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Effects of Levodopa on Vowel Articulation in Patients with Parkinson's Disease

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ABSTRACT

Objectives. The effects of levodopa on articulatory dysfunction in patients with Parkinson's disease remain inconclusive. This study aimed to investigate the effects of levodopa on isolated vowel articulation and motor performance in patients with moderate to severe Parkinson's disease, excluding speech fluctuations caused by dyskinesia.

Methods. 21 patients (14 males and 7 females) and 21 age- and sex- matched healthy subjects were enrolled. Together with motor assessment, the patients phonated five Japanese isolated vowels (/a/, /i/, /u/, /e/, and /o/) 20 times before and 1 h after levodopa treatment. We made the frequency analysis of each vowel and measured the first and second formants. From these formants we constructed the pentagonal vowel space area which should be the good indicator for articulatory dysfunction of vowels. In control subjects, only speech samples were analyzed. To investigate the sequential relationship between plasma levodopa concentrations, motor performances, and acoustic measurements after treatment, entire drug cycle tests were performed in 4 patients.

Results. The pentagonal vowel space area was significantly expanded together with motor amelioration after levodopa treatment, although the enlargement is not enough for the space area of control subjects. Drug cycle tests revealed that sequential increases or decreases in plasma levodopa levels after treatment correlated well with expansion or decrease of the vowel space areas and improvement or deterioration of motor manifestations.

Conclusions. Levodopa expanded the vowel space area and ameliorated motor performance, suggesting that dysfunctions in vowel articulation and motor performance in patients with Parkinson's disease are based on dopaminergic pathology.

INTRODUCTION

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons primarily in the substantia nigra [16]. Dopaminergic impairment is associated with a variety of motor and nonmotor deficits, and the most characteristic symptoms are muscular rigidity, tremor, bradykinesia, and postural instability [20].

In addition, up to 70% of the patients with PD (PD patients) develop distinctive hypokinetic dysarthria [26]. Parkinsonian dysarthria is characterized by a monotony of pitch and loudness, decreased stress, a variable rate of speech, imprecise consonants, and a breathy and harsh voice [1,6]. These disturbances are attributed to bradykinesia and hypokinesia of speech organ movements [3,11].

Although levodopa is shown to be the most reliable pharmacological treatment for PD, its effect on parkinsonian dysarthria remains inconclusive. Some previous studies showed the improvement in phonation [29] and speech intelligibility [8,9] after treatment, while others revealed no effects of dopaminergic therapy on articulation [27,34,35], phonatory parameters [12,13,34], and prosody [17,33,34].

With regard to the articulatory dysfunction in PD patients, some kinematic and electromyographic studies focusing on the neurophysiology of speech articulators showed beneficial effects of levodopa on labial rigidity [4], lip muscle activation patterns [22], and mandibular movements [37], whereas others described no changes in tongue force measurements [7] and oral pressure [36] after medication. Moreover, acoustic studies reported no significant improvement in articulatory parameters after dopaminergic treatment; Skodda et al. [34] examined 23 patients with early-stage PD and found no significant improvement in articulation after short-term and long-term levodopa treatment, although they found some single individuals with amelioration. Poluha et al. [27] investigated 10 patients with mild to severe PD and found no change in acoustic measurements.

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In patients with the advanced stage of disease, however, chronic levodopa treatment is complicated by dyskinesia, which may have an additional impact on speech performance [9,34]. Dyskinesia can cause vocal tract instability that induces excessive formant fluctuations, even during steady vowel articulation [11]. Therefore, in our study, isolated vowels were used for acoustic analyses to exclude the influence of dyskinesia, although many previous studies used embedded vowels during reading tasks [8,9,13,27,34,35]. During reading tasks, including the combination of consonants and vowels, it may be difficult to extract steady-state vowel formants because of a coarticulatory effect, particularly in the presence of dyskinesia.

For the index of acoustic parameters showing dysarthria, we measured the vowel space area (VSA) obtained from characteristic resonant frequencies determining each vowel, namely first formant (F1) and second formant (F2). The movements of the tongue, lips, and jaw form vowels by creating oropharyngeal resonating cavities, which amplify certain frequency bands of the voice spectrum. These harmonics, called formants, show their typical distinct peaks of acoustic energy in each vowel. The F1 and F2 formant are essential in determining each vowel articulation. The plotting of F1 frequency as a function of F2 for 5 vowels (/a/, /i/, /u/, /e/, and /o/) provides a graphic display of a pentagonal vowel space area (pVSA). It has been well established that, in most types of dysarthria, the VSA is reduced because of the limited movement of articulators, which lead to formant centralization and disturbance of vowel articulation [31,32,40]. Thus, the analysis of vowel formants and the pVSA should be a good indicator of vowel articulation in parkinsonian dysarthria.

Taking these problems into consideration, this study aimed to investigate the effects of levodopa on isolated vowel articulation, motor performance, and perceptual speech assessment in patients with moderate to severe PD before (OFF state) and 1 h after (ON state confirmed by motor improvements) levodopa administration and to compare the results of acoustic analysis for PD patients after treatment with those for healthy subjects. Further to investigate the sequential relationship between plasma levodopa levels, motor responses, and articulatory measurements after treatment, the entire levodopa cycle tests were performed in 4 patients with advanced PD.

SUBJECTS AND METHODS

Patients and healthy subjects

Twenty-one patients (14 males, 7 females; age range, 49–88 years; mean age, 65.6 years) with idiopathic PD who were hospitalized at the National Center Hospital of Neurology and Psychiatry and 21 sex- and age- matched control subjects participated in this study. PD diagnosis was based on UK Parkinson's Disease Society Brain Bank Criteria [19]. The disease duration averaged 8.7 (2.5–26) years. The mean Hoehn–Yahr stage was 3.7 (3–5) in the worst OFF state and 3.0 (2–4.5) in the best ON state. None of these patients experienced the on–off phenomenon during examination. Eleven patients had developed dyskinesias. All patients scored ≥1 on "speech" item 18 of the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) during the OFF state.

Twenty patients were receiving dopaminergic therapy comprising levodopa, various dopamine agonists, MAO-B inhibitors, COMT inhibitors, and amantadine, as well as anticholinergic drugs and droxidopa before hospitalization, with the mean duration of levodopa therapy being 5.8 (0.5–23) years. One patient (Case 7) was newly diagnosed with PD at hospitalization and had no history of prior medication. Eligible patients were all native Japanese speakers (Tokyo dialect, standard Japanese) with no hearing disorders. Severe cognitive deterioration was ruled out by the Mini-Mental State Examination Test (MMSE); all patients scored ≥24. The demographic and clinical characteristics of the patients are summarized in Table I.

This study was approved by the ethics committee of the National Center Hospital of Neurology and Psychiatry, and all patients provided informed consent prior to study participation.

Experimental procedure

Tests for PD patients were performed early in the morning. Medication and food were withheld from 9:00 pm on the evening prior to the test till completion. Levodopa treatment (levodopa 100 mg/carbidopa 10 mg) was administered per os at 8:00 am. Before and 1 h after medication, speech samples were recorded for each patient using a tape recorder (TCM48, Sony, Tokyo, Japan) and digital IC recorder (DM-20, Olympus, Tokyo, Japan) with a microphone positioned 5 cm from the lips according to the standard protocol for vowel phonation. Motor performance was evaluated using UPDRS-III and finger tapping counts of the more afflicted side (tapping of thumb and pointing finger from a distance of 3 cm for 15 s; the average of 3 trials was used for analysis), and perceptual speech impairment was assessed using item 18 of the UPDRS-III. All patients were responsive to levodopa as judged by UPDRS-III and finger tapping, confirming that they were in the ON state 1 h after medication (Table I).

For the control subjects, only speech samples were recorded without medication and motor tests.

Table I. Summary of Clinical Characteristics of Subjects

Case number	Age & sex	Duration of disease (years)	Duration levodopa therapy (years)	Usual drugs*	UPDRS part III		UPDRS speech item 18		Finger tapping counts (/15sec)		Hoehn & Yahr stage		Dyskinesia (ON)†	MMSE
					OFF	ON	OFF	ON	OFF	ON	Best on	Worst off		
1	70M	16	6	S,C,Pr,T	72	40	2	1	34	46	4.5	5	++	30
2	49M	4	3	S,C,Pr,T	20	8	2	2	43	51	3	3	+	27
3	78F	26	23	S,C,Pr,Am	47	28	2	2	37	47	4	4.5	++	28
4	67M	7	4	M,Pr,E,A	38	14	2	1	40	56	2.5	4	+	30
5	64M	7	3	M,E	35	24	1	1	42	52	3	3	+	30
6	88F	5	2	S,Pr	44	35	2	1	36	43	4.5	5	−	24
7	60F	2.5	0	None	24	10	1	1	44	54	3	3	−	25
8	76M	7	4	S,Am	43	34	1	1	31	40	4.5	5	−	24
9	68M	6.5	6.5	S,C,Pr,Am	19	14	1	1	43	54	2.5	3	−	29
10	68F	6	2	S,C,Pr,D	35	17	1	1	43	52	3	3	−	24
11	52M	4	3.5	M,Pr	17	8	1	1	42	52	2	3	−	30
12	57M	14	6.5	M,R	40	23	1	1	31	52	3	4.5	+	30
13	56M	9	8	S,P,Se,E,A	43	17	2	2	19	35	2.5	4.5	+	30
14	68M	10	8	M,C,Pr,Se	20	10	1	1	41	50	3	3	+	29
15	65F	11	10	S,Se,Am	20	8	1	1	43	53	2	3	−	26
16	61M	8	8	S,C,R,Am	26	9	1	1	45	56	2.5	3	−	30
17	55F	6	5	S,C	34	14	1	1	38	56	3	3.5	+	30
18	65M	14	9	S,Pr,E,D	46	18	2	1	39	50	2.5	4.5	+	24
19	65F	7.5	7	M,R,E	36	20	2	1	37	46	3.5	4	++	30
20	74M	5	0.5	S	33	14	2	2	44	56	3	3	−	26
21	71M	7	2	M,P,Se	18	8	1	1	48	55	2	3	−	28

* Traditionally utilized anti-parkinsonian drugs: levodopa/carbidopa (S), levodopa/benserazide (M), pergolide (P), talipexole (T), cabergoline (C), ropinirol (R), pramipexole (Pr), entacapone (E), selegiline (Se), amantadine (Am), droxidopa (D), and anticholinergic agents (A). † Presence of dyskinesia: absent (−), mild (+), severe (++).

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination.

Measurement of vowel formants and pentagonal vowel space area (pVSA)

Articulatory function was assessed using 5 Japanese vowels /a/, /i/, /u/, /e/, and /o/. All subjects were asked to phonate each isolated vowel for over 0.4 s in a series at a comfortable frequency and intensity level. In PD patients with chronic levodopa treatment, involuntary movements such as dyskinesia in the muscles of the oropharyngeal tract, which provide vocal tract instability, can cause excessive fluctuations in acoustic measurements during vowel articulation. To avoid this difficulty, patients repeated each vowel 20 times, and an acceptable 15 of 20 speech samples which showed steady-state vowel formant without influence of dyskinesia were selected for acoustic analysis. In the acoustic analysis of each isolated vowel used in our study, oropharyngeal dyskinesia could be well identified as the excessive fluctuation of F1 and/or F2 formant tracking with various amplitude and duration [11].

Formant frequency was analyzed using computer software (SUGI Speech Analyzer 1.0.0.4, Fujitsu–Animo, Yokohama, Japan). Both wideband spectrographic displays and linear predictive coding (LPC) spectra were used to determine formant frequencies. The F1 and F2 formant values of each respective vowel were measured using a 32-ms window centered at the temporal midpoint of each vowel to decrease the effects of articulatory onset and offset [29]. These formant data (F1/a/, F1/i/, F1/u/, F1/e/, F1/o/, F2/a/, F2/i/, F2/u/, F2/e/, and F2/o/, where F1/a/ is the frequency of first formant of the vowel /a/, F2/o/ is the frequency of the second formant of the vowel /o/, and so on) were based on 15 repetitions and were separately averaged for each individual before and after treatment. The average of 15 formants of each respective vowel was used as a representative of the speech variable of each patient. The pVSA was then constructed by plotting F1 frequency as a function of F2 frequency for the 5 vowels and figured for each patient before and after levodopa treatment. In the healthy subjects without involuntary movement, they phonated each vowel 15 times from which F1, F2, and pVSA were determined.

Levodopa cycle test and determination of plasma levodopa concentrations

To investigate the sequential relationships between plasma levodopa concentrations, acoustic parameters and motor responses after medication in 3 patients (Case 4, 6, and 7), plasma levodopa concentrations were determined in parallel with recording of speech samples and examination of motor performance just before and 0.5, 1, 2, 3, and 4 h after medication delivered in one drug cycle. In one patient (Case 1), two cycles of levodopa treatment were administered continuously in series for 10 h after the first administration.

To measure plasma levodopa concentrations, blood samples (2 ml) were collected in heparinized syringes chilled on ice and promptly centrifuged at 2000 rpm. $HClO_4$ (50 µl of 60%) was added to 500 µl of supernatant and the whole solution was stirred and centrifuged at 14,000 rpm for 20 min at 4°C. The resulting supernatant was applied to high-performance liquid chromatography (CoulArray; ESA) for determination of levodopa concentrations. The detail of the assay method was reported elsewhere [24].

Statistical analyses

SPSS Statistics for Windows (version 22.0, IBM Corp., Armonk, NY, USA) was used for statistical analyses. The paired t-test was separately performed to examine group differences in acoustic variables (F1/a/, F1/i/, F1/u/, F1/e/, F1/o/, F2/a/, F2/i/, F2/u/, F2/e/, F2/o/, and pVSA) before and 1 h after treatment. The results of mean pVSA between PD patients after treatment and healthy subjects were compared using t-test. The level of significance was set at $p = 0.05$. In addition, to control the familywise error rate, statistical analysis for each set of F1 and F2 formants of 5 vowels was tested using the adjusted significant level at $p = 0.01$ for the Bonferroni method.

RESULTS

(1) F1, F2 frequencies and pVSA in the control subjects

One of the examples of the demographic recordings of acoustic waveform, wide-band sound spectrogram, F1 and F2 frequencies of 5 vowels phonated by a control subject was shown in Figure 1A. The mean frequency of F1/a/, F1/i/, F1/u/, F1/e/ and F1/o/ value of 21 healthy subjects was 814 ± 81, 338 ± 60, 444 ± 91, 583 ± 75 and 588 ± 62 Hz, and the mean frequency of F2 /a/, F2/i/ F2/u/, F2/e/ and F2/o/ was 1291 ± 124, 2308 ± 231, 1069 ± 183, 1984 ± 208 and 931 ± 98 Hz, respectively. The size of the pVSA for each subject was calculated by Euclidean distances between the F1 and F2 coordination of 5 corner vowels /a/, /e/, /i/, /u/, and /o/ in the F1–F2 plane. The mean pVSA was 305037 ± 68773 Hz2 (Figure 1B).

(2) Analysis of motor and perceptual speech performance of PD patients in the OFF and ON state

The mean motor score of all 21 patients as measured by the UPDRS-III improved with levodopa treatment from 33.8 ± 13.1 in the OFF state to 17.8 ± 9.4 in the ON state ($p < 0.001$). Finger tapping counts per 15 s were also increased from 39.0 ± 6.3 to 50.3 ± 5.5 after treatment ($p < 0.001$) (Table I). Global speech impairment as assessed by item 18 of the UPDRS-III was comparable before and after treatment (1.43 ± 0.51 vs. 1.19 ± 0.40).

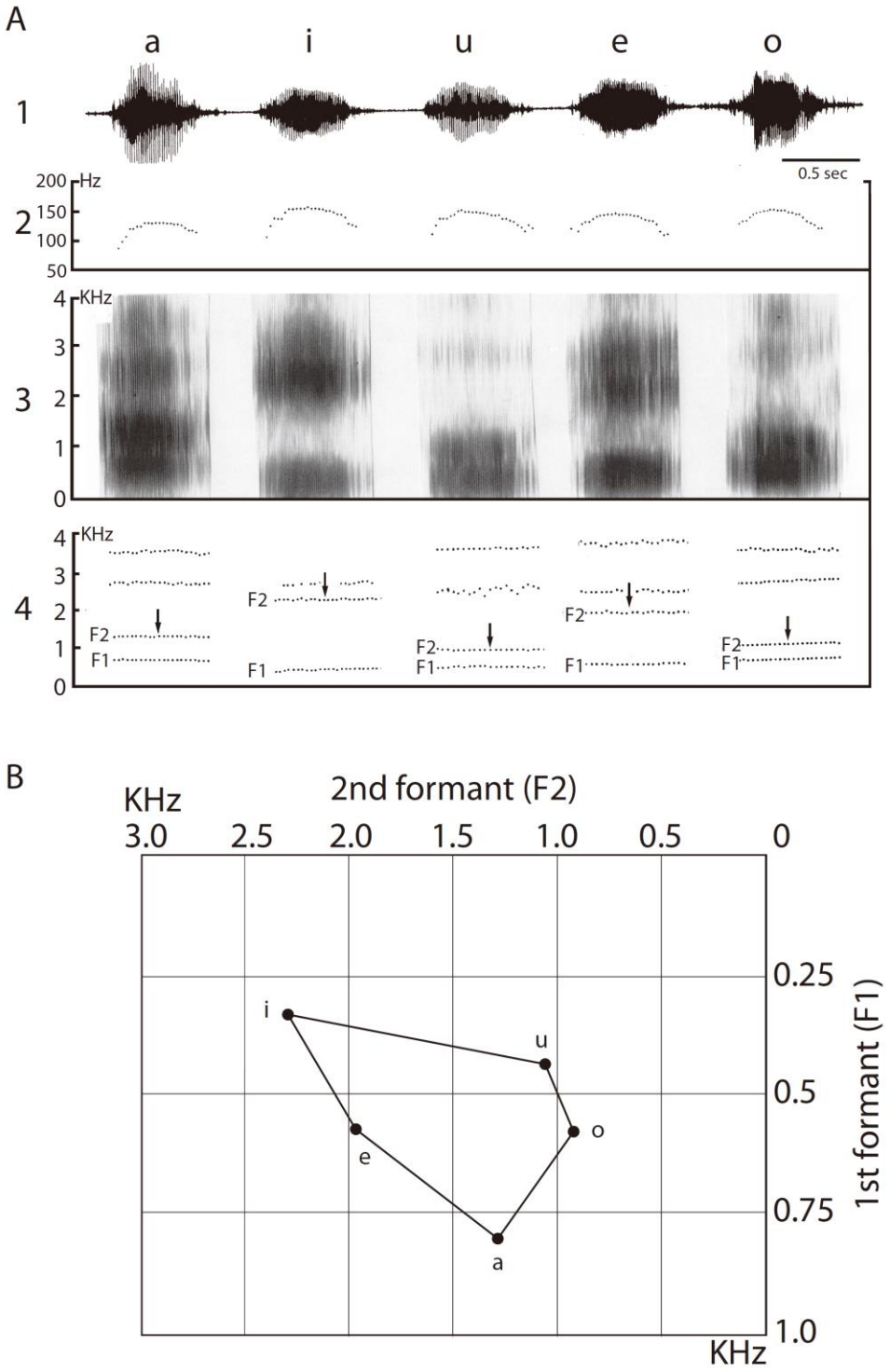

Figure 1. (A) shows demographic recording of acoustic waveform (1), fundamental frequency, F0 (2), wideband sound spectrogram (3), and formant tracking (4) of 5 isolated vowels phonated by a healthy subject. The thick vertical arrows indicate the temporal midpoint of phonated vowel sounds when F0, F1 and F2 values were determined. (B) shows the pentagonal vowel space area (pVSA) obtained from the mean F1 and F2 frequencies of each vowel of 21 control subjects.

(3) Formant analysis of 5 isolated vowels and pVSA of PD patients in the OFF and ON state

Figure 2A shows an example indicating changes in the F1 and F2 formants for each vowel of a PD patient (Case 4) in the OFF and ON state. Each point (●) indicates the mean F1 and F2 values for each vowel obtained from 15 phonations. In the ON state, both F1 and F2 frequency increased for vowel /a/, F1 decreased and F2 increased for vowel /i/, both F1 and F2 decreased for vowel /u/, F1 and F2 frequency increased for vowel /e/, and F1 increased and F2 decreased for vowel /o/.

Using the relationship between the F1 and F2 frequencies for the 5 vowels of this patient in the OFF and ON state, pVSAs were constructed (Figure 2B). Levodopa treatment dramatically expanded the pVSA (encircled with solid line), which was compressed in the OFF state (dotted line). For the other 20 patients, the F1 and F2 formant frequencies were measured and pVSAs were constructed in a similar manner. Figure 3 shows the changes in the pVSA for each of the 21 patients in the OFF and ON states. Each histogram indicates the pVSA of an individual patient before (gray histogram) and after (black histogram) treatment. In 16 of the 21 patients, pVSA increased after treatment, whereas in other patients (Cases 7, 8, 10, 12, and 14), there was no marked increase in pVSA. The mean pVSA for the 21 patients significantly expanded from 190421 ± 84178 to 241171 ± 72610 Hz2 after treatment (95% CI = −72722.2 to −28837.8, $p < 0.001$). However this expanded pVSA after levodopa treatment (241171 ± 72610 Hz2) was smaller than pVSA of control subjects (305037 ± 68773 Hz2) and the difference of pVSA between control subjects and patients after treatment was significant (95% CI = −107721.2 to −19321.7, $p = 0.006$).

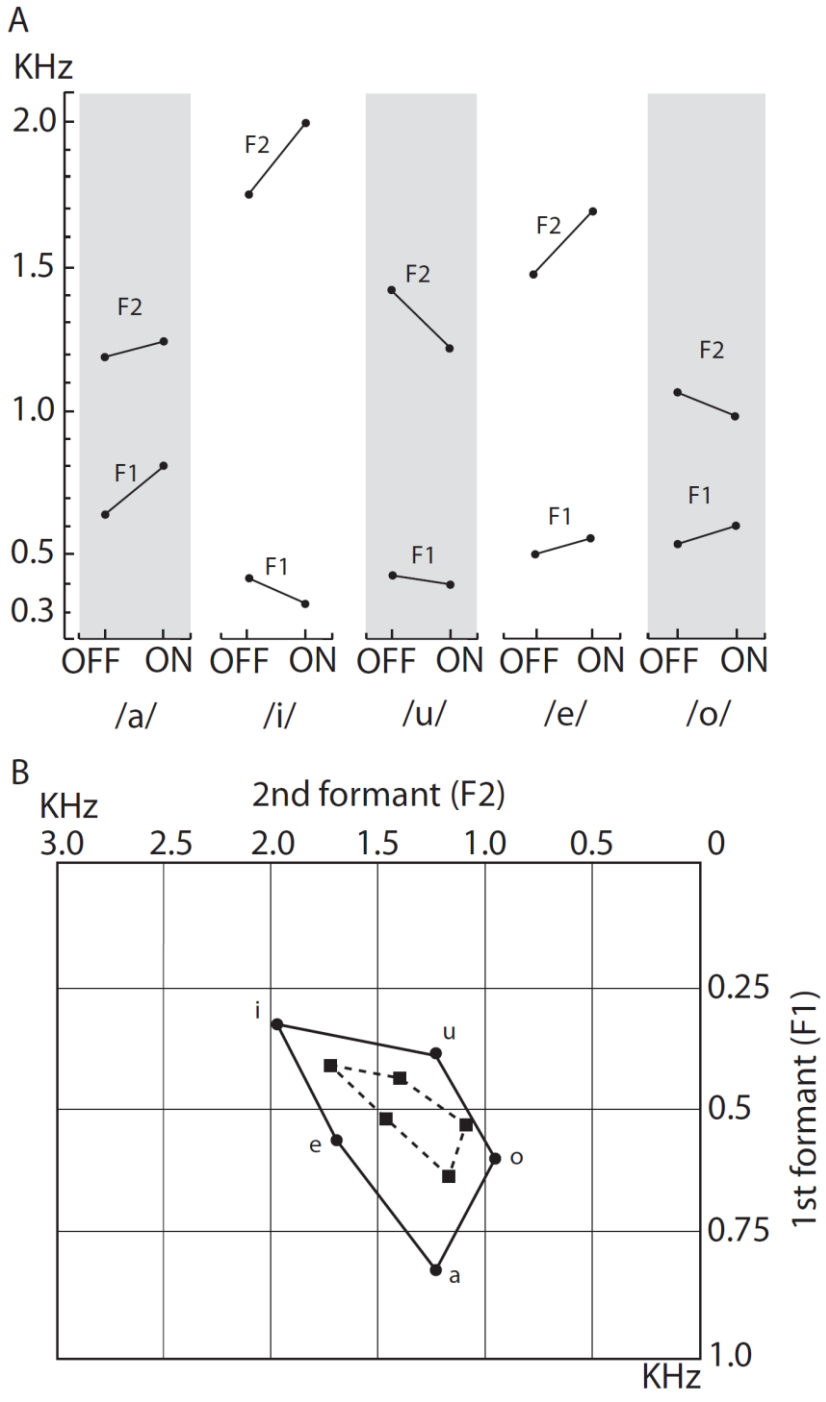

Figure 2. (A) Changes in the F1 and F2 formants of 5 vowels in the OFF and ON states in a single patient (Case 4). (B) Pentagonal vowel space areas obtained from the same patient in the OFF (■) and ON (●) states.

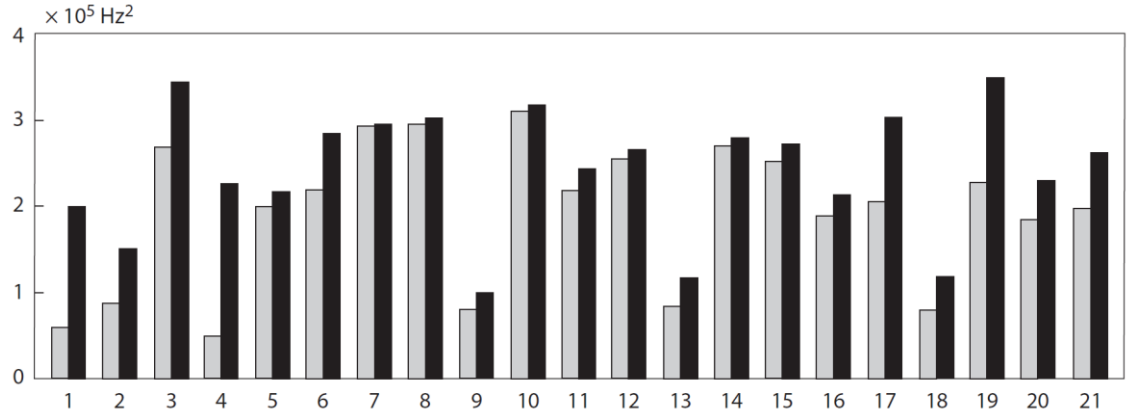

Figure 3. Pentagonal space areas obtained from each of the 21 patients with Parkinson's disease before (gray histogram) and after (black histogram) levodopa treatment.

(4) Changes in the F1 and F2 formants after levodopa treatment

Table II shows the changes in each of the F1 and F2 formants of the respective vowels in the 21 patients before and after treatment. Although the pattern of formant changes varied among individuals, F1 increased significantly and F2 did not change for vowel /a/, F1 decreased and F2 increased significantly for vowel /i/, both F1 and F2 did not change for vowel /u/, F1 increased significantly and F2 did not change for vowel /e/, and F1 did not change and F2 decreased significantly for vowel /o/.

Statistical analysis of the effects of levodopa on the complete set of F1 formants of the 5 vowels, with the adjusted significance level at $p = 0.01$ that controls familywise error rate, indicated that F1/a/ and F1/e/ increased ($p < 0.001$ and $p = 0.008$, respectively) and F1/i/ decreased ($p = 0.01$) after levodopa administration. With regard to the set of F2 formants, F2/i/ increased ($p = 0.004$) and F2/o/ decreased ($p = 0.008$) after treatment.

Table II.

A. Differences in each of the F1 formants for 5 vowels between OFF and ON state

		OFF		ON		95% CI		p
		Mean	SD	Mean	SD	Lower bound	Upper bound	
F1 (Hz)	/a/	736	98	790	87	−77.5	−29.3	< 0.001
	/i/	419	40	403	36	4.1	27.8	0.01
	/u/	454	43	450	36	−10.7	17.4	0.626
	/e/	532	52	550	53	−30.4	−5.2	0.008
	/o/	570	58	573	68	−16.7	11.0	0.671

B. Differences in each of the F2 formants for 5 vowels between OFF and ON state

		OFF		ON		95% CI		p
		Mean	SD	Mean	SD	Lower bound	Upper bound	
F2 (Hz)	/a/	1319	158	1330	149	−33.5	12.9	0.366
	/i/	2245	315	2304	280	−95.5	−21.6	0.004
	/u/	1366	200	1342	199	−11.9	60.2	0.178
	/e/	1939	259	1970	229	−65.0	4.0	0.08
	/o/	963	120	939	116	7.0	41.5	0.008

Abbreviations: SD, standard deviation; CI, confidence interval.

(5) Sequential relationship between plasma levodopa concentrations, motor performances, and pVSAs across levodopa cycle test

On the basis of the present results that show clear expansion of pVSA 1 h after levodopa administration, we further applied the entire levodopa cycle test in 4 patients (Case 1, 4, 6, and 7) to investigate whether the patterns of sequential changes in the F1 and F2 formants for the 5 vowels and pVSAs were indeed reflected by an increase/decrease in plasma levodopa levels and amelioration/deterioration of motor manifestation after medication (Figure 4). This is because the effectiveness of levodopa can vary among patients because of the difference in the pharmacokinetic and pharmacodynamics features of each individual, particularly patients with advanced PD and motor fluctuations [10].

In 3 patients (Case 4, 6, and 7), plasma levodopa levels, motor performances, and pVSAs before, 0.5 h after, and every 1 h after levodopa administration were determined as shown in Figure 4A-C. The plasma levodopa level

reached its peak within 1 h after medication and gradually declined after that. The temporal sequence of an increase/decrease in plasma levodopa levels after treatment agreed quite well with that of an increase/decrease in finger tapping counts and that of an expansion/decrease in the pVSA. In one patient (Case 1), two drug cycle tests were performed in series (Figure 4D). In this patient, there was a clear period of wearing off of motor response, which occurred 5 h after the first levodopa administration, when the plasma levodopa level was gradually declining. At the onset of this wearing off, a much greater and abrupt decrease in pVSA as well as a deterioration in motor response was found. The sleep benefit phenomenon [18] was observed not only for motor performance but also for the pVSA in this patient. Notably, the second levodopa administration reproduced the results of the first cycle in this patient and 3 other patients. Although the pattern of changes in the plasma levodopa levels, motor responses, and involuntary movements varied among single individuals, it should be noted that sequential changes in the plasma levodopa levels were in parallel with those in pVSAs and motor performances, even in the presence of dyskinesia and motor fluctuations.

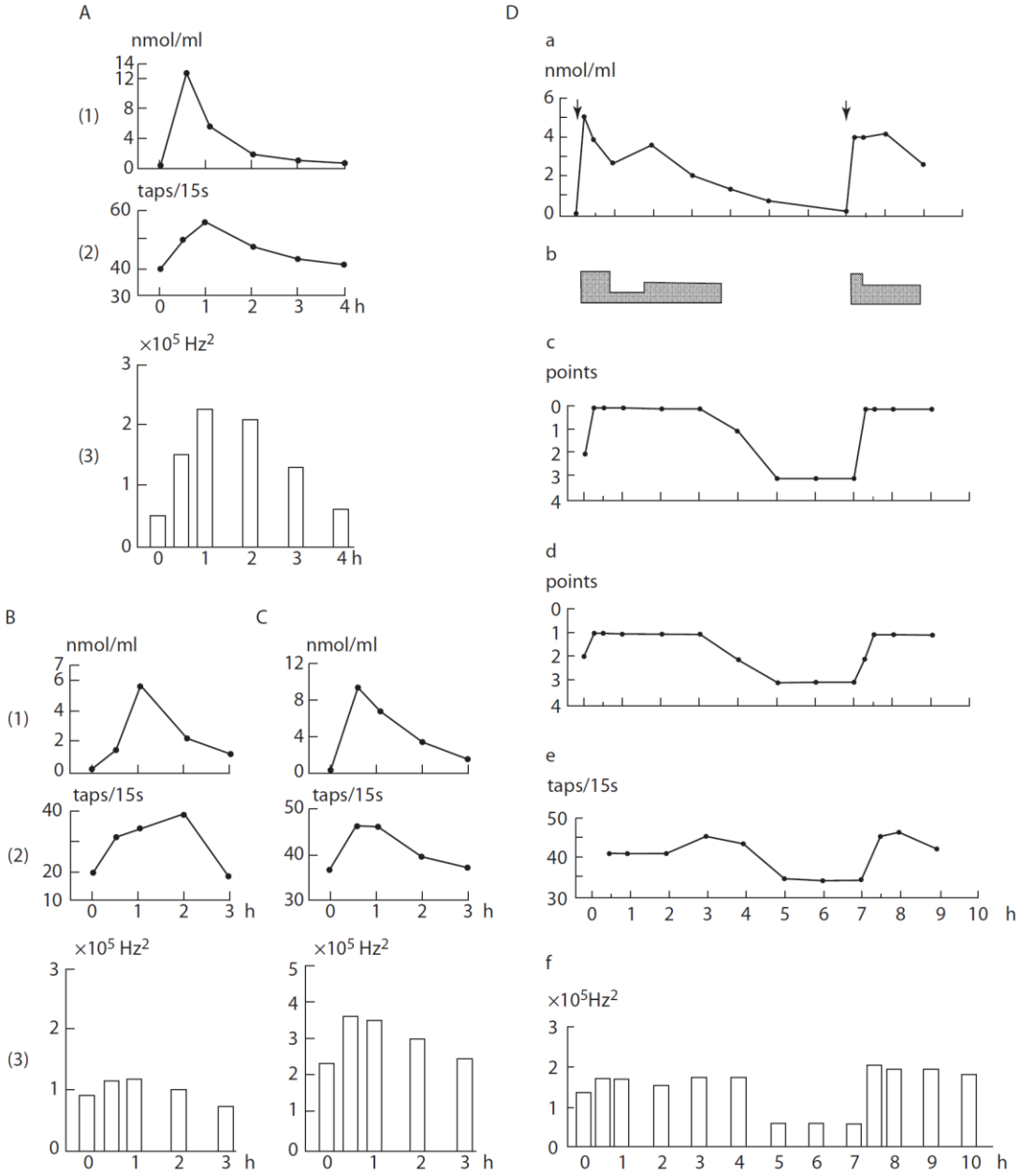

Figure 4. Sequential changes in plasma levodopa levels, motor performance, and pVSAs before and after levodopa treatment in 4 patients [Case 1 (D), 4 (A), 13 (B), and 19 (C)]. (A), (B), and (C) indicate sequential changes in plasma levodopa levels (1), finger tapping counts (2), and pVSAs (3), respectively. (D) shows the result from two levodopa cycle tests and indicates the sequential changes in plasma levodopa levels (a), appearance of dyskinesia (b), UPDRS-III scores for resting tremors (c) and rigidity (d) in the afflicted arm, finger tapping counts (e), and pVSAs (f). Downward arrows indicate levodopa administration.

DISCUSSION

The present study, which examined the effects of levodopa on vowel articulation in patients with PD, revealed significant expansion in pVSA as well as an improvement in motor performance after treatment. This result was consistent with those of previous kinematic and electromyographic studies focusing on the neurophysiology of speech articulators, which showed the beneficial effects of levodopa [4,22,37]. Sapir et al. [31] reported that intensive voice treatment with Lee Silverman Voice Treatment significantly expanded the VSA and improved vowel articulation. Therefore, expansion of pVSA after levodopa treatment in our study suggests that levodopa is responsible for the improvement of vowel articulation in patients with parkinsonian dysarthria.

On the other hand, some acoustic studies reported no significant improvement in vowel articulation after dopaminergic treatment in patients with PD [11, 12]. The discrepancy in results between previous studies and our study may have occurred because of methodological inconsistencies such as different disease stage and different procedure of acoustic sampling. Skodda et al. [34] found no significant improvement in articulation in early PD patients (Hoehn–Yahr stage, $\leq$2.5) after levodopa treatment, although they found some single individuals with amelioration. We cannot compare this result to ours because we studied patients with moderate to severe PD stages (Hoehn–Yahr stage, 3–5 in the worst OFF state). Poluha et al. investigated patients with mild to severe PD (Hoehn–Yahr stage, 2–5) and found no change in acoustic measurements [27]. However, the sampling number of investigated patients of their study was small for statistical analysis and they did not refer to dyskinesia in patients with advanced PD. Dyskinesia may cause the instability of articulators, which induces excessive formant fluctuations during articulations [11].

With regard to the difference in acoustic sampling, acoustical analyses in the previous studies were based on embedded vowels during reading tasks [8,13,27,34,35], although it is known that speech performance may be influenced by the type of task [14,15,23,38,39]. During reading tasks including the combination of consonants and vowels, it may be difficult to extract the steady-state vowel formants because of coarticulatory effects, particularly during the appearance of involuntary movements such as dyskinesia. To avoid these difficulties, we used isolated vowels for acoustic analyses in order to measure steady-state vowel formants and exclude the influence of dyskinesia. In our study, five isolated Japanese vowels were selected for formant analysis because Japanese is a mora language, with the 5 vowels being the basis of almost all syllabary (morae) containing 1 of the 5 vowels as an essential unit of mora. Even a single isolated vowel (/a/, /i/, /u/, /e/, or /o/) has a meaning by itself in Japanese (/a/, exclamation in English; /i/, stomach; /u/, cormorant; /e/, picture; and /o/, tail). The acoustic analysis of isolated vowels therefore enabled us to determine steady-state vowel formants accurately. In addition, to minimize the intraspeaker variability in formant values, in our study, each vowel was phonated for over 0.4 s 20 times, and 15 acceptable samples that were free from fluctuations due to dyskinesia were selected and averaged for analysis.

With regard to the VSA, it has been reported that the VSA of PD patients is compressed compared with that of healthy subjects [35, 40]. This is in good agreement with our present result. Sapir et al. [31,32] and Roy et al. [28] reported that, in most types of dysarthria, limitations in articulator movements lead to inadequate vowel formation by restriction of formant production, which is characterized by the lowering of normally high frequency formants and elevation of normally low frequency formants. These changes, in turn, result in a decrease in the VSA, namely formant centralization. From this perspective, it is interesting to note that for the complete set of F1 formants of the 5 vowels in our study, levodopa significantly increased F1/a/ and F1/e/ and decreased F1/i/, whereas for the set of F2 formants, it significantly increased F2 /i/ and decreased F2 /o/ (Table II). That is, levodopa increased high frequency formants, decreased low frequency formants, and increased the pVSA, which was centralized in the OFF state as shown in Figures 2 and 3. These results may indicate that levodopa enables patients to make sufficient upward–downward and forward–backward movements of the tongue as well as movements of the jaws and lips, which are restricted in the OFF state [21, 32].

It is to be noted that the levodopa effect was not enough to make complete improvement of dysarthria of vowel articulation. The mean pVSA of the patients after levodopa treatment expanded only to 79% of that obtained in the control subjects (Figure 1 and 3). However, this is true for the effect of levodopa on motor manifestation as seen in the changes of Hoehn–Yahr stage and UPDRS-III during OFF and ON state in the patients (Table I). It should be further studied whether this is due to the partial effect of levodopa on dysarthria or to the severity of the disease in each patient.

The levodopa cycle test in 4 patients revealed that sequential increase/decrease in the plasma levodopa concentration was in parallel with expansion/reduction in pVSAs and amelioration/deterioration of motor performances (Figure 4). These results accord well with the report showing that lip force increases/decreases with an increasing/decreasing plasma levodopa level during the levodopa drug cycle [5]. Although the sample number of our drug cycle test is too small to make statistical analysis, together with the results showing the expansion of pVSA in 21 patients after levodopa administration (Figure 3), the parallel time sequence of plasma levodopa concentrations, motor responses and acoustic performances during the entire drug cycle in 4 patients may strongly

suggest that dysfunctions in vowel articulation and motor manifestations in PD patients are both based on dopaminergic pathology.

The mean fundamental frequency (F0) of 15 phonations of each respective vowel was measured together with the F1 and F2 formants before and after levodopa administration (Figure 1A) because formant frequency values can be affected by the change in F0 frequency of the respective vowels by the order of an octave [2,25,30]. However, in our study, the increase in the F0 frequency of each vowel phonated by all patients after levodopa administration was limited within 10–30 Hz (data not shown), which is far from one octave. It is unlikely that changes in the F1 and F2 frequency were affected only by an increase in F0 in the ON state.

In contrast to the finding of pVSA expansion, global speech impairment as assessed by item 18 of the UPDRS-III was comparable before and after treatment, and this perceptual assessment identified only 5 patients (23.8%) with speech improvement in our sample (Table I) and showed poor sensitivity for the detection of the effects of levodopa on speech deficits. Clarification of the relationship between acoustic variables quantified by formant analysis and speech intelligibility scored by perceptual analysis requires further investigation.

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