




ORIGINAL RESEARCH

Abnormal Pulmonary Venous Filling: An Adjunct Feature in the Computed Tomography Pulmonary Angiogram Assessment of Chronic Thromboembolic Pulmonary Hypertension

Deepa Gopalan , MBBS, MSc; Anna Nordgren-Rogberg, MD, PhD; Elizabeth Phuong Vi Le, MA; Holly Pavey, MSc; Jason Tarkin , MD, PhD; Sven Nyrén, MD, PhD; William Auger, MD, PhD; Peter Lindholm , MD, PhD

BACKGROUND: Hypodense filling defects within the pulmonary veins on computed tomography described as pulmonary vein sign (PVS) have been noted in acute pulmonary embolism and shown to be associated with poor prognosis. We evaluated venous flow abnormalities in chronic thromboembolic pulmonary hypertension (CTEPH) to determine its usefulness in the computed tomography assessment of CTEPH.

METHODS AND RESULTS: Blinded retrospective computed tomography analysis of 50 proximal CTEPH cases and 3 control groups—50 acute pulmonary embolism, 50 nonthromboembolic cohort, and 50 pulmonary arterial hypertension. Venous flow reduction was assessed by the following: (1) presence of a filling defect of at least 2 cm in a pulmonary vein draining into the left atrium, and (2) left atrium attenuation (>160 Hounsfield units). PVS was most prevalent in CTEPH. Compared with all controls, sensitivity and specificity of PVS for CTEPH is 78.0% and 85.3% (95% CI, 64.0–88.5 and 78.6–90.6, respectively) versus 34.0% and 70.7% (95% CI, 21.2–48.8 and 62.7–77.8) in acute pulmonary embolism, 8.0% and 62% (95% CI, 2.2–19.2 and 53.7–69.8) in nonthromboembolic and 2.0% and 60% (95% CI, 0.1–10.7 and 51.7–67.9) in pulmonary arterial hypertension. In CTEPH, lobar and segmental arterial occlusive disease was most commonly associated with corresponding absent venous flow. PVS detection was highly reproducible (Kappa=0.96, 95% CI, 0.90–1.01, $P<0.001$).

CONCLUSIONS: PVS is easy to detect with higher sensitivity and specificity in CTEPH compared with acute pulmonary embolism and is not a feature of pulmonary arterial hypertension. Asymmetric enhancement of pulmonary veins may serve as an additional parameter in the computed tomography assessment of CTEPH and can be used to differentiate CTEPH from pulmonary arterial hypertension.

Key Words: chronic thromboembolic disease ■ CTEPH ■ CTPA ■ pulmonary hypertension ■ pulmonary vein sign

Chronic thromboembolic pulmonary hypertension (CTEPH) classified under group 4 pulmonary hypertension (PH) is a complication of pulmonary embolism and a major cause of chronic PH leading to right-sided heart failure and death.¹ Despite considerable progress in the understanding

of its pathophysiology and emergence of a successful multi-therapeutic approach, CTEPH remains an underdiagnosed disease.

A large proportion of patients with suspected CTEPH or breathlessness of unknown cause will undergo a computed tomography pulmonary angiogram

Correspondence to: Deepa Gopalan, MBBS, MSc, Department of Physiology and Pharmacology, Karolinska Institutet, Solnavägen 9 (Biomedicum) 171 65 Solna, Sweden. E-mail: deepa.gopalan@ki.se and deepa.gopalan@btopenworld.com

Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018075>

For Sources of Funding and Disclosures, see page 11.

© 2020 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Absent or heterogenous pulmonary venous flow (pulmonary vein sign), a computed tomography pulmonary angiogram feature of thromboembolic disease, has higher sensitivity in chronic thromboembolic pulmonary hypertension compared with acute pulmonary embolism.
- Pulmonary arterial occlusive disease in the lobar and segmental levels is more commonly associated with absent pulmonary venous flow in the corresponding lobe compared with eccentric nonocclusive or partially occlusive clots, web disease, and stenoses.
- Pulmonary vein sign is not a feature of pulmonary arterial hypertension.

What Are the Clinical Implications?

- Pulmonary vein sign can be used in conjunction with arterial abnormalities in the computed tomography pulmonary angiogram assessment of chronic thromboembolic pulmonary hypertension.
- Asymmetric enhancement of pulmonary veins should prompt a search for chronic thromboembolic pulmonary hypertension, particularly when there is evidence of pulmonary hypertension on a computed tomography pulmonary angiogram.

Nonstandard Abbreviations and Acronyms

CTEPH	chronic thromboembolic pulmonary hypertension
CTPA	computed tomography pulmonary angiogram
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
PV	pulmonary vein
PVS	pulmonary vein sign
VQ	ventilation-perfusion

(CTPA). Unlike acute pulmonary embolism (PE) imaging where CTPA is acknowledged as the reference standard, many institutions prefer ventilation-perfusion (VQ) scintigraphy as the initial test of choice in the investigation of CTEPH. While there are publications advocating the superiority of VQ scintigraphy,^{2,3} CTPA has been shown to be noninferior to VQ in diagnosing CTEPH.⁴ Anecdotally, low-volume nonspecialist centers have been known to miss CTEPH diagnosis if they relied solely on CTPA, while high-volume specialist institutions are more successful in using CTPA both for diagnosis

and operability assessment. This is substantiated by a recent publication demonstrating the inconsistencies in computed tomography (CT) interpretation among radiologists.⁵ Thus, there is a real need to improve the sensitivity of CTEPH diagnosis on CTPA because it will reduce the need for downstream testing.

There is abundant imaging literature describing the pulmonary arterial abnormalities of CTEPH on CTPA since the first angiographic description,⁶ but meager information regarding the macroscopic appearances of the pulmonary veins (PV). The extraparenchymal PV are well delineated on a CTPA. Although variations may occur in the number, diameter, and drainage pattern, the veins typically show uniform density similar to that of the left atrium (LA). Thus far, pulmonary venous flow heterogeneity on CTPA in patients with CTEPH has not been previously documented, although this phenomenon, described as pulmonary vein sign (PVS) or insufficient contrast medium filling, has been noted in patients with acute PE.⁷⁻⁹ Heterogeneous pulmonary venous flow has been postulated to be the result of diminished venous return into an underfilled LA. We performed this observational study to look for either absence of flow or heterogeneous flow with nonuniform contrast medium distribution in 1 or more PV in patients with CTEPH in order to assess its usefulness as an additional parameter in the CTPA assessment of CTEPH.

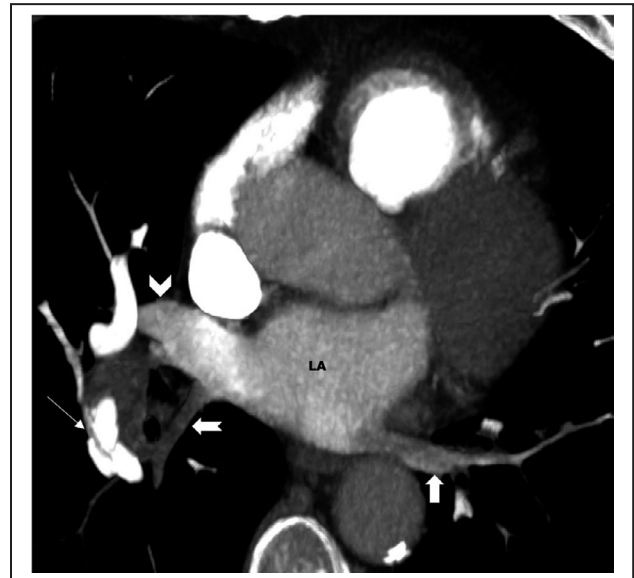


Figure 1. CTPA axial view at the level of the LA in a CTEPH case.

There is normal enhancement (score 1) in the right upper lobe pulmonary vein (chevron), heterogeneous enhancement (score 2) in left lower lobe pulmonary vein (block arrow) and absent flow (score 3) in the right lower lobe pulmonary vein (notched arrow). There is a trifurcation web in the right lower lobe pulmonary artery (thin arrow). CTEPH indicates chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiogram; and LA, left atrium.

METHODS

The authors declare that all supporting data are available within the article (Method S1).

A retrospective case–control review was performed with approval from the local Institutional Review Board. Informed consent from the patients was not required for this study.

Cases

Patients with CTEPH who were referred between 2011 and 2019 for pulmonary endarterectomy to a PH specialist center and who underwent the surgery were included. Fifty-three consecutive cases with confirmed CTEPH had preoperative CTPA. For patients with more

than 1 CTPA, the most recent CT closest in timing to the surgery was selected. Three patients were excluded because they did not fit the CT selection criteria (see Exclusions below).

Controls

Three patient groups had undergone CTPA for a variety of reasons except CTEPH. This includes 50 acute PE, 50 nonthromboembolic cases that were taken to be “normals” insofar as having no acute or chronic PE, and 50 patients with pulmonary arterial hypertension (PAH) (Group 1 PAH). The clinical request for CTPA in the first 2 groups was to exclude acute PE. The CT data sets were collected from 1 institution to ensure uniformity in the acquisition

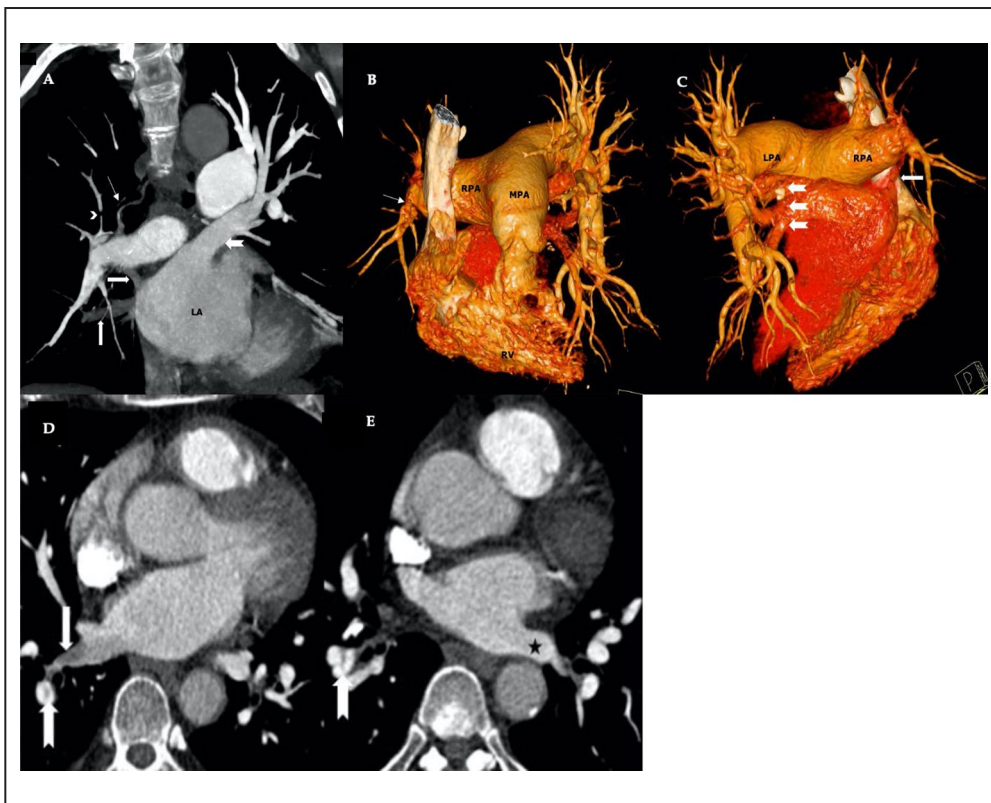


Figure 2. Pulmonary venous flow abnormalities in CTEPH.

CTPA coronal view (A), anterior (B) and posterior (C) volume-rendered technique (VRT) in a 45-year-old woman with CTEPH. Pulmonary arterial abnormalities are asymmetrically worse on the right with proximal stenosis (chevron, A) and segmental occlusions in the upper lobe, lobar occlusion in middle lobe, and trifurcation stenosis with post stenotic dilatation in the lower lobe (thin arrow, B). Note the pressure-overloaded hypertrophied right ventricle (RV, B) and dilated bronchial artery (thin arrow, A). On A, there is absent flow in the right middle and lower lobe pulmonary veins (block arrows). Note normal caliber vein with good enhancement in left upper lobe (notched arrow). The posterior VRT image on (C) elegantly demonstrates normal upper, lingula, and lower lobe veins on the left (notched arrows) and small caliber upper (block arrow) and absent middle and lower lobe veins on the right. In a different subject who also has CTEPH, CTPA axial views (D and E), there is heterogeneous flow in the right inferior pulmonary vein (block arrow, D) and a proximal web (notched arrow, D) in the corresponding segmental artery. The complex web is better demonstrated on a lower slice (E). There is normal flow in the left inferior pulmonary vein (black star, E). CTEPH indicates chronic thromboembolic pulmonary hypertension; CTPA, computed tomography pulmonary angiogram; LA, left atrium; and MPA, RPA, LPA, main, right, and left pulmonary arteries.

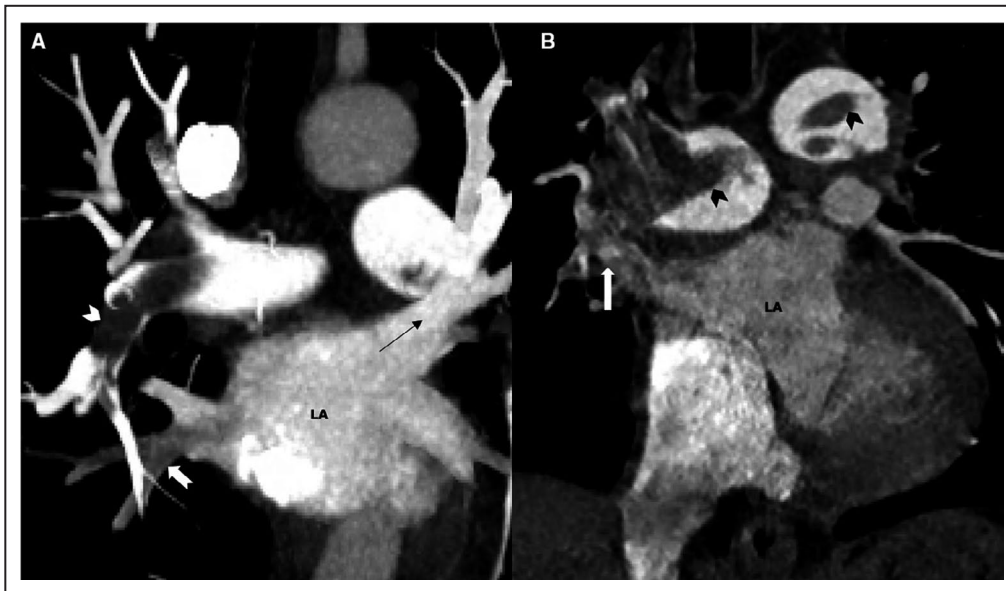


Figure 3. CTPA coronal views at the level of the left atrium (LA) from 2 different patients with acute PE.

There is absent flow in the right inferior pulmonary vein (notched arrow, **A**) with central intraluminal thrombus in the corresponding right lower lobe pulmonary artery (white chevron). Note normal flow in left upper lobe pulmonary vein (thin black arrow). There is heterogeneous flow in right superior pulmonary vein (block arrow, **B**) with central clot in the main and right pulmonary arteries (black chevron). CTPA indicates computed tomography pulmonary angiogram; and PE, pulmonary embolism.

protocol and were randomly selected from the radiology department's picture archiving and communication system with the closest age and sex match. These were acquired on a single-source 128-multislice configuration (Somatom Definition AS+; Siemens AG, Berlin and Munich, Germany). Scanning was performed in a craniocaudal direction from lung apices to bases. Omnipaque 350 (100 mL) was administered at 5 mL/s with a 40-mL saline chaser. Bolus tracking was used with region of interest in the pulmonary artery and trigger values of 100 HU. The images were reconstructed at 1-mm intervals using Siemens iterative reconstruction method, SAFIRE (Sinogram Affirmed Iterative Reconstruction, strength 3). CTPA for the PAH

group was chosen from the institution's PH database and had a female preponderance because of a higher number of idiopathic PAH cases, known to be more prevalent in females.

Grading of PV

The appearances of the 4 major PV were scored according to a visual grading system of 1 to 4: 1=Normal flow; 2=Heterogeneous flow; 3=Absent flow; and 4=unable to comment (Figure 1). Normally, the PV have a uniform density consistent with that of the LA. Scores 2 and 3 were defined by the following criteria adapted from previous publications^{8,9}—(1) Filling defect in at least 2 cm of a PV and (2) LA attenuation >160 HU.

Table 1. Baseline Characteristics

	All Patients	Cases		Controls		
		CTEPH	PAH	Acute PE	Nonthromboembolic	All
N	200	50	50	50	50	150
Age, y (±SD)	56.3±16.7	59.9±12.3	48.9±15.7	61.2±17.1	55.0±18.5	55.1±17.8
<i>P</i> value	0.004*	0.900	0.427	0.073
Females, n (%)	101 (51)	17 (34)	32 (64)	26 (52)	26 (52)	84 (56)
<i>P</i> value	0.002†	0.069	0.069	0.007†

P values refer to comparisons of control groups to cases with CTEPH as reference. CTEPH indicates chronic thromboembolic pulmonary hypertension; n, number of patients; PAH, pulmonary arterial hypertension; and PE, pulmonary embolism.

*Significant Tukey Honestly Significant Difference *P* value.

†Significant even after Bonferroni correction.

Table 2. Prevalence of PVS Score 3

	Cases	Controls			
	CTEPH	PAH	Acute PE	Nonthromboembolic	All
n	50	50	50	50	150
PVS sign present, n (%)	39 (78.0)	1 (2.0)	17 (34.0)	4 (8.0)	22 (14.7)
P value	...	<0.001*	<0.001*	<0.001*	<0.001*
Sensitivity (%) (CI)	78.0 (64.0–88.5)	2.0 (0.1–10.7)	34.0 (21.2–48.8)	8.0 (2.2–19.2)	...
Specificity (%) (CI)	85.3 (78.6–90.6)	60.0 (51.7–67.9)	70.7 (62.7–77.8)	62.0 (53.7–69.8)	...

P values refer to comparisons of control groups with CTEPH cases as reference. CTEPH indicates chronic thromboembolic pulmonary hypertension; n, number of patients; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; and PVS, pulmonary venous sign.

*Significant even after Bonferroni correction.

Exclusions

Three patients with CTEPH had poor opacification of the LA (LA <160 U) and were excluded at the outset. Two patients (1 in the acute PE and 1 in the nonthromboembolic group) had beam-hardening artifacts in the right upper lobe PV and 2 patients (1 CTEPH and 1 PAH) had partial anomalous pulmonary venous drainage involving 1 PV. These were also excluded from the analysis.

Image Analysis

The data sets were anonymized and cases and controls were mixed randomly before the assessment. Evaluation was performed by 2 radiologists (R1, a cardiovascular radiologist with 15 years' experience, and R2, a thoracic radiologist with 3 years' experience) and a cardiovascular imaging fellow (cardiologist) with 1 years' experience. Axial CTPA images (mediastinal and pulmonary embolism window setting) and multiplanar reformatted (coronal and sagittal) images with slice thickness varying between 1 and 3 mm were analyzed on a Sectra Picture Archiving and Communication System workstation.

In addition to appearances of the PV, concomitant data regarding the pulmonary arterial appearances such as acute PE or chronic thromboembolic disease—occlusion, eccentric wall adherent thrombus, arterial bands/webs, stenosis, reduced caliber segmental and subsegmental vessels (Figures 2 and 3) as well as a range of

Table 3. Age- and Sex-Adjusted Multivariate Regression Model for CTEPH Versus Pooled Controls (Non-CTEPH)* on the Odds of PVS

Variable	Odds Ratio	95% CI	P Value
Group: CTEPH (Ref)	1		
Non-CTEPH	0.052	(0.023, 0.121)	<0.0001
Age	1.024	(0.998, 1.050)	0.071
Sex: female (Ref)	1		
Male	2.419	(1.100, 5.318)	0.028

CTEPH indicates chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; and PVS, pulmonary venous sign.

*Pooled controls includes PAH, PE, and nonthromboembolic.

nonvascular findings (consolidation, atelectasis, pulmonary fibrosis, lung nodule/mass, airways disease, and pleural effusion) were collected. In cases of disagreement between the reviewers, a consensus reading was performed after individual assessment was completed.

Statistical Analysis

Data were analyzed using SPSS Statistics (version 25, IBM Corp) and Microsoft Excel. Continuous variables were compared between cases and control groups using 1-way ANOVA with Tukey's post-hoc Honestly Significant Difference test or an unpaired Student *t* test, as appropriate. Categorical variables were compared between cases and control groups using Pearson's χ^2 test; where $n < 5$, Fisher's exact test was used. A $P < 0.05$ was considered statistically significant, with Bonferroni correction applied as appropriate to control for multiple comparisons. Sensitivity and specificity values were calculated for the PVS (score 3 and score 2) in CTEPH, acute PE, PAH, and nonthromboembolic groups, respectively, versus all other groups. 95% CI were calculated as "exact" Clopper-Pearson CI. Positive predictive value and negative predictive value estimates were not calculated because these parameters depend on disease prevalence, which is unavailable in a case-control study. The odds of having the PVS sign if a patient is in each of the control groups compared with being in the CTEPH group was assessed by fitting a univariate logistic regression model. A multivariable regression model was fitted to allow further adjustment for age and sex. Interobserver agreement was assessed using Fleiss' kappa statistics ($\kappa < 0.20$, poor agreement; $\kappa = 0.21$ – 0.40 , fair agreement; $\kappa = 0.41$ – 0.60 , moderate agreement; $\kappa = 0.61$ – 0.80 , good agreement; $\kappa = 0.81$ – 1.00 , very good agreement).

RESULTS

This study included 200 patients: 50 CTEPH cases, and 150 controls (3 groups); mean \pm SD age of 56.3 (± 16.7)

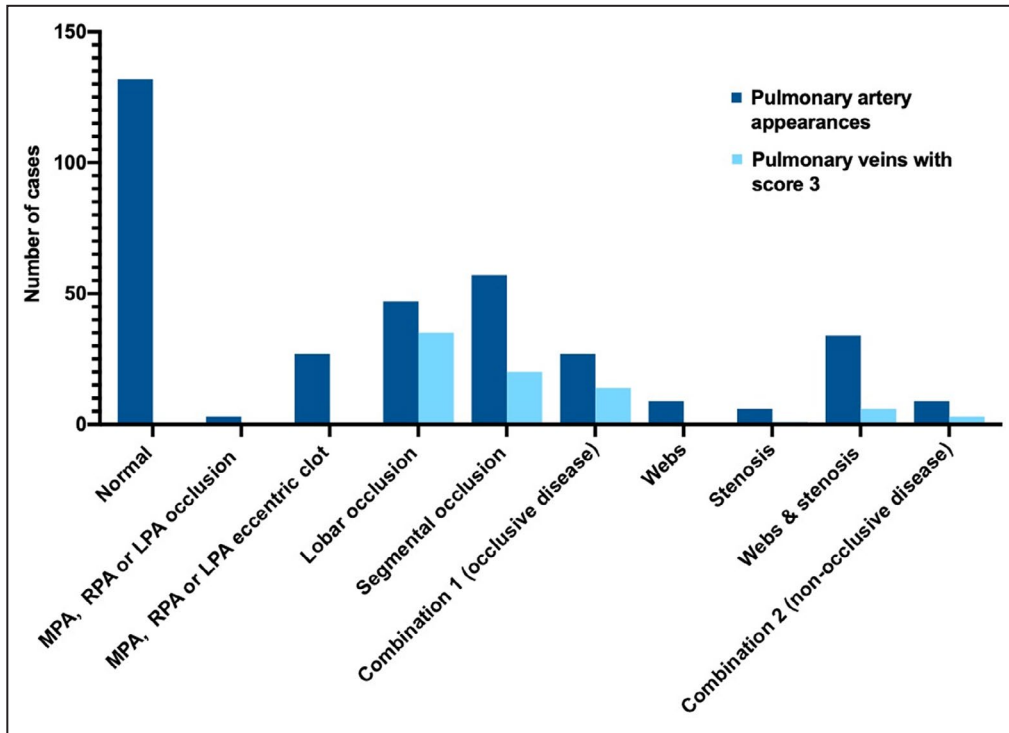


Figure 4. Distribution of pulmonary arterial changes corresponding to PVS score 3 in CTEPH. Thirty-nine of 50 CTEPH cases had PVS score 3 giving rise to 351 arterial points (6 matched and 3 unmatched arterial points per case). In total 79 veins had score 3. CTEPH indicates chronic thromboembolic pulmonary hypertension; LPA, left pulmonary artery; MPA, main pulmonary artery; PE, pulmonary embolism; RPA, right pulmonary artery; and PVS, pulmonary vein sign.

years. CTEPH cases had a mean age of 59.9 (±12.3) years. Table 1 illustrates the baseline characteristics of all patients included in this study. A 1-way ANOVA analysis with post-hoc Tukey Honestly Significant Difference test revealed that patients with PAH were younger than ($P=0.004$) patients with CTEPH. There were no statistically significant differences in age between CTEPH and acute PE or nonthromboembolic groups, respectively. χ^2 analysis showed that CTEPH cases in this sample were more likely to be male (66%) than the control groups (44%), $P=0.007$.

Table 4. PVS Score 3 and 2 Corresponding to Different Pulmonary Arterial Abnormalities

	Occlusive Disease*	Non-Occlusive Disease
PVS score 3 corresponding to different pulmonary arterial abnormalities		
PVS score 3	69	10
No PVS score 3	62	39
<i>P</i> value	...	<0.001
PVS score 2 corresponding to different pulmonary arterial abnormalities		
PVS score 2	32	24
No PVS score 2	67	53
<i>P</i> value	...	0.870

PVS indicates pulmonary venous sign.
*Reference.

PVS Score 3 (Absent Flow)

The number of patients with score 3 in at least 1 PV were evaluated. Thirty-nine of 50 (78%) of CTEPH cases had a score of 3 in at least 1 PV. The prevalence of the PVS sign score 3 in the different groups is shown in Table 2.

The PVS sign score 3 is more prevalent in CTEPH than in any other control group ($P<0.001$). Compared with all the controls, the PVS sign has a sensitivity of 78.0% (95% CI, 64.0–88.5) and a specificity of 85.3% (95% CI, 78.6–90.6) for CTEPH. A multivariable regression model demonstrated that the PVS is still more prevalent in the CTEPH group compared with the other control groups after adjusting for age and sex. Detailed information on the odds ratios for the age- and sex-adjusted multivariate model is shown in Table 3.

PVS Score 2 (Heterogeneous Flow)

The number of patients with score 2 in at least 1 PV were evaluated (Table S1). Thirty-three of 50 (66%) CTEPH cases had a score of 2 in at least 1 PV. When using a score of 2 rather than a score of 3, the sensitivity of the PVS for CTEPH decreases from 78% to 66%. However, the prevalence of the PVS score 2 in CTEPH is still significantly higher than in the other control groups ($P<0.001$).

Distribution of Pulmonary Arterial Changes in Veins With Abnormal Flow

Pulmonary arterial abnormalities were evaluated at the main, lobar, segmental, and subsegmental levels and classified into different categories such as lobar or segmental occlusion, eccentric nonocclusive thrombus, webs, and stenosis and combination changes. For each case, there are 6 matched arterial and venous points (upper, middle/lingula, and lower). Because the 3 proximal pulmonary arteries (main, right, and left pulmonary artery) do not have corresponding matching veins, the venous changes were evaluated at the lobar level. The distributions of the pulmonary arterial changes corresponding to PVS are elaborated in Figure 4 and Figure S1.

In CTEPH, pulmonary venous flow abnormalities were more frequently observed in the lower and middle lobes compared with the upper lobes (Figure S2). No normal pulmonary arterial segment was associated with absent PV flow but a small (6.6%) number had heterogeneous flow. Pulmonary arterial occlusive disease in the lobar and segmental levels were most commonly associated with absent flow in the corresponding vein when compared with eccentric nonocclusive or partially occlusive clots, web disease, and stenotic segments ($P<0.001$) (Table 4). However, there was no significant difference in heterogenous PV flow between the occlusive and non-occlusive pulmonary arterial disease groups.

PVS Score 3 CTEPH Versus Acute PE

Absent PV flow is more prevalent in CTEPH versus acute PE ($P<0.001$) (Table 5). When compared with acute PE, PVS score 3 has a sensitivity of 78% and specificity of 66% for CTEPH. The sign has low-to-moderate sensitivity and specificity for acute PE (34.0% and 22.0%, respectively).

PVS Score 3 CTEPH Versus PAH

The distribution of different Group 1 PAH causes and the corresponding PV scoring is elaborated in Figure 5. Only 1 case (connective tissue disease–associated PH with large pleural effusion) had PVS score 3 (Figure 6). There were no morphological intraluminal pulmonary arterial abnormalities in this cohort. Absent PV flow is more prevalent in CTEPH versus PAH ($P<0.001$). When compared with PAH, PVS score 3 has a sensitivity of 78% and specificity of 98% in CTEPH. The sign has very low sensitivity and specificity for PAH (2.0% and 22.0%, respectively) (Table 5).

PVS Score 3 in Nonthromboembolic Group

In the nonthromboembolic group, there were miscellaneous findings that are elaborated in Figure 7. In this cohort,

Table 5. PVS Score 3 Comparative Sensitivity and Specificity Values for CTEPH Versus Acute PE, PAH, and Nonthromboembolic Disease

PVS Score 3 in CTEPH vs Acute PE: Sensitivity and Specificity Values are Calculated as CTEPH vs Acute PE; and Acute PE vs CTEPH, Respectively		
	CTEPH	Acute PE
PVS score 3	39 (78%)	17 (34%)
No PVS score 3	11 (22%)	33 (66%)
Sensitivity (%) (CI)	78.0 (64.0–88.5)	34.0 (21.2–48.8)
Specificity (%) (CI)	66.0 (51.2–78.8)	22.0 (11.5–36.0)
PVS Score 3 in CTEPH vs PAH: Comparative Sensitivity and Specificity Values for CTEPH vs PAH; and PAH vs CTEPH, Respectively		
	CTEPH (n=50)	PAH (n=50)
PVS score 3	39 (78%)	1 (2%)
No PVS score 3	11 (22%)	49 (98%)
Sensitivity (%) (CI)	78.0 (64.0–88.5)	2.0 (0.1–10.7)
Specificity (%) (CI)	98.0 (89.4–100.0)	22.0 (11.5–36.0)
PVS Score 3 in CTEPH vs Nonthromboembolic: Comparative Sensitivity and Specificity Values for CTEPH vs Nonthromboembolic; and Nonthromboembolic vs CTEPH, Respectively		
	CTEPH (n=50)	Nonthromboembolic (n=50)
PVS score 3	39 (78%)	4 (8%)
No PVS score 3	11 (22%)	46 (92%)
Sensitivity (%) (CI)	78.0 (64.0–88.5)	8.0 (2.2–19.2)
Specificity (%) (CI)	92.0 (80.8–97.8)	22.0 (11.5–36.0)

CTEPH indicates chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PE, pulmonary embolism; and PVS, pulmonary venous sign.

4 (8%) patients (lobar consolidation, extrinsic compression by a neuroendocrine tumor, sarcoid with severe fibrotic lung disease, and severe idiopathic pulmonary fibrosis) had PVS score 3 (Figure 8). Absent PV flow is more prevalent in CTEPH versus nonthromboembolic controls ($P<0.001$). When compared with the nonthromboembolic group, PVS score 3 has a sensitivity of 78% and specificity of 92% for CTEPH. The sign has very low sensitivity and specificity for the nonthromboembolic cohort (8.0% and 22.0%, respectively) (Table 5).

In terms of reproducibility of detection and categorization of the PVS, the overall Fleiss' Kappa statistics showed that there was very high agreement between the 3 readers, $\kappa=0.96$ (95% CI, 0.90–1.01), $P<0.001$ (Table S2).

DISCUSSION

Our results show that in CTEPH, pulmonary venous flow is significantly compromised when there is

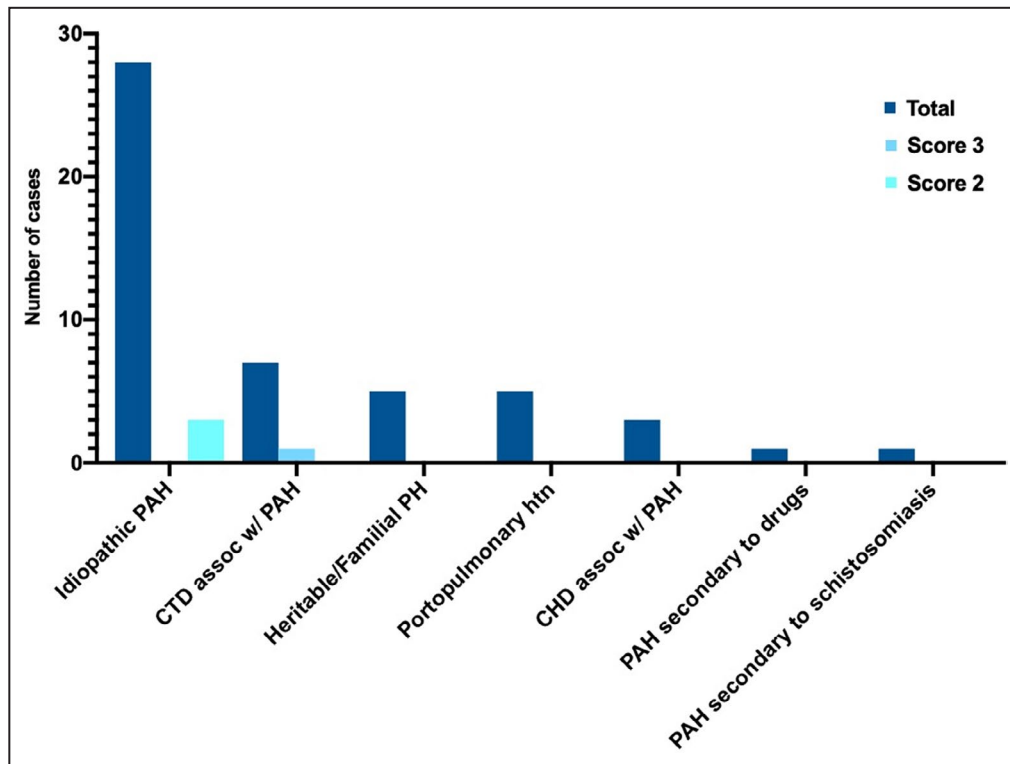


Figure 5. PV score and diagnoses in the PAH control group.

PV scoring in the 50 controls with PAH demonstrated score 3 in 1 patient and score 2 in 3 patients. CHD indicates congenital heart disease; CTD, connective tissue disease; htn, hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; and PV, pulmonary vein.

proximal occlusion in the pulmonary arteries and that this can be readily visualized by CTPA. It is not surprising that the abnormal venous flow was more common in the lower lobe veins because clinicopathological studies have demonstrated that CTEPH is more predominant in the lower lobes.¹⁰

The pulmonary arterial, capillary, and venular segments serve to preserve the synchrony between right ventricular (RV) output and left ventricular filling. A multitude of factors such as blood viscosity, vascular compliance, and transmural pressures influence the propagation of blood flow in the pulmonary circulation, which is pulsatile. The flow pattern in the large extraparenchymal PV is also dependent on dynamic changes in left atrial pressure occurring throughout the cardiac cycle.¹¹

Under normal conditions, the lung has a dual vascular supply from the pulmonary and bronchial arteries and therefore, pulmonary venous drainage is rarely affected. Hypoxic vasoconstriction is a homeostatic mechanism that is intrinsic to the pulmonary vasculature. Intrapulmonary arteries constrict in response to alveolar hypoxia, diverting blood from the suboptimally aerated alveoli to better-oxygenated lung segments, thereby optimizing VQ matching and systemic oxygen delivery. Thus, regionalized pulmonary venous

hypoperfusion may be the result of hypoxic vasoconstriction and may account for the PV abnormalities observed in the nonthrombotic control groups. It is very important not to misinterpret the poor PV opacification as thrombus.

In CTEPH, with chronic occlusion or narrowing of the pulmonary arteries within segments of the lung parenchyma, the altered pulmonary venous flow pattern observed in this study may simply be a reflection of this compromise in arterial flow. Alternative explanations for the reduction in pulmonary venous return might be based on the cardiac pathology known to develop in CTEPH. Chronic pulmonary arterial obstruction causes resistance to continuous blood flow and also alters the flow pulsatility because of an increase in arterial impedance, a measure of RV afterload. Pathophysiological studies have shown that the increase in pulmonary vascular resistance is related to the extent of obstruction, severity of vascular remodeling, reflex or biochemically mediated vasoconstriction of the pulmonary arterial bed, and reflex hypoxemia.^{12,13} Over time, there is progressive RV dilatation and adaptive remodeling with hypertrophy, reduction in stroke volume, and functional decline as the RV is unable to maintain that level of systolic stress. The decrease in RV stroke volume leads to



Figure 6. CTPA coronal view in a patient with connective tissue disease–associated pulmonary hypertension.

There is absent flow in the left inferior pulmonary vein (notched arrow). There is a large left pleural effusion (white triangle) and dependent atelectasis (white star) in the left lower lobe. On the right, there is a small pleural effusion with mild basal atelectasis and normal flow in the corresponding inferior pulmonary vein. CTPA indicates computed tomography pulmonary angiogram; and LA, left atrium.

reduced pulmonary venous return with LA underfilling and impaired left ventricular diastolic function. Concomitant right atrial enlargement causes compression and further reduction in the LA size. However, the observation that PVS was not a significant feature in the PAH group speaks against this mechanism as the primary reason for the relatively high frequency of pulmonary venous abnormalities observed in the CTEPH cohort.

Correlation between CTPA finding of PVS and catheter pulmonary angiography can be obtained from the balloon pulmonary angioplasty literature. The overall success of the procedure is graded on restoration of both pulmonary arterial and venous flow.¹⁴ Close attention is paid by balloon pulmonary angioplasty operators to identify target lesions with poor venous return. The goal of each balloon treatment is to adequately dilate the lesion and restore prompt pulmonary venous return. Repeat dilations with bigger balloons are performed if there is <50% increase in angiographic vessel size and an increase of pulmonary venous backflow is documented.¹⁵ Given the angiographic importance placed on the pulmonary venous flow, detection of the PVS can be used not only to aid in the CT diagnosis of CTEPH but can potentially also be useful in evaluating the effects of balloon pulmonary angioplasty on postprocedural imaging.

Small case series have reported insufficient contrast medium filling of the PV in the more severe cases

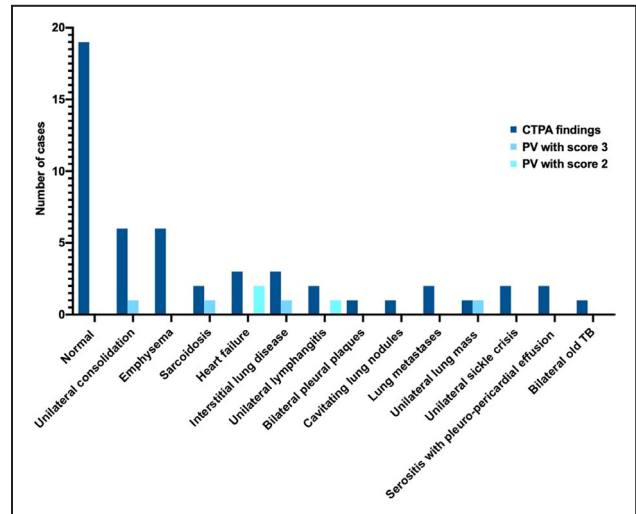


Figure 7. Miscellaneous findings on CTPA in the nonthrombotic cohort.

PV scoring in 50 nonthromboembolic controls demonstrated score 3 in 4 patients and score 2 in 3 patients. CTPA indicates computed tomography pulmonary angiogram; PV, pulmonary vein; and TB, tuberculosis.

of acute pulmonary embolism with significant pulmonary vascular obstruction and failure of the right side of the heart.^{7–9} The sign has been postulated as a potential risk stratification tool because its presence has been shown to be associated with higher mean PE index and poor prognosis. In our acute PE group, absent PV flow had a sensitivity of 34%. This is in agreement with previous publications, which have reported sensitivities of 33% and 36%, respectively.^{8,9} The authors speculated that significant imbalance of the VQ ratio because of severe hypoxia in acute PE results in diminished venous return, giving rise to flow disturbance, but as we have shown in the CTEPH group, there might also be a simple flow phenomenon in acute PE.

Although it is beyond the scope of this article to elaborate on the technical parameters for CTPA acquisition, it is important to understand that while PVS is easily identifiable in CTEPH, its presence is dependent on achieving a balance between good opacification of the pulmonary vasculature and homogeneous opacification of the LA. A high-quality CTPA is essential to ensure that the CTEPH diagnosis is not missed.

Computer-aided detection for automated diagnosis of acute PE on CTPA has evolved over the decades and has been shown to be more sensitive in the detection of peripheral emboli, particularly for inexperienced readers.¹⁶ As yet, there is no commercially available CT software for automated identification of CTEPH, but emerging machine learning tools are apposite for the detection and risk stratification of thromboembolic disease and pulmonary

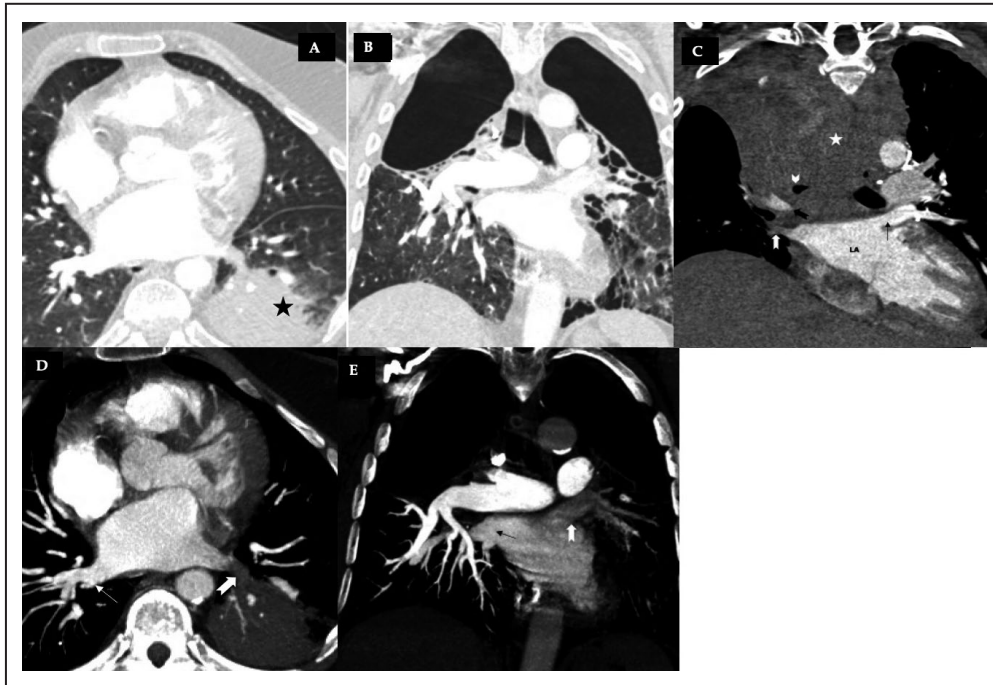


Figure 8. Pulmonary venous flow abnormalities in nonthromboembolic cohort.

Left Panel (A, D): CTPA axial view in a patient with left lower lobe consolidation (black star, A). There is absent flow in the corresponding left inferior pulmonary vein (notched arrow, D) compared with the normal flow in right inferior pulmonary vein (thin white arrow). Middle Panel (B, E): CTPA coronal view in a patient with fibrocavitary sarcoidosis (lung window, B). There is absent flow in the left superior pulmonary vein (notched arrow, E) compared with the normal flow in right pulmonary vein (thin black arrow). Right Panel (C): CTPA coronal view in a patient with primary pulmonary neuro-ectodermal tumor. Large heterogeneous soft tissue mass (white star) is causing compression of the pulmonary artery (black notched arrow), right superior pulmonary vein (white notched arrow), and bronchus (white chevron). There is absent flow in the right superior pulmonary vein compared with the normal flow in left superior pulmonary vein (thin black arrow). CPTA indicates computed tomography pulmonary angiogram.

hypertension. It is now feasible to do highly accurate pulmonary artery–vein segmentation on CT using a fully automated machine learning algorithm.¹⁷ Therefore, the incorporation of the PV sign into a machine learning algorithm for CTPA diagnosis of CTEPH should be achievable and has the potential to improve the consistency and diagnostic confidence in observers.

Limitations of this study include the following. First, a subjective evaluation method was used for assessment of the pulmonary venous flow. However, there was high interobserver reproducibility (κ 0.96) between the readers with different levels of experience for CTPA assessment. Secondly, it was difficult to blind observers to the presence or absence of either acute or chronic PE. Thirdly, the absence of delayed phase imaging precluded evaluation of the relationship of the bronchial circulation and the observed pulmonary venous changes. The dual-energy CT literature has demonstrated that in chronic thromboembolic disease, perfusion defects in the early phase

show improved parenchymal enhancement in the late phase; this has been attributed to contribution from the systemic collaterals.^{18,19} It is possible that patients with CTEPH with PVS in the arterial phase CTPA may show improvement in the pulmonary venous flow on delayed phase CT, but this is speculative and would require prospective evaluation. Finally, the sample is biased towards the proximal CTEPH population and hence the utility of PVS in distal CTEPH remains unknown. Because the latter group of patients exhibit very few pulmonary vascular signs on CTPA, it is important to clarify the usefulness of PVS in this cohort. While we have shown that PVS is not a feature of PAH, it is necessary to systematically investigate other groups of PH, particularly those associated with dysfunction of the left side of the heart and multifactorial pathogenesis, as these may affect its prevalence and accuracy. Prospective multicenter studies with large numbers of patients are needed to evaluate the correlation between the pulmonary venous abnormalities and hemodynamic severity of the disease.

In conclusion, our study has shown that PVS on CTPA has higher sensitivity and specificity for CTEPH, compared with the other control groups (acute PE, PAH, and nonthromboembolic). Furthermore, PVS is more prevalent in CTEPH compared with acute PE. Additionally, PVS is not a feature of PAH. Therefore, asymmetric enhancement of PV should prompt a search for CTEPH, particularly when there is evidence of PH on CTPA. PVS is relatively easy to see on CTPA, as shown by the high concordance between the independent blinded observers with varying levels of expertise in our study, and therefore can be used as an aide-memoire in the CTPA interpretation of thromboembolic disease and pulmonary hypertension.

ARTICLE INFORMATION

Received July 2, 2020; accepted September 21, 2020.

Affiliations

From the Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden (D.G., A.N.-R., P.L.); Imperial College Healthcare NHS Trust, London, United Kingdom (D.G.); Department of Radiology Solna, Karolinska University Hospital, Stockholm, Sweden (A.N.-R., S.N.); Department of Medicine (E.P.L., J.T.) and Division of Experimental Medicine and Immunotherapeutics (H.P.), University of Cambridge, United Kingdom; Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden (S.N.); Temple University Hospital, Philadelphia, PA (W.A.); and Department of Emergency Medicine, University of California San Diego, San Diego, CA (P.L.).

Sources of Funding

None.

Disclosures

Gopalan reports consultancy work for Bayer and Actelion. William Auger reports consultancy work for Bayer. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S2

Figures S1–S2

REFERENCES

- Kim NH, Delcroix M, Jais X. Chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2019;53:1801915.
- Tunari N, Gibbs SJ, Win Z, Gin-Sing W, Graham A, Gishen P, Al-Nahas A. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. *J Nucl Med*. 2007;48:680–684.
- Soler X, Kerr KM, Marsh JJ, Renner JW, Hoh CK, Test VJ, Morris TA. Pilot study comparing SPECT perfusion scintigraphy with CT pulmonary angiography in chronic thromboembolic pulmonary hypertension. *Respirology*. 2012;17:180–184.
- He J, Fang W, Lv B, He JG, Xiong CM, Liu ZH, He ZX. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector computed tomography pulmonary angiography with pulmonary angiography. *Nucl Med Commun*. 2012;33:459–463.
- Rogberg AN, Gopalan D, Westerlund E, Westerlund E, Lindholm P. Do radiologists detect chronic thromboembolic disease on computed tomography? *Acta Radiol*. 2019;60:1576–1583.
- Auger WR, Fedullo PF, Moser KM, Buchbinder M, Peterson KL. Chronic major-vessel thromboembolic pulmonary artery obstruction: appearance at angiography. *Radiology*. 1992;182:393–398.
- Zhang H, Ma Y, Song Z, Lv J, Yang Y. Predictive value of insufficient contrast medium filling in pulmonary veins in patients with acute pulmonary embolism. *Medicine (Baltimore)*. 2017;96:e7926.
- Ermin S, Çinkooğlu A, Susam S, Batum Ö, Yılmaz U. A new perspective for pulmonary thromboembolism radiology: 'Pulmonary vein sign'. *Clin Respir J*. 2018;12:2653–2658.
- Souza LVS, Zanon M, Souza AS, Irion K, Penha D, Alves GRT, Marchiori E, Hochegger B. "Pulmonary Vein Sign" for pulmonary embolism diagnosis in computed tomography angiography. *Lung*. 2017;195:769–774.
- Blauwet LA, Edwards WD, Tazelaar HD, McGregor CG. Surgical pathology of pulmonary thromboendarterectomy: a study of 54 cases from 1990 to 2001. *Hum Pathol*. 2003;34:1290–1298.
- Keren G, Sherez J, Megidish R, Levitt B, Laniado S. Pulmonary venous flow pattern—its relationship to cardiac dynamics. A pulsed Doppler echocardiographic study. *Circulation*. 1985;71:1105–1112.
- Simonneau G, Torbicki A, Dorfmüller P, Kim N. The pathophysiology of chronic thromboembolic pulmonary hypertension. *Eur Respir Rev*. 2017;26:160112.
- Delcroix M, Vonk Noordegraaf A, Fadel E, Lang I, Simonneau G, Naeije R. Vascular and right ventricular remodeling in chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2013;41:224–232.
- Kataoka M, Inami T, Kawakami T, Fukuda K, Satoh T. Balloon pulmonary angioplasty (percutaneous transluminal pulmonary angioplasty) for chronic thromboembolic pulmonary hypertension. A Japanese Perspective. *JACC Cardiovasc Interv*. 2019;12:1382–1388.
- Lang I, Meyer B, Ogo T, Matsubara H, Kurzyna M, Ghofrani G, Mayer E, Brenot P. Balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension. *Eur Respir Rev*. 2017;26:160119.
- Engelke C, Schmidt S, Bakai A, Auer F, Marten K. Computer-assisted detection of pulmonary embolism: performance evaluation in consensus with experienced and inexperienced chest radiologists. *Eur Radiol*. 2008;18:298–307.
- Nardelli P, Jimenez-Carretero D, Bermejo-Pelaez D, Washko GR, Rahaghi FN, Ledesma-Carbayo MJ, San Jose Estepar R. Pulmonary artery–vein classification in CT images using deep learning. *IEEE Trans Med Imaging*. 2018;37:2428–2440.
- Hong YJ, Kim JY, Choe KO, Hur J, Lee H-J, Choi BW, Kim YJ. Different perfusion pattern between acute and chronic pulmonary thromboembolism: evaluation with two-phase dual-energy perfusion CT. *AJR Am J Roentgenol*. 2013;200:812–817.
- Koike H, Sueyoshi E, Sakamoto I, Uetani M. 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.

SUPPLEMENTAL MATERIAL

Table S1. Prevalence of PVS score 2.

	Cases	Controls			
	CTEPH	PAH	Acute PE	Non-TE	All
n	50	50	50	50	150
PVS sign present – n (%)	33 (66)	3 (6)	12 (24)	3 (6)	18 (12)
p-value	-	<0.001*	<0.001*	<0.001*	<0.001*
Sensitivity (%) (C.I.)	66.0 (51.2-78.8)	6.0 (1.3-16.6)	24.0 (13.1-38.2)	6.0 (1.3-16.6)	-
Specificity (%) (C.I.)	88.0 (81.7-92.73)	68.0 (59.9-75.4)	74.0 (66.2-80.8)	68.0 (59.9-75.4)	-

*C.I., 95% confidence intervals; n, number of patients; p-values refer to comparisons of control groups with CTEPH cases as reference; * significant even after Bonferroni correction*

PVS: Pulmonary Venous Sign; **CTEPH:** Chronic thromboembolic pulmonary hypertension;

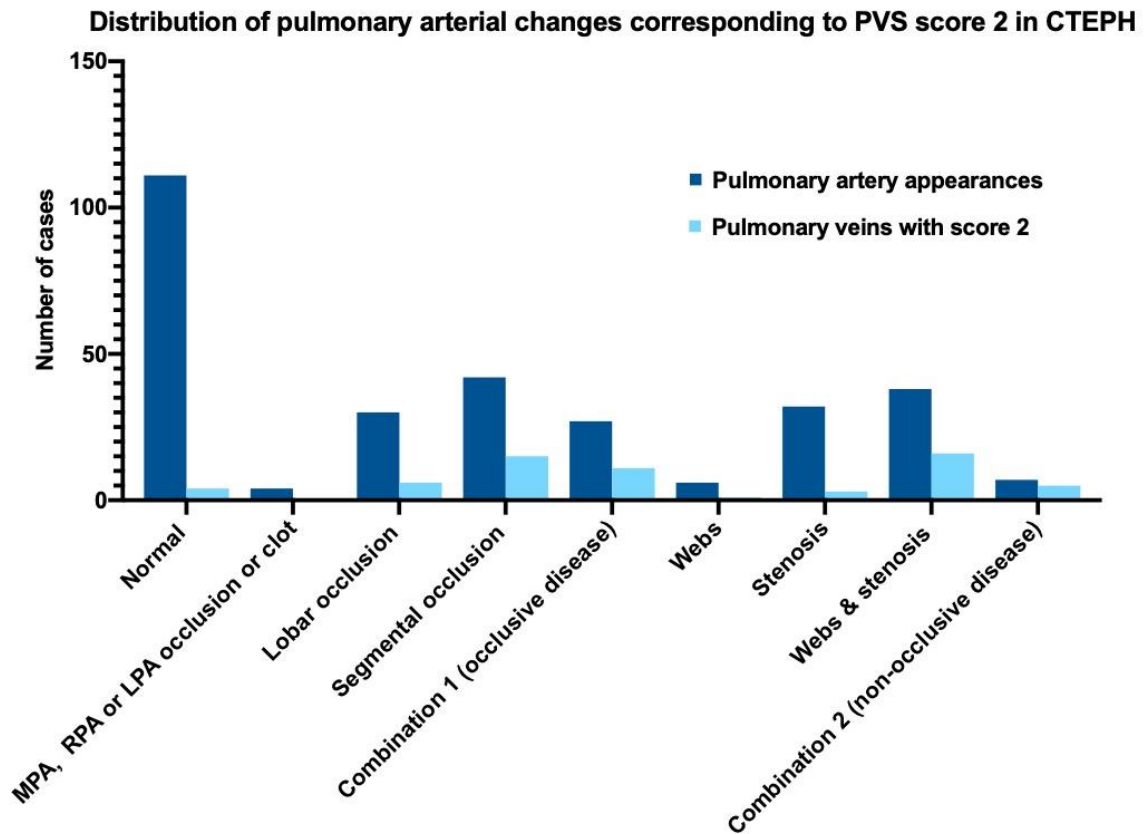
PAH: Pulmonary arterial hypertension; **PE:** Pulmonary embolism; **Non-TE:** Non-thromboembolic.

Table S2. Fleiss' Kappa statistics.

	Kappa	P Value	95% Confidence Intervals
Overall	0.96	<0.001	0.90 to 1.01
PV rating category			
1 (Normal)	0.97	<0.001	0.90 to 1.05
2 (Heterogenous)	0.92	<0.001	0.84 to 0.99
3 (Absent flow)	0.96	<0.001	0.88 to 1.03
4 (Unable to comment)	1.00	<0.001	0.93 to 1.07

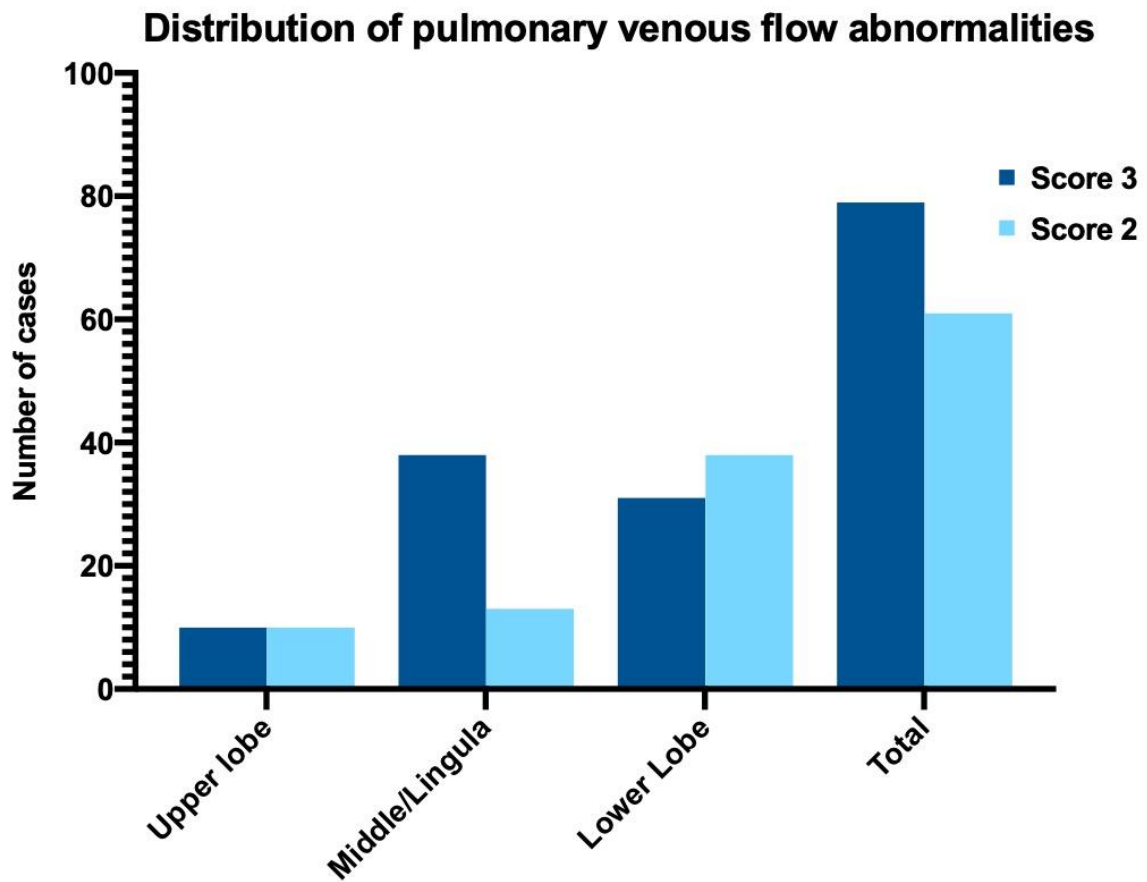
PV: Pulmonary Vein

Figure S1.



33/50 CTEPH cases had PVS score 2 giving rise to 297 arterial points (6 matched & 3 unmatched arterial points per case). In total 61 veins had score 2.

Figure S2.



The pulmonary venous flow abnormalities are more frequently observed in the middle and lower lobes compared to the upper lobes.