Dynamic-Ventilatory Digital Radiography in Air Flow Limitation: A Change in Lung Area Reflects Air Trapping

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Keywords
Air flow limitation · Chronic obstructive pulmonary disease · Digital radiography · Lung area changes · Pulmonary function

Abstract
Objective: The aim of this study was to determine the utility of dynamic-ventilatory digital radiography (DR) for pulmonary function assessment in patients with airflow limitation.
Methods: One hundred and eighteen patients with airflow limitation (72 patients with lung cancer before surgery, 35 patients with chronic obstructive pulmonary disease [COPD], 6 patients with asthma, and 5 patients with asthma-COPD overlap syndrome) were assessed with dynamic-ventilatory DR. The patients were instructed to inhale and exhale slowly and maximally. Sequential chest X-ray images were captured in 15 frames per second using a dynamic flat-panel imaging system. The relationship between the lung area and the rate of change in the lung area due to respiratory motion with respect to pulmonary function was analyzed.

Results: The rate of change in the lung area from maximum inspiration to maximum expiration (Rs ratio) was associated with the RV/TLC ratio \( r = 0.48, p < 0.01 \) and the percentage of the predicted FEV1 \( r = -0.33, p < 0.01 \) in patients with airflow limitations. The Rs ratio also decreased in an FEV1-dependent manner. Conclusion: The rate of change in the lung area due to respiratory motion evaluated with dynamic DR reflects air trapping. Dynamic DR is a potential tool for the comprehensive assessment of pulmonary function in patients with COPD.

Introduction
Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality [1]. Indeed, COPD is a preventable and treatable disease that is characterized by persistent symptoms and airflow limitation [2]. Spirometry is required to establish the diagnosis of COPD [3]. A postbronchodilator FEV1/FVC <0.70 con-
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firms persistent airflow limitation. While postbronchodilator spirometry is required for the diagnosis and assessment of COPD, assessing the degree of reversibility of the airflow limitation to make therapeutic decisions is no longer recommended [4]. Patient-reported outcomes, including the burden of symptoms (dyspnea, activity limitations, and health-related quality of life), are pivotal in assessing the efficacy of interventions for COPD [5].

A recent study has reported the utility of dynamic digital radiography (DR) using a flat-panel detector (FPD) [6]. Dynamic DR provides sequential chest X-ray images during respiration with lower radiation than conventional X-ray fluoroscopy and CT [7]. These images reflect respiratory kinetics, which may be effective for evaluating pulmonary function in patients with lung disease [8]. Patients with severe COPD have decreased and slower diaphragmatic motion during forced breathing [9]. The diaphragmatic motion during tidal breathing in a standing position is larger and faster in COPD patients than in healthy subjects [10]. However, little is known about the role of dynamic DR in evaluating pulmonary function in COPD.

In the current study, we determined the utility of dynamic DR in evaluating pulmonary function in patients with airflow limitation.

**Patients and Methods**

**Subjects**

Between December 2015 and April 2019, 185 patients underwent dynamic-ventilatory DR at our institution for assessing several conditions. Among them, 129 patients with airflow limitation (FEV<sub>1</sub>/FVC < 0.70 at prebronchodilator spirometry) were initially enrolled in this study. Although all of these patients were assessed with dynamic-ventilatory DR, 11 patients with airflow limitation were excluded because pulmonary function testing using the helium dilution technique was not performed. Furthermore, the 118 patients with airflow limitation consisted of 72 patients with lung cancer before surgery, 35 definite COPD patients with postbronchodilator FEV<sub>1</sub>/FVC < 0.70, 6 patients with asthma, and 5 patients with asthma-COPD overlap syndrome. The median Brinkman index of the 118 subjects was 833. All examinations in this study were performed when patients were stable. The cancers (median size: 21 mm, locations: 26 on the right upper lobe, 8 on the right middle lobe, 15 on the right lower lobe, 13 on the left upper lobe, and 10 on the left lower lobe) did not affect lung/diaphragm movements. The characteristics of the patients are shown in Table 1.

**Dynamic-Ventilatory DR**

Sequential chest X-ray images were obtained during respiration using a dynamic FPD imaging system (Konica Minolta, Inc., Tokyo, Japan), consisting of an indirect-conversion FPD (PaxScan, 4343CB; Varex Imaging Corporation, Salt Lake City, UT, USA), and X-ray generator/tube capable of pulsed irradiation (DHF-155HI/UH-6QC-07E; Hitachi, Ltd.). To be a reliable diagnostic tool, the system must have a high homogeneity and uniformity in X-ray pulses. Except for the breathing pattern, imaging is performed in the same way as a conventional chest examination (i.e., the standing position and posteroanterior [PA] direction). For an accurate evaluation of pulmonary function, it is crucial to include 1 respiratory cycle within a limited amount of time with good reproducibility. Therefore, it is recommended to use an automatic voice system and to train patients in advance. The total patient dose is adjustable by changes in the imaging time, imaging rate, and source-to-image distance (SID), and can be less than the dose limit for 2 projections (PA + LA) recommended by the International Atomic Energy Agency (IAEA). In this study, the exposures were obtained using the following parameters: 100 kV; 50 mA; 2.5 ms; 15 frames per second; and 2.0 m from the SID. The entrance surface dose to the detector is approximately 0.21 mSv in 14 s.

**Study Design**

All of the patients were instructed to breathe deeply in the standing position under voice guidance. The patients inhaled and exhaled slowly, followed by maximal inhalation and exhalation for 5 s. Breath holding lasted for 2 s at each maximum inspiration timing and maximum expiration time (Fig. 1a). The sequential chest X-ray images for a total of 14 s were captured in 15 frames per second with the dynamic DR system. The lung areas at maximum inspiration (S<sub>In</sub>) and maximum expiration timing (S<sub>Ex</sub>) were measured. The rate of change in the lung areas due to respiratory motion (from maximum inspiration to maximum expiration, and from maximum expiration to maximum inspiration) was defined as the R<sub>S<sub>Ex</sub></sub> to <sub>In</sub> <sub>Ex</sub> and R<sub>R<sub>Ex</sub></sub> to <sub>In</sub> <sub>Ex</sub> ratios, respectively. The Rs ratios were calculated as follows:

\[
R_{S(In to Ex)} = \frac{(S_{Ex} - S_{In})}{S_{In}} \quad \text{and} \quad R_{S(Ex to In)} = \frac{(S_{In} - S_{Ex})}{S_{Ex}}
\]

**Table 1. Characteristics of the patients**

|                          | n   |
|--------------------------|-----|
| Gender, females/males    | 31/87 |
| Age, years               | 71.4±7.7 |
| BMI, kg/m<sup>2</sup>     | 22.9±3.3 |
| Smoking history (Brinkman index) | 833 (0–3,000) |
| Pulmonary function       |     |
| VC, % of predicted       | 114.2±18.2 |
| FVC, % of predicted      | 113.6±18.2 |
| FEV<sub>1</sub>, % of predicted | 95.9±27.3 |
| FEV<sub>1</sub>/FVC ratio | 0.59±0.1 |
| MMEF, % of predicted     | 28.0±14.0 |
| FRC, % of predicted      | 109.4±18.9 |
| RV, % of predicted       | 119.7±25.1 |
| TLC, % of predicted      | 110.9±14.5 |
| RV/TLC ratio             | 0.40±0.1 |
| DLCO, % of predicted     | 62.7±20.8 |

Except for smoking history, data are presented as the mean ± SD. Smoking history is presented as the median (range). MMEF, maximal mid-expiratory flow.
Hand switch ON

Take in a deep breath, keep inhaling, keep inhaling...

Breathe out slowly as far as you can, keep exhaling...

Take in a deep breath, keep inhaling... go go! Relax

5 s No exposure

X-ray pulse

Diaphragm level

Maximum inspiration

Maximum expiration

Maximum inspiration

Breath holding for 2 s

Breath holding for 2 s

Inspiratory phase

Expiratory phase

Inspiratory phase

Rs(\text{In to Ex}) = \frac{S_{\text{Ex}} - S_{\text{In}}}{S_{\text{In}}},

Rs(\text{Ex to In}) = \frac{S_{\text{In}} - S_{\text{Ex}}}{S_{\text{Ex}}}.

A case of normal pulmonary function

A case of COPD

Fig. 1. a Sequential chest X-ray images during respiration were obtained using a dynamic FPD system and X-ray generator capable of pulsed irradiation. Except for the breathing manner, imaging was performed in the same way as a conventional chest examination, i.e., the standing position and the PA direction. Subjects inhaled and exhaled slowly and maximally. The exposures were taken using the following parameters: 120 kV; 50 mA; 2.5 ms; 15 frames/s; and 2.0 m from the SID. The entrance surface dose to the detector was approximately 0.21 mSv in 14 s. b The lung area was measured at the maximum inspiration timing (S_{\text{In}}) and the maximum expiration timing (S_{\text{Ex}}). The rate of change in the lung area was calculated as follows: Rs_{\text{In to Ex}} = \frac{S_{\text{Ex}} - S_{\text{In}}}{S_{\text{In}}},

Rs_{\text{Ex to In}} = \frac{S_{\text{In}} - S_{\text{Ex}}}{S_{\text{Ex}}}.
Examples for measuring the lung areas are shown in Figure 1b (see also suppl. online videos; for all online suppl. material, see www.karger.com/doi/10.1159/000506881).

The relationships between $S_{\text{In}}$, $S_{\text{Ex}}$, $R_{\text{In}}$ and $R_{\text{Ex}}$, and the data (e.g., VC, FVC, FEV$_1$, FRC, RV, and TLC) obtained based on conventional pulmonary function tests were assessed in the 118 patients with airflow limitation. The severity of airflow limitation was defined as follows: mild airflow limitation, FEV$_1$ $\geq 80\%$ of predicted; moderate airflow limitation, $50\% \leq$ FEV$_1$ $< 80\%$ of predicted; and severe airflow limitation, FEV$_1$ $< 50\%$ of predicted.

**Pulmonary Function Tests**

Spirometry tests were performed with a computerized spirometer (Chestac-9900; Chest, Tokyo, Japan) according to the ATS/ERS Task Force [11]. The measurements were obtained before and 15 min after inhalation of albuterol (400 µg) and used to diagnose and classify COPD according to the GOLD criteria [2]. Lung volumes were also measured using the multi-breath helium dilution method.

**Data Analysis**

Data except smoking history are presented as means $\pm$ SD. Statistical differences between the groups were analyzed using the Mann-Whitney U test, Kruskal-Wallis test, or Fisher exact test. Results with values of $p < 0.05$ were considered statistically significant. Correlations between parameters were assessed using Spearman’s rank correlation coefficient. Correlations were considered weak if $\leq 0.30$, moderate if $0.30–0.60$, and strong if $> 0.60$.

**Results**

$S_{\text{In}}$ was associated with VC, FRC, RV, and TLC (VC vs. $S_{\text{In}}$, $r = 0.67$; FVC vs. $S_{\text{In}}$, $r = 0.75$; RV vs. $S_{\text{In}}$, $r = 0.56$; TLC vs. $S_{\text{In}}$, $r = 0.55$; $p < 0.05$) but not FEV$_1$. The relationship between the Rs ratio and pulmonary function are shown in Table 2. The Rs$_{\text{(In to Ex)}}$ was significantly associated with the RV/TLC ratio ($r = 0.48$; $p < 0.05$). The Rs$_{\text{(In to Ex)}}$ was also associated with the percentage of predicted FEV$_1$ ($r = 0.33$; $p < 0.05$). The patients with airflow limitations had a significant decrease in the Rs$_{\text{(In to Ex)}}$ in a FEV$_1$-dependent manner (Kruskal-Wallis test, $p < 0.05$; Fig. 2). These results were nearly equal to the Rs$_{\text{(Ex to In)}}$.

**Discussion**

In this study, we have shown that the rate of change in the lung area due to respiratory motion reflects air trapping in patients with airflow limitations such as COPD. The lung area at the time of maximum inspiration ($S_{\text{In}}$) was associated with lung volume (VC, FRC, RV, and TLC). The rate of change in the lung area from maximum inspiration/expiration was assessed using Spearman’s rank correlation coefficient.

![Fig. 2. The patients with airflow limitation (AL) showed a significant decrease in the Rs in an FEV$_1$-dependent manner (Kruskal-Wallis test, $p < 0.05$). The Rs ratio represents the rate of change in the lung area due to respiratory motion. Means $\pm$ SD. Mild AL, FEV$_1$ $\geq 80\%$ of predicted; $n = 89$; moderate AL, $50\% \leq$ FEV$_1$ $< 80\%$ of predicted; $n = 23$; severe AL, FEV$_1$ $< 50\%$ of predicted; $n = 6$; Rs ratio, $(S_{\text{Ex}} - S_{\text{In}})/S_{\text{In}}$; $S_{\text{In}}/S_{\text{E}}$, the lung area at the time of maximum inspiration/maximum expiration.](image-url)
using dynamic DR. Herein, we showed the rate of lung area change during forced breathing in patients with airflow limitation correlated with air trapping indicators, such as the RV/TLC ratio, and their activities using the same dynamic-ventilatory DR system. Some studies have shown a correlation between pulmonary function and diaphragmatic mobility based on evaluations with other modalities. Scheibe et al. [13] and Dos Santos Yamaguti et al. [12] demonstrated a correlation between diaphragmatic mobility and pulmonary function test results, such as FEV$_1$ and RV, using ultrasonography. Thus, ultrasonography may provide an alternative method for investigating pulmonary function using a safe, noninvasive technique that is easy to access. Unlike these results, dynamic measurements using diaphragm ultrasonography provide a relatively poor measure of pulmonary function in relation to whole-body plethysmography. Unal et al. [14] also demonstrated a correlation between diaphragmatic movement and FEV$_1$ using MR fluoroscopy. In addition to decreased diaphragmatic mobility in COPD, previous studies [15, 16] have reported that quantitative CT findings, such as peak attenuation of the bronchial wall and the expiratory/inspiratory ratio of the mean lung density, correlate with airflow limitation indicators such as FEV$_1$, FEF$_{25-75\%}$, and specific airway conductance. Yamada et al. [10] also reported that the craniocaudal gradients of the maximum pixel value rate of change in COPD patients were significantly lower than in healthy subjects in dynamic DR. Evaluation of pulmonary function with dynamic-ventilatory DR has some advantages compared with other modalities. Specifically, dynamic-ventilatory DR can be performed in a standing or sitting position, which reflects physiologically relevant daily activities. Dynamic-ventilatory DR does not require a technique that depends on the operator. The radiation dose of dynamic-ventilatory DR is lower than that of conventional X-ray fluoroscopy and CT. The sequential chest X-ray images during respiration provided by dynamic-ventilatory DR make it easy to understand the respiratory kinetics of the chest.

The results of Rs$_{(\text{In to Ex})}$ and Rs$_{(\text{Ex to In})}$ showed the same tendency. This finding may be due to the breathing maneuver. In the current study, the patients inhaled and exhaled slowly and maximally. If the study had been conducted with forced breathing, there may have been a difference between Rs$_{(\text{In to Ex})}$ and Rs$_{(\text{Ex to In})}$ because of air trapping. Unlike previous studies [9, 12–14], and the results herein that showed decreased maximal diaphragmatic motion in patients with severe COPD, Yamada et al. [10] reported that diaphragmatic motion during tidal breathing in a standing position is larger and faster in COPD patients than in healthy subjects. This compensatory motion of the diaphragm is thought to be one of the characteristic features of tidal breathing in patients with COPD [9]. The difference in diaphragmatic motion between tidal and maximal breathing in patients with severe COPD may help to elucidate the mechanism underlying severe COPD.

There is only a weak correlation between FEV$_1$, symptoms, and impaired health status in patients with COPD [17, 18]. The peripheral airway limitation traps gas during expiration, resulting in hyperinflation. The hyperinflation develops even in early-stage COPD, and it is the main mechanism underlying exertional dyspnea [19, 20]. The GOLD guidelines recommend a combined COPD assessment incorporating patient-reported outcomes, risk of exacerbations, and spirometric classification [2]. The “ABCD” tool for therapeutic decisions provides information pertaining to symptom burden and risk of exacerbation. Herein, we showed that the Rs ratio was associated with the RV/TLC ratio and the percentage of predicted FEV$_1$. Dynamic-ventilatory DR can be an alternative assessment tool that reflects both the severity of airflow limitation and air trapping in patients with COPD. Bronchodilators, such as long-acting muscarinic antagonists, act on the peripheral airways and reduce gas trapping, thus improving dyspnea and exercise capacity [21]. Dynamic-ventilatory DR is also an indicator of therapy outcome due to a reduction in gas trapping. While the ABCD assessment consists of patient symptoms and their history of exacerbation, the assessment has a limited ability to predict mortality [22, 23]. The BODE index, which consists of the body mass index, percent of predicted FEV$_1$, modified Medical Research Council grades, and the distance walked in 6 min, is superior to the FEV$_1$ in predicting mortality [24]. Dynamic-ventilatory DR may be promising for predicting mortality because the Rs ratio reflects activities of COPD patients as well as the percent of predicted FEV$_1$ and the RV/TLC ratio. Further studies are warranted to evaluate COPD patient activities and mortality with dynamic-ventilatory DR.

The limitations of the study listed below deserve consideration. First, there are only 35 definite COPD cases with a postbronchodilator FEV$_1$/FVC < 0.70 in this study. Larger cohorts of definite COPD patients are needed to validate the findings of this study. Second, we did not assess pulmonary function based on changes in radiographic lung density. Although previous studies indicated that ventilation defects could be detected as decreased changes in radiographic lung density [8, 25], further studies are
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In conclusion, the dynamic-ventilatory DR is a potential tool for comprehensive assessment of COPD patients.

Statement of Ethics

This study was approved by the Medical Ethics Committee of the Kanazawa University Hospital (registration No. 1729). All patients gave informed consent to participate.

Disclosure Statement

The authors report no conflicts of interest.

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