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Effects of Bronchodilators on Regional Lung Sound Distribution in Patients with Chronic Obstructive Pulmonary Disease

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Key Words
Lung sound · Pulmonary function · Impulse oscillometry

Abstract
Background: Bronchodilators have been reported to influence regional lung ventilation in patients with chronic obstructive pulmonary disease (COPD), which may change regional lung sound distribution. Vibration response imaging (VRI) is a lung imaging system for the assessment of breath sounds. ***Objective:*** To evaluate the effects of a short-acting β_2-agonist (SABA) on the regional distribution of lung sounds in COPD patients. ***Methods:*** A double-blind crossover trial was performed to compare the treatment of COPD patients with an SABA (20 μg of inhaled procaterol) versus a placebo. The percentage of regional lung sound energy [quantitative lung data (QLD)] was evaluated with VRI. VRI, spirometry, and impulse oscillometry (IOS) were performed immediately before and 30 min after SABA administration. ***Results:*** Ten male patients (69.6 ± 14.2 years of age, percentage predicted forced expiratory volume in 1 s: 43.8 ± 16.9%) were evaluated. The use of an SABA produced significant functional improvements in the spirometric and IOS measurements. Among the homogeneous emphysema patients (n = 7), the upper-lung QLD decreased (from 24.2 ± 5.8 to 18.8 ± 6.1%, $p < 0.05$) and the lower-lung QLD increased (from 37.9 ± 12.7 to 46.1 ± 14.3%, $p < 0.05$) following SABA inhalation. However, the significant redistribution of the regional lung QLD to the lower-lung field was not observed in 2 of the 3 inhomogeneous emphysema patients. ***Conclusion:*** The additional use of an SABA by COPD patients improved their pulmonary function, which was accompanied by changes in regional lung air flow. The distribution of emphysematous lesions and the bronchial reactivity to SABA appeared to affect the redistribution of the lung sounds following bronchodilator administration.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world [1]. This disease is characterized by progressive expiratory flow limitation, which leads to incomplete lung emptying and pulmonary hyperinflation, especially during exercise. Pulmonary hyperinflation can cause flattening of the diaphragm, which can impair the piston-like downward displacement capacity of that organ. Symptomatic COPD patients are usually treated with bronchodilators, such as long-acting inhaled anticholinergics and long-acting β_2-agonists [2–4]. Inhaled short-acting β_2-agonists (SABAs) have a relatively rapid onset of action and are used as a standard method to reduce symptoms in

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patients with COPD [5, 6]. These bronchodilators have been reported to produce improvements in exercise tolerance, health-related quality of life, and the exacerbation rate by improving airflow and hyperinflation [7].

Aliverti et al. [8] reported that the use of salbutamol increased forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and inspiratory capacity (IC); it also reduced resting functional residual capacity. The salbutamol-induced decrease in the functional residual capacity was accomplished by decreasing the volume of the abdomen rather than that of the total chest wall. These bronchodilator effects appeared to cause a change in regional lung ventilation.

Kirby et al. [9] used magnetic resonance imaging with inhaled hyperpolarized ^{3}He to evaluate regional structure-function measurements in COPD subjects, and they reported a change in gas distribution following bronchodilator administration. Kirby et al. suggested that the newly ventilated lung regions were not more emphysematous than the lung regions of interest that participated in ventilation prior to bronchodilator administration. Furthermore, they concluded that the bronchodilator use caused a reduction in regional gas trapping. The elucidation of the relationship between regional lung structure and regional ventilation following bronchodilator administration in COPD patients, in whom the distribution of emphysematous or bronchial lesions is thought to vary, may provide new insights for evaluating the clinical benefits of bronchodilators for individual patients. However, the use of magnetic resonance imaging with inhaled hyperpolarized ^{3}He is limited by high costs and poor accessibility.

Airflow in the lung vibrates the airway wall and produces breath sounds. A correlation between breath sound recordings and the regional distribution of pulmonary ventilation has been reported, particularly in studies comparing acoustic findings with data obtained with radioactive gases in normal subjects [10, 11]. Regional lung sounds may be influenced by improvements in regional lung ventilation induced by bronchodilator administration. Vibration response imaging (VRI) is a commercially available acoustic lung imaging system that displays breath sound energy distribution as a dynamic grey-scale image [12–15]. VRI is a noninvasive, radiation-free technique that requires minimal patient effort and can be transported to the bedside [16, 17]. We recently reported that the locations of central airway obstructions and the outcomes of procedures could be reliably identified by analyzing the specific patterns of lung images obtained with the use of VRI [18]. Additionally, reports of the application of VRI in the diagnosis of obstructive pulmonary diseases have been published [19–21].

We postulated that SABA-induced changes in regional lung ventilation would alter regional lung sound distributions, which would be influenced by lung architecture or bronchial responsiveness to SABAs among COPD patients. We conducted a pilot study to examine the effects of an SABA on pulmonary function and the accompanying changes in lung sound distribution using VRI in patients with moderate-to-severe COPD.

Methods

Subjects

We recruited 11 patients who had been previously diagnosed with moderate-to-severe COPD according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). All the patients were ex-smokers, and the inclusion criteria were a postbronchodilator FEV_1/FVC ratio of <0.7 and a predicted FEV_1 of <80%. The predicted values of the spirometric measurements were derived from the guidelines of the Japanese Respiratory Society [22]. Patients were excluded from the study if they had received a clinical diagnosis of asthma or bronchiectasis. The ethics committee of the St. Marianna University School of Medicine approved this study, and written informed consent was obtained from all the participants. This study is registered with the University Hospital Medical Information Network (UMIN-CTR, No. UMIN000003174).

Study Design

The study was conducted as a double-blind, randomized, crossover trial and was performed at a single center (St. Marianna University Hospital, Kanagawa, Japan). The patients received either a single 20-μg dose of inhaled procaterol (an inhaled SABA, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) or a placebo on each of the two study days, which were separated by 4 weeks. A pharmacist advised the patients on how to use the inhaler devices on each study day. The patients were permitted to continue using long-acting bronchodilators, such as tiotropium, salmeterol, transdermal turobuterol or theophylline, throughout the duration of the study. All of the tests were performed at approximately the same time of day. The tests were performed in the following order: impulse oscillometry (IOS), VRI, and spirometry. The patients underwent a 6-min walking test (6MWT) at the end of each study day.

Pulmonary Function Tests

Spirometry was performed with a calibrated spirometer (HI-801, Chest M.I., Inc., Tokyo, Japan). Prior to testing, calibration checks were performed using a 3-liter calibration syringe, with ambient air to ensure correct equipment function. Spirometry was performed before and 30 min after inhaler use according to the American Thoracic Society guidelines. FVC, IC, FEV_1, maximum expiratory flow rate at 50% of FVC, and maximum expiratory flow rate at 25% of FVC were recorded. For IOS (Masterscreen IOS; Erich Jaeger, Hoechberg, Germany), the subjects supported their cheeks, while impulses were applied during tidal breathing. The average inspiratory and expiratory respiratory resistance (R) and reactance (X) values were calculated at 5 Hz (R5, R5ins, R5exp, X5, X5ins, and X5exp). Additionally, the respiratory resistance at

20 Hz (R20) and the resonant frequency were recorded. The IOS measurements were performed in triplicate and the mean IOS values were used for further analysis.

VRI Recordings

The VRIxp System (Deep Breeze, Ltd., Or Akiva, Israel) is a computer-based acoustic lung imaging platform that was developed to acquire, quantify, monitor, and store breath sounds. Breath sounds were recorded using the VRI device as previously described [12, 13] with 7-row arrays; 6-row arrays were used if the height of the subject was less than 165 cm. Each subject was seated in a quiet environment with their hands resting in their laps. The right and left planar arrays were placed symmetrically on the subject's back using a low-vacuum, computer-controlled method. The two bottom-row arrays were positioned at approximately the same height as the two arrays that were parallel to the vertebral column. The recording was performed over a 12-second period, while the subject took deep, regular breaths at a rate of 15–20 breaths per minute. VRI software (Deep Breeze) was used to calculate the regional quantitative lung data (QLD). The breathing of each subject was recorded at least 3 times, and the VRI recording with the highest technical quality was chosen for evaluation.

High-Resolution Computed Tomography

All of the patients were scanned with a 64-detector CT scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan). The CT was conducted during a deep inspiration breath-hold with the patient in the supine position. Prior to the CT examination, each patient was carefully instructed on how to breathe during the examination. The CT parameters for the inspiratory scans were as follows: collimation 0.5 mm, 120 kVp, 200 mA, gantry rotation time 0.5 s, and beam pitch 0.83 (table feed per gantry 53 and collimation beam width 64). All images were reconstructed using a standard algorithm, with a slice thickness of 1 mm and a reconstruction interval of 0.5 mm.

The CT images were transferred to a personal computer for the quantitative analysis of emphysema. Three CT slices were selected from each series of CT scans for each subject. The upper cranial slice was obtained 1 cm above the upper margin of the aortic arch, the middle slice was obtained 1 cm below the carina, and the lower caudal slice was obtained 1 cm below the right inferior pulmonary vein. These CT images were then analyzed using a semiautomatic image processing program (Image J version 1.40 g, a public domain Java image-processing program available at http://rsb.info.nih.gov/ij/). This program uses a semiautomatic threshold technique to isolate the lungs from other tissues and structures, and it selects all of the pixels between –500 and –1,024 HU. Minimal user intervention was required to exclude the nonlung structures that satisfied the threshold criteria, such as the trachea, blood vessels, and large bronchi near the hilum. Low-attenuation areas (LAA) between –950 and –1,024 HU were then identified as emphysema in the upper-, middle-, and lower-lung fields. A threshold value of –950 HU was selected because this threshold has been macroscopically and microscopically validated for thin-section CT studies of the extent of emphysema [23]. The percentage of the LAA that was less than –950 HU for the entire lung area (%LAA) was calculated for both the right and left sides of the upper-, middle-, and lower-lung fields as follows: %LAA = (LAA/each whole-lung area) × 100 (%). We defined emphysema-dominant COPD as an averaged regional %LAA of more than 25%, and we defined heterogeneous emphysema as a greater than 25% difference between the %LAAs of three lung fields.

Table 1. Characteristics of subjects (n = 10)

Males/females	10/0
Age, years	69.6±14.2
Range	32–80
Body mass index	22.1±3.1
Smoking status	ex-smoker
Smoking history, pack-years	68.9±37.0
Baseline lung function	
FVC, % predicted	80.9±17.2
FEV_1, % predicted	43.8±16.9
Ratio of FEV_1/FVC	42.0±9.1
GOLD stage	
II	5
III	4
IV	1
Medication for COPD	
Long-acting inhaled anticholinergics	10
Long-acting β_2-agonists	4
Inhaled	2
Transdermal	2
Inhaled corticosteroids	0
Theophylline compound	3
Supplemental oxygen	1

Values represent number or mean ± SD.

Statistical Analysis

The data are expressed as means ± standard deviation. The measurements of IOS, spirometry, and regional lung QLD before and after the inhalation of procaterol or placebo were compared. These paired data were compared using the Wilcoxon t test. $p < 0.05$ was considered to be statistically significant.

Results

Between 13 February 2010 and 11 June 2011, 11 patients were recruited; however, a VRI sensor array could not be attached to 1 patient due to the bony nature of the structure of his back. Thus, statistical analyses were performed for 10 patients. The patient characteristics and pulmonary function data are shown in table 1. Four patients were treated with tiotropium, 2 with tiotropium and salmeterol, 2 with tiotropium and theophylline, 1 with tiotropium and transdermal tulobuterol, and 1 with tiotropium, transdermal tulobuterol and theophylline. Two patients were prescribed an inhaled SABA for use as required. One of these patients needed an inhaled SABA every morning (07:00), whereas the other patient could forgo the inhaled SABA for more than 8 h before the administration of the study medication.

No adverse events were reported after the inhalation of the study drugs. The placebo had no effect on the pul-

Table 2. Procaterol effects on regional lung airflow

	Placebo		Procaterol	
	before inhalation	after inhalation	before inhalation	after inhalation
Spirometry				
FVC, l	2.63±0.45	2.64±0.44	2.66±0.58	2.80±0.58
IC, l	1.82±0.42	1.81±0.06	1.75±0.43	1.89±0.44*
FEV_1, l	1.12±0.35	1.12±0.31	1.15±0.37	1.25±0.40*
MEFR50%	0.47±0.21	0.47±0.19	0.48±0.21	0.55±0.23*
MEFR25%	0.20±0.08	0.18±0.06	0.22±0.10	0.23±0.10
IOS				
R5, kPa/l/s	0.37±0.10	0.40±0.12	0.38±0.10	0.31±0.10*
R5insp	0.33±0.08	0.32±0.09	0.31±0.10	0.27±0.08*
R5exp	0.40±0.12	0.44±0.15	0.42±0.12	0.33±0.11**
R20, kPa/l/s	0.23±0.05	0.24±0.06	0.24±0.08	0.20±0.04*
R5 – R20, kPa/l/s	0.14±0.08	0.16±0.09	0.13±0.07	0.11±0.08*
X5, kPa/l/s	–0.19±0.08	–0.21±0.11	–0.19±0.10	–0.17±0.13
X5insp	–0.16±0.04	–0.16±0.05	–0.15±0.06	–0.13±0.06*
X5exp	–0.22±0.12	–0.26±0.20	–0.21±0.15	–0.22±0.23
Resonant frequency, Hz	23.4±5.9	24.2±5.6	22.4±5.9	19.9±6.5**
QLD, %				
Right				
Upper	10.5±4.0	11.2±4.7	12.8±4.0	9.8±5.2*
Middle	16.4±6.5	16.6±4.9	20.3±6.3	16.5±6.4
Lower	17.7±11.3	16.9±9.1	20.5±12.0	18.6±10.6
Left				
Upper	14.9±7.9	13.1±4.7	11.8±4.0	12.5±5.6
Middle	21.1±5.3	20.8±6.8	16.9±5.4	18.4±5.0
Lower	19.4±7.8	21.3±7.6	17.7±10.3	24.2±11.8*

Continuous valuables before and after inhalation were tested with Wilcoxon's t test. Values are represented as means ± standard deviation. * $p < 0.05$, ** $p < 0.01$. MEFR50% = Maximum expiratory flow rate at 50% of FVC; MEFR25% = maximum expiratory flow rate at 25% of FVC; R20 = respiratory resistance at 20 Hz; X = respiratory reactance; insp = values measured during inspiration; exp = values measured during expiration.

monary function tests or regional lung QLD (table 2). Procaterol use significantly increased IC, FEV_1 and maximum expiratory flow rate at 50% of FVC, according to the spirometry results, and produced significant changes in the IOS parameters, excluding the X5 and X5exp values (table 2). There were no significant differences in the 6MWT distances between the procaterol and placebo groups (procaterol: 430 ± 56 m, placebo: 428 ± 59 m). Although the right upper-lung QLD was significantly reduced (from 12.8 ± 4.0 to 9.8 ± 5.2%, $p < 0.05$), and the left lower-lung QLD was significantly increased (from 17.7 ± 10.3 to 24.2 ± 11.8%, $p < 0.05$) after procaterol inhalation (table 2), there were no significant changes in the total upper, middle, or lower QLDs.

To study the effects of structural changes in the lungs on lung sound distribution, we compared the distribution of emphysematous lesions as indicated by the chest high-resolution CT (HRCT) results and the procaterol effects on the regional lung QLD (table 3). Among the patients with homogeneous emphysema (n = 7), the total QLD of the upper lung was significantly decreased after procaterol inhalation, whereas the total QLD of the lower lung was significantly increased (fig. 1; upper-lung QLD: from 24.2 ± 5.8 to 18.8 ± 6.1%, $p < 0.05$; lower-lung QLD: from 37.9 ± 12.7 to 46.1 ± 14.3%, $p < 0.05$). Figure 2 shows the HRCT findings and the VRI recordings for case 3. This subject was a 77-year-old male with stage 2 COPD (predicted FEV_1 = 51.5%, predicted FVC = 91.9%) and an average %LAA of 51.5%. Procaterol inhalation decreased the upper-lung QLD and increased the lower-lung QLD. In case 4 (upper-lung-dominant emphysema) and case 6 (non-emphysema-dominant COPD with a higher %LAA in the lower-lung field), the regional lung sound energy shifted from the emphysematous field to a more pre-

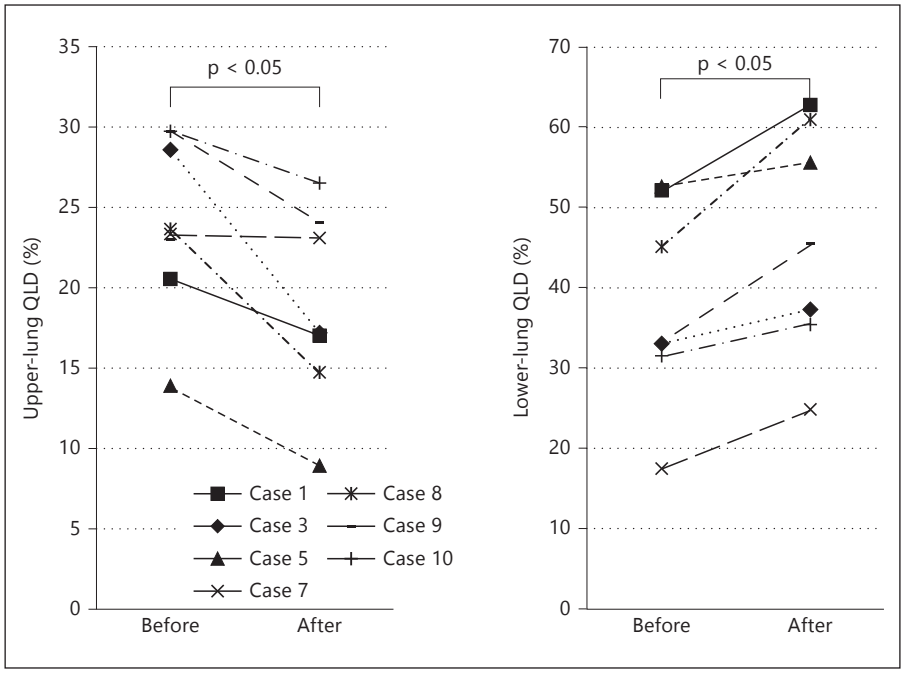

Fig. 1. Among the patients with homogeneous emphysema (n = 7), the total QLD of the upper lung was significantly decreased after procaterol inhalation, whereas the total QLD of the lower lung was significantly increased (upper-lung QLD: from 24.2 ± 5.8 to 18.8 ± 6.1%, $p < 0.05$; lower-lung QLD: from 37.9 ± 12.7 to 46.1 ± 14.3%, $p < 0.05$).

Table 3. Distribution of emphysematous lesions on chest HRCT and procaterol effects on regional lung QLD

	%LAA				Change in QLD, %[a]		
	upper	middle	lower	phenotype	upper	middle	lower
Case 1	77.6	79.8	68.3	hom-E	–3.55	–7.22	10.78
Case 2	59.0	42.0	23.6	het-E	8.30	4.55	–12.87
Case 3	57.9	44.9	51.8	hom-E	–11.38	6.98	4.40
Case 4	58.0	42.0	31.6	het-E	–3.30	–3.97	7.25
Case 5	36.5	27.7	33.2	hom-E	–4.94	1.94	3.00
Case 6	8.7	7.6	20.6	non-E	10.82	–4.84	–5.98
Case 7	57.8	52.2	52.0	hom-E	–0.29	–7.10	7.39
Case 8	37.1	33.2	19.4	hom-E	–8.93	–6.93	15.86
Case 9	22.9	21.1	33.9	hom-E	–5.63	–6.79	12.40
Case 10	69.5	68.1	65.2	hom-E	–3.23	–0.69	3.90

hom-E = Homogeneous emphysema; het-E = heterogeneous emphysema; non-E = emphysema nondominant.
[a] QLD of after inhalation – QLD of before inhalation.

served lung field (upper to lower in case 4 and lower to upper in case 6). However, the QLD of the most emphysematous fields increased after bronchodilator use in case 2. Figure 3 shows the HRCT and VRI data for case 2, a 73-year-old male with stage 3 COPD (predicted FEV_1 = 33.0%, predicted FVC = 65.1%) and an average %LAA of 41.6%. His bilateral upper-lung QLD was increased after procaterol inhalation, whereas the bilateral lower-lung QLD was decreased.

Discussion

This is the first study to simultaneously evaluate the effects of bronchodilator use on pulmonary function and regional lung sound distribution in patients with COPD. We found that an SABA (procaterol) caused improvements in pulmonary function that were accompanied by changes in regional lung sound distribution in moderate-to-severe COPD patients, whereas the placebo caused no

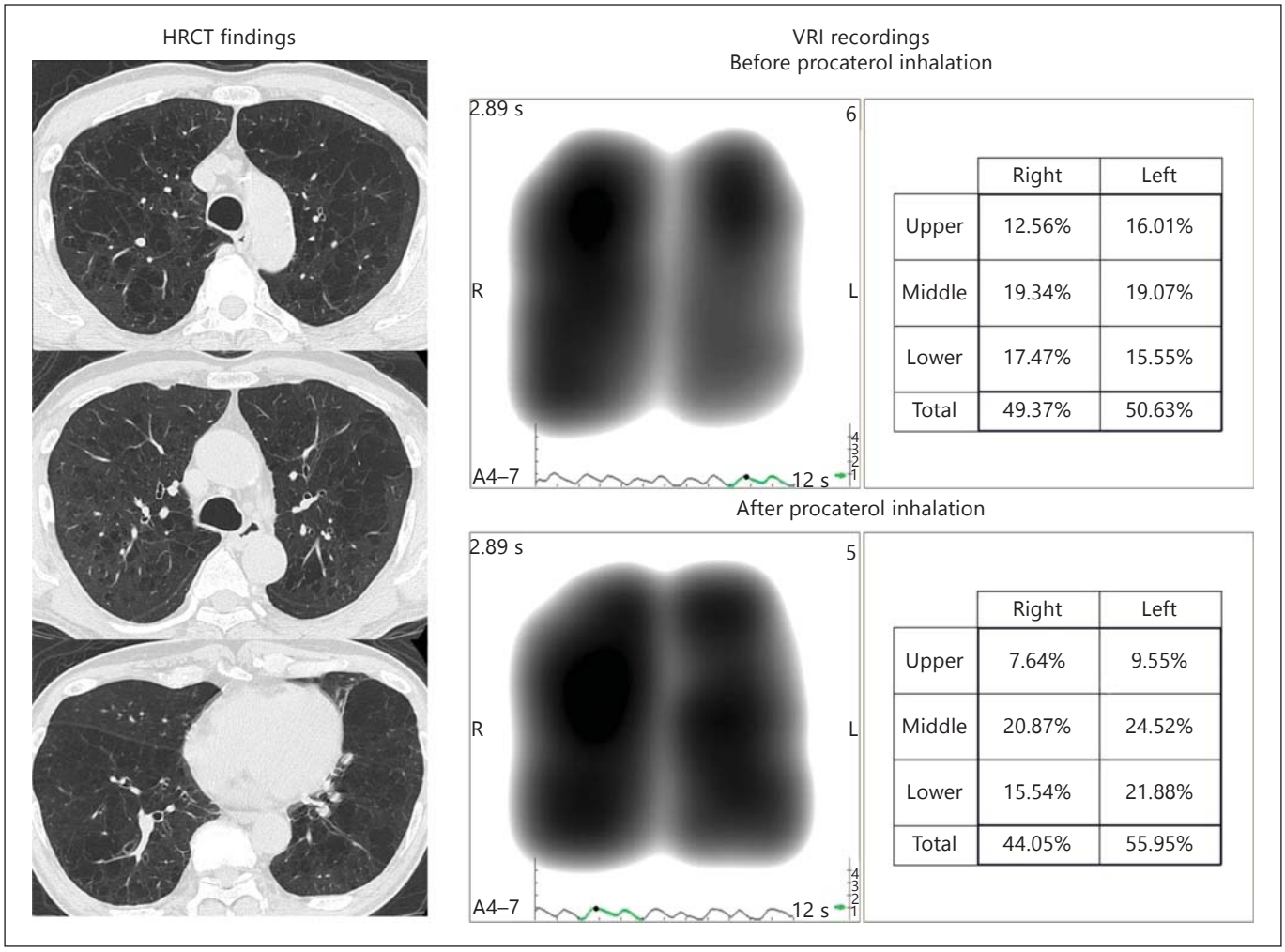

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Fig. 2. HRCT and VRI data for case 3, a 77-year-old male with stage 2 COPD (predicted FEV_1 = 51.5%, predicted FVC = 91.9%) with homogeneous emphysema and an average %LAA of 51.5%. Procaterol inhalation decreased the upper-lung QLD and increased the lower-lung QLD.

significant changes. However, the patterns of change in lung sound distribution after bronchodilator use were different between COPD patients with homogeneous emphysema and other types of COPD patients.

In homogeneous emphysema, the redistribution of vibration energy to lower-lung regions after bronchodilator use may be a surrogate marker of improved diaphragm movement. In inhomogeneous emphysema, the relationship between regional lung structure and the airflow shift after bronchodilator use may vary between patients. Hatipoğlu et al. [24] reported that an SABA (albuterol) relieved dyspnea and enhanced respiratory muscle output, which could be explained by a lengthening of the diaphragm due to decreased lung volume. Bronchodilator administration appears to improve diaphragm movement by deflating the lungs, which may lead to increased ventilation of the lower-lung field and an airflow shift to that field. Dellinger et al. [16] reported the redistribution of vibration energy to lower-lung regions in pressure-targeted modes of mechanical ventilation and speculated that the physiological mechanism might involve an increase in the downward movement of the diaphragm. Therefore, prior to this study, we expected that the pulmonary function improvements caused by bronchodilators might be accompanied by incremental changes in lower-lung breath sound energy. Indeed, we observed this relationship in patients with homogeneous emphysema. In 7 homogeneous patients, the regional lung QLD,

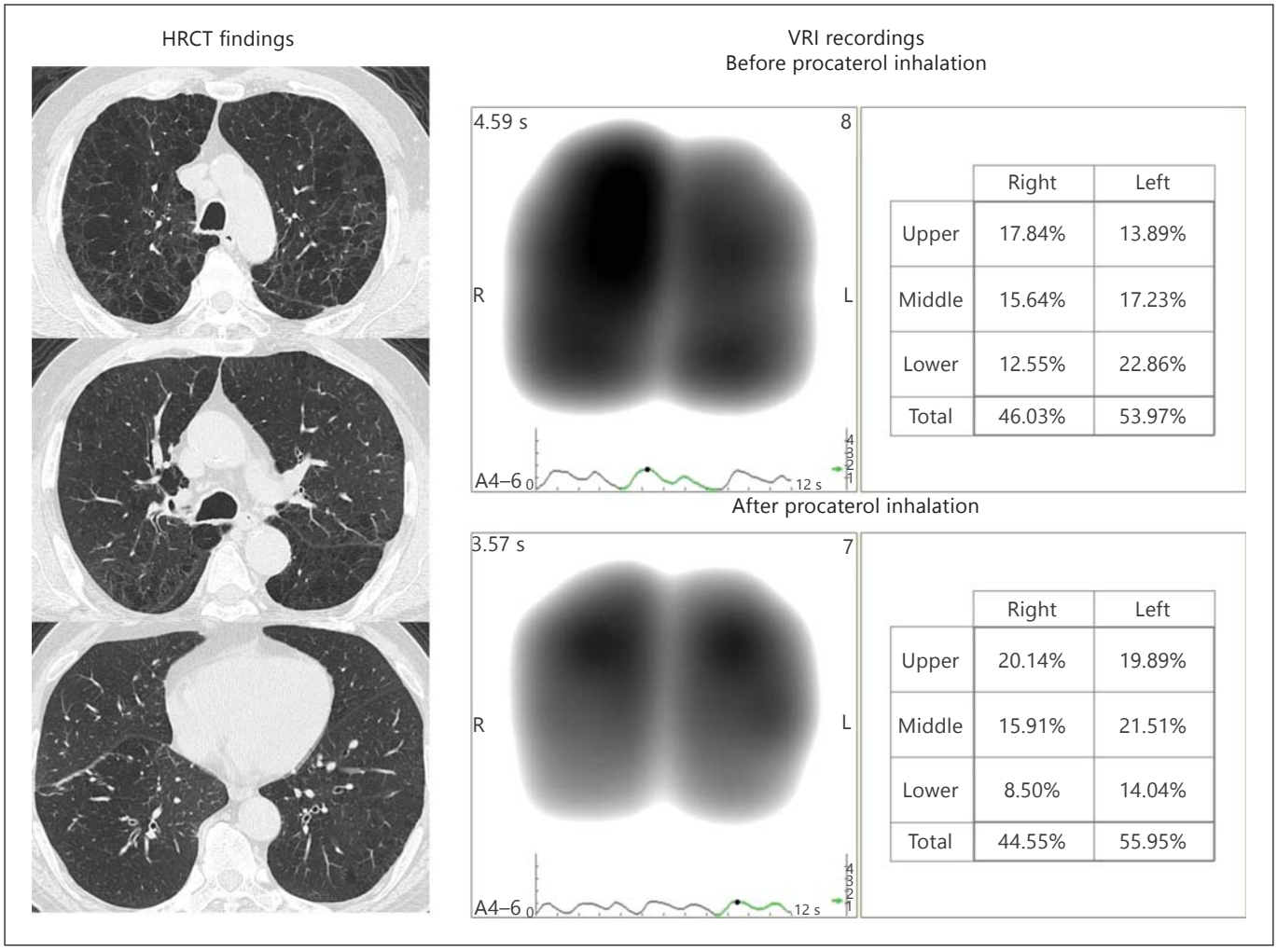

Fig. 3. HRCT and VRI data for case 2, a 73-year-old male with stage 3 COPD (predicted FEV_1 = 33.0%, predicted FVC = 65.1%) with nonhomogeneous emphysema and an average %LAA of 41.6%. His bilateral upper-lung QLD was increased after procaterol inhalation, whereas his bilateral lower-lung QLD was decreased.

which was considered a possible surrogate marker for regional lung airflow, was decreased in the upper-lung field and increased in the lower-lung field after SABA inhalation. In patients with homogeneous emphysema, analyzing lung sound distributions may be useful for assessing diaphragm movement after COPD treatment.

We considered the changes in lung sound distribution following bronchodilator administration that were observed in the patients with heterogeneous emphysema and nonemphysema COPD to be influenced by heterogeneities in the lung structure, such as differences in the distribution of emphysematous lesions or in the reactivity of the bronchus to inhaled bronchodilators. In COPD, bronchodilators are delivered primarily to the more normal lung regions [9]. This effect is beneficial for ventilation-perfusion matching. In this study, we found that the regional lung QLD of the more preserved lung regions was increased in one case of upper-lung-dominant emphysema and in one case of non-emphysema-dominant COPD. In these cases, the bronchodilator was thought to cause an airflow shift to the more normal lung field, and the increase in the regional QLD appeared to reflect this phenomenon.

However, we observed one case of heterogeneous emphysema in which the regional lung QLD of the relatively emphysematous upper lung increased after bronchodilator inhalation. In this case, the bronchodilator use actually changed the regional lung sound distribution, albeit

in an apparently discordant manner. If the increase in regional lung QLD reflected an airflow shift to the more damaged part of the lung, the ventilation-perfusion mismatch of this case may have been worsened. Not all COPD patients benefit from bronchodilator therapy, and there is only a weak relationship between the changes in spirometric parameters and the subsequent exercise capacity [25]. However, this patient experienced an improvement in the 6MWT distance (459–473 m), with a lower drop in SpO_2 levels during the 6MWT (from 10 to 7%) following procaterol inhalation. Therefore, a worsening of his ventilation-perfusion mismatch appeared to be unlikely.

One possible mechanism of bronchodilator activity in this case is that in bronchi dilated by SABA, the turbulence caused by airflow may decrease, which reduces the regional lung sound intensity. Conversely, the bronchi of more diseased lungs may not dilate sufficiently after SABA inhalation without a change in the regional lung sound intensity. As a result, the relative intensity of the lung sounds (QLD) throughout the diseased lung field is increased. Because this theory is based on speculation alone, further studies using quantitative CT or radioactive gases are required to find out the reason for this phenomenon. The relationship between regional lung structure and changes in regional lung sounds after bronchodilator use may vary, especially among heterogeneous or nonemphysematous COPD patients.

In this study, the use of long-acting bronchodilators was continued to avoid aggravating the patients' conditions. We also investigated whether the use of SABA really produced genuine physiological effects on the daily management of moderate-to-severe COPD. Because the effect of SABAs on spirometry is thought to be ameliorated by the regular use of long-acting bronchodilators, we added IOS as a more sensitive assessment to elucidate the physiological effects of an SABA [26, 27]. We found significant improvements using both IOS and spirometric assessments.

Although this was a pilot study with a small number of participants, we discovered changes in lung sound distribution accompanied by pulmonary function improvements following bronchodilator use by COPD patients. The redistribution of vibration energy to the lower-lung regions after treatment may be a surrogate marker for improved diaphragm movement, especially among homogeneous emphysema patients. Larger studies are needed to elucidate the relationships among lung architecture, the bronchial response to treatment, and changes in regional lung sound distribution.

In conclusion, the addition of SABA treatment in moderate-to-severe COPD patients improved pulmonary function, which was accompanied by a change in regional lung airflow. In homogeneous emphysema patients, the redistribution of vibration energy to lower-lung regions after bronchodilator administration may be a surrogate marker for the deflation of lungs accompanied by an improvement in the diaphragm movement. In inhomogeneous emphysema, the relationship between regional lung structure and the airflow shift after bronchodilator use may vary between patients.

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Financial Disclosure and Conflicts of Interest

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