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RESEARCH ARTICLE

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Quantitative pulmonary perfusion in acute pulmonary embolism and chronic thromboembolic pulmonary hypertension

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Abstract

Current methods for quantifying perfusion from computed tomography pulmonary angiography (CTPA) often rely on semi-quantitative scoring systems and requires an experienced evaluator. Few studies report on absolute quantitative variables derived from the images, and the methods are varied with mixed results. Dual-energy CTPA (DE-CTPA) enables automatic quantification of lung and lobar perfusion with minimal user interaction by utilizing machine learning based software. We aimed to evaluate differences in DE-CTPA derived quantitative perfusion variables between patients with acute pulmonary embolism (PE) and chronic thromboembolic pulmonary hypertension (CTEPH). This retrospective, single-center, observational study included 162 adult patients diagnosed with PE ($n = 81$) or CTEPH ($n = 81$) and scanned using dual-energy CT between 2020 and 2023. Mann–Whitney U tests and permutational analysis of variance (PERMANOVA) were used for comparative analyses. We found whole lung perfusion blood volume to be lower ($p < 0.001$) in PE patients (median 3399 mL [2554, 4284]) than in CTEPH patients (median 4094 mL [3397, 4818]). The same was observed at single lung and lobar level. PERMANOVA encompassing all perfusion variables showed a difference between the two groups (F-statistic = 13.3, $p = 0.002$). Utilizing logistic regression, right and left lower lobe perfusion blood volume showed some ability to differentiate between PE and CTEPH with area under the receiver operation characteristics curve values of 0.71 (95% CI: 0.56; 0.84) and 0.72 (95% CI: 0.56; 0.86). Pulmonary perfusion is lower in patients with PE than patients with CTEPH, highlighted by differences in DECT-derived perfusion blood volume. Quantitative perfusion variables might be useful to differentiate between the two diseases.

KEYWORDS
cardiovascular disease, computed tomography pulmonary angiography, dual-energy computed tomography, machine learning, pulmonary circulation

Acute pulmonary embolism (PE) is the third most common cause of cardiovascular death,[1] characterised by embolization of thrombotic material from the deep veins to the pulmonary circulation.[1,2] Chronic thromboembolic pulmonary hypertension (CTEPH) is an underdiagnosed but debilitating disease with a prevalence of 26–38 cases/million adults.[3] Untreated, CTEPH has a 3-year mortality of 90%.[4–6] PE is characterised by a sudden increase in afterload in response to acute obstruction and vasoconstriction. CTEPH is caused by a progressive increase in afterload as a result of chronic obstruction and vasculopathy.[2,4,5,7] For both diseases, this compromises pulmonary perfusion and may be fatal if the right ventricle cannot compensate. Methods for diagnosis and severity assessment should consider both location of obstructions, and extent of pulmonary perfusion.

Traditional CT pulmonary angiography (CTPA) provides high quality and accurate information on location of acute or chronic emboli and is the imaging method of choice for diagnosis of PE.[2,6] It is routinely used in diagnosis and assessment of CTEPH patients.

Technological innovations in CT scanners enable simultaneous acquisition of dual-energy scan data and CTPA when dual-energy scan mode (DE-CTPA) is utilised. Reconstructed images from DE-CTPA such as pulmonary perfusion blood volume (PBV) images provide information on iodine distribution within lungs which can be assessed qualitatively and quantified in entire lung or lobes.[8–28] Qualitative assessment or scoring of PBV images has proven useful for severity stratification and diagnosis of both diseases with a diagnostic accuracy approximate to or higher than V/Q SPECT, but requires interpretation by trained radiologists.[15,26,27,29–33] The underlying premise of assessing pulmonary perfusion is decreased iodine distribution as a marker of decreased pulmonary perfusion in presence of pulmonary vascular obstruction, vasoconstriction or vasculopathy. Most studies describe the use of qualitative assessment of perfusion defects on PBV images in patients with acute PE and CTEPH[15,16,26,34–36] or use of non-absolute values or ratios based on zones instead of lobes.[19,23,24]

Advances in machine-learning based image processing of DE-CTPA enables automatic lung and lobe segmentation to obtain user-independent, quantitative perfusion data with absolute values,[28,37,38] concurrent with CTPA, without the need for additional scans. The aim of this study was to evaluate whether DE-CTPA could detect and characterize differences in quantitative lung and lobar perfusion metrics between CTEPH and PE patients.

METHODS

Subjects and data collection

This retrospective study included all patients admitted to the Department of Cardiology at Aarhus University Hospital for treatment of acute PE or CTEPH between February 2020 and February 2023. Patients were identified using the regional registry of patients and filtered by date, department, and diagnostic code to include all patients who had the diagnosis confirmed (Figure 1).

From electronic patient records on the day of the patients' initial diagnostic workup, we recorded demographics and comorbidities, systemic blood pressure, heart rate (HR), lactate, troponin-I, fibrin D-dimer, N-terminal pro-brain natriuretic peptide (NT-proBNP), 6-min walking distance (6-MWD), Borg dyspnoea scale, simplified pulmonary embolism severity index (sPESI), and World Health Organisation Functional Class (WHO FC). From right heart catheterisation (RHC) and transthoracic echocardiography, we recorded pulmonary blood pressure, cardiac output (CO), pulmonary vascular resistance (PVR), saturation, tricuspid regurgitation-gradient (TR), and tricuspid annular plane systolic excursion (TAPSE).

We classified acute PE patients into four categories according to the European Society of Cardiology Risk Stratification table from current guidelines.[2] For CTEPH patients, pulmonary hypertension was defined as a mean pulmonary arterial pressure (PAP) > 25 mmHg as it was the consensus at the time of diagnosis.[6] The study was approved by the institutional review board and informed consent was waived for this study.

DE-CTPA acquisition and image analysis

Patients were scanned on clinical indication in second-generation, dual-source, 128-slice multidetector-row CT scanners (SOMATOM Definition Flash, Siemens Healthineers). Images were routinely reconstructed as traditional CTPA for diagnosis and evaluation of pulmonary parenchymal-, vascular-, and thrombotic/embolic lesion characteristics, PBV images for visualization of pulmonary perfusion (Figure 2) and scoring of perfusion defects, and high and low energy image sets for further software analysis, the latter being the focus of this study.

CTEPH patients were scanned with tube voltages set to 100 kVp with 220 reference mAs and 140 kVp with 187 mAs. Other settings included 0.28-second gantry rotation time, 0.85:1 pitch factor, and 64 × 0.6 mm detector configuration. A 10 mL test bolus (350 mg/mL) of iodine contrast was used to determine scan delay followed by a

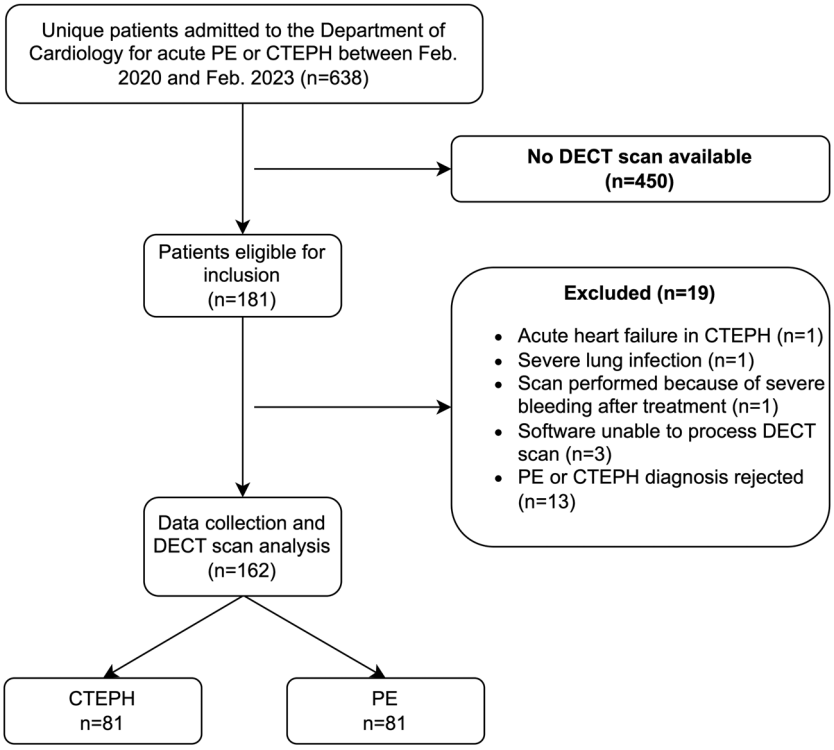

FIGURE 1 Patient inclusion flow. Patient inclusion flowchart detailing patient identification process, primary screening, inclusion cohort, and final cohort after exclusions.

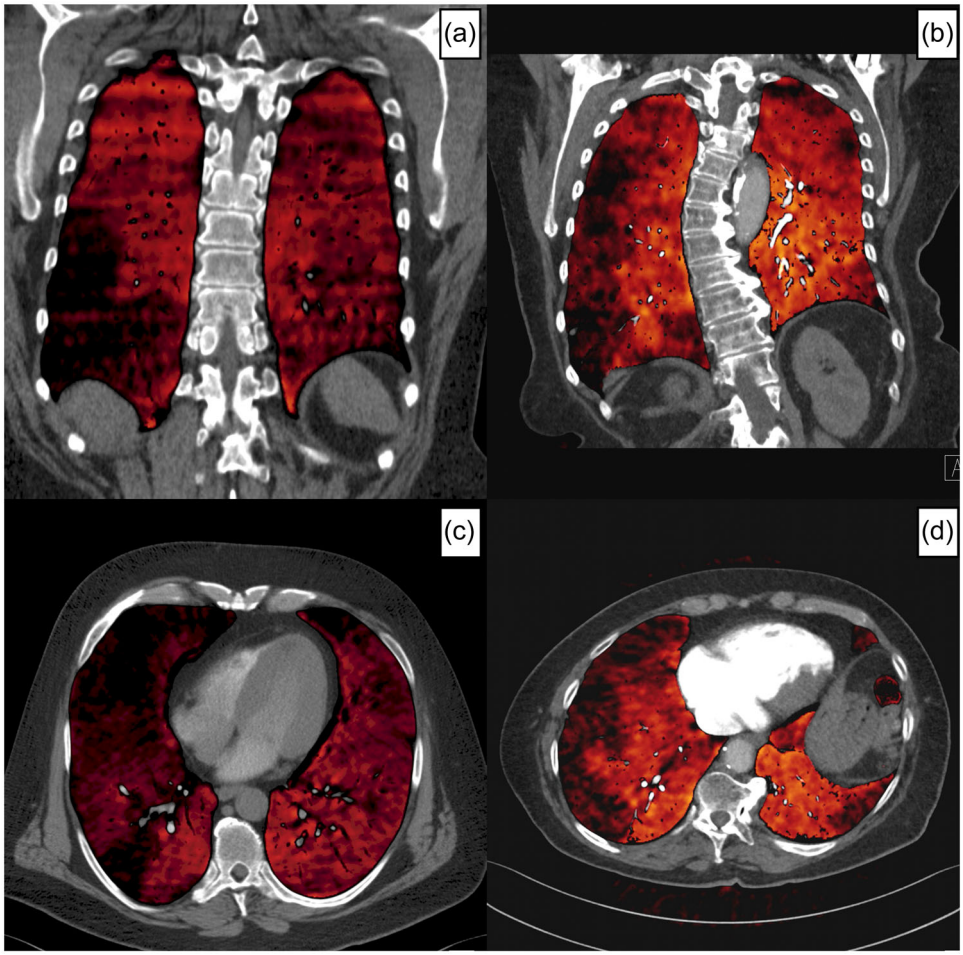

FIGURE 2 Representative lung perfusion blood volume images. Representative lung perfusion blood volume images from a patient with acute PE in coronal (a) and transversal (c) view, and a patient with CTEPH in coronal (b) and transversal view (d). CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism.

45 ml bolus (350 mg/mL) for CT acquisition at an injection rate of 5 mL/s. Images were reconstructed at 1 mm slice thickness with 0.5 mm increments. Acute PE patients were scanned with tube voltages set to 100 kVp with 180 reference mAs and 140 kVp with 153 reference mAs. Additional settings included 0.28-second gantry rotation time, 0.85:1 or 0.95:1 pitch factor, and 64×0.6 mm detector configuration. Contrast injection protocol did not differ. Images were reconstructed at 1- or 1.5-mm slice thickness with 0.5 mm increments.

After de-identification, the 100 and 140 kVp image datasets were exported offline and processed with a standalone, machine-learning based software for quantitative lung perfusion analysis (DE Lung Isolation, eXamine, Siemens Healthineers) (Supporting Information S1: Figure S1). This software automatically segments each lung and lobe, and calculates quantitative perfusion metrics for both lungs, right- and left lung, and each lobe based on attenuation differences between tissues, air, and iodine on material decomposition images of iodine concentration. The output variables included pulmonary PBV in millilitres (mL).

PBV images were visually assessed to determine the extent of perfusion defects in each lobe using a 4-point scale (grade 0 = no defect; grade 1 = mild, <25%; grade 2 = moderate, 25%–50%; grade 3 = severe, >50%). A total PBV score was calculated as the sum of all lobar scores with 15 being the highest possible score. Further, the main pulmonary artery (PA) and descending aorta (dAo) diameter was measured on the plane perpendicular to the direction of the vessel to create the PA/dAo ratio.

Statistical analysis

We used R for statistical analysis. We assessed data distribution by visual inspection of histograms and QQ plots, and Shapiro–Wilks test. Descriptive statistics are presented as means with standard deviations (mean ± SD) for normally distributed variables and medians with interquartile ranges (median [IQR]) for non-normally distributed variables. We used either Mann–Whitney *U* test or Student's *t*-test for singular comparisons. For multivariate comparison, we performed permutational multivariate analysis of variance (PERMANOVA). We created contingency tables for lung PBV scores and used Fischer's exact test to test the differences between the groups. Using Spearman's rho correlation coefficient, we evaluated correlation between perfusion and clinical variables for all patients, while perfusion, lung PBV score, and RHC variables were evaluated for CTEPH patients. For significant results, we performed stepwise multivariate logistic regression to further investigate the relationship between perfusion variables and the chosen dependent variables.

We performed binomial logistic regression to explore whether PBV variables could predict the disease group. The data was randomly split into a training set (70% of data) and a validation set (30% of data) to evaluate the discriminatory ability of the models by calculating the area under the receiver operating characteristic curve (AUC), and positive and negative predictive value. We considered AUC values between 0.7 and 0.8 to be fair/moderate, between 0.8 and 0.9 to be excellent, and >0.9 to be outstanding. We calculated the cut-off values for the optimal sensitivity and specificity using Youden's index. Variables that were not-normally distributed were $\log_2$-transformed for logistic regression and $\log_e$-transformed for multivariate linear regression. We considered a p-value < 0.05 to be statistically significant.

RESULTS

Patient characteristics

Initial screening to identify patients with acute PE or CTEPH identified 638 unique patients and DE-CTPA images were available for 181 patients. We excluded six patients during data collection due to acute heart failure ($n = 1$) or severe lung infection ($n = 1$) being the reason for admission; the scan being performed after treatment ($n = 1$); or the software being unable to process images ($n = 3$). A small group of patients ($n = 13$) with a tentative diagnosis of PE or CTEPH had the diagnosis dismissed and were excluded from the study during file review.

The final cohort included 162 patients with confirmed PE ($n = 81$) or CTEPH ($n = 81$) (Figure 1).

The acute PE and CTEPH groups were equally distributed in number of patients, age, and sex. The prevalence of coagulopathies was equal, while diabetes was more prevalent with acute PE patients, and chronic heart failure and chronic lung disease were more prevalent in CTEPH patients (Table 1).

There were no differences in systemic blood pressure and TAPSE, but heart rate was elevated in PE patients ($p < 0.001$), and the TR-gradient was higher in CTEPH patients ($p < 0.001$) (Table 2).

Qualitative assessment

All 81 PE patients were found to have filling defects consistent with PE on their CTPA exams. Of these, 13 lesions caused either sub- or total occlusion of a vessel and stenosis was found in one patient. Wall-adherent, eccentric and organized thromboemboli were found in 73 of the CTEPH patients. Of these, 62 lesions caused

TABLE 1 Patient characteristics.

		Acute PE	CTEPH
(n)		81	81
Age (median [IQR])		68 [60,76]	71 [61,78]
Sex	Female	36 (44.4)	35 (43.2)
Coagulopathy	Anti-phospholipid syndrome	1 (1.2)	0
	Factor V leiden	1 (1.2)	3 (3.7)
	Protein C deficiency	0	1 (1.2)
	None or unknown	78 (96.3)	75 (91.6)
Chronic heart failure	Yes	6 (7.4)	39 (48.2)
Chronic lung disease	Yes	12 (14.8)	25 (30.9)
Diabetes	Type I	0	1 (1.2)
	Type II	13 (16.1)	3 (3.7)
sPESI (median [IQR])		1 [1,2]	
ESC risk stratification class[a]	Low	4 (5.0)	
	Intermediate-low	25 (31.2)	
	Intermediate-high	45 (56.2)	
	High	6 (7.5)	
WHO FC	1		1 (1.4)
	2		26 (35.6)
	3		44 (60.3)
	4		2 (2.7)

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; IQR, interquartile range; PE, pulmonary embolism; Sex, sex assigned at birth; sPESI, simplified pulmonary embolism severity index; WHO FC, World Health Organisation functional class.

Note: Variables are presented as number and percentage of patients in a disease group, unless otherwise stated.

[a]From current European Society of Cardiology guidelines.[2]

sub-occlusion ($n = 4$) or total occlusion ($n = 58$) of a vessel. One or more additional characteristics of chronic thromboembolism were present in all CTEPH patients, including webs ($n = 22$), bands ($n = 27$), intimal thickening ($n = 8$), abrupt narrowing of the vessel ($n = 11$), beading ($n = 28$), tortuosity ($n = 1$), and stenosis ($n = 38$).

CTEPH patients had a higher prevalence of emphysema ($n = 11$ vs. n = 7), fibrosis ($n = 11$ vs. $n = 5$), and/or mosaic attenuation patterns ($n = 27$ vs. $n = 2$) compared to PE patients. Conversely, PE patients had a higher prevalence of atelectasis ($n = 33$ vs. $n = 19$), infarcts ($n = 11$ vs. $n = 7$), and pleural effusion ($n = 14$ vs. $n = 5$) compared to CTEPH patients. Ground glass opacification was similar between the groups ($n = 21$ vs. $n = 23$).

Comparison of perfusion variables

Whole lung PBV was higher in CTEPH patients compared to acute PE patients with a median volume of 4103 mL [3405, 4830] compared to 3399 mL [2554, 4284] ($p < 0.001$). This was also true for lung and lobar PBV (Figure 3b–d).

PERMANOVA analysis encompassing all PBV variables showed a difference between the two groups (F-statistic = 13.3, $p = 0.002$) after testing for homogeneity of variance. We performed random label shuffling of the disease groups, and after 1000 permutations, the median F-statistic was 0.49 [0.17, 1.34] and was different from the observed F-statistic ($p < 0.001$).

Lung PBV score and PA/dAo ratio

Median total PBV defect score did not differ between the groups with median scores of 12 [10, 14] for CTEPH-compared to 13 [10, 14] for acute PE ($p = 0.44$). The distribution of grades for each lobe was similar between the groups, except for the right upper lobe ($p = 0.01$), where PE patients had a higher prevalence of grade 1 and

TABLE 2 Comparison of median values for clinical variables.

	Acute PE	CTEPH	p
Mean arterial blood pressure (mmHg)	100 [89, 106]	99 [92, 108]	0.596
Heart rate (1/min)	92 [81, 107]	76 [67,87]	<0.001
Peripheral arterial saturation, oximetry (%)	95 [93,97]	94 [92,95]	0.025
TAPSE (mm)	17 [13,20]	19 [15,23]	0.117
TR-gradient (mmHg)	45 [35,56]	65 [49,80]	<0.001
Lactate (mmol/L)	1.50 [1.10, 2.10]	0.80 [0.62, 1.10]	<0.001
Troponin I (ng/L)	242 [50, 657]		
Fibrin D-dimer (mg/L)	9.10 [6.27, 18.30]		
6-min walking distance (meters)		365 [210, 450]	
Borg(CR10)-scale		6 [3,7]	
NT-proBNP (ng/L)		653 [227, 2134]	
mPAP (mmHg)		42 (10)	
PVR (WU)		6.8 [4.7, 9.7]	
Cardiac output (L/min)		4.5 [3.5, 5.5]	
Cardiac index (L/min/m^2)		2.3 [1.9, 2.8]	

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; IQR, interquartile range; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; PE, pulmonary embolism; PVR, pulmonary vascular resistance; TAPSE, tricuspid annular plane systolic expulsion; TR, tricuspid regurgitation; WU, Wood units.

Note: Variables are presented as median [IQR].

3, and CTEPH patients a higher prevalence of grade 2 and grade X (Supporting Infomation S1: Figure S2).

PA/dAo ratio was higher in CTEPH patients with a median of 1.26 [1.15, 1.45]) compared to 1.06 [1, 1.21] in acute PE patients ($p < 0.0001$). (Supporting Information S1: Figure S3).

Correlation analysis

PBV variables showed mostly poor correlation with clinical and RHC variables (Table 3). For CTEPH patients, CO and most PBV variables were correlated, though the strength and direction of the relationships were poor (rho = 0.18–0.30).

Multivariate logistic regression revealed a significant association between right lung PBV and CO ($p = 0.014$). For every 1% increase in right lung PBV, the estimated increase in CO was 0.33% (95% CI: 0.07; 0.58) with an R^2 of 0.077.

PA/dAo correlated with mPAP (rho = 0.37, $p < 0.001$) albeit poorly. There was no significant relationship between PA/dAo and PVR, CO or CI ($p = 0.23$–0.50). Total PBV defect score did not correlate to PVR, CO, CI, or mPAP ($p = 0.14$–0.84).

Differentiation between disease groups

The odds-ratios of lobar PBV were predictors of disease groups (Table 4). In patients with suspected PE or CTEPH, the odds of having CTEPH instead of acute PE increases by 3.66 (95% CI: 1.69; 8.80) when right lower lobe PBV doubles, and by 2.42 (95% CI: 1.29; 5.13) when left lower lobe PBV doubles.

Right- and left lower lobe PBV demonstrated a fair ability to discriminate between the diseases in the validation data set (Figure 4). The AUC for the right lower lobe was 0.71 (95% CI: 0.56; 0.84). We determined the optimal cut-off to be 0.54 using Youden's index. This resulted in a sensitivity of 0.69 (95% CI: 0.51; 0.88), a specificity of 0.69 (95% CI: 0.51; 0.87), a positive predictive value of 0.67 (95% CI: 0.48; 0.86), and a negative predictive value of 0.72 (95% CI: 0.54; 0.90).

For the left lower lobe, the AUC was 0.72 (95% CI: 0.56; 0.86). Applying a cut-off of 0.47, the sensitivity was 0.87 (95% CI: 0.73; 1), specificity was 0.58 (95% CI: 0.39; 0.77), positive predictive value was 0.64 (95% CI: 0.48; 0.81), and negative predictive value was 0.83 (95% CI: 0.66; 1). Models combining two or more PBV variables did not improve AUC values.

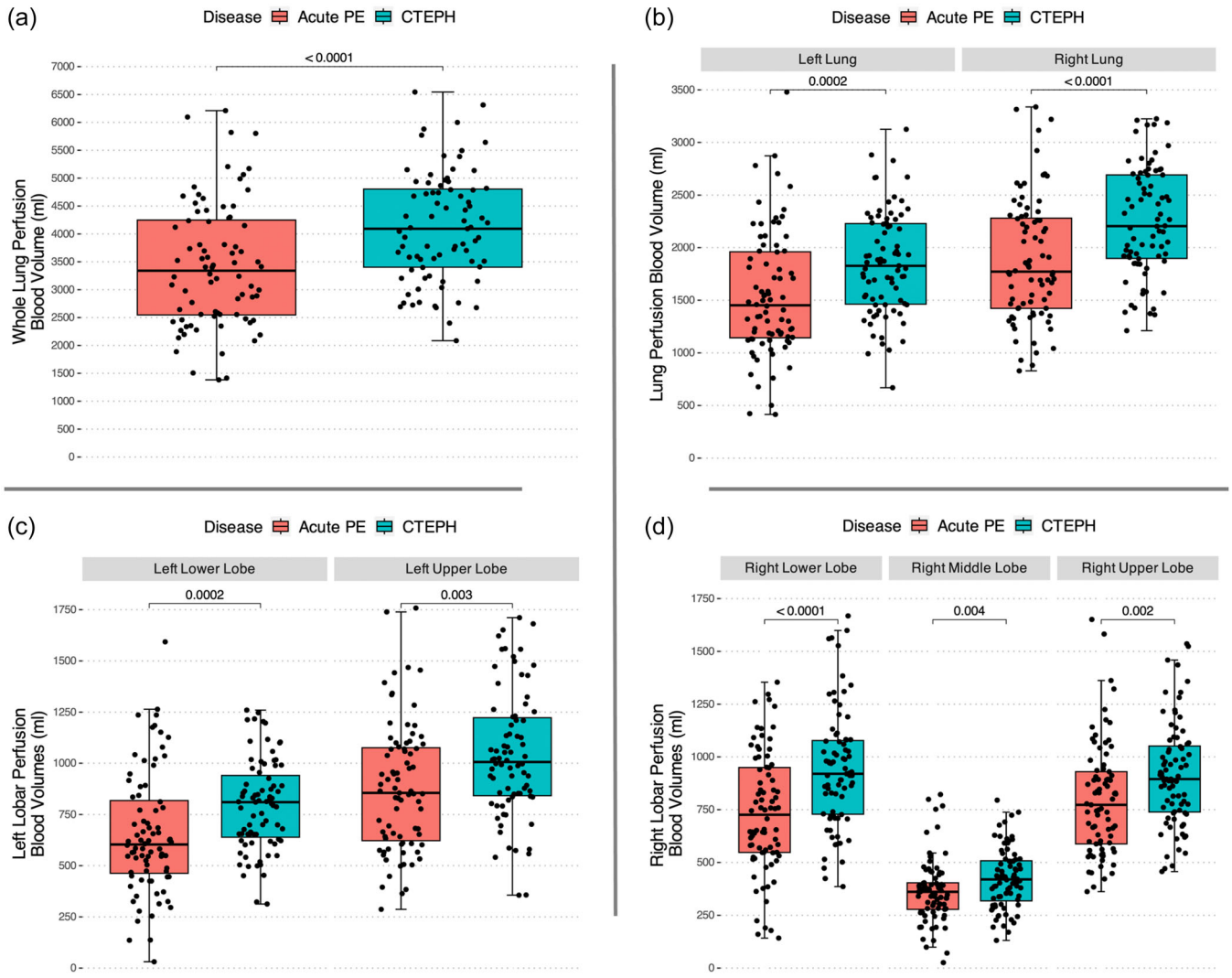

FIGURE 3 Comparison of median perfusion blood volumes. Boxplots summarizing median [IQR] perfusion blood volume differences between acute PE and CTEPH patients. Whole lung blood volume (a), lung (b), and lobar (c, d) blood volumes are presented as median [IQR] with error bars. Each dot represents an individual. CTEPH, chronic thromboembolic pulmonary hypertension; IQR, interquartile range; PE, pulmonary embolism.

TABLE 3 Correlation table for perfusion blood volume variables.

	Right upper Rho	Right middle Rho	Right lower Rho	Left upper Rho	Left lower Rho	Right lung Rho	Left lung Rho	Whole lung Rho
mPAP	0.03	−0.12	0.06	−0.02	−0.07	−0.01	−0.06	−0.04
Cardiac output	0.18*	0.27*	0.20	0.25*	0.30**	0.28*	0.29*	0.30**
Cardiac index	0.04	0.14	0.12	0.15	0.17	0.15	0.19	0.18
PVR	−0.09	−0.22	−0.06	−0.10	−0.21	−0.16	−0.17	−0.18

Abbreviations: mPAP, mean pulmonary arterial pressure; PBV, perfusion blood volume; PVR, pulmonary vascular resistance; Rho, Spearman's rank correlation coefficient.

Note: Correlation table from Spearman's rank correlation tests between PBV variables and selected hemodynamic variables.

*$p < 0.05$; **$p < 0.01$.

TABLE 4 Prediction of disease group.

Perfusion blood volume (mL)	Odds-ratio (95% CI)	p	AUC (95% CI)
Right upper lobe	3.30 (1.41; 8.30)	0.007	0.65 (0.49; 0.80)
Right middle lobe	2.20 (1.08; 4.75)	0.036	0.62 (0.46; 0.78)
Right lower lobe	3.66 (1.69; 8.80)	0.002	0.71 (0.56; 0.84)
Left upper lobe	3.13 (1.49; 7.12)	0.004	0.61 (0.44; 0.76)
Left lower lobe	2.42 (1.29; 5.13)	0.012	0.72 (0.56; 0.86)

Abbreviations: AUC, area under the receiver operation characteristics curve; CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism.

Note: Coefficients are presented as odds-ratios of being in the CTEPH group relative to the acute PE group.

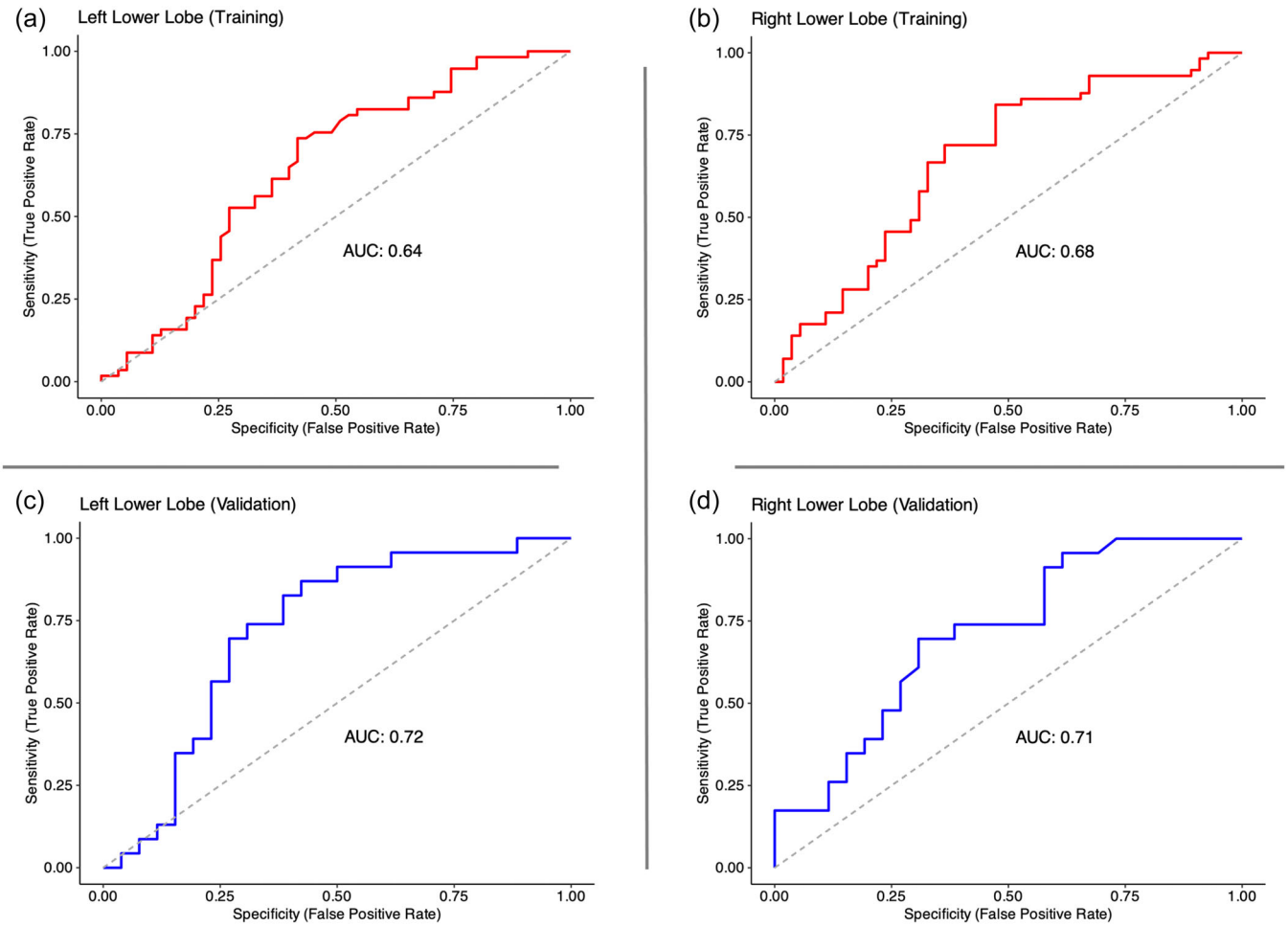

FIGURE 4 Receiver operating characteristics curves. ROC-curve for left lower lobe PBV training (a) and validation (c) data set, and right lower lobe PBV training (b) and validation (d) data set. AUC, area under the curve; PBV, perfusion blood volume; ROC, receiver operating characteristic.

DISCUSSION

Median whole lung, lung, and lobar perfusion blood volume were higher in CTEPH patients compared to acute PE patients, and right- and left lower lobes showed a fair ability to differentiate between acute PE and CTEPH. CO and PBV variables were correlated in CTEPH patients, but correlation between PBV variables and other RHC and clinical parameters were poor, both for all patients, and in separate disease groups.

The pulmonary perfusion differences between the diseases may be explained by the differences between an

acute, decompensated disease phenotype and a chronic, compensated disease phenotype. The prevalence of bronchopulmonary collaterals is increased and may contribute up to 30% of pulmonary blood flow in CTEPH patients. This may register as higher perfusion values in areas hypoperfused by normal pulmonary vasculature.[16,17,39] Ammari et al.[40] found that 44% of acute PE patients had a cardiac index (CI) < 2.2 L/min/m^2 and that TAPSE predicted reduced CI. RHC was not performed in acute PE patients, but TAPSE and TR-gradient are reduced compared to the CTEPH patients. It is likely that CI is lower than the 2.3 L/min/m^2 we found in the CTEPH group.

PA/dAo ratio was higher in CTEPH patients compared to PE patients. PA diameter is often dilated in CTEPH patients as the right ventricle attempts to compensate for the increased PVR over time.[4,41,42]

Total PBV defect score did not differ between CTEPH and PE patients and the distribution of grading was similar across the lobes. Though perfusion patterns might differ between the two diseases,[16,43–45] the size of the perfusion defect on a lobar level may be the same.

Total PBV defect score and PA/dAo ratio correlated poorly with mPAP, PVR, CO, and CI. This is inconsistent with Takagi et al.[35] However, their study mainly included female patients, and included DECT scans and RHC from both preoperative workups and postoperative follow-ups.

Comparison of methods

Our study utilizes automatic, user-independent quantification of pulmonary perfusion. Other studies have reported on the use of quantitative lung perfusion from DE-CTPA for evaluating clinical severity in CTEPH and acute PE separately.[19,21,22,24,28,46]

Few involve both diseases or involve different quantitative perfusion parameters, and the results are divergent.[23,47] Both find that quantitative perfusion metrics differs between diseases, but one finds CTEPH patients had lower perfusion metrics compared to acute PE patients.[23] This study had few patients in the PE group ($n = 13$) compared to the CTEPH group ($n = 53$). Conversely, the study with comparable results to ours had a similar number of patients in the PE ($n = 57$) and CTEPH ($n = 52$) groups. Both found similar results for discriminating between the disease groups with AUC ranging from 0.67 to 0.77. The three studies were retrospective and single center. We identified patients who already had an acute PE or CTEPH diagnosis and excluded those without a DECT scan. We did not include a control group. The two other studies identified patients who underwent DECT for suspected PE or CTEPH, or for suspected CTEPH, but included incidental PE patients as well. They included the patients where PE or CTEPH was not found as control groups. Nallasamy et al.[23] found moderate diagnostic accuracy when differentiating between the control group ($n = 80$) and CTEPH/CTED patients, but not when differentiating between PE and the control group. The divergent results from ours and inconsistency in diagnostic performance might be explained by the substantial differences in group sizes. Gertz et al.[47] found a similar diagnostic accuracy when differentiating between a combined group of CTEPH and PE patients ($n = 109$) and the control group ($n = 22$), but group sizes are skewed.

Singh et al.[28] found that mean lobar PBV variables were lower in acute PE patients compared to patients without PE and mean right lower lobe PBV was lower in patients with occlusive PE compared to patients with non-occlusive PE. While not directly comparable to our patients, the method is the same, and shows that varying degrees of obstruction (or no obstruction) affect pulmonary perfusion and that DECT can estimate these differences.

Arru et al.[37] investigated differences in quantitative perfusion metrics for patients with COVID-19, with and without PE. We found a significant difference in mean whole lung PBV between patients with and without PE. Mean whole lung PBV was lower in patients with adverse outcomes (death, hospital stay duration >10 days, and intubation). This study demonstrates the applicability for estimating perfusion differences, while exploring the potential for risk assessment and outcome prediction.

Both studies only include PE patients. Including a group of CTEPH patients helps expand the scope to a chronic manifestation of the disease and provides valuable insight into differences beyond hemodynamics, biochemical markers, and clinical presentation.

Clinical perspectives

We were able to replicate that quantitative perfusion variables correlated with variables from RHC in CTEPH patients.[19,21,46] The results differ, some reporting negative and some positive correlations, and the strength of the correlations varies. These differences may be explained by differences in data collection and inclusion/exclusion criteria.

Meinel et al.[21] found negative correlations between PAP and quantitative perfusion, but only included 25 patients and RHC was performed within a large timeframe relative to DECT (6 months before to 6 months after).

Tsutsumi et al.[46] included 58 patients who underwent DECT for detailed examination or follow-up of CTEPH.

They found positive correlation with PAP and negative correlation with CI. They excluded patients who underwent treatment with BPA or PTEA, explaining that RHC was performed at varying time intervals relative to DECT or after treatment. The time interval between RHC and DECT is not stated. We included patients regardless of treatment, and RHC was performed within 1 day of DECT, except for a small number of cases ($n = 5$).

This emphasizes the need for prospective studies with study designs including both diseases. Prospective studies with timepoints before and after treatment of each disease, possibly with additional follow-up, would help investigate the feasibility of quantitative perfusion from DECT for evaluation of severity, prognosis, treatment response, and outcome prediction.

LIMITATIONS

Several limitations should be addressed. This study was retrospective and without follow-up, making it prone to selection bias. We included all patients with DE-CTPA-scans and only excluded patient where the diagnosis was refuted, software was unable to process the images, or other diagnoses were the primary concern. Further, no specific outcome was registered. The main objective was to estimate differences in lung PBV between the two diseases. The lack of follow-up makes this study unable to evaluate changes after treatment, where quantitative lung perfusion may have potential.

DE-CTPA images were unavailable for 450 patients. The DECT scanner was one of several CT scanners used in the Department and acute PE patients were scanned in the first available scanner.

The study had a low prevalence of acute PE patients in the low and high-risk group compared to the intermediate-low and intermediate-high risk groups which should be noted when extrapolating the results. Low risk patients are not normally admitted to the Dept. of Cardiology. All patients regardless of risk group were included in the analyses.

Calculation of quantitative perfusion variables is based on attenuation differences between soft tissue, air, and iodine on PBV images.[10,45] As such, it is affected by atelectasis, fibrosis, consolidation, infection, collateral supply, beam-hardening artifacts and motion artifacts from the diaphragm. In our study, CTEPH patients had a higher prevalence of emphysema and fibrosis which may affect perfusion values in some areas of the lung, while PE patients had a higher prevalence of atelectasis and infarcts which may do the same, but we cannot exclude a bias in the perfusion variables between PE and CTEPH patients.

CONCLUSIONS

DE-CTPA can estimate differences in quantitative lung and lobar perfusion variables between acute PE and CTEPH patients, and these variables might contribute to classifying patients into correct disease groups.

AUTHOR CONTRIBUTIONS

Jacob V. Hansen handled application for IRB approval, identified patients eligible for inclusion, performed statistical analysis, and drafted the manuscript. Jacob. V. Hansen and Mette. W. Poulsen collected patient data, processed DECT scans, and recorded results. Jacob. V. Hansen, Mads. D. Lyhne, Jens. E. Nielsen-Kudsk, Asger Andersen and Mannudeep. K. Kalra conceptualized the study and the design. All authors contributed to the interpretation of the results and have critically revised the manuscript. The final version for submission was approved by all authors.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was approved by the institutional review board and informed consent was waived for this retrospective analysis. All CT scans were deidentified before export to a secure device. All data extracted from the patients' electronic records are kept on a secure server operated by Aarhus University and will be deleted after a designated amount of time as mandated by Danish Data Protection Act and national laws.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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