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A Possible, Non-Invasive Method of Measuring Dynamic Lung Compliance in Patients with Interstitial Lung Disease Using Photoplethysmography

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Background: Measuring lung compliance is useful for evaluating progression of interstitial lung disease (ILD), because reduced lung compliance due to fibrosis progression is the main cause of decreased vital capacity. However, because insertion of a balloon into the esophagus is invasive, lung compliance is rarely measured. A recently developed method uses fingertip photoplethysmography to estimate intrathoracic pressure. This method non-invasively measures lung dynamic compliance (Cdyn) by simultaneously measuring tidal volume. We evaluated the efficacy of this method in assessing ILD.

Methods: This single-center, cross-sectional, observational study evaluated the efficacy of this method in patients with ILD and healthy controls. The primary outcome was estimated Cdyn (eCdyn), as determined with this method. We also evaluated baseline characteristics that are potential confounding factors for eCdyn.

Results: Median eCdyn was significantly lower in the ILD group (n = 14) than in the control group (n = 49) (0.122 vs. 0.183; P = 0.011). In univariate regression analysis, eCdyn was significantly correlated with height, weight, forced vital capacity, forced expiratory volume in 1 second, diffusing capacity for carbon monoxide, and usual interstitial pneumonia. In multivariate regression analysis, weight (β = 0.49, P = 0.011) and usual interstitial pneumonia (β = 0.52, P = 0.007) were significantly correlated with eCdyn.

Conclusions: Using photoplethysmography, we noted a significant reduction in Cdyn in patients with ILD. This novel non-invasive method is a promising tool for evaluating fibrosis progression in ILD.

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Key words: lung compliance, photoplethysmography, respiratory function tests, pulse wave analysis, interstitial lung disease

Introduction

Interstitial lung disease (ILD) describes a large group of disorders, most of which cause progressive scarring of lung tissue. The most common subtype of idiopathic ILD is idiopathic pulmonary fibrosis (IPF), histologically diagnosed as usual interstitial pneumonia (UIP). IPF is a progressive, fibrotic lung disease that is characterized by hypoxia and diminishing lung volume and leads to respiratory failure[1]. The pulmonary function test (PFT), an essential tool for evaluating ILD progression, usually shows a restrictive defect with decreased vital capacity and diffusing capacity for carbon monoxide (DLco). However, in patients with severe restrictive lung diseases, PFT is often impractical, especially for measuring DLco. Non-invasive techniques are therefore required to evaluate lung function when following patients with ILD.

Volume change per unit pressure change is known as lung compliance[2]. Lung compliance is a useful measure

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of the lung's ability to stretch and expand. An increase in fibrous tissue in the human lung reduces its normal compliance. Conversely, compliance is increased in pulmonary emphysema and in the normal aging lung. Because reduced lung compliance due to fibrosis progression is the main cause of decreased vital capacity, measuring lung compliance is useful for evaluating ILD progression. Because intrathoracic pressure is difficult to directly measure, esophageal pressure is measured instead[3]. However, insertion of a balloon into the esophagus is invasive; thus, lung compliance is rarely measured in hospitals and clinics.

Previous studies reported a correlation between intrathoracic pressure and pulsus paradoxus (a minimum drop in systolic pressure of 10 mm Hg during inspiration[4]). Pulsus paradoxus can be seen in breathing disorders such as severe asthma[5] and chronic airway disease[6]. Shiomi et al.[7,8] reported that pulsus paradoxus, along with significant end-diastolic negative esophageal pressure, might be present during obstructive sleep apnea. During inspiration in a closed upper airway, right ventricle filling increases, with interventricular septum displacement. This limits left ventricle filling by reducing its compliance, thus lowering left ventricular stroke volume and decreasing arterial blood pressure.

Nanba et al.[9] used pulse wave signals to estimate the relative degree of intrathoracic pressure variation. A first variation signal is obtained from the peak of pulse wave amplitude. A second variation signal is obtained from the peak of the first variation signal. Based on the difference between the first and second variation signals, the relative degree of variation in intrathoracic pressure is predicted. In a patient with sleep apnea syndrome who underwent 111 assessments, intrathoracic pressure estimated from pulse wave signals was strongly correlated with that from esophageal pressure (r = 0.85).

The DENSO Corporation (Aichi, Japan) has developed a new method that uses fingertip photoplethysmography with a pulse wave sensor to estimate intrathoracic pressure[10]. By simultaneously measuring tidal volume in the flow sensor unit, this method non-invasively measures lung dynamic compliance (Cdyn). This study aimed to evaluate the efficacy of this system for assessing ILD with restrictive lung function.

Materials and Methods

Study Design and Population

This single-center, cross-sectional, observational study enrolled patients with ILD (ILD group) and healthy controls (control group) from the Nippon Medical School Hospital during the period from February 2017 through July 2018. Patients with ILD were diagnosed according to the American Thoracic Society/European Respiratory Society guidelines[11]. We enrolled patients who satisfied all the inclusion criteria (age ≥20 years; FVC %predicted <80%; presence of ILD regardless of cause; and written informed consent) and none of the exclusion criteria (FEV_1/FVC <70%, presence of respiratory diseases other than ILD expected to affect PFT, and presence of atrial fibrillation or serious arrhythmia expected to affect pulse wave analysis). We excluded patients with upper airway obstruction by assessing upper airway lesions on chest CT or peak flow reduction with flattening on the flow-volume loop of PFT. Moreover, we excluded patients with >10% emphysema on high-resolution CT, as defined by low attenuation areas delimited by an extremely thin wall (<1 mm). This study was approved by the ethics committee of the Nippon Medical School Hospital (28-09-650) and conducted in accordance with the principles articulated in the Declaration of Helsinki.

We recorded patients' demographic data (age, sex, height, and weight) at baseline and calculated body mass index (BMI: weight in kilograms divided by the square of the height in meters). PFT was performed with a spirometer in the control group and measured lung function indices, including FVC, FEV_1, and FEV_1/FVC. PFT was performed with a lung function instrument and computer processing [CHESTAC 8900 (NIHON KOHDEN, Tokyo, Japan)] for the ILD group. The parameters recorded were FVC, FEV_1, FEV_1/FVC, and DLco. We also calculated lung function indices as percentages of predicted normal values and measured arterial blood gases and alveolar-arterial oxygen difference in the ILD group. To analyze background factors, we divided the ILD group into two subgroups (UIP and non-UIP) according to the American Thoracic Society/European Respiratory Society diagnostic criteria[12]. In this study, UIP was defined as a UIP pattern or possible UIP pattern on high-resolution CT.

eCdyn Measurement

We measured Cdyn with an intrathoracic pressure calculation device (**Fig. 1A**) and was as estimated Cdyn (hereinafter referred to as eCdyn). The results for each procedure are presented as the mean of three independent measurements taken with the participant in a seated position.

The pulse wave sensor unit extracts the respiration signal by measuring a pulse wave signal with a fingertip

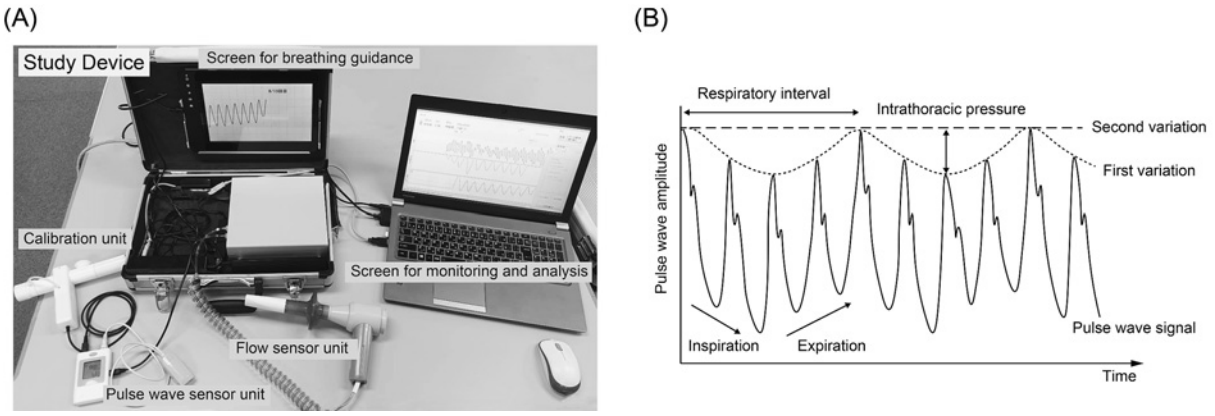

Fig. 1 (A) eCdyn was measured using fingertip photoplethysmography with a pulse wave sensor. The device comprises a pulse wave sensor unit, an intraoral pressure sensor unit (calibration unit), a flow sensor unit, a screen for breathing guidance to participants, and a screen for monitoring and analysis.
(B) Example of a screenshot of the output of the device. Note the continuous records of inspiratory and expiratory pulse wave signals recorded with the fingertip photoplethysmography device. The display reads out the amplitude measured from the first variation signal and second variation signal.

photoplethysmography device when participants are breathing at different depths along a time axis. The amplitude of the respiration signal is measured (**Fig. 1B**), and for each breath the relative degree of variation in intrathoracic pressure is estimated.

Pressure resistance due to airway resistance can be eliminated by breathing with a mouthpiece that is attached to an air intake port with strong inspiratory resistance (calibration unit). Thus, the degree of variation, which is a preset amplitude of the intraoral pressure signal, and intrathoracic pressure signal are equalized. The ratio of the degree of variation expressed by the intraoral pressure signal to that expressed by the pulse wave signal is calculated as the calibration factor.

The flow sensor unit measures tidal volume (total of 13 times at a rate of approximately 15 breaths/min) to represent the natural respiration of the participants at rest and is targeted at 30% to 60% of the VC of the participants.

Estimated on the basis of the pulse wave signal, the relative degree of variation in intrathoracic pressure is multiplied by the calibration factor to calculate the absolute value of intrathoracic pressure. Dividing the tidal volume by the absolute value of the intrathoracic pressure yields eCdyn.

Outcome Measure

The primary outcome was eCdyn of patients with ILD compared with that of healthy controls. Cdyn was reported to be 0.1 to 0.4 L/cmH_2O for healthy controls[13] and 0.093 ± 0.042 L/cmH_2O for patients with ILD[14]. The optimal cutoff value of eCdyn for ILD, measured non-invasively, was 0.1 L/cmH_2O [sensitivity, 14/21 (66%); specificity, 20/20 (100%)] (unpublished data). We therefore measured sensitivity and specificity for ILD in this device when setting the cutoff value of eCdyn to 0.1 L/cmH_2O. The coefficient of variation (CV: ratio of standard deviation to mean) is useful for comparing the degree of variation from one data series to another, even if the means drastically differ. We estimated the calculated CV at every measured eCdyn, estimated as the main index of reliability and repeatability of this device. To evaluate the clinical value of eCdyn measured with this device, we also evaluated baseline characteristics that are potential confounding factors for eCdyn.

Statistical Analysis

We used non-parametric statistics because of our small sample size and the non-normal distribution of most of our variables. We present continuous variables as medians with interquartile ranges and categorical variables as numbers and percentages. We used the Mann-Whitney U test (continuous variables) and Fisher exact test (categorical variables) to identify significant differences between groups. Using the baseline characteristics of the ILD group as independent variables, we performed linear regression analyses with eCdyn as the dependent variable. To examine interrelations among statistically significant variables, we calculated correlation coefficients with the Spearman rank test. To investigate correlations of eCdyn with baseline characteristics, we performed multivariate regression analyses with eCdyn as the dependent variable and the other variables as independent variables. We excluded potential confounders from the analyses and

Table 1 Baseline characteristics of participants in the control group and ILD group

Variables	Control group	ILD group	*P* value
No.	49	14	
Age (yr)	37 (31.5–44.0)	71 (68.5–74.0)	<0.001*
Sex, male (n)	33 (67%)	9 (64%)	1.00
Height (cm)	169 (163–174)	160.5 (149.8–165.3)	0.002*
Weight (kg)	60.0 (54.5–70.0)	57.9 (51.5–74.0)	0.72
BMI (kg/m^2)	21.0 (20.1–22.5)	23.9 (22.8–27.0)	0.002*
FVC (L)	4.19 (3.45–4.72)	1.68 (1.51–2.06)	<0.001*
FVC %predicted	97.5 (90.6–104.5)	65.0 (47.5–72.5)	<0.001*
FEV_1 (L)	3.55 (3.12–3.82)	1.46 (1.28–1.75)	<0.001*
FEV_1 %predicted	92.4 (90.4–98.5)	79.8 (64.4–92.9)	0.013*
FEV_1/FVC (%)	81.3 (79.0–88.7)	83.8 (80.0–94.6)	0.35

Data are presented as median and interquartile range
* Results of Mann-Whitney U test or Fisher exact test
ILD = interstitial lung disease
BMI = body mass index

used adjusted R^2 to evaluate the model's fitness for a given data set. We performed statistical analyses using JMP14 (SAS Institute Inc., Cary, NC, USA). A two-sided *P* value of <0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics

Our study included 14 patients with a diagnosis of ILD and 49 healthy controls (**Table 1**). Age was significantly higher, and height, FVC, FVC %predicted, FEV_1, and FEV_1 %predicted were significantly lower, in the ILD group than in the control group. Most patients with ILD had a restrictive pattern on PFT (FVC %predicted <70). However, FEV_1/FVC did not significantly differ between the two groups. **Table 2** summarizes the baseline characteristics of the ILD group. We recorded demographic features, including smoking status, arterial blood gas analysis results, and DLco. Of the 14 patients with ILD, 8 (57%) and 6 (43%) were classified as having UIP and non-UIP, respectively.

Clinical Outcome

Median eCdyn was significantly lower in the ILD group (0.122) than in the control group (0.183; $P = 0.011$, **Fig. 2A**). Mean (± SD) eCdyn was 0.195 ± 0.074 in the control group and 0.136 ± 0.066 in the ILD group. The average of standard deviations from all eCdyn measurements in individual patients was 0.024; thus, the CV of eCdyn was 18%. When we set the cutoff value for eCdyn to 0.1 L/cmH_2O, the sensitivity and specificity to ILD was 6/14 (43%) and 49/49 (100%), respectively.

Table 3 shows the results of univariate regression analysis. eCdyn was significantly correlated with height, weight, BMI, FVC, FEV_1, and DLco. We noted a statistically significant inverse correlation between eCdyn and FEV_1/FVC and no significant correlation between eCdyn and predicted lung function, as indicated by FVC %predicted ($P = 0.087$) or DLco %predicted ($P = 0.36$). The correlation coefficients among these variables are shown in **Table 4**. We noted that height and weight were strongly correlated ($r = 0.84$, $P < 0.05$), as were FVC and FEV_1 ($r = 0.95$, $P < 0.05$) and FVC and DLco ($r = 0.80$, $P < 0.05$).

Figure 2B shows a comparison of the UIP and non-UIP groups. Median eCdyn was significantly lower in the UIP group (0.080) than in the non-UIP group (0.191; $P = 0.017$). Among the 6 patients with eCdyn of <0.1, 5 were in the UIP group.

To investigate correlations of eCdyn with other variables, we performed multivariate regression analyses with eCdyn as the dependent variable and weight, FVC, and UIP as independent variables. Because height, FEV_1, and DLco were strongly correlated with weight and FVC (**Table 4**), we excluded these factors from the analysis. Moreover, BMI was excluded because it was strongly correlated with weight. **Table 5** shows standardized partial regression coefficients and standard errors for eCdyn. The adjusted R^2 of eCdyn in the model was 0.77. Both weight ($\beta = 0.49$, $P = 0.011$) and UIP ($\beta = 0.52$, $P = 0.007$) were significantly correlated with eCdyn in the model. There was no significant correlation between FVC and eCdyn ($\beta = 0.19$, $P = 0.30$).

Table 2 Baseline characteristics of ILD group

Variables	ILD group	UIP	Non-UIP	*P* value
No.	14	8	6	
Pack-yr of smoking† (no.)	42.5 (30.0–88.8)	47.0 (31.9–84.4)	38.5 (0.0–88.8)	0.46
PaO_2 at rest‡ (Torr)	76.8 (52.8–87.3)	63.8 (49.6–82.1)	82.7 (66.4–97.2)	0.12
A-aDO_2 (Torr)	33.0 (15.3–47.0)	41.3 (18.2–44.6)	23.4 (9.9–76.7)	0.85
DLco	8.50 (7.20–12.09)	8.08 (6.67–9.36)	11.5 (7.81–14.36)	0.17
DLco %predicted	58.8 (44.9–74.1)	45.2 (38.7–68.2)	63.8 (53.4–89.4)	0.13

Data are presented as median and interquartile range
† 1 pack-yr = 1 year smoking 20 cigarettes per day
‡ Obtained while breathing room air
ILD = interstitial lung disease
A-aDO_2 = alveolar-arterial oxygen difference
DLco = diffusing capacity for carbon monoxide
UIP = usual interstitial pneumonia

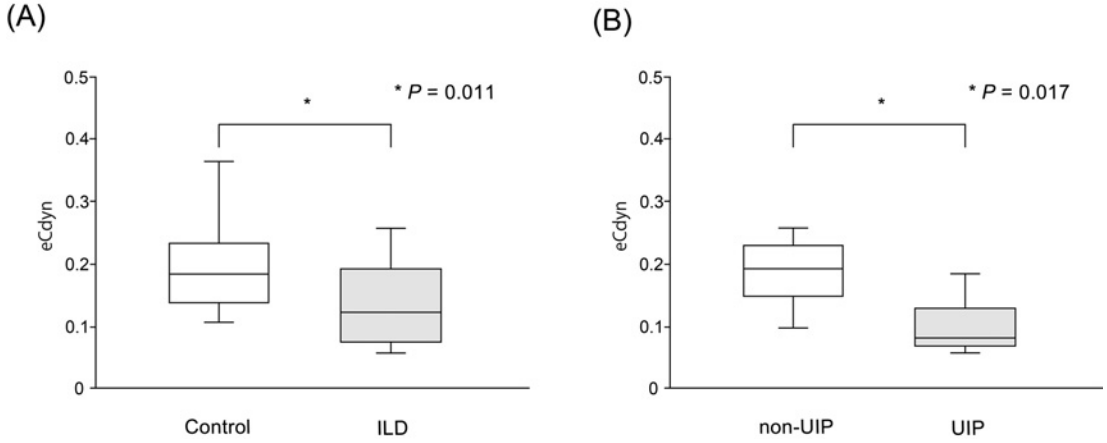

Fig. 2 (A) Box and whisker plots of eCdyn in 14 patients with interstitial lung disease and 49 healthy controls. Box plot shows median and 25th–75th percentiles (interquartile range). Whiskers show the minimum and maximum values. Note the difference between the two groups. **P* = 0.011.
(B) Box and whisker plots of eCdyn in 8 patients in the UIP group and 6 patients in the non-UIP group. Box plot shows median and 25th–75th percentiles (interquartile range). Whiskers show the minimum and maximum values. Note the difference between the two groups. **P* = 0.017.

Discussion

In this study, eCdyn was significantly lower in the ILD group than in the control group. With a cutoff value of 0.1 L/cmH_2O for eCdyn, the sensitivity and specificity for ILD was 6/14 (43%) and 49/49 (100%), respectively. Our data suggest that pulse wave is useful for measuring lung compliance. To our knowledge, no other study has assessed lung compliance by using a pulse wave sensor. We also evaluated the performance of the device by calculating CV and found that eCdyn varied by ±18%. Baydur et al.[15] reported that the intra-individual CV measured with an esophageal balloon was <10%. The range of variation in this study is large, and more-precise measurement results are required for clinical application.

As expected, eCdyn was significantly correlated with FVC and DLco. Several studies reported that DLco and lung compliance were markedly lower as compared with FVC reduction in ILD[16,17]. Fulmer et al. reported that, in patients with IPF, lung compliance was correlated with VC and TLC but not with DLco[18]. Therefore, our findings support the hypothesis that eCdyn measured using this device reflects the physiological condition of ILD with restrictive lung function.

eCdyn was also significantly correlated with height and weight. West et al.[2] reported that lung compliance depends on lung size: lung compliance is larger for a human lung than for a mouse lung. Conversely, Sutherland et al. reported that increasing adiposity reduced lung compliance caused by increased fat surrounding the chest wall and abdomen[19]. Because height was strongly

Table 3 Univariate regression analysis with eCdyn as the dependent variable in the ILD group

Dependent Variable	Independent Variables	β†	SE‡	Adjusted R^2	*P* value
eCdyn	Age	0.16	0.05	0.06	0.59
	Height	0.59	0.03	0.30	0.049*
	Weight	0.67	0.02	0.41	0.008*
	BMI	0.56	0.08	0.26	0.037*
	Pack-years of smoking	0.20	0.00	0.04	0.50
	PaO_2 at rest	0.13	0.02	0.07	0.66
	A-aDO_2	–0.18	0.01	0.05	0.55
	FVC	0.69	0.48	0.43	0.006*
	FVC %predicted	0.47	0.02	0.16	0.087
	FEV_1	0.54	0.58	0.23	0.048*
	FEV_1 %predicted	0.18	0.01	0.05	0.54
	FEV_1/FVC	–0.59	0.03	0.30	0.027*
	DLco	0.68	0.10	0.40	0.016*
	DLco %predicted	0.29	0.01	0.01	0.36

* Results of univariate regression analysis.
† β = standardized partial regression coefficient
‡ SE = standard error of the standardized partial regression coefficient
ILD = interstitial lung disease
eCdyn = estimated lung dynamic compliance
BMI = body mass index
A-aDO_2 = alveolar-arterial oxygen difference
DLco = diffusing capacity for carbon monoxide

Table 4 Correlations between significant variables

	Height	Weight	FVC	FEV_1	FEV_1/FVC	DLco
Height	x	0.84*	0.62*	0.60*	–0.11	0.39
Weight		x	0.52	0.41	–0.34	0.47
FVC			x	0.95*	–0.37	0.80*
FEV_1				x	–0.09	0.73*
FEV_1/FVC					x	–0.46
DLco						x

Spearman rank correlation coefficients
*$P < 0.05$
DLco = diffusing capacity for carbon monoxide

correlated with weight, eCdyn was positively correlated with weight. Here, we found no significant correlation of eCdyn with FVC %predicted or DLco %predicted. A potential problem is the effect that age and height, which are used for predicted lung function, have on lung compliance. eCdyn may be related to multiple confounding factors. In particular, the structural effects of advancing age on the respiratory system must be identified, to distinguish pathologic changes from those caused by the normal aging process. Aging reportedly increases lung compliance by decreasing lung elastisity[2,20]. However, Galetke et al. showed that lung compliance decreased with increasing age[12]. Mahler et al. revealed that advancing age increases the stiffness of the chest wall and decreases respiratory muscle strength[21]. Thus, the total compliance of the respiratory system could decrease with advancing age.

In the control group, we found no significant correlation of eCdyn with age ($P = 0.66$), height ($P = 0.42$), weight ($P = 0.66$), or BMI ($P = 0.90$). Establishing a regression equation (based on factors such as age, sex, height, and weight) for predicting eCdyn was difficult. In the future, eCdyn must be analyzed by adjusting for age, height, and weight.

In the ILD group, 12 of 14 patients were current or former smokers, and the median pack-years of smoking was

Table 5 Multivariate regression analysis with eCdyn as the dependent variable in the ILD group

Dependent Variable	Independent Variables	β†	SE‡	Adjusted R^2	*P* value
eCdyn	Weight	0.49	0.02		0.011*
	FVC	0.19	0.63		0.30
	UIP	0.52	0.31		0.007*
				0.77	

* Results of multivariate regression analysis
† β = standardized partial regression coefficient
‡ SE = standard error of the standardized partial regression coefficient
eCdyn = estimated lung dynamic compliance
ILD = interstitial lung disease
UIP = usual interstitial pneumonia

42.5. Hanley et al.[22] reported that lung compliance was higher in smokers with IPF than in nonsmokers. In pulmonary emphysema, lung compliance is increased by alteration of elastic tissue in the lung[2]. In this study, we excluded patients with obstructive lung disease (FEV_1/FVC <70%) and those with emphysema (patients with >10% emphysema on high-resolution CT). We noted a significant inverse correlation between eCdyn and FEV_1/FVC (P = 0.027). This result was affected by a decrease in FVC due to ILD. Mean (± SD) eCdyn was 0.135 ± 0.023 in patients with no emphysema (n = 9) and 0.138 ± 0.031 in patients with <10% emphysema on high-resolution CT (n = 5). We found no significant correlation between these groups (P = 0.95).

The various spirometric indices reflect airflow obstruction of different airways. Forced expiratory flow at 50% FVC ($FEF_{50\%}$) reflects mid/small airways. Forced expiratory flow when 75% of the FVC has been expired ($FEF_{75\%}$) reflects small airways. Takishima et al.[23] reported that the $FEV_{50\%}/FEV_{75\%}$ ratio indicates small-airway obstruction and does not exceed 3.0 in the healthy controls. In the ILD group, the mean (± SD) $FEV_{50\%}/FEV_{75\%}$ ratio was 2.92 ± 0.56. We found no significant correlation between eCdyn and pack-years of smoking (P = 0.50). These results reflect the absence of smoking-related airflow obstruction affecting eCdyn measurements in this study.

The median eCdyn was significantly lower in the UIP group than in the non-UIP group in univariate regression analysis. No other baseline characteristic significantly differed between the two groups (**Table 2**). Only FVC (P = 0.14) and FVC %predicted (P = 0.06) tended to decrease in the UIP group. Nevertheless, UIP was a significant variable in multivariate analysis for eCdyn, suggesting that it is a potential independent factor in decreasing compliance of FVC. Keogh et al.[24] reported that most results from animal studies are consistent with the concept that the relationships of static volume and pressure in ILD is determined more by fibrosis than by inflammation. Plantier et al.[25] suggested that reductions in lung compliance are strongly correlated with the severity of lung fibrosis. In 7 patients with end-stage IPF requiring mechanical ventilation, Cdyn was considerably reduced (0.019 ± 0.002 L/cmH_2O)[26]. The role of this method in assessing fibrosis progression in ILD should be further evaluated during analyses of different parameters, such as quantitative assessment of lung fibrosis using high-resolution CT.

Modern ventilators continuously display Cdyn even without measurement of esophageal pressure[27]. Monitoring is useful for optimizing ventilator management. However, it is seldom performed in the clinical assessment of chronic respiratory disease because of the invasiveness of mechanical ventilation. Analysis of pulse wave signals during mechanical ventilation might identify new relationships between respiration and pulse wave.

Our study has some limitations. First, we must identify factors that could obstruct pulse wave signal analysis. Pulse wave signals cannot be analyzed in patients with atrial fibrillation. The effects of cardiovascular disease should be considered when assessing pulse wave signals; however, this study did not evaluate circulatory dynamics in detail. Further examination of the effects of cardiac diseases and arteriosclerosis in pulse wave analysis is necessary. Second, Cdyn decreases with increasing respiratory frequency, which is a concern[28]. Furthermore, Woolcock et al.[29] reported that the respiratory frequency dependence of compliance was strong with obstruction

in peripheral airways. In this study, we measured, as a guide, a rate of approximately 15 breaths/min. However, we also need to measure eCdyn at varying respiratory frequencies. In addition, airflow limitation should be assessed with the forced oscillation technique. Third, we did not measure esophageal pressure with the esophageal balloon method. To evaluate the accuracy of the present device's measurements, we need to conduct a comparative study with Cdyn measured using the aforementioned method. Finally, this single-center study included only 14 patients with ILD. To assess the reliability and reproducibility of this method, the same patient must be assessed at different time points. Studies using larger case groups are necessary to further elucidate the mechanism of this method of measuring intrathoracic pressure.

In conclusion, using fingertip photoplethysmography, we noted a significant reduction in Cdyn in patients with ILD. This novel non-invasive method is a promising tool for evaluating fibrosis progression in ILD. Further validation studies are required.

Author contributions: Conceptualization and Methodology: K.A., R.O., K.S., S.K., A.A. Literature search: K.A. Study design: K.A., Y.S., A.A. Resources: R.O., K.S., S.K. Data collection: K.A., Y.S., T.T., T.K., H.H. Supervision: Y.S., A.G. Analysis of data: K.A., Y.S. Manuscript preparation: K.A. Review of manuscript: K.A., Y.S., K.K., M.S., A.G., A.A.

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References

1. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000 Feb;161(2 Pt 1):646–64.
2. West JB, Luks AM. West's Respiratory Physiology: The Essentials. 10th edition: Philadelphia, PA: Wolters Kluwer; 2016. p. 112–3.
3. Baydur A, Behrakis PK, Zin WA, Jaeger M, Milic-Emili J. A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis. 1982 Nov;126 (5):788–91.
4. Shabetai R, Fowler NO, Fenton JC, Masangkay M. Pulsus paradoxus. Journal Clin Invest. 1965;44(11):1882–98.
5. Knowles GK, Clark TJ. Pulsus paradoxus as a valuable sign indicating severity of asthma. Lancet. 1973 Dec 15;2 (7842):1356–9.
6. Settle HP Jr, Engel PJ, Fowler NO, et al. Echocardiographic study of the paradoxical arterial pulse in chronic obstructive lung disease. Circulation. 1980 Dec;62 (6):1297–307.
7. Shiomi T, Guilleminault C, Stoohs R, Schnittger I. Leftward shift of the interventricular septum and pulsus paradoxus in obstructive sleep apnea syndrome. Chest. 1991 Oct;100(4):894–902.
8. Shiomi T, Guilleminault C, Maekawa M, Nakamura A, Yamada K. Flow velocity paradoxus and pulsus paradoxus in obstructive sleep apnea syndrome. Chest. 1993 May;103(5):1629–31.
9. Nanba S, Ohsaki R, Toshiaki S. Apparatus and method for electronically predicting pleural pressure from pulse wave signal. 2002. U.S. Patent No. 6669632 [Internet]. n.d. [cited 2020 Aug 3]. Available from: https://patents.google.com/patent/US6669632B2/en?oq=6669632
10. Osaki R, Kurosawa S. Intrathoracic pressure calculation device and intrathoracic pressure calculation method 2018. U.S. Patent No. 20180199839 [Internet]. n.d. [cited 2020 Aug 3]. Available from: https://patents.google.com/patent/US20180199839A1/en?oq=20180199839
11. American Thoracic Society, European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med. 2002 Jan 15;165(2):277–304.
12. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011 Mar;183(6):788–824.
13. Galetke W, Feier C, Muth T, Ruehle KH, Borsch-Galetke E, Randerath W. Reference values for dynamic and static pulmonary compliance in men. Respir Med. 2007 Aug;101 (8):1783–9.
14. Faisal A, Alghamdi BJ, Ciavaglia CE, et al. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. Am J Respir Crit Care Med. 2016 Feb 1;193(3):299–309.
15. Baydur A, Cha EJ, Sassoon CS. Validation of esophageal balloon technique at different lung volumes and postures. J Appl Physiol (1985). 1987 Jan;62(1):315–21.
16. Yernault JC, de Jonghe M, de Coster A, Englert M. Pulmonary mechanics in diffuse fibrosing alveolitis. Bull Physiopathol Respir (Nancy). 1975 Mar-Apr;11(2):231–44.
17. American Thoracic Society, European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002 Aug;166(4):518–624.
18. Fulmer JD, Roberts WC, von Gal ER, Crystal RG. Morphologic-physiologic correlates of the severity of fibrosis and degree of cellularity in idiopathic pulmonary fibrosis. J Clin Invest. 1979 Apr;63(4):665–76.
19. Sutherland TJ, McLachlan CR, Sears MR, Poulton R, Hancox RJ. The relationship between body fat and respiratory function in young adults. Eur Respir J. 2016 Sep;48(3): 734–47.
20. Turner JM, Mead J, Wohl ME. Elasticity of human lungs in relation to age. J Appl Physiol. 1968 Dec;25(6):664–71.
21. Mahler DA, Rosiello RA, Loke J. The aging lung. Clin Geriatr Med. 1986 May;2(2):215–25.
22. Hanley ME, King TE Jr, Schwarz MI, Watters LC, Shen AS, Cherniack RM. The impact of smoking on mechanical properties of the lungs in idiopathic pulmonary fibrosis

and sarcoidosis. Am Rev Respir Dis. 1991 Nov;144(5): 1102–6.
23. Takishima T, Sasaki T, Takahashi K, Sasaki H, Nakamura T. Direct-writing recorder of the flow-volume curve and its clinical application. Chest. 1972 Mar;61(3):262–6.
24. Keogh BA, Crystal RG. Clinical significance of pulmonary function tests. Pulmonary function testing in interstitial pulmonary disease. What does it tell us? Chest. 1980 Dec; 78(6):856–65.
25. Plantier L, Cazes A, Dinh-Xuan AT, Bancal C, Marchand-Adam S, Crestani B. Physiology of the lung in idiopathic pulmonary fibrosis. Eur Respir Rev. 2018 Mar 31;27(147): 170062.
26. Nava S, Rubini F. Lung and chest wall mechanics in ventilated patients with end stage idiopathic pulmonary fibrosis. Thorax. 1999 May;54:390–5.
27. Macnaughton PD. New ventilators for the ICU--usefulness of lung performance reporting. Br J Anaesth. 2006 Jul;97(1):57–63.
28. Otis AB, McKerrow CB, Bartlett RA, et al. Mechanical factors in distribution of pulmonary ventilation. J Appl Physiol. 1956 Jan;8(4):427–43.
29. Woolcock AJ, Vincent NJ, Macklem PT. Frequency dependence of compliance as a test for obstruction in the small airways. J Clin Invest. 1969 Jun;48(6):1097–106.

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