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.

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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-

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 ($FEV_1/FVC < 0.70$ 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 $FEV_1/FVC < 0.70$, 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-

Table 1. Characteristics of the patients

<i>n</i>	118
Gender, females/males	31/87
Age, years	71.4±7.7
BMI, kg/m ²	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 ₁ , % of predicted	95.9±27.3
FEV ₁ /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.

155H II/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_{In}) and maximum expiration timing (S_{Ex}) 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 Rs_(In to Ex) and Rs_(Ex to In) ratios, respectively. The Rs ratios were calculated as follows:

$$Rs_{(In\ to\ Ex)} = (S_{Ex} - S_{In})/S_{In}, \text{ and}$$

$$Rs_{(Ex\ to\ In)} = (S_{In} - S_{Ex})/S_{Ex}.$$

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_{In}) and the maximum expiration timing (S_{Ex}). The rate of change in the lung area was calculated as follows: $RS_{(In\ to\ Ex)} = (S_{Ex} - S_{In})/S_{In}$, $RS_{(Ex\ to\ In)} = (S_{In} - S_{Ex})/S_{Ex}$.

Fig. 2. The patients with airflow limitation (AL) showed a significant decrease in the Rs in an FEV₁-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, FEV₁ $\geq 80\%$ of predicted; $n = 89$; moderate AL, $50\% \leq \text{FEV}_1 < 80\%$ of predicted; $n = 23$; severe AL, FEV₁ $< 50\%$ 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.

Table 2. Relationship between Rs ratio and pulmonary function in patients with airflow limitation ($n = 118$)

	Rs _(In to Ex) ratio		Rs _(Ex to In) ratio	
	<i>r</i>	<i>p</i> value	<i>r</i>	<i>p</i> value
VC	-0.29	<0.01	0.29	<0.01
FVC	-0.28	<0.01	0.28	<0.01
FEV ₁	-0.33	<0.01	0.33	<0.01
FEV ₁ /FVC	-0.19	0.04	0.19	0.04
MMEF	-0.26	<0.01	0.26	<0.01
FRC	-0.14	0.12	0.15	0.11
RV	0.31	<0.01	-0.31	<0.01
TLC	-0.01	0.93	0.01	0.94
RV/TLC ratio	0.48	<0.01	-0.47	<0.01
DLCO	-0.12	0.18	0.12	0.18

Rs ratio represents the rate of change in the lung area due to respiratory motion. 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/expiration; MMEF, maximal mid-expiratory flow. Correlations between parameters were assessed using Spearman's rank correlation coefficient.

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_{In} , $\text{Rs}_{(\text{In to Ex})}$, $\text{Rs}_{(\text{Ex to In})}$, and the data (e.g., VC, FVC, FEV₁, 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, FEV₁ $\geq 80\%$ of predicted; moderate airflow limitation, $50\% \leq \text{FEV}_1 < 80\%$ of predicted; and severe airflow limitation, FEV₁ $< 50\%$ 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 ≤ 0.30 , moderate if $0.30-0.60$, and strong if > 0.60 .

Results

S_{In} was associated with VC, FRC, RV, and TLC (VC vs. S_{In} , $r = 0.67$; FRC vs. S_{In} , $r = 0.75$; RV vs. S_{In} , $r = 0.56$; TLC vs. S_{In} , $r = 0.55$; $p < 0.05$) but not FEV₁. The relationship between the Rs ratio and pulmonary function are shown in Table 2. The $\text{Rs}_{(\text{In to Ex})}$ was significantly associated with the RV/TLC ratio ($r = 0.48$; $p < 0.05$). The $\text{Rs}_{(\text{In to Ex})}$ was also associated with the percentage of predicted FEV₁ ($r = -0.33$; $p < 0.05$). The patients with airflow limitations had a significant decrease in the $\text{Rs}_{(\text{In to Ex})}$ in a FEV₁-dependent manner (Kruskal-Wallis test, $p < 0.05$; Fig. 2). These results were nearly equal to the $\text{Rs}_{(\text{Ex to In})}$.

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_{In}) was associated with lung volume (VC, FRC, RV, and TLC). The rate of change in the lung area from maximum inspiration to maximum expiration (Rs ratio) was associated with the RV/TLC ratio and percent of predicted FEV₁ in patients with airflow limitation and COPD. The Rs ratio decreased in an FEV₁-dependent manner in patients with airflow limitation. These results are consistent with previous studies [9, 12–14] which reported decreased diaphragmatic mobility in COPD patients using other modalities. Hida et al. [9] reported decreased and slower diaphragmatic motion during forced breathing in patients with severe COPD when in the standing position

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 FEV₁ 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 FEV₁ 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 FEV₁, 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 $Rs_{(In\ to\ Ex)}$ and $Rs_{(Ex\ to\ In)}$ 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 $Rs_{(In\ to\ Ex)}$ and $Rs_{(Ex\ to\ In)}$ 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 FEV₁, 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 FEV₁. 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 FEV₁, modified Medical Research Council grades, and the distance walked in 6 min, is superior to the FEV₁ 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 FEV₁ 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 FEV₁/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

needed to confirm the relationship between pulmonary function and changes in radiographic lung density. Third, it has been reported that the synchrony of respiratory movements between the pulmonary lobes is limited or lost in patients with more severe airflow limitation in the study using 4-dimensional dynamic-ventilation CT [26]. Although this study focused on the rate of change in the lung area, future studies need to find indices that indicate nonuniformity in respiratory movement using dynamic-ventilatory DR and show their associations with respiratory function and symptoms. Finally, the results of this study were analyzed in 1 cycle of slow-maximum breathing for each participant considering the radiation dose. To confirm reproducibility, repeated analysis of each participant's multicycle breathing is desirable. Furthermore, other parameters from dynamic-ventilatory DR should be analyzed in order to verify the clinical utility of dynamic-ventilatory DR. For example, the use of lateral chest X-ray and dynamic measurements during breathing may also be effective.

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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