OPEN

Assessment of Severity in Chronic Thromboembolic Pulmonary Hypertension by Quantitative Parameters of Dual-Energy Computed Tomography

Yoshinori Tsutsumi, RT,† Shingo Iwano, MD, PhD,‡ Naoki Okumura, MD, PhD,§ Shiro Adachi, MD, PhD,§ Shinji Abe, RT, PhD,* Takahisa Kondo, MD, PhD,§ Katsuhiko Kato, MD, PhD,† and Shinji Naganawa, MD, PhD‡*

Objective: The objective of this study was to assess the correlation between dual-energy computed tomography quantitative parameters and hemodynamics in patients with chronic thromboembolic pulmonary hypertension.

Methods: Dual-energy computed tomography of 52 chronic thromboembolic pulmonary hypertension patients were evaluated retrospectively. The mean lung perfused blood volume (lung PBV) and the mean pulmonary artery (PA) enhancement measured at pulmonary parenchymal phase were compared with the hemodynamics by Spearman rank correlation coefficient (r_s) and receiver operating characteristic analysis.

Results: Lung PBV was correlated with mean pulmonary arterial pressure ($r_s = 0.47$, $P < 0.001$). Pulmonary artery enhancement was correlated with cardiac index ($r_s = -0.49$, $P < 0.001$) and pulmonary vascular resistance ($r_s = 0.48$, $P < 0.001$). The areas under the curves were 0.86 for lung PBV to predict mean pulmonary arterial pressure of >50 mm Hg and 0.86 for PA enhancement to predict pulmonary vascular resistance of >1000 dyne·s/cm^5.

Conclusions: Lung PBV and PA enhancement could be indicators of hemodynamics.

Key Words: Dual-energy computed tomography, chronic thromboembolic pulmonary hypertension, hemodynamics

(*J Comput Assist Tomogr* 2020;44: 578–585)

Chronic thromboembolic pulmonary hypertension (CTEPH) is a specific type of pulmonary hypertension (PH) caused by obstructive vascular remodeling, which lead to increase pulmonary artery (PA) pressure and right heart failure.[1,2] The development of CTEPH has been suggested to be associated with acute pulmonary embolism.[1–3] The incidence of CTEPH within 2 years after acute symptomatic pulmonary embolism has been reported to range from 0.1% to 9.1%.[3]

Chronic thromboembolic pulmonary hypertension is defined as the presence of multiple chronic organized occlusive thromboembolisms in the pulmonary arteries, which accompany PH with a mean pulmonary arterial pressure (mPAP) of 25 mm Hg or more and a pulmonary arterial wedge pressure of 15 mm Hg or less.[1,2] Diagnosis of CTEPH is confirmed by pulmonary arteriography or contrast-enhanced computed tomography (CT) based on the findings of mismatched lung perfusion using pulmonary ventilation/perfusion scintigraphy.[1,2]

The contrast-enhanced CT findings of CTEPH in the PA are a complete obstruction or partial filling defects such as vessel narrowing, intimal irregularities, and bands and webs caused by chronic organized blood clots.[2,4,5] In addition, the dilatation of the main PA diameter is known to be associated with PH.[6–10] The diameter ratio of the main PA to the ascending aorta (rPA) measured on a CT image is widely used as a noninvasive diagnostic method for PH.[8–10] The rPA is also known to correlate with the mPAP.[8,10] Recently, dual-energy computed tomography (DE-CT) has enabled us to analyze lung perfused blood volume (lung PBV) and is able to generate an iodine map image similar to that obtained by pulmonary perfusion scintigraphy. Its diagnostic utility for the evaluation of pulmonary perfusion in CTEPH has been reported to be equivalent to pulmonary perfusion scintigraphy.[11–13]

Right heart catheterization (RHC) is invasive but essential to evaluate the hemodynamics of CTEPH. The mPAP and pulmonary vascular resistance (PVR) obtained by RHC is one of the prognostic factors in CTEPH patients.[14–16] Therefore, it may be useful to identify high-risk patients by noninvasive CT examination. A few studies reported that quantitative or visual assessment of lung PBV significantly correlated with clinical parameters such as mPAP, PVR, or mosaic attenuation pattern in CTEPH patients.[17–19] It should be noted however that a correlation between quantitative evaluation using DE-CT and hemodynamic severity has not been demonstrated. Therefore, the purpose of this study was to consider whether contrast-enhanced DE-CT could be used to assess the severity of CTEPH.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the institutional review board of Nagoya University Hospital (approval number 2017-0291) with waivers of informed consent from all participants. From April 2014 to July 2017, 58 consecutive patients who underwent DE-CT for the detailed examination or follow-up of CTEPH were treated at our institution. The diagnosis of CTEPH was confirmed by ventilation/perfusion scintigraphy, RHC, and pulmonary arteriography. Patients who underwent pulmonary endarterectomy or balloon pulmonary angioplasty were not included in this study, because of the various time intervals between CT and RHC that were performed before or after treatments. If multiple examinations were performed on a patient during the study period, only the first DE-CT examination was analyzed. This is because multiple examinations become a confounding factor to evaluate CT and RHC parameters. Three patients were excluded because of the presence of pulmonary disease (interstitial pneumonia, atypical mycobacterial disease, or emphysema). One patient was excluded because

From the *Department of Radiological Technology, Nagoya University Hospital; Departments of †Radiological and Medical Laboratory Sciences, ‡Radiology, and §Advanced Medicine in Cardiopulmonary Disease, Nagoya University Graduate School of Medicine, Aichi, Japan.

Received for publication December 23, 2019; accepted April 24, 2020.

Correspondence to: Katsuhiko Kato, MD, PhD, Department of Radiological and Medical Laboratory Sciences, Nagoya University Graduate School of Medicine, 1-20, Daikominami 1-chome, Higashi-ku, Nagoya 461-8673, Japan (e-mail: KatoKt@met.nagoya-u.ac.jp).

The authors declare no conflict of interest.

DOI: 10.1097/RCT.0000000000001052

the cardiac output (CO) was potentially reduced by a large pericardial effusion. Two patients who were previously diagnosed with CTEPH but did not meet the PH criteria during follow-up were also excluded. The remaining 52 patients (20 male and 32 female; median age, 65.5 years) were evaluated retrospectively.

Dual-energy computed tomography and RHC were performed within 6 months (median, 29.5 days; range, 15–160 days) of each other. There was one case where the patient started anticoagulation therapy between DE-CT and RHC.

CT Acquisition Protocol

Data acquisition was performed using a dual-source CT (Somatom Definition Flash; Siemens Healthcare, Forchheim, Germany) with the following CT scan protocol: tube voltage, 80 kV and 140 kV (Sn); collimation, 64 × 0.6 mm; gantry rotation speed, 0.33 seconds; helical pitch, 0.65; caudocranial scan direction; and automatic tube current modulation (CARE dose 4D; Siemens Healthcare, Forchheim, Germany). The radiation doses (CT dose index and dose-length product) were recorded for each examination. Contrast medium was administered into the right antecubital vein according to the following criteria based on weight: less than 40 kg, 80 mL at a rate of 3.3 mL/s, 300 mg iodine/mL iopromide (Proscope 300; Alfresa Pharma, Osaka, Japan); 40 to 55 kg, 96 mL at a rate of 4 mL/sec, 320 mg iodine/mL ioversol (Optiray 320; Guerbet Japan, Tokyo, Japan); and 55 kg or more, 96 mL at a rate of 4 mL/s, 370 mg iodine/mL iopamidol (Iopamiron 370; Bayer Healthcare, Tokyo, Japan), followed by 20 mL saline at 4 mL/s using a dual-head power injector (Dual Shot GX7; Nemoto Kyorindo, Tokyo, Japan). Scans were started using a bolus-tracking method 6 seconds after a threshold of 80 Hounsfield units (HU) in the ascending aorta was attained. We defined this timing as the pulmonary parenchymal phase, which provided adequate contrast enhancement from the PA to the pulmonary vein and allowed visualization of the peripheral PA. In our institution, this scan phase was used to evaluate CTEPH. Both 80 kV and 140 kV (Sn) images were reconstructed with a medium soft convolution kernel (D30f) at 1-mm slice thickness and 1-mm increments.

Image Analysis

The iodine-enhanced images called lung PBV were generated by the 80 kV and 140 kV (Sn) data sets from the application based on a 3-material decomposition method. The lung PBV values were measured using software supplied with DE-CT system (syngo CT Workplace, lung PBV; Siemens Healthcare, Forchheim, Germany). The lung PBV value was defined with the following parameters: Hounsfield scale, air of −1000 HU on both 80 kV and 140 kV (Sn) data sets, soft tissue of 60 HU on 80 kV and 55 HU on 140 kV (Sn); contrast medium ratio, 3.01; analysis range, −930 HU to −600 HU; and smoothing process range, 6. Bilateral lungs were divided into 3 zones (upper, middle, and lower), and the mean lung PBV values were calculated, except in the right upper zone to avoid artifacts caused by the presence of the iodine contrast agent in the superior vena cava and the subclavian vein (Figs. 1A, B). Whole lung PBV values were also calculated. The mean PA enhancements were measured by placing a circular region of interest (ROI) in the pulmonary trunk (Fig. 1C) to evaluate right heart function. The diameter of the PA and the ascending aorta was measured at the level of the bifurcation of the pulmonary trunk to calculate the diameter

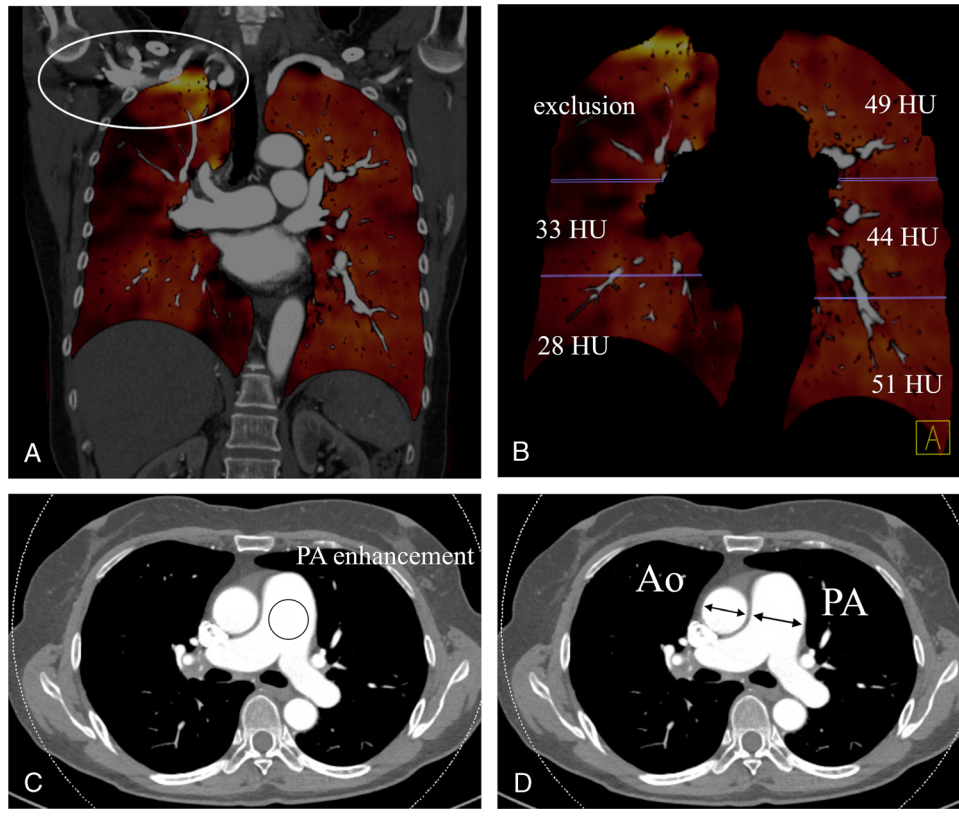

FIGURE 1. The DE-CT images with chronic thromboembolic PH. Lung PBV image shows the artifacts caused by the presence of iodine contrast medium in the subclavian vein (A). Bilateral lungs were divided into 3 zones, and the mean lung PBV values were calculated except the right upper zone (B). The mean PA enhancements (C) and the diameter ratio of the PA to the ascending aorta (Ao) (D) were measured at the level of bifurcation of the main PA.

TABLE 1. Patient Characteristics and Measurements

		Body Weight (Contrast Medium)			
	Number, Median (Range)	<40 kg (300 mgI)	40–55 kg (320 mgI)	≥55 kg (370 mgI)	*P*
Patients, n	52	2	17	33	NA
Male/female, n	20/32	0/2	5/12	15/18	0.249*
Age, y	65.5 (21–80)	69 (69)	70 (52–78)	60 (21–80)	0.273
BMI, kg/m^2	23.8 (16.1–42.1)	17.8 (16.1–19.4)	20.4 (16.2–25.5)	25.4 (18.7–42.1)	<0.001
WHO-FC (II, III, IV)	21, 28, 3	0, 2, 0	7, 10, 0	14, 16, 3	0.411*
Type (central/distal)	28/24	2/0	9/8	17/16	0.924*
mPAP, mm Hg	42.5 (23–66)	38 (37–39)	40 (23–66)	43 (25–62)	0.954
sRVP, mm Hg	73.5 (27–129)	70.5 (69–72)	78 (42–129)	73 (27–95)	0.644
RAP, mm Hg	6 (1–16)	3.5 (2–5)	5 (1–12)	7 (1–16)	0.111
CO, L/min	4.31 (2.48–9.62)	3.90 (3.05–4.74)	4.01 (2.48–9.62)	4.32 (3.01–7.22)	0.557
Cardiac index, L/min/m^2	2.55 (1.61–5.80)	3.00 (2.31–3.68)	2.68 (1.61–5.80)	2.43 (1.89–3.69)	0.222
PVR, dyne·s/cm^5	576 (166–1676)	667 (573–760)	581 (166–1676)	559 (166–1115)	0.679
Lung PBV, HU	36.3 (24.0–55.2)	29.2 (26.8–31.6)	35.8 (30.4–41.8)	38.6 (24.0–55.2)	0.459
W-lung PBV, HU	36 (24–55)	27.5 (24–31)	35 (30–40)	39 (25–55)	0.091
PA enhancement, HU	554 (340–898)	527 (488–565)	593 (350–898)	545 (340–837)	0.538
Ao enhancement, HU	443 (281–621)	378 (364–393)	452 (281–607)	442 (289–621)	0.624
PA-Ao enhancement, HU	116 (−18.3–366)	148 (94.9–200)	122 (−18.3 to 291)	114 (−2 to 366)	0.545
Scan timing, s	24.0 (16.0–35.0)	22.0 (16.0–28.0)	23.0 (18.2–30.3)	24.0 (19.0–35.0)	0.132
rPA	1.09 (0.73–2.00)	1.10 (1.03–1.17)	1.05 (0.73–1.53)	1.10 (0.82–2.00)	0.229
CTDI vol, mGy	10.8 (6.50–16.2)	7.86 (7.68–8.03)	9.29 (6.50–11.4)	11.7 (7.67–16.2)	<0.001
DLP, mGy·cm	390 (220–684)	270 (263–276)	333 (220–401)	427 (283–684)	<0.001

*χ^2 test.

Ao indicates ascending aorta; BMI, body mass index; CTDI vol, CT dose index volume; DLP, dose length product; mgI, mg iodine/mL; NA, not applicable; WHO-FC, World Health Organization functional classification; w-lung, whole lung.

ratio (Fig. 1D).[8–10] The scan timing was calculated from the time difference between contrast medium injection start time and the image acquisition start time.

Assessment of Hemodynamic Data

We reviewed the following RHC results: right arterial pressure (RAP), systolic ventricular pressure (sRVP), mPAP, CO,

TABLE 2. Correlation Between DE-CT Parameters and Body Weight With Hemodynamics

Parameters	Lung PBV	W-Lung PBV	PA Enhancement	rPA	Body Weight
Hemodynamics	r_s (95% CI) *P* Value	r_s (95% CI) *P* Value	r_s (95% CI) *P* Value	r_s (95% CI) *P* Value	r_s (95% CI) *P* Value
mPAP	0.47 (0.23–0.66) <0.001	0.35 (0.09–0.57) 0.010	0.20 (−0.07 to 0.45) 0.149	0.07 (−0.21 to 0.34) 0.612	−0.13 (−0.38 to 0.15) 0.377
sRVP	0.44 (0.19–0.63) 0.001	0.3 (0.03–0.53) 0.033	0.14 (−0.13 to 0.40) 0.306	0.008 (−0.27 to 0.28) 0.955	−0.22 (−0.47 to 0.05) 0.110
RAP	0.32 (0.05–0.54) 0.022	0.34 (0.08–0.56) 0.013	−0.09 (−0.35 to 0.19) 0.533	0.17 (−0.11 to 0.42) 0.229	0.42 (0.16–0.62) 0.002
CO	−0.02 (−0.29 to 0.25) 0.873	−0.03 (−0.30 to 0.24) 0.812	−0.59 (−0.74 to −0.37) <0.001	0.08 (−0.20 to 0.34) 0.596	0.37 (0.11–0.58) 0.007
Cardiac index	−0.03 (−0.30 to 0.24) 0.824	−0.14 (−0.40 to 0.14) 0.325	−0.49 (−0.68 to −0.25) <0.001	0.01 (−0.26 to 0.28) 0.939	−0.09 (−0.36 to 0.19) 0.516
PVR	0.31 (0.04–0.53) 0.027	0.21 (−0.07 to 0.46) 0.132	0.48 (0.23–0.66) <0.001	−0.06 (−0.33 to −0.22) 0.679	−0.35 (−0.57 to −0.08) 0.012

W-lung indicates whole lung.

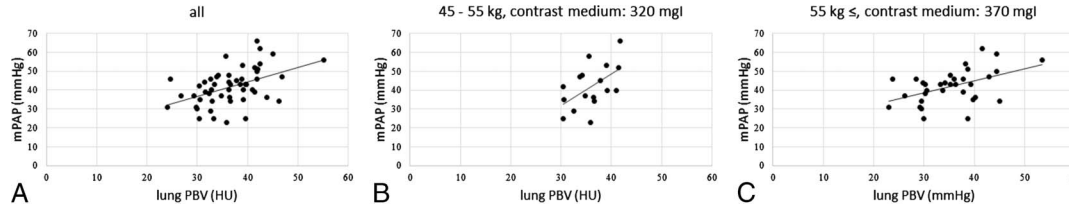

FIGURE 2. Correlation between the mean lung PBV and mPAP in different injection protocols based on body weight. The mean lung PBV was significantly correlated with mPAP in all patients (A) or the group of weight 55 kg or more (C), but not statistically significant in the group of weight 45 to 55 kg (B).

cardiac index, and PVR. Cardiac output was determined by the thermodilution method, and cardiac index was defined as the CO divided by the body surface area. Pulmonary vascular resistance (dyne·s/cm^5) was calculated as follows: (mPAP − pulmonary artery wedge pressure)/CO × 80.

Statistical Analysis

The Mann-Whitney *U* test was used for comparing the patient characteristics or measurements. The χ^2 test was used categorical variables. Spearman rank correlation coefficient (r_s) with 95% confidence interval (CI) and *P* value was used to compare DE-CT quantitative parameters and body weight with the hemodynamics values measured by RHC. The correlation between scan timing and DE-CT parameters was also evaluated, because our image acquisition protocol might have a significant effect on the DE-CT parameters. Furthermore, contrast medium injection protocols were divided based on patient weight, and the correlation coefficient between lung PBV and hemodynamics was analyzed for each group. The group weighing less than 40 kg was excluded because there were only 2 patients. Multivariate linear regression analysis was performed whether DE-CT parameters were independent predictor of hemodynamics in which variables were significantly correlated with hemodynamics in bivariate analysis. In this analysis, body weight was included to the analysis factors to evaluate the effect of the scan protocol.

The data of mPAP and PVR were dichotomized according to the following criteria: mPAP >50 mm Hg and PVR > 1000 dyne·s/cm^5. The reference values of these prognostic and severity factors were determined based on previous studies.[14–16] Areas under the curves (AUCs) for receiver operating characteristic (ROC) analysis were performed to evaluate the ability of mPAP and PVR to perform as prognostic criteria. The Youden index method was used to determine the cutoff value and calculate the sensitivity and the specificity.

Analyses were performed using Microsoft Excel 2013 and the statistical software BellCurve for Excel (version 2.15; Social Survey Research Information Co, Ltd, Tokyo, Japan) and R for windows (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria). A *P* value of <0.05 was considered to indicate statistical significance.

RESULTS

Patient characteristics, measurements of RHC, and DE-CT examination are shown in Table 1. An mPAP greater than 50 mm Hg was observed in 9 examinations, and a PVR greater than 1000 dyne·s/cm^5 was shown in 7 examinations. These patients were considered to have severe CTEPH.

The correlation between DE-CT parameters and body weight with RHC hemodynamics is shown in Table 2. The mean lung PBV was significantly correlated with mPAP (r_s = 0.47; 95% CI, 0.23–0.66; *P* < 0.001) (Fig. 2A), sRVP (r_s = 0.44; 95% CI, 0.19–0.63; *P* = 0.001), RAP (r_s = 0.32; 95% CI, 0.05–0.54; *P* = 0.022), and PVR (r_s = 0.31; 95% CI, 0.04–0.53; *P* = 0.027). There was no significant correlation between lung PBV and CO or cardiac index. Whole lung PBV was correlated with mPAP (r_s = 0.35; 95% CI, 0.09–0.57; *P* = 0.010); however, the correlation coefficient was lower than that for lung PBV calculated while excluding the right upper zone. Pulmonary artery enhancement was negatively and significantly correlated with CO (r_s = −0.59; 95% CI, −0.74 to −0.37; *P* < 0.001) and cardiac index (r_s = −0.49; 95% CI, −0.68 to −0.25; *P* < 0.001), and positively and significantly correlated with PVR (r_s = 0.48; 95% CI, 0.23–0.66; *P* < 0.001). The rPA was not correlated with RHC hemodynamic parameters. The body weight was positively and significantly correlated with RAP (r_s = 0.42; 95% CI, 0.16–0.62; *P* = 0.002) and CO (r_s = 0.37; 95% CI, 0.11–0.58; *P* = 0.007), and negatively and significantly correlated with PVR (r_s = −0.35; 95% CI, −0.57 to −0.08; *P* = 0.012). On the other hand, the body weight was not significantly correlated with mPAP, sRVP, and cardiac index. The multivariate linear regression analysis indicated that both the lung PBV and the body weight were significantly correlated with RAP (standardized partial regression coefficient [β] = 0.27, *P* = 0.033, and β = 0.39, *P* < 0.001, respectively; Table 3). The PA enhancement was significantly correlated with CO (β = −0.56, *P* < 0.001), whereas the body weight was not significantly correlated with CO (β = 0.18, *P* = 0.121). The PA enhancement was significantly correlated with PVR (β = 0.39, *P* = 0.121). The body weight was

TABLE 3. Multivariate Linear Regression Analysis for Predicting Hemodynamics Based on DE-CT Parameters and Body Weight

Variable	Lung PBV			PA Enhancement			Body Weight		
Hemodynamics	***B* (95% CI)**	**β**	***P***	***B* (95% CI)**	**β**	***P***	***B* (95% CI)**	**β**	***P***
RAP	0.16 (0.01–0.30)	0.27	0.033	NA	NA	NA	0.09 (0.03–0.16)	0.39	<0.001
CO	NA	NA	NA	−0.006 (−0.008 to −0.003)	−0.56	<0.001	0.017 (−0.005 to 0.038)	0.18	0.121
PVR	9.07 (−3.58 to 21.7)	0.18	0.156	0.94 (0.31–1.56)	0.39	0.004	−6.53 (−11.9 to −1.14)	−0.30	0.019

B indicates partial regression coefficient; NA, not applicable; β, standardized partial regression coefficient.

TABLE 4. Correlation Between Lung PBV and Hemodynamics in Different Injection Protocol Based on Body Weight

Body Weight	40–55 kg (320 mgI)		≥55 kg (370 mgI)	
Hemodynamics	**r_s (95% CI)**	***P***	**r_s (95% CI)**	***P***
mPAP	0.45 (−0.04 to 0.76)	0.071	0.48 (0.16–0.70)	0.005
sRVP	0.46 (−0.03 to 0.77)	0.064	0.49 (0.17–0.71)	0.004
RAP	0.20 (−0.31 to 0.62)	0.443	0.26 (−0.09 to 0.55)	0.143
CO	−0.46 (−0.77 to 0.03)	0.062	0.07 (−0.28 to 0.41)	0.689
Cardiac index	−0.37 (−0.72 to 0.14)	0.146	0.16 (−0.19 to 0.47)	0.369
PVR	0.59 (0.15–0.83)	0.013	0.28 (−0.07 to 0.57)	0.117

also negatively and significantly correlated with PVR ($\beta = -0.30$, $P = 0.019$). However, lung PBV was not significantly correlated with PVR ($\beta = 0.18$, $P = 0.156$).

The scan timing was not significantly correlated with lung PBV ($r_s = 0.02$; 95% CI, −0.26 to 0.29; $P = 0.912$), whole lung PBV ($r_s = 0.04$; 95% CI, −0.23 to 0.31; $P = 0.760$), PA enhancement ($r_s = 0.11$; 95% CI, −0.17 to 0.37; $P = 0.455$), and rPA ($r_s = 0.24$; 95% CI, −0.03 to 0.48; $P = 0.081$).

Table 4 shows the correlation between lung PBV and hemodynamics in different injection protocols based on body weight. In the group weighing 45 to 55 kg, the mean lung PBV was not significantly correlated with mPAP ($r_s = 0.45$; 95% CI, −0.04 to 0.76; $P = 0.071$) (Fig. 2B), CO ($r_s = -0.46$; 95% CI, −0.77 to 0.03; $P = 0.062$), or cardiac index ($r_s = -0.37$; 95% CI, −0.72 to 0.14; $P = 0.146$). There was, however, a significant correlation between lung PBV and PVR ($r_s = 0.59$; 95% CI, 0.15–0.83; $P = 0.013$). Conversely, in the group weighing 55 kg or more, lung PBV was correlated with mPAP ($r_s = 0.48$; 95% CI, 0.16–0.70; $P = 0.005$) (Fig. 2c), but not with CO, cardiac index, and PVR.

Figure 3 shows the ROCs curves for identifying the criteria of prognostic and severity factors for CTEPH. The optimal cutoff values were decided by the Youden index (Table 5). Figure 4 shows representative lung PBV images in case of different severity. At the criterion of mPAP greater than 50 mm Hg, the AUC values were lung PBV (0.86; 95% CI, 0.74–0.98; $P < 0.001$), PA enhancement (0.69; 95% CI, 0.50–0.89; $P = 0.049$), and rPA (0.67; 95% CI, 0.49–0.84; $P = 0.060$), respectively. The optimal cutoff value, sensitivity, and specificity of lung PBV were 41.4 HU, 0.78 and 0.86, respectively. At the criterion of PVR greater than 1000 dyne·s/cm^5, the AUC values were significant for PA enhancement (0.80; 95% CI, 0.59–1.00; $P = 0.0045$), but not for lung PBV (0.67; 95% CI, 0.42–0.92; $P = 0.18$) and rPA (0.58; 95% CI, 0.32–0.85; $P = 0.539$). The optimal cutoff value, sensitivity, and specificity of PA enhancement were 614 HU, 0.86 and 0.73, respectively.

DISCUSSION

In this study, we examined the correlation between quantitative parameters (lung PBV, PA enhancement, rPA) obtained from DE-CT and hemodynamics in patients with CTEPH. The lung PBV value was positively correlated with mPAP. There have been few studies comparing the quantitative value of lung PBV with the RHC dataset. Meinel et al[17] reported that lung PBV values relative to PA enhancement were correlated negatively with mPAP. This discrepancy may be caused by a difference in the acquired DE-CT scan phase because of the configuration of the bolus-tracking method. In our study, the bolus-tracking ROI was placed on the ascending aorta. Therefore, the DE-CT scan is acquired in the pulmonary parenchymal phase in which the PA and vein are adequately filled with the contrast medium. On the other hand, in the study of Meinel et al,[17] the bolus-tracking ROI was placed on the pulmonary trunk. Hence, their DE-CT scans were performed predominantly in a PA phase which was earlier than ours.

The difference in scan timing due to placing the ROI in the ascending aorta may reflect the degree of pooling in the pulmonary vascular system. Meinel et al[20] also demonstrated that enhancement of the pulmonary trunk and the enhancement difference between the pulmonary trunk and left atrium significantly influenced PBV values. On the other hand, the scan timing in the pulmonary

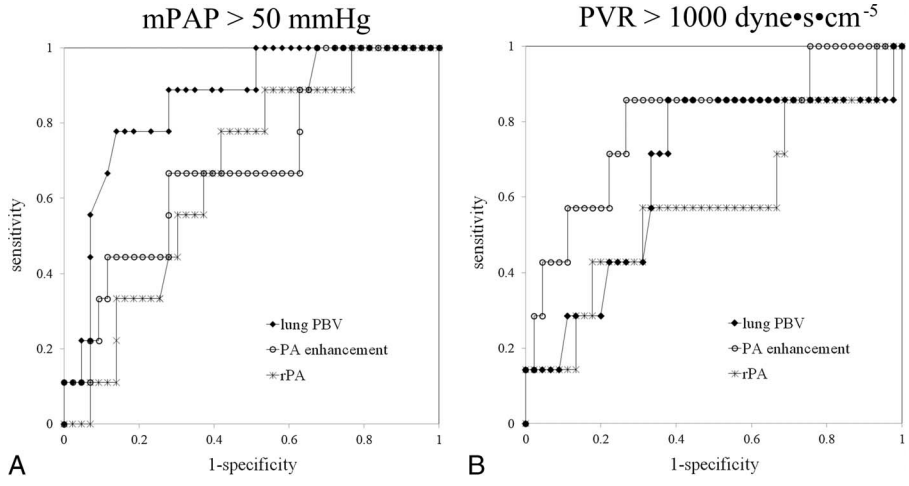

FIGURE 3. The ROCs curves for identifying the criteria of prognostic and severity factors for CTEPH.

TABLE 5. Sensitivities and Specificities Obtained From the Optimal Cutoff Value to Identify the Criterion

A. mPAP >50 mm Hg

DE-CT Parameter	Cutoff Value	Sensitivity (95% CI)	Specificity (95% CI)	Odds Ratio
Lung PBV, HU	41.4	0.78 (0.66–0.89)	0.86 (0.77–0.95)	21.6
PA enhancement, HU	614	0.67 (0.54–0.79)	0.72 (0.60–0.84)	5.17
rPA	1.10	0.78 (0.66–0.89)	0.58 (0.45–0.72)	4.86

B. PVR >1000 dyne·s/cm^5

DE-CT parameter	Cutoff value	Sensitivity (95% CI)	Specificity (95% CI)	Odds Ratio
Lung PBV, HU	37.8	0.86 (0.76–0.95)	0.62 (0.49–0.75)	9.88
PA enhancement, HU	614	0.86 (0.76–0.95)	0.73 (0.61–0.85)	16.5
rPA	1.04	0.57 (0.44–0.71)	0.69 (0.56–0.81)	2.95

parenchymal phase was not correlated with lung PBV. Therefore, the lung PBV can be used to directly assess the contrast effect in pulmonary parenchymal. In CTEPH, obstruction of the peripheral PA causes increases in mPAP and PVR, and decreases in circulation from the PA to venous return of the contrast medium. Consequently, the pooling of contrast medium in pulmonary vessels might result in increased lung PBV values. Lung PBV values evaluated using different scan timings may be important to explain the difference in pulmonary circulation in patients with CTEPH.

We performed subgroup analysis to evaluate the correlation between lung PBV and hemodynamics for each weight-based protocol. Although the results showed no statistical significance, lung PBV tended to be correlated with hemodynamics in the group weighing 45 to 55 kg. On the other hand, lung PBV was correlated with mPAP in the group weighing 55 kg or more. This result might have been affected by sample size, because mPAP was not correlated with body weight. Takagi et al[18] reported that a high-contrast enhancement of the PA was obtained by injecting a contrast medium at a constant rate of iodine per body weight. Adjusting the contrast medium injection method according to weight may be useful in improving the diagnostic accuracy of lung PBV value.

We also confirmed that PA enhancement was negatively correlated with CO and cardiac index, that is, an increase PA enhancement suggested a decrease in CO associated with right heart failure. Pulmonary hypertension in CTEPH is caused by obstruction of pulmonary arteries with an organized thrombus and vascular remodeling of small vessels.[21,22] Progression of PH leads to right heart failure and decreased CO. As a result, the dilution effect of the contrast medium in the pulmonary trunk decreases, and increases the PA enhancement.[23,24]

The prognosis of patients with CTEPH is related to the degree of pulmonary arterial pressure. Untreated CTEPH patients with mPAP above 50 mm Hg have an extremely poor prognosis, in which the 2-year survival rate is approximately 20%.[14] Pulmonary artery endarterectomy is the first option for curative treatment with CTEPH, although several studies reported that a preoperative PVR of more than 1000 dyne·s/cm^5 was a mortality risk factor.[15,16] For this reason, hemodynamic assessment by a noninvasive method is helpful for determining the management of CTEPH. The results of ROC analysis are useful for clinical use of lung PBV and PA enhancement value. Derlin et al[25] reported that quantitative assessment of the extent of the perfusion defect in CTEPH on a lung perfusion SPECT/CT with 99mTc–human serum albumin was able to diagnose mPAP greater than 50 mm Hg with a sensitivity of 88% and specificity of 64%. In this study, the lung PBV value was able to diagnose mPAP greater than 50 mm Hg with a sensitivity of 78% and specificity of 87%.

The rPA value showed no significant correlation with mPAP. It has been reported that rPA correlates with mPAP or strongly suggests PH based on the criteria of an rPA larger than 1.[8–10] Takagi et al[18] report that rPA was positively correlated with mPAP in CTEPH patients; however, approximately 80% of patients were

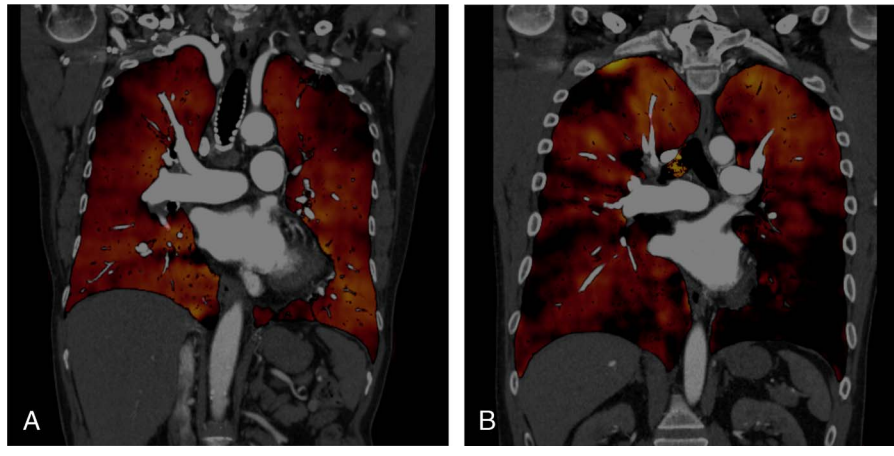

FIGURE 4. Representative lung PBV images with color map. Yellow areas are high lung PBV value, and dark red or black areas are low lung PBV value. In severe case (mPAP, 66 mm Hg; PVR, 996 dyne·s/cm^5), there were high lung PBV value areas in both lungs. The mean lung PBV value was 41.8 HU (A). By contrast, in mild case (mPAP, 25 mm Hg; PVR, 261 dyne·s/cm^5), the mean lung PBV value was 33.2 HU (B).

treated with pulmonary endarterectomy or balloon pulmonary angioplasty (mean rPA, 0.98; mPAP, 24 mm Hg). The difference between the results might be due to the different target patients. Our result is consistent with a study by Corson et al[26] that showed that the correlation coefficient between rPA and mPAP was low or not significant only in the PH patients. Therefore, the rPA value is a morphological parameter caused secondarily by high pulmonary arterial pressure and a quantitative parameter established for diagnosing patients with CTEPH, although the lung PBV value that is the hemodynamic parameter might able to diagnose the severity of CTEPH more accurately.

Our study has several limitations. First, this study was performed retrospectively at a single center in a limited number of patients. Second, the right upper zones of the lungs were excluded from the region of measurement because of the inaccuracy of the lung PBV measurement owing to the artifact caused by the dense contrast medium flowing from the subclavian vein to the superior vena cava. However, if huge defects are in the excluded area, the lung PBV value may be imprecise. Hence, it is necessary to confirm visually that there are no huge defects in the right upper zone on the lung PBV images. Third, the scan timing of DE-CT might affect the quantitative values of DE-CT. Our results include the influence of the systemic collateral supply from bronchial arteries or intercostal arteries.[27–29] When there are widespread defects in lung PBV, regardless of central or distal type of CTEPH, the mean lung PBV value might have been increased by collateral blood supply. It was impossible to assess how much this must have influenced the lung PBV values in this study. If faster DE-CT could scan during both the PA phase and the pulmonary circulation phase, the relationship between the degree of contrast enhancement of the aorta and the potential influence of collateral circulation might be explained. Further study is needed on the degree of influence of the systemic collateral supply on lung PBV.

In conclusion, the lung PBV value was positively correlated with mPAP and PVR, and PA enhancement was negatively correlated with both CO and cardiac index and positively correlated with PVR under the condition that DE-CT scan was performed in the pulmonary parenchymal phase. Furthermore, it was confirmed that the quantitative values of lung PBV and PA enhancement were able to identify severe CTEPH patients specified according to the criterion of mPAP greater than 50 mm Hg or PVR greater than 1000 dyne·s/cm^5. In conclusion, lung PBV and PA enhancement could be indicators of hemodynamics, and noninvasive quantitative DE-CT parameters could therefore guide the CTEPH management.

REFERENCES

1. Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2016;37:67–119.
2. Wilkens H, Konstantinides S, Lang IM, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): updated recommendations from the Cologne Consensus Conference 2018. *Int J Cardiol*. 2018;272:69–78.
3. Lang IM, Pesavento R, Bonderman D, et al. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. *Eur Respir J*. 2013;41:462–468.
4. Castañer E, Gallardo X, Ballesteros E, et al. CT diagnosis of chronic pulmonary thromboembolism. *Radiographics*. 2009;29:31–50; discussion 50–3.
5. Ruggiero A, Screaton NJ. Imaging of acute and chronic thromboembolic disease: state of the art. *Clin Radiol*. 2017;72:375–388.
6. Kuriyama K, Gamsu G, Stem RG, et al. CT-determined pulmonary artery diameters in predicting pulmonary hypertension. *Invest. Radiol*. 1984;19:16–22.
7. Edwards PD, Bull RK, Coulden R. CT measurement of main pulmonary artery diameter. *Br J Radiol*. 1998;71:1018–1020.
8. Ng CS, Wells AU, Padley SP. A CT sign of chronic pulmonary arterial hypertension: the ratio of main pulmonary artery to aortic diameter. *J Thorac Imaging*. 1999;14:270–278.
9. Sanal S, Aronow WS, Ravipati G, et al. Prediction of moderate or severe pulmonary hypertension by main pulmonary artery diameter and main pulmonary artery diameter/ascending aorta diameter in pulmonary embolism. *Cardiol Rev*. 2006;14:213–214.
10. Colin GC, Gerber BL, de Meester de Ravenstein C, et al. Pulmonary hypertension due to left heart disease: diagnostic and prognostic value of CT in chronic systolic heart failure. *Eur Radiol*. 2018;28:4643–4653.
11. Nakazawa T, Watanabe Y, Hori Y, et al. Lung perfused blood volume images with dual-energy computed tomography for chronic thromboembolic pulmonary hypertension: correlation to scintigraphy with single-photon emission computed tomography. *J Comput Assist Tomogr*. 2011;35:590–595.
12. Dournes G, Verdier D, Montaudon M, et al. Dual-energy CT perfusion and angiography in chronic thromboembolic pulmonary hypertension: diagnostic accuracy and concordance with radionuclide scintigraphy. *Eur Radiol*. 2014;24:42–51.
13. Masy M, Giordano J, Petyt G, et al. Dual-energy CT (DECT) lung perfusion in pulmonary hypertension: concordance rate with V/Q scintigraphy in diagnosing chronic thromboembolic pulmonary hypertension (CTEPH). *Eur Radiol*. 2018;28:5100–5110.
14. Riedel M, Stanek V, Widimsky J, et al. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. *Chest*. 1982;81:151–158.
15. Jamieson SW, Kapelanski DP, Sakakibara N, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. *Ann Thorac Surg*. 2003;76:1457–1464.
16. Mayer E, Jenkins D, Lindner J, et al. Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry. *J Thorac Cardiovasc Surg*. 2011;141:702–710.
17. Meinel FG, Graef A, Thierfelder K, et al. Automated quantification of pulmonary perfused blood volume by dual-energy CTPA in chronic thromboembolic pulmonary hypertension. *Rofo*. 2014;186:151–156.
18. Takagi H, Ota H, Sugimura K, et al. Dual-energy CT to estimate clinical severity of chronic thromboembolic pulmonary hypertension: comparison with invasive right heart catheterization. *Eur J Radiol*. 2016;85:1574–1580.
19. Hoey ET, Mirsadraee S, Pepke-Zaba J, et al. Dual-energy CT angiography for assessment of regional pulmonary perfusion in patients with chronic thromboembolic pulmonary hypertension: initial experience. *Am J Roentgenol*. 2011;196:524–532.
20. Meinel FG, Graef A, Sommer WH, et al. Influence of vascular enhancement, age and gender on pulmonary perfused blood volume quantified by dual-energy-CTPA. *Eur J Radiol*. 2013;82:1565–1570.
21. Humbert M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. *Eur Respir Rev*. 2010;19:59–63.
22. Galie N, Kim NH. Pulmonary microvascular disease in chronic thromboembolic pulmonary hypertension. *Proc Am Thorac Soc*. 2006;3:571–576.
23. Fleischmann D. How to design injection protocols for multiple detector-row CT angiography (MDCTA). *Eur. Radiol*. 2005;15:E60–E65.

24. Bae KT, Heiken JP, Brink JA. Aortic and hepatic contrast medium enhancement at CT. Part II. Effect of reduced cardiac output in a porcine model. *Radiology*. 1998;207:657–662.

25. Derlin T, Kelting C, Hueper K, et al. Quantitation of perfused lung volume using hybrid SPECT/CT allows refining the assessment of lung perfusion and estimating disease extent in chronic thromboembolic pulmonary hypertension. *Clin Nucl Med*. 2018;43: e170–e177.

26. Corson N, Armato SG III, Labby ZE, et al. CT-based pulmonary artery measurements for the assessment of pulmonary hypertension. *Acad Radiol*. 2014;21:523–530.

27. Remy-Jardin M, Duhamel A, Deken V, et al. Systemic collateral supply in patients with chronic thromboembolic and primary pulmonary hypertension: assessment with multi-detector row helical CT angiography. *Radiology*. 2005;235:274–281.

28. Hong YJ, Kim JY, Choe KO, et al. Different perfusion pattern between acute and chronic pulmonary thromboembolism: evaluation with two-phase dual-energy perfusion CT. *Am J Roentgenol*. 2013;200:812–817.

29. Koike H, Sueyoshi E, Sakamoto I, et al. Clinical significance of late phase of lung perfusion blood volume (lung perfusion blood volume) quantified by dual-energy computed tomography in patients with pulmonary thromboembolism. *J Thorac Imaging*. 2017;32:43–49.