Introduction

Patients suffering from central airway obstruction (CAO) can receive significant relief from life-threatening symptoms through interventional bronchoscopy. Performing interventional procedures at the exact location of the obstruction can provide the greatest functional benefit to patients [1–10].

We have applied multi-modal, objective assessments using technologies such as endobronchial ultrasonography, three-dimensional computed tomography scans, and impulse oscillation systems (IOS) to provide useful information on collapsible segments and choke points in CAO patients [10–14]. To evaluate the effects of intervention during the procedure, we have recently introduced airway pressure assessment. The lateral airway pressure is measured during intervention to physiologically evaluate tracheal obstruction, and we have found that lateral airway pressure measurement can estimate the need for additional procedures [13]. The abovementioned measurements provide valuable visual and physiological information on CAO that is essential for a favorable outcome after intervention.

Regarding physiological assessment, we have noticed distinct flow-volume curve patterns specific to the type of obstruction [10]. Although flow-volume curves are widely used and easy to perform in daily clinical settings, they cannot discriminate between the left and right lungs. Furthermore, in patients with bronchial obstruction, pulmonary function tests may not change significantly after intervention [16].

In patients with CAO, airflow in the lungs is severely disturbed by the obstructed airway. The airflow asynchrony in both lungs due to unilateral bronchial obstruction may be applicable as a physiological indicator in bronchial obstruction. Airflow asynchrony in central airway obstruction with bronchial involvement may provide useful physiological information for interventional bronchoscopy.
chrony may be evaluated by the difference in the left and right lung respiratory sound development in tidal breathing.

Airflow in the lung vibrates the airway wall and produces lung sounds. A correlation between lung 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 [16,17]. Recently, Shi et al. reported that measurements of regional ventilation distribution by lung sound were comparable to those obtained by electrical impedance tomography in a piglet model [18].

Lung sound recordings are evaluated quantitatively and qualitatively by computer software [18–27]. We reported that the location of the CAO and procedural outcomes were reliably identified according to specific patterns of lung sound distribution. Especially in unilateral bronchial obstruction, there was a consistent difference in the lung sound dynamics and intensity between the lungs. We found that the development of lung sound intensity of the obstructed side lagged behind that of the preserved side [19].

In bronchial asthma, asynchrony of the left and right lung sounds were detected by analyzing the gap between intensity peaks [25]. We speculated that analysis of left and right lung asynchrony using lung sound analysis might be a useful marker for main bronchial obstruction and as an outcome measurement for interventional bronchoscopy.

**Methods**

Between May 2007 and December 2011, we performed a prospective study that was approved by the Research Ethics Committee at St. Marianna University School of Medicine. Written informed consent was obtained from all patients.

Adult patients previously diagnosed with CAO were enrolled and classified into three groups: tracheal, bronchial and extensive obstruction (defined as an obstruction extending from the trachea, including the carina, to the bronchi). Lung sound analysis, pulmonary function tests (PFTs), and the modified Medical Research Council (MMRC) scale were measured before and after intervention.

For lung sound analysis, the vibration response imaging (VRI) device (VRIxp System, Deep Breeze, Or-Akiva, Israel) was used as previously described [19–22,26,27]. The VRIxp System is a computer-based acoustic lung imaging platform that was developed to acquire, quantify, monitor and store breath sounds. Breath sounds were recorded 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

**Table 1. Characteristics of patients with central airway obstruction.**

| Type of central airway obstruction n = 50 | Tracheal | Bronchial | Extensive |
|-----------------------------------------|---------|----------|-----------|
| n = 12                                  |         |          |           |
| n = 18                                  |         |          |           |
| n = 20                                  |         |          |           |
| Age, yr                                 | 57.5    | 51.7     | 58.1      |
| Range                                   | 35–77   | 17–71    | 34–75     |
| Sex                                     | Male    | 9        | 11        |
|                                         | Female  | 3        | 7         |
|                                         |         | 14       | 6         |
| Diagnosis                               |         |          |           |
| Lung cancer                             | 4       | 5        | 11        |
| Esophageal cancer                       | 2       | 2        |           |
| Thyroid cancer                          | 1       |          |           |
| Metastasis of colon cancer              | 1       |          |           |
| Germinal tumor                          | 1       |          |           |
| Tuberculosis                            | 8       | 4        |           |
| Wegener granulomatosis                  | 3       |          |           |
| Relapsing polychondritis                |         | 2        |           |
| Post intubation tracheal obstruction    | 2       |          |           |
| Others                                  | 1       | 2        | 1         |

**Figure 1. Receiver operating characteristic (ROC) validation of the gap index in the diagnosis of bronchial involvement in patients with central airway obstruction (CAO).** ROC validation of the gap index revealed that a cut-off point of 0.06 seconds showed 76.3% sensitivity, 91.7% specificity, and 80% accuracy in the differentiation between CAO with bronchial involvement (bronchial = 18 and extensive = 20) and tracheal obstruction (n = 12).

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Table 2. Pulmonary function tests and lung sound recordings of patients with central airway obstruction.

|                          | Central airway obstruction n = 50 |       |       |
|--------------------------|----------------------------------|-------|-------|
|                          | Tracheal (n = 12) | Bronchial (n = 18) | Extensive (n = 20) |
| Pulmonary function tests | FVC (l) | 2.98±0.34 | 2.67±0.16 | 2.32±0.15 |
|                          | (FVC/predFVC, %) | (83.9 ± 6.5) | (80.6 ± 4.0) | (68.0 ± 3.4)* |
|                          | FEV1 (l) | 1.09±0.18 | 1.65±0.11* | 1.39±0.12 |
|                          | (FEV1/predicted FEV1, %) | (39.7 ± 6.9) | (59.6 ± 3.8)** | (49.1 ± 3.4) |
|                          | FEV1/FVC(%) | 39.6±6.4 | 62.7±3.1** | 60.1±3.2** |
|                          | PEF (l/sec) | 1.85±0.22 | 4.54±0.46*** | 2.75±0.27 |
| Lung sound recordings     | Gap Index (sec) | 0.039±0.011 | 0.216±0.050* | 0.190±0.044* |

Comparisons between tracheal obstruction group and CAO with bronchial involvement (bronchial and extensive obstruction group) were performed by one-way ANOVA with Dunnett adjustment.

Values are represented as mean ± standard error *p<0.05, **p<0.01, ***p<0.001.

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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. Each subject was recorded at least three times, and the VRI recording with the highest technical quality was chosen for evaluation. Lung sound intensity was plotted over time (12 seconds) for each lung, with time on the x-axis and decibels on the y-axis. The timing of the inspiratory and expiratory lung sound intensity peaks was compared for the left and right lungs [25]. The gap index was defined as the absolute value of the average of gaps (seconds) between the lung sound intensity peaks of both lungs for the duration of 12 seconds.

Multiple detector computed tomography (MDCT) was performed with a 64-detector row CT scanner (Aquilion-64, Toshiba Medical Systems, Otawara, Japan) as previously described [28,29]. The degree of bronchial obstruction was defined using the following formula, in which “CSA” stands for “cross-sectional area”; (CSA of less stenotic main bronchus – CSA of more stenotic main bronchus) / CSA of less stenotic main bronchus [15].

Statistical Analysis

Data are reported as mean ± standard error (SE) unless otherwise indicated. All analyses were performed using SAS software (Release 9.2; SAS Institute, Cary, NC, USA). Significance tests were two-sided, and p values of 0.05 or less were defined as significant. One-way ANOVA with Dunnett adjustment was used to evaluate the difference in pulmonary function tests and lung sound recordings between tracheal obstruction group and CAO with bronchial involvement (bronchial and extensive obstruction group). Significant differences in MMRC, PFTs and lung sound recordings before and after intervention were evaluated using the Wilcoxon signed-rank test. The Mann-Whitney test was used to evaluate the significant difference in the gap index between two different severity stages of bronchial obstruction.

Results

Patient characteristics

Fifty cases of CAO were included in this study. There were 34 male and 16 female participants with a mean age of 55.6 years. CAO cases were diagnosed by bronchoscopy and chest CT and classified into three groups: tracheal (n = 12), bronchial (n = 18) and extensive obstruction (n = 20). Thirty-six cases were treated with combination therapy, including balloon dilatation, ablation, and stenting; 11 were treated with balloon dilatation alone; and 3 were treated with mechanical resection alone (Table 1).

Lung sounds and pulmonary function tests from 50 cases were recorded before and after intervention.

MMRC, PFTs and lung sound recordings before and after interventional bronchoscopy

For lung sound recordings before intervention, gap indexes for bronchial and extensive obstruction cases were significantly higher than those of tracheal obstruction (Table 2; tracheal: 0.039±0.011 seconds; bronchial: 0.216±0.050 seconds, p<0.05; extensive: 0.190±0.044 seconds, p<0.05). Receiver operating characteristics (ROC) validation of the gap index revealed that a cut-off point of 0.06 seconds showed 76.3% sensitivity, 91.7% specificity, and 80% accuracy in the differentiation between CAO with bronchial obstruction.
involvement (bronchial = 18 and extensive = 20) and tracheal obstruction (n = 12) (Figure 1).

After intervention, there were significant improvements in dyspnea for all groups (Table 3; tracheal p < 0.01, bronchial p < 0.001, extensive p < 0.001). In the bronchial obstruction group, no significant improvement was observed in PFTs after intervention. However, the gap index was significantly reduced after intervention (Table 3; 246.2%, p < 0.05). In 14 patients with bronchial obstruction, MDCT scans before and after intervention were available and the degrees of bronchial obstruction were analyzed (Table 4). Figure 2 shows a correlation between the gap index and the degree of bronchial obstruction in the bronchial obstruction group. A gap index of more than 0.06 sec was observed only when the degree of bronchial obstruction was more than 80%. The gap index in cases with 80% or more unilateral bronchial obstruction (0.18 ± 0.04 seconds) was significantly higher than that of patients with less than 80% obstruction (0.02 ± 0.01 seconds, p < 0.01). The relationship between the baseline of the gap index and the improvement in MMRC in 38 patients with bronchial involvement (bronchial = 18 and extensive = 20) is shown in Table 5. The clinical responder rates were 79.3% for gap indexes over 0.06 seconds and 55.6% for gap indexes of 0.06 seconds or under.

Figure 3 represents a patient with lung adenocarcinoma. The tumor protrudes from the right side of the trachea and obstructs the right main stem bronchus. The development of lung sound intensity in the right lung, especially in the lower lung field, was weaker and lagged behind that of the left lung (Lung sound distribution, Video S1 left panel: VRI before intervention; Video S1 right panel: VRI after intervention, online data supplement. The biphasic curve at the bottom stands for inspiratory and expiratory lung sound intensity). After intervention, these asynchronies were mostly resolved.

Figure 4 shows the bronchoscopic, CT and lung sound recordings (Lung sound distribution, Video S2 left panel: VRI before intervention; VRI before intervention; Video S1 right panel: VRI after intervention, online data supplement.

| Cases          | Degree of obstruction | Gap Index (sec) |
|----------------|-----------------------|-----------------|
| Before         | After                 | Before          | After          |
| 63 yr (Male)   | 99.7%                 | 68.4%           | 0.057          | 0              |
| 37 yr (Male)   | 92.3%                 | 88.0%           | 0.574          | 0.021          |
| 65 yr (Female) | 85.6%                 | 71.2%           | 0.064          | 0.021          |
| 64 yr (Male)   | 98.1%                 | 58.3%           | 0.097          | 0              |
| 63 yr (Male)   | 93.0%                 | 83.5%           | 0.425          | 0.306          |
| 17 yr (Female) | 97.5%                 | 93.1%           | 0.567          | 0              |
| 62 yr (Male)   | 99.6%                 | 47.7%           | 0.255          | 0.043          |
| 57 yr (Male)   | 87.2%                 | 85.5%           | 0.021          | 0.106          |
| 62 yr (Male)   | 90.6%                 | 74.8%           | 0.064          | 0.019          |
| 45 yr (Male)   | 90.9%                 | 42.1%           | 0.073          | 0.043          |
| 26 yr (Male)   | 89.9%                 | 92.8%           | 0.019          | 0.106          |
| 71 yr (Female) | 83.9%                 | 19.4%           | 0.208          | 0.043          |
| 25 yr (Female) | 99.3%                 | 99.2%           | 0.038          | 0.043          |
| 61 yr (Female) | 96.9%                 | 95.2%           | 0.34           | 0.413          |

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before intervention; Video S2 right panel: VRI after intervention, online data supplement) of a patient with lung adenocarcinoma. Her left main stem bronchus was severely obstructed, and the development of lung sound intensity in the left lung lagged behind the right. After intervention, these asynchronies were mostly resolved.

**Discussion**

In this study, the left and right lung asynchrony found to be significant at 80% or more bronchial obstruction. These findings revealed that patients with bronchial obstruction and with obvious asynchrony of both lungs displayed a higher responder rate for dyspnea. Furthermore, after intervention for bronchial obstruction, the dyspnea scale and the gap index significantly improved, although the spirometric assessment was unable to show these significant improvements. To our knowledge, this is the first prospective investigation demonstrating the usefulness of left and right lung asynchrony in the diagnosis and treatment of CAO patients.

Although PFTs such as flow-volume curves are important in the assessment of total lung function, PFTs require patient effort and cannot always be performed in CAO patients with severe dyspnea. IOS does not require forced breath maneuvers and provides useful information on collapsible segments. IOS measurements have been proven to correlate with symptomatic improvements after interventional bronchoscopy in tracheal obstruction [14]. However, IOS cannot also discriminate between the left and right bronchial obstructions.

Although we have applied bronchoscopy and three-dimensional computed tomography scans for evaluating bronchial obstructions, non-invasive, reliable and physiological assessment tools for bronchial obstruction are required for outcome assessment after interventional bronchoscopy.

In patients with bronchial obstruction, airflow of the obstructed side lags behind that of the preserved side. This airflow asynchrony in both lungs may be applicable as a physiological indicator in bronchial obstruction. Lung sounds have been used as a surrogate for regional lung airflow [16–7]. Recently, Shi et al. reported that measurements of regional ventilation distribution by VRI were comparable to those obtained by electrical impedance tomography [18]. Lung sound recordings are effort-independent, noninvasive, and can be applied even in critical cases [19,23]. The left and right lung sound asynchrony induced by bronchial obstruction can be evaluated by the gap index. Wang and colleagues reported significant asynchrony between the left and right lungs in asthma exacerbations [25]. They also demonstrated that the asynchrony

**Table 5.** Relation between the baseline of the degree of gap index and the change in MMRC scale after interventional bronchoscopy in cases with bronchial involvement.

| Gap index of pre-intervention (sec) | $\Delta$ MMRC | 0 | $\geq1$ | Responders (%) |
|------------------------------------|----------------|---|--------|----------------|
| 0–0.06                             | 4              | 5 | 5/9 (55.6%) |
| 0.06<                              | 6              | 23 | 23/29 (79.3%) |

Definition of abbreviations: MMRC = modified Medical Research Council.

$\Delta$ MMRC = change in MMRC scale.

Responders = improvement in MMRC scale by 1 or more.

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**Figure 3.** Bronchoscopic and CT findings, flow-volume loops and lung sound recordings for extensive obstruction (before, A–E; after, F–J). This figure shows data of a patient with lung adenocarcinoma. The tumor protrudes from the right side of the trachea and obstructs the right main stem bronchus. The development of lung sound intensity in the right lung, especially the lower lung field, was weaker and lagged behind the left lung (right, red; left, blue). After intervention, these asynchronies were mostly resolved.

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was significantly reduced, and clinical improvements were noted following treatment.

In this study we found significant asynchrony between the left and right lungs in CAO with bronchial involvement, and patients with a baseline gap index above 0.06 seconds showed a higher responder rate for dyspnea after the intervention. The clear asynchrony in both lungs is thought to be an important finding in planning treatment procedures in CAO patients.

In the outcome assessment of interventional bronchoscopy for bronchial stenosis cases, PFTs may not change significantly after intervention [19]. In this study, the dyspnea scale and the gap index were significantly improved after intervention although there were no significant improvements for PFTs. The evaluation of left and right lung asynchrony may provide a distinct prospective point-of-view in the assessment of interventional outcomes for cases with bronchial obstruction.

Recently, there have been extensive developments in functional imaging related to regional lung function, such as the Xenon ventilation CT [29] and hyperpolarized MRI [30]. These methods are unique and promising due to the high spatial and temporal resolution of respiratory disease morphology and ventilation volumetry. Although the applications of these methods require irradiation or a long acquisition time that limits the accessibility for patients in critical condition at this time, innovation of the functional imaging field will provide ideal methods for evaluating left and right lung asynchrony.

A limitation of this study was the difficulty in sensor attachment to the bony posterior chest wall, which resulted in excluding thinner patients with a BMI of 19 or less. Lower body weight is not uncommon in the Japanese population, especially in the older population. Further improvements in sensor attachment are expected.

Supporting Information

**Video S1 Lung sound distribution (1).** Left panel: VRI before intervention. Right panel: VRI after intervention. The development of lung sound intensity in the right lung, especially in the lower lung field, was weaker and lagged behind that of the left lung. After intervention, these asynchronies were mostly resolved. The biphasic curve at the bottom stands for inspiratory and expiratory lung sound intensity. (MP4)

**Video S2 Lung sound distribution (2).** Left panel: VRI before intervention. Right panel: VRI after intervention. The development of lung sound intensity in the left lung lagged behind the right. After intervention, these asynchronies were mostly resolved. The biphasic curve at the bottom stands for inspiratory and expiratory lung sound intensity. (MP4)

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Author Contributions

Conceived and designed the experiments: MM TM. Performed the experiments: MM HK HN HH TI. Analyzed the data: MM. Contributed reagents/materials/analysis tools: MM. Contributed to the writing of the manuscript: MM TI TM.

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Figure 4. Bronchoscopic and CT findings, flow-volume loops and lung sound recordings for bronchial obstruction (before, A–E; after, F–J). The left bronchus was severely stenotic as a result of lung adenocarcinoma. The development of lung sound intensity in the left lung lagged behind the right lung (right, red; left, blue). After intervention, these asynchronies were mostly resolved. doi:10.1371/journal.pone.0105327.g004
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