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A new noninvasive method for measurement of dynamic lung compliance from fluctuations on photoplethysmography in respiration

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Running Title: Dynamic lung compliance with application of PPG

New & Noteworthy: Our newly developed method for measuring dynamic lung compliance (Cdyn) in combination with changes in estimated intrathoracic pressure from fluctuations on photoplethysmography with respiration and lung volume measured simultaneously by spirometry showed good linear regression between the estimated Cdyn and the Cdyn measured with an esophageal balloon, and he estimated percentage of predicted Cdyn (%Cdyn) showed significantly lower values in patients with interstitial lung disease (ILD) than in healthy subjects and d chronic obstructive pulmonary disease (COPD) patients, and significant correlations with vital capacity and lung diffusion capacity.

Keywords: pulse wave, intrathoracic pressure, esophageal pressure, interstitial lung disease, chronic obstructive pulmonary disease

Conflicts of Interest Disclosure: This study was supported by collaborative research expenses from Denso Corporation.

Abstract

Lung compliance is important in interstitial lung disease (ILD). However, the measurement requires placement of an esophageal pressure probe, and is therefore not done in routine clinic practice. This study was performed to develop and verify a new noninvasive method for estimation of dynamic lung compliance (Cdyn) with a photoplethysmograph (PPG) of pulse wave representing as the changes of absorbance of green LED for hemoglobin, and to examine its usefulness. A system for measuring Cdyn in combination with changes in estimated pleural pressure (Ppl) from the fluctuations on PPG with respiration and lung volume measured simultaneously by spirometry was developed, and verified to show correspondence with the estimated Ppl and the esophageal pressure (Pes), estimated Cdyn, and Cdyn measured with an esophageal balloon. Furthermore, the estimated percentage of predicted Cdyn (% Cdyn) was compared among healthy subjects (HS) (n = 33) and patients with chronic obstructive pulmonary disease (COPD) (n = 31) and ILD (n = 30). Both the estimated Ppl and Cdyn were significantly correlated with the Pes (r = 0.89) and measured Cdyn (r = 0.63), respectively. The estimated %Cdyn in ILD showed significant lower values than those in HS and COPD. The estimated %Cdyn was significantly related to percentage of predicted vital capacity (VC) (r = 0.57, P < 0.01) and percentage of predicted diffusion capacity of carbon monoxide (DLCO) (r = 0.50, P < 0.01) in patients with ILD. These findings suggested that the newly developed noninvasive and convenient method for Cdyn estimation using a combination of PPG and

55 spirometry may be useful for the assessment of lung fibrosis in ILD.

56

57 **Introduction**

58 Static lung compliance (Cst) is the lung compliance under static conditions, whereas dynamic lung
59 compliance (Cdyn) is the lung compliance during tidal breathing. Cst is affected by lung elastic recoil
60 pressure. Cst shows higher values in emphysema and lower values in interstitial lung disease (ILD).
61 In chronic obstructive pulmonary disease (COPD), Cdyn varies in accordance with the severity of
62 emphysema and airway diseases (1, 2). Although there is volume loss in the progressive stage of ILD
63 and no correlations were observed between standard physiological parameters, such as vital capacity
64 (VC), total lung capacity (TLC), and diffusion capacity of carbon monoxide (DLCO), and pathological
65 severity, Cst was strongly correlated with the degree of fibrosis assessed by scoring of lung biopsies
66 (3). Reductions in Cdyn occur to the same extent as reductions in Cst in subjects with ILD (4).
67 Therefore, Cdyn can be used as an index of lung elasticity in ILD, and may be useful for evaluation
68 of disease progression or efficacy of therapeutic regimens. However, determination of Cdyn requires
69 measurement of esophageal pressure (Pes) with an esophageal balloon. Pes has been used as an
70 estimate of pleural pressure (Ppl) since 1949 when Buytendijk pioneered the technique (5). Lung
71 compliance measurement therefore requires placement of a Pes probe, which is invasive and not
72 routinely done in clinical settings. Therefore, a new noninvasive and convenient method for evaluation

of lung compliance is required.

Systolic and diastolic blood pressures vary with respiration, reaching a minimum when Ppl is at its lowest during inspiration and reaching a maximum during expiration when Ppl is greatest (6). The most likely additional mechanism is the decrease in left ventricular stroke volume during inspiration (7, 8). Shiomi et al. demonstrated interventricular shift to the diastolic left ventricle, inducing flattening of the left ventricle with pulsus paradoxus during non-REM sleep in obstructive sleep apnea (OSA) (9), and also reported that more negative Pes was significantly correlated with increased right ventricular internal end-diastolic dimension and decreased left ventricular internal end-diastolic dimension monitored by echocardiography during sleep in children with OSA (10). Therefore, the mechanism underlying the variation of stroke volume with respiration has been considered to be as follows: the more negative Ppl during inspiration induces an increase in venous return, which results in an increase in end-diastolic right ventricular volume and interventricular shift to the left ventricle, and decreased end-diastolic left ventricular volume and stroke volume. However, Buda et al. (11) reported that during the Müller maneuver, left ventricular end-diastolic volume increased and the stroke volume and cardiac output were significantly decreased. It was suggested that the marked intrathoracic negative pressure affected left ventricular function by increasing left ventricular transmural pressure, which resulted in an increase in afterload.

The photoplethysmograph (PPG) waveform, well known as the pulse oximeter waveform, is an

amplified and highly filtered measurement of light absorption by the local tissue over time, and represents the changes of peripheral blood volume. It has been demonstrated that the variation of stroke volume with respiration reflects the fluctuation of pulse wave on photoplethysmography (PPG) (12). That is, the fluctuation in PPG may reflect the swing of Ppl with respiration. If the within-breath changes in PPG correspond to the changes in Ppl, it would be possible to estimate Cdyn in combination with changes in Ppl estimated from the fluctuation of PPG and the simultaneous measurement of lung volume by spirometry.

We have developed a new noninvasive system for measurement of Cdyn in combination with changes in Ppl estimated from fluctuations on PPG with respiration and lung volume measured simultaneously by spirometry, confirmed the correspondence of the Cdyn estimated from PPG and the Cdyn measured with an esophageal balloon, and compared the Cdyn estimated by PPG among healthy adult volunteers and patients with COPD and ILD.

Materials and methods

1. Subjects

Three healthy subjects (HS; mean age: 43 ± 14 years old, range: 32 – 58 years) in experiment 1; 28 HS, 14 patients with stable COPD (GOLD classification: stage 1, n = 7; 2, n = 6; 3, n = 1), and 10 patients with ILD in experiment 2 (Table 1); and 33 HS, 31 patients with stable COPD (GOLD

classification: stage 1, n = 8; 2, n = 14; 3, n = 4; 4, n = 5), and 30 patients with ILD in experiment 3 (Table 2) who were different from the subjects in experiment 2 were recruited between April 2013 and May 2016. All subjects were Japanese. Subjects who showed arrhythmia and atrial fibrillation, had peripheral circulatory failure, or were diagnosed with heart failure, renal failure, or impaired cognitive function were excluded from the study. Patients with ILD due to scleroderma were excluded in experiment 2 because scleroderma may involve esophageal contractility and elastance, and therefore may affect the relevance of Pes with regard to reflecting Ppl. Seven patients with COPD were treated with long-acting bronchodilators (LABD), three with LABD and inhaled corticosteroid (ICS), and four received no therapy. Three patients with ILD were treated with oral steroids, two were treated with anti-fibrotic agent, and five received no therapy. Long-term oxygen therapy was prescribed in two patients with COPD and one patient with ILD in experiment 2. Seventeen patients with COPD were treated with LABD, nine were treated with LABD and ICS, and five received no therapy. Seven patients with ILD were treated with oral steroids, five were treated with immunosuppressive agents, one was treated with anti-fibrotic agent, and sixteen received no therapy. Long-term oxygen therapy was prescribed in eight patients with COPD and four patients with ILD in experiment 3. All subjects were given an adequate explanation of the study and provided written informed consent. This study was conducted in accordance with the International Conference on Harmonization-Good Clinical Practice and the Declaration of Helsinki (2008), and was approved by the Shinshu University of

Medical Ethics Committee (approval number: 2291, May 8, 2014).

2. Methods

2.1. Protocol

The fluctuations in PPG signals with respiration were monitored as changes in absorbance of reflected light from a green LED and were affected by various factors. Therefore, it was necessary to convert from changes in PPG signals to changes in pressure, and to calibrate with the changes in pressure at airway opening (Pao) with respiration under loading with inspiratory negative pressure in each measurement. Experiment 1 was performed to examine the correspondence between the changes in Pao and Pes, and between the estimated Ppl from PPG and Pes to verify the calibration method. Experiment 2 was performed to verify the correspondence between the estimated Cdyn from PPG and Cdyn measured by Pes in the population including HS and patients with COPD and ILD. Experiment 3 was performed to compare the estimated Cdyn among HS and patients with COPD and ILD who were different from the subjects in experiment 2, and to examine the relationships with pulmonary function.

2.1.1. Experiment 1: Verification of calibration method and correspondence with Ppl estimated from PPG and Pes

145 The method for calibration by loading inspiratory negative resistance was verified with an esophageal
146 balloon. Briefly, an esophageal balloon was inserted into each of three HS who were attached to a PPG
147 and spirometer with inspiratory negative resistive load and breathed 12 times at 4 s/breath with the
148 tidal volume gradually increasing from about 0.3 L to 0.8 L. The changes in pressure Pao and Pes were
149 measured simultaneously to verify the correspondence between both measurements. After calibration,
150 the resistive device was removed, and breathing was continued in the same manner with measurement
151 of the changes in estimated Ppl and Pes simultaneously, and the coincidence of both measurements
152 was verified. The data of Pao, Pes, and the intrathoracic pressure estimated from PPG fluctuation were
153 collected from three healthy subjects.

154 2.1.2. Experiment 2. Comparison of the estimated Cdyn from PPG and the Cdyn measured by the
155 method using an esophageal balloon

156 Twenty-eight HS, 14 patients with COPD, and 10 patients with ILD underwent pulmonary function
157 tests, including spirometry, lung volume, diffusing capacity, and ventilator unevenness, followed by
158 determination of estimated Cdyn in combination with PPG and spirometry. Finally, all subjects
159 underwent measurement of Cst and Cdyn by the method using an esophageal balloon, and the results
160 were compared with the estimated Cdyn determined by PPG.

161 2.1.3. Experiment 3. Comparison of the estimated Cdyn from PPG among HS, patients with stable
162 COPD, and patients with ILD

Thirty-three HS, 31 patients with COPD, and 30 patients with ILD underwent pulmonary function tests followed by determination of estimated Cdyn in combination with PPG and spirometry. We did not measure Cst and Cdyn using an esophageal balloon in this experiment. The estimated Cdyn, expressed as percentage of predicted Cdyn (%Cdyn), from PPG was compared among these subjects.

2.2. Methods for the estimation of Cdyn

2.2.1. Development of a system for the estimation of Cdyn

A reflection-type PPG using a green LED with a wavelength of 525 nm developed by Denso Corporation (Kariya, Japan) was used in this study. The device showed good absorption for hemoglobin and a small degree of surface reflection on the skin, and used an alternating current (AC) amplifier corresponding to the lower limit of 0.1 Hz to sensitively detect respiratory components superimposed on PPG. This device was attached to the right index finger. The position of finger was adjusted at the height of heart although the estimation of intrathoracic pressure did not largely affect by the position of finger. Figures 1A and 1B show the changes in PPG corresponding to tidal breathing. Ppl was estimated from PPG according to the method reported by Kimura (12). The y-axis showed changes in absorbance, which reflected the intravascular blood volume and were decreased in inspiration and increased in expiration. First, we calculated the difference (PPa) between the envelope line of each peak percussion pulse wave (line (1) in Figure 1A) and the envelope line of the peak

181 percussion pulse wave at expiration (line (2) in Figure 1A). As the amplitude of the pulse wave is
182 affected by systolic pressure, the amount of light from outside, and the attachment with the skin (13),
183 it was necessary to correct the PPa by the amplitude of the pulse wave (PWa). The changes in PPa/PWa
184 with respiration are shown in Figure 1B.

185 The changes in absorption of PPG corresponding to the changes in Ppl were converted to changes
186 in pressure. For calibration, inspiratory resistance was loaded by the attachment of a resistive device
187 (5 $cmH_2O/L/s$) to the side opposite the site of attachment of the spirometer mouthpiece (Figure 2A).
188 When the inspiratory resistance was loaded, the changes in Pao were equal to the changes in Ppl. The
189 signals of Pao and PPG were inputted into the same computer system and automatically synchronized.
190 The sampling frequency was 100 Hz and there was no time lag, and the changes in absorption
191 (PPa/PWa) corresponded to the changes in Pao. We determined the slope of the regression line between
192 the changes in PPa/PWa and Pao (Figure 2B), and converted changes in absorption to changes in
193 pressure.

194 2.2.2. Determination of estimated Cdyn

195 Figure 3 shows the system for determination of estimated Cdyn. A reflection-type PPG was attached
196 to the right second finger that was placed on a cushion to avoid movement. Subjects were attached to
197 a PPG and a nose clip and mouthpiece attached to a flow sensor were applied. The subjects breathed
198 according to the instructions provided by a picture displayed on a personal computer (PC) and voice

199 on the PC. Subjects breathed at a rate of 4 s/breath and the tidal volume was gradually increased from
200 about 0.3 L to 0.8 L over 12 breaths. First, calibration was performed under loading with negative
201 inspiratory pressure for 12 breaths, and the slope of the regression line was obtained. After removal of
202 the resistance device, subjects breathed at 4 s/breath and the tidal volume was gradually increased in
203 the same manner as in calibration (Figure 4). The PPa/PWa was converted to change in estimated Ppl
204 using the slope of the regression line in each measurement and the Cdyn was calculated by linear
205 regression analysis between the estimated Ppl and tidal volume.
206
207 2.3. Pulmonary function test including lung compliance measured with an esophageal balloon
208 Spirometry, lung volume of FRC and airway resistance (Raw) determined by body plethysmography,
209 lung diffusion capacity for carbon monoxide (DLCO) determined by the single-breath method, and
210 the N_2 phase III slope of single-breath N_2 washout (ΔN_2), a marker of ventilation unevenness, were
211 measured using a Chestac-8900 (Chest Co., Ltd.). The lung volumes and DLCO were represented as
212 the percentage of predicted value. For the predicted values of forced expiratory volume in 1 s (FEV_1)
213 and vital capacity (VC), Japanese local reference data (25) developed by the Japanese Respiratory
214 Society were adopted, and the predicted values for DLCO and lung volumes (FRC, RV, and TLC)
215 measured by body plethysmography were determined with the formulas of Nishida *et al*. (15) and
216 Boren *et al*. (16), respectively.

Both Cst and Cdyn were measured by the esophageal balloon method using a body box (Chestac 8900; Chest Co., Ltd.) as reported previously (2). We used an esophageal balloon as an accessory of a Chestac-8800 pulmonary function testing system (Chest Co., Ltd.). The balloon length was 120 mm and total length including the tube was 1010mm, the outside diameter was 2.5 mm and inside diameter was 1.5 mm. The optimal volume of air in the balloon was 0.2 mL. Before the test, the nasal cavity was anesthetized with xylocaine spray, and the esophageal balloon catheter (Chest Co., Ltd.) was passed through the nose. The balloon was drawn 10 cm from the position where the change in balloon pressure synchronized with the respiration was reversed, and the distance was measured 10 cm from the nostril. First, after maximum inspiration, the subjects were asked to exhale from maximum inspiratory level to maximum expiratory level in increments of 300 – 500 mL. We drew a lung pressure–volume curve using transpulmonary pressure (Ptp) (the difference between Pao and Pes) and lung volume. Regression analysis was performed using a sigmoidal equation. Regression analysis was performed using a sigmoidal equation of the form, $V = a + b\ [1 + e^{-(P-c)/d}]^{-1}$ (17). The Cst was calculated as the slope between resting expiratory level (FRC level) and 500-mL inspiratory level, and the Ptp at the point of maximum inspiration (Pes max) was also measured. Subsequently, we measured Cdyn and lung resistance (R_L) at a resting respiratory rate of 0.25 Hz, and the last five breaths were analyzed breath-by-breath. Cdyn and R_L were obtained. For the predicted values of Cst and Cdyn, the formula reported by Galetke et al (18). were adopted.

235

236 **5. Statistical analysis**

237 Values are shown as the means ± SD. The data distribution of the variables in the various groups was
238 first assessed with Bartlett's test. As the data for the variables did not show a normal distribution, the
239 variables were compared with the Kruskal-Wallis test followed by multiple comparisons among
240 groups with the nonparametric Steel-Dwass test. Cut-off values of estimated %Cdyn to differentiate
241 ILD from HS and COPD were calculated by receiver operator characteristic (ROC) curve analysis,
242 with sensitivity and specificity determined in each case. All statistical analyses were performed using
243 StatFlex version 6 for Windows (Artech Co., Ltd., Osaka, Japan). Spearman's rank correlation
244 coefficient was used for bivariate correlation analysis. Orthogonal distance regression analysis
245 (Python 5.8; Python Software Foundation, Wilmington, DE) and Bland–Altman analysis (R ver. 4.0.2;
246 The R Project for Statistical Computing, Vienna, Austria) were also performed to verify the
247 correspondence of Cdyn measured using PPG and the esophageal balloon. In all analyses, $P < 0.05$
248 was taken to indicate statistical significance.

249

250 **Results**

251 Experiment 1: Verification of calibration method and correspondence with Ppl estimated from PPG
252 and Pes

253 The data were collected from three healthy subjects (A, B, C). Thirty-eight data in subject A, 33 in
254 subject B, and 111 in subject C were collected. The correlation coefficients between Pao and Pes,
255 estimated intrathoracic pressure and Pes were 0.996 and 0.996 in subject A, 0.997 and 0.988 in subject
256 B, and 0.997 and 0.982 in Subject C, respectively. Figure 5A shows scatter plots using total 182 breath-
257 by breath data of three healthy volunteers and linear regression analysis of the changes in Pao and Pes.
258 The correlation coefficient was 0.98, which was a high value and the slope was 1.05, which showed
259 almost the same value as Pes. Therefore, the changes in Pao corresponded closely with the changes in
260 Pes.
261 Figure 5B shows the relationship between the changes in Pes and Ppl estimated by PPG using all
262 breath-by-breath data in three healthy volunteers. There was a significant correlation ($r = 0.89$)
263 between the changes in Pes and the estimated Ppl from PPG. The slope was 0.92, indicating that the
264 estimated Ppl was almost same as Pes.
265
266 Experiment 2. Comparison of the estimated Cdyn from PPG and the Cdyn measured with an
267 esophageal balloon
268 Table 1 shows the characteristics and results of pulmonary function tests. The patients with COPD
269 showed mild to moderate airflow obstruction (FEV_1: 41.5% – 94.1%, stage 1/2/3: 7/6/1 patients),
270 increased residual volume, hyperinflation, and ventilation unevenness. Twelve of 14 patients showed

decreased diffusion capacity. Cst, %Cst (% of predicted Cst), and R_L were increased, but there was no significant difference in %Cdyn between HS and COPD groups. Patients with ILD showed decreased lung volume and diffusion capacity and ventilation unevenness, and both %Cst and %Cdyn were significantly decreased and R_L was increased. As shown in Figure 6A, there was a significant correlation between Cdyn measured from Pes and the Cdyn estimated from PPG ($r = 0.63$). Orthogonal distance regression analysis was also performed to verify the correspondence of Cdyn measured by the two methods. The confidence interval of the y-intercept was from 0.003 to 0.062, almost including 0, and the confidence interval of the slope was from 0.579 to 1.009, including 1. Figure 6B shows a Bland–Altman plot of differences in %Cdyn measured by the two methods. The mean difference was −2.39 % between EP-%Cdyn and PPG-Cdyn, and the 95% limit of agreement (LOA) had an upper limit of 30.9 % and lower limit of −35.7 %. No apparent systematic errors in the measurement of PPG-%Cdyn were found. However, measurement errors were found in a few patients. These findings suggested that the values of Cdyn measured by the two methods were almost consistent with each other.

Experiment 3. Comparison of the estimated Cdyn from PPG among healthy subjects, patients with stable COPD, and patients with ILD

Figure 7 shows the %Cdyn estimated from PPG among HS, patients with COPD, and patients with

289 ILD. Although there was no significant difference in estimated %Cdyn between the HS and COPD
290 groups, the estimated %Cdyn in the ILD group (35.4 ± 12.3 %) was significantly lower compared
291 with the HS group (60.0 ± 15.8 %, $P < 0.01$) and the COPD group (66.7 ± 41.9 %, $P < 0.01$). The
292 estimated %Cdyn was significantly related with %VC (r = 0.57, $P < 0.01$) and %DLCO (r = 0.50, $P <$
293 0.01) in patients with ILD (Fig. 8). ROC analysis was performed to quantify the diagnostic
294 performance of %Cdyn to detect ILD using the area under the curve (AUC) on ROC analysis (Fig. 9).
295 The AUCs on ROC analysis to differentiate ILD from HS and COPD patients were 0.896 (confidence
296 interval: 0.813-0.979) and 0.786 (confidence interval: 0.670-0.902), respectively. Sensitivity and
297 specificity to differentiate from HS was 80.0 % and from COPD was 64.5 %, respectively, when the
298 cut-off value for estimated %Cdyn was 45.2 % for HS and 42.9 % for COPD patients.
299
300 **Discussion**
301 Although there have been a number of reports regarding the fluctuation of PPG in respiration, there
302 have been no attempts to estimate lung compliance (19). In the present study, we have developed a
303 new method for the estimation of Cdyn in combination with changes in estimated Ppl based on the
304 fluctuation of PPG with respiration and lung volume measured simultaneously by spirometry. On
305 linear regression analysis, a good correlation was observed between estimated Ppl from PPG and Pes
306 measured by the esophageal balloon method. Furthermore, the estimated Cdyn from PPG and Cdyn

307 measured by the esophageal balloon method were almost the same. The Cdyn and % Cdyn in the ILD
308 group was significantly lower than those in the HS and COPD groups and showed significant
309 correlations with %VC and %DLCO. ROC analysis demonstrated that the estimated %Cdyn showed
310 good diagnostic performance for ILD. These findings suggested that the new noninvasive and
311 convenient method for estimation of Cdyn may be useful for the assessment of lung fibrosis in ILD.
312 Kimura et al. (12) demonstrated that marked intrathoracic negative pressure in inspiration induced
313 by occluding the upper airway increased intrathoracic blood volume and decreased peripheral blood
314 volume in anesthetized dogs. Shiomi et al. (9, 10) demonstrated that more negative Pes was
315 significantly correlated with increased right ventricular internal end-diastolic dimension and decreased
316 left ventricular internal end-diastolic dimension monitored by echocardiography when pulsus
317 paradoxus was found during sleep in OSA. However, Buda et al. (11) reported that left ventricular
318 end-diastolic volume increased and the stroke volume and cardiac output were significantly decreased
319 during large, sustained changes in intrathoracic pressure by the Müller maneuver. It is suggested that
320 the marked intrathoracic negative pressure affects left ventricular function by increasing left
321 ventricular transmural pressure, which results in an increase of afterload. These interactions between
322 intrathoracic pressure and hemodynamics may induce PPG fluctuation in respiration. Furthermore, the
323 compensatory offset of blood volume and air content into the thorax, that is interaction between lung
324 compliance and hemodynamic effect of ventilation (inspiration, expiration), may be able to modify

the measurement of estimated Cdyn from PPG.

Noninvasive surrogate markers of Pes using PPG have been reported, especially in OSA (31). For example, pulse transit time (PTT), which is the time interval for a pulse wave to travel between two locations in the arterial system, showed reasonable correlations between the amplitude oscillations (ΔPTT) and the magnitude of negative Ppl swings assessed by Pes monitoring (20). However, the specificity and interobserver variability were not assessed, and PTT is not a valid surrogate marker for Pes monitoring. Forehead venous pressure (FVP) has been reported to be useful for measurement of respiratory effort derived from a combination of physiological signals obtained from a recorder affixed to the forehead (ARES™ Unicorder; Advanced Brain Monitoring, Carlsbad, CA), composed of red and infrared LEDs to detect the fluctuations in PPG amplitude, a piezoresistive silicone absolute pressure sensing chip to measure changes in forehead venous pressure, and 3-axis MEM accelerometer to measure subtle motions associated with respiration in patients with sleep disordered breathing (21). This device is believed to allow monitoring of respiration-related changes in volume or pressure in the veins of the skin on the forehead, and has been shown to be suitable as an alternative measure of respiratory effort. However, its reproducibility and validity with respect to Pes monitoring have not been determined. In the present study, a significant correlation was observed between the fluctuation of PPG and the changes in Pes during tidal breathing, and we were able to estimate the changes in Ppl from PPG. A significant correlation was also observed between the Cdyn estimated from PPG and the

343 Cdyn measured using the esophageal balloon method, and the two values of Cdyn were almost
344 identical. Therefore, the estimated Cdyn by the newly developed method can be used as a surrogate
345 marker of Cdyn.
346 In the pulmonary function test, an absolute or relative decline in forced vital capacity (FVC), DLCO,
347 and 6-minute walking distance (6MWD) are markers for predicting progression of fibrosis and
348 therapeutic efficacy in progressing fibrosing ILD (22). In nonspecific interstitial pneumonia and
349 idiopathic pulmonary fibrosis, severely decreased DLCO, exertional desaturation, and a decrease in
350 FVC identify patients at particular risk of mortality (23). However, change over time in shortness of
351 breath scores was associated with change in FVC, quality of life score, and 6MWD, but not DLCO
352 (24). On the other hand, it has been demonstrated that reductions of lung compliance occur early in
353 IPF (4, 25). Although no correlations between decreased lung volume or DLCO and pathological
354 severity have been observed, Cst was shown to be strongly correlated with the degree of fibrosis
355 assessed by scoring of lung biopsies (3). Reductions in Cdyn occur to the same extent as reductions in
356 Cst in subjects with ILD (4). Cdyn is decreased with the reduction of lung volume. The decrease of
357 Cdyn resulted from reduced lung volume has been suggested to be due to increased airway resistance
358 and airway closure at small airways (26, 27). It was suggested that the decreased Cdyn in ILD may be
359 due to not only increased elasticity of lungs but also decreased lung volume. Therefore, it may become
360 possible to assess multidimensionally by the addition of Cdyn as a biomarker of lung fibrosis to

conventional pulmonary function testing. However, measurement of lung compliance is not routinely done in a clinical setting because it is invasive and the equipment required is expensive. In the present study, the estimated Cdyn and %Cdyn in ILD showed not only significantly lower values than those in HS and COPD groups, but also significant correlations with loss of lung volume and decreased gas transfer, and was demonstrated to show good diagnostic performance for ILD. Therefore, the estimated Cdyn that can be obtained noninvasively and conveniently by our newly developed method may be useful for the assessment of lung fibrosis in ILD, and will contribute to the screening and management of ILD as a new physiological marker.

Limitations

This study had several limitations. First, sample size was comparatively small for comparison of the estimated Cdyn among HS, patients with COPD, and patients with ILD. Second, Cdyn is decreased with increased age (27) and the age was not matched between HS and COPD or ILD. Although there was no report about the reference values of Cdyn in Japanese normal subjects. Cdyn was expressed as the percentage of predicted value with the formula reported by Galetke et al (18). However, the predicted value of Cst and Cdyn may be suggested to be higher values for Japanese because the mean %Cst and %Cdyn in healthy subjects were 72.5% and 57.2%, respectively. Third, the pulse volume waveform contains a complex mixture of the influences of arterial, venous, autonomic, and respiratory

379 systems on the central and peripheral circulation (28). The PPG signal is comprised of the AC
380 component and DC component. The pulsatile waveform (AC component) is attributed to changes in
381 the interrogated blood volume with each heartbeat and varies slowly due to respiration and
382 sympathetic nervous system activity (DC component) (29). The pulse waveform variation with
383 respiration has also been shown to be significantly correlated with the changes in systolic pressure
384 variation, and to be a sensitive indicator of hypovolemia (13). In the present study, the PPa, was
385 corrected by the amplitude of the pulse wave because this value is affected by the systolic pressure,
386 the amount of light from outside, and the conditions of attachment to the skin. In addition, the
387 measurement of estimated Cdyn was calibrated by the changes in Pao when the inspiratory negative
388 pressure was loaded in each measurement. However, PPG may be affected by multiple factors, such
389 as vasoconstriction, vasodilation, tissue congestion, and circulating blood volume (16). Further studies
390 are required to examine these effects on the measurement. Fourth, we did not use the Baydur's
391 maneuver to check the correct positioning of the balloon because the Chestac-8800 did not have a
392 function to check the balloon position. Fifth, the value of the estimated Cdyn in HS was lower than
393 that reported previously (0.15 ± 0.04 in this study vs. 0.29 ± 0.11 L/cmH_2O) (18). However, the value
394 of estimated Cdyn was almost the same as Cdyn measured by the conventional method. Sixth, the
395 estimated Cdyn may be affected by respiratory pattern. However, it was demonstrated that there were
396 no significant differences in changes in Ppl between "intercostal" and "abdominal" breathing (30).

Conclusion

The estimated Ppl and Cdyn from the fluctuation of PPG in respiration were significantly correlated with Pes and Cdyn, respectively. The estimated %Cdyn in ILD was significantly lower than in HS and COPD groups, and was significantly correlated with %VC and %DLCO. The newly developed method for estimation of Cdyn in combination with PPG and spirometry may be useful for the assessment of lung fibrosis in ILD.

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CONFLICTS OF INTEREST

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491

492 Figure Legends

493 Figure 1. Method for extraction of respiratory component superimposed on PPG

494 A. Changes in the absorbance of PPG corresponding to tidal breathing. Line (1), envelope line of each

495 peak percussion pulse wave; line (2), envelope line of peak percussion pulse wave at expiration; PWa,

496 amplitude of the pulse wave; PPa, line (2)–(1). B. Changes in PPa/PWa corresponding to tidal

497 breathing.

498 Abbreviations: PPG, photoplethysmograph.

499

500 Figure 2. Method of calibration

501 A. A device for negative pressure loading in inspiration was attached to the side opposite the

502 mouthpiece during calibration. B. Regression line between the changes in pressure at the airway

503 opening (Pao) and absorbance of PPG corresponding to tidal breathing under negative inspiratory

504 pressure load. The slope of the regression line was obtained (coefficient value) for calibration. C.

505 Conversion from changes in PPG absorbance to changes in pressure by calibration.

506

507 Figure 3. System for measurement of lung dynamic compliance (Cdyn) in combination with

508 photoplethysmography (PPG) and spirometry.

509

510 Figure 4. Measurement and calculation of estimated lung dynamic compliance (Cdyn).

511 Tidal breathing at a cycle of 4 s/breath was gradually increased from about 0.3 L to 0.8 L according

512 to guidance (dashed line in upper panel), and simultaneously the changes in intrathoracic pressure

513 estimated from PPG (solid line in upper panel) were measured. B. Scatter plot of tidal volume and

514 changes in estimated intrathoracic pressure. The slope represents Cdyn..

515

516 Figure 5. A. Comparison of the changes in esophageal pressure (Pes) measured using an esophageal

517 balloon and pressure at the airway opening (Pao) when negative pressure was loaded in three healthy

518 adult volunteers. B. Relationship between Pes measured using an esophageal balloon and intrathoracic

519 pressure estimated from photoplethysmography (PPG).

520

521 Figure 6. A. Relationship between lung dynamic compliance (Cdyn) measured from esophageal

522 pressure (EP-Cdyn) and Cdyn estimated from photoplethysmography (PPG) (PPG-Cdyn). Open

523 circles: healthy subjects; open squares: patients with chronic obstructive pulmonary disease (COPD);

524 open triangles: patients with interstitial lung disease (ILD). There was a significant correlation between

525 the Cdyn measured by the two methods. B. Bland–Altman plot of differences in % of predicted Cdyn

526 measured from esophageal pressure and %Cdyn estimated from PPG (n = 52). Solid lines represent

527 mean differences, and dashed lines represent 1.96 SD of the difference from the mean. PPG,

528 photoplethysmography.

529

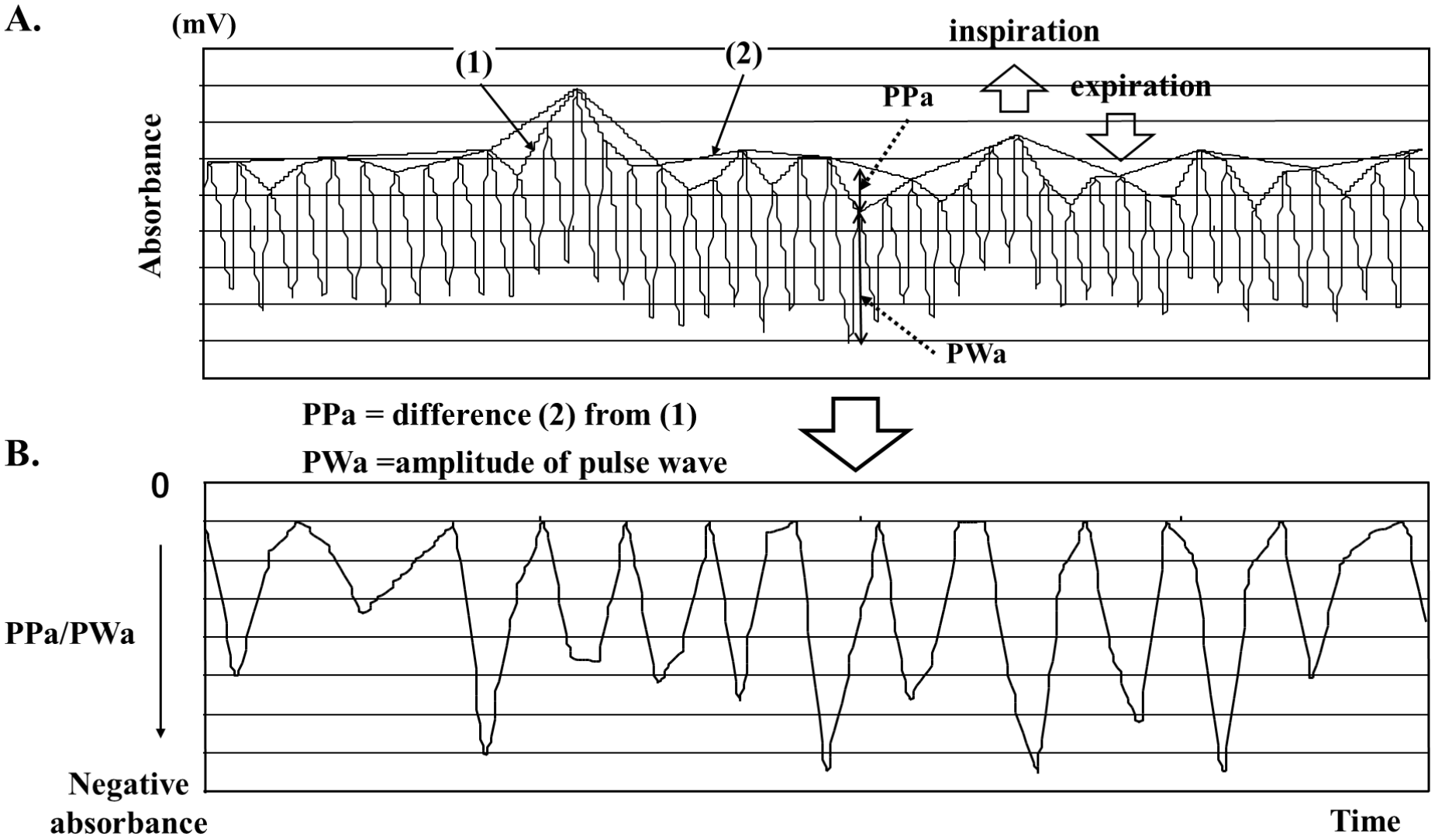
530 Figure 7. Comparison of the estimated lung dynamic compliance (Cdyn) from photoplethysmography
531 (PPG) among healthy subjects (HS) (n = 33) and patients with chronic obstructive pulmonary disease
532 (COPD, n = 31) and interstitial lung disease (ILD, n = 30).

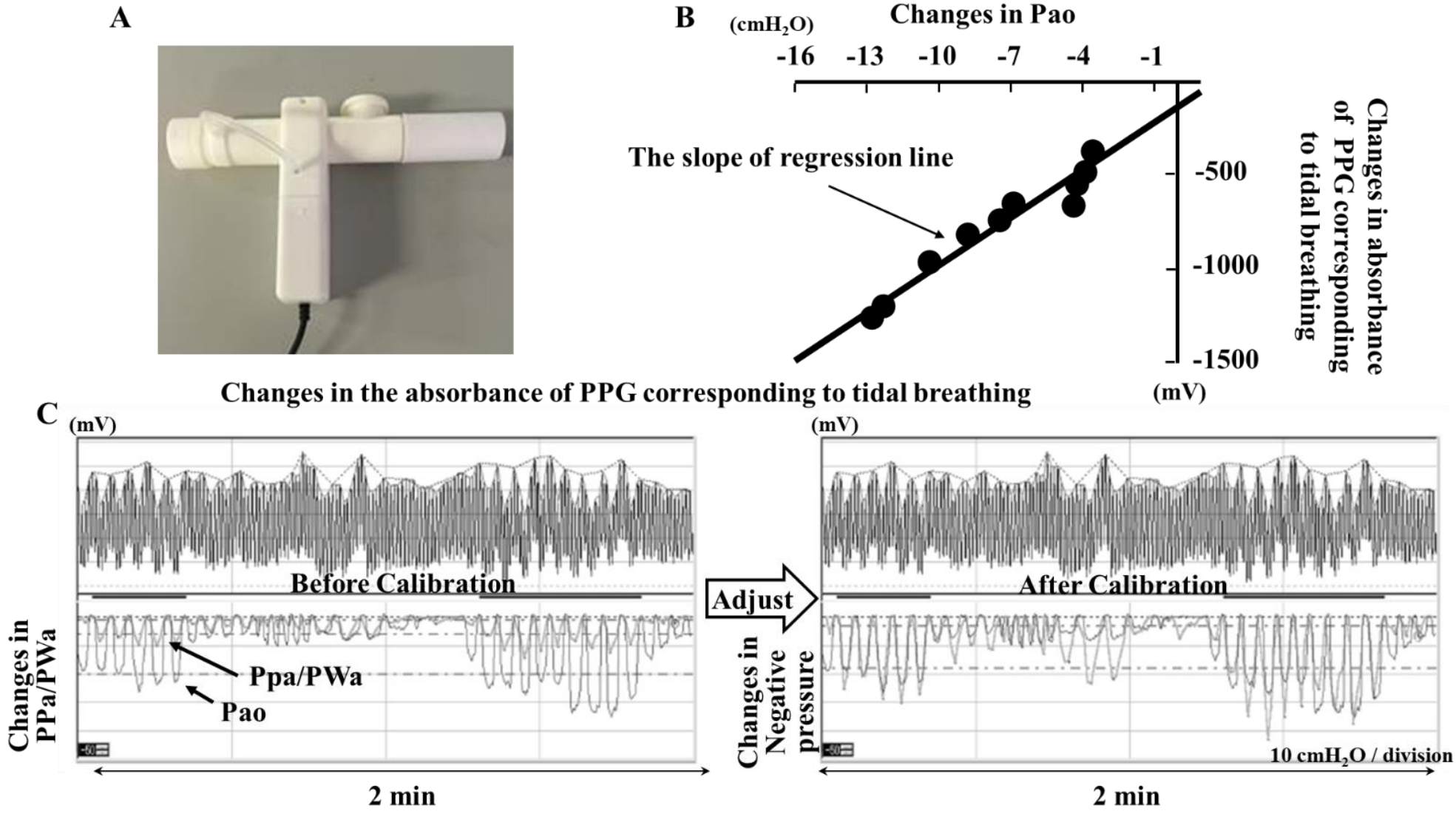
533

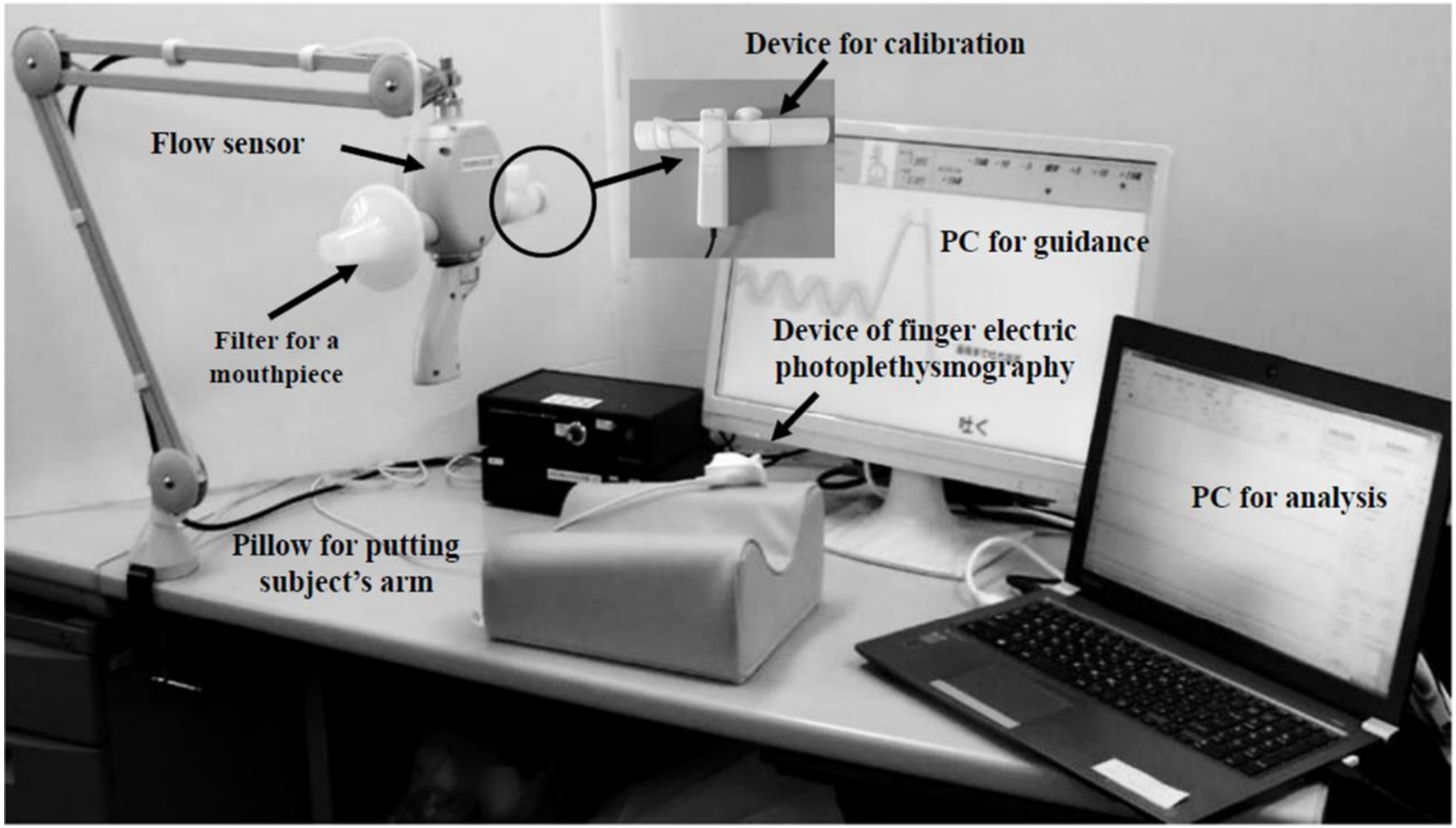
534 Figure 8. Relationship between the estimated lung dynamic compliance (Cdyn) from
535 photoplethysmography (PPG) and vital capacity (VC) (left panel) and lung diffusion capacity for
536 carbon monoxide (DLCO) (right panel). Cdyn, VC, and DLCO were represented as the % of
537 predicted Cdyn, VC, and DLCO (%Cdyn, %VC, %DLCO), respectively (12, 18, 24).
538 The estimated Cdyn was significantly and positively correlated with VC and DLCO.

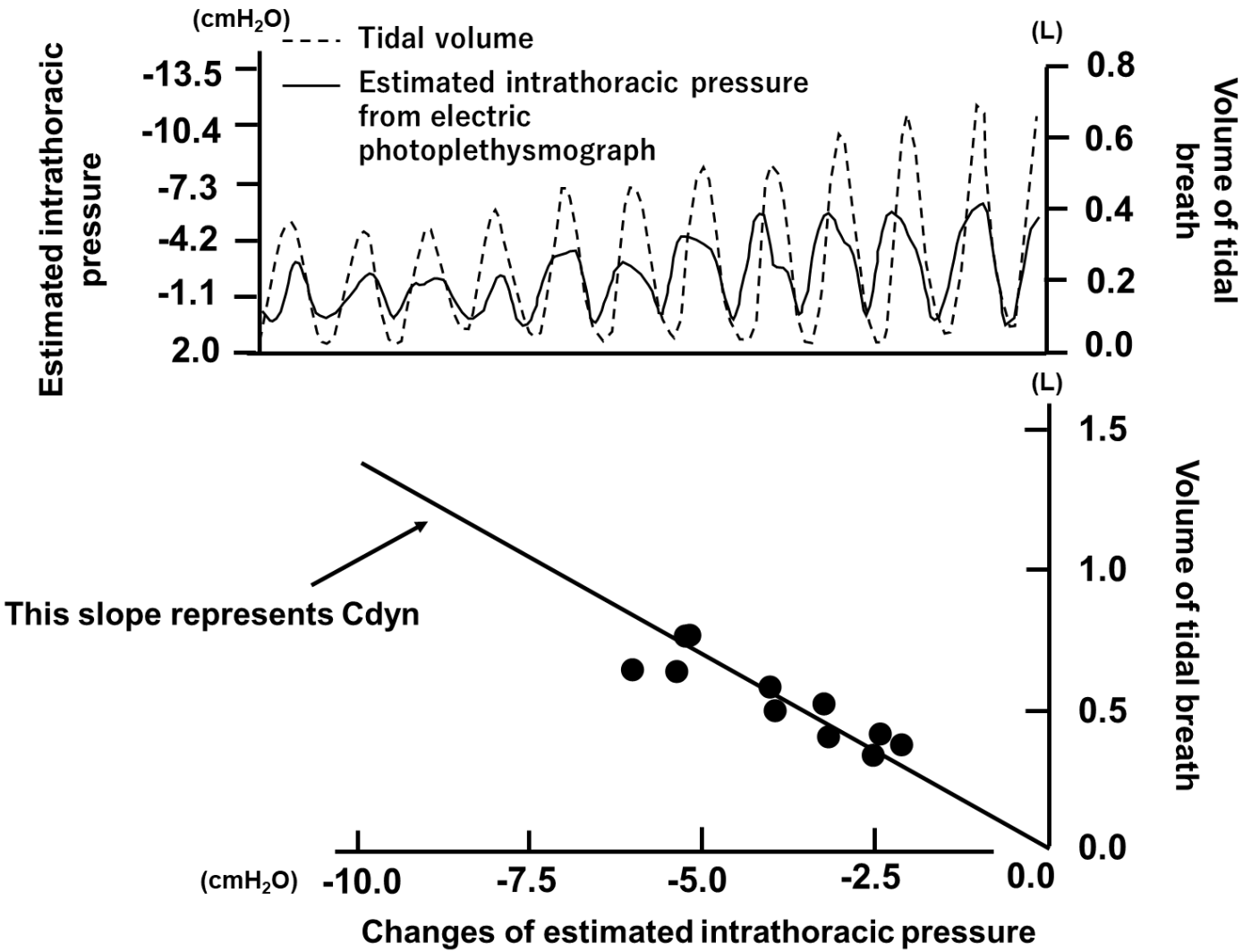
539

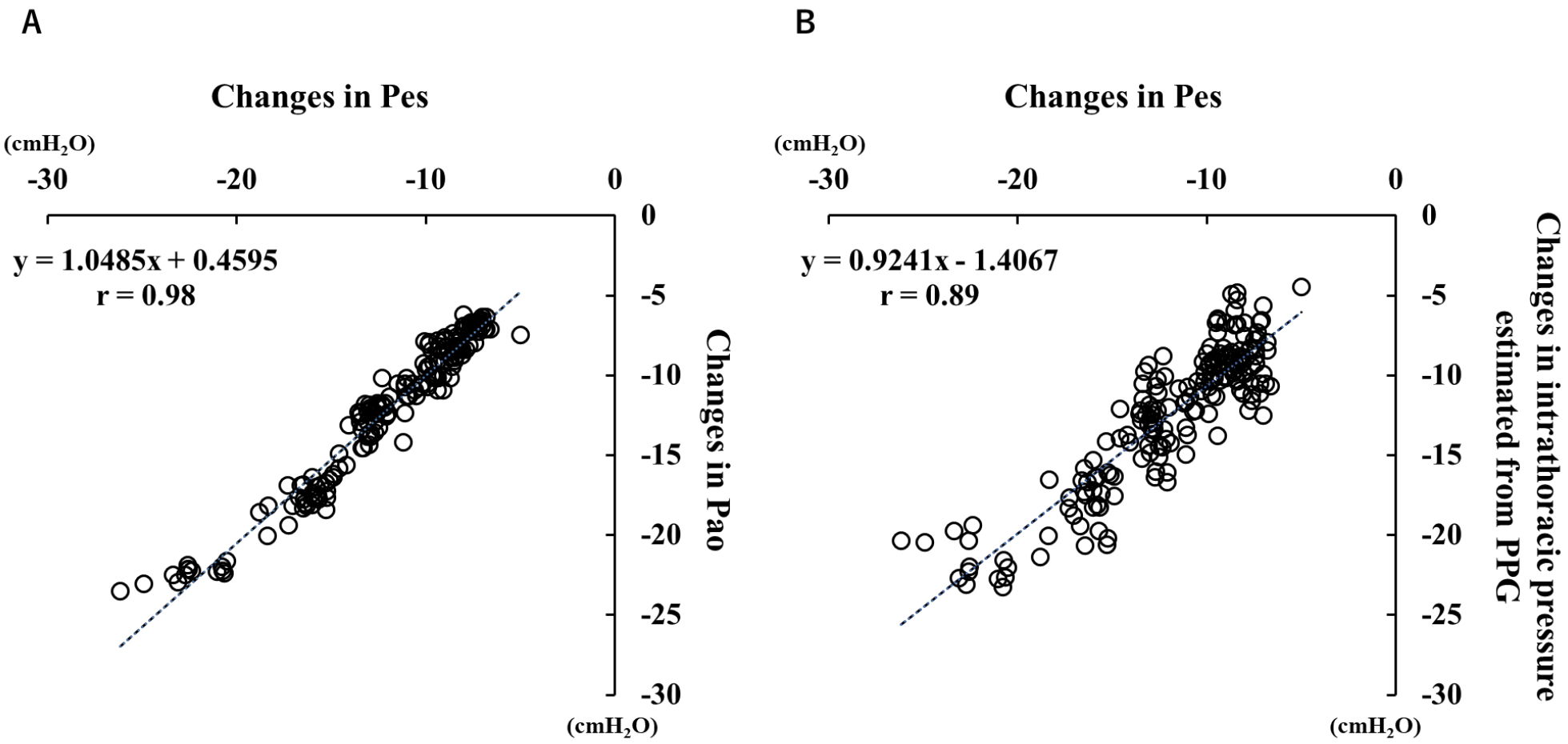
540 539 Figure 9: Receiver operator characteristic (ROC) curve analysis to differentiate
541 estimated % of predicted Cdyn (%Cdyn) in interstitial lung disease (ILD) from those in
542 healthy subjects (HS) (Fig.9A) and from chronic obstructive pulmonary disease (COPD)
543 (Fig. 9B). The bars were the upper and lower bounds. The area under the curve (AUC)
544 on ROC analysis to differentiate ILD from HS and COPD patients were 0.896 (95%
545 confidence interval (CI): 0.813-0.979) and 0.786 (95%CI: 0.670-0.902), respectively.

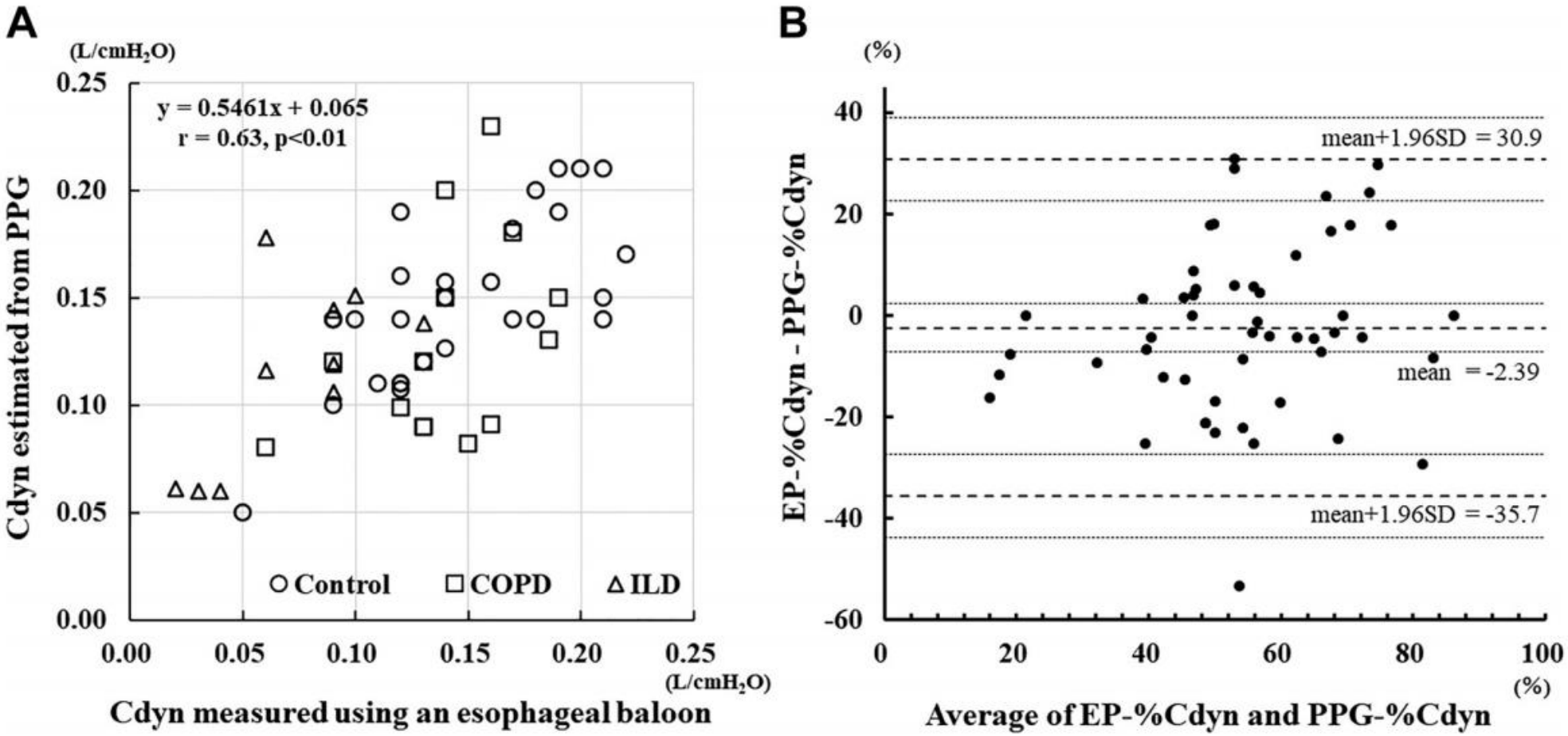

A.
(mV)
inspiration
(1)
(2)
PPa
expiration
Absorbance
PWa
PPa = difference (2) from (1)
PWa =amplitude of pulse wave
B.
0
PPa/PWa
Negative
absorbance
Time

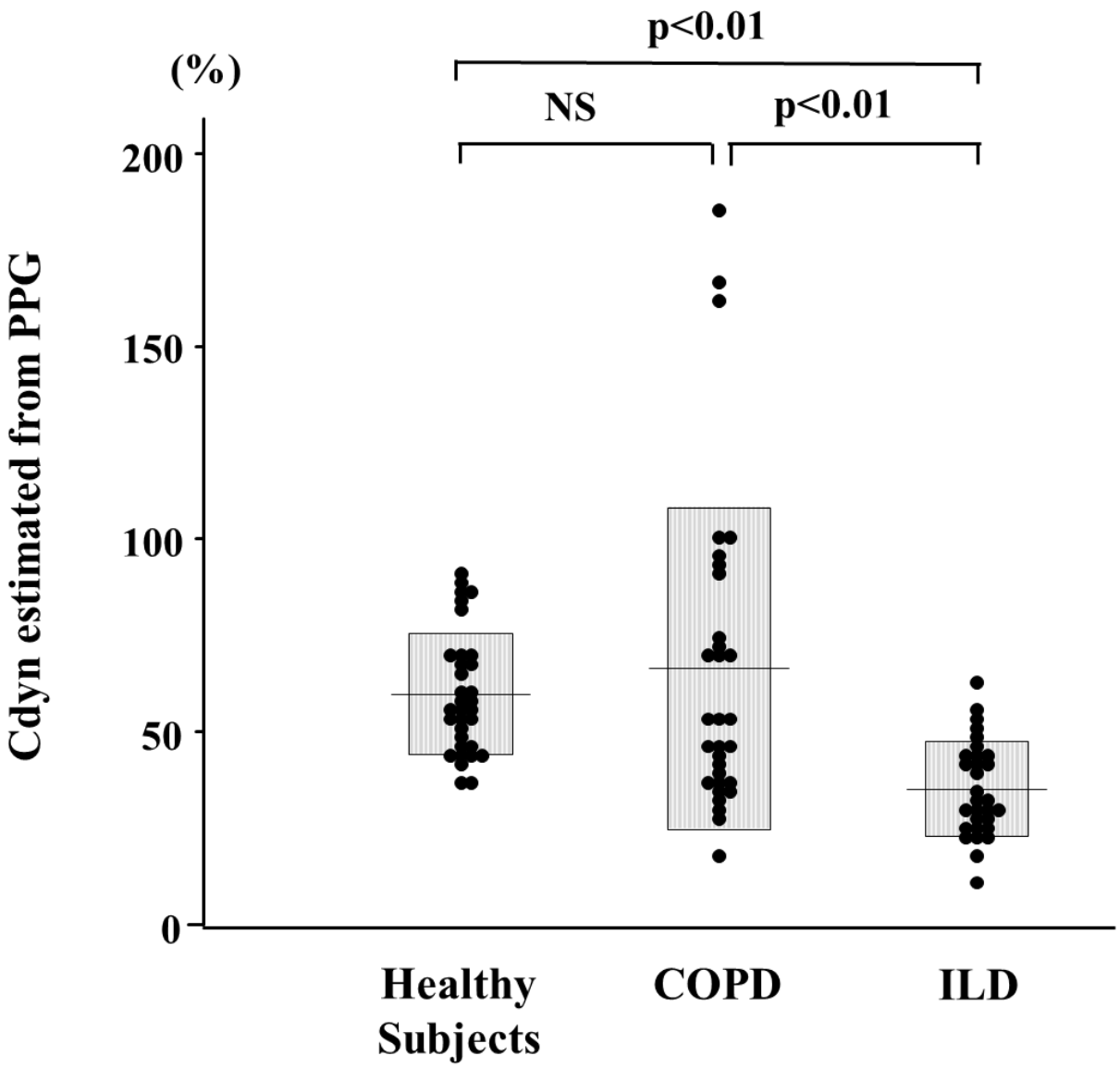

A
B
(cmH2O)
Changes in Pao
-16
-13
-10
-7
-4
-1
The slope of regression line
-500
-1000
-1500
(mV)
Changes in absorbance of PPG corresponding to tidal breathing
Changes in the absorbance of PPG corresponding to tidal breathing
C
(mV)
Before Calibration
Changes in PPa/PWa
Ppa/PWa
Pao
2 min
Adjust
(mV)
After Calibration
Changes in Negative pressure
10 cmH2O / division
2 min

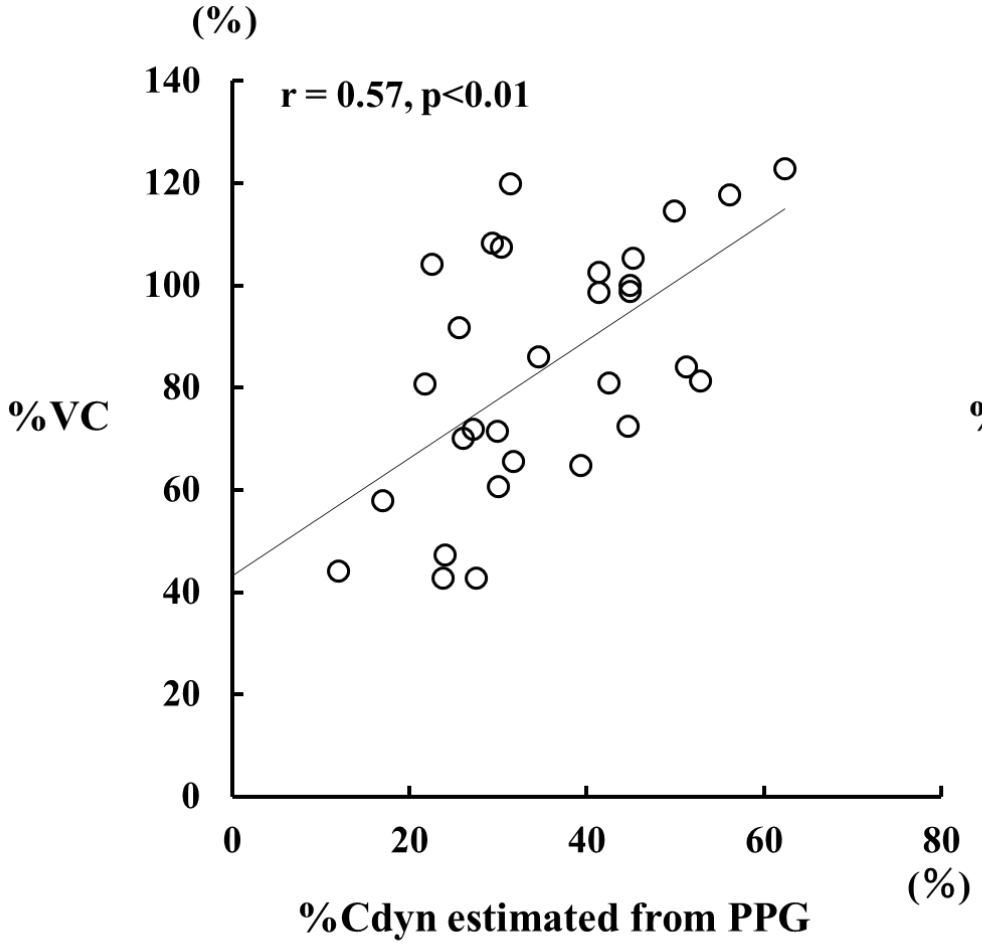

Device for calibration
Flow sensor
PC for guidance
Filter for a mouthpiece
Device of finger electric photoplethysmography
PC for analysis
Pillow for putting subject's arm

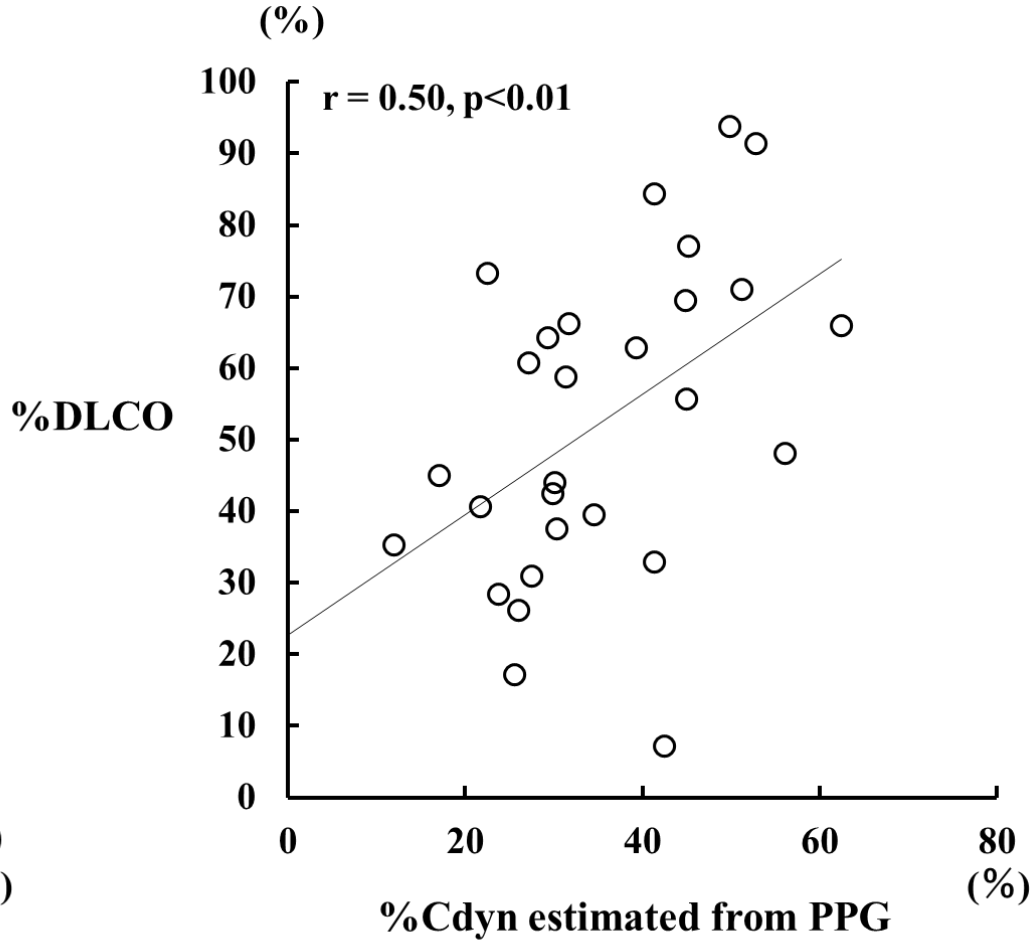

(cmH2O)
Tidal volume
Estimated intrathoracic pressure from electric photoplethysmograph
(L)
Estimated intrathoracic pressure
-13.5
-10.4
-7.3
-4.2
-1.1
2.0
0.8
0.6
0.4
0.2
0.0
Volume of tidal breath
(L)
1.5
1.0
0.5
0.0
Volume of tidal breath
This slope represents Cdyn
(cmH2O)
-10.0
-7.5
-5.0
-2.5
0.0
Changes of estimated intrathoracic pressure


A
Changes in Pes
(cmH2O)
-30
-20
-10
0
y = 1.0485x + 0.4595
r = 0.98
0
-5
-10
-15
-20
-25
-30
Changes in Pao
(cmH2O)
B
Changes in Pes
(cmH2O)
-30
-20
-10
0
y = 0.9241x - 1.4067
r = 0.89
0
-5
-10
-15
-20
-25
-30
Changes in intrathoracic pressure estimated from PPG
(cmH2O)


A
(L/cmH2O)
y = 0.5461x + 0.065
r = 0.63, p<0.01
Cdyn estimated from PPG
0.25
0.20
0.15
0.10
0.05
0.00
Control
COPD
ILD
0.00
0.05
0.10
0.15
0.20
0.25
(L/cmH2O)
Cdyn measured using an esophageal baloon
B
(%)
EP-%Cdyn - PPG-%Cdyn
40
20
0
-20
-40
-60
mean+1.96SD = 30.9
mean = -2.39
mean+1.96SD = -35.7
0
20
40
60
80
100
(%)
Average of EP-%Cdyn and PPG-%Cdyn


p<0.01
(%)
NS
p<0.01
200
150
100
50
0
Cdyn estimated from PPG
Healthy Subjects
COPD
ILD


(%)
r = 0.57, p<0.01
%VC
140
120
100
80
60
40
20
0
0
20
40
60
80
(%)
%Cdyn estimated from PPG


(%)
r = 0.50, p<0.01
%DLCO
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
(%)
%Cdyn estimated from PPG

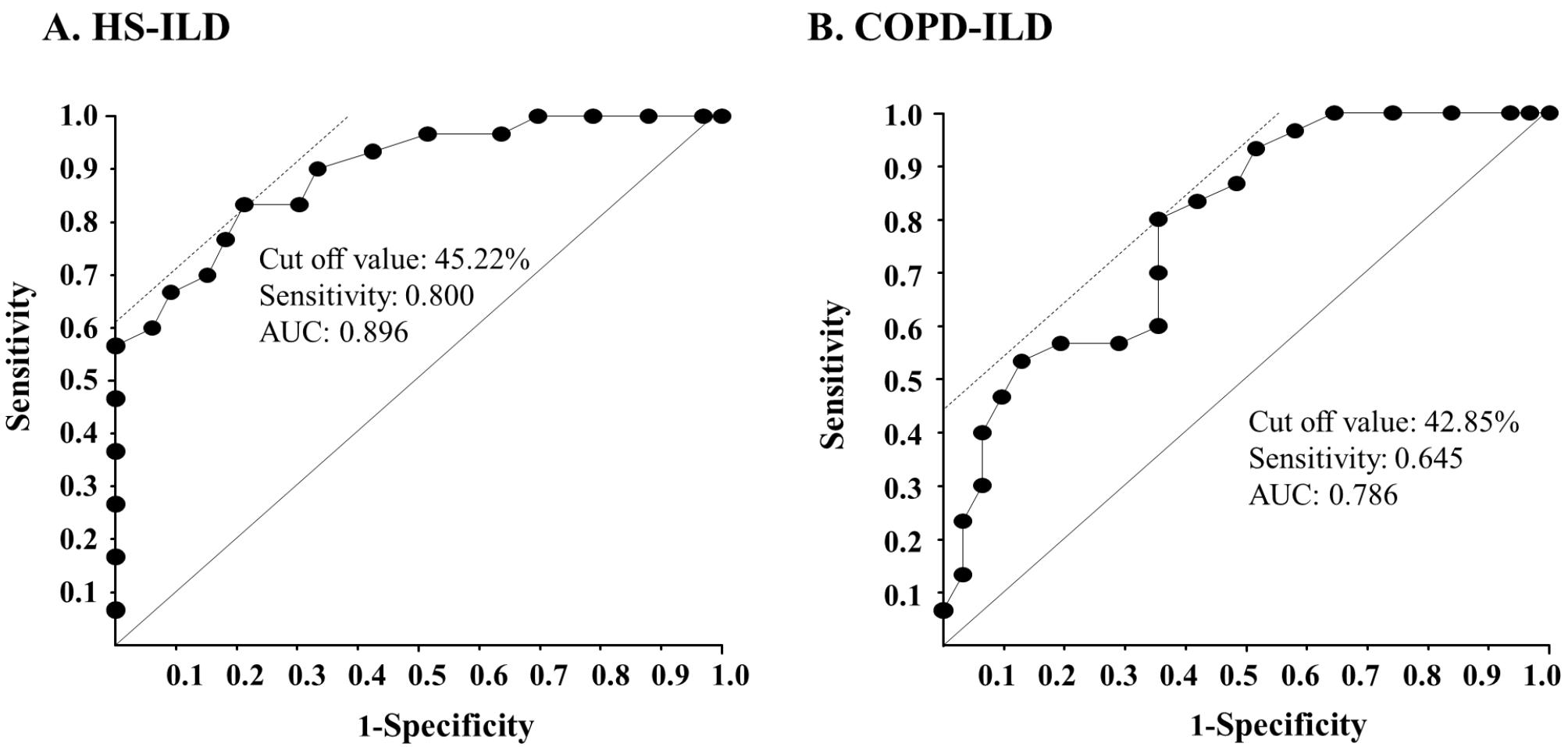

A. HS-ILD
Sensitivity
1-Specificity
Cut off value: 45.22%
Sensitivity: 0.800
AUC: 0.896
B. COPD-ILD
Sensitivity
1-Specificity
Cut off value: 42.85%
Sensitivity: 0.645
AUC: 0.786

Table 1. Characteristics and results of pulmonary function test of healthy subjects (HS) and patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) in experiment 2.

	HS	COPD	ILD
Number	28	14	10
Age, years old	57.5 ± 16.1	75.4 ± 8.2 **	68.1 ± 11.1
Sex, male/female	28/0	14/0	9/1
BMI, kg/m^2	23.4 ± 3.5	21.0 ± 1.8 **	22.3 ± 6.6 †
Smoking history, pack×year	5.4 ± 8.2	34.7 ± 18.2 **	27.4 ± 23.1 *
Number of having smoking history	10	14	8
VC, % of predicted value	105.6 ± 10.0	113.3 ± 14.3	76.4 ± 25.6 **††
FEV_1, % of predicted value	105.1 ± 9.8	74.9 ± 15.9 **	72.3 ± 23.9 **
FEV_1/FVC, %	81.8 ± 6.0	53.2 ± 12.3 **	77.7 ± 9.5 ††
FRC, % of predicted value	100.8 ± 14.9	109.9 ± 24.7	77.4 ± 17.3**††
RV, % of predicted value	119.6 ± 19.0	179.3 ± 61.2 **	103.7 ± 16.9 *††
TLC, % of predicted value	121.1 ± 20.8	131.1 ± 19.7	84.7 ± 17.8 **††
RV/TLC, %	33.8 ± 6.2	43.5 ± 9.0 **	41.3 ± 8.6 *
DLCO, % of predicted value	100.7 ± 15.5	65.5 ± 25.5 **	53.3 ± 16.6 **

DLCO/V_A, % of predicted value	121.7 ± 21.0	80.1 ± 36.5 **	93.4 ± 25.0 **
ΔN_2, %	1.09 ± 0.48	9.79 ± 23.95 **	7.81 ± 10.90 **
CV, L	0.65 ± 0.30	1.03 ± 0.54 *	0.51 ± 0.25
CV/VC, %	16.2 ± 6.9	29.9 ± 20.2 *	20.9 ± 11.9 ††
Cst, L/cmH_2O	0.22 ± 0.08	0.33 ± 0.11 **	0.17 ± 0.25 **††
Cst, % of predicted value	72.5 ± 25.5	116.3 ± 36.4 **	59.5 ± 86.5 **††
Pes max, cmH_2O	−24.4 ± 6.7	−13.8 ± 6.8 **	−29.3 ± 13.9 †
Cdyn, L/cmH_2O	0.15 ± 0.04	0.14 ± 0.04	0.07 ± 0.03 **††
Cdyn, % of predicted value	57.2 ± 17.1	60.4 ± 15.2	29.9 ± 14.9 **††
R_L, cmH_2O/L/s	1.94 ± 0.73	3.19 ± 1.77 **	5.40 ± 4.15**

Values are means ± SD. The lung volumes and DLCO were represented as the percentage of reference value, and Cst and Cdyn were also represented as the percentage of reference value. *$P < 0.05$ and **$P < 0.01$ vs. HS, †$P < 0.05$ and ††$P < 0.01$ vs. COPD.

Abbreviations: BMI, body mass index; Cst, static lung compliance; Pes max, maximum difference between esophageal and oral pressure at the level of total lung capacity; Cdyn, dynamic lung compliance; R_L, lung resistance.

Table 2. Characteristics and results of pulmonary function test of healthy subjects (HS) and patients with chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD)

	HS	COPD	ILD
Number	33	31	30
Age, years	57.6 ± 15.1	74.6 ± 8.6 **	70.0 ± 13.2 **
Sex, male/female	32/1	30/1	16/14 **††
BMI, kg/m^2	23.0 ± 2.4	22.4 ± 3.7	23.3 ± 3.5
Smoking history, pack×year	7.3 ± 12.2	38.3 ± 26.8 **	19.0 ± 29.0 *††
Number of having smoking history	13	31	12
VC, % of predicted value	105.1 ± 9.4	93.9 ± 24.8 *	83.9 ± 24.2 **
FEV_1, % of predicted value	103.5 ± 11.2	65.1 ± 27.9 **	97.5 ± 25.6 ††
FEV_1/FVC, %	81.5 ± 6.3	52.0 ± 15.6 **	82.3 ± 13.4 ††
FRC, % of predicted value	102.9 ± 14.4	120.5 ± 31.9 **	96.2 ± 33.9 †
RV, % of predicted value	133.3 ± 29.1	181.7 ± 55.9 **	98.9 ± 38.7 **††
TLC, % of predicted value	117.5 ± 13.0	127.5 ± 21.5 *	93.2 ± 24.8 **††
RV/TLC, %	34.6 ± 6.7	48.9 ± 10.2 **	39.0 ± 9.9 ††
DLCO, % of predicted value	101.9 ± 14.4	62.9 ± 25.8 **	52.5 ± 22.1 **
DLCO/V_A, % of predicted value	120.5 ± 20.2	79.3 ± 33.0 **	88.2 ± 36.8 **

ΔN_2, %	1.14 ± 0.61	4.48 ± 2.99 **	2.66 ± 1.74 **†
CV, L	0.64 ± 0.27	0.61 ± 0.42	0.45 ± 0.28 *
CV/VC, %	16.2 ± 6.5	19.0 ± 11.3	19.1 ± 13.6 **

Values are means ± SD. The lung volumes and DLCO were represented as the percentage of reference value. *$P < 0.05$ and **$P < 0.01$ vs. HS, †$P < 0.05$ and ††$P < 0.01$ vs. COPD.

Abbreviations: BMI, body mass index; CV, closing volume, CV/VC; CV/vital capacity (VC).