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Treatment Response Evaluation by Computed Tomography Pulmonary Vasculature Analysis in Patients With Chronic Thromboembolic Pulmonary Hypertension

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Objective: To quantitatively assess the pulmonary vasculature using non-contrast computed tomography (CT) in patients with chronic thromboembolic pulmonary hypertension (CTEPH) pre- and post-treatment and correlate CT-based parameters with right heart catheterization (RHC) hemodynamic and clinical parameters.

Materials and Methods: A total of 30 patients with CTEPH (mean age, 57.9 years; 53% female) who received multimodal treatment, including riociguat for ≥ 16 weeks with or without balloon pulmonary angioplasty and underwent both non-contrast CT for pulmonary vasculature analysis and RHC pre- and post-treatment were included. The radiographic analysis included subpleural perfusion parameters, including blood volume in small vessels with a cross-sectional area ≤ 5 mm^2 (BV5) and total blood vessel volume (TBV) in the lungs. The RHC parameters included mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), and cardiac index (CI). Clinical parameters included the World Health Organization (WHO) functional class and 6-minute walking distance (6MWD).

Results: The number, area, and density of the subpleural small vessels increased after treatment by 35.7% (P < 0.001), 13.3% (P = 0.028), and 39.3% (P < 0.001), respectively. The blood volume shifted from larger to smaller vessels, as indicated by an 11.3% increase in the BV5/TBV ratio (P = 0.042). The BV5/TBV ratio was negatively correlated with PVR (r = -0.26; P = 0.035) and positively correlated with CI (r = 0.33; P = 0.009). The percent change across treatment in the BV5/TBV ratio correlated with the percent change in mPAP (r = -0.56; P = 0.001), PVR (r = -0.64; P < 0.001), and CI (r = 0.28; P = 0.049). Furthermore, the BV5/TBV ratio was inversely associated with the WHO functional classes I–IV (P = 0.004) and positively associated with 6MWD (P = 0.013).

Conclusion: Non-contrast CT measures could quantitatively assess changes in the pulmonary vasculature in response to treatment and were correlated with hemodynamic and clinical parameters.

Keywords: Chronic thromboembolic pulmonary hypertension; Computed tomography; Pulmonary vasculature; Hemodynamics; Treatment response

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease characterized by unresolved pulmonary embolisms and pulmonary artery obstruction, resulting in increased pulmonary vascular resistance

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(PVR) and progressive right ventricular dysfunction [1,2]. Interventional treatment for CTEPH involves pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA) [3-6]. Additionally, riociguat, a soluble guanylate cyclase stimulator, is prescribed to patients with inoperable or recurrent CTEPH [7,8].

The current diagnostic method and treatment response evaluation of CTEPH require invasive right heart catheterization (RHC) to assess hemodynamic parameters [9], with inherent risks of invasive procedural complications [10]. The contrast injection needed during catheterization expels patients with renal insufficiency or anaphylactic history from undergoing examination [11]. Recent advances in computer-based image analysis have facilitated complex volumetric assessments of vascular morphology [12,13], which can be used to assess the pulmonary vasculature in non-enhanced computed tomography (CT) in patients with CTEPH. The radiographic feature "pruning of distal pulmonary vessels" can be used as a non-invasive substitute to evaluate disease severity; the quantification methods are still under investigation [14,15].

Few studies have simultaneously investigated radiographic pulmonary vasculature measures, RHC hemodynamic parameters, and clinical parameters in patients with CTEPH [16-18]. Therefore, this study aimed to quantitatively assess the pulmonary vasculature using non-contrast CT pre- and post-treatment and correlate the image parameters with RHC hemodynamic and clinical parameters to evaluate the implications of the CT parameters in evaluating CTEPH disease severity and treatment efficacy.

MATERIALS AND METHODS

Study Design and Patients

This retrospective study was approved by National Taiwan University Hospital Research Ethics Committee (approval number:202106058RINB) and adhered to the tenets of the Declaration of Helsinki and its amendments. The need for written informed consent was waived because of the retrospective nature of the study.

CTEPH diagnosis was previously reported, according to the following criteria after at least 3 months of anticoagulation therapy [3,19]: 1) mismatched ventilation/perfusion defects on lung scintigraphy; 2) specific pulmonary angiography features, including ring-like stenosis, slits, webs, slits, and subtotal/total occlusions; 3) mean pulmonary artery pressure (mPAP) ≥ 25 mmHg; and 4) pulmonary arterial wedge pressure ≤ 15 mmHg. The diagnostic algorithm followed at our institution is in line with that proposed by the American College of Cardiology [9]. Patients with suspected CTEPH underwent both contrast-enhanced and non-contrast thoracic CT simultaneously to confirm the thromboembolic basis of pulmonary hypertension and to exclude the differential diagnosis of acute thromboembolism. Imaging characteristics that differentiate CTEPH from acute thromboembolism include vascular, collateral, pulmonary hypertension, and lung parenchymal signs [20,21]. Subsequently, the patients underwent RHC to examine hemodynamic parameters for the diagnosis of CTEPH. All the study patients were reviewed by an institutional multidisciplinary team.

The study inclusion criteria were as follows: patient aged 20 years, diagnosed with CTEPH, inoperable for PEA, received riociguat for at least 16 weeks ± BPA, and underwent both RHC and CT pulmonary vasculature analyses pre- and post-treatment. The administration of riociguat for at least 16 weeks was in line with the findings of the landmark CHEST-1 trial, demonstrating that 16 weeks of riociguat treatment improved exercise capacity and PVR in patients with CTEPH [7]. As shown in Figure 1, patients who discontinued riociguat treatment before the end of 16 weeks (n = 1), those with incomplete post-treatment RHC data (n = 2), or those with incomplete post-treatment CT pulmonary vasculature analysis data (n = 3) were excluded. For the three patients who did not receive post-treatment CT evaluation, personal reasons, such as inconvenience with transportation or reluctance to receive radiation exposure, were documented.

The time points for post-treatment evaluation (RHC, non-contrast CT, and clinical parameters) were varied based on the discretion of the treating physician and willingness of the patient, and all evaluations were scheduled within 1 week. Clinical parameters, including demographic characteristics, World Health Organization (WHO) functional class, 6-minute walking distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP) level, and hemodynamic information from pre- and post-treatment RHC, were collected. All RHCs were performed by the same team, and resting hemodynamic measurements were used in the analysis. RHC hemodynamic data included mPAP, right atrial pressure, pulmonary arteriole wedge pressure, right ventricular systolic pressure, and cardiac output (CO) obtained using the thermodilution technique via a 7-Fr Swan-Ganz catheter. The cardiac index (CI) and PVR were calculated based on the following standard formulas: for CI, CO is divided by the body surface

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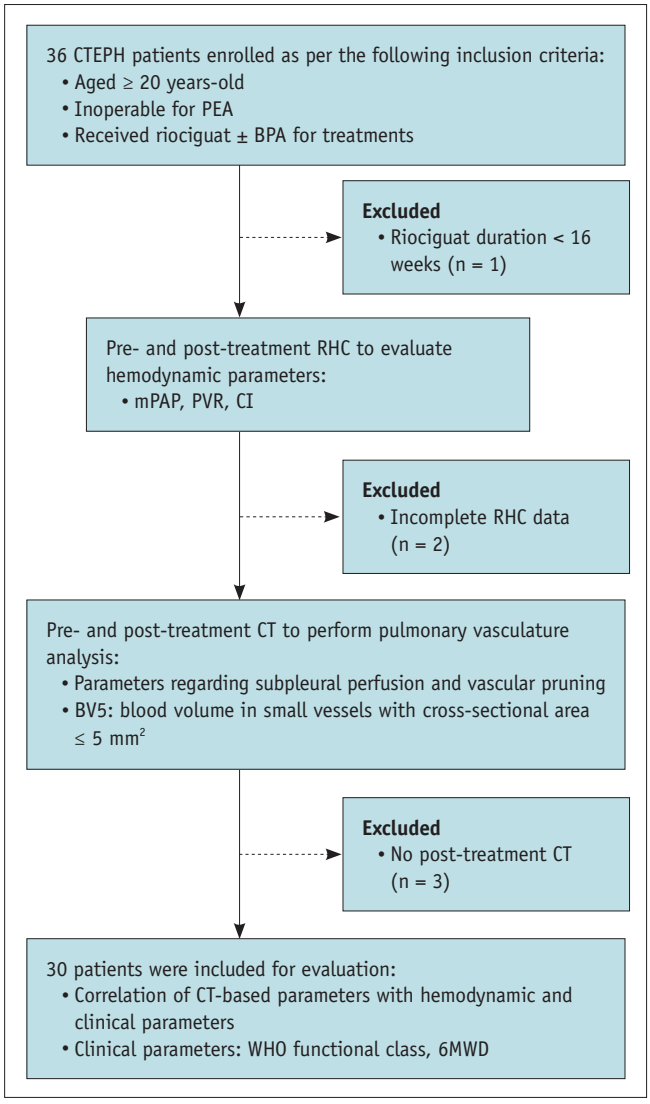

Fig. 1. Flowchart of the study. From 2011 to 2019, 36 patients with chronic thromboembolic pulmonary hypertension (CTEPH) met the inclusion criteria of age ≥ 20 years, are inoperable for pulmonary endarterectomy (PEA), and received riociguat ± balloon pulmonary angioplasty (BPA) for treatment. One patient presented with riociguat duration of less than 16 weeks and is excluded, two are excluded because they did not receive post-treatment right heart catheterization (RHC) to evaluate hemodynamic parameters, and three are excluded because they did not undergo post-treatment computed tomography (CT) pulmonary vasculature analysis. A total of 30 patients are included in this evaluation. mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular resistance, CI = cardiac index, WHO = World Health Organization, 6MWD = 6-minute walking distance

area; for PVR, the pulmonary arteriole wedge pressure is subtracted from mPAP and then divided by CO.

CT Pulmonary Vasculature Analysis

Pulmonary CT was scheduled within 1 week prior to RHC examination (median, 3 days; range, 0–7 days). Inspiratory non-contrast CT examinations covering the entire thorax were performed in a supine position using a Siemens Somatom Definition AS+ or Siemens Sensation 64 CT Scanner (Siemens Healthcare). Image reconstruction was performed using the soft convolution kernel of B40f. Alternatively, CT was performed using a GE LightSpeed VCT (GE Medical System) and Aquilion ONE scanner (Canon Medical Systems), and image reconstruction was performed using the soft convolution kernel–CHEST and FC08, respectively. The acquisition parameters were 120 kVp, 250–350 mA (based on body weight), 350 ms rotation time, and 0.5–0.625 mm section thickness. All the acquired CT images were reconstructed to a slice thickness of 1 mm for further analysis.

Lung segmentation and pulmonary vasculature analyses were performed using the Aview® system (Coreline Soft, Inc.). Briefly, the lungs and lobes were segmented, and three-dimensional (3D) reconstructed images of the lung segments and intraparenchymal vasculature were generated. The pulmonary vessels were extracted using a threshold of -750 HU. Initially, extracted vessels were refined in detail as twigs of lung vascular structures using region-growing and weighted minimum spanning tree algorithms with an orientation vector field. The lung at a depth of 6 mm from the pleural surface was defined as the "subpleural" region. An example of 3D pulmonary vascular reconstruction pre- and post-treatment is shown in Figure 2.

Severe CTEPH can result in vascular pruning and poor subpleural perfusion. Radiographic pulmonary vasculature parameters provide a quantitative assessment of subpleural perfusion and vascular pruning. In this study, small vessels were defined as those with a cross-sectional area ≤ 5 mm^2 (BV5). Total number of small vessels in the subpleural region, area of vessels in the subpleural section, and density of small vessels in the subpleural area (vessel count/cm^2) were calculated. The number and area of subpleural small blood vessels were normalized across the study cohort by dividing by the patient's total lung volume and are presented as vessel count/dL lung and mm^2/dL lung, respectively.

Blood vessel volume was determined as a function of the vascular cross-sectional area of the total lung. The total blood vessel volume (TBV) was determined as the total volume of the intraparenchymal pulmonary vasculature in the lungs. The fractions of blood volume in vessels with a BV5 and cross-sectional area > 10 mm^2 (BV > 10) within the total long volume were calculated. Cut-offs ≤ 5 mm^2 and > 10 mm^2

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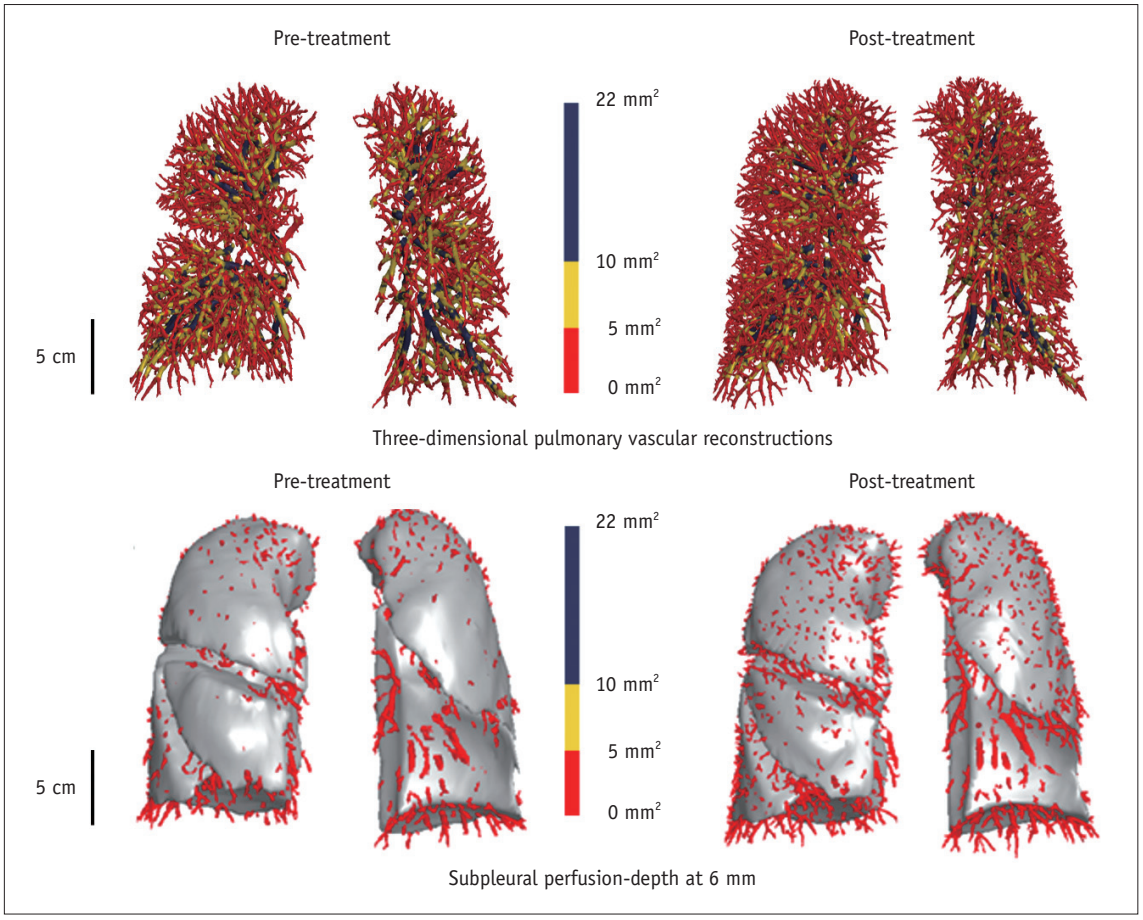

Fig. 2. Example of three-dimensional pulmonary vascular reconstruction pre- and post-treatment in a patient with chronic thromboembolic pulmonary hypertension. Computed tomography-based three-dimensional pulmonary vascular reconstructions in a 54-year-old female with chronic thromboembolic pulmonary hypertension (CTEPH). The color indicates the cross-section of the vessel, with red representing small vessels with a cross-sectional area ≤ 5 mm^2. Pretreatment imaging (left panel) shows a reduction in the volume of peripheral small vessels, termed "vascular pruning." The patient received riociguat treatment for 12 months without balloon pulmonary angioplasty. Post-treatment imaging (right panel) shows a significant increase in subpleural perfusion and improvement in vascular pruning. Regarding hemodynamic parameters, the mean pulmonary artery pressure decreases from 44.0 mmHg to 34.0 mmHg, pulmonary vascular resistance decreases from 14.1 woods unit to 10.7 woods unit, and cardiac index increases from 19 L/min/m^2 to 2.0 L/min/m^2. Quantitative radiographic pulmonary vasculature also showed improvement, with the number, area, and density of subpleural small vessels improving from 25.1 vessel count/dL lung to 43.9 vessel count/dL lung, 107.9 mm^2/dL lung to 130.9 mm^2/dL lung, and 0.6 vessel count/cm^2 to 1.0 vessel count/cm^2, respectively. In addition, the blood volume is shifted from larger vessels to smaller vessels, as evidenced by the increase in the ratio of blood volume in vessels with cross-sectional area ≤ 5 mm^2 (to the total blood volume, from 45.0% to 53.1%).

were selected based on previous research that quantified vascular pruning on CT scans [12,22].

Statistical Analyses

Statistical assistance was provided by the Clinical Trial Bioinformatics and Statistical Center, founded by the Department of Medical Research at National Taiwan University Hospital. Continuous variables are expressed as mean ± standard deviation, while dichotomous variables are expressed as numbers and proportions. The percent change was the change in the values (post-treatment value minus pre-treatment value) divided by the pre-treatment value and multiplied by 100. Pre- and post-treatment differences were evaluated using a paired-sample *t*-test. Pearson correlation analysis was used to determine the linear association between radiographic pulmonary vasculature measures and RHC hemodynamic parameters, where the regression parameter *b* was the slope of the regression line, the sign of the correlation coefficient *r* (i.e., positive or negative) defined the direction of the relationship, and the absolute value of the correlation coefficient *r* indicated the strength of the correlation [23]. One-way analysis of variance

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(ANOVA) was used to determine statistically significant differences in radiographic pulmonary vasculature measurements between different clinical categories grouped by WHO functional class or 6MWD [24]. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 22.0; IBM). Statistical *P*-value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics and Changes between Before and After Treatment

A total of 30 patients with CTEPH were included in this study. The median duration from the prescription of riociguat treatment to post-treatment evaluations (RHC, non-contrast CT, and clinical parameters) was 24.1 months (range: 4.0–

Table 1. Patient Characteristics and Changes Across Treatment (n = 30)

Variables	Pre-treatment	Post-treatment	Percent-change[§]	*P*
Clinicodemographic characteristics				
Age, yr	57.9 ± 13.8	-	-	-
Sex, female	16 (53)	-	-	-
Hypertension	14 (47)	-	-	-
Diabetes mellitus	5 (17)	-	-	-
Smoker	6 (20)	-	-	-
Body mass index, kg/m^2	24.0 ± 3.7	24.3 ± 3.9	1.2	0.350
WHO functional class				< 0.001[†]
I	1	12	-	
II	15	14	-	
III	11	3	-	
IV	3	1	-	
6MWD	397.6 ± 101.7	437.0 ± 118.3	9.9	0.019[†]
NT-proBNP, pg/mL	2063.2 ± 3197.7	992.8 ± 1417.2	-51.9	0.013[†]
Radiographic pulmonary vasculature measures[‡]				
Total lung volume, L	3.7 ± 1.4	3.7 ± 1.3	0.6	0.600
Number of subpleural small vessels, vessel count/dL lung*	25.5 ± 11.7	34.6 ± 14.1	35.7	< 0.001[†]
Subpleural vessel area, mm²/dL lung*	127.6 ± 72.5	144.6 ± 62.8	13.3	0.028[†]
Density of subpleural small vessels, vessel count/cm^2	0.5 ± 0.2	0.7 ± 0.3	39.3	< 0.001[†]
BV5, mL	86.9 ± 47.3	106.8 ± 55.2	22.9	0.006[†]
BV > 10, mL	47.0 ± 23.9	51.2 ± 24.9	8.9	0.013[†]
TBV, mL	203.4 ± 96.4	227.0 ± 104.8	11.8	0.006[†]
BV5/TBV ratio, %	41.3 ± 5.5	46.0 ± 6.3	11.3	0.042[†]
BV > 10/TBV, %	23.6 ± 4.2	22.8 ± 4.5	-3.4	0.279
Hemodynamic parameters				
mPAP, mmHg	42.9 ± 9.9	34.4 ± 9.7	-19.8	< 0.001[†]
Right atrial pressure, mmHg	8.7 ± 4.8	8.0 ± 4.5	-8.0	0.355
Pulmonary arteriole wedge pressure, mmHg	12.6 ± 5.9	13.1 ± 5.5	3.9	0.446
Cardiac output, L/min	3.5 ± 1.3	4.0 ± 1.0	14.3	0.029[†]
Cardiac index, L/min/m^2	2.2 ± 0.7	2.4 ± 0.6	9.1	0.025[†]
PVR, woods unit	9.7 ± 4.4	5.9 ± 2.9	-39.1	< 0.001[†]
Right ventricular systolic pressure, mmHg	71.3 ± 19.9	59.1 ± 18.1	-17.1	< 0.001[†]

Values are presented as mean ± standard deviation or number (%) unless otherwise specified. Of the 30 patients, 24 and 6 had improved and stationary WHO functional classes, respectively, after treatment. *Indices were divided by the patient's total lung volume to normalize the number and area of subpleural blood vessels across the study cohort, [†]Significance was tested using the paired-sample *t*-test, with *P*-values < 0.05 considered statistically significant, [‡]The lung at a depth of 6 mm from the pleural surface was defined as the "subpleural" region, and "small vessels" were defined as vessels with a cross-sectional area ≤ 5 mm^2, [§]Percent-change was the change in values (post-treatment value minus pre-treatment value), divided by the pre-treatment value, multiplied by 100. WHO = World Health Organization, NT-proBNP = N-terminal pro-brain natriuretic peptide, 6MWD = 6-minute walking distance, BV5 = blood volume in vessels with cross-sectional area ≤ 5 mm^2, TBV = total blood volume, BV > 10 = blood volume in vessels with cross-sectional area > 10 mm^2, mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular resistance

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78.7 months), and most patients were prescribed a riociguat dosage of 2.5 mg three times daily. A total of 20 patients (67%) received PBA intervention during the treatment period, and the median number of BPA interventions was 3 (range: 1–6). The patient characteristics and changes across treatments are presented in Table 1. After treatment, the WHO functional class improved, and the 6MWD increased. Among the RHC hemodynamic parameters, mPAP, PVR, and right ventricular systolic pressure decreased, whereas CO and CI increased after treatment.

The severity of CTEPH has been associated with vascular pruning and poor subpleural perfusion. As shown in Table 1, quantification of radiographic pulmonary vasculature parameters showed a significant increase in subpleural perfusion and improvement in vascular pruning after treatment. The number, area, and density of the subpleural small vessels increased after treatment by 35.7% ($P < 0.001$), 13.3% ($P = 0.028$), and 39.3% ($P < 0.001$), respectively. The blood volume shifted from larger to smaller vessels, as indicated by the 11.3% increase in the BV5/TBV ratio ($P = 0.042$). These results indicate that the increased blood volume in the small vessels revealed less severe vascular pruning following CTEPH treatment.

Correlation between Radiographic Pulmonary Vasculature and Hemodynamic Parameters

The correlations between radiographic pulmonary vasculature and hemodynamic parameters are shown in Table 2. Although there was no correlation between mPAP and radiographic pulmonary vasculature measurements, PVR and CI were correlated with radiographic pulmonary vasculature measurements (Fig. 3). PVR showed a significant negative correlation with the number, area, and density of the measured subpleural small vessels and BV5/TBV ratio. For example, per 1-wood-unit increase in PVR, number of subpleural small vessels, subpleural vessel area, subpleural small vessel density, and BV5/TBV ratio decreased by 1.19 vessel count/dL lung ($P = 0.003$), 4.20 mm^2/dL lung ($P = 0.032$), 0.03 vessel count/cm^2 ($P = 0.002$), and 0.34% ($P = 0.035$), respectively. These results indicate that the more severe the PVR, the more severe the vascular pruning. A reciprocal pattern was observed for CI. Unlike PVR, CI showed a significant positive correlation with the measured subpleural small vessel number, area, density, and BV5/TBV ratio, indicating that improvement in vascular pruning and increased subpleural perfusion after treatment were associated with better cardiac function.

Table 2. Correlation between Radiographic Pulmonary Vasculature Measures and Hemodynamic Parameters (n = 30, with Two Datasets per Patient, Pre- and Post-treatment, Resulting in a Total of 60 Datasets)

Radiographic Pulmonary Vasculature Measures‡	mPAP			PVR			Cardiac Index		
	Correlation Coefficient, *r*	Slope *b* (95% Confidence Interval)	*P*	Correlation Coefficient, *r*	Slope *b* (95% Confidence Interval)	*P*	Correlation Coefficient, *r*	Slope *b* (95% Confidence Interval)	*P*
Number of subpleural small vessels, vessel count/dL lung*	-0.12	-0.16 (-0.50 to 0.18)	0.342	-0.37	-1.19 (-1.97 to -0.42)	0.003†	0.47	9.44 (4.72 to 14.17)	< 0.001†
Area of subpleural vessel, mm^2/dL lung*	0.09	0.18 (-1.52 to 1.89)	0.826	-0.26	-4.20 (-8.26 to -0.15)	0.032†	0.33	33.3 (7.92 to 58.63)	0.011†
Density of subpleural small vessels, vessel count/cm^2	-0.12	-0.01 (-0.01 to 0.01)	0.368	-0.40	-0.03 (-0.04 to -0.01)	0.002†	0.43	0.18 (0.08 to 0.28)	< 0.001†
BV5/TBV ratio, %	-0.19	-0.11 (-0.25 to 0.04)	0.147	-0.26	-0.34 (-0.70 to 0.01)	0.035†	0.33	2.95 (0.76 to 5.13)	0.009†
BV > 10/TBV ratio, %	0.09	0.03 (-0.07 to 0.14)	0.515	0.08	0.08 (-0.18 to 0.34)	0.544	-0.21	-1.34 (-2.98 to 0.31)	0.111

*Values were divided by each patient's total lung volume to normalize the number and area of subpleural blood vessels across the study cohort, †Significance was tested using Pearson correlation analysis, with *P*-values < 0.05 considered statistically significant, ‡The lung at a depth of 6 mm from the pleural surface was defined as the "subpleural region," and "small vessels" were defined as vessels with cross-sectional area ≤ 5 mm^2. BV5 = blood volume in vessels with cross-sectional area ≤ 5 mm^2, TBV = total blood volume, BV > 10 = blood volume in vessels with cross-sectional area > 10 mm^2, mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular resistance

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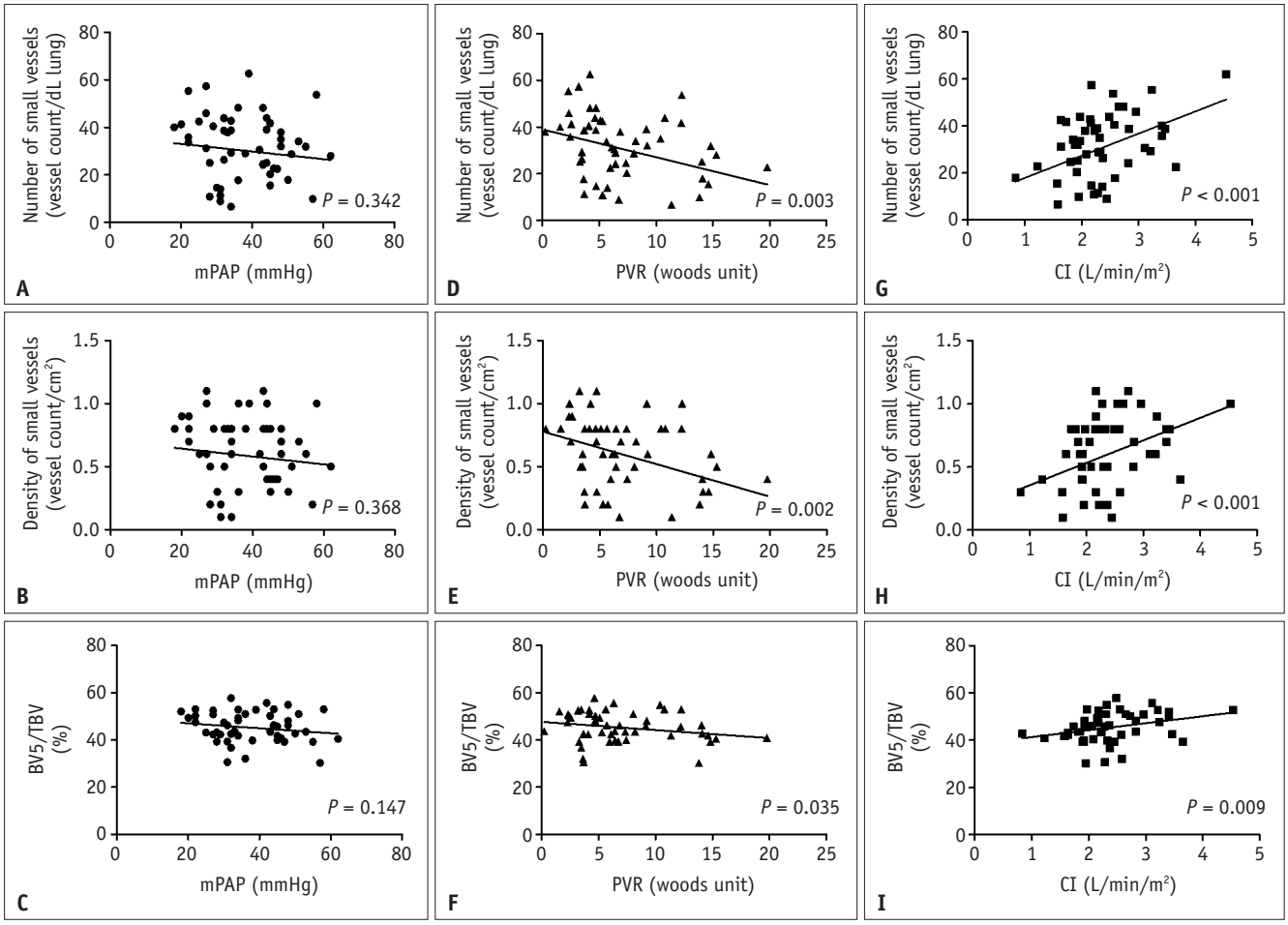

Fig. 3. Correlation between the radiographic pulmonary vasculature and hemodynamic parameters. Scatterplots demonstrating the relationships between radiographic pulmonary vasculature and hemodynamic parameters are shown. **A-C:** Mean pulmonary artery pressure (mPAP). **D-F:** Pulmonary vascular resistance (PVR). **G-I:** Cardiac index (CI). *P*-values were obtained using Pearson's correlation analysis. PVR is significantly negatively correlated with radiographic pulmonary vasculature measurements, whereas CI is significantly positively correlated with radiographic pulmonary vasculature measurements. BV5 = blood volume in vessels with cross-sectional area ≤ 5 mm^2, TBV = total blood volume

Correlation between Percent Changes Across Treatment in Radiographic Pulmonary Vasculature and Hemodynamic Parameters

In the analysis of the correlations between percent changes across treatments in the radiographic pulmonary vasculature and hemodynamic parameters (Table 3), patterns similar to those obtained for absolute measures were observed. As illustrated in Figure 4, percentage changes in mPAP, PVR, and CI were significantly correlated with percentage changes in radiographic pulmonary vasculature measures. For example, a 1% reduction in PVR was significantly correlated with 0.97%, 0.53%, 1.08%, and 0.25% increases in the number ($P < 0.001$), area ($P = 0.030$), and density ($P = 0.003$) of the measured subpleural small vessels and BV5/TBV ratio ($P < 0.001$), respectively. The percent change in the above-mentioned radiographic pulmonary vasculature measures was significantly correlated with the percent change in CI. For example, a 1% increase in CI was significantly correlated with 0.40%, 0.47%, 0.66%, and 0.09% increase in the number ($P = 0.040$), area ($P = 0.004$), and density ($P = 0.021$) of the subpleural small vessels and BV5/TBV ratio ($P = 0.049$), respectively. Although no significant correlation was found between the absolute measures of mPAP and radiographic pulmonary vasculature measures, significant negative correlations were observed for the corresponding relative changes. For example, a 1% reduction in mPAP was significantly correlated with 0.88% and 1.17% increases in the number ($P = 0.015$) and density of subpleural small vessels ($P = 0.019$), respectively, and a 0.29% increase in the BV5/TBV ratio ($P = 0.001$).

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Table 3. Correlation between the Percent-change in Radiographic Pulmonary Vasculature Measures and Hemodynamic Parameters Across Treatment (n = 30)

Radiographic Pulmonary Vasculature Measures‡	Percent-change* in mPAP			Percent-change* in PVR			Percent-change* in Cardiac Index		
	Correlation Coefficient, *r*	Slope *b* (95% Confidence Interval)	*P*	Correlation Coefficient, *r*	Slope *b* (95% Confidence Interval)	*P*	Correlation Coefficient, *r*	Slope *b* (95% Confidence Interval)	*P*
Percent-change in subpleural small vessel number	-0.44	-0.88 (-1.57 to -0.19)	0.015†	-0.62	-0.97 (-1.45 to -0.49)	< 0.001†	0.33	0.40 (-0.05 to 0.85)	0.040†
Percent-change in subpleural vessel area	-0.15	-0.22 (-0.79 to 0.35)	0.439	-0.40	-0.53 (-0.99 to -0.05)	0.030†	0.51	0.47 (0.16 to 0.77)	0.004†
Percent-change in subpleural small vessel density	-0.42	-1.17 (-2.13 to -0.20)	0.019†	-0.53	-1.08 (-1.75 to -0.41)	0.003†	0.42	0.66 (0.11 to 1.21)	0.021†
Percent-change in BV5/TBV	-0.56	-0.29 (-0.45 to -0.12)	0.001†	-0.64	-0.25 (-0.37 to -0.13)	< 0.001†	0.28	0.09 (-0.03 to 0.20)	0.049†
Percent-change in BV > 10/TBV	0.49	0.40 (0.13 to 0.68)	0.006†	0.61	0.39 (0.20 to 0.59)	< 0.001†	-0.12	-0.06 (-0.25 to 0.13)	0.521

*Percentage change was the change in values (post-treatment value – pre-treatment value) divided by the pre-treatment value multiplied by 100, †Significance was tested using Pearson correlation analysis, with *P*-values < 0.05 considered statistically significant, ‡The lung at a depth of 6 mm from the pleural surface was defined as the "subpleural region," and "small vessels" were defined as vessels with cross-sectional area ≤ 5 mm^2. BV5 = blood volume in vessels with cross-sectional area ≤ 5 mm^2, TBV = total blood volume, BV > 10 = blood volume in vessels with cross-sectional area > 10 mm^2, mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular resistance

These results indicate that effective treatment resulted in increased pulmonary distal perfusion and improved vascular pruning, and the treatment response can be substituted by radiographic pulmonary vasculature measures.

Associations between Radiographic Pulmonary Vasculature Parameters and Clinical Parameters

The associations between absolute measures of the radiographic pulmonary vasculature and clinical parameters, WHO functional class and 6MWD, are shown in Figure 5 and Supplementary Table 1. WHO functional classes I–IV were inversely associated with the number (P = 0.015) and density (P = 0.016) of subpleural small vessels and BV5/TBV ratio (P = 0.004). For instance, the mean values of the subpleural small vessel numbers were 39.5, 29.0, 23.0, and 22.0 vessel counts/dL lung for WHO functional classes I, II, III, and IV, respectively. Furthermore, decreased 6MWD (< 350 m) was associated with decreased numbers (P = 0.008), area (P = 0.003), and density (P = 0.023) of measured subpleural small vessels and BV5/TBV ratio (P = 0.013). For instance, the mean values of the subpleural small vessel numbers were 41.8, 30.6, and 22.7 vessel counts/dL lung for patients with 6MWD > 500 m, 350–500 m, and < 350 m, respectively.

DISCUSSION

To the best of our knowledge, this is the largest study that simultaneously investigated the radiographic pulmonary vasculature measures, RHC hemodynamic parameters, and clinical outcomes and found that the pulmonary vasculature measures from non-invasive non-contrast CT scans (i.e., the number, area, and density of subpleural small vessels and BV5/TBV ratio) provided a quantitative assessment of the pulmonary vasculature changes in response to treatment and correlated with the hemodynamic parameters from invasive RHC and clinical outcomes in patients with CTEPH. Importantly, CT-based pulmonary vasculature measurements provide image biomarkers that could substitute invasive catheter-based CTEPH parameters, which can be used to evaluate treatment response and disease severity.

Radiographic pulmonary vasculature measures are important in predicting lung health and patient survival [22,25]. Modern CT-based measures are more detailed in assessing the pulmonary vasculature distribution, particularly the peripheral pulmonary perfusion than prior CT-based measurements reflecting the diameters of the cardiac ventricle, cardiac atrium, ascending aorta, and

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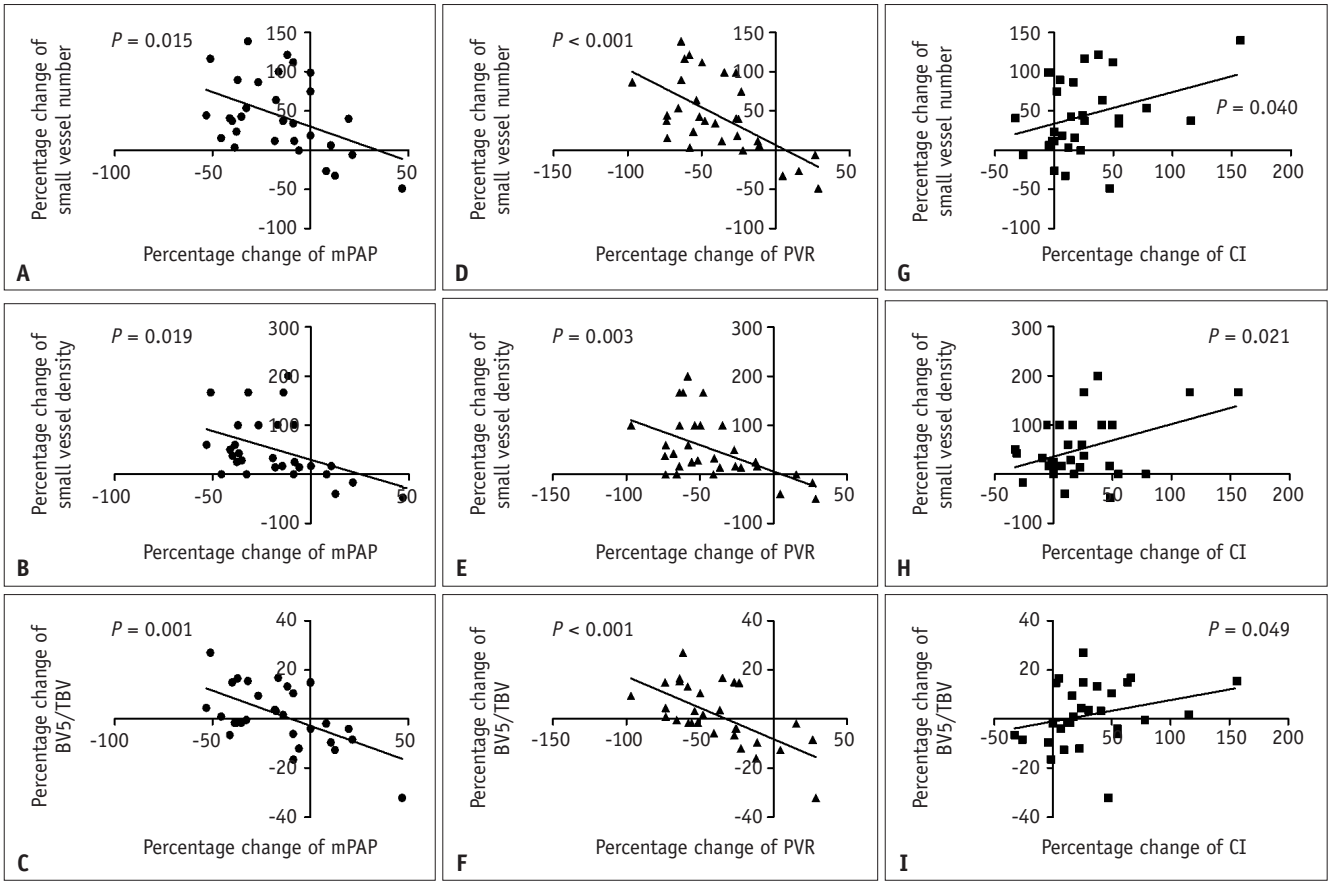

Fig. 4. Correlation between percent-changes (pre- to post-treatment) in the radiographic pulmonary vasculature and hemodynamic parameters. Scatterplots demonstrating the relationships between post-treatment percent change in the radiographic pulmonary vasculature and hemodynamic parameters are shown. **A-C:** Mean pulmonary artery pressure (mPAP). **D-F:** Pulmonary vascular resistance (PVR). **G-I:** Cardiac index (CI). Percent change (% change) is the change in the values (post-treatment value minus pre-treatment value) divided by the pre-treatment value multiplied by 100. *P*-values are obtained using Pearson's correlation analysis. The percentage reduction in mPAP and PVR is significantly correlated with the percentage increment in the measured number and density of subpleural small vessels and the ratio of blood volume in vessels with cross-sectional area ≤ 5 mm^2 (BV5) to the total blood volume (TBV). Additionally, the percentage increment in the CI is significantly correlated with the percentage increment values in the above-mentioned radiographic pulmonary vasculature measurements.

pulmonary arteries [17]. In 2016, Rahaghi et al. [16] demonstrated altered pulmonary vascular morphology using quantitative CT analysis in patients with CTEPH. Compared with individuals without pulmonary vascular disease, BV5 density in patients with CTEPH was correlated with CI and stroke volume. These observations are in line with our study, which showed that the density of subpleural small vessels and BV5/TBV were significantly correlated with PVR and CI. In contrast, BV > 10/TBV, as a negative control, showed no obvious association with hemodynamic parameters.

The present study evaluated the usefulness of CT-based pulmonary vasculature measures in patients who underwent medical treatment with riociguat, whereas previous studies applied CT-based pulmonary vasculature measures in patients who underwent BPA and demonstrated that CT-derived pulmonary blood volume and vessel densities were indicators of the treatment effect [18,26]. In the present study, while the absolute CT-driven vascular parameters correlated well with the PVR and CI but not the absolute values of the mPAP, the relative change in the mentioned parameters showed good correlations. Increased mPAP is related to multiple modalities, including pulmonary rarefaction, vasoconstriction, vascular remodeling, and intravascular plexiform or thrombotic lesions at the level of the small pulmonary arteries [27], which may not directly reflect the absolute pulmonary vascular volume or density but can be considered an indicator of disease severity [28]. Furthermore, we found that peripheral small vessels were a major component of improvements in vessel density and blood volume. Most importantly, the increase in the density

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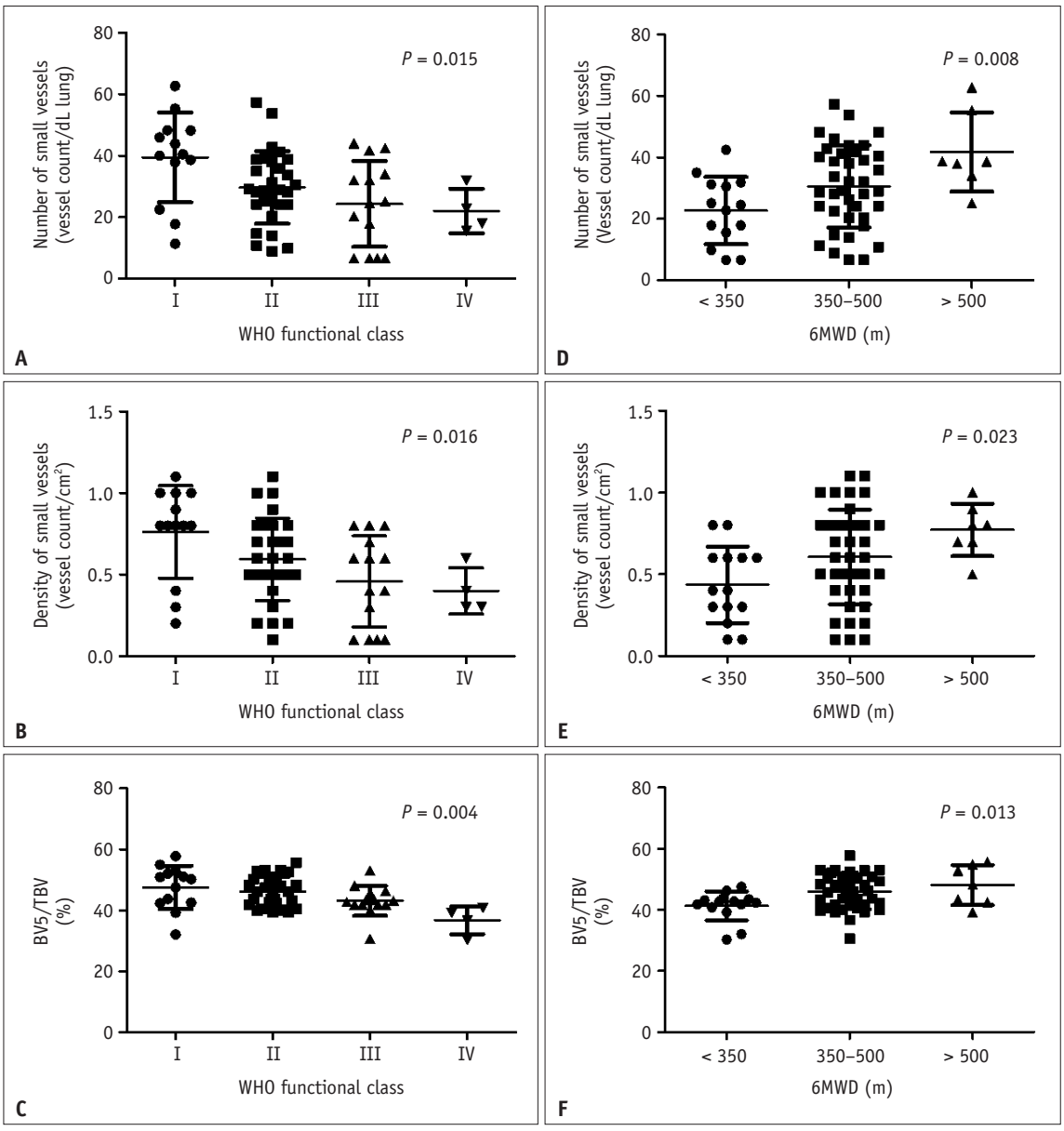

Fig. 5. Association between the radiographic pulmonary vasculature and clinical parameters. Comparisons of the radiographic pulmonary vasculature between the clinical parameters of the World Health Organization (WHO) functional class (I–IV) **(A-C)** and 6-minute walking distance (6MWD, < 350 m, 350–500 m, and > 500 m) **(D-F)**. P-values are obtained using a one-way analysis of variance. The WHO functional classes I–IV are inversely associated with radiographic pulmonary vasculatures, whereas 6MWD is positively associated with radiographic pulmonary vasculature. BV5 = blood volume in vessels with cross-sectional area ≤ 5 mm^2, TBV = total blood volume

of subpleural small vessels and BV5/TBV correlated well with improvements in hemodynamic and clinical parameters. These results establish the role of peripheral perfusion and BV5/TBV as imaging biomarkers for evaluating patients with CTEPH and as potential predictors of treatment response.

Pulmonary vasculature analysis was based on images obtained from non-contrast CT; accordingly, the measured vasculature could have included some occluded vessels without perfusion. Non-contrast CT cannot differentiate intravascular thromboembolic lesions by direct vascular signs such as filling defects; therefore, the quantification of the subpleural pulmonary vasculature in the present study may include both non-obstructive small vessels with adequate perfusion and thrombosed small arterioles without perfusion. Nevertheless, objective changes in the number, area, diameter, and volume of subpleural pulmonary vessels may still provide information on pulmonary circulation based on a published study establishing the histology-

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radiology correlation of pulmonary microvasculature [29]. Contrast-enhanced CT, in addition to dual-energy CT angiography, provides pulmonary perfusion imaging, evaluates thrombi in the pulmonary vasculature, and may be considered as an additional tool for lung perfusion analysis of the lung microcirculation [30]; however, inter-subject variability of contrast injection volume, enhancement intensity, and post-contrast timing of scanning all make image standardization challenging for unbiased vasculature analysis. Thus, pulmonary vasculature analysis on dual-energy CT angiography is not currently performed, and supportive investigation is warranted to overcome these obstacles.

Echocardiography, another non-invasive tool, provides an indirect parameter to calculate the mPAP for the diagnosis of pulmonary hypertension (for instance, the tricuspid regurgitation velocity [TRV]); however, poor quality Doppler signals or severe free-flowing tricuspid regurgitation could result in inaccurate estimation of the peak TRV signal and inaccurate calculation of the mPAP values [31]. Thus, when screening patients with suspected pulmonary hypertension, information obtained from echocardiography can only grade the probability of pulmonary hypertension instead of confirmation of the diagnosis [32].

The present study had some limitations. First, post-treatment examinations, including RHC, non-contrast CT, and clinical parameters, were not performed on the same day but over a span of 1 week; the median of 3 days between CT and RHC examinations suggests that the influence of the time difference was relatively minor. Second, due to the retrospective nature of the study, the timing of post-treatment evaluation performed in the present study varied and may not match that of the best clinical treatment response. However, the inclusion criteria limited the enrolled patients with CTEPH to those who received at least 16 weeks of riociguat treatment, thus reducing this concern. Third, the correlation coefficient r between the absolute values of radiographic pulmonary vasculature measures and hemodynamic parameters ranged from 0.2–0.5, indicating a weak-to-moderate correlation [23], which may be due to the limited number of patients or nonlinear relationship between the variables, considering that the calculation of PVR or CI involves multiple variables, including CO, body surface area, pulmonary arteriole wedge pressure, and mPAP. Regardless of the weak-to-moderate correlation, the existence of statistical significance may still provide evidence for the application of radiographic pulmonary vasculature measures in patients with CTEPH. Fourth, for the chronological comparison of pulmonary vasculature analysis in the same patient, conditions involving postoperative pulmonary infection, pleural effusion, or underlying chronic obstructive pulmonary disease, bronchiectasis, or asthma [33-35], should be considered, as these lead to major changes in pulmonary vasculature structures and may introduce bias in the interpretation of pulmonary vasculature changes after CTEPH treatment.

In conclusion, CT-based pulmonary vasculature measures provided a quantitative assessment of pulmonary vasculature changes in response to treatment and correlated with invasive pulmonary hemodynamic and clinical parameters in patients with CTEPH. Thus, they may provide information for the evaluation of disease severity and treatment efficacy. Overall, non-contrast CT has the advantages of non-invasiveness and avoidance of contrast media allergy and nephropathy, benefiting patients with impaired renal function or a history of allergy. Non-enhanced CT can provide image biomarkers that can substitute for invasive catheter-based CTEPH parameters. Further large-scale prospective studies investigating RHC and CT vasculature analysis parameters are needed to validate our findings and enable pulmonary vasculature measures as biomarkers for diagnostic, phenotyping, and prognostic purposes in patients with CTEPH.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2022.0675.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due privacy and ethical concerns, but are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

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