
Ventilation–Perfusion Scintigraphy Is More Sensitive than Multidetector CTPA in Detecting Chronic Thromboembolic Pulmonary Disease as a Treatable Cause of Pulmonary Hypertension

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Pulmonary hypertension (PH) is a progressive disease with a poor prognosis. Identifying chronic thromboembolic pulmonary disease as a cause of PH has major clinical implications as these patients could be potentially offered a surgical cure. Ventilation–perfusion (V/Q) scintigraphy has a high sensitivity to detect embolic disease but its value has been challenged with the emergence of multidetector CT pulmonary angiography (CTPA). We compared the value of V/Q scintigraphy with CTPA in detecting chronic thromboembolic pulmonary disease. **Methods:** We retrospectively reviewed the results of V/Q scintigraphy and CTPA performed on patients who had been referred to the Pulmonary Hypertension Service at Hammersmith Hospital between 2000 and 2005. A total of 227 patients (85 males, 142 females; age range, 18–81 y; mean age, 42 y) had all tests done at Hammersmith Hospital and were included in the study. Interpretation of scans was according to the modified PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) criteria. CTPA was considered as suggestive of chronic thromboembolic pulmonary disease if it showed visualization of the thrombus or webs, recanalization, perfusion abnormalities, stenosis, or strictures. Standard pulmonary angiography was performed via femoral approach. In 90% of the cases, CTPA and V/Q scintigraphy were performed within 10 d. **Results:** Seventy-eight patients (group A) had a final diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) and 149 (group B) had non-CTEPH etiology. Among group A, V/Q scintigraphy was reported as high probability in 75 patients, intermediate probability in 1 patient, and low probability in 2 patients. CTPA was positive in 40 patients and negative in 38 patients. Among group B, V/Q scintigraphy was reported as low probability in 134, intermediate probability in 7, and high probability in 8 patients. CTPA was negative in 148 patients and false-positive in 1 patient. Statistical analysis showed V/Q scintigraphy to have a sensitivity of 96%–97.4% and a specificity of 90%–95%. CTPA showed a sensitivity

of 51% and a specificity of 99%. **Conclusion:** Our results demonstrate that V/Q scintigraphy has a higher sensitivity than CTPA in detecting CTEPH as a potential curable cause of PH.

Key Words: chronic thromboembolic pulmonary hypertension; V/Q scintigraphy; multidetector CTPA

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Pulmonary hypertension (PH) is a progressive disease with a poor prognosis, defined as a mean pulmonary artery pressure > 25 mm Hg (>30 mm Hg during exertion) measured during right heart catheterization. It can present as an idiopathic condition or as a complication of various medical conditions, including chronic cardiac and pulmonary diseases (1–3).

An accurate diagnosis of the cause of pulmonary hypertension determines the management and prognosis. Patients with chronic thromboembolic pulmonary hypertension (CTEPH) represent a distinct category of PH as they can potentially be offered curable surgery in the form of pulmonary endarterectomy. This operative procedure has gained wide acceptance and achieved good success rates, with a reported mortality rate of 4%–8% (4–7).

Without treatment, the prognosis of CTEPH is very poor, with a quoted survival rate of 30% over a period of 5 y for patients with mean pulmonary artery pressure > 30 mm Hg (8,9).

Recent literature have shown that up to 3.8% of patients diagnosed with acute pulmonary embolism (PE) develop CTEPH at 2-y follow-up (10) and suggest that the incidence of CTEPH is much higher than previously thought (10,11). Furthermore, up to 63% of patients diagnosed with CTEPH may not have a previous history of documented PE (12).

Identifying CTEPH as the cause of PH is facilitated by several imaging techniques, including ventilation–perfusion

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(V/Q) scintigraphy, multidetector CT pulmonary angiography (CTPA), high-resolution CT (HRCT), pulmonary digital subtraction angiography (DSA), and, more recently, magnetic resonance angiography (13,14).

The introduction of spiral CTPA has challenged the role of V/Q scanning in diagnosing acute PE (15). In the United Kingdom, it has become the first line of the investigation in patients with suspected acute PE (16).

Further advances in CT technology, with the introduction of multidetector CTPA and multiplanar reconstruction have further improved the sensitivity and specificity of this technique with small studies quoting values of 96% and 98%, respectively (17). However, a recent large multicenter study has shown these figures to be lower, with a sensitivity of 83% and a specificity of 96% for CTPA, with even a lower sensitivity for segmental (68%) and subsegmental (25%) branches (18).

This has been adopted by PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) II investigators and is reflected in the new guidelines published in January 2007, which have approved multidetector CTPA as the first-line imaging procedure in most patients suspected of having PE (19).

However, the sensitivity of multidetector CTPA in detecting chronic thromboembolic pulmonary disease remains variable. There are few publications in this respect, including a study published by Pitton et al. showing multidetector CTPA to have a sensitivity of 70.4% for segmental and 63.6% for subsegmental branches when compared with pulmonary DSA (20).

On the other hand, several studies have shown that high-probability and intermediate-probability V/Q scintigraphy has a high sensitivity and specificity for distinguishing patients with chronic pulmonary thromboembolic disease from other causes of PH, to the extent that normal V/Q scintigraphy can comfortably rule out CTEPH (21–27). To our knowledge, there is no published study that compares the value of V/Q scintigraphy with that of multidetector CTPA in the diagnosis of CTEPH. Our aim was to perform a head-to-head comparison of the 2 techniques.

MATERIALS AND METHODS

We retrospectively reviewed the results of V/Q scintigraphy and CTPA performed on 500 patients with PH referred to Hammersmith Hospital, London, between 2000 and 2005. Patients selected for inclusion were those who had all of their imaging tests performed at Hammersmith Hospital rather than in the referring hospitals. Of the 500 patients, 227 (85 males, 142 females; age range, 18–81 y; mean age, 42 y) fulfilled these criteria. For such retrospective review neither ethical approval nor informed consent was required. The imaging reports have been retrieved from the Hammersmith Hospital picture archiving and communication system (PACS) archive. The final diagnosis of CTEPH or non-CTEPH was obtained from the Hammersmith Hospital Pulmonary Hypertension Service case records. The information obtained from medical history, laboratory tests, and other investigations—such as echocardiography, CTPA, V/Q, right heart cardiac cath-

eterization, and pulmonary angiography—was used to obtain a final diagnosis.

The identification of the PH clinical class (e.g., CTEPH vs. non-CTEPH etiology) was made in all patients in accordance with the guidelines of the European Society of Cardiology and the American College of Chest Physicians (1–3).

V/Q Scintigraphy

V/Q scintigraphy was performed using ^{99m}Tc -labeled macroaggregated albumin (^{99m}Tc -MAA) and ^{81m}Kr gas (^{81}Kr). Images were acquired using an ECAM dual-head γ -camera (Siemens Medical Solutions USA, Inc.). The perfusion images were acquired after intravenous administration of 100 MBq of ^{99m}Tc -MAA with the patient in the supine position. The images were acquired in 4 standard projections (anterior, posterior, right posterior oblique, and left posterior oblique) with a medium-energy, general-purpose collimator. An energy window of 20% centered on the energy peak of ^{99m}Tc (140 keV), and a matrix of 128×128 pixels was used and approximately 400,000 counts accumulated per view. Ventilation images using ^{81m}Kr were acquired immediately after each perfusion view. ^{81m}Kr was inhaled through a mouthpiece. The acquisition parameters were the same as those used for the perfusion study, but the 20% window was centered on the energy peak of ^{81m}Kr (190 keV). Images were reported from a Hermes workstation (Nuclear Diagnostics) by experienced nuclear medicine physicians. Images were interpreted according to the modified PIOPED criteria (28,29). A high-probability scan was suggestive of chronic thromboembolic pulmonary disease, whereas a low-probability scan was suggestive of nonchronic thromboembolic pulmonary disease etiology. For intermediate-probability scans, 2 separate datasets were produced and analyzed. In one dataset, intermediate-probability scans were considered as suggestive of chronic thromboembolic pulmonary disease and, in the other dataset, the intermediate-probability scans were considered as not suggestive of chronic thromboembolic pulmonary disease. This was in accordance with previous similar studies (22).

Multidetector CTPA

CTPA was acquired with multidetector row CT scanners. The first 24 studies were acquired with a Somatom Four Plus CT scanner (Siemens Medical Solutions) using 4×3 mm collimation and 2.5-mm reconstruction. From March 2002, the remaining 203 studies were acquired on a Light Speed CT scanner (GE Healthcare), using 8×1.25 mm collimation with 1.25-mm reconstruction. A bolus injection of 100 mL of nonionic iodinated contrast medium (300 mg/mL) was administered intravenously via a peripheral cannula at 4 mL/s via a power injector with a variable-start delay. This was determined using automatic bolus trigger software with a circular region of interest positioned at the level of main pulmonary trunk. The images were acquired in the cranio-caudal direction with the z -axis coverage and the field of view chosen to include the entire thorax, from the apex to the base of the lungs.

All CTPA was reported by experienced radiologists using PACS workstations (GE Healthcare) as well as Siemens and General Electric workstations to assess multiplanar reconstructions. A report was considered as suggestive of chronic thromboembolic pulmonary disease if it stated visualization of the thrombus, calcified thrombus, recanalization, sudden change in vessel caliber, strictures, poststenotic dilatation, webs, or perfusion abnormality (30–34). The presence of mosaic perfusion, defined as areas of

increased and decreased attenuation and vascularity without evidence of destruction or displacement of pulmonary vessels, was also noted. However, its presence alone in the absence of other signs was not considered as diagnostic of chronic thromboembolic pulmonary disease (35–37).

Pulmonary DSA

The indications for referring patients for pulmonary DSA included (a) clinical suspicion of CTEPH, (b) at least one positive imaging modality for chronic thromboembolic pulmonary disease, and (c) whether the patient was being assessed for pulmonary thrombendarterectomy. Pulmonary DSA was performed in 61 patients by experienced vascular radiologists via a femoral venous approach using a 7-French Grollman pigtail catheter (William Cook Europe) placed in the main pulmonary trunk. More selective studies of the intrapulmonary artery branches were performed in some patients with a 7-French headhunter catheter (Cordis Europa). Images were obtained with an HDI 5000 fluoroscopy unit (Philips) after administration of 20 mL of nonionic iodinated contrast medium (300 mg/mL), per DSA run, at 7 mL/s via a pump injector or by hand injection with a maximum volume limit of 300 mL. The minimum projections per hemithorax included frontal and posterior oblique projections, with extra views obtained as required.

RESULTS

All 227 patients included in this analysis had both V/Q scintigraphy and CTPA performed at Hammersmith Hospital, with most (90%) of the CTPA being performed within 10 d from the V/Q scintigraphy and 73% being performed within 48 h. When chronic thromboembolic pulmonary disease was highly suspected, pulmonary DSA was performed in patients who were clinically fit to undergo pulmonary endarterectomy.

In patients with CTEPH (group A, $n = 78$ patients), the final diagnosis was confirmed by pulmonary DSA in 61 patients. In the remaining 17 patients, there was strong clinical and imaging suspicion of chronic thromboembolic pulmonary disease. However, these patients did not consent to surgery or were considered unfit for surgery and, therefore, not referred for pulmonary DSA.

In patients with non-CTEPH (group B, $n = 149$ patients), the clinical and imaging data did not suggest thromboembolic etiology, so there was no clinical indication to refer them for pulmonary DSA. The final diagnosis of PH of nonthromboembolic etiology was achieved by a consensus based on clinical and imaging data discussed at a multidisciplinary meeting.

Patients with CTEPH: Group A

CTPA was reported as showing features suggestive of chronic thromboembolic pulmonary disease in 40 of 78 patients but was falsely negative in 38 of 78 cases, giving a sensitivity of 51%. The V/Q scintigraphy showed high probability in 75 patients, intermediate probability in 1 patient, and low probability in 2 patients. When the intermediate-probability scans were considered suggestive of chronic thromboembolic pulmonary disease (grouped with the high probability), the V/Q sensitivity was 97.4%, and when

intermediate probability was considered as negative for chronic thromboembolic pulmonary disease (grouped with low probability), the sensitivity was 96% (Tables 1 and 2).

Patients with Non-CTEPH: Group B

CTPA did not show features suggestive of chronic thromboembolic pulmonary disease in 148 of 149 patients with one false-positive case. V/Q scintigraphy showed low probability in 134 patients, high probability in 8 patients, and intermediate in 7 patients.

The specificity of CTPA was 99%. The V/Q specificity was 90% when the intermediate-probability scans were analyzed as suggestive of chronic thromboembolic pulmonary disease and 95% when the intermediate scans were considered negative for chronic thromboembolic pulmonary disease (Tables 1 and 2).

Mosaic Perfusion

Mosaic perfusion was reported in 53 of the total 227 CTPA scans (23.34%). Among those, 43 (18.94%) were in group A and 10 (4.41%) were in group B.

Thus, the CTPA showed evidence of mosaic perfusion in 55% (43/78) of patients with CTEPH (group A).

DISCUSSION

The sensitivity and specificity of the V/Q scintigraphy in diagnosing chronic thromboembolic pulmonary disease shown in our study are similar to those of a smaller group (75 patients with PH) studied by Worsley et al. (22). They found that the combination of high- and indeterminate-probability V/Q scintigraphy had a sensitivity of 100% for detecting patients with CTEPH; however, the specificity was 86% (22). Other studies have also highlighted the value of V/Q scintigraphy in the diagnosis of CTEPH (21–27).

In our study, we approach the V/Q scintigraphy analysis from 2 perspectives. First (V/Q (1)), we considered both the high- and intermediate-scans as suggestive of chronic pulmonary thromboembolic disease, which resulted in a sensitivity of 97.4%, specificity of 90%, accuracy of 92.5%, negative predictive value (NPV) of 98.5%, and positive predictive value (PPV) 83.5%, respectively (Table 2).

When we analyzed the data considering just the high-probability scans as suggestive of chronic pulmonary thromboembolic disease (V/Q (2)), the sensitivity was 96.2%, whereas the specificity increased to 94.6%. The overall accuracy was 95.2% with a NPV of 97.9% and a PPV of 90.3% (Table 2).

TABLE 1
Summary of V/Q Scans and CTPA Results

Group	V/Q			CTPA	
	Low probability	Intermediate probability	High probability	Negative	Positive
A ($n = 78$)	2	1	75	38	40
B ($n = 149$)	134	7	8	148	1

TABLE 2

Summary of Performance Indicators for V/Q Scintigraphy and CTPA

Indicator	Scintigraphy		CTPA
	V/Q (1)*	V/Q (2)†	
Sensitivity (%)	97.4	96.2	51.3
Specificity (%)	90	94.6	99.3
Accuracy (%)	92.5	95.2	82.8
NPV (%)	98.5	97.9	79.7
PPV (%)	83.5	90.3	97.6

*Intermediate with high-probability scans as indicative of CTEPH.

†Only high-probability scans as indicative of CTEPH.

NPV = negative predictive value; PPV = positive predictive value.

TABLE 3

Summary of False-Positive V/Q Scans

V/Q	Diagnosis
Intermediate probability (n = 7)	IPAH (n = 4)
	IPAH and emphysema (n = 1)
	ASD and pulmonary fibrosis (n = 1)
High probability (n = 8)	Pulmonary fibrosis (n = 1)
	IPAH (n = 3)
	PVOD (n = 1)
	APAH and ASD (n = 2)
	Scleroderma and pulmonary fibrosis (n = 1)
	Apical bullae: apical mismatch on V/Q (n = 1)

IPAH = idiopathic pulmonary arterial hypertension; ASD = atrial septal defect; PVOD = pulmonary venoocclusive disease; APAH = associated pulmonary arterial hypertension.

The sensitivity of CTPA in our study was significantly lower compared with V/Q scintigraphy in detecting chronic thromboembolic pulmonary disease changes. However, it was similar with that reported by Pitton et al., who had analyzed 994 vessel segments in 14 patients with CTEPH and had both CTPA and selective pulmonary DSA (20). Their analysis showed CTPA to be significantly inferior to selective DSA, with a 67% overall concordance in diagnosing CTEPH. Furthermore, the nonocclusive changes of the vessels were significantly underdiagnosed by CT, with a concordance between CT and DSA of 23.1% (20).

False-Negative V/Q Scintigraphy

The 2 patients from group A who had their V/Q scintigraphy interpreted as low probability did not have the diagnosis of CTEPH confirmed on pulmonary DSA. The final diagnosis was made by CTPA, which showed calcified thrombus in one patient and narrowed but patent pulmonary arterial branches in the other patient. By corroborating the patient clinical history and the CT findings, it was concluded that these patients most likely had previous PE and the pulmonary vessels had recanalized.

V/Q scintigraphy that was interpreted as intermediate probability was confirmed on pulmonary DSA to be CTEPH. The CT was reported as showing severe emphysematous changes but failed to show signs of CTEPH. It was the V/Q result together with the clinical history that prompted the clinicians to request pulmonary DSA.

False-Positive V/Q Scintigraphy

Eight V/Q scans were reported as high probability and 7 were reported as intermediate probability among the non-CTEPH group. None of these patients had pulmonary DSA. The clinical diagnoses were idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension associated with atrial septal defect, pulmonary venoocclusive disease, and PH related to parenchymal lung disease, such as emphysema or pulmonary fibrosis (Table 3).

Mosaic Attenuation Pattern

The combination of a mosaic pattern and disparity in the size of segmental vessels on HRCT was found in a study by Bergin et al. to reliably distinguish patients with CTEPH (33). Similarly, Schwickert et al. analyzed the CT findings in 75 patients diagnosed with CTEPH and found mosaic perfusion in 77% (34). However, the mosaic perfusion pattern can also be found in patients with PH due to other causes (31–37), and up to 12% of patients with idiopathic pulmonary arterial hypertension will have mosaic perfusion on CTPA (35). In our study, mosaic perfusion was present in only 55% of the CTPA performed in group A patients and 20% of group B patients. This confirms that, although the mosaic pattern is more common in CTEPH, it is not a specific feature.

CONCLUSION

Our findings confirm that normal V/Q scintigraphy practically rules out the presence of CTEPH, whereas normal CTPA does not exclude the presence of CTEPH. In contrast, the presence of high probability on V/Q scintigraphy makes CTEPH the most likely diagnosis, although other conditions—including pulmonary venoocclusive disease—may result in similar findings. Our results suggest that grouping intermediate-probability with low-probability V/Q scans as indicative of non-CTEPH etiology would maintain a high sensitivity and improve specificity, NPV, and PPV. We have shown that V/Q scintigraphy, which is widely available and easy to perform, has a higher sensitivity than multidetector CTPA as well as very good specificity in detecting chronic pulmonary thromboembolic disease as a potential curable cause of PH.

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