

**Pulmonary arterial hypertension with abnormal V/Q single-photon emission computed
tomography**

Short title: Chan, V/Q SPECT and pulmonary hypertension

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Abstract

Objectives: This study aims to evaluate the incidence and clinical outcomes of abnormal ventilation/perfusion (V/Q) SPECT without thromboembolism, especially in group I pulmonary arterial hypertension (PAH) patients.

Background: AHA/ACC and ESC guidelines recommend V/Q scan for screening for chronic thromboembolic pulmonary hypertension (CTEPH). The significance of patients with abnormal V/Q SPECT but no thromboembolism demonstrated in further investigations remained unclear. A distinct pattern of global patchy changes not typical of thromboembolism is recognised but guidelines for reporting these in the context of pulmonary hypertension is lacking.

Methods: A total of 136 patients underwent V/Q SPECT and right heart catheterization showing mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg were included. V/Q SPECT were reported using EANM criteria for pulmonary embolism followed by CT pulmonary angiography (CTPA) screening for positive thromboembolisms and further invasive pulmonary angiogram for distal thromboembolisms. The abnormal V/Q SPECT images were further analysed according to perfusion pattern into focal or global perfusion defects.

Results: V/Q SPECT showed thromboembolic disease in 44 patients but 19 of these have no thromboembolisms demonstrated by pulmonary angiography. 15/19 (78.9%) of these patients had group I PAH and the majority had diffuse patchy perfusion defects. After re-defining V/Q SPECT images according to the perfusion pattern, those with global perfusion defects had higher mPAP compared to patients with focal perfusion defects and normal scans (mean difference +13.9 mmHg and +6.2 mmHg respectively, $p=1.54 \times 10^{-4}$) as well as higher pulmonary vascular resistance (mean difference +316.6 ARU and +226.3 ARU respectively, $p=0.004$). Among patients with PAH, global perfusion defects were associated with higher all-cause mortality with hazard ratio 5.63 (95% CI 1.11-28.5) compared to those with focal or no perfusion abnormalities.

Conclusion: There is a high incidence of abnormal V/Q SPECT scans in non-thromboembolic PH.

Further studies are needed to investigate the poor outcome associated with abnormal V/Q SPECT in the context of PAH.

Condensed abstract:

The incidence and clinical outcomes of abnormal ventilation/perfusion (V/Q) SPECT without thromboembolism remains unclear. Using current reporting guidelines, 43% patients had positive V/Q SPECT but no demonstrable thromboembolisms in corroborating pulmonary angiography. When analysing V/Q SPECT images according to the perfusion pattern, those with global perfusion defects had higher mPAP, pulmonary vascular resistance, and all-cause mortality compared to patients with focal perfusion defects or normal scans. Hence we found a high incidence of abnormal V/Q SPECT scans in non-thromboembolic pulmonary hypertension. In this cohort, abnormal V/Q SPECT in the context of pulmonary arterial hypertension was a poor prognostic marker.

Abbreviation list: Chronic thromboembolic pulmonary hypertension (CTEPH); computed tomography (CT); European Association of Nuclear Medicine (EANM); European society of cardiology (ESC); pulmonary hypertension (PH); pulmonary arterial hypertension (PAH); V/Q (Ventilation/perfusion); SPECT (Single photon emission computed tomography)

Introduction

Pulmonary hypertension (PH) is a severe condition with historically poor prognosis.(1) With certain disease-modifying therapies and traditional therapies, and with transplant, the outcome has been altered radically in certain subgroup of patients. Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially treatable cause of PH with anticoagulation and pulmonary endarterectomy(2), hence the ACCF/AHA consensus(3) and ESC guideline(4) both recommend ventilation/perfusion (V/Q) scan as a pivotal tests in the initial assessment to screen for CTEPH. Further investigations such as computed tomography (CT) or conventional pulmonary angiography is then indicated if V/Q scan is positive.(4) In pulmonary hypertension, planar V/Q scintigraphy has 97.4% sensitivity compared to 51% for computed tomography pulmonary angiography (CTPA) for detection of chronic thromboembolic disease.(5)

The advent of V/Q single-photon emission computed tomography (SPECT) has overcome some of the limitations of planar V/Q imaging, offering even higher sensitivity (80-100%), specificity (93-100%) and accuracy (94%) in thromboembolic diseases.(6) Compared to planar V/Q scans, the 3-dimensional tomography image from SPECT allow more accurate diagnose of thromboembolic disease while differentiating other lung pathologies such as chronic obstructive pulmonary disease, interstitial lung disease, and veno-occlusive disease.(7) The European Association of Nuclear Medicine (EANM) has established a diagnostic criteria for interpreting thromboembolic disease based on focal V/Q mismatches in segmental and subsegmental pulmonary arteries.(8) It is however recognised that patients with abnormal V/Q SPECT sometimes might not have significant thromboembolic disease demonstrated on confirmatory pulmonary angiography.(9) Some patients also have abnormal patchy and heterogeneous perfusion defect on V/Q SPECT images which are difficult to classify.(7,9,10) The functional significance of these abnormal V/Q SPECT results in PH remains unclear. We sought to evaluate the incidence and clinical significance of abnormal V/Q SPECT in the context of patients with pulmonary hypertension who had no detectable thromboembolism in corroborating investigations.

Methods

Patient cohort and characterisation of pulmonary hypertension

Patients referred to the National Pulmonary Hypertension service at the Royal Free NHS Foundation Trust typically undergo V/Q scanning at the Royal Free Hospital if this has not been previously performed. Patients undergone V/Q scan subsequent to 2013 were studied as SPECT V/Q was introduced at that date. We have included all patients who had SPECT V/Q between 2013 and January 2016 at the Royal Free within three months of their initial diagnostic right heart catheterisation in this study. The study complied with the Declaration of Helsinki and was approved by institutional review board.

Right heart catheterisation (RHC) was performed according to ESC guidelines.⁽⁴⁾ PH is defined as mean pulmonary arterial pressure ≥ 25 mmHg on right heart catheterization.⁽⁴⁾ The aetiology of PH was defined according to World Health Organisation (WHO) classifications.⁽¹¹⁾ Echocardiogram was used to assess left heart disease. Spirometry and CT scans of the chest were performed in all patients. We have excluded patients clinically diagnosed with significant left heart and lung disease.

V/Q SPECT were interpreted according to EANM criteria, and these patients were then screened for thromboembolic disease (**Figure 1**). Six minute walking distance and functional class was assessed in all patients. We obtained data on whether therapy with pulmonary vasodilators was initiated and on whether the patient was treated with anticoagulation. The patients were followed up after V/Q SPECT and right heart catheterisation and all-cause mortality were recorded.

V/Q SPECT

V/Q SPECT scans were performed as part of the initial assessment. The scans were acquired using triple-head (Philips Irix) gamma camera equipped with low energy, high resolution, and parallel-hole collimators. Perfusion studies were performed after injection of 100 MBq of ^{99m}Tc -

macroaggregated albumin (99mTc-MAA) (CIS Bio International (MAA); Mallinckrodt Medical (99mTc) during two respiratory cycles. Ventilation scans were performed during quiet tidal inhalation of 81mKr (190keV; Sandwell and West Birmingham NHS trust) or 99mTc-Technegas (140keV, Cyclomedica). All scans were clinically reported by experienced nuclear medicine physicians at the Royal Free Hospital based on clinical indications provided by the treating physicians at the time of the scan. 'Positive scans' are those that meet the EANM reporting criteria for pulmonary thromboembolic disease.(8) All scans were subsequently reviewed for the purposes of this study by one of the authors (M.H) blinded to all clinical information. The scans were then re-analysed according to the pattern of perfusion defect into a) normal scans with no perfusion defects; b) focal perfusion defects which indicate segmental or subsegmental obstruction but not fulfilling EANM criteria for thromboembolism; and c) global perfusion defects. Where there was a discrepancy between the two reports, the blinded report was used.

Statistical analysis

Continuous variables are summarised using the mean \pm standard error (SE) for normally distributed data, and medians for non-normally distributed data. Categorical variables are described as a percentage and analysed using χ^2 or Fisher's exact test where appropriate. Linear regression model was used to compare between patients with abnormal V/Q SPECT but no thromboembolism and those with normal V/Q SPECT scans. For comparison between 3 groups (normal, focal defect, and global defects on V/Q SPECT), one-way analysis of variance (ANOVA) test was used with Bonferroni post-hoc analysis on significant associations. Analysis of covariance (ANCOVA) test was used for adjusted analyses. All analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL), and Graphpad Prism 6.0.

Results

High incidence of positive V/Q SPECT in non-thromboembolic PH

A total of 244 patients underwent V/Q SPECT and right heart catheterisation (RHC) for pulmonary hypertension assessment between 2013 and 2016, of these 136 patients had PH confirmed on RHC. Suspected thromboembolism on V/Q SPECT was reported in 44 patients according to EANM criteria. After further corroborating investigations including CTPA confirmed positive thromboembolism in 10 patients, and 10 patients had previous established diagnosis of CTEPH, 24 patients with none or negative CTPA results further underwent conventional pulmonary angiogram, which identified thromboembolism in 5 patients. This gives a total of 19 patients with positive V/Q SPECT but no thromboembolic disease detectable on conventional invasive pulmonary angiography and 15 (78.9%) of these patients had group I PAH (**Figure 1 and Table 1**). Among those with negative V/Q SPECT, 60 (65.2%) patients had group I PAH. 27 (29.3%) patients were anticoagulated at baseline for other co-morbidities such as atrial fibrillation. There were no significant demographic differences or difference in pulmonary haemodynamics or baseline function (functional class or six-minute walk distance) between those with positive V/Q SPECT and those without (**Figure 2**)

Perfusion defects on V/Q SPECT is associated with haemodynamic severity

The V/Q SPECT imaging of the 75 patients with group I PH were re-analyzed according to the pattern of perfusion defects (**Figure 3**). There were minimal discrepancies with inter-class correlation coefficient of 0.98 (95% CI 0.97-0.99). Majority of patients with focal perfusion defects had subsegmental mismatches which are non-diagnostic for thromboembolism. The remaining patients with focal or global perfusion defects on V/Q SPECT all had CT pulmonary angiogram, and targeted invasive pulmonary angiography in selected cases to exclude distal thromboembolisms. Compared to those with normal V/Q SPECT, there are more group I PAH in patients with global perfusion defects (χ^2 test $p=0.022$), in particular there were more patients with systemic sclerosis (Fisher exact test, $p=0.019$). Among patients with group I PAH, ANOVA test between the three groups of perfusion defects there were significant differences in mPAP ($F(2,72)=9.93$, $p=1.54 \times 10^{-4}$), and PVR

($F(2,72)=5.9$, $p=0.004$). (**Table 2 and Figure 4**) The associations persisted after adjustment for multiple comparison with Bonferroni corrections. Post-hoc analysis showed no significant differences between patients with normal V/Q and focal V/Q defects for both mPAP ($p=0.18$) and PVR ($p=0.60$). The associations remained significant after adjusting for vasodilator and baseline anticoagulation therapy, with mPAP ($F(2,72)=7.48$, $p=0.0011$) and PVR ($F(2,72)=3.80$, $p=0.027$), as well as after Bonferroni corrections. The associations were similar in a subgroup analysis focusing on patients with systemic sclerosis, mPAP ($F(2,36)=8.27$, $p=0.001$) and PVR ($F(2,36)=4.12$, $p=0.023$).

High mortality rate in group I PAH with global perfusion defects on V/Q SPECT

Patients were followed up for a median of 372.7 ± 200 days. All-cause mortality occurred in 6 patients with group I PAH, and all had global perfusion defects on V/Q SPECT. The underlying diagnosis of these patients included 3 with idiopathic PAH, 2 with systemic sclerosis and 1 with other connective tissue disorder. Among patients with group I PAH, those with global perfusion defects on V/Q SPECT had significantly worse survival compared to those with normal or focal perfusion defects on V/Q SPECT (Log-rank $p=0.037$), with hazard ratio 5.63 (95% CI 1.11-28.5) calculated with Mantel Haenszel approach described by Bernstein et al.(12)

Discussion

There was a high incidence (43.1%) of PH patients in our cohort with positive V/Q SPECT scan results but no thromboembolism demonstrable in corroborating investigations. After diagnostic screening the 19 patients with positive V/Q SPECT all had no detectable thromboembolism on conventional invasive pulmonary angiography, the current 'gold standard'.(13,14) None of the patients with negative V/Q SPECT subsequently had thromboembolism detected in other modalities of investigations, which demonstrates that the high negative predictive value of a normal V/Q scan also pertains to patients with PAH.

We found a false positive rate of 43% (specificity 67%) amongst patients with PAH. A previous study looked at a mixed group of pulmonary hypertension aetiologies and found a lower false positive rate of 5-10% using planar V/Q scanning.(5) Our study utilised V/Q SPECT which offers better accuracy for detecting segmental and subsegmental pulmonary embolisms.(6)

Pulmonary arterial hypertension is associated with pruning of pulmonary vessels and in early nuclear medicine studies patchy perfusion defects have been described.(9,10) Attempts were also made to quantify the heterogeneity of perfusion defect, and was shown to be predictive of pulmonary systolic pressures.(15) We have found that these perfusion defects are often reported as pulmonary emboli using current, sensitive, V/Q SPECT scanning and contemporary reporting criteria. To our knowledge, this has not previously been described.

Global perfusion defects on V/Q SPECT scanning were associated with a severe PAH phenotype, with more adverse pulmonary haemodynamics and higher mortality. This finding suggests that the V/Q scan may have utility beyond the exclusion of pulmonary thromboembolic disease. In particular, such global perfusion defects could reflect obliteration of distal pulmonary vessels, a pathological feature that precede anticipates progression to right ventricular failure.(14,16) This could offer a non-invasive assessment to identify patients with more severe PAH. Prospective studies would be helpful to establish whether perfusion defects on V/Q scanning provide independent prognostic information and whether they may identify patients who would benefit from specific therapies.

Study limitations

The limitations of this study follow from its observational single centre design. Although invasive pulmonary angiograms were not routinely performed in all patients, we have only described as 'false positive' in those with negative conventional pulmonary angiograms, and true positive CTEPH cases were confirmed with either CTPA or conventional pulmonary angiograms. The subgroup analysis

included group I PH patients which are still a heterogeneous group but nevertheless all have arterial stiffness/vasoconstriction. The correlations between V/Q SPECT and severity of PH were also consistent when only patients with systemic sclerosis were included. The associations with pulmonary vascular resistance gave further mechanistic insight that V/Q SPECT images might be related to arterial pathologies. Further studies of V/Q SPECT in subtypes of group I PH is needed to investigate the correlation with the underlying pulmonary arterial pathology. A larger series of patients studied prospectively will also be helpful to confirm the worse outcome of patients with global perfusion defects on V/Q SPECT.

Taken together, pulmonary arterial hypertension is associated with frequent perfusion abnormalities detectable on V/Q SPECT scanning which are not due to thromboembolic disease, and which may reflect the severity of the disease as evidence by worse pulmonary haemodynamics and poorer prognosis. Further prospective study of these associations is merited.

Clinical Perspectives

Competency in Medical knowledge: There is a high incidence (43%) of pulmonary hypertensive patients with positive ventilation/perfusion (V/Q) SPECT but no demonstrable thromboembolisms in corroborating pulmonary angiography. In the context of pulmonary arterial hypertension, the presence of global perfusion defects on perfusion scan are associated with worse pulmonary haemodynamics and clinical outcome, and this may be because these defects reflect more severe pulmonary vasculopathy.

Translational Outlook: V/Q scans are currently recommended by guidelines as screening tool for chronic thromboembolic pulmonary hypertension. Insights into the interpretation of perfusion defects in pulmonary arterial hypertension provides a non-invasive method to assess disease severity/progression, and to guide treatment options.

Disclosures

We declare no conflict of interests

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Figure legends

Figure 1. Diagnostic screening for excluding thromboembolic disease in pulmonary hypertension.

CTPA, computed tomography pulmonary angiogram; PA, pulmonary angiogram; PH, pulmonary hypertension; RHC, right heart catheterization; V/Q SPECT, ventilation-perfusion single photon emission computed tomography

Figure 2. Mean pulmonary arterial pressure in group I PAH patients with positive V/Q SPECT

According to EANM interpretation criteria, cases with thromboembolism demonstrable in pulmonary angiograms were excluded. Line denotes mean \pm 95% CI

Figure 3. V/Q SPECT interpretation by pattern of perfusion defects.

A) normal scan; B) focal wedge shape perfusion defect consistent with pulmonary embolism; C) global heterogenous perfusion defects with no embolism demonstrated in subsequent investigations

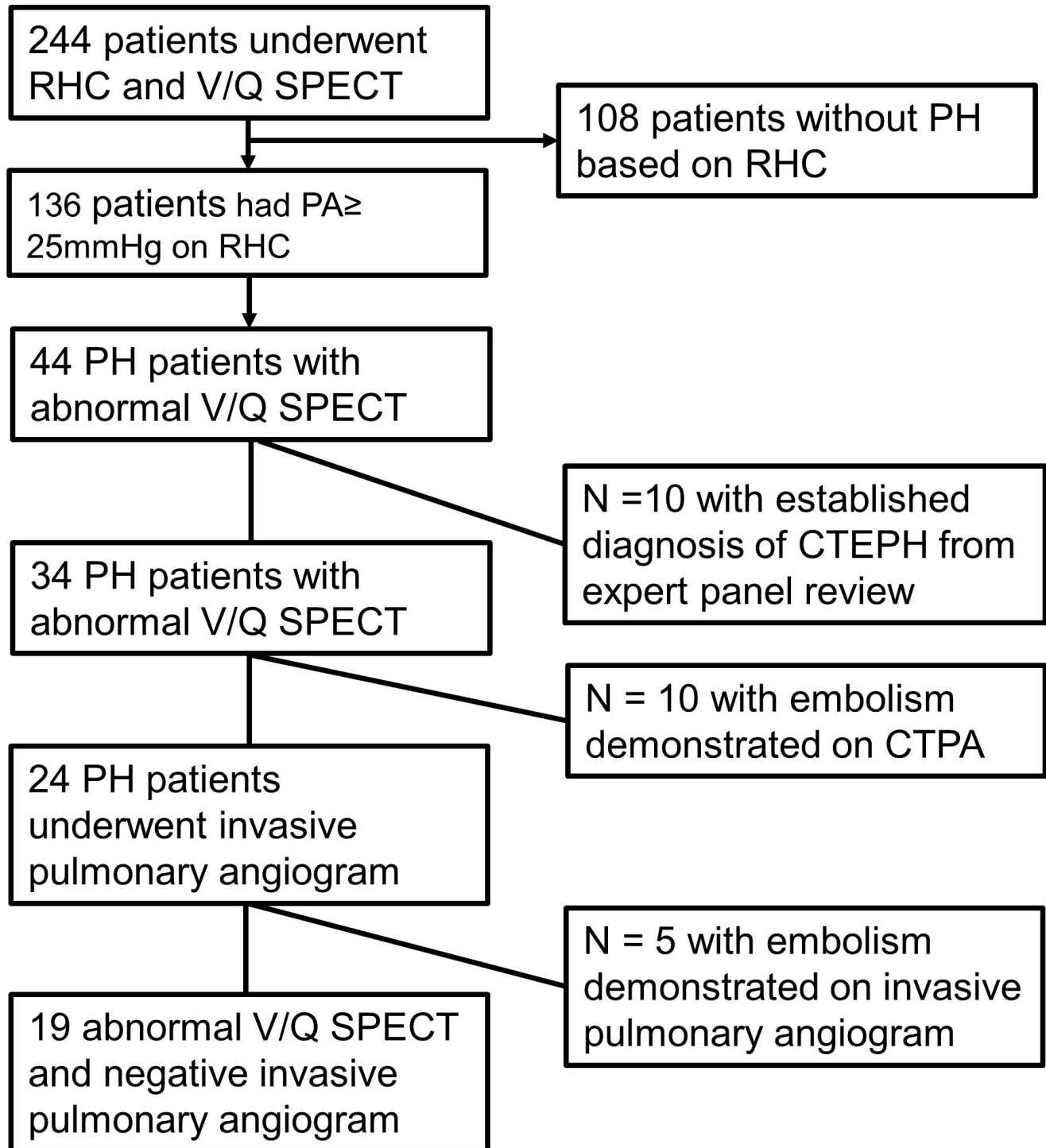
Figure 4. Mean pulmonary arterial pressure in group I PAH patients according to the perfusion defects on V/Q SPECT

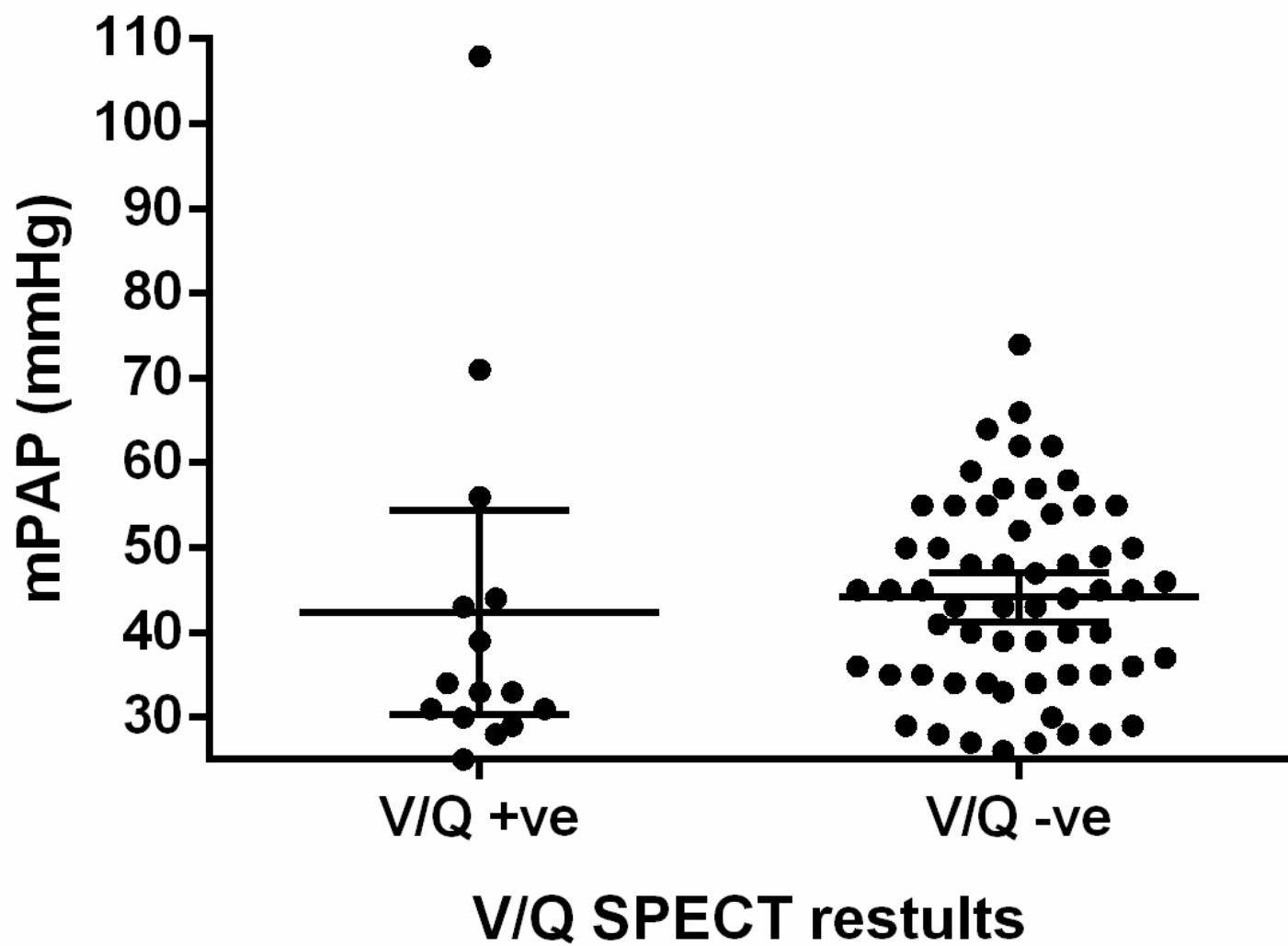
Table 1. Baseline characteristics for patients with pulmonary hypertension. 6MWD, 6-minute walk distance; CTEPH, chronic thromboembolic pulmonary hypertension; HIV, human immunodeficiency virus; PAH, pulmonary arterial hypertension

	Positive V/Q SPECT without thromboembolic disease	Negative V/Q SPECT for thromboembolic disease
n	19	92
Mean age	59.8±18.2	63.8±15.1
Gender (male,%)	2 (10.5%)	28 (30.4%)
Aetiology:		
Group I (PAH)	15 (78.9%)	60 (65.2%)
1.1 Idiopathic	2 (10.5%)	7 (7.6%)
1.4.1 Systemic sclerosis	8 (42.1%)	31 (33.7%)
1.4.1 Other connective tissue disease	2 (10.5%)	14 (23.3%)
1.4.3 Portal hypertension	0 (0%)	6 (10%)
1' veno-occlusive disease	2 (10.5%)	1 (1.7%)
1.4.4 secundum atrial septal defect with left-to-right shunt	1 (5.6%)	1 (1.7%)
Group II (left heart disease)	2 (11.1%)	17 (18.5%)
Group III (Lung disease)	1 (5.3%)	11 (12.0%)
Group V (unclear/multifactorial)	1 (5.6%)	4 (4.3%)
WHO functional class		
I or II	44.4%	16.0%
III	44.4%	64.0%
IV	11.1%	20.0%
6MWD on initial assessment	273.5±174.7	255.1±134.0
Management		
Vasodilator	15 (78.9%)	55 (59.8%)
Baseline anticoagulation status	11 (57.9%)	27 (29.3%)

Table 2. Associations between V/Q SPECT results and right heart catheterisation haemodynamics in patients with group I PH. Results expressed in mean±standard error. ARU, absolute resistance unit; CO, cardiac output; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance

	Normal V/Q SPECT	Focal perfusion defects on V/Q SPECT	Global perfusion defects on V/Q SPECT	p-value
Group I PAH (n)	6	25	44	
mPAP (mmHg)	42.7±4.2	35.0±1.6	48.9±2.2	1.54x10 ⁻⁴
PCWP (mmHg)	13.5±6.9	10.9±0.6	10.5±0.5	0.14
PVR (ARU)	506.3±129.7	416.0±45.9	732.6±65.4	0.004
Cardiac index (L/min/m²)	3.00±0.4	3.1±0.2	2.80±0.1	0.32
PA oxygen saturations (%)	66.3±4.2	69.8±1.9	66.2±1.5	0.33





Perfusion defects

Normal

Focal

Global

Perfusion
Ventilation



Perfusion
Ventilation



