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博 士 論 文

Usefulness of the Six-minute Walk Test as a Screening Test for Pulmonary Arterial Enlargement in COPD

（COPD 患者の肺動脈拡張スクリーニングテストとしての 6 分間歩行試験の有用性）

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Usefulness of the Six-minute Walk Test as a Screening Test for Pulmonary Arterial Enlargement in COPD

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Six-min walk test, chronic obstructive pulmonary disease, exercise-induced oxygen desaturation, pulmonary artery

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Abstract:

Purpose: Pulmonary hypertension and exercise-induced oxygen desaturation (EID) influence acute exacerbation of chronic obstructive pulmonary disease (COPD). Computed tomography (CT)-detected pulmonary artery (PA) enlargement is independently associated with acute COPD exacerbations. Associations between PA to aorta (PA:A) ratio and EID in patients with COPD have not been reported. We hypothesised that the PA:A ratio correlated with EID and results of the 6-min walk test (6MWT) would be useful for predicting the risk associated with PA:A > 1.

Patients and methods: We retrospectively measured lung function, 6MWT, emphysema area, and PA enlargement on CT in 64 patients with COPD. The patients were classified into groups with PA:A ratio ≤ 1 and > 1. Receiver-operating characteristic (ROC) curves were used to determine the threshold values with the best cutoff points to predict patients with PA:A > 1.

Results: The PA:A > 1 group had lower forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1:FVC ratio, diffusion capacity of lung carbon monoxide (D_{LCO}), 6-min walk distance (6MWD) and baseline peripheral oxygen saturation (SpO_2), lowest SpO_2, highest modified Borg Scale results, percentage low-attenuation are (LAA%), and history of acute COPD exacerbations ≤ 1 year and worse BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise) index results ($p < 0.05$). Predicted PA:A >1 was determined for SpO_2 during 6MWT (best cutoff point: 89%, area under the curve [AUC] 0.94, 95% confidence interval 0.88–1). SpO_2 < 90% during 6MWT showed a sensitivity of 93.1, specificity of 94.3, positive predictive values of 93.1, negative predictive values of 94.3, positive likelihood ratios of 16.2, and negative likelihood ratios of 0.07.

Conclusion: Lowest SpO_2 during 6MWT may predict CT-measured PA:A ratios, and lowest SpO_2 <89% during 6MWT is excellent for detecting pulmonary hypertension in COPD.

Introduction

Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with accelerated loss of lung function, poor quality of life and mortality.[1,2] These events can be predicted by numerous clinical factors, including prior exacerbations, airflow obstruction, symptom burden, gastroesophageal reflux, and leukocytosis.[3] It is important to detect COPD exacerbations early and minimise their severity.

Patients with COPD frequently experience significant decreases in oxygen saturation during exercise attributed to the imbalance between oxygen delivery and exercise-induced demand.[4] Exercise-induced oxygen desaturation (EID) is reported to be associated with hospitalisation and mortality in patients with COPD.[5] The 6-min walking test (6MWT) has been suggested as the preferred measure to identify patients with COPD and EID.[6] EID occurs frequently during 6MWT in patients with COPD.[7] EID has been related to forced expiratory volume in 1 s (FEV_1), diffusion capacity of lung carbon monoxide (D_{LCO}), amount of emphysema and baseline oxygen saturation.[8–10]

Pulmonary hypertension (PH) is an important factor contributing to acute exacerbation of COPD.[11] PH appears when airflow limitation is severe, and is associated with chronic hypoxemia. Pulmonary vascular remodelling in COPD is the main cause of increased pulmonary artery (PA) pressure, and is thought to result from the combined effects of hypoxia, inflammation and capillary loss in severe emphysema.[12] The presence of PH has been shown to increase the hospitalisation rate and mortality of patients with COPD.[13,14] Computed tomography (CT)-detected PA enlargement is independently associated with acute exacerbations of COPD.[15] The PA-to-aorta (PA:A) ratio measured by CT scan outperforms echocardiography for diagnosing resting PH in patients with severe COPD.[16] A PA:A >1 indicates lower oxygen saturation at rest

than a PA:A <1.[15] However, there are no reports on the association between PA:A and EID in patients with COPD.

We hypothesised that the PA:A correlates with the presence of EID and that 6MWT results are useful for predicting the risk of having a PA:A >1. The present study aimed to examine the relationship between PA:A and EID and develop a simple screening tool by determining the appropriate cut-off score on 6MWT to predict a PA:A >1 in patients with COPD.

Patients and methods

Study design and patient selection

This study analysed regularly treated outpatients with COPD between 2014 and 2015 at the Kobe City Medical Center West Hospital. A total of 64 patients with COPD were included after applying the exclusion criteria in this study (Figure 1). The criteria for diagnosing COPD were a smoking history (≥20 pack-years) and post-bronchodilator FEV_1/forced vital capacity (FVC) < 70%. Furthermore, we used the following inclusion criteria to define COPD clinically, all of which had to be fulfilled: symptoms, including cough, sputum production, wheezing, dyspnea, a smoking history (≥20 pack-years), existence of emphysema on chest CT, and a physician diagnosis of COPD.[17–21] Study-exclusion criteria were as follows: history of lung surgical procedures, exacerbation-related hospitalization 3 months before 6MWT, and patients on long-term oxygen therapy. This study was approved by the ethics committee of Kobe University (N287). All the participants provided written or oral informed consent.

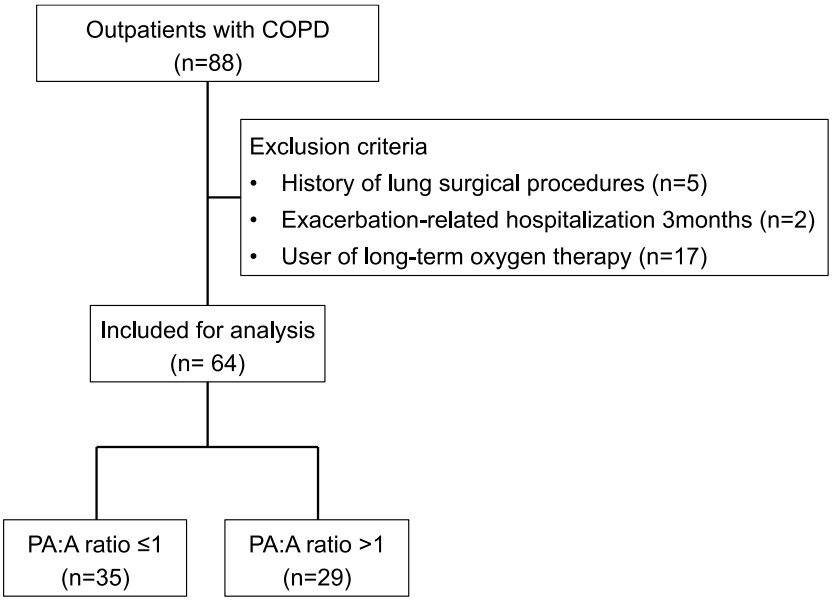

Figure 1 Patients flow diagram

Abbreviations: PA, pulmonary artery; A, aorta.

Clinical Characterisation

Assessments

A chest physician performed the physical examination for all outpatients. This examination included an assessment of body weight, height, and medical history (eg, pulmonary embolism and sleep apnea syndrome), GOLD (Global Initiative for Obstructive Lung Disease) grade 0–4, history of acute exacerbations of COPD within the previous year, COPD Assessment Test (CAT), level of dyspnea (using the modified Medical Research Council [mMRC] dyspnoea scale), post-bronchodilator spirometry, D_{LCO}, 6MWT (according to international recommendations), emphysema area, and PA enlargement on CT. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. GOLD 0 was defined as current and former smokers with a normal post-bronchodilator ratio of FEV_1: FVC exceeding 0.7 and an FEV_1 of at least 80%, symptoms, including cough, sputum production, wheezing and dyspnea, smoking

history (≥20 pack-years), existence of emphysema on chest CT, and a physician diagnosis of COPD.[17–21]

Six-minute walk test

The 6MWT was performed according to the 2002 American Thoracic Society guidelines.[22] Participants were asked to walk indoors on a flat, round, 25 m walking course supervised by a physician and physical therapist. A practice 6MWT was not undertaken. Subjects were encouraged using standard methodology every minute of the 6MWT. A pulse oximeter (WristOx 3150; Nonin Medical, Plymouth, MN, USA) with a finger probe measured peripheral oxygen saturation (SpO_2) during 6MWT, and 6MWT-analysis software (WristOx 2; Star Product, Tokyo, Japan) was used. In addition, a modified Borg scale was used to quantify the levels of dyspnea perceived by subjects at each minute during 6MWT. EID was defined as a nadir SpO_2 <90%, SpO_2 ≤88% and ΔSpO_2 ≥4%.[23–25]

Measuring the PA:A ratio

One reviewer, blinded to hemodynamic information, analysed CT scans (Optima CT 660 Discovery; GE Healthcare, Little Chalfont, UK). Measurements of the diameter of the main PA and the diameter of the aorta (A) at the level of the bifurcation were used to calculate the PA:A ratio, as previously reported.[14–16] In cases where the aorta was not uniform in diameter, two measurements were taken 90° apart and the larger diameter used. PA was measured on the line that joins the origin of the left PA and the centre of the adjacent ascending aorta on the axial section at the level of PA bifurcation.[26] CT-measured relative PA enlargement was defined as PA:A >1 (Figure 2).[14–16]

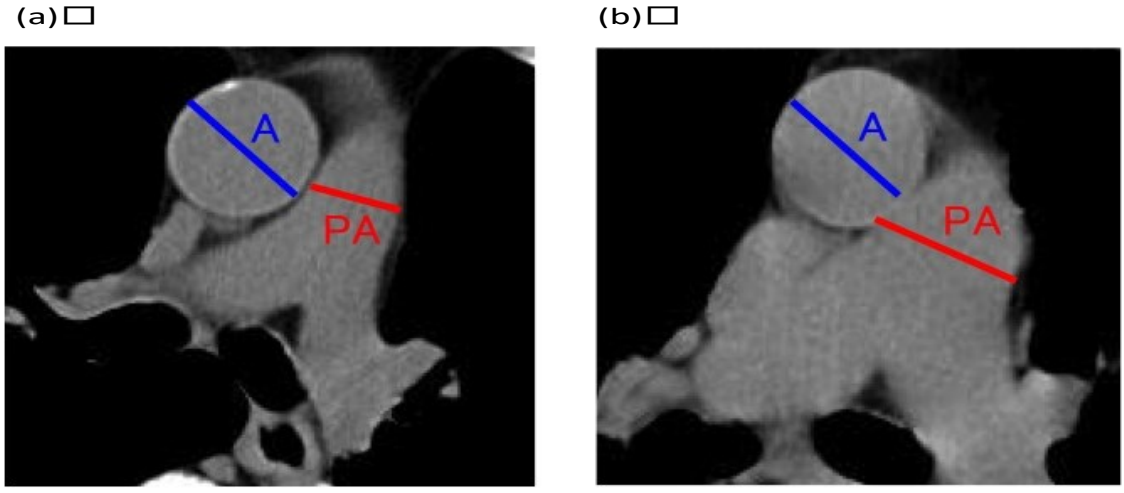

Figure 2. Measurement of the PA and A diameters at the PA bifurcation.

Notes: (A) PA:A ≤1, (B) PA:A >1. The κ-values for intraobserver and interobserver agreements for detecting PA:A >1 were 0.87 (95% confidence interval 0.74–0.99) and 0.75 (95% confidence interval 0.58–0.91), respectively.

Abbreviations: PA, pulmonary artery; A, aorta.

Statistical Analysis

Results are expressed as counts or median (interquartile range). Data are presented as means and standard deviations or as proportions, as appropriate. Cohen's κ-coefficient measured intraobserver and interobserver agreements for CT measurements of the PA:A ratio. Bivariate analyses were performed with the use of a Pearson's χ^2 test for categorical data and Mann–Whitney U-test for continuous data when appropriate. The Spearman's rank-correlation coefficient was determined for relationships between the PA:A ratio, lung function parameters, 6MWT parameters, and CT parameters. Receiver operating characteristic (ROC) curves were used to determine the threshold values with the best sensitivity and specificity to predict PA:A > 1, with the best being defined as the point on the ROC curve with the shortest distance from the upper-left corner. Sensitivity, specificity, positive/negative predictive value (PPV/NPV), and positive/negative likelihood were calculated for lung-function parameters and 6MWT parameters of exacerbation-risk factors on the basis of a previous study.[6,27,28]

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R project (R Foundation for Statistical Computing, Vienna, Austria).[29] More precisely, it is a modified version of R Commander designed to add statistical functions frequently used in biostatistics, and *P*-values <0.05 were considered statistically significant.

Results

The current analysis comprised 64 patients who were separated into groups on the basis of PA:A >1 (n = 29) and ≤1 (n = 35). Participants had a mean age of 73 (68–79) years. Fifty were male (78.1%) and 14 were female (21.9%). The κ-values for intraobserver and interobserver agreements for detecting PA:A >1 were 0.87 (95% confidence interval [CI] 0.74–0.99) and 0.75 (95% CI 0.58–0.91), respectively.

Differences in the PA:A ratio between both groups were driven by the diameter of PA (2.9 [2.7–3.3] cm in PA:A ≤ 1 vs. 3.7 [3.5–3.9] cm in PA:A >1, *P*= 0.002), because no differences were detected in the diameter of aortae (3.7 [3.4–3.9] cm vs. 3.5 [3.3–3.7] cm, *P*= 0.20). There were no significant differences between the two groups with regard to age, sex, BMI, pack-years, mMRC dyspnea scale, GOLD, COPD assessment test, baseline pulse rate, baseline modified Borg Scale (*P*> 0.05). On the other hand, there were significant differences between the two groups with regard to FEV_1 (71.6% [60.5%–80.8%] vs. 52.6% [39.6%–72.1%], *P*= 0.013), FVC (82.3% [50.3%–93.6%] vs. 75.8% [42.7%–86.0%], *P*= 0.04), FEV_1:FVC ratio (68% [61%–73.3%] vs. 53.8% [48.8%–69.4%], *P*= 0.023), $\%D_{LCO}$ (72.5% [55.5%–82.9%] vs. 44.6% [37.7%–49.6%], *P*= 0.005), BODE (BMI, obstruction [airflow], dyspnea, and exercise performance) index (2 [1–3] vs. 4 [2–5], *P*< 0.001), 6-min walking distance (6MWD; 450 m

[400–510.5] vs. 325 m [238–466], $P< 0.001$), baseline SpO_2 (97% [95%–97.5%] vs. 95% [93%–96%], $P= 0.001$), lowest SpO_2 (92% [91%–94%] vs. 86% [84%–88%], $P< 0.001$), highest modified Borg Scale result (2 [0–5] vs. 5 [2–5], $P= 0.04$), low-attenuation area (LAA; 6.8% [2.8%–14.7%] vs. 25.4% [11.3%–33.4%], $P< 0.001$), and history of acute exacerbations of COPD within the previous year (1 [2.9%] vs. 7 [24.1%], $P= 0.019$) (Table 1).

The PA:A ratio demonstrated a significant linear correlation with lowest SpO_2 ($r= -0.68$, $r^2= 0.46$; $P< 0.001$), $\%D_{LCO}$ ($r= -0.61$, $r^2= 0.37$; $P< 0.001$), 6MWD ($r= -0.43$, $r^2= 0.18$; $P< 0.001$), BODE index ($r= 0.41$, $r^2= 0.17$; $P< 0.001$), baseline SpO_2 ($r= -0.36$, $r^2= 0.13$; $P= 0.003$), LAA% ($r= 0.36$, $r^2= 0.13$; $P= 0.004$), FVC ($r= -0.34$, $r^2= 0.12$; $P= 0.006$), FEV_1 ($r= -0.29$, $r^2= 0.08$; $P= 0.019$) and highest pulse rate ($r= 0.26$, $r^2= 0.07$; $P= 0.035$) (Table 2).

Using ROC curves, the threshold values with the best cutoff point, sensitivity, and specificity to predict PA:A >1 were determined for SpO_2 during 6MWT (best cutoff points 89%, area under curve [AUC] 0.94, 95%CI 0.88–1), D_{LCO} (best cutoff points 51%, AUC 0.87, 95%CI 0.78–0.96), 6MWD (best cutoff points 388m, AUC 0.75, 95%CI 0.62–0.87), BODE index (best cutoff points 4, AUC 0.74, 95%CI 0.61–0.87) (Table 3, Figure 3). The performance data on the 6MWT and lung function for predicting PA enlargement are depicted in Table 4. $SpO_2 < 90\%$, $SpO_2 \leq 88\%$, and $\Delta SpO_2 \geq 4\%$ during 6MWT were 94.3 (80.8–99.3), 97.1 (85.1–99.9), and 45.7 (28.8–63.4), respectively, for specificity, 93.1 (77.2–99.2), 95.8 (78.9–99.9) and 59.6 (44.3–73.6), respectively, for positive predictive value, and 16.2 (4.2–62.8), 27.7 (4–193.3), and 1.8 (1.3–2.4), respectively, for positive likelihood ratios.

Table 1 General characteristics of the patients with PA:A ≤1 and PA:A >1

Variable	PA:A ≤1 (n=35)	PA:A >1 (n=29)	*P-value*
Age (years)	71 (66.5–76.5)	78 (70–79)	0.06[b]
Male sex (%)	28 (80)	22 (75.9)	0.76[a]
Body mass index (kg/m^2)	21.1 (19.5–23.4)	22.4 (20.4–24.7)	0.33[b]
Smoking history (pack-years)	40 (26.8–60)	40 (35–50)	0.49[b]
PE	0	1 (3.4%)	0.45[a]
SAS	1 (2.8%)	0	1[a]
GOLD (0/1/2/3/4)	14/3/13/4/1	7/2/8/11/1	0.14[a]
mMRC (0/1/2/3/4)	1/7/22/5/0	0/2/21/5/1	0.36[a]
COPD Assessment Test (points)	15 (8–22)	14 (11.5–22)	0.62[b]
BODEindex (points)	2 (1–3)	4 (2–5)	<0.001[b]
FEV_1 (% of predicted value)	71.6 (60.5–80.8)	52.6 (39.6–72.1)	0.013[b]
FVC (% of predicted value)	82.3 (50.3–93.6)	75.8 (42.7–86)	0.04[b]
FEV_1:FVC ratio	68 (61–73.3)	53.8 (48.8–69.4)	0.023[b]
D_{LCO} (% of predicted value)	72.5 (55.5–82.9)	44.6 (37.7–49.6)	0.005[b]
RV/TLC (%)	43.7 (37.4–48.6)	48.8 (39.8–53.8)	0.12[b]
LAA (%)	6.8 (2.8–14.7)	25.4 (11.3–33.4)	<0.001[b]
Admission for exacerbation	1 (2.9)	7 (24.1)	0.019[a]
6MWD (m)	450 (400–510.5)	325 (238–446)	<0.001[b]
Baseline SpO_2 (%)	97 (95–97.5)	95 (93–96)	0.001[b]
Lowest SpO_2 (%)	92 (91–94)	86 (84–88)	<0.001[b]
Baseline PR (bpm)	74 (69.5–81.5)	77 (70–88)	0.28[b]
Highest PR (bpm)	108 (98–115.5)	112 (108–120)	0.014[b]
Baseline modified Borg Scale	0 (0–0)	0 (0–0.5)	0.1[b]
Highest modified Borg Scale	2 (0–5)	5 (2–5)	0.04[b]
Diameter of aorta (cm)	3.7 (3.4–3.9)	3.5 (3.3–3.7)	0.2[b]
Diameter of pulmonary artery (cm)	2.9 (2.7–3.3)	3.7 (3.5–3.9)	0.002[b]

Notes: Data presented as counts (%) or median (interquartile range). *P*-values calculated by [a]Pearson's χ^2 test (categorical) and [b]Mann–Whitney *U*-test (continuous).

Abbreviations: PA, pulmonary artery; A, aorta; PE, pulmonary embolism; SAS, sleep apnoea syndrome; GOLD, Global Initiative for Obstructive Lung Disease; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; BODE, body mass index, airflow obstruction, dyspnoea and exercise; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; DLCO, diffusion capacity of lung carbon monoxide; RV/TLC, residual volume/total lung capacity; LAA%, the percentage of the lung field occupied by low attenuation areas; 6MWD, 6-minute walking distance; Baseline SpO2, resting SpO2 before 6MWT; Lowest SpO2, nadir SpO2 during the 6MWT; Baseline PR, resting pulse rate before 6MWT; highest PR, Highest value of pulse rate during 6MWT; Baseline modified Borg Scale, resting modified Borg Scale before 6MWT; Highest modified Borg Scale, highest value of modified Borg Scale during 6MWT

Table 2 Linear relationships between PA:A ratio, lung function, and index of 6MWT

Variable	*r*	r^2	*P-value*[a]
Lowest SpO_2 (%)	-0.68	0.46	<0.001
D_{LCO} (% of predicted value)	-0.61	0.37	<0.001
6MWD (m)	-0.43	0.18	<0.001
BODE index	0.41	0.17	<0.001
Baseline SpO_2 (%)	-0.36	0.13	0.003
LAA (%)	0.36	0.13	0.004
FVC (% of predicted value)	-0.34	0.12	0.006
FEV_1 (% of predicted value)	-0.29	0.08	0.019
Highest PR (bpm)	0.26	0.07	0.035

Notes: [a]*P*-value calculated by Spearman's rank-correlation coefficient.

Abbreviations: PA, pulmonary artery; A, aorta; 6MWT, 6-minute walking test; Lowest SpO_2, nadir SpO_2 during the 6MWT; DLCO, diffusion capacity of the lung carbon monoxide; 6MWD, 6-min walking distance; BODE index, body mass index, obstruction (airflow), dyspnoea and exercise; Baseline SpO_2, resting SpO_2 before 6MWT; LAA, low-attenuation areas; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; Highest PR, highest value of pulse rate during 6MWT

Table 3 Cut off points and ROC-curve parameters for the prediction of PA:A ratio > 1

Variable	Best cutoff	AUC (95% CI)	Sensitivity	Specificity
Lowest SpO_2 (%)	89	0.94 (0.88–1)	86.2	93.1
D_{LCO} (%)	51	0.87 (0.78–0.96)	79.3	85.7
6MWD (m)	388	0.75 (0.62–0.87)	69	80
BODE index (points)	4	0.74 (0.61–0.87)	58.6	85.7

Abbreviations: ROC, receiver-operating characteristic; PA, pulmonary artery; A, aorta; AUC, area under the curve; Lowest SpO_2, nadir SpO_2 during the 6MWT; DLCO, diffusion capacity of lung carbon monoxide; 6MWD, 6-minute walking distance; BODE index, body mass index, obstruction (airflow), dyspnoea and exercise; CI, confidence interval.

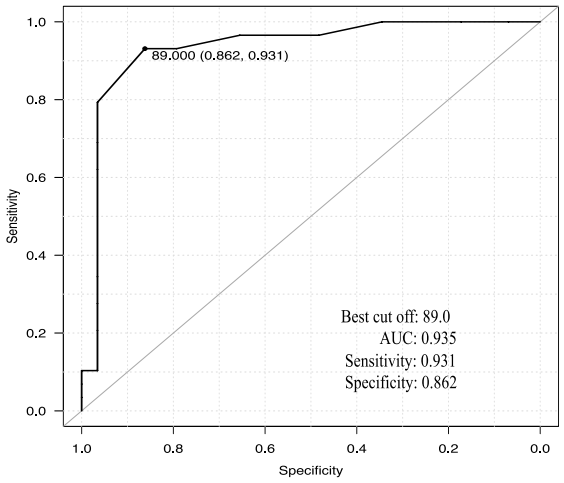

Figure 3 Receiver operator characteristic curve with lowest SpO_2 during 6MWT identifying PA:A ratio > 1

Abbreviations: lowest SpO_2, nadir SpO_2 during the 6MWT; 6MWT, 6-min walking test; PA, pulmonary artery; A, aorta; AUC, area under the curve.

Table 4 The performance data of 6MWT and lung function for PA:A ratio > 1

Variable	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	+LR (95% CI)	-LR (95% CI)
SpO_2 <90%	93.1 (77.2–99.2)	94.3 (80.8-99.3)	93.1 (77.2-99.2)	94.3 (80.8-99.3)	16.2 (4.2-62.8)	0.07 (0.02-0.28)
SpO_2 ≤88%	79.3 (60.3-92)	97.1 (85.1-99.9)	95.8 (78.9–99.9)	85 (70.2–94.3)	27.7(4–193.3)	0.21(0.1–0.44)
ΔSpO_2 ≥4%	96.6 (82.0–99.9)	45.7 (28.8–63.4)	59.6 (44.3–73.6)	94.1 (71.3–99.9)	1.8 (1.3–2.4)	0.08 (0.01–0.54)
Baseline SpO_2 ≤95%	58.6 (38.9–76.5)	71.4 (53.7–85.4)	63.0 (42.4–80.6)	67.6 (50.2–82.0)	2.1 (1.1–3.8)	0.58 (0.36–0.94)
6MWD <350 m	58.6 (38.9–76.5)	82.9 (66.4–93.4)	73.9 (51.6–89.8)	70.7 (54.5–83.9)	3.4 (1.6–7.5)	0.50 (0.32–0.80)
SpO_2 <90% and 6MWD <350m	51.7 (32.5–70.6)	97.1 (85.1–99.9)	93.8 (69.8–99.8)	70.8 (55.9–83.0)	18.1 (2.5–128.9)	0.50 (0.34–0.73)
SpO2 ≤88% and 6MWD <350m	51.7 (32.5–70.6)	100 (85.5–100)	100 (69.8–100)	71.4 (56.7–83.4)	-	0.48 (0.33–0.70)
ΔSpO_2 ≥4% and 6MWD <350m	55.2 (35.7–73.6)	91.4 (76.9–98.2)	84.2 (60.4–96.6)	71.1 (55.7–83.6)	6.4 (2.1–19.9)	0.49 (0.32–0.74)
FEV_1 <80%	79.3 (60.3–92.0)	31.4 (16.9–49.3)	48.9 (34.1–63.9)	64.7 (38.3–85.8)	1.2 (0.9–1.5)	0.65 (0.28–1.56)
FEV_1 <50%	44.8 (26.4–64.3)	85.7 (69.7–95.2)	72.2 (46.5–90.3)	65.2 (49.8–78.6)	3.1 (1.3–7.8)	0.64 (0.45–0.92)
D_{LCO} <50%	75.9 (56.5–89.7)	85.7 (69.7–95.2)	81.5 (61.9–93.7)	81.1 (64.8–92.0)	5.3 (2.3–12.3)	0.28 (0.15–0.54)

Abbreviations: PPV, positive predictive values; NPV, negative predictive values; +LR, positive likelihood; −LR, negative likelihood; 6MWT, 6-min walking test; Baseline SpO_2, resting SpO_2 before 6MWT; 6MWD, 6-min walking distance; FEV_1, forced expiratory volume in 1 s; DLCO, diffusion capacity of the lung carbon monoxide

Discussion

We were able to reveal three main findings in the present study. First, we found a strong association between PA:A ratio and lowest SpO_2 during 6MWT. For this reason, a consistent finding in patients with COPD is the close relationship between severity of hypoxemia and PA pressure or pulmonary vascular resistance, supporting a major role for alveolar hypoxia.[30] Alveolar hypoxia causes constriction of the resistance PAs, and sustained alveolar hypoxia induces pulmonary vascular remodelling.[28] Pathological studies of lung specimens from patients with COPD have shown extensive pulmonary vascular remodelling with prominent intimal thickening and medial hypertrophy. For this reason, chronic alveolar hypoxia plays an important role in pulmonary vascular remodelling.[28] In a previous study, patients with PA:A >1 showed lower resting SpO_2, higher usage rates of supplemental oxygen, and an indirect association with EID.[15] In the present study, the lowest SpO_2 during 6MWT to predict PA:A > 1 was considered to be a beneficial result based on the ROC curves. Lowest SpO_2 < 89% during the 6MWT is excellent in the detection of PH. These results suggest that the lowest SpO_2 during 6MWT is a

very helpful measure and screening test for PA:A ratio. For example, it might be possible to easily screen for pulmonary artery expansion by means of the 6MWT in home-care situation, where it would be difficult to perform CT imaging.

Second, with regard to the relationship between PA:A ratio and lung function, correlations were observed among FEV_1, D_{LCO}, and LAA. One of the factors that may play a role in causing PH to advance in patients with COPD is the destruction of lung parenchyma, leading to loss of part of the pulmonary vascular bed,[30,31] and the burden of airway remodelling influencing PA-pressure increase.[28] A previous study included patients with airflow-obstruction severity greater than moderate, and our study included mild airflow obstruction and smokers with normal spirometry.[15] Therefore, regardless of the severity of airflow-obstruction, PA enlargement may be progressing. Undiagnosed COPD is a problem worldwide.[18] GOLD 0 has been reported to be an exacerbation risk; therefore,[18] early detection and not just spirometry evaluation is important from multiple perspectives.[18,32] From the viewpoint of early detection of PA enlargement, a definition of EID as SpO_2 <90% may be a good start.

Third, there are many causes for acute COPD exacerbations. However, these findings may imply that PA:A >1 is one of the multiple risk factors for acute COPD exacerbations. One reason for this is that PA:A is associated with PH[16] and PH is also a risk factor for acute COPD exacerbations.[33] Furthermore, a previous study reported an association between the PA:A ratio and acute COPD exacerbation.[15] These results suggest that screening for the PA:A ratio without CT using the 6MWT may indicate the risk for acute COPD exacerbations at an early stage.

Limitation

This study had some limitations, including small size, single-center experience, and retrospective design. In addition, this study also included COPD subjects who did not fit the GOLD criteria. Furthermore, because healthy controls do not have respiratory symptoms and there are no control data for the measurement items pertaining to such individuals, healthy controls were not included in the present study. However, it has been reported that the presence of clinical symptoms and low D_{LCO} in smokers, even with normal spirometry, increases the risk of progression to airflow obstruction in COPD.[17–20] Therefore, the present study's results during the 6MWT could be useful to screen for PH at an early COPD stage, even in GOLD 0 patients. Finally, according to a previous study, left ventricular dysfunction causes PA enlargement. However, echocardiography was not performed in all subjects, and this information could not be included because it was unavailable from the medical history, although we observed clinically relevant associations between CT-measured PA:A ratios and 6MWT results.

Conclusion

The current study's findings suggest that there is a strong association between PA:A ratio and lowest SpO_2 during 6MWT. 6MWT is a simple, noninvasive, and reproducible measurement tool. Lowest SpO_2 during 6MWT is a very helpful measurement to predict PA:A ratio on CT, and lowest SpO_2 <89% during the 6MWT is excellent to screen for PH in COPD.

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Author contributions

YO was involved in the conception, hypothesis, outline and design of the study, data acquisition, analysis, and interpretation, drafting the article, and its revision prior to submission. MK, YF, and HY were involved in the conception, hypothesis, outline, and design of the study, data acquisition, and revision of the article prior to submission. AI was involved in the conception, hypothesis, outline, and design of the study, data acquisition and analysis, drafting the article, and its revision prior to submission. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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