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A Prospective, Comparative Study of Planar and Single-photon Emission Computed Tomography Ventilation/Perfusion Imaging for Chronic Thromboembolic Pulmonary Hypertension

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Short title: Planar and SPECT V/Q imaging for CTEPH

ABSTRACT

Objectives

The study compared the diagnostic performance of Planar Ventilation/perfusion (V/Q) and V/Q Single-photon computed tomography (SPECT), and determined whether combining perfusion scanning with low-dose computed tomography (Q-LDCT) may be equally effective in a prospective study of patients with chronic thromboembolic pulmonary hypertension (CTEPH) patients.

Background

V/Q scanning is recommended for excluding CTEPH during the diagnosis of pulmonary hypertension (PH). However, Planar V/Q and V/Q SPECT techniques have yet to be compared in patients with CTEPH.

Methods

Patients with suspected PH were eligible for the study. PH attributable to left heart disease or lung disease was excluded, and patients whose PH was confirmed by right heart catheterization and who completed Planar V/Q, V/Q-SPECT, Q-LDCT, and pulmonary angiography were included. V/Q images were interpreted and patients were diagnosed as instructed by the 2009 EANM guidelines, and pulmonary angiography analyses were used as a reference standard.

Results

A total of 208 patients completed the study, including 69 with CTEPH confirmed by pulmonary angiography. Planar V/Q, V/Q-SPECT, and Q-LDCT were all highly effective for diagnosing CTEPH, with no significant differences in sensitivity or specificity observed among the three techniques (Planar V/Q [sensitivity/specificity]: 94.20%/92.81%; V/Q-SPECT: 97.10%/91.37%,

Q-LCDT: 95.65%/90.65%). However, V/Q-SPECT was significantly more sensitive (V/Q-SPECT: 79.21%; Planar V/Q: 75.84%, p=0.012; Q-LDCT: 74.91%, p<0.001), and Planar V/Q was significantly more specific (Planar V/Q: 54.14%; V/Q-SPECT 46.05%, p<0.001; Q-LDCT: 46.05%, p=0.001) than the other two techniques for identifying perfusion defects in individual lung segments.

Conclusions

Both Planar V/Q and V/Q-SPECT were highly effective for diagnosing CTEPH, and Q-LDCT may be a reliable alternative method for patients who are unsuitable for ventilation imaging.

Keywords: pulmonary hypertension, chronic thromboembolic pulmonary hypertension, ventilation/perfusion scanning, low-dose computed tomography

Abbreviations

CTEPH: chronic thromboembolic pulmonary hypertension

PH: pulmonary hypertension

V/Q: ventilation/perfusion

LDCT: low-dose computed tomography

PE: pulmonary embolism

mPAP : mean pulmonary arterial pressure

PAWP: pulmonary artery wedge pressure

TPR: total pulmonary resistance

PVR: Pulmonary vascular resistance

PPV: positive predictive value

NPV: negative predictive value

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is classified as group 4 pulmonary hypertension (PH) in guidelines published by the European Society of Cardiology (ESC) and European Respiratory Society (ERS) (*1*). It is characterized by the presence of macroscopic thromboembolic lesions in the proximal or distal pulmonary arteries and microscopic pulmonary vasculopathy (*2)*, which impede blood flow and increase pressure in the pulmonary arteries. The lesions also produce regions of the lungs that are adequately ventilated during inhalation but inadequately perfused by the pulmonary circulation, and these ventilation/perfusion (V/Q) mismatches can be detected, with high sensitivity and specificity, via imaging techniques that map both ventilation (V) and perfusion (Q) in the lungs (i.e., V/Q scanning) (*3*). Thus, V/Q scanning is the recommended procedure for identifying or excluding the presence of CTEPH during the diagnosis of patients with PH (*1*).

Two primary methods of V/Q scanning are currently available: planar V/Q scintigraphy, which was first introduced in the 1960s and produces 2-dimensional images, and V/Q single photon emission computed tomography (SPECT), a more advanced, 3-dimensional technique. Of the two, V/Q-SPECT is less likely to produce non-diagnostic scans and is more sensitive for diagnosing acute pulmonary embolism (PE) (*4,5*); however, the techniques have yet to be compared in patients with CTEPH. Furthermore, some evidence indicates that acute PE can also be diagnosed by combining a perfusion scan with chest X-ray or thoracic CT (*6*), which suggests that ventilation scanning may also be unnecessary for the diagnosis of CTEPH. Thus, the study described in this report was designed to

compare the diagnostic performance of Planar V/Q, V/Q-SPECT, and a combination of perfusion SPECT with low-dose CT (Q-LDCT) in a prospective study of patients with CTEPH. Pulmonary angiography assessments, which were once considered the gold standard for PE diagnosis, were also conducted to serve as a single, unambiguous benchmark for calculations of sensitivity, specificity, and accuracy.

MATERIALS AND METHODS

Study Design and Study Population

This study complied with the amended Declaration of Helsinki and was approved by the Institutional Review Board of Fuwai Hospital (Ethical approval No.402); all participants provided informed consent. Patients referred to the National Center for Cardiovascular Disease and Fuwai Hospital for suspected PH were recruited prospectively from February 2016 to September 2018 and diagnosed according to the algorithm published in the Guidelines on Diagnosis and Treatment of PH by the ESC and ERS (*1*) (Fig. 1). Patients diagnosed with PH attributable to left heart disease or lung disease were excluded before the V/Q scanning procedure was attempted; additional exclusion criteria included failure to complete right heart catheterization or pulmonary angiography, and a resting mean pulmonary arterial pressure (mPAP) of less than 25 mmHg upon catheterization. Patients whose PH diagnosis was confirmed via right heart catheterization and who completed the Planar V/Q, V/Q-SPECT, Q-LDCT, and pulmonary angiography procedures were included in the study. Our previous experience at the Center indicated that ~35% of recruited patients would be diagnosed with CTEPH via our benchmark assessment (pulmonary angiography); thus, planned enrollment was ~200,

yielding populations of ~70 patients in the CTEPH group and ~130 patients in the non-CTEPH group. Based on the anticipated sensitivity (95%) and specificity (90%) scores, with a 2-sided significance (alpha) of 0.05, these sample sizes would estimate the performance of each technique for diagnosing CTEPH in patients with a precision of less than 5% (one-half of the width of the 95% confidence interval).

Planar V/Q, V/Q SPECT, and Q-LDCT

V/Q scanning and chest LDCT were performed with hybrid SPECT/CT cameras (SymbiaT16 SPECT-CT, Siemens, Germany; Discovery NM640 SPECT-CT, GE, USA). The imaging protocols were conducted over two days with a dual-head gamma camera equipped with low energy, high-resolution, parallel-hole collimators. On the first day, planar perfusion scintigraphy, SPECT perfusion imaging, and chest LDCT were performed consecutively. For planar perfusion scintigraphy, patients were in the supine position and intravenously injected with 111-185 MBq of ^{99m}Tc-macroaggregated albumin (2-7×10^5 macroaggregated albumin particles); then, planar perfusion imaging was performed with a matrix size of 256×256 in eight views (anterior, posterior, left anterior oblique, left lateral, left posterior oblique, right anterior oblique, right lateral, and right posterior oblique), and a total of 500 kilocounts per projection were collected. Immediately after planar acquisition, SPECT images were acquired with a matrix size of 64×64, zoom 1.0, and 3° per frame over 360°, and the duration of each projection was 10 s. Chest LDCT was performed without contrast enhancement and with the following parameters: pitch 1.25, rotation time 1.0 s, effective tube current-time product 30 mAs, and tube voltage 120 kV; Filtered back projection was used for CT

reconstruction. CT image reconstruction was performed with commonly used parameters for slice thickness (2.5 mm) and increments (1.25 mm). On the second day, ventilation planar and SPECT scanning was performed. Patients inhaled 20-30 MBq ^{99m}Tc-Technegas (Technegas Generator, Australia); then, ventilation planar scanning was conducted in the same manner as perfusion planar scanning, and SPECT ventilation images were acquired immediately afterward with zoom 1.0 and 3° per frame over 360°. The duration of each projection was 15 s. Reconstruction for both SPECT perfusion and ventilation imaging was performed via ordered subset expectation maximization with eight subsets and two iterations. The estimated effective radiation dose from V/Q scanning was 2.1 mSv, the average dose-length product for chest LDCT was 153.5 mGy*cm, and the average measured effective dose was 2.1 ± 0.62 mSv. Total effective dose (V/Q +LDCT) was 4.2 mSv.

Image Interpretation

V/Q and LDCT images were interpreted by two experienced nuclear physicians who were blinded to clinical results, and diagnosis was determined via consensus reading. To avoid recall bias, Planar V/Q images were reviewed first, V/Q SPECT images were reviewed one week later, and the LDCT and fused Q-LDCT images were reviewed one week after V/Q-SPECT images were reviewed. V/Q images from both planar and SPECT imaging were interpreted, and a diagnosis of PE was determined, according to the 2009 EANM Guidelines for Ventilation/perfusion Scintigraphy (*7*); the guidelines do not differentiate between acute PE or CTEPH and, consequently, any perfusion defect meeting the criteria is classified as PE. A V/Q mismatch in at least one segment or two subsegments that conformed to the pulmonary vascular anatomy was considered diagnostic for PE, while multiple

V/Q abnormalities that were not typical for specific diseases were considered nondiagnostic for PE. Criteria for the absence of PE were a normal perfusion pattern conforming to the anatomic boundaries of the lungs; in the absence of mismatch, matched or reversed mismatch V/Q defects of any size, shape or number; or a mismatch that did not have a lobar, segmental or subsegmental pattern. LDCT and fused Q-LDCT images in axial, coronal, and sagittal planes were displayed for review with 3-dimentional registration software (Xeleris 3 Functional Imaging Workstation, GE). LDCT and Q-SPECT images were reviewed separately, and any perfusion defect in the absence of a CT abnormality was identified as a mismatch; mismatches in at least one segment or two subsegments from Q-LDCT imaging was considered diagnostic for PE. (Figs. 2A and 2B).

Pulmonary Angiography and Pulmonary Hemodynamic Measurements

Pulmonary angiography was performed with an Allura Xper FD10/10 angiographic apparatus (Philips, Holland, Amsterdam, The Netherlands); 25 images were obtained per second with a matrix size of 1024×1024, and all images were collected with the same imaging parameters. The patient's right or left common femoral vein was cannulated, and a 6F-sheath (Cordis, Bridgewater, New Jersey, USA) was introduced. For angiograms of the main pulmonary arteries, a power injector was used to deliver 30-40 mL of iohexol (Omnipaque 350, GE Health-Ireland, Shanghai, China) through a 6-F pigtail catheter (Cordis) at a rate of 15–20 mL/s. For subselective studies, a hand or power injector was used to deliver 10-15 mL of the contrast material through a 5-F curved tip catheter (Cordis) at approximately 5-8 mL/s. Anterior and supplemental oblique projections were obtained, and all images were evaluated by two experienced physicians.

Hemodynamic parameters (mean right atrial pressure, mPAP, and pulmonary artery wedge pressure [PAWP]) were recorded during right-heart catheterization within one week after V/Q scanning. Cardiac output (CO) was calculated as the mean value of three measurements obtained via the thermodilution method, and pulmonary vascular resistance (PVR) and total pulmonary resistance (TPR) were calculated with the following equations: PVR=(mPAP－PAWP)/CO; TPR=mPAP/CO.

Statistical Analysis

Continuous data were expressed as mean ± standard deviation, and categorical data were expressed as frequency and percentage (%). Differences between the two groups were analyzed for significance with the unpaired Student t test for continuous variables and with the Fisher exact test for categorical variables. Pulmonary angiograph was used as a benchmark for evaluating the diagnostic performance of each method. Differences in sensitivity, specificity, and accuracy were analyzed with the McNemar test, and the kappa value was estimated to determine the degree of agreement between each method and pulmonary angiography. All statistical analyses were performed with SPSS 19.0 software (SPSS Inc., Chicago, IL, USA), and significance was defined as a 2-tailed p value of <0.05.

RESULTS

Patient Baseline Characteristics

Ninety patients were excluded from the study: 11 with PH attributable to left heart disease or lung disease, 58 who failed to complete the right heart catheterization or pulmonary angiography

procedures, and 21 whose resting mPAP was less than 25 mmHg upon right heart catheterization. A total of 208 patients were included in the study (Table 1), 69 of whom (33.2%) were diagnosed with CTEPH when evaluated via pulmonary angiography. There were no non-diagnostic decisions during V/Q interpretation. Of the 139 patients with non-CTEPH diagnoses, 135 patients were diagnosed with Group 1 PH (idiopathic pulmonary arterial hypertension [PAH], 69; heritable PAH, 3; and PAH associated with connective tissue disease, 27, congenital heart disease, 35, and pulmonary veno-occlusive disease, 1) and 4 were diagnosed with Group 5 PH (PH associated with fibrosing mediastinitis, 1, and PH of unclear mechanisms, 3).

Diagnostic Performance of Planar V/Q and V/Q-SPECT

When pulmonary angiography was used as the benchmark for CTEPH diagnosis, Planar V/Q had a sensitivity of 94.20% and a specificity of 92.81%, while V/Q SPECT had a sensitivity of 97.10% and a specificity of 91.37%. Neither sensitivity nor specificity differed significantly between Planar V/Q and V/Q SPECT. Calculations of accuracy, as well as positive and negative predictive values (PPV and NPV, respectively), were also similar between techniques (Accuracy: Planar V/Q, 93.27%; V/Q-SPECT, 93.27%. PPV: Planar V/Q, 86.67%; V/Q-SPECT, 84.81%. NPV: Planar V/Q, 96.99%; V/Q-SPECT: 98.45%) (Table 2), while kappa analyses indicated that the results from both techniques were in good agreement with each other (kappa=0.897) and with the results from pulmonary angiography (Planar V/Q vs pulmonary angiography: kappa=0.851; V/Q SPECT vs pulmonary angiography: kappa=0.854).

The effectiveness of Planar V/Q and V/Q-SPECT for identifying perfusion defects was also evaluated segmentally for the 69 patients whose CTEPH diagnoses were confirmed via pulmonary angiography. Assessments were based on a 20-segment lung model, and the results obtained from the interpretation of Planar V/Q and V/Q-SPECT images for each individual segment were compared to the results of benchmark assessments (pulmonary angiography) in the same segment. A total of 1380 lung segments were evaluated. An average of 12.91±4.9 segments per patient displayed a mismatched pattern on Planar V/Q scan, while V/Q-SPECT detected 13.94±4.8 mismatched segments per patient. 861 segments were positive for PE when evaluated via pulmonary angiography, compared to 891 and 962 that displayed mismatches when evaluated via Planar V/Q and V/Q-SPECT, respectively. Thus, mismatched segments were more frequently identified via V/Q-SPECT than Planar V/Q, and this increase was accompanied by a correspondingly higher sensitivity score (Planar V/Q, 75.84%; V/Q-SPECT, 79.21%; p=0.012) (Table 3). However, specificity scores were significantly lower for V/Q-SPECT than for Planar V/Q analyses (Planar V/Q, 54.14%; V/Q-SPECT, 46.05%; $p<0.001$), while measures of accuracy (Planar V/Q, 67.68%; V/Q-SPECT, 66.74%), PPV (planar V/Q, 73.29%; V/Q-SPECT, 70.89%), and NPV (Planar V/Q, 57.46%; V/Q-SPECT, 57.18%) for the two techniques were similar. Thus, although mismatched segments were more likely to be correctly identified via V/Q-SPECT than Planar V/Q, V/Q-SPECT also led to a greater number of false CTEPH indicators, and the overall accuracy of the two techniques was similar.

Diagnostic Performance of Q-LDCT

When patients were evaluated via Q-LDCT, 79 were positive and 129 were negative for CTEPH. 66 of the CTEPH-positive and 126 of the CTEPH-negative patients were diagnosed with or without CTEPH, respectively, via pulmonary angiography, and calculations of sensitivity (95.65%), specificity (90.65%), accuracy (92.31%), PPV (83.54%), and NPV (97.67%) for Q-LDCT analyses of individual patients did not differ significantly from the corresponding calculations for Planar V/Q or V/Q SPECT (Table 2). For segmental analyses, defects were identified as mismatches between perfusion (Q-SPECT) and CT images in at least one segment or two subsegments, and our results indicated that Q-LDCT was significantly less sensitive (74.91%; $p<0.001$) than V/Q-SPECT, significantly less specific (46.05%; $p=0.001$) than planar V/Q, and significantly less accurate (64.06%; $p=0.005$ versus V/Q planar, $p=0.003$ versus V/Q-SPECT) than either of the other two techniques (Table 3).

DISCUSSION

V/Q scanning was first established in the 1960s and, after more than a half-century of development, has become the first-line imaging technique for diagnosing PE because of its noninvasiveness, low radiation burden, and high sensitivity. The ESC/ERS Joint Task Force recommends that V/Q scanning be used to identify or exclude CTEPH during an early stage of the algorithm for diagnosing PH, and their accompanying report suggests that V/Q-SPECT may be more effective than Planar V/Q (*1*), but the two techniques have yet to be rigorously compared. Thus, this investigation is the first to prospectively evaluate the effectiveness of Planar V/Q and V/Q-SPECT for CTEPH diagnosis in a large group of patients with PH, and our results confirmed that both techniques were highly effective for detecting or excluding CTEPH in individual patients, with no significant

differences in sensitivity, specificity, or accuracy. Our results also indicate that Q-LDCT could be a reliable alternative method for identifying CTEPH in patients with PH when ventilation methods are unavailable.

V/Q-SPECT is considered more accurate than Planar V/Q for evaluations of acute PE by an increasing majority of physicians and researchers (*8*). However, previous investigations of the diagnostic performance of lung-scanning technology for CTEPH have yielded varying results (*9,10*), and extrapolating the findings from studies of acute PE to CTEPH may be problematic, especially since the benchmark parameter for many of the acute PE studies was generated from a composite of measures, such as clinical symptoms, laboratory tests, observations at follow-up and, sometimes, Planar V/Q or V/Q-SPECT. Pulmonary angiography is rarely performed now, because CT angiography is less-invasive with similar diagnostic accuracy (*11*). Nevertheless, conventional X-ray pulmonary angiography is often required to identify patients with CTEPH who may benefit from pulmonary endarterectomy or pulmonary balloon angioplasty and can be performed during right heart catheterization (*12*). Thus, pulmonary angiography was chosen as the benchmark for the studies reported here, because it is unambiguous, reliable, and clinically relevant for studies of CTEPH.

Although both acute PE and CTEPH are caused by the obstruction of pulmonary arteries, their underlying pathologies differ substantially. For example, the pulmonary artery obstructions in patients with CTEPH are more diffuse and multisegmental, as demonstrated by our observation that the patients with CTEPH in this study typically displayed V/Q mismatches in the majority (~13 out of 20)

of lung segments. Obstructions in a single small segment or subsegment are also very unlikely to cause CTEPH but not uncommon in patients with acute PE. Furthermore, PH is a fundamental component of the CTEPH diagnosis and is characterized by the remodeling of pulmonary vessels, including the narrowing or distortion of distal pulmonary arteries, which can lead to microvasculature embolism but no evidence of thrombosis during anatomical imaging (even pulmonary angiography). For these reasons, the apparent superiority of V/Q-SPECT to Planar V/Q for diagnosing acute PE may not be translatable to patients with CTEPH. Notably, PH itself can also lead to perfusion defects that are detectable via Planar V/Q or V/Q-SPECT (*13,14*), which likely explains, at least in part, the occurrence of false-positive cases in our study.

The results from our investigation indicated that V/Q-SPECT was more sensitive than Planar V/Q for identifying mismatches in individual segments or subsegments, which is consistent with the results from previous reports (*15-17*). Notably, the results from a pilot study by Soler, et al., also indicated that SPECT perfusion scanning was more sensitive than Planar V/Q for detecting segmental pulmonary artery obstructions in patients with CTEPH; however, the ventilation scans were conducted with ^{133}Xe gas and performed only in the planar mode, because SPECT ventilation was not available (*18*). In principle, this increased sensitivity may lead to unnecessary diagnoses and overtreatment of clinically insignificant defects in patients with acute PE (*19*), but this concern is less relevant in patients with CTEPH, for whom lifelong anticoagulant therapy is recommended. Perhaps more importantly, these observations suggest that V/Q-SPECT may be superior to Planar V/Q for identifying vessels that can be targeted during pulmonary endarterectomy and pulmonary balloon

angioplasty (*20,21*), which are the most promising treatments for improving symptoms and prognoses in eligible patients with CTEPH (*12*). Thus, although our results suggested that V/Q-SPECT is no more effective than Planar V/Q for diagnosing CTEPH in individual patients, its greater sensitivity may be advantageous for certain therapeutic approaches and for postoperative assessments of newly acute PE (*22*).

Despite detailed guidelines recommending that V/Q scanning be conducted for all patients in whom PH is suspected, only 57% of patients registered in the Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative underwent V/Q scanning (*23*). This discrepancy may be partially attributable to the broad availability of more routine clinical procedures, such as chest X-ray or CT, and as SPECT/CT hybrid imaging systems become more common, the popularity of Q-LDCT–based diagnostic techniques may increase accordingly. Recent attempts to measure the accuracy of Q-LDCT have been somewhat inconsistent (*24-26*), chiefly because specificity estimates have ranged from 94% to as low as 51%, but the implications of these investigations (like those comparing the effectiveness of Planar V/Q and V/Q-SPECT) are difficult to interpret for CTEPH diagnoses, because they were conducted retrospectively in patients with PE and are confounded by the use of composite benchmarks. Thus, our observation (from a prospective study with an unambiguous and clinically relevant benchmark) that CTEPH can be effectively diagnosed via Q-LDCT could have a substantial impact on patient care, particularly for individuals whose clinical instability or symptoms (e.g., severe dyspnea) preclude ventilation imaging. Q-LDCT examinations also require less time than V/Q scanning and could provide information about other thoracic

pathologies (e.g. pneumonia, bullous emphysema, tumors) that may lead to perfusion abnormalities; however, the results from our segmental analyses suggest that the technique may be less accurate than either V/Q-SPECT or Planar V/Q for identifying the precise location of perfusion defects. The concurrent presence of parenchymal conditions in patients with CTEPH can be depicted on CT images (e.g. ground-glass opacification) resulting matched Q-LDCT pattern, which leaded to the diagnosis of absence of PE. This condition resulted more false-negative results of Q-LDCT, which can lower its sensitivity.

Study Limitations

Because this study was conducted in a single national cardiovascular disease and PH referral center, the calculated PPVs and NPVs will only be valid for patient populations in which the incidence of CTEPH is high. Our study is also limited by sample size, which may not be sufficient to exclude differences in the performance of diagnostic modalities, and by the inclusion of patients with pulmonary arteritis, which may impact our specificity measurements. Arteritis assessments are not recommended in the ESC/ERS Joint Task Force algorithm, and V/Q imaging alone typically cannot differentiate between arteritis and PE, but the condition can be identified via clinical observation; nevertheless, only nine arteritis cases were included in our study, so they are unlikely to have significantly influenced our results. Our study was also restricted to the diagnostic performance of V/Q imaging, so future studies are needed to determine whether the use of V/Q imaging can be expanded to include therapeutic applications, such as pulmonary endarterectomy and pulmonary balloon angioplasty (*27*).

CONCLUSION

The results from this investigation indicated that both Planar V/Q and V/Q-SPECT were highly effective for detecting or excluding CTEPH in patients with PH, with no significant differences in sensitivity, specificity, or accuracy observed between the two techniques. Q-LDCT may be a reliable alternative method for identifying CTEPH in patients who are unsuitable for ventilation imaging; however, V/Q-SPECT appeared to be superior to both methods for identifying perfusion defects in individual lung segments.

Conflict of Interest

None.

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Key Points

Question

Does the diagnostic performance of Planar V/Q, V/Q-SPECT, and Q-LDCT comparable in

patients with CTEPH?

Pertinent Findings

The prospective study showed Planar V/Q and V/Q-SPECT were highly effective for diagnosing CTEPH, and V/Q-SPECT was more sensitive for identifying mismatches segmentally.

Implication for Patient Care

Results from the study support the use of both Planar V/Q and V/Q SPECT for diagnosing CTEPH and Q-LDCT may be a reliable alternative method for patients who are unsuitable for ventilation imaging.

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Figure 1

Summary of patient disposition.

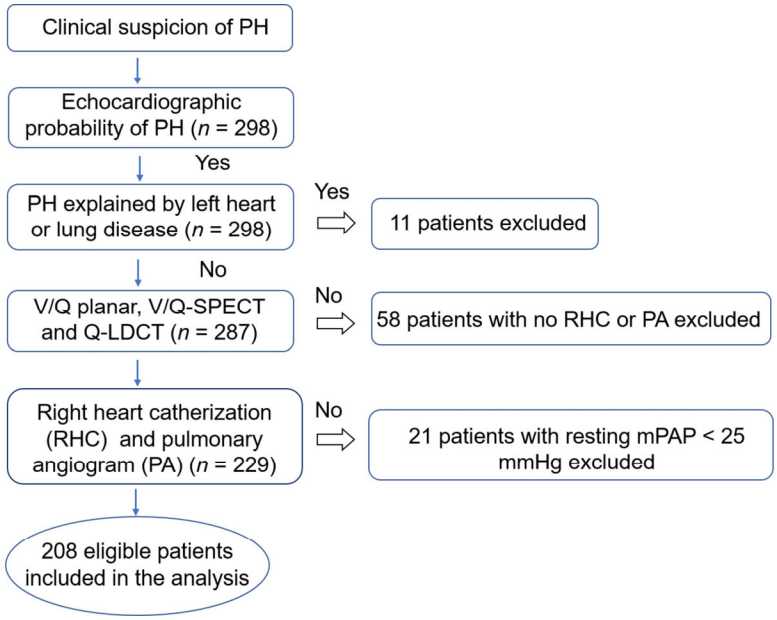

Figure 1. Summary of patient disposition.

Figure 2A

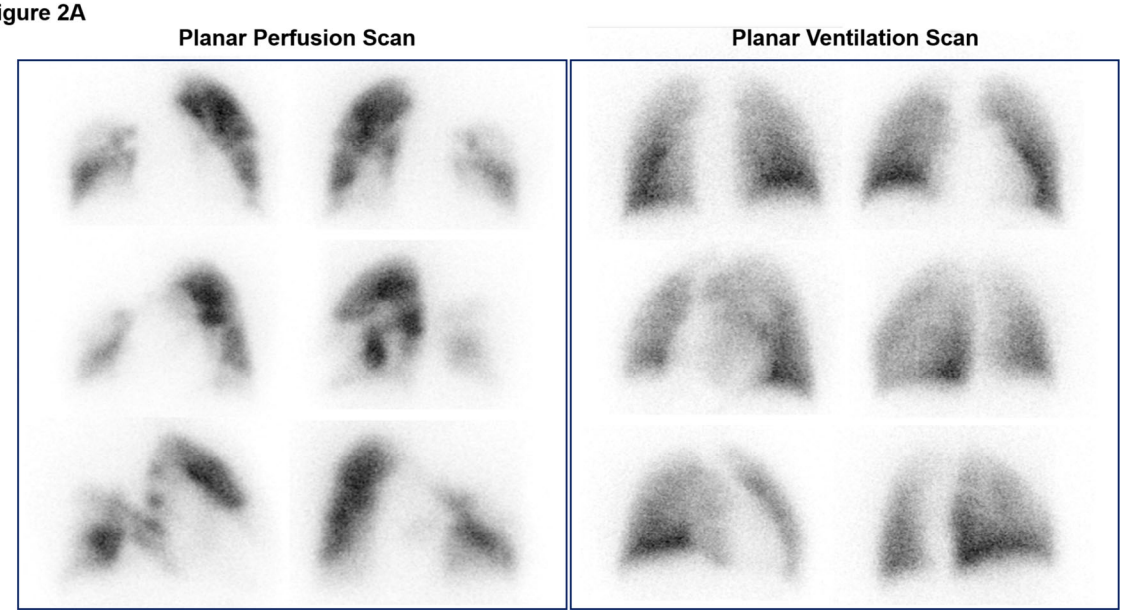

Figure 2B

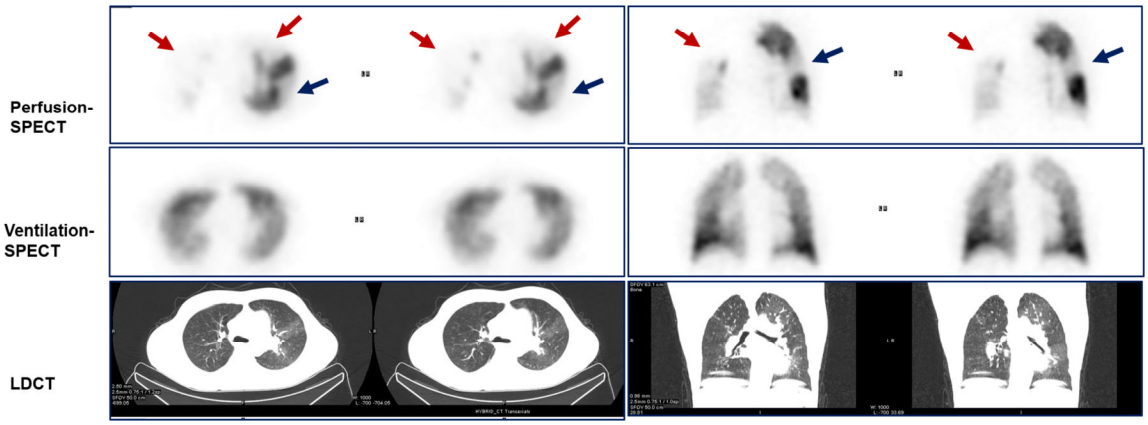

Figure 2. Representative Planar V/Q, V/Q-SPECT, and Q-LDCT images from a patient with CTEPH. **A)** Planar V/Q images show multiple segmental and subsegmental mismatched perfusion defects throughout the right lung and in the anterior segment, lingular segments, and basal segments of the left lung. **B)** Consistent with the findings from Planar V/Q, V/Q-SPECT and Q-LDCT images revealed mismatched perfusion defects in the right lung and the anterior segment of the left lung (red arrow); however, the posterior segment of the left lung (blue arrow) displays a mismatched perfusion defect in V/Q-SPECT and Q-LDCT images but not in Planar V/Q images.

Table 1. Patient baseline characteristics

	All patients (N=208)	**CTEPH (N=69)**	**Non-CTEPH (N=139)**
Age (years)	42.0±15.6	54.1±13.1	36.1±13.2
Sex (female**, %**)	140 (67.3%)	37 (53.6%)	103 (74.1%)
NYHA (n)			
I	9	0	9
II	94	29	65
III	97	39	58
IV	8	1	7
RHC			
mRAP (mmHg)	6.8±5.3	7.7±6.3	6.4±4.7
mPAP (mmHg)	53.2±15.9	48.3±11.4	55.6±17.3
mPAWP (mmHg)	8.9±4.1	10.2±4.3	8.3±3.8
CI (L/min/m^2)	2.8±0.8	2.7±0.7	2.9±0.9
PVR (Wood units)	10.8±6.2	9.3±4.5	11.8±7.0
TPR (dyn*s*cm^2)	1037.6±502.3	930.0±393.9	1087.0±539.0
Blood test			
Big ET-1 (pmol/L)	0.5±0.6	0.6±0.7	0.5±0.5
NT-proBNP (pg/mL)	1286.0±1816.0	1492.2±1735.7	1183.6±1851.7
D-Dimer (ng/ml)	618.7±1677.0	927.5±2478.7	465.4±1058.1
6MWD (m)	421.4±46.1	371.7±74.6	437.4±95.8

RHC: right heart catherization; mRAP: mean right atria pressure; mPAP: mean right pulmonary artery pressure; mPAWP: mean pulmonary artery wedge pressure; CI: cardiac index; PVR: pulmonary vascular resistance; TPR: total pulmonary resistance; Big ET-1: big endothelin-1; NT-proBNP: N-terminal pro b-type natriuretic peptide; 6MWD: 6-minute walking distance.

Table 2. Diagnostic performance for detecting or excluding CTEPH in patients.

	Sensitivity (95%CI)	Specificity (95%CI)	Accuracy (95%CI)	PPV (95%CI)	NPV (95%CI)
V/Q Planar	94.20% (88.55%-99.86%)	92.81% (88.46%-97.16%)	93.27% (89.84%-96.70%)	86.67% （78.79%-94.54%）	96.99% (94.05%-99.93%)
V/Q SPECT	97.10% (93.04%-101.16%)	91.37% (86.64%-96.09%)	93.27% (89.84%-96.70%)	84.81% (76.72%-92.90%)	98.45% (96.29%-100.61%)
Q-LDCT	95.65% (90.72%-100.59%)	90.65% (85.75%-95.55%)	92.31% (88.66%-95.96%)	83.54% (75.19%-91.90%)	97.67% (95.04%-100.31%)

V/Q: ventilation/perfusion, SPECT: single-photon emission computed tomography, Q-LDCT: perfusion scanning combined with low dose computed tomography, PPV: positive predictive value, NPV: negative predictive value, 95%CI: 95% confidence interval.

Differences in diagnostic performance of three imaging are not statistically significant.

Table 3. Detection or exclusion of V/Q mismatches in lung segments

	Sensitivity (95%CI)	Specificity (95%CI)	Accuracy (95%CI)	PPV (95%CI)	NPV (95%CI)
V/Q Planar	75.84% (72.98%-78.71%)	54.14% (49.84%-58.44%)	67.68% (65.21%-70.15%)	73.29% (70.38%-76.20%)	57.46% (53.07%-61.86%)
V/Q SPECT	79.21% (76.49%-81.93%)	46.05% (41.75%-50.35%)	66.74% (64.25%-69.23%)	70.89% (68.02%-73.77%)	57.18% (52.41%-61.94%)
Q-LDCT	74.91% (72.01%-77.81%)	46.05% (41.75%-50.35%)	64.06% (61.52%-66.59%)	69.73% (66.76%-72.70%)	52.53% (47.92%-57.13%)
*P V/Q SPECT vs Planar	0.012	<0.001	0.449		
Q-LDCT vs Planar	0.582	0.001	0.005		
V/Q SPECT vs Q-LDCT	<0.001	1.000	0.003		

V/Q: ventilation/perfusion, SPECT: single-photon emission computed tomography, Q-LDCT: perfusion scanning combined with low dose computed tomography, PPV: positive predictive value; NPV: negative predictive value, 95%CI: 95% confidence interval.

*P values were obtained with McNemar test.