DOI: 10.1002/pul2.12423

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRi | WILEY

Novel evaluation of pulmonary hypertension associated with chronic lung disease using perfusion SPECT/CT: A pilot study

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Abstract

In pulmonary hypertension (PH) associated with chronic lung disease (CLD), identifying patients who would benefit from pulmonary vasodilators is a significant clinical challenge because the presence of PH is associated with poorer survival. This study evaluated the severity of pulmonary circulation impairment in patients with CLD-PH using pulmonary perfusion single-photon emission computed tomography/computed tomography (SPECT/CT). This single-center, observational study enrolled patients with CLD-PH who had a mean pulmonary arterial pressure (PAP) ≥ 25 mmHg, as confirmed by right heart catheterization. The primary outcome was to measure the percentage of pulmonary perfusion defect (%PPD), calculated by dividing the perfusion defect volume from perfusion SPECT images by the lung volume from CT scan images. The secondary outcome was to assess the correlation between %PPD and baseline characteristics. The median %PPD was 52.4% (interquartile range, 42.5%–72.3%) in 22 patients. In multivariate linear regression analysis, both forced vital capacity ($\beta = 0.58$, $p = 0.008$) and mean PAP ($\beta = 0.68$, $p = 0.001$) were significantly correlated with %PPD. In conclusion, significant correlation between mean PAP and %PPD in patients with CLD-PH was observed. This noninvasive assessment of %PPD may be useful for evaluating the severity of pulmonary circulation impairment in CLD-PH.

Abbreviations: %PPD, percentage of pulmonary perfusion defect; CI, cardiac index; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; CPFE, combined pulmonary fibrosis and emphysema; CTEPH, chronic thromboembolic pulmonary hypertension; DLco, diffusing capacity for carbon monoxide; DLco/VA, DLco divided by alveolar volume; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, Pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; RHC, right heart catheterization; SPECT, single-photon emission computed tomography; SPECT/CT, SPECT combined with CT; SUV, standardized uptake volume; V/Q, ventilation/perfusion; WHO-FC, World Health Organization functional classification.

Funding information
None

KEYWORDS
perfusion imaging, phosphodiesterase 5 inhibitors, pulmonary hypertension, single-photon emission computed tomography/computed tomography, vasodilator agents

Pulmonary hypertension (PH) is characterized by an increase in blood pressure in the pulmonary arteries and deterioration of right ventricular function. PH is classified into five subgroups based on similarities in pathophysiology and clinical management. Group 3 represents PH associated with chronic lung disease (CLD).[1,2] The presence of PH in patients with CLD has been linked to poorer survival.[3] Pulmonary vasodilator therapy using pulmonary arterial hypertension (PAH)-targeted drugs is not generally recommended for CLD-PH because of a lack of evidence regarding their efficacy and potential exacerbation of ventilation–perfusion mismatch and hypoxia.[4] However, CLD-PH could potentially include patients with Group 1 (PAH) phenotype. Previous studies have investigated the presence of responders to pulmonary vasodilator therapy, particularly phosphodiesterase-5 inhibitor, in patients with CLD-PH.[5–9] Recently, inhaled treprostinil, which is a synthetic analog of prostacyclin, had been approved by the US Food and Drug Administration for the treatment of PH due to interstitial lung disease (ILD) based on improvements in 6-min walk distance.[10] Vascular remodeling associated with microangiopathy is a fundamental pathological feature of PH. The degree of microangiopathy in pulmonary circulation is correlated with the severity of the disease, vasodilator response, and prognosis of patients with PH. Consequently, accurately identifying patients with CLD-PH who would benefit from pulmonary vasodilator therapy based on their responsiveness is a significant clinical challenge.

Ventilation/perfusion (V/Q) scintigraphy is one of the standard imaging procedures for diagnosing chronic thromboembolic pulmonary hypertension (CTEPH), a subset of Group 4. In patients with PAH, perfusion is typically normal or heterogeneous, with small peripheral, unmatched, and/or nonsegmental defects.[11,12] However, the functional significance of conventional scintigraphy in CLD-PH remains uncertain due to the complex impact of CLD on the underlying microangiopathy. The introduction of V/Q single-photon emission computed tomography (SPECT) has addressed many of the limitations of planar V/Q scintigraphy. In particular, V/Q SPECT combined with computed tomography (SPECT/CT) offers high diagnostic accuracy in distinguishing pulmonary embolism from other lung diseases.[13] Generally, pulmonary perfusion SPECT is performed using conventional free-breathing acquisitions; lung motion during image acquisition can degrade image quality and obscure small perfusion defects. The conformity between pulmonary perfusion SPECT and CT at the bottom of the lung is low because the acquisition timing of CT is deep-inspiratory breath-hold. Recent studies have described a technique that involves performing SPECT during intermittent deep-inspiratory breath-hold of the respiratory cycle.[14] This technique may improve the detection of small defects and the accuracy of SPECT/CT fusion images by minimizing misregistration resulting from lung motion. However, this imaging modality is yet to be established for the functional evaluation of pulmonary circulation impairment. Figure 1 shows the difference between free-breathing and deep-inspiratory breath-hold perfusion SPECT/CT imaging performed at our hospital in a patient with CLD-PH. We used this methodology for our SPECT/CT imaging.

The current study aimed to assess the effectiveness of deep-inspiratory breath-hold perfusion SPECT/CT as a screening tool for evaluating the severity of pulmonary circulation impairment in patients with CLD-PH.

METHODS

Study design and population

This single-center observational study was conducted at the Nippon Medical School Hospital and included patients with CLD from February 2017 to December 2019. This study was approved by the Ethics Committee of Nippon Medical School Hospital (29-04-753). Written informed consent was obtained from all patients.

Patients aged ≥18 years with CLD who underwent right heart catheterization (RHC) were assessed for the study. The underlying CLDs included chronic obstructive pulmonary disease (COPD), ILD, and combined pulmonary fibrosis and emphysema (CPFE). The diagnosis of these CLDs was based on relevant guidelines for ILD,[15] COPD,[16] or pivotal clinical reports for CPFE.[17,18] Patients with CTEPH were excluded based on V/Q SPECT findings with segmental mismatched V/Q defects. Patients with findings, such as small peripheral or nonsegmental defects, were enrolled. Finally, treatment-naive patients with CLD-PH who had a mean pulmonary arterial pressure (PAP) of ≥25 mmHg, as confirmed by RHC, were enrolled in the study.

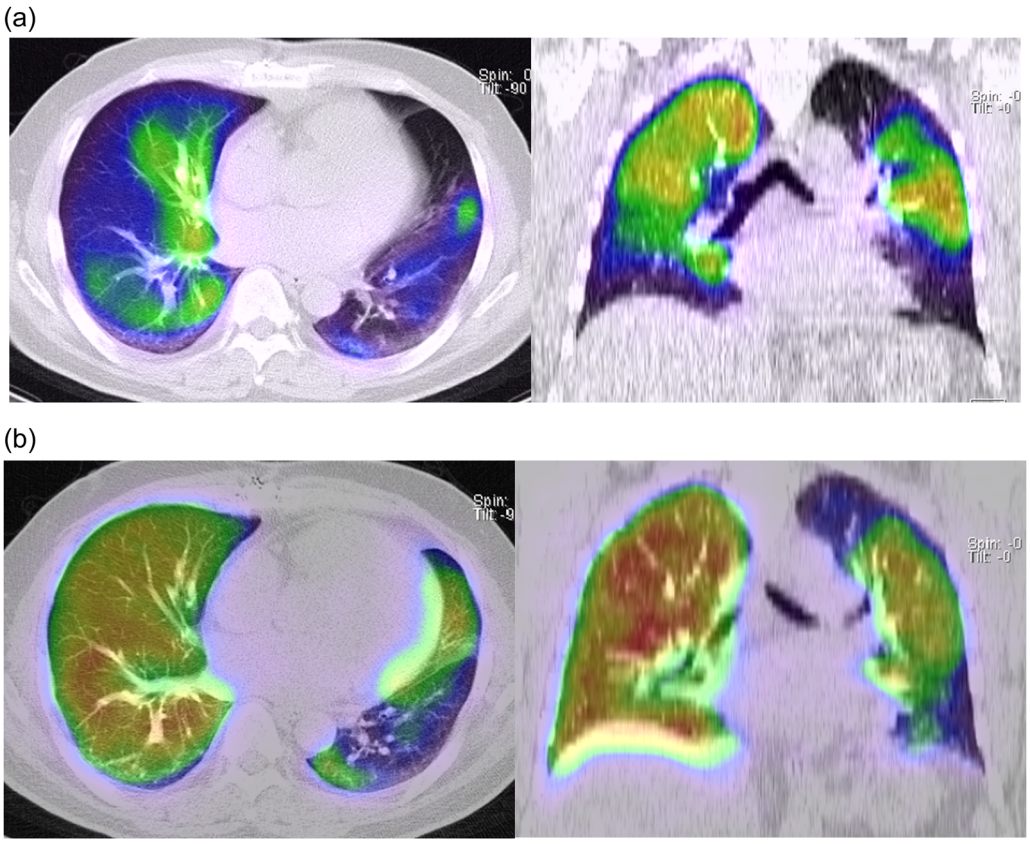

FIGURE 1 Difference between free-breathing (a) and deep-inspiratory breath-hold (b) perfusion SPECT/CT imaging in a patient with CLD-PH at our hospital. Deep-inspiratory breath-hold SPECT imaging (displayed using color) shows a distribution close to the lung field on chest CT imaging (displayed using grayscale) by minimizing misregistration resulting from lung motion. CLD, chronic lung disease; CT, computed tomography; PH, pulmonary hypertension; SPECT, single-photon emission computed tomography; SPECT/CT, SPECT combined with CT.

Data collection

Baseline characteristics were recorded, including gender, age, World Health Organization functional classification (WHO-FC), arterial blood gas analysis including alveolar-arterial oxygen difference (A-aDO2), and plasma N-terminal pro-B-type natriuretic peptide levels. Pulmonary function tests were conducted using a lung function instrument with computer processing, and the following parameters were recorded: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC, diffusing capacity for carbon monoxide (DLco), and DLco divided by alveolar volume ($DLco/V_A$). Pulmonary hemodynamic indices were assessed through RHC, including mean right atrial pressure (RAP), systolic PAP, mean PAP, pulmonary arterial wedge pressure (PAWP), cardiac output (CO) assessed by thermodilution, cardiac index (CI; calculated as CO divided by body surface area), and pulmonary vascular resistance (PVR; calculated as [mean PAP − PAWP]/CO). Mixed venous blood was simultaneously drawn from the pulmonary artery to measure mixed venous oxygen tension.

The percentage of pulmonary perfusion defect (%PPD) using SPECT/CT

The examinations were conducted using the SPECT/CT hybrid system Symbia T2, which uses a dual-head gamma camera with a two-row, multisection CT scanner (Siemens Healthcare Japan). Pulmonary perfusion SPECT was performed in synchrony with intermittent deep-inspiratory breath-hold cycles. The radiotracer 99mTechnetium macroaggregated albumin was used and administered at a dose of 370 MBq, which is the standard dose for free-breathing perfusion SPECT. Next, a low-dose chest CT scan was performed during deep-inspiratory breath-holding, and hybrid SPECT/CT images were created by combining the SPECT and CT images through hardware fusion. To visually distinguish SPECT and CT images, the former were displayed in

TABLE 1 Baseline characteristics of patients with pulmonary hypertension associated with chronic lung disease.

Characteristics	Total ($N = 22$)		COPD ($N = 7$)		ILD ($N = 7$)		CPFE ($N = 8$)		p Value[a]
Gender male, No. (%)	19 (86)		5 (71)		6 (86)		8 (100)		0.27
Age (year)	68	(65–72)	67	(65–69)	71	(65–72)	69	(61–73)	0.84
WHO-FC II/III/IV, No.	5/16/1		2/5/0		1/5/1		2/6/0		0.65
Arterial blood gas analysis									
PaO_2 at rest (Torr)	55.0	(50.1–62.5)	48.1	(46.0–50.6)	60.0	(55.0–65.0)	55.5	(52.1–64.6)	0.007*
$PaCO_2$ at rest (Torr)	39.3	(35.5–44.6)	41.0	(33.7–58.5)	43.6	(38.0–47.6)	37.8	(34.3–39.3)	0.18
A-aDO_2 (Torr)	55.4	(44.3–62.6)	56.3	(37.5–57.6)	46.2	(43.3–57.1)	63.2	(46.9–72.9)	0.19
Plasma NT-proBNP (pg/mL)	383	(193–1229)	592	(221–1273)	274	(98–710)	538	(203–3334)	0.42
Pulmonary function tests									
FVC (L)	2.59	(1.81–3.11)	2.80	(2.13–3.40)	1.64	(1.41–1.86)	3.07	(2.66–3.21)	<0.001*
FVC% predicted	82.5	(57.8–91.3)	88.8	(83.3–95.0)	47.7	(43.8–60.4)	88.6	(80.8–100.5)	0.001*
FEV_1 (L)	1.78	(1.16–2.43)	1.16	(0.75–2.17)	1.56	(1.14–1.86)	2.59	(2.30–2.80)	0.002*
FEV_1% predicted	76.9	(55.4–101.6)	46.3	(39.3–75.4)	59.5	(58.4–91.2)	105.5	(91.5–122.4)	0.003*
FEV_1/FVC (%)	81.3	(59.6–91.6)	41.4	(35.2–63.8)	95.1	(81.5–100.0)	86.4	(80.0–87.5)	<0.001*
DLco% predicted	26.6	(22.4–33.6)	28.4	(22.2–37.7)	25.4	(25.4–30.9)	25.3	(22.7–32.3)	0.94
DLco/V_A% predicted	28.4	(23.4–36.7)	24.7	(16.4–32.6)	54.0	(54.0–60.5)	29.4	(24.3–39.7)	0.030*
Right heart catheterization									
Mean RAP (mmHg)	5.0	(3.0–7.3)	7.0	(3.0–9.0)	4.0	(1.0–7.0)	4.5	(3.0–9.3)	0.41
Systolic PAP (mmHg)	61.0	(49.8–70.3)	56	(45.0–81.0)	60	(53.0–70.0)	64	(42.5–76.0)	0.98
Mean PAP (mmHg)	36.5	(29.8–42.8)	37	(30.0–54.0)	36	(29.0–38.0)	40	(27.5–44.3)	0.75
PAWP (mmHg)	10.5	(7.0–12.0)	10	(6.0–12.0)	10	(8.0–11.0)	12	(5.3–15.0)	0.52
CO (L/min)	4.5	(3.9–4.8)	4.6	(4.1–4.8)	4.6	(4.3–5.2)	3.8	(2.9–4.6)	0.10
CI ($L/min/m^2$)	2.8	(2.3–3.1)	3.0	(2.6–3.2)	3.0	(2.7–3.3)	2.3	(1.8–2.7)	0.023*
PVR (WU)	6.3	(4.7–7.9)	6.6	(4.0–7.9)	5.5	(4.6–7.2)	6.7	(5.4–8.9)	0.45
PvO_2 (Torr)	34.0	(30.2–37.0)	36.5	(32.8–39.0)	32.3	(30.2–35.8)	30.3	(26.1–35.9)	0.14
Perfusion SPECT/CT									
%PPD (%)	52.4	(42.5–72.3)	70.3	(35.5–81.0)	44.0	(43.0–55.5)	60.0	(44.2–73.0)	0.55

Note: Data are presented as medians and interquartile ranges unless otherwise indicated.

Abbreviations: %PPD, percentage of pulmonary perfusion defect; A-aDO_2, alveolar-arterial oxygen difference; CI, cardiac index; CO, cardiac output; COPD, chronic obstructive pulmonary disease; CPFE, combined pulmonary fibrosis and emphysema; DLco, diffusing capacity for carbon monoxide; DLco/VA, DLco divided by alveolar volume; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PvO_2, mixed venous oxygen tension; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; SPECT/CT, single-photon emission combined with computed tomography; WHO-FC, World Health Organization functional classification.

[a]Results of the Kruskal–Wallis test or Fisher's exact test.

*$p < 0.05$.

color, whereas the latter were displayed in grayscale. For quantitative analysis with standardized uptake volume (SUV), we previously investigated the optimal cutoff level of maximum radioactivity in lung perfusion SPECT images in 1% increments in healthy subjects. In this study, SUV was identified as regions with up to 31% of the maximum counts, and the accumulation volume was calculated with a three-dimensional (3D) volume of interest greater than 31% of the SUV. Moreover, lung volume was measured using the 3D volume of interest from the CT scan images. Lung perfusion defect volume was calculated as the difference between lung volume and the accumulation volume. %PPD was then calculated by dividing the lung perfusion defect volume by the lung

volume. All calculations from the fused images were performed using the Symbia T2 workstation (Siemens Healthcare Japan).

Outcome measures

The primary outcome of this study was to measure the %PPD in patients with CLD-PH. The secondary outcome was to assess the correlation between %PPD and baseline characteristics of the patients to evaluate the clinical value of a given %PPD.

Statistical analysis

Given the small sample size and nonnormal distribution of most variables, nonparametric statistics were used in this study. Continuous variables were reported as medians with interquartile ranges (IQRs), while categorical variables were presented as numbers and percentages. The Mann–Whitney *U* test, Kruskal–Wallis test (for continuous variables), or Fisher's exact test (for categorical variables) were used to determine significant differences between groups. Univariate and multivariate linear regression analyses were conducted, with %PPD serving as the dependent variable and the baseline characteristics of patients with CLD-PH as independent variables. Potential confounders were excluded from the analyses, and the adjusted R^2 value was used to assess the model's fitness for a given data set. All statistical analyses were conducted using JMP®14 software (SAS Institute Inc.). A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 30 patients with CLD who underwent RHC were assessed for eligibility. After excluding total seven patients from the analysis due to a mean PAP of <25 mmHg (four patients), collagen tissue diseases (two patients), and incomplete data (one patient), the remaining 22 patients were included in this study and underwent pulmonary V/Q SPECT/CT. There were no cases with segmental defects on V/Q SPECT that clearly indicated CTEPH. Table 1 summarizes the baseline characteristics of the patients with CLD-PH. The median age of these patients was 68 years (IQR, 65–72 years). Among these patients, seven were classified into the COPD group, seven in the ILD group, and eight in the CPFE group. Most patients in all groups were categorized as WHO-FC II or III. The median mean PAP was 37 mmHg for the COPD group, 36 mmHg for the ILD group, and 40 mmHg for the CPFE group ($p = 0.75$). The median PVR was 6.6 WU for the COPD, 5.5 WU for ILD, and 6.7 WU for CPFE group ($p = 0.45$). In terms of lung function parameters, FEV_1 and FEV_1/FVC were significantly lower in the COPD group than in other groups. In addition, FVC and FVC% predicted were significantly lower, while DLco/V_A% predicted was significantly higher in the ILD group than in other groups. Furthermore, FEV_1% predicted was significantly higher, whereas CI was significantly lower in the CPFE group than in other groups.

Clinical outcomes

The median %PPD for all 22 patients was 52.4% (IQR, 42.5%–72.3%) and for each group was 70.3% (IQR, 35.5%–81.0%) in the COPD group, 44.0% (IQR, 43.0%–55.5%) in the ILD group, and 60.0% (IQR, 44.2%–73.0%) in the CPFE group (Figure 2).

Table 2 shows the results of the univariate linear regression analysis with %PPD as the dependent

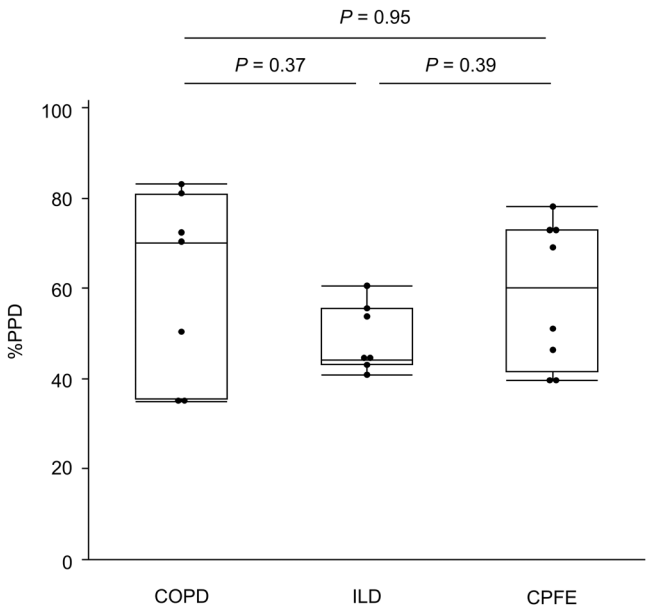

FIGURE 2 Box and whisker plots depict the percentage of pulmonary perfusion defect (%PPD) in different patient groups: chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and combined pulmonary fibrosis and emphysema (CPFE). The bottom and top of the box represent the first and third quartiles, whereas the band inside the box indicates the median. The whiskers represent the minimum and maximum values observed.

TABLE 2 Univariate linear regression analysis with the percentage of pulmonary perfusion defect.

	Total ($N = 22$)		COPD ($N = 7$)		ILD ($N = 7$)		CPFE ($N = 8$)	
Variables	***R***	***p* Value**	***R***	***p* Value**	***R***	***p* Value**	***R***	***p* Value**
Age (year)	−0.32	0.15	−0.35	0.44	−0.52	0.23	−0.36	0.38
Arterial blood gas analysis								
PaO_2 at rest (Torr)	−0.31	0.15	−0.08	0.87	0.28	0.54	−0.74	0.038*
$PaCO_2$ at rest (Torr)	−0.39	0.071	−0.67	0.10	0.04	0.93	−0.48	0.23
A-aDO_2 (Torr)	0.40	0.064	0.81	0.027*	−0.36	0.43	0.26	0.54
Plasma NT-proBNP, (pg/mL)	−0.19	0.40	−0.22	0.63	−0.20	0.66	−0.45	0.27
Pulmonary function test								
FVC (L)	0.53	0.011*	0.77	0.043*	−0.54	0.21	0.54	0.16
FVC% predicted	0.35	0.11	0.23	0.62	−0.46	0.30	0.35	0.39
FEV_1 (L)	0.29	0.18	0.56	0.19	−0.70	0.080	0.61	0.10
FEV_1% predicted	0.11	0.62	0.38	0.40	−0.46	0.29	0.24	0.57
FEV_1/FVC (%)	−0.13	0.58	0.48	0.27	−0.90	0.006*	0.49	0.22
DLco% predicted	−0.27	0.27	−0.17	0.72	0.79	0.42	−0.57	0.14
DLco/V_A% predicted	−0.48	0.042*	−0.52	0.23	0.79	0.42	−0.61	0.11
Right heart catheterization								
Mean RAP (mmHg)	0.41	0.056	−0.15	0.74	0.26	0.58	0.88	0.004*
Systolic PAP (mmHg)	0.62	0.002*	0.87	0.011*	0.84	0.018*	0.31	0.45
Mean PAP (mmHg)	0.66	<0.001*	0.77	0.041*	0.80	0.030*	0.43	0.29
PAWP (mmHg)	0.28	0.20	−0.35	0.43	0.49	0.26	0.65	0.079
CO (L/min)	−0.002	0.99	0.50	0.25	−0.54	0.21	−0.004	0.99
CI (L/min/m^2)	−0.06	0.80	0.31	0.50	−0.20	0.66	−0.13	0.76
PVR (WU)	0.57	0.006*	0.76	0.047*	0.87	0.011*	0.13	0.76
PvO_2 (Torr)	0.12	0.63	0.55	0.26	−0.40	0.37	0.06	0.92

Abbreviations: A-aDO_2, alveolar-arterial oxygen difference; CI, cardiac index; CO, cardiac output; COPD, chronic obstructive pulmonary disease; CPFE, combined pulmonary fibrosis and emphysema; DLco, diffusing capacity for carbon monoxide; DLco/VA, DLco divided by alveolar volume; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ILD, interstitial lung disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PvO_2, mixed venous oxygen tension; PVR, pulmonary vascular resistance; RAP, mean right atrial pressure; SPECT/CT, single-photon emission combined with computed tomography; WHO-FC, World Health Organization functional classification.

*$p < 0.05$.

TABLE 3 Multivariate linear regression analysis with %PPD.

Dependent variable	Independent variables	β	SE	Adjusted R^2	*p* Value
%PPD (%)	FVC (L)	0.58	0.48		0.008*
	DLco/V_A% predicted	0.14	0.02		0.50
	Mean PAP (mmHg)	0.68	0.03		0.001*
				0.62	

Abbreviations; %PPD, percentage of pulmonary perfusion defect; DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; PAP, pulmonary arterial pressure; SE, standard error of the standardized partial regression coefficient; V_A, alveolar volume; β, standardized partial regression coefficient.

*$p < 0.05$.

TABLE 4 Univariate linear regression analysis with mean PAP.

Dependent variable	Independent variables	*R*	*p* Value
Mean PAP (mmHg)	%PPD (%)	0.66	<0.001*
	FVC (L)	0.14	0.54
	DLco/V_A% predicted	0.43	0.073

Abbreviations; %PPD, percentage of pulmonary perfusion defect; DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; PAP, pulmonary arterial pressure; V_A, alveolar volume.
*$p < 0.05$.

variable. In all 22 patients, %PPD was found to be significantly correlated with FVC, systolic PAP, mean PAP, and PVR. However, there was a statistically significant inverse correlation between %PPD and DLco/V_A% predicted. To further investigate the correlation of %PPD and other variables, multivariate regression analyses were conducted with %PPD as the dependent variable and FVC, DLco/V_A% predicted and mean PAP as independent variables. Systolic PAP and PVR were excluded from the analysis due to their strong correlation with mean PAP considering the method of calculation. Table 3 shows the standardized partial regression coefficients and standard errors for %PPD. The adjusted R^2 of %PPD in the model was 0.62. Furthermore, both FVC ($\beta = 0.58$, $p = 0.008$) and mean PAP ($\beta = 0.68$, $p = 0.001$) were significantly correlated with %PPD in the model. However, there was no significant relationship between DLco/V_A% and %PPD ($\beta = 0.14$, $p = 0.50$). Table 4 summarizes the results of the univariate linear regression analysis with mean PAP as the dependent variable and %PPD, FVC, and DLco/VA% predicted as the independent variables. %PPD was found to be independently associated with PAP than FVC and DLco/VA% predicted. Figure 3 shows the relationship between %PPD and mean PAP, with each group identified by separate symbols.

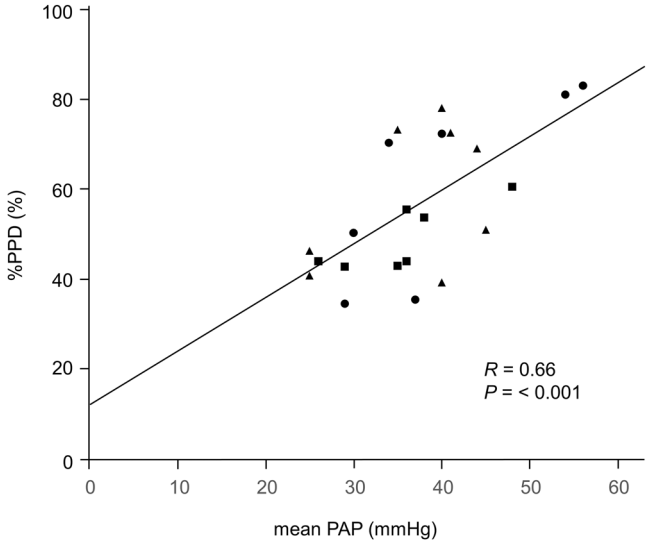

FIGURE 3 Relationship between the percentage of pulmonary perfusion defect (%PPD) and mean pulmonary arterial pressure (PAP) in all 22 patients with pulmonary hypertension associated with chronic lung disease. Circles: chronic obstructive pulmonary disease group; triangles: interstitial lung disease group; squares: combined pulmonary fibrosis and emphysema group. Continuous line represents the regression line. There is a significant correlation between mean PAP and %PPD ($R = 0.66$, $p < 0.001$).

DISCUSSION

This study revealed a significant correlation between the mean PAP and the %PPD in multivariate linear regression analysis. To the best of our knowledge, no previous studies have investigated %PPD in patients with CLD-PH using pulmonary perfusion SPECT/CT. These findings indicate that the noninvasive assessment of %PPD can be a valuable screening tool for evaluating the severity of pulmonary circulation impairment in patients with CLD-PH.

The functional significance of abnormal scintigraphy findings in patients with PH remains unclear. Scott reported that quantifying the heterogeneity of perfusion defects could be predictive of pulmonary systolic pressures.[19] Chan et al. reported that global perfusion defects on SPECT were associated with a severe PAH phenotype characterized by adverse pulmonary hemodynamics and higher mortality rates.[20] In addition, previous reports have demonstrated that global perfusion defects may reflect pathological features related to the obliteration of distal pulmonary vessels due to the progression of right ventricular failure.[21,22] These findings indicate that pulmonary perfusion SPECT may have potential utility beyond its traditional role in excluding pulmonary embolism.

COPD not only affects the airways but also the entire lung. Patients with COPD have been observed to have a higher risk of hypercoagulability.[23] This can lead to various vascular complications, including ischemic heart disease, congestive heart failure, pulmonary vascular changes, and pulmonary embolism.[24] Although PH has long been recognized in a subset of patients with CLD, there are still unanswered questions regarding its underlying pathophysiology. Matsuoka et al. reported a significant negative correlation between the severity of PAP in severe emphysema and the percentage of the total cross-sectional area of small pulmonary vessels less than

5 mm^2 on CT scans.[25] Jögi et al. reported that V/Q SPECT could help identify comorbid diseases in patients with COPD.[26] Unlike COPD, ILD is characterized by unperfused cystic air spaces, probably due to vascular obliteration, while ventilation is typically preserved. Strickland et al. demonstrated that this V/Q mismatch observed on scintigraphy could differentiate between ILD and COPD.[27] However, the significance of using scintigraphy to evaluate CLD-PH has yet to be established.

In our study, we did not find a significant correlation between the %PPD and mean PAP in patients with CPFE ($p = 0.29$, Table 2). However, a strong correlation between %PPD and mean RAP was observed ($p = 0.004$). One possible explanation for these findings is the hemodynamics of patients with CPFE. The CI was found to be significantly lower in patients with CPFE (median: 2.3 L/min/m^2) than in those with COPD (median: 3.0 L/min/m^2) and ILD (median: 3.0 L/min/m^2) ($p = 0.023$, Table 1). In addition, PAWP tended to be higher in patients with CPFE (median: 12 mmHg) than in those with COPD (median: 10 mmHg) and ILD (median: 10 mmHg). Based on these hemodynamic findings, we assume that left heart failure may have influenced right heart failure and contributed to the observed %PPD.

In the present study, we observed a significant correlation between FVC and %PPD in the multivariate linear regression analysis. %PPD tended to be lower in patients with ILD (median: 44%) than in those with COPD (median: 70.3%) and CPFE (median: 60.0%) (Figure 2). We hypothesized that ILD with low FVC may have contributed to the lower %PPD observed in this group. However, the relationship between %PPD and FVC varied depending on the underlying CLD associated with PH. In the ILD group, we observed that %PPD tended to increase as FVC decreased. However, in the COPD and CPFE groups, %PPD tended to decrease as FVC decreased. Evaluating the significance of FVC in the CPFE group was challenging because patients with CPFE often have nominally normal lung volumes because of the presence of both ILD and COPD. Consequently, FVC is a complex confounding factor for %PPD and should be further investigated in a larger study population.

Our study has several limitations. First, the analysis of %PPD could be affected by factors other than PH, and it is important to identify these factors that may impact the accuracy of %PPD measurements. Contrast-enhanced CT was performed in patients included in the follow-up study and was not routinely performed in other patients. Therefore, there was a possibility that CTEPH could not be completely ruled out using V/Q SPECT alone. Further investigations are needed to examine the effects of hemodynamics, microangiopathy, and imaging artifacts on perfusion SPECT/CT. In this study, SUV in the lung perfusion SPECT images was identified as regions with up to 31% of the maximum counts; however, further investigation is required to determine the optimal cutoff level. Second, the calculation of %PPD did not incorporate the evaluation of pulmonary ventilation scintigraphy. It would be valuable to assess the quantitative calculation method of pulmonary perfusion scintigraphy, including the ventilation scintigraphy results. Third, this study included patients with different background lung diseases, such as COPD and ILD, which have distinct impacts on perfusion SPECT/CT. COPD may also have different effects on %PPD measurements between emphysema and nonemphysema. It is necessary to separately evaluate the effects on %PPD measurements for each specific background lung disease by enrolling a larger number of patients with CLD-PH. Finally, our pilot study was conducted at a single-center and had a limited sample size of 22 patients with CLD-PH. Multivariate regression analysis with a larger sample size should be conducted to evaluate %PPD using the three independent variables. In addition, there was no control arm for CLD without PH. Larger studies with larger case groups and conducted at different time points are necessary to assess the reliability and reproducibility of %PPD.

In conclusion, our study revealed a significant correlation between mean PAP and %PPD in multivariate linear regression analysis. This suggests that noninvasive assessment of %PPD may be a valuable tool for evaluating the severity of pulmonary circulation impairment in patients with CLD-PH.

AUTHOR CONTRIBUTIONS

Kenichiro Atsumi: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; writing—original draft; and writing—review and editing. **Yoshimitsu Fukushima**: Conceptualization; data curation; formal analysis; investigation; methodology; project administration and writing—original draft. **Yosuke Tanaka**: Conceptualization; methodology; and supervision. **Shunichi Nishima**: Data curation and investigation. **Toru Tanaka**: Data curation and investigation. **Masahiro Seike**: Supervision and writing—review and editing. **Yoshiaki Kubota**: Data curation and investigation. **Hiroshi Kimura**: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision and writing—review and editing.

ACKNOWLEDGMENTS

The authors would like to thank Enago for editing the draft of this manuscript. The authors have no funding to report.

CONFLICT OF INTEREST STATEMENT

Hiroshi Kimura worked in an endowment department supported by an unrestricted grant to Nippon Medical School from Actelion Pharmaceuticals Japan. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Ethics Committee of Nippon Medical School Hospital (29-04-753). Written informed consent was obtained from all patients.

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REFERENCES

1. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34–41.
2. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015;46(4):903–75.
3. Weitzenblum E, Hirth C, Ducolone A, Mirhom R, Rasaholinjanahary J, Ehrhart M. Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. Thorax. 1981;36(10):752–8.
4. Seeger W, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galiè N, Ghio S, Gibbs S, Martinez FJ, Semigran MJ, Simonneau G, Wells AU, Vachiéry JL. Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol. 2013;62(25 Suppl):D109–16.
5. Hurdman J, Condliffe R, Elliot CA, Swift A, Rajaram S, Davies C, Hill C, Hamilton N, Armstrong IJ, Billings C, Pollard L, Wild JM, Lawrie A, Lawson R, Sabroe I, Kiely DG. Pulmonary hypertension in COPD: results from the ASPIRE registry. Eur Respir J. 2013;41(6):1292–301.
6. Tanabe N, Taniguchi H, Tsujino I, Sakamaki F, Emoto N, Kimura H, Takamura K, Hanaoka M, Nishimura M, Tatsumi K. Multi-institutional retrospective cohort study of patients with severe pulmonary hypertension associated with respiratory diseases. Respirology. 2015;20(5):805–12.
7. Vitulo P, Stanziola A, Confalonieri M, Libertucci D, Oggionni T, Rottoli P, Paciocco G, Tuzzolino F, Martino L, Beretta M, Callari A, Amaducci A, Badagliacca R, Poscia R, Meloni F, Refini RM, Geri P, Baldi S, Ghio S, D'Alto M, Argiento P, Sofia M, Guardamagna M, Pezzuto B, Vizza CD. Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: a randomized controlled multicenter clinical trial. J Heart Lung Transplant. 2017;36(2):166–74.
8. Tanabe N, Kumamaru H, Tamura Y, Taniguchi H, Emoto N, Yamada Y, Nishiyama O, Tsujino I, Kuraishi H, Nishimura Y, Kimura H, Inoue Y, Morio Y, Nakatsumi Y, Satoh T, Hanaoka M, Kusaka K, Sumitani M, Handa T, Sakao S, Kimura T, Kondoh Y, Nakayama K, Tanaka K, Ohira H, Nishimura M, Miyata H, Tatsumi K. Multi-institutional prospective cohort study of patients with pulmonary hypertension associated with respiratory diseases. Circ J. 2021;85(4):333–42.
9. Vizza CD, Hoeper MM, Huscher D, Pittrow D, Benjamin N, Olsson KM, Ghofrani HA, Held M, Klose H, Lange T, Rosenkranz S, Dumitrescu D, Badagliacca R, Claussen M, Halank M, Vonk-Noordegraaf A, Skowasch D, Ewert R, Gibbs JSR, Delcroix M, Skride A, Coghlan G, Ulrich S, Opitz C, Kaemmerer H, Distler O, Grünig E. Pulmonary hypertension in patients with COPD. Chest. 2021;160(2):678–89.
10. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, Allen R, Feldman J, Argula R, Smith P, Rollins K, Deng C, Peterson L, Bell H, Tapson V, Nathan SD. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med. 2021;384(4):325–34.
11. Powe JE, Palevsky HI, McCarthy KE, Alavi A. Pulmonary arterial hypertension: value of perfusion scintigraphy. Radiology. 1987;164(3):727–30.
12. Worsley DF, Palevsky HI, Alavi A. Ventilation-perfusion lung scanning in the evaluation of pulmonary hypertension. J Nucl Med. 1994;35(5):793–6.
13. Lu Y, Lorenzoni A, Fox JJ, Rademaker J, Vander Els N, Grewal RK, Strauss HW, Schöder H. Noncontrast perfusion single-photon emission CT/CT scanning. Chest. 2014;145(5):1079–88.
14. Suga K, Kawakami Y, Iwanaga H, Tokuda O, Matsunaga N. Automated breath-hold perfusion SPECT/CT fusion images of the lungs. Am J Roentgenol. 2007;189(2):455–63.
15. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schünemann HJ. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824.

16. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013;187(4):347–65.
17. Cottin V. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J. 2005;26(4):586–93.
18. Cottin V, Cordier JF. The syndrome of combined pulmonary fibrosis and emphysema. Chest. 2009;136(1):1–2.
19. Scott JA. Pulmonary perfusion patterns and pulmonary arterial pressure. Radiology. 2002;224(2):513–8.
20. Chan K, Ioannidis S, Coghlan JG, Hall M, Schreiber BE. Pulmonary arterial hypertension with abnormal V/Q single-photon emission computed tomography. JACC Cardiovasc Imaging. 2018;11(10):1487–93.
21. Rich JD, Rich S. Clinical diagnosis of pulmonary hypertension. Circulation. 2014;130(20):1820–30.
22. Bloodworth NC, West JD, Merryman WD. Microvessel mechanobiology in pulmonary arterial hypertension: cause and effect. Hypertension. 2015;65(3):483–9.
23. Voelkel NF, Cool CD. Pulmonary vascular involvement in chronic obstructive pulmonary disease. Eur Respir J Suppl. 2003;46:28–32s.
24. Holguin F, Folch E, Redd SC, Mannino DM. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. Chest. 2005;128(4):2005–11.
25. Matsuoka S, Washko GR, Yamashiro T, Estepar RSJ, Diaz A, Silverman EK, Hoffman E, Fessler HE, Criner GJ, Marchetti N, Scharf SM, Martinez FJ, Reilly JJ, Hatabu H. Pulmonary hypertension and computed tomography measurement of small pulmonary vessels in severe emphysema. Am J Respir Crit Care Med. 2010;181(3):218–25.
26. Jögi J, Ekberg M, Jonson B, Bozovic G, Bajc M. Ventilation/perfusion SPECT in chronic obstructive pulmonary disease: an evaluation by reference to symptoms, spirometric lung function and emphysema, as assessed with HRCT. Eur J Nucl Med Mol Imaging. 2011;38(7):1344–52.
27. Strickland NH, Hughes JM, Hart DA, Myers MJ, Lavender JP. Cause of regional ventilation-perfusion mismatching in patients with idiopathic pulmonary fibrosis: a combined CT and scintigraphic study. Am J Roentgenol. 1993;161(4):719–25.

How to cite this article: Atsumi K, Fukushima Y, Tanaka Y, Nishima S, Tanaka T, Seike M, Kubota Y, Kimura H. Novel evaluation of pulmonary hypertension associated with chronic lung disease using perfusion SPECT/CT: a pilot study. Pulm Circ. 2024;14:e12423. https://doi.org/10.1002/pul2.12423