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ORIGINAL ARTICLE

Effects of Rehabilitative Intervention for Augmenting Cough Function in Patients with Multiple System Atrophy

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Objectives: One of the causes of death in patients with multiple system atrophy (MSA) is aspiration pneumonia caused by cough dysfunction. This study aimed to identify an effective approach to improve coughing and to explore the establishment of criteria for the use of gastrostomy based on cough and respiratory dysfunctions. **Methods:** Eighteen probable MSA patients participated in the study. They were categorized into air stacking and non-air stacking groups. First, we investigated how the inspiration volume changes by applying maximum insufflation capacity (MIC). Second, peak cough flow (PCF) was measured by different cough augmentation methods: 1) spontaneous coughing (SpC); 2) SpC with MIC (SpC+MIC); 3) SpC with manually assisted cough (MAC) (SpC+MAC); and 4) SpC with MIC and MAC (SpC+MIC+MAC). Among these four conditions, PCF values were compared to determine the most effective approach for cough augmentation. Receiver operating characteristic analysis was performed on percent forced vital capacity (%FVC) to determine an index for discriminating PCF below160 L/min, which indicates a high risk of suffocation, involving SpC and SpC+MIC. **Results:** Inspiration volume increased significantly with MIC in both groups ($P<0.05$), and PCF increased significantly with MIC in the air stacking group ($P<0.01$). PCF could not be maintained at 160 L/min when %FVC fell below 59%, even when MIC was applied. **Conclusions:** PCF increases with MIC in patients with MSA. It may be meaningful to consider the timing of gastrostomy introduction based on the severity of cough and respiratory dysfunction.

Key Words: cough; gastrostomy; multiple system atrophy; pneumonia; ROC curve

INTRODUCTION

Multiple system atrophy (MSA) is a rare and progressive neurodegenerative disease.[1,2] It was previously classified as olivopontocerebellar atrophy, Shy-Drager syndrome, or striatonigral degeneration.[2,3] According to natural history studies of the patients with MSA, the average life expectancy from the onset of motor symptoms is 9.8 years, and the mean age of onset is 60 years.[4,5] Aspiration pneumonia is one of the causes of death in patients with MSA.[6] Generally, aspiration pneumonia is caused by a decrease in cough function.[7] Previous studies revealed the effectiveness of rehabilitative interventions aimed at strengthening the cough function in the presence of neuromuscular diseases such as Duchenne muscular dystrophy and amyotrophic lateral sclerosis.[8,9] Some studies on respiratory function in MSA have conclud-

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ed that respiratory function is maintained, whereas others found that it gradually deteriorates.[10,11] Importantly, vocal cord dysfunction is associated with life-threatening events such as upper airway obstruction, nocturnal sleep apnea syndrome, and stridor. In addition, vocal cord dysfunction can lead to the impairment of coughing.[12] However, there has been no report of efforts seeking effective cough augmentation maneuver in the presence of MSA. In addition, gastrostomy has also been performed in clinical settings for MSA patients with inadequate coughing.[1,6] After a search of the literature, it appears that no study has examined the timing of gastrostomy based on cough and respiratory functions in MSA. Clarification of the timing would promote the planning of therapeutic interventions and collaborative decision making on treatment. Therefore, the aims of this study were to: 1) identify the most effective approach to improve cough function, and 2) explore conditions requiring therapeutic intervention, such as gastrostomy, based on cough and respiratory functions.

MATERIALS AND METHODS

Ethical Considerations

This study was approved by the Medical Ethics Committee of the International University of Health and Welfare School of Medicine (Approval number: 21-Im-006) and was conducted in accordance with the principles of the Declaration of Helsinki. We registered our study with the University Hospital Medical Information Network (UMIN) Center before starting examination (UMIN-CTR ID: UMIN000045378). All procedures were conducted after subjects provided written informed consent.

Participants

We conducted a single-facility and hospitalized care study. This study was a non-randomized, prospective intervention study (a cross-sectional study) using data from the International University of Health and Welfare Ichikawa Hospital Intractable Disease Center from 1 July 2021 through to 31 May 2023. Study participants were recruited from patients admitted to the Department of Neurology of our hospital. In addition, we asked the MSA registry, which collects information on MSA patients from medical institutions, to introduce this study and recruit patients.

The study used the following inclusion criteria: 1) clinical diagnosis of probable MSA based on the second consensus diagnostic criteria[13]; 2) no cardiopulmonary diseases such as chronic obstructive pulmonary disease, myocardial infarction, cardiac insufficiency or similar conditions; 3) no malignant disease; 4) no neurological or neuromuscular diseases other than MSA; 5) no acute or chronic inflammatory or infectious diseases; 6) no tracheostomy and/or artificial ventilation before the study; 6) capable of verbal communication; and 7) no cognitive impairment as confirmed by a Mini-Mental State Examination (MMSE) score below 21 and a Frontal Assessment Battery (FAB) score less than 13).

Outcome Measures

Respiratory function, including vital capacity (VC), percent vital capacity (%VC), and percent forced vital capacity (%FVC), was assessed by spirometry (Autospiro AS-407; Minato Medical Science, Japan). Respiratory muscle strength such as percent maximal inspiratory mouth pressure (%PImax) and percent maximal expiratory mouth pressure (%PEmax) were assessed using a respiratory muscle strength-measuring device (IOP-01; Kobata Gauge, Japan) by oral manometry.[14] These measurements were recorded while the patient wore a nose plug and the mouthpiece was firmly held in place by hand to prevent air leaks. Both respiratory function assessment and respiratory muscle strength testing were conducted after the patient was allowed to practice the measurement once. All data obtained in percent predicted values were adjusted for height, weight, age, and sex by the assessment device.

Forced insufflation using a resuscitation bag (single-use resuscitation bag adult; Philips, The Netherlands) is an assistance maneuver that can be used to achieve maximum insufflation capacity (hereinafter, this technique is referred to as MIC).[15] A pressure gauge (disposable manometer; MPI, Japan) and a simple spirometer (Haloscale standard respirometer; nSpire Health, UK) were attached to the resuscitation bag to measure the pressure and expiratory volume, respectively.[16] The participants used a face mask (cough assist face mask; Philips) to cover the nose and mouth to prevent air leaks. In addition, an LIC Trainer (Carter Technologies, Japan) with a one-way valve was used to prevent any expiration leak during forced insufflation with a resuscitation bag.[17] To perform MIC, this study used three forced air pressures: 20, 30, and 40 cmH_2O, and the expiratory volume was measured. A manually assisted cough (MAC) is a technique in which a hand is placed on the upper or lower rib cage and pushed inward at the same time as the patient coughs.[18] This technique assists expiration by pushing the ribcage from the outside. Inspiratory volume measured without any respiratory maneuver refers to VC.

Cough function was measured as peak cough flow (PCF) by

connecting a face mask to a peak flow meter (Mini-Wright™ Standard Peak Flow Meter; Clement Clarke International, UK).[15] Previous research has established ways to strengthen cough function in patients with neuromuscular diseases by using inhalation assistance, exhalation assistance, or both.[15] Therefore, in this study, we applied MIC as inhalation assistance and MAC as exhalation assistance. PCF was measured by employing four different cough augmentation methods: 1) spontaneous coughing (coughing without any assistance) (SpC); 2) SpC with MIC (SpC+MIC); 3) SpC with MAC (SpC+MAC); and 4) SpC with MIC and MAC (SpC+MIC+MAC).[8,15] For each condition, PCF was measured three times and the maximum value was used. The order of measurement for each pattern was randomly selected.

The Unified Multiple System Atrophy Rating Scale (UMSARS) parts 1, 2, 4, and Hoehn & Yahr scale (H&Y) were used to assess the severity of disease for all participants. UMSARS part I assesses impairments affecting activities of daily living (12 items), and UMSARS part 2 assesses impairments affecting motor function (14 items). UMSARS part 4 is the global disability score. Each item is scored from 0 (unaffected/normal) to 4 (severe impairment).[19] H&Y is a parkinsonian motor impairment severity scale from stage 1 (unilateral symptoms) to stage 5 (wheelchair bound or bed ridden).[20] In addition, the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part 3 was used to assess the severity of motor function. It has 18 questions (33 scoring items). Each item scores from 0 (normal) to 4 (severe) and total scores are obtained from the sum of each item score.[21] The Scale for the Assessment and Rating of Ataxia (SARA) was used to assess ataxia. The total score can range from 0 (without ataxia) to 40 (most severe) based on eight assessment points: gait (0–8 points); stance (0–6 points); sitting (0–4 points); speech disturbance (0–6 points); finger chase (0–4 points); nose–finger test (0–4 points); fast alternating hand movement (0–4 points); and heel–shin slide (0–4 points).[22]

Vocal cord movement can be impaired in MSA patients. When the vocal cords do not open or close completely and become fixed in the midline position, it is a contributing factor to stridor and nocturnal sleep apnea syndrome, which are potentially life-threatening conditions.[10,12] However, coughing requires the ability to close the vocal cords and hold the breath.[23] Vocal cord dysfunction in MSA patients means that some may be unable to hold their breath, leading to decreased cough strength. Therefore, in this study, participants were divided into two groups based on their ability to hold their breath: the air stacking group and the non-air stacking group.[8] Patients in the air stacking group were able to hold their breath without leakage during measurement of maximum insufflation capacity, whereas patients in the non-air stacking group could not fully hold their breath at the lowest pressure for MIC of 20 cmH_2O. For cough function evaluation, two critical values of PCF (270 and 160 L/min) are used as criteria for assessing cough strength. When PCF is less than 270 L/min, it becomes difficult for an individual to produce sufficient sputum, and other methods of sputum excretion are required.[15,24] When PCF falls below 160 L/min, sputum drainage becomes impossible and suction or endotracheal intubation is required.[24–26] These two points are important when assessing cough function and performing interventions aimed at improving cough strength.

Statistical Analysis

Statistical analysis software (SPSS statistics version 27; IBM, Armonk, NY, USA) was used to analyze all data. Data are expressed as mean (±SD) for parametric variables and ordinal data. The numbers and percentages are reported for nominal data and the ratio scale. The paired *t*-test was performed for two data obtained by changing the conditions for a matched sample. The two-sample *t*-test was used to compare parametric variables between the air stacking and non-air stacking groups. Fisher's exact test was used to analyze categorical data. The differences among the four cough assistance methods were analyzed by repeated measures analysis of variance (ANOVA) and compared by multiple comparison. Cut-off values (CVs) of PCF below 270 L/min or below 160 L/min at SpC and SpC+MIC in %FVC were examined using the receiver operating characteristic (ROC) curve. The area under the curve (AUC), Sensitivity (Sen.), and Specificity (Spe.) were calculated. The Youden index (Sensitivity+Specificity−1) was calculated at all points of the ROC curve to determine the potential CV.

RESULTS

This study included 24 consecutive patients with probable MSA. Of the 24 patients, 6 did not meet the inclusion criteria. Of the 6 patients, 3 were on a tracheostomy ventilator, 2 showed cognitive decline, and 1 refused to participate in the study. Therefore, this study examined 18 consecutive patients with MSA.

The demographic backgrounds of the patients are shown in **Table 1**. Of the 18 patients, 12 were able to hold their breath (air stacking group). The other 6 patients were unable to hold their breath (non-air stacking group). Regarding the

Table 1. Participant information

	All	Air stacking group	Non-air stacking group	P value
Basic information				
n	18	12	6	-
Sex (F/M)	8/10	5/7	3/3	n.s.
Height (cm)	164.33 (±9.33)	165.58 (±9.89)	161.83 (±8.33)	n.s.
Weight (kg)	58.92 (±16.63)	60.32 (±16.57)	56.13 (±17.96)	n.s.
BMI (kg/m^2)	21.70 (±5.09)	21.78 (±4.43)	21.55 (±6.69)	n.s.
Age at onset (years)	56.45 (±8.33)	56.00 (±9.99)	57.33 (±3.88)	n.s.
Disease duration (months)	50.56 (±30.49)	47.83 (±34.50)	56.00 (±22.10)	n.s.
Sub-type (P/C)	7/11	3/9	4/2	n.s.
Cognitive function				
MMSE (/30)	26.25 (±6.92)	27.50 (±1.72)	24.17 (±11.41)	n.s.
FAB (/18)	15.31 (±1.78)	15.00 (±1.63)	15.60 (±2.19)	n.s.
Basic respiratory and motor function				
%VC	70.39 (±23.84)	80.25 (±20.28)	50.67 (±18.11)	<0.01
%FVC	66.72 (±24.59)	78.50 (±20.23)	43.17 (±12.50)	<0.01
%PImax	55.66 (±37.80)	69.84 (±36.24)	27.30 (±22.81)	<0.05
%PEmax	41.82 (±26.40)	58.26 (±19.64)	23.52 (±12.74)	<0.01
H&Y total	4.05 (±0.99)	3.67 (±0.98)	4.83 (±0.41)	<0.01
SARA (/40)	21.67 (±7.87)	18.50 (±6.02)	28.00 (±7.67)	<0.05
MDS-UPDRS Part 3 (/132)	53.22 (±24.51)	42.42 (16.95)	74.83 (23.86)	<0.01
UMSARS Part 1 (/48)	26.06 (±9.42)	21.33 (±6.47)	35.50 (±7.01)	<0.01
UMSARS Part 2 (/56)	25.50 (±11.15)	20.92 (±9.27)	34.67 (±9.10)	<0.01
UMSARS Part 4 (/5)	3.00 (±1.19)	2.41 (±0.90)	4.17 (±0.75)	<0.01

Data are presented as number or mean (±SD).
BMI, body mass index; Sub-type P, Parkinsonian; Sub-type C, cerebellar; n.s., not significant.

basic information and the cognitive function, no significant difference was observed between the groups. However, %VC, %FVC, %PImax, and %PEmax were significantly higher in the air stacking group than in the non-air stacking group. Scores for H&Y, SARA, MDS-UPDRS part 3, and UMSARS part 1, part 2, and part 4 were significantly higher in the non-air stacking group than in the air stacking group.

Figure 1 shows the inspiratory volume changes with the use of MIC in both groups. In the air stacking group (squares), the mean inspiratory volume without MIC was 2884.2 (±1138.4) mL and that with MIC was 3570.8 (±1174.6) mL. The application of MIC significantly increased inspiratory volume ($P<0.01$). In the non-air stacking group (diamond symbols), the mean inspiratory volume without MIC was 1701.7 (±769.3) mL and that with MIC was 2308.3 (±1040.4) mL. Similarly, the respiratory volume was significantly increased with the use of MIC ($P<0.05$). **Figure 2** shows the changes in PCF with application of MIC and MAC. **Figure 2a** shows that PCF in the air stacking group (solid line) was significantly increased with the use of MIC (from 316.7±129.0 L/min to 372.5±141.9 L/min, $P<0.01$). In the non-air stacking group (dotted line), the use of MIC increased PCF from 123.3±89.1 L/min to 161.7±88.9 L/min, but the increase was not significant ($P=0.13$). **Figure 2b** shows the changes of PFC with the use of MAC. Application of MAC in the air stacking group (solid line) produced no significant difference (from 316.7±129.0 L/min to 328.3±123.6 L/min, $P=0.73$). Similarly, the use of MAC in the non-air stacking group (dotted line) showed no significant difference (from 123.3±89.1 L/min to 155.0±100.1 L/min, $P=0.25$). **Figure 2c** shows the change of PCF when both MIC and MAC were applied. This combined application of MIC and MAC significantly increased PCF in the air stacking group (solid line) (from 316.7±129.0 L/min to 368.3±116.6 L/min, $P<0.01$). However, this combined application did not produce a significant increase of PCF in the non-air stacking group (dotted line) (from 123.3±89.1 L/min to 163.3±74.2 L/min, $P=0.11$).

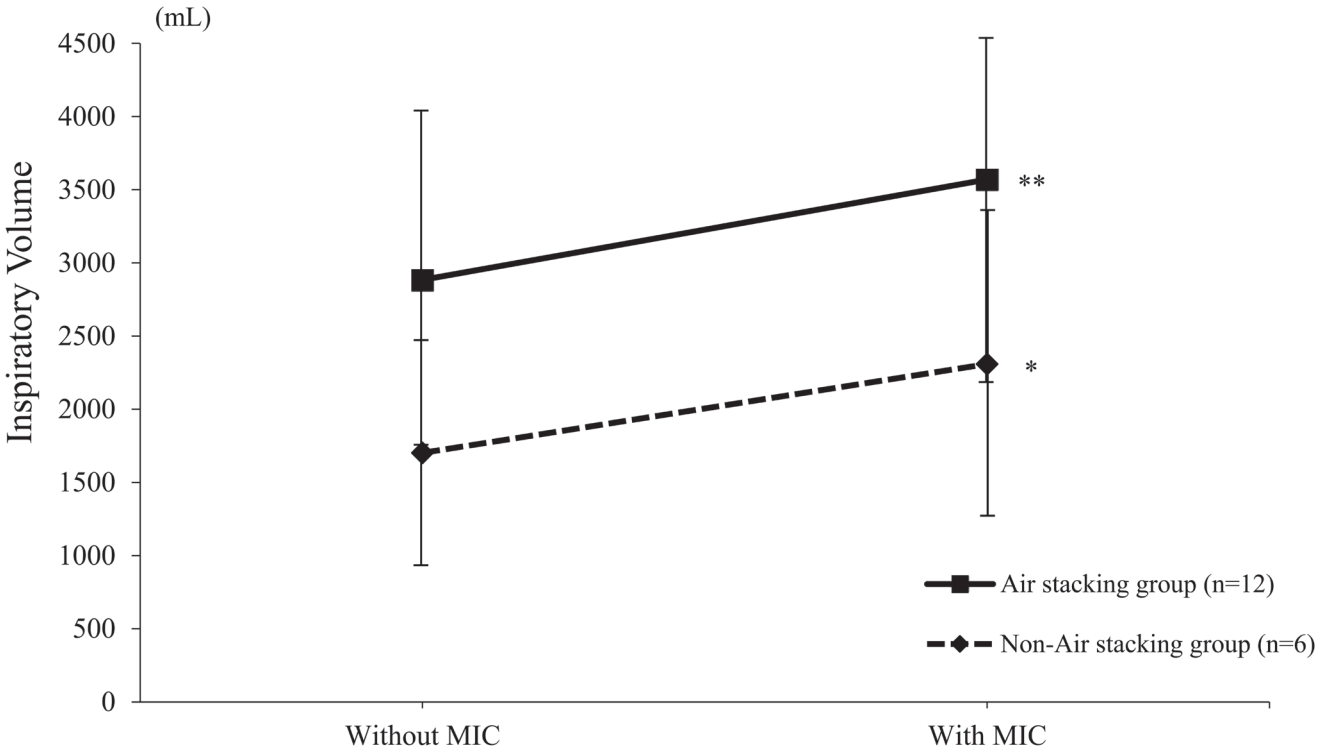

Fig. 1. Difference in inspiratory volume caused by the use of MIC in the air stacking group (squares) and the non-air stacking group (diamond symbols). Inspiratory volume measured without MIC refers to vital capacity.

The results of ROC analysis are presented in **Fig. 3. Figure 3a** shows that the %FVC cut-off value for discriminating SpC below 270 L/min was 74.5% (AUC=0.852, Sensitivity=0.778, Specificity=0.889, P<0.05), and **Fig. 3b** shows that the %FVC cut-off value for discriminating SpC below 160 L/min was 59.0% (AUC=0.958, Sensitivity=0.917, Specificity=1.0, P<0.01). Similarly, the %FVC cut-off value for discriminating SpC+MIC below 270 L/min was 70.5% (AUC=0.935, Sensitivity=0.818, Specificity=1.0, P<0.01, **Fig. 3c**), and the %FVC cut-off value for discriminating SpC+MIC below 160 L/min was 59.0% (AUC=0.946, Sensitivity=0.786, Specificity=1.0, P<0.01, **Fig. 3d**).

DISCUSSION

To the best of our knowledge, this is the first report to clearly indicate that an effective rehabilitative approach can improve cough function in MSA patients. First, we observed that inspiratory volume was significantly increased by MIC. Second, we found that PCF was successfully augmented by MIC in the air stacking group. Third, it seemed difficult to maintain PCF at 160 L/min when %FVC fell below 59% even though MIC was provided.

A previous study reported that MSA with predominant cerebellar ataxia was more common than Parkinsonian type MSA in Japan.[27] In addition, there was no significant difference after a disease duration of approximately 5 years when patients with MSA were divided into those with and without vocal cord dysfunction.[28] Therefore, MSA patients in this study are equivalent to those in natural history studies.

This study revealed that the inspiratory volume in patients with MSA could be significantly increased by applying MIC (**Fig. 1**). In the cough function of healthy subjects, deep inspiration before coughing reaches 85%–90% of the inspiratory volume, and a total cough volume of about 2.3 L is reached to achieve sufficient PCF.[29] In addition, a pre-cough lung volume is essential to generate an effective cough in patients with neuromuscular disease whose inspiratory and expiratory muscles are severely impaired.[30] At the time of this study, %VC, %FVC, %PImax, and %PEmax had already decreased in both groups (**Table 1**). For patients with MSA who have difficulty achieving sufficient deep inspiration without assistance, application of MIC may be recommended as an essential method to facilitate deep inspiration before coughing.

PCF was found to be significantly improved by provid-

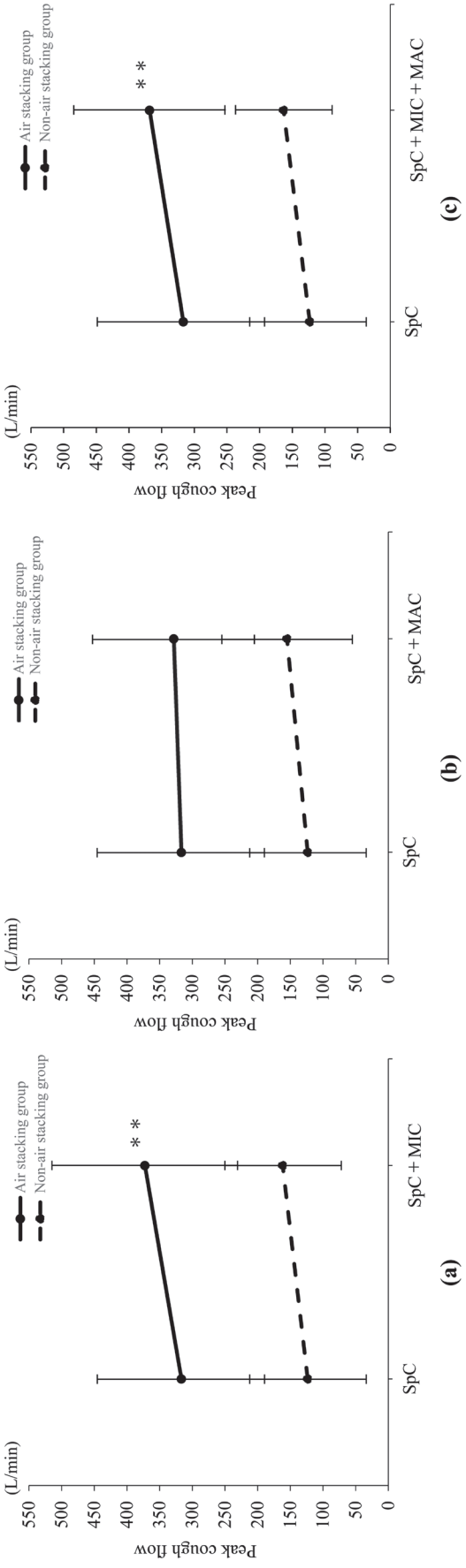

Fig. 2. Comparison of PCF in the air stacking group (solid line) and non-air stacking group (dotted line) and the effects of different cough augmentation methods. (a) Change of PCF with MIC (SpC + MIC); (b) change of PCF with MAC (SpC + MAC); (c) change of PCF with combined application of MIC and MAC (SpC + MIC + MAC).

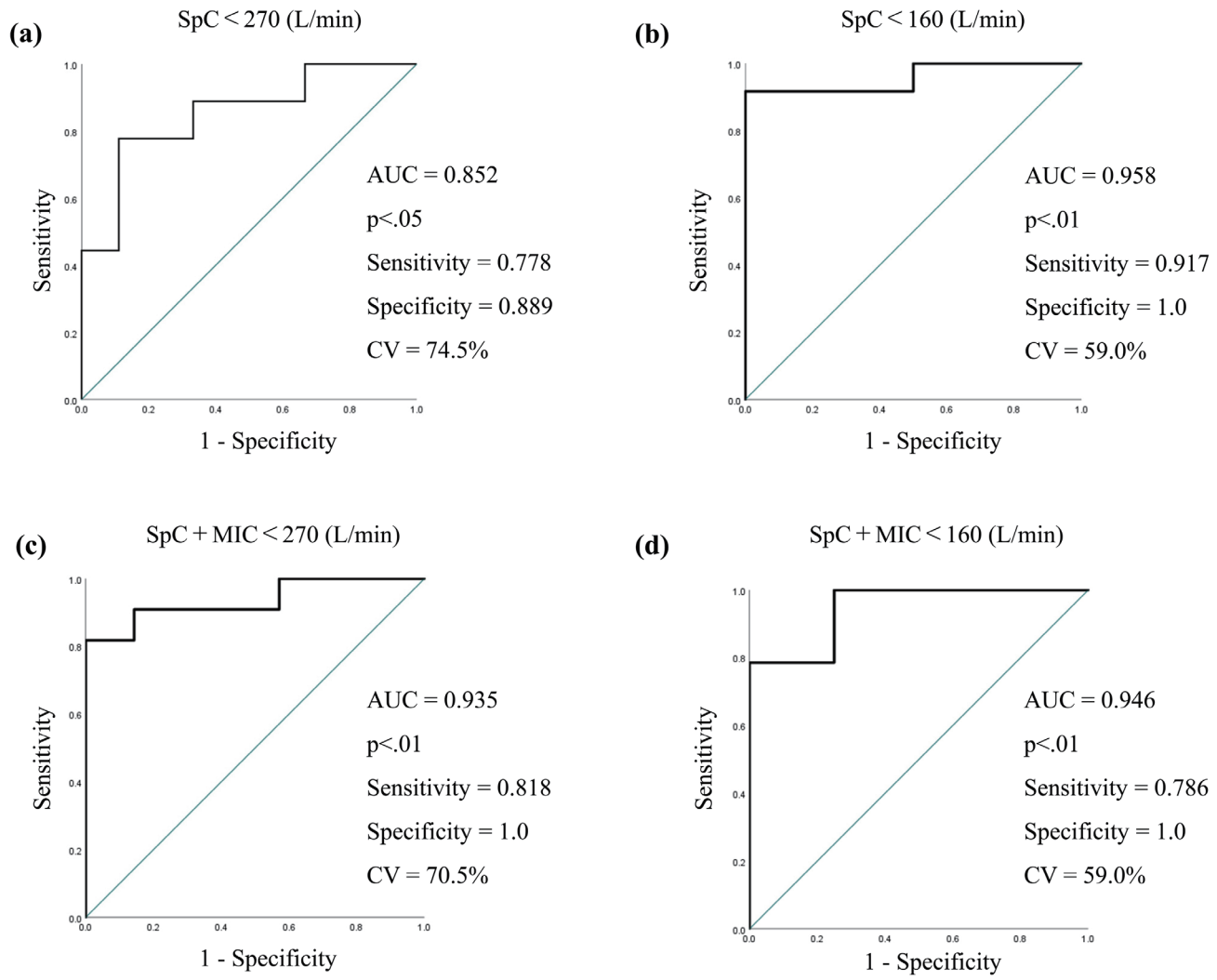

Fig. 3. ROC analysis of %FVC. Plots show %FVC cut-off values for: (a) discriminating SpC below 270 L/min, (b) discriminating SpC below 160 L/min, (c) discriminating SpC+MIC below 270 L/min, and (d) discriminating SpC+MIC below 160 L/min.

ing MIC (**Fig. 2**). However, in the non-air stacking group, various cough assistance methods including MIC and MAC did not lead to a significant increase in PCF. Improvement in PCF with the use of MIC is likely caused by lengthening of the expiratory muscles by sufficient inspiration (length–tension relationship), which increases intrathoracic pressure and leads to strong PCF.[25] In this study, expansion of the expiratory muscle group and increase in intrathoracic pressure may be caused by MIC. However, even in the air stacking group, MAC alone did not improve PCF. A study investigating the limitations of cough augmentation found MAC to be ineffective in patients with neuromuscular disease with a VC greater than 1910 mL.[31] For patients in this study who could achieve a sufficient inspiratory volume, it was considered that compression of the thorax alone would not lead to PCF improvement. In the non-air stacking group, cough augmentation with MIC and/or MAC did not improve PCF. By applying positive pressure, it was possible to achieve deep inspiration greater than the VC. However, the inability of some patients to hold their breath may have rendered any increase in intrathoracic pressure as insufficient because of air leakage. Therefore, in MSA patients with insufficient ability to hold their breath, it may be difficult to increase PCF with MIC and/or MAC.

According to the ROC curve results, when %FVC is 74.5% or lower, spontaneous cough strength is less than 270 L/min. However, by adding MIC to assisted coughing, the cut-off value was maintained at 70.5%, indicating that effective ex-

pectoration could be extended to that point. Previous studies reported that MIC is improved by intervention even though VC decreases as the disease progresses.[32] Increasing the pre-cough inspiratory volume by MIC may extend the period of clinically effective sputum expectoration. However, when %FVC is 70.5% or lower even with MIC, PCF becomes less than 270 L/min. In general, when PCF falls below 270 L/min, other coughing methods should be considered.[15,24] Therefore, when %FVC falls below 70.5%, the methods of cough augmentation performed in this study are not effective, and other cough augmentation methods such as the mechanical insufflation-exsufflation need to be considered. Furthermore, it was found that PCF could not be maintained at 160 L/min when %FVC fell below 59% even when MIC was performed. It is known that PCF below 160 L/min signifies insufficient secretion clearance, and endotracheal intubation may be necessary.[24–26] Patients with MSA present with dysphagia.[6] Swallowing difficulty can lead to pneumonia and suffocation. Gastrostomy tube feeding is usually performed for MSA patients showing repeated episodes of aspiration.[6] From the results of this study, the introduction of gastrostomy tube feeding for patients with MSA should be considered when the cough function and respiratory function are insufficient.

This study has some limitations. First, the total of 18 out of 24 consecutive patients who participated in this study was a small sample size. There are approximately 12,000 MSA patients in Japan. Because MSA is a rare disease, the sample size in previous studies on MSA in Japan was generally in the range of 20 to 50 people over a 5-year research period. Considering the low prevalence of MSA in Japan, the result of this study is clinically meaningful, although the sample size for our study was small. Future studies should be performed with more participants to improve the accuracy of research results. Second, this study was conducted as a single-facility intervention. A single source of patients could be insufficient to make a trial of viable size and may be associated with bias of the subjects and the risk of overestimation of intervention results when compared with a multicenter trial. In addition, after extensive research, we found no previous studies on rehabilitative interventions for respiratory muscle strength or cough strength. Given the rare nature of this disease, multicenter collaborative research should be conducted in the future. Third, this study used a cross-sectional study design. In future studies, it is desirable to assess the long-term effects of cough augmentation techniques as applied in this study for MSA patients. In particular, the effects of these techniques when they are applied repeatedly should be clarified.

CONCLUSION

By applying positive pressure with MIC, it was possible to increase inspiratory volume just before coughing and to enhance PCF. Furthermore, when %FVC was less than 59%, the effect of cough augmentation became insufficient. Therefore, the results of this study indicate the performance cut-off when consideration should be given to the necessity of securing safe nutritional intake via gastrostomy.

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CONFLICTS OF INTEREST

Mieko Ogino received honoraria for lecturing from Takeda Pharmaceutical. The remaining authors declare no conflict of interest.

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