1.4, patchy decreased group: 3.6±3.0, predominantly posterior decreased group as compared to the other two groups: P＜0.05 and P＜0.05, respectively). About the analysis of the relationship between the types of SPECT findings and the total disease progression of PD-related motor dysfunction including therapeutics was achieved by comparing the groups using another surrogate values calculated by dividing the UPDRS Part

Table 3. On Decrease Ext (%) under normal conditions following anti-PD drugs administration for each VOI at the lobe level

a

| | On Decrease Ext (%) |
|---|---|
| Frontal lobe | 22.2±13.0 |
| Parietal lobe | 22.3±18.4 |
| Temporal lobe | 15.2±10.4 |
| Occipital lobe | 12.4±8.2 |
| Limbic system | 22.2±10.7 |
| Midbrain | 16.3±25.7 |
| Pons | 3.5±12.3 |
| Medulla Oblongata | 1.7±4.8 |
| Carebellum | 12.1±17.0 |
| Lentiform nucleus | 32.4±37.7 |

b

| | Off Decrease Ext (%) | On Decrease Ext (%) | Off-On Decrease Ext (%) |
|---|---|---|---|
| Frontal lobe | 19.5±9.9 | 24.2±12.3 | −4.7±5.2* |
| Parietal lobe | 19.7±16.6 | 18.4±19.4 | 1.3±5.8 |
| Temporal lobe | 11.0±10.8 | 9.7±9.2 | 1.3±3.5 |
| Occipital lobe | 10.0±9.9 | 6.9±8.1 | 3.2±5.8 |
| Limbic system | 17.6±7.4 | 20.5±8.6 | −2.9±4.1* |
| Midbrain | 6.7±19.0 | 9.0±22.0 | −2.3±4.1* |
| Pons | 2.7±10.0 | 2.7±9.2 | 0.02±1.2 |
| Medulla Oblongata | 1.2±4.5 | 1.1±4.1 | 0.1±0.3 |
| Carebellum | 9.8±23.5 | 12.6±27.2 | 2.9±6.9 |
| Lentiform nucleus | 21.5±31.8 | 18.0±32.0 | 3.5±5.5 |

*$P < 0.05$

a; No. 1〜43 The steady state 2 hours after anti-PD drugs administration. b; No. 30〜43 The difference of Decrease Ext (%) before and after anti-PD drugs administration.

III score during On-time by the disease duration. The results revealed that progression was also the most gradual in the predominantly posterior decreased group (0.9±0.6), which had a significant difference to that of the patchy decreased group (3.0±2.4, $P < 0.05$).

**2. Correlation between the percentage of decreased VOI coordinates in lobe level regional blood flow and clinical features**

To more objectively assess the decreased blood flow distributions of the 43 subjects, we calculated the rate of steady-state distribution of decrease in the lobe level regional blood flow after taking anti-PD drugs (On Decrease Extent). The results are shown in Table 3a. The frontal lobe, parietal lobe, limbic system, and lentiform nucleus had relatively high scores of On Decrease Extent, and the temporal lobe, and occipital lobe, midbrain including substantia nigra, and cerebellum showed moderate scores. The ratios of decreased blood flow area were small in the pons and medulla oblongata. In addition, the analysis of 14 subjects that underwent SPECT studies both before and after anti-PD drug administration indicated that the area of decreased blood flow in each of the frontal lobe, limbic system, and midbrain significantly expanded after drugs administration. In contrast, it tended to decrease in size in the occipital lobe, cerebellum, and lentiform nucleus, though with no significance (Table 3b).

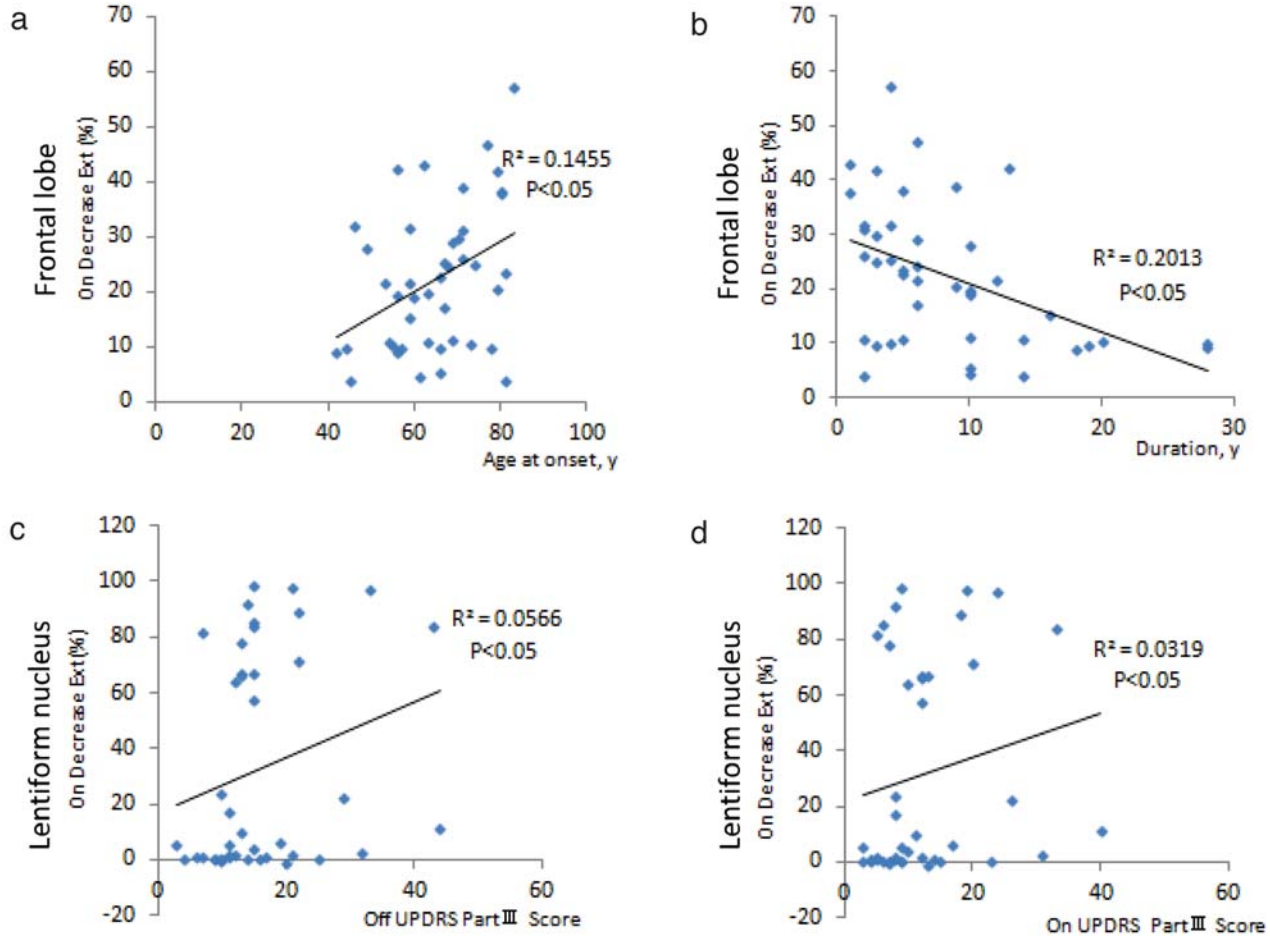


Figure 2. We investigated the correlation between the lobe level distribution rates of regional cerebral blood flow decrease, calculated by SPECT data, and clinical features.
a and b: The distribution rate of regional blood flow decrease in the frontal lobe was correlated, positively with age at onset and negatively with disease duration ($P<0.05$ and $P<0.05$, respectively). c and d: The distribution rate of regional blood flow decrease in the lentiform nucleus was correlated, both with the Off-time UPDRS Part III score during trough state and the On-time UPDRS Part III score after anti-PD drugs administration ($P<0.05$ and $P<0.05$, respectively).

### 3. Correlation between the distribution rate of the decreased regional blood flow in the SPECT findings, obtained from each before and after anti-PD drug administration, and clinical features

We investigated the correlation between the distribution rate of the reduced regional cerebral blood flow for each lobe during On-time, and their associated clinical features. In the frontal lobe, there was a significantly positive correlation between the decreased blood flow distribution rate and age at onset, and was a negative correlation between the decreased blood flow distribution rate and disease duration (Fig. 2a and b, $P<0.05$ and $P<0.05$, respectively). In addition, the analysis of the lentiform nucleus, indicated that there was a significantly positive correlation between the decreased blood flow distribution rate and the UPDRS Part III scores each of before and after anti-PD drug administration (Fig. 2c and d, $P<0.05$ and $P<0.05$, respectively). Correlations

were not observed between decreased cerebral blood flow distribution rates and clinical features in the other regions.

We also investigated into the relationship between the distribution rates of the decreased regional cerebral blood flow during Off-time, and clinical features in 14 subjects who underwent SPECT study before drugs administration, which brought no significant correlations for any of the regions.

**4. Correlation between changes in the distribution of decreased regional cerebral blood flow affected by anti-PD drugs and clinical features**

We investigated the correlation between the changes in the distribution of the decreased regional cerebral blood flow, as (Off–On) Decrease Extent (%), and clinical features of the 14 subjects that underwent SPECT examinations both before and after anti-PD drug administration.

The distribution of the decreased regional cerebral blood flow after anti-PD drugs administration in the frontal lobe tended to dynamically expand, and the rate of expansion was significantly correlated with the degree in improvement of motor symptoms [Off-time–On-time UPDRS Part III] (Fig. 3, $P<0.05$). On the contrary, the distribution of the decreased re-

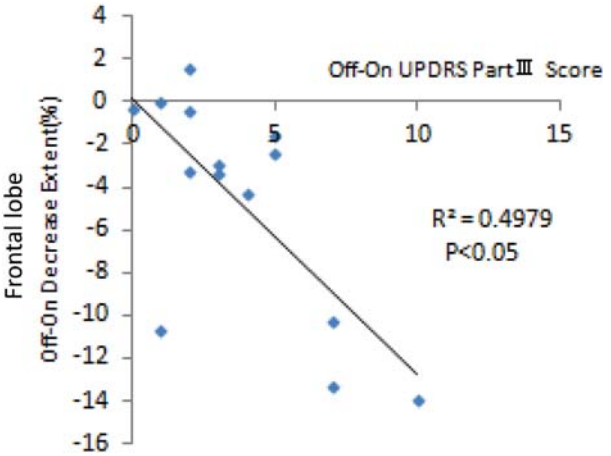


Figure 3. In the frontal lobes of 14 subjects who underwent SPECT examinations before and after anti-PD drugs administration (Table 1: patient No. 30～43), there had a significant correlation between the degree of expansion in the distribution rate of regional blood flow decrease (Off–On Decrease Extent [%]) and the degree in improvement of motor symptoms (Off–On UPDRS Part III score, $P<0.05$).

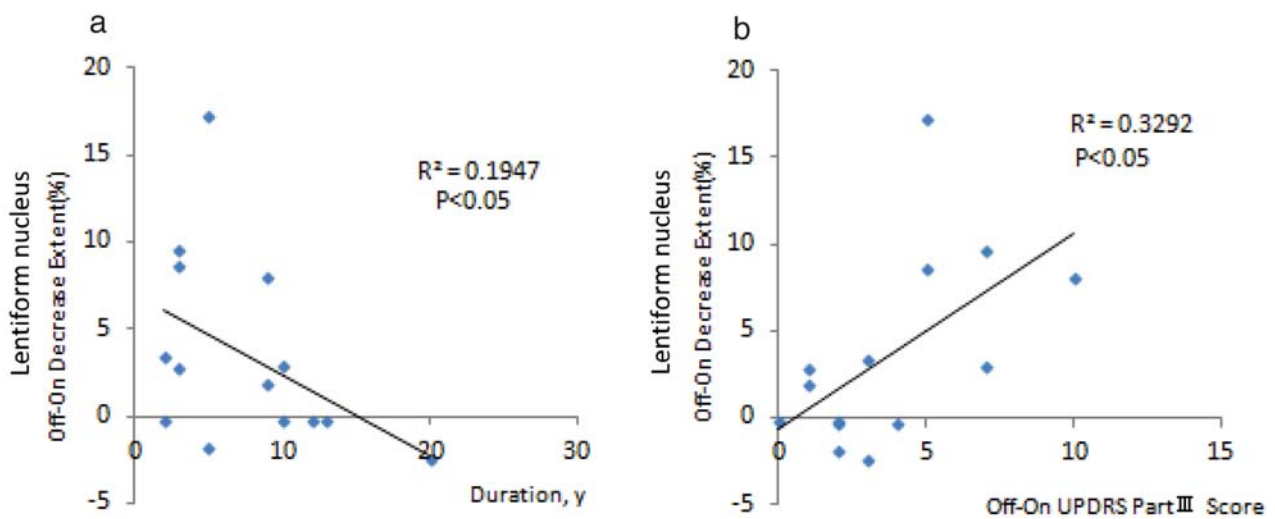


Figure 4. a: In the lentiform nuclei of 14 subjects who underwent SPECT examinations before and after anti-PD drugs administration (Table 1: patient No. 30～43), the recovering in blood flow decrease after drugs administration correlated negatively with disease duration ($P<0.05$). b: And also, it correlated positively with the degree in improvement of motor symptoms ($P<0.05$).

gional blood flow in the lentiform nucleus tended to dynamically decline, in other words, blood flow tended to improve, by the anti-PD drugs administration. Significantly, the rate of this dynamic improvement of blood flow was inversely correlated with disease duration, and was positively correlated with the rate of improvement in motor symptoms (Fig. 4a and b, $P < 0.05$ and $P < 0.05$, respectively).

## DISCUSSION

Although there have been numerous studies using SPECT investigating changes in cerebral blood flow with PD, their results have not elucidated some consistent conclusions. Really, cerebral blood flow SPECT is commonly applied for the patients as one of clinical examinations of PD, though limiting to visual assessments of decreased blood flow distribution patterns in many cases. Therefore, there remains room for improvement regarding its usefulness in clinical and diagnostic applications. Our visual assessments of the decreased cerebral blood flow distribution under steady-state conditions allowed us to classify the subjects into the three groups of predominantly anterior decreases, predominantly posterior decreases, and patchy decreases. Our comparison of the clinical features among the groups indicated that the predominantly anterior decrease group was relatively older at onset (69.9 years), and had a relatively shorter duration of 4.9 years. In contrast, the predominantly posterior decrease group was significantly younger age at onset of 56.7 years old than those in the predominantly anterior decrease group, and had significantly the longest duration of 14.2 years among these three groups. More meaningfully, the predominantly anterior decreased group, although exhibiting a good response to the drugs, tended to have more quickly progressing disease pathology. The predominantly posterior decreased group also had a relative good response to the drugs, but was different from the predominantly anterior decreased group as disease progression was relatively slow. The patchy decrease group exhibited the worst drug response of all three groups, as well as the worst disease progression, and NET extrapyramidal deterioration. Although the study is a retrospective and will be expected to conduct with larger subjects, these results of steady-state SPECT data could be useful for planning systematically the therapeutic strategies based on considering necessity of the long-term treatment with PD.

In this SPECT study, we quantitatively ascertained the lobe level regional changes in cerebral blood flow in patients with PD using VOI analysis, then conducted a detailed investigation of the relationship between changes in cerebral blood flow and the clinical condition of PD. Under usual medical settings, we have interpreted serial SPECT findings without precisely taking into consideration the real-time effects of drugs. Therefore, we tried to elucidate the time-related effects of anti-PD drugs on regional cerebral blood flow, by performing SPECT examinations on each patient both before and after drug administration. The results indicated that the distribution of the regional blood flow reduction in the frontal lobe, limbic system and midbrain tended to expand after drugs administration. Although the cause of this is unclear, at least in the midbrain, anti-PD drugs administration may cause for a negative feedback on some remaining dopaminergic neurons.

Concerning the lentiform nucleus, we analyzed the relationship between the distribution of its regional blood flow reduction and the clinical conditions of motor symptoms. Then

UPDRS Part III scores of both pre- and post-administrations were positively correlated with the distribution rate of regional blood flow decrease after drugs administration, meaning that the better the motor function was, no matter how the patient during Off-time or On-time, the smaller the distribution of regional blood flow decrease in the lentiform nucleus would be. Moreover, the extent of recovering for the decreased blood flow distribution after drugs administration was significantly related to the degree of improvement in motor symptoms by the drugs. Previously, there has been reported that breakdown of dopaminergic neurons in rats exhibited increased regional blood flow in the lentiform nucleus after L-dopa administration measured by autoradiography[13]. The other reports of cerebral blood flow measurements obtained using Xe-CT and SPECT before and after L-dopa therapy revealed significantly elevated levels in the basal ganglia[14)~17)]. And researches into dopamine metabolism in the basal ganglia using [$^{18}$F]DOPA PET and [$^{123}$I]$\beta$-CIT SPECT have reported a decline in the uptake into the corpus striatum[18], indicating that the degree of the decline in ligand uptake was correlated with PD severity, and moreover, these declines in uptake indicated that some recovery was achieved by the anti-PD drugs. In light of these previous reports, the results of our study suggest that steady-state condition of decreased regional blood flow and the extent of its dynamic recovering in the lentiform nucleus might reflect disease progression of PD and the responding capacity to the anti-PD drugs, respectively. And considering together with the fact in this study that there was a negative correlation between the recovering in blood flow decrease and disease duration, a decline in response to the drugs resulted from the longer-term medication of PD could be depended upon blood flow dynamism in the lentiform nucleus.

Our SPECT analysis of the frontal lobe indicated that there was no significant correlation between steady-state distribution of regional blood flow decrease before taking anti-PD drugs and any item of the clinical features (data not shown). Therefore, steady-state decrease in the frontal lobe regional blood flow may have minimal direct relation to the pathological condition of PD. On the other hand, the distribution rate of regional blood flow decrease after anti-PD drugs administration correlated positively to age at onset and negatively to the disease duration but did not correlate with the extrapyramidal symptoms. In addition, after taking drugs, the distribution of regional blood flow decrease dynamically expanded as compared to that before drugs administration, and this expansion negatively correlated to the change in improvement of motor symptoms of [Off-time–On-time UPDRS Part III]. In other words, the more the anti-PD drugs worked, the larger the distribution of regional blood flow decrease in the frontal lobe would be. The mechanism of this dynamic expansion in the distribution of regional blood flow decrease in the frontal lobe after taking anti-PD drugs could not be elucidated within the scope of this study. However, considered in the results of previous brain functional imaging studies using magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI) and other techniques, the mechanism may involve the regulation of non-selective blood flow based on secondary efficient selection via the activation of networks in the frontal lobe, including the prefrontal area and the supplementary motor area, that would be induced in association with the alleviation of dopaminergic transmitting dysfunction in the

basal ganglia by the administration of anti-PD drugs[19)~21)].

Recently, the development of highly disease specific tracers made resulted in the more active conduction of functional images of dopamine brain metabolism using [$^{18}$F]-DOPA PET and dopamine transporter (DAT) SPECT. Studies on [$^{18}$F]-DOPA PET have reported a metabolic increase in the ventral portion of the putamen and metabolic decline in the parietal lobe[22)]. In addition, DAT SPECT studies have revealed decreased uptake within the corpus striatum, particularly in the unaffected side of the putamen during the incipient stage of the disease[23)], that is attracting attention as a method for the diagnosis of PD in the prodromal stage, but that is inappropriate as a determinant of disease severity because of not having correlation with the UPDRS score[24)]. Nevertheless, cerebral blood flow SPECT has the substantial merit of using a standardized tracer of low-cost, and being universally and simply available. We believe that significance of both steady-state change in cerebral blood flow and its dynamism by the effect of drugs in PD, as shown by our cerebral blood flow SPECT study, should make the treatment of patients with PD more elaborate and fruitful.

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