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Evaluation of the pharynx and upper esophageal sphincter motility using high-resolution pharyngeal manometry for Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is associated with a high incidence of dysphagia. Aspiration pneumonia due to dysphagia is a major cause of death in patients with PD, and therefore accurately evaluating dysphagia should help improve prognosis. It has been reported that the severity of dysphagia does not always correlate with the Hoehn and Yahr (H&Y) stage for classifying PD severity. However, no reports have quantitatively evaluated the relationship between severity of dysphagia and H&Y stage. High-resolution pharyngeal manometry (HRPM) is a quantitative method that can be used to measure swallowing pressure from the velopharynx to the entry of the upper esophageal sphincter (UES). We used HRPM to measure swallowing pressure in 51 patients with PD. As PD progresses, atrophy and degeneration of the pharyngeal muscles become more pronounced, which contributes to dysphagia. However, thus far there is no quantitative clinical evidence for this pathological change. To evaluate the relationship between severity of underlying PD and dysphagia, patients were categorized by H&Y stage, as follows: stage II in four patients, stage III in 23, stage IV in 14, and stage V in 10. In patients with H&Y stages II, III, IV, and V, the respective velopharyngeal pressures were 179.8 ± 32.5, 157.6 ± 62.2, 172.2 ± 48.9, and 107.4 ± 44.0 mmHg, the mesopharyngeal pressures were 126.8 ± 53.2, 121.6.1 ± 50.4, 142.1 ± 57.8, and 61.4 ± 19.6 mmHg, the residual UES pressure were -8.0 ± 10.8, 10.3 ± 16.1, 16.5 ± 37.9, and 11.2 ± 16.2 mmHg, and the resting UES pressure were 49.5 ± 30.0, 15.8 ± 25.7, 1.85 ± 14.1, and -1.2 ± 12.2 mmHg. Patients with severe PD demonstrated significantly decreased velopharyngeal and oropharyngeal pressures, along with incomplete UES opening and contraction. HRPM can detect subtle abnormalities by quantifying swallowing pressure in patients with PD. Evaluating swallowing pressure with HRPM provides insights into neuromuscular dysfunction that causes abnormal pressure generation during pharyngeal swallowing in patients with PD.

1. Introduction

Parkinson's disease (PD) is highly prevalent in older people, a fact that is particularly important in aging societies [1]. PD affects approximately 1% of the world's population, and incidence rates increase with age [2]. In Japan, the crude incidence was 18.4 per 100,000 population per year in 2004 [3]. PD is a progressive, neurodegenerative disease that primarily in[1–37,39–47]volves degeneration of substantia nigra dopaminergic neurons and is characterized by the presence of cardinal motor symptoms such as bradykinesia, tremor, rigidity, and loss of postural reflexes [4,5]. Dysphagia occurs in 75–100 % of patients with PD [6,7]. Screening for dysphagia is important because 2.4–13.6 % of patients with dysphagia develop aspiration pneumonia [8,9], which leads to hospitalization [8,10,11] and is a major cause of death in individuals with PD [10,12–14]. Videofluoroscopy (VF) and videoendoscopy (VE) are widely used to visualize and evaluate the swallowing dynamics of the pharynx and soft palate, the residue after passage, laryngeal penetration, and tracheal aspiration [15–18]. However, both VF and VE are qualitative rather than quantitative assessment techniques.

High-resolution pharyngeal manometry (HRPM) can quantitatively evaluate the extent of dysphagia from the velopharynx to the entry of the upper esophageal sphincter (UES)(F). HRPM can reveal subtle changes in swallowing-related pressure in patients with PD [17,19,20]. In addition, it avoids the radiation exposure and interobserver differences associated with VF [21]. HRPM can be performed even without any bolus [22]. It has been suggested that HRPM is safe for evaluating dysphagia in patients with PD who are at risk of aspiration. It has been

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reported that the severity of dysphagia does not always correlate with the Hoehn and Yahr (H&Y) stage for classifying PD severity [17]. However, no studies thus far have quantitatively evaluated the relationship between severity of dysphagia and each H&Y stage. In addition, several reports have demonstrated that HRPM reveals abnormal swallowing pressure in patients with PD, but only in limited regions of interest, such as the UES or pharynx, and only in the early and middle stages of PD [23–26].

We hypothesized that patients with early and advanced PD would exhibit quantitative differences in swallowing pressure as measured by HRPM over a broad area, from the pharynx to the UES.

Therefore, this study used HRPM to evaluate swallowing pressure from the pharynx to the UES in patients with PD, and analyzed the relationship between swallowing pressure and H&Y stage, a well-known severity classification system for PD.

2. Materials and methods

2.1. Subjects

The study subjects were 51 outpatients with PD who were referred to our department from April 2014 to March 2016. All patients with PD were diagnosised by neurologists, treated with antiparkinsonian drugs, and visited an otorhinolaryngological outpatient clinic for screening of dysphagia. Exclusion criteria were neurological diseases other than PD, severe dementia with no capacity for self-determination, severe dyskinesia of the head and neck (which would interfere with HRPM recording), mental depression, head and neck cancer, severe cardiovascular disease, severe respiratory disease, or previous surgery for swallowing dysfunction or conditions of the central nervous system. All patients had stable PD at the time of inclusion. At the time of the study, all patients were taking levodopa as monotherapy (n = 39) or in combination with other antiparkinsonian drugs (n = 12). The number of different antiparkinsonian drugs taken was two in ten patients and three in two patients. The mean duration since diagnosis was 7.8 years (range 1.8–22.5). At the time of the study, 41 patients could ingest food orally while 10 could not. Written informed consent was obtained from all subjects.

2.2. Classification of clinical severity

The clinical severity of PD was defined using the H&Y scale, which categorizes patients from stage I to stage V, as follows: stage I, unilateral involvement; stage II, bilateral involvement; stage III, PD with impaired balance; stage IV, able to walk and stand unassisted but otherwise markedly incapacitated; stage V, unable to walk [27]. All diagnoses of PD at our hospital were confirmed by a neurologist, and H&Y staging was performed by the neurology team.

2.3. HRPM

HRPM (Starr Medical, Tokyo, Japan) was used to evaluate swallowing pressures from the velopharynx through the UES in all patients and control subjects. The manometry catheter had an outer diameter of 4 mm, with 20 circumferential pressure sensors that were spaced 1 cm apart. The inputs from all sensors were averaged and recorded as the mean pressure. The system was calibrated to record pressures between −50 mmHg and 300 mmHg. The catheter was calibrated before each use according to the manufacturer's specifications.

2.4. HRPM measurement methodology

First, 1% pantetheine spray was applied through one nasal passage. The manometric catheter was then lubricated using 2% lidocaine jelly to ease its passage through the pharynx; to prevent it from being inserted into the trachea, its position was confirmed using a flexible fiberscope introduced into the other nasal passage.

Patients then rested for approximately 30 s because the pharyngeal reflex is increased after catheter insertion. We next asked patients to say "Papapa," and confirmed the position of the soft palate with the velopharynx closed. We verified the sensor number on the catheter by inserting a flexible fiberscope into the same nasal passage, and determined the position of the velopharynx, epiglottis, and UES after using a flexible fiberscope to ensure that the distal tip of the catheter was located in the cervical esophagus.

During the examination, patients sat comfortably in an exam chair and looked straight ahead with the chin in a neutral position. We asked patients to swallow saliva five times, and analyzed the data from all five swallows. No bolus was used because patients with PD have a high risk of aspiration and choking. Pressure waveforms were separated into three regions of interest (Fig. 1a,b). The velopharynx is the superior-most region of pharyngeal swallowing-related pressure as the soft palate contacts the posterior and lateral portions of the nasal cavity to close off this area and prevent liquid from entering [28]. The mesopharynx is the pressure region between the velopharynx and UES, with pressure contributions from the tongue base, pharyngeal walls, and laryngeal structures [29]. The UES, which separates the hypopharynx from the esophagus [30], lies below the mesopharynxis and is closed tightly at rest, thus exerting pressure [31].

After inserting the catheter through the nasal cavity and into the UES, we measured the mean pressure values after at least five dry swallows. Means and SDs of the maximal velopharyngeal (VP) pressure, maximal mesopharyngeal (MP) pressure, basal UES pressure, and residual UES pressure were recorded. Time is shown on the x-axis and the distance from the nostril is indicated on the y-axis. Pressure is color-coded (Fig. 1). Each evaluation lasted between 1 and 2 h, with the goal of maintaining a constant examination period after patients took antiparkinsonian drugs [32].

2.5. Statistical analysis

Differences in manometric variables between patients with each stage of PD were assessed by the one way ANOVA or the Kruskal–Wallis test. The Dunn method was used for post hoc analysis. Values are presented as average ± standard deviation. A significance level of $\alpha = 0.05$ was determined a priori. Manometric variables were assessed using Prism 7 software (GraphPad, La Jolla, CA, USA). A p value of <0.05 was considered to indicate significance.

3. Results

All HRPM procedures were completed without complications. Thirty-three patients were males and 18 were females, and their mean age was 74.4 (range, 55–88) years. Treatment with anti-Parkinsonism drugs (e.g., L-DOPA and dopamine agonists) was provided to all 51 subjects.

The H&Y PD classification was stage II PD in four patients, stage III in 23, stage IV in 14, and stage V in 10; the mean age in each group was 74.3 (range, 65–83), 72.5 (range, 61–88), 75.0 (range, 64–86), and 77.9 (range, 73–83) years, respectively. Patients characteristics are shown in Table 1.

Patients with PD showed differences in the velopharynx, mesopharynx, and UES regions on topographic images (Fig. 1). Tables 2a and 2b shows swallowing pressures in patients with PD. The VP pressure was significantly higher in stage IV than stage V ($p = 0.032$) (Fig. 2). The MP pressure differed significantly between stage III and stage V ($p = 0.006$) and between stage IV and stage V ($p = 0.0009$) (Fig. 3). There was no significant difference in residual UES pressure between stages (Fig. 4). Finally, the resting UES pressure was significantly higher in stage II than stage IV ($p = 0.042$) (Fig. 5).

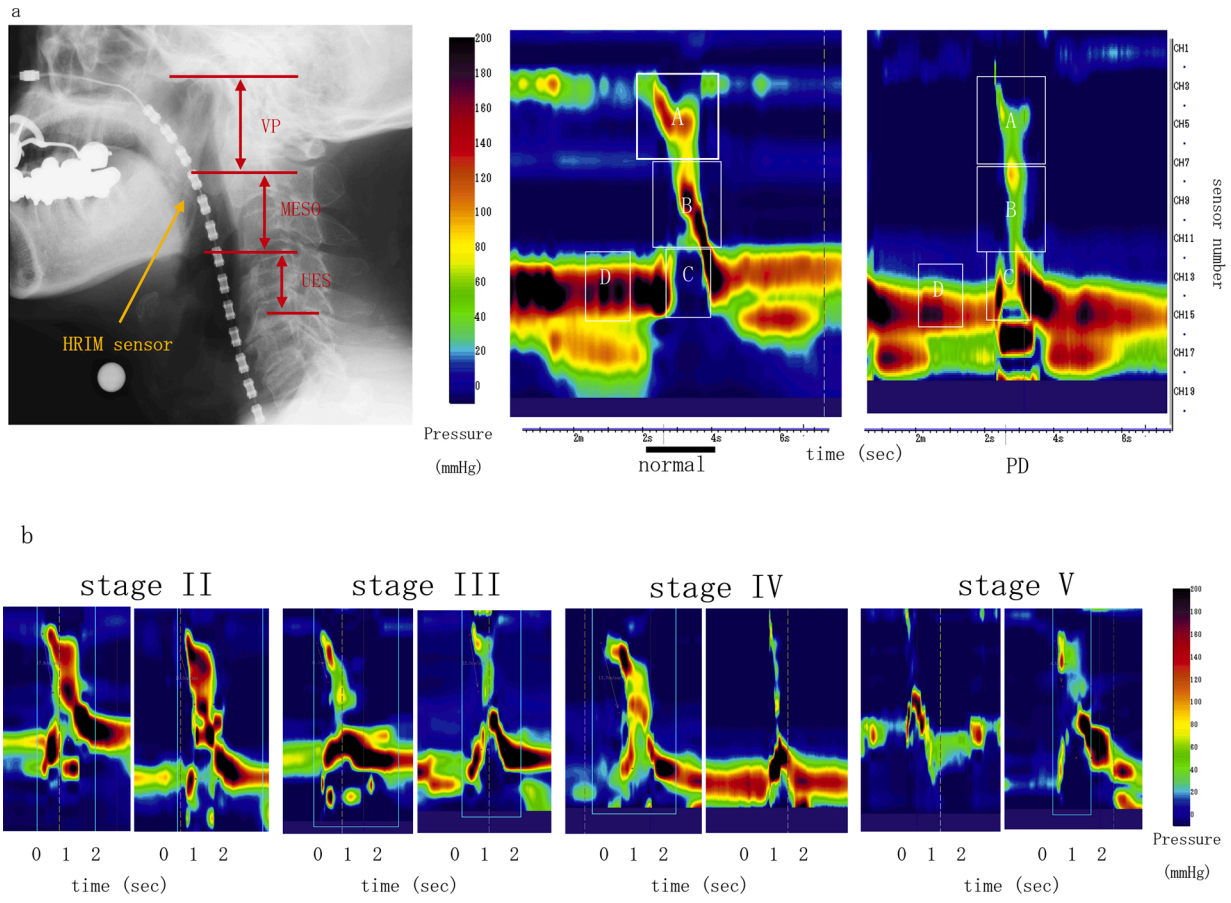

Fig. 1. (a) Simultaneous videofluoroscopy with anatomical referents (left).
high-resolution pharyngeal manometry of healthy control (center) and high-resolution pharyngeal manometry of PD (right).
VP: veropharyngeal.
MESO: mesopharyngeal.
UES: upper esophageal sphincter.
Time is on the x-axis(black bars indicate 2 s) and distance from nasal nostril is on the y-axis. Each pressure is assigned a color (legend left). When swallowing, we can observe construction of the VP muscle zone (A), MESO muscle zone(B), and relaxation of UES muscle zone(C). At rest, we could observe construction of the UES muscle zone (D). (b) High resolution pharyngeal manometry sample spatiotemporal plot from each stage in patients with Parkinson disease.
(Hoehn and Yahr stage classification).

Table 1
Patients characteristics and Hoehn and Yahr stage score in PD patients.

	Hoehn and Yahr (H&Y) staging			
	II	III	IV	V
number	4	23	14	10
age(yr)	74.3 ± 6.6	72.5 ± 7.8	75.0 ± 6.9	77.9 ± 5.2
Sex(m/f)	3/1	15/8	8/6	9/1
Levodopa (n)				
Total	4	23	14	10
Monotherapy	4	19	10	6
In combination	0	4	4	4
Daily dose of levodopa (mg) (mean (SD))	200(71)	448(147)	418(142)	550(150)
Range of daily dose of levodopa (mg)	100−300	300−900	300−800	400−900
Agonists (n)	0	1	3	3
Selegiline (n)	0	3	2	2
Duration since diagnosis(yr) (mean(SD))	3.2(1.5)	6.9(3.8)	9.2(5.4)	9.6(6.2)
Oral intake/non oral intake (n)	4/0	20/3	13/1	4/6

Table 2a
Summary data of swallowing pressure in patients with PD for each stage.

	Stage II	Stage III	Stage IV	Stage V	P value
VP(mmHg)	179.8 ± 32.5	157.6 ± 62.2	172.2 ± 48.9	107.4 ± 44.0	0.0174*
MESO(mmHg)	126.8 ± 53.2	121.6 ± 50.4	142.1 ± 57.8	61.4 ± 19.6	0.0024**
Residual UES (mmHg)	−8.0 ± 10.8	10.3 ± 16.1	16.5 ± 37.9	11.2 ± 16.2	0.2679
Resting UES (mmHg)	49.5 ± 30.0	15.8 ± 25.7	1.85 ± 14.1	−1.2 ± 12.2	0.0256*

Values are means ± SD.
One way ANOVA,P*<.05, p**<.01.

4. Discussion

Dysphagia occurs frequently among patients with PD [33]. Swallowing function deteriorates in all phases, including the oral cavity, pharyngeal, and esophageal phases [34,35]. Clinically, patients with PD have an increased incidence of dysphagia, which is characterized by reduced MP pressure and UES dysfunction, the latter caused by impairment or failure of sphincter relaxation [23,34,35]. Neuropathologically, patients with PD demonstrate pharyngeal muscle fiber

Table 2b
Comparison of swallowing pressure in patients with PD for each stage.

	VP	MESO	Resudial UES	Resting UES
Stage II vs stage III	>0.99	>0.99	0.375	0.462
Stage II vs stage IV	>0.99	>0.99	0.666	0.042[a]
Stage II vs stage V	0.093	0.159	0.392	0.070
Stage III vs stage IV	>0.99	>0.99	>0.99	0.555
Stage III vs stage V	0.096	0.011[a]	>0.99	0.960
Stage IV vs stage V	0.032[a]	0.001[b]	>0.99	>0.99

Dunn method for post hoc analysis.
[a] $p < .05$.
[b] $p<01$.

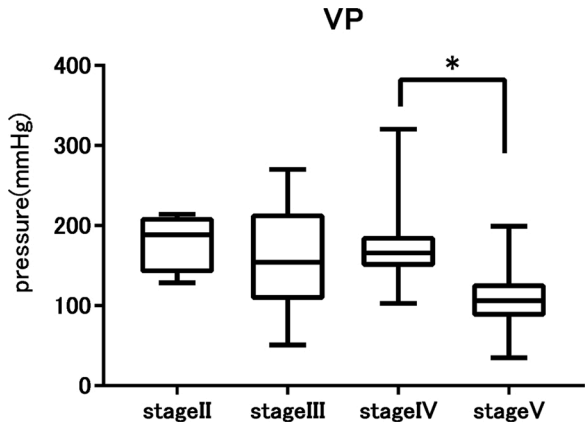

Fig. 2. Veropharyngeal pressure for each stage in patients with PD.
*p < .05.
ANOVA, Dunn's test post hoc Error bar: standard error.

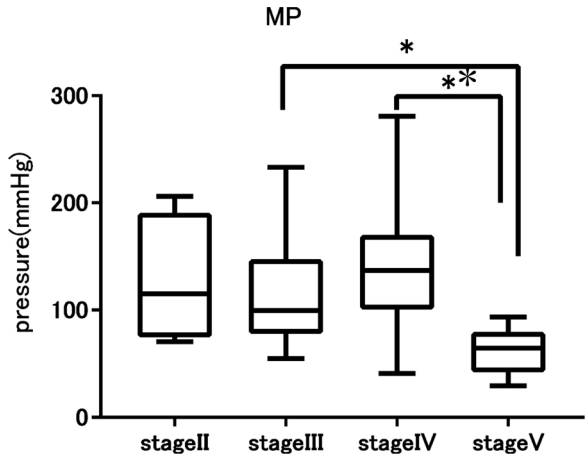

Fig. 3. Meso pharyngeal pressure for each stage in patients with PD.
*p < .05, **<.01.
ANOVA, Dunn's test post hoc Error bar: standard error

atrophy and muscle fiber transformation [36]. Pharyngeal muscle fibers are categorized as either slow or fast [36]. In patients with PD, a decrease in muscle fiber size, a reduced number of fast-twitch (type I) fibers, and an increase in slow-twitch (type II) fibers may cause functional changes in the intrinsic force-generating capacity of pharyngeal muscles and reduce their strength and contractile speed during swallowing [36]. Additionally, muscle fiber atrophy and transformation from type II to type I might cause a decrease in force and thus result in abnormal swallowing pressure.

However, it has been difficult to quantitatively evaluate the degree of clinical dysfunction from the pharynx to the UES because the

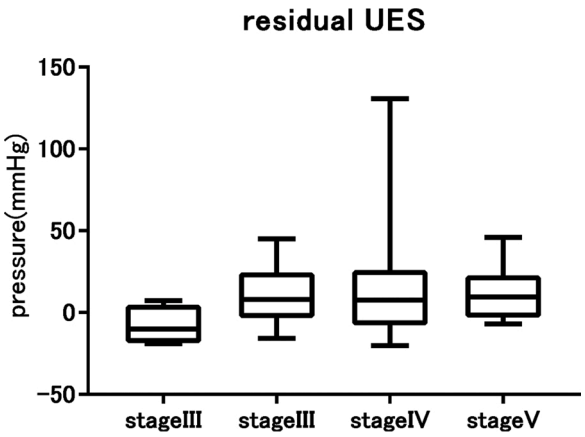

Fig. 4. Resudial UES pressure for each stage in patients with PD.
ANOVA, Dunn's test post hoc Error bar: standard error.

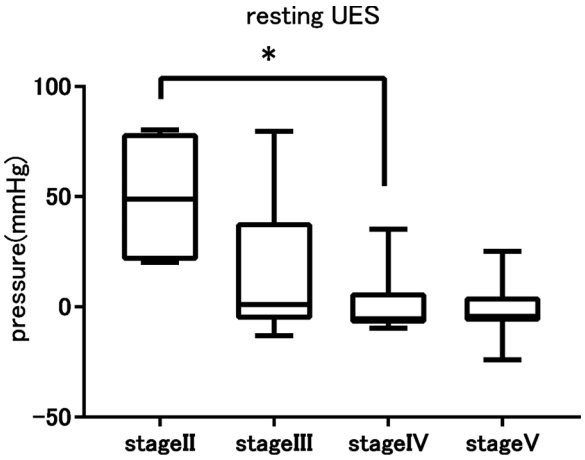

Fig. 5. Resting UES for each stage in patients with PD.
*p < .05.
ANOVA, Dunn's test post hoc Error bar: standard error.

movements involved are highly complex. Our study is the first to demonstrate that HRPM provides clear information on swallowing pressure at different stages of PD.

Two previous studies used HRPM to compare swallowing pressure between patients with early-stage PD (stages I, II, and III) and healthy controls, and showed that the maximum VP pressure was significantly lower in the patients with PD than in the healthy controls [23,24]. Those reports did not compare early- and advanced-stage PD. One study indicated that dysphagia was present in 68 % of patients with advanced-stage PD (stages IV and V) [37]. In addition, another study reported that 64 % of patients who developed aspiration pneumonia had stage IV or V disease [9],. Thus, we should evaluate swallowing pressures in patients with all stages of PD so as to determine how the swallowing pressure in each region is associated with disease stage.

In our study, VP pressure was significantly reduced in stage V. With HRPM, VP pressure reflects VP closure. VP function plays an important role not only in swallowing but also in articulation. A previous study showed that 96 % of patients with advanced-stage PD had poor velopharyngeal closure and difficulty with speech [37]. On the other hand, in patients with early- to mid-stage PD, only the timing of VP closure was affected, and not VP pressure [38]. Unlike this study, however, VP pressure was not evaluated at each stage.

In this study, MP pressure was significantly reduced in stage V (Fig. 3). Consistent with this finding, a previous report showed no significant decline in MP pressure in early- or mid-stage PD [23]. However,

no studies have compared MP pressure in each advanced stage. A videofluoroscopic swallowing study demonstrated that a vertical epiglottis showed no movement during ingestion in any patients with stage V PD [39]. Motion of the epiglottis is influenced by the function of the mesopharynx. The above reports support the results of our HRPM-based study.

Previous classifications of PD have been based on early, mid, and late stages. In our study, there were significant differences in both MP and VP pressures for each mid or advanced stage.

The UES pressure is relatively low; it even reaches sub-atmospheric pressures during swallowing, usually when there is high pressure in the velopharynx and mesopharynx, and it rapidly increases with a gradual return to baseline pressure [27,40–42]. Several studies reported that the residual UES pressure was higher and the resting UES pressure was lower in patients with advanced-stage PD than in those in earlier stages [25,40,43,44]. It is possible that patients with PD cannot physiologically achieve sufficient relaxation and contraction of the UES. In our study, the residual UES pressure was not significantly increased in any stage. The residual pressure is also affected by the function of pharyngeal muscles other than the cricopharyngeal muscle.

It was reported that the residual UES pressure was significantly positively correlated with bolus volume (3 mL, 5 mL, 10 mL of water, thick liquid, and paste) [45]. In our study, patients swallowed saliva rather than bolus due to their risk of aspiration or suffocation. It has been suggested that the residual UES pressure varies according to examination method. However, in two studies the resting UES pressure did not seem to be affected by the bolus volume [45,46]. The resting UES pressure is a function of cricopharyngeal muscle activity, which is controlled by the vagal nerve. The pathological process in PD initially involves the dorsal motor nucleus of the vagal nerve [47]. Without compensation by the glossopharyngeal nerve, the resting UES pressure may be directly influenced by PD severity. In addition, L-DOPA is not effective for the degeneration of the vagal nerve [12]. These reports may explain why resting UES pressure is reduced in patients with PD beginning at a relatively early stage. However, the relation between residual and resting UES pressures remains unclear.

In this study, we showed that swallowing pressures differed between stages of PD, and that HRPM clarified how neuromuscular function leads to abnormal pressure generation during pharyngeal swallowing in patients with PD. Further prospective studies are necessary to validate these clinical and neuropathological findings. HPRM will likely be an important technique for determining swallowing-related treatments and oral intake [23,24], both of which influence the nutritional condition and quality of life of patients with PD. As such, swallowing pressure should be evaluated at each PD stage.

This study had several limitations. The number of patients with PD in each stage was small. Since this study enrolled relatively few patients with stage I or II PD, large-scale comparison of patients with early and advanced PD stages is required. Evaluating swallowing pressure at all stages of PD may help determine swallowing-related treatment strategies and improve long-term outcomes. Furthermore, measurements of swallowing pressure amplitudes were performed only when patients swallowed saliva; other experimental conditions would be informative.

5. Conclusion

The results of HRPM demonstrated quantitative changes in swallowing pressure between stages of PD. HRPM is a safe, simple, and convenient method for evaluating swallowing function in patients with PD.

CRediT authorship contribution statement

Kenkichiro Taira: Conceptualization, Methodology, Software, Data curation, Writing - original draft, Visualization, Resources, Investigation. **Kazunori Fujiwara:** Conceptualization, Methodology, Software, Supervision, Validation, Writing - review & editing, Resources. **Takahiro Fukuhara:** Validation, Supervision. **Satoshi Koyama:** Formal analysis, Data curation. **Tsuyoshi Morisaki:** Validation. **Hiromi Takeuchi:** Supervision, Validation.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2020.106447.

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