VENTILATION PERFUSION LUNG SCAN IN PULMONARY VENO-OCCCLUSIVE DISEASE

Andrei Seferian¹²³, Badia Helal⁴, Xavier Jaïs¹²³, Barbara Girerd¹²³, Laura C. Price⁶, Sven Günther¹²³, Laurent Savale¹²³, Peter Dorfmüller⁵, Florence Parent¹²³, Olivier Sitbon¹²³, Marc Humbert¹²³, Gérald Simonneau¹²³, David Montani¹²³

¹ Université Paris-Sud, Faculté de Médecine, Kremlin-Bicêtre, F-94276, France
² AP-HP, Centre de Référence de l’Hypertension Pulmonaire Sévère, Service de Pneumologie et Réanimation Respiratoire, Hôpital Antoine Béclère, Clamart, F-92140, France
⁴ Service de Médecine Nucléaire, Hôpital Antoine Béclère, Clamart, F-92140, France
⁵ Service d’Anatomie Pathologique, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, F-92350, France
⁶ Department of Pulmonary Hypertension, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK

Corresponding author:
David Montani, MD, PhD
Centre de Référence de l’Hypertension Pulmonaire Sévère, Service de Pneumologie, Hôpital Antoine Béclère, Assistance Publique, Hôpitaux de Paris, Université Paris-Sud 11, 157 rue de la Porte de Trivaux, 92140 Clamart, France.
Tel: (33) 1 45 37 47 79; Fax: (33) 1 46 30 38 24;
e-mail: david.montani@abc.aphp.fr

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ABSTRACT

Pulmonary veno-occlusive disease (PVOD), a rare form of pulmonary arterial hypertension (PAH) requires histological proof for definitive diagnosis; however lung biopsy is not recommended in PAH. Recent conjoint ERS/ESC guidelines, suggest that unmatched perfusion defects on ventilation/perfusion (V/Q) lung scan, in PAH patients, may suggest PVOD.

The aim of our study was to evaluate V/Q lung scans in a large cohort of PVOD and idiopathic or heritable PAH patients.

V/Q lung scans from 70 patients with idiopathic or heritable PAH and 56 patients with confirmed or highly probable PVOD were reviewed in a double-blind manner. The vast majority of V/Q lung scans was normal or without significant abnormalities, in both groups. No differences in ventilation or perfusion lung scans were observed between PAH and PVOD patients (all p values >0.05). Furthermore, no differences were observed between confirmed (n=31) or highly-probable PVOD (n=25). Unmatched perfusion defects were found in 7 (10%) idiopathic PAH patients and 4 (7.1%) PVOD patients (p>0.05).

Unmatched perfusion defects were rarely seen in a large cohort of idiopathic or heritable PAH and PVOD patients. Future recommendations should be amended according to these results suggesting that V/Q lung scan is not useful in discriminating PVOD from idiopathic PAH.

Key-words: Guidelines, pulmonary arterial hypertension, pulmonary veno-occlusive disease, V/Q lung scan
ABBREVIATIONS LIST:

6MWD: six minute walk distance

_BMPR2_: bone morphogenetic protein receptor II

CI: cardiac index

CO: cardiac output

CTEPH: chronic thromboembolic pulmonary hypertension

DLCO: diffusing lung capacity of carbon monoxide

ERS: European Respiratory Society

ESC: European Society of Cardiology

NYHA FC: New York Heart Association functional class

HIV: human immunodeficiency virus

HRCT: high resolution computer tomograph

mPAP: mean pulmonary arterial pressure

NO: nitric oxide

PAH: pulmonary arterial hypertension

PCWP: pulmonary capillary wedge pressure

PH: pulmonary hypertension

PVOD: pulmonary veno-occlusive disease

PVR: pulmonary vascular resistance

SvO₂: mixed venous oxygen saturation

V/Q lung scan: ventilation perfusion lung scan

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a severe condition characterized by vascular cell proliferation and remodeling of small pulmonary arteries that causes elevated pulmonary
vascular resistance, leading to right heart failure and death [1-3]. The most recent clinical classification proposed during the 4th World symposium of pulmonary hypertension divides pulmonary hypertension (PH) into 5 different groups, PAH being the first subgroup, including idiopathic and heritable PAH, drugs and toxins induced PAH, and PAH associated with coexisting conditions (connective tissue disease, HIV infection, portal hypertension, congenital heart disease, schistosomiasis and chronic haemolytic anaemia) [2, 4, 5]. One of the prominent changes of the recent guidelines was to move pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH) from separate categories into a single subcategory of PAH (group 1’) [2]. Pulmonary veno-occlusive disease (PVOD) is a rare form of PAH that remains poorly understood and is both difficult to diagnose and treat [6-11]. PVOD shares many similarities with idiopathic PAH, in particular clinical features and hemodynamic characteristics, and therefore it can be difficult to distinguish PVOD from idiopathic PAH [8]. PVOD patients exposed to PAH-specific treatments may develop abrupt and potentially life-threatening deterioration due to severe pulmonary oedema [8, 12, 13].

A definitive diagnosis of PVOD requires histological examination of lung samples showing extensive and diffuse occlusion of pulmonary veins by fibrous tissue and intimal thickening involving preferentially venules and small veins in lobular septa [10, 14]. However, lung biopsy for histological confirmation of PVOD is a high risk procedure and therefore it is not recommended[11]. We have recently demonstrated that a non-invasive approach including suggestive findings on high-resolution computed tomography (HRCT) of the chest, diffusing lung capacity of carbon monoxide (DLCO) and bronchoalveolar lavage, can be helpful to screen for PVOD patients [8, 15, 16].

In recent conjoint European Respiratory Society (ERS) and European Society of Cardiology (ESC) guidelines for diagnosis and treatment of pulmonary hypertension [4, 5], it has been
suggested that unmatched perfusion defects may also suggest the diagnosis of PVOD. However, this statement is based on few isolated reports of PVOD patients with “high probability V/Q lung scan” with multiple segmental perfusion defects in perfusion lung scan, mimicking proximal CTEPH [17].

The aim of this study was to evaluate the frequency of abnormalities in ventilation and perfusion lung scans, and the potential interest of this investigation as a non-invasive approach to differentiate PVOD from idiopathic or heritable PAH.
METHODS

Subjects

We retrospectively reviewed 56 consecutive V/Q lung scans at time of diagnosis for patients with confirmed (n=31) or highly probable (n=25) PVOD, referred to the French Reference Centre for Pulmonary Hypertension (Université Paris Sud 11, Hôpital Antoine Béclère, Clamart, France) between 2000 and 2009 (Group “PVOD”). The diagnosis of PVOD was considered as “highly probable” if patients fulfilled the following characteristics: precapillary pulmonary hypertension, presence of 2 or more radiological abnormalities on high-resolution computed tomography of the chest (including lymph node enlargement, centrilobular ground-glass opacities and septal lines), low DLCO or occult alveolar haemorrhage. Diagnosis of PVOD was considered as confirmed PVOD when histological proof of veno-occlusive disease was available or when patients with signs of “highly probable” disease developed pulmonary edema after initiation of specific PAH therapy. Histological proof of veno-occlusive disease was based on hematoxylin-eosin-safran staining of biopsies (n=1), post-mortem (n=1), or lungs obtained after lung transplantation (n=10). The pathologic hallmark of PVOD was defined as an extensive and diffuse obstruction of pulmonary veins and venules by intimal fibrosis, cellular proliferation and muscularization [10, 18-20]. As control group, we reviewed 70 consecutive V/Q lung scans at time of diagnosis for patients with idiopathic or heritable PAH (Group “PAH”) diagnosed between 2007 and 2009.

Patients with drugs and toxin induced PAH or PAH associated with other medical conditions were not included in the study. After obtaining written informed consent, point mutations and large rearrangements of BMPR2 gene were researched in 72 patients (38 PAH patients and 34 PVOD patients) as previously described [20].
Haemodynamic measurements

Precapillary PH was defined as mPAP ≥25 mmHg with a normal PCWP (≤15 mmHg). mPAP, PCWP, right atrial pressure (RAP) and mixed venous oxygen saturation (SvO₂) were recorded. Cardiac output (CO) was measured by the standard thermodilution technique. The cardiac index (CI) was calculated as the CO divided by the body surface area and systolic index as the CI divided by heart rate. Pulmonary vascular resistance (PVR) was calculated as (mPAP-PCWP)/CO and was expressed in Wood units. Baseline hemodynamic data and response to acute vasodilator testing with inhaled nitric oxide (NO) were performed for all subjects. A NO challenge (10 ppm for 5-10 minutes) was used and a positive acute response was defined as a reduction of mPAP of more than 10 mmHg to reach an absolute value of mPAP lower than 40 mmHg and an increased or unchanged CO [3, 21].

Clinical and functional assessment

Routine evaluation at baseline included medical history and physical examination. Age at diagnosis and clinical status assessed by modified New-York Heart Association functional class (NYHA FC) were recorded at diagnosis [3]. A non-encouraged 6-minute walk test according to the American Thoracic Society recommendations [22] was performed with the recording of the 6-minute walk distance (6MWD). Pulmonary function tests, including diffusing lung capacity of carbon monoxide (DLCO) were also assessed.

Ventilation/Perfusion lung scan

Ventilation imaging was carried out with Tc-99m-Technegas followed by perfusion imaging using 180 MBq Tc-99m-human albumin macroaggregates. Six or eight views were taken using a high-resolution parallel-hole collimator and were reviewed in double blind. Quantitative V/Q lung scan was not considered necessary. The exams were characterized as
normal, with non-systematized defects or with segmental/subsegmental defects in ventilation and perfusion. Segmental defects were defined as the presence of abnormalities in ventilation or perfusion for >75% of a pulmonary segment. Subsegmental defects were defined as the presence of abnormalities in ventilation or perfusion for 25-75% of a pulmonary segment, while non-systematized defects on the exam meant <25% abnormalities.

**Statistical Analysis**

Statistical analysis was performed using Stat View version 5.0 (Abacus Concepts Inc., Berkley, CA). Data are presented as mean ± standard deviation unless stated otherwise. Comparisons between PVOD and PAH patients were assessed by Student t test and Z-test for comparing proportions. A p value <0.05 was considered statistically significant and the z value was calculated for a 95% confidence interval.
RESULTS

Characteristics of PVOD and PAH patients at diagnosis

Demographic, clinical, hemodynamic and functional characteristics of PVOD (n=56) and PAH patients (n=70) at diagnosis are shown in Table 1. PVOD was confirmed in 31 patients (55%) [histological confirmation (n=12)] and was considered highly probable in 25 patients (45%). Age at diagnosis was broadly similar in PVOD and PAH patients (50.2 ± 18.4 versus 53.9 ± 18.9 respectively, p=0.13). Sex ratio was significantly different, with a female/male ratio of 0.5 in the PVOD group and 1.6 in the PAH group (p<0.01). Forty-three (76%) PVOD patients and 56 (80%) PAH patients were in NYHA FC III, while 12 (21.2%) PVOD and 3 (4.3%) PAH were in NYHA FC class IV (p=0.003). 6MWD was significantly lower in PVOD patients, as compared to PAH patients (241±172 versus 299±163, p=0.02). Regarding haemodynamic parameters, no significant differences were observed in mPAP, PCWP, PVR and SvO2 between PVOD and PAH patients (all p values>0.05), except for CI (2.3±0.6 versus 2.6±0.9, respectively, p=0.01). DLCO was significantly lower in PVOD patients as compared to idiopathic PAH patients (31.3±18.9 and 61.7±21.3, p<0.001). BMPR2 mutations were found in 3 of the 38 PAH patients tested and none of the 34 PVOD patients tested.

Analysis of the V/Q lung scans in PVOD and idiopathic PAH patients

Results of perfusion and ventilation of V/Q lung scans in PVOD and PAH patients are shown in Figure 1. Normal perfusion was observed in 51 (72.9%) PVOD patients and 46 (82.1%) PAH patients (p=0.3). Segmental or subsegmental defects were observed in 4 (7.1%) PVOD patients and 5 (7.1%) PAH patients (p=0.72). Non-systematized defects were observed in the same proportion in both groups (20% and 10.7%, respectively, p=0.24).

In ventilation, no statistically relevant difference was observed between PAH and PVOD patients: normal ventilation [59 (84.3%) versus 48 (85.7%), p=0.97], non-systematized
defects [10 (14.3%) versus 7 (12.5%), p=0.97] and segmental or subsegmental defects [1 (1.4%) versus 1 (1.7%), p=0.58].

**Analysis of patients with non-matched perfusion defects**

In the 126 patients included in this study, 11 (8.7%) patients had non-matched perfusion defects, including 7 (10%) PAH and 4 (7.1%) PVOD patients (3 confirmed disease and 1 highly probable). Individual data of these 11 patients are presented in Table 2. The clinical history of the 11 patients with non-matched perfusion defects was analyzed in detail in order to find arguments that could explain the V/Q lung scan results. Two PAH patients had a previous history of acute pulmonary embolism with a delay between diagnosis of PAH/PVOD and pulmonary embolism of 26 and 60 months, respectively, associated in one patient with deep vein thrombosis and therefore prior use of anticoagulant therapy. One PAH patient had a history of superficial vein thrombosis with a 3-month period of anticoagulation therapy. In 8 patients, no clinical history of thromboembolic disease was found.

The epidemiological, clinical, functional and haemodynamic characteristics of the 11 patients with non-matched perfusion defects at the time of diagnosis were compared with those having matched or no perfusion defects (n=115) (Table 3). NYHA FC, 6MWD, haemodynamic characteristics and DLCO measurements were similar in both groups, except for a significantly higher CI in patients with non-matched defects (2.93±0.84 versus 2.51±0.84,, p=0.03).

**V/Q lung scan analysis of patients with histological confirmed PVOD**

In histologically confirmed PVOD patients (n=12), 8 (66.6%) patients had a normal perfusion, 2 (16.6%) had non-systematized and 2 (16.6%) had segmental or subsegmental defects. Regarding ventilation, 9 (75%) patients had a normal ventilation at the V/Q lung
scan, 2 (16.6%) had non-systematized ventilation defects and 1 (8.3%) had segmental ventilation defects.

We present in Figure 2 an illustrative case of a PVOD patient with HRCT highly suggestive of PVOD, histological proofs of PVOD and normal V/Q lung scan. Among the other histologically confirmed PVOD patients, only one (8.3%) had a non-matched segmental perfusion defect on V/Q lung scan and histological exam found venular and capillary involvement characteristic of PVOD associated with thrombotic lesions (Figure 3). In this selected case, HRCT of the chest showed typical PVOD findings including septal lines, centrolobular ground-glass opacities and mediastinal lymph node enlargement associated with mosaic perfusion. Pulmonary angiography revealed attenuation of peripheral pulmonary arteries without radiological signs of chronic thromboembolic disease.
DISCUSSION

PVOD is a rare and severe condition with a poor prognosis that requires an early diagnosis because of the need for specific management including high dose diuretics, careful management of specific PAH therapy and early referral for lung transplantation [11, 13, 23, 24]. The main risk for these patients is the development of acute pulmonary oedema with the use of PAH specific drugs (prostacyclin, prostacyclin analogues, endothelin receptor antagonists or phosphodiesterase 5 inhibitors), that may promote fluid extravasation from the capillaries to the alveolus by acting mainly as arteriolar vasodilators against a venular obstruction due to specific remodeling [8, 12, 13]. The definitive diagnosis of PVOD requires histological examination of lung tissue samples. As lung biopsy is a high risk procedure in the setting of PAH, it is not recommended, and histological proof of PVOD is usually retrospectively obtained after death or lung transplantation[8, 11]. Therefore a reliable non-invasive approach is needed for the diagnosis of PVOD. We recently demonstrated that HRCT of the chest showing septal lines, ground-glass opacities and lymph node enlargement, low DLCO and presence of intra-alveolar hemorrhage on bronchoalveolar lavage may be helpful to discriminate patients with highly probable PVOD.

The V/Q lung scan is a relatively inexpensive and widely available investigation, recommended in the management and diagnosis of pulmonary hypertension to screen for CTEPH because of its higher sensitivity than computed tomography [4, 5, 25, 26]. A normal or low probability V/Q lung scan effectively excludes CTEPH with a high sensitivity and specificity [4, 5]. Recent ERS/ESC guidelines also affirm that unmatched perfusion is a caveat because these defects are also seen in PVOD, suggesting that V/Q lung scan may be helpful to screen PVOD patients [4, 5].
To our knowledge, this assertion in the recent ERS/ESC guidelines is based on a series of 3 cases of PVOD, where patients with high probability V/Q lung scans and negative angiograms for arterial obstruction had a focal “downstream” process suggestive of PVOD at angiography, which was confirmed histologically in 2 of the cases [17].

The present study reviews the V/Q lung scans at time of diagnosis for confirmed or highly probable PVOD and idiopathic or heritable PAH patients. There was no difference in lung perfusion between PVOD and PAH patients and the same proportion of segmental or subsegmental perfusion defects (7.1%) was observed in both groups. Furthermore, there is a non-statistically significant trend toward a higher proportion of non-systematized perfusion defects in PAH patients (20%) than in PVOD patients (10.8%). These perfusion abnormalities may be due to \textit{in situ} thrombosis which have been described in histological samples of idiopathic PAH [27-29]. Based on this observation, Rich \textit{et al} demonstrated, in a period when no specific PAH therapy was available that anticoagulation may improve survival of idiopathic PAH patients. Regarding ventilation, we have found no significant differences between the percentage of non-systematized and segmental/subsegmental defects between PVOD and PAH [30]. It has been clearly demonstrated that HRCT may discriminate PVOD patients among idiopathic PAH patients, by showing abnormalities suggestive of PVOD (septal lines, ground glass opacities and lymph node enlargement)[8, 15]. Therefore, it could be suspected that PVOD may be associated with more frequent abnormal ventilation on V/Q lung scan, as compared to PAH patients. However, our data confirmed that ventilation defects were not, significantly associated with PVOD signs on HRCT. Interestingly, we present an illustrative case of a PVOD patient in Figure 2 with a highly suggestive HRCT, a histological confirmation and a normal V/Q lung scan. In conclusion, PAH and PVOD are two entities, which do not influence \textit{per se} the distribution of the radionuclide substance in ventilation, having similar both flow and volumes measured by pulmonary functional tests; however an
abnormal ventilation may signify an incorrect maneuver or the presence of other lung disease [7]. The rare association of non-matched perfusion defects and the diagnosis of PVOD or idiopathic PAH suggest the absence of correlation between abnormal V/Q lung scan and the diagnosis of PVOD, either confirmed histologically or highly probable.

In our study, we found 11 patients (7 PAH and 4 PVOD patients) with non-matched perfusion defects. Three PAH patients had non-matched perfusion defects and a history of thromboembolic events (two had a previous acute pulmonary embolism that required anticoagulation therapy, and a third patient had a superficial vein thrombosis more than 5 years prior to PAH diagnosis), whereas none of the 4 PVOD patients had a history of thromboembolic events. We further analyzed the clinical and haemodynamic data from these patients and found no statistically significant difference between them and the rest of the patients, with the exception of a higher mean cardiac index. This finding does not support the idea that more severe PAH patients have a greater risk for \textit{in situ} thrombosis due to low CI [31, 32]. However, our data suggest that no haemodynamic characteristics seem to be associated with perfusion scan abnormalities. Based on these results, it can therefore be suggested that low cardiac index was not a risk factor of \textit{in situ} thrombosis in PAH or PVOD patients. In our cohort, \textit{BMPR2} mutation was observed only in 3/72 PAH or PVOD patients that could not allow to conclude on the impact of \textit{BMPR2} mutations on V/Q lung scan; however, these 3 PAH patients with \textit{BMPR2} mutations had no specific abnormalities. In particular, none of the 6 patients with non-matched perfusion defects and genetic testing had \textit{BMPR2} mutations. In this context, it could be interesting to evaluate other characteristics, such as age, gender or deficiency of coagulation in a large cohort of PAH patients to find predictive factors of \textit{in situ} thrombosis in these patients, and better understand the impact of anticoagulant in these disorders.
To our knowledge, no systematic analysis of V/Q lung scans has already been performed in a cohort of PAH or PVOD patients of this size. European guidelines suggesting a role for V/Q lung scanning in PVOD patients was based on the analysis of a selected report of 3 PVOD patients showing that non-matched perfusion lung scans may be not necessarily associated with proximal CTEPH. These observations may be in accordance with our results, because in our cohort of well-characterized PVOD patients, we found 4 PVOD patients with non-matched pulmonary defects in a period of 8 years. However, these abnormalities were not specific of PVOD and were observed in the same proportion in PAH patients. Of the 3 patients with non-matched perfusion defects reported by Bailey et al [17], 2 had no history of thromboembolic events and PVOD diagnosis was confirmed by histology. The last case had a presumed diagnosis of pulmonary embolism made during pregnancy, and was treated with oral anticoagulation therapy for 3 years before the diagnosis of pre-capillary pulmonary hypertension was made. HRCT in this patient showed features compatible with the diagnosis of PVOD, and the diagnosis of PVOD was suggested by focal venous obstructions at venography. The authors hypothesized that the distribution of radionuclide particles during perfusion scanning may be altered by the high downstream resistance due to venular involvement, resulting in regional differences in pulmonary blood flow. Our analysis showed no clinical or haemodynamic difference between the PAH and PVOD patients with non-matched perfusion defects, with, if anything, cardiac index being higher in those with non-matched V/Q defects (Table 3).

Our study is the first large-scale systematic analysis of V/Q lung scans in a substantial cohort of PVOD patients. In our study, a limitation was that only 12 PVOD patients had the diagnosis confirmed histologically, while the rest we used the established non-invasive diagnostic criteria. However, because of the rarity of PVOD and the contraindication of lung biopsy in these patients, the proportion of histologically confirmed PVOD in fact represents
one of the most important series of those with a confirmed diagnosis. Another strength was that all patients that had non-matched perfusion defects were further investigated by CT scan and/or angiography in order to rule out the possibility of CTEPH. The low number of patients having a BMPR2 mutation could not give us information of a specific V/Q pattern for this subgroup, although it cannot be excluded that such a status may be associated with non-matched perfusion defects.

In conclusion, non-matched perfusion defects on V/Q lung scans are an uncommon observation in idiopathic or heritable PAH and PVOD patients and V/Q lung scanning may mimic CTEPH in the same proportion in both conditions. Even if PVOD is characterized by abnormalities on HRCT of the chest, abnormalities in ventilation lung scans are infrequent and observed in the same proportion in idiopathic PAH patients. Our data suggest also that non-matched perfusion defects are not associated with more pronounced haemodynamic impairment and the hypothesis of in situ thrombosis induced by low cardiac output should be therefore reconsidered. According to our results, the role of V/Q lung scans in the diagnostic algorithm for pulmonary hypertension should be modified in future guidelines: although V/Q lung scanning remains essential for the screening of CTEPH patients, it may not be such a useful tool to discriminate PVOD.
**TABLE 1** Demographic, clinical, haemodynamic, functional characteristics and heritable PAH status at diagnosis of PVOD and PAH patients.

<table>
<thead>
<tr>
<th></th>
<th>PVOD n=56</th>
<th>PAH n=70</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, yrs (mean±SD)</td>
<td>50 ± 18</td>
<td>54 ± 18</td>
<td>0.13</td>
</tr>
<tr>
<td>Gender, female/male (ratio)</td>
<td>19/37 (0.5)</td>
<td>43/27 (1.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>NYHA FC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2 (3.5%)</td>
<td>11 (15.7%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>43 (76.7%)</td>
<td>56 (80%)</td>
<td>0.003</td>
</tr>
<tr>
<td>IV</td>
<td>11 (19.8%)</td>
<td>3 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>6MWD, m (mean±SD)</td>
<td>240±173</td>
<td>299±163</td>
<td>0.02</td>
</tr>
<tr>
<td>mPAP, mmHg(mean±SD)</td>
<td>53±12</td>
<td>53±15</td>
<td>0.46</td>
</tr>
<tr>
<td>PCWP, mmHg(mean±SD)</td>
<td>9±4</td>
<td>8±4</td>
<td>0.14</td>
</tr>
<tr>
<td>CO, L/min (mean±SD)</td>
<td>3.97±1.4</td>
<td>4.57±1.7</td>
<td>0.01</td>
</tr>
<tr>
<td>CI, L/min/m²(mean±SD)</td>
<td>2.34±0.6</td>
<td>2.63±0.9</td>
<td>0.01</td>
</tr>
<tr>
<td>PVR, mmHg/L/min(mean±SD)</td>
<td>12.6±8</td>
<td>11.7±8</td>
<td>0.25</td>
</tr>
<tr>
<td>SvO₂, % (mean±SD)</td>
<td>61±10.</td>
<td>61±10</td>
<td>0.33</td>
</tr>
<tr>
<td>DLCO, % pred (mean±SD)</td>
<td>31.3±18.9</td>
<td>61.7±21.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMPR2 status (%)</td>
<td>0/34 (0%)</td>
<td>3/38 (8%)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

% pred: percent of predicted value; 6MWD: 6-minute walk distance; BMPR2: bone morphogenetic protein receptor type 2; CI: cardiac index; CO: cardiac output; DLCO: diffusion capacity of carbon monoxide; SvO₂: mixed venous oxygen saturation; mPAP: mean pulmonary artery pressure; NYHA FC: New York Heart Association functional class, PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance.
TABLE 2. Clinical history, *BMPR2* status and clinical, functional, haemodynamic and radiological characteristics of the patients with non-matched perfusion defects on V/Q lung scans

<table>
<thead>
<tr>
<th>Patient</th>
<th>History of thromboembolic disease</th>
<th>Group</th>
<th>BMPR2 mutation screening</th>
<th>NYHA FC</th>
<th>6MWD, m</th>
<th>mPAP, mmHg</th>
<th>CI, L/min/m²</th>
<th>PVR, mmHg/L/min</th>
<th>HRCT of the chest</th>
<th>Angiography</th>
<th>Anticoagulant treatment prior to the PAH diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no</td>
<td>PAH</td>
<td>N/A</td>
<td>III</td>
<td>383</td>
<td>41</td>
<td>2.3</td>
<td>5.1</td>
<td>normal</td>
<td>not performed</td>
<td>no</td>
</tr>
<tr>
<td>2</td>
<td>history of deep vein thrombosis and pulmonary embolism</td>
<td>PAH</td>
<td>N/A</td>
<td>III</td>
<td>N/A</td>
<td>65</td>
<td>2.2</td>
<td>19.7</td>
<td>mosaic perfusion</td>
<td>very narrow peripheral vascular structures; no signs of CTED</td>
<td>yes</td>
</tr>
<tr>
<td>3</td>
<td>no</td>
<td>PAH</td>
<td>negative</td>
<td>III</td>
<td>340</td>
<td>61</td>
<td>2.2</td>
<td>9.9</td>
<td>mosaic perfusion</td>
<td>not performed</td>
<td>no</td>
</tr>
<tr>
<td>4</td>
<td>history of superficial vein thrombosis</td>
<td>PAH</td>
<td>N/A</td>
<td>III</td>
<td>395</td>
<td>39</td>
<td>3.9</td>
<td>3.2</td>
<td>not performed</td>
<td>signs of CTED only at the level of the median lobe artery</td>
<td>yes</td>
</tr>
<tr>
<td>5</td>
<td>history of pulmonary oedema</td>
<td>PAH</td>
<td>negative</td>
<td>III</td>
<td>N/A</td>
<td>49</td>
<td>2.4</td>
<td>8.9</td>
<td>apical bilateral mosaic perfusion</td>
<td>very narrow peripheral vascular structures; no signs of CTED</td>
<td>yes</td>
</tr>
<tr>
<td>6</td>
<td>no</td>
<td>PAH</td>
<td>negative</td>
<td>II</td>
<td>390</td>
<td>42</td>
<td>3.6</td>
<td>6.6</td>
<td>normal</td>
<td>not performed</td>
<td>no</td>
</tr>
<tr>
<td>7</td>
<td>no</td>
<td>PAH</td>
<td>negative</td>
<td>III</td>
<td>395</td>
<td>53</td>
<td>3.1</td>
<td>10.0</td>
<td>normal</td>
<td>not performed</td>
<td>no</td>
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<tr>
<td>8</td>
<td>no</td>
<td>confirmed PVOD</td>
<td>negative</td>
<td>III</td>
<td>318</td>
<td>59</td>
<td>2.5</td>
<td>9.8</td>
<td>nodules; mediastinal lymphadenopathy</td>
<td>not performed</td>
<td>no</td>
</tr>
<tr>
<td>9</td>
<td>no</td>
<td>Highly probable PVOD</td>
<td>negative</td>
<td>III</td>
<td>453</td>
<td>35</td>
<td>2.8</td>
<td>4.3</td>
<td>bilateral ground glass opacities; mediastinal lymphadenopathy;</td>
<td>not performed</td>
<td>no</td>
</tr>
<tr>
<td>10</td>
<td>no</td>
<td>confirmed PVOD</td>
<td>N/A</td>
<td>III</td>
<td>315</td>
<td>59</td>
<td>4.9</td>
<td>5.9</td>
<td>septal lines; nodules; mediastinal lymphadenopathy;</td>
<td>very narrow peripheral vascular structures; no signs of CTED</td>
<td>no</td>
</tr>
<tr>
<td>11</td>
<td>no</td>
<td>confirmed PVOD</td>
<td>N/A</td>
<td>II</td>
<td>N/A</td>
<td>40</td>
<td>2.2</td>
<td>8.7</td>
<td>Septal lines; mediastinal lymphadenopathy; nodules mosaic perfusion</td>
<td>very narrow peripheral vascular structures; no signs of CTED</td>
<td>no</td>
</tr>
</tbody>
</table>

6MWD: 6-minute walk distance; BMPR 2: bone morphogenetic protein receptor type 2; CI: cardiac index; CTED: chronic thromboembolic disease; NYHA FC: New York Heart Association functional class; mPAP: mean pulmonary artery pressure, N/A: not available; NYHA: New York Heart Association; PVR: pulmonary vascular resistance;
**TABLE 3** Demographic, clinical, haemodynamic and functional characteristics of patients with non-matched perfusion defects on the V/Q lung scan *versus* patients with normal or matched perfusion defects

<table>
<thead>
<tr>
<th></th>
<th>Patients with non matched perfusion defects</th>
<th>Patients with normal V/Q lung scans or matched defects</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=11</td>
<td>n=115</td>
<td></td>
</tr>
<tr>
<td>Diagnosis, PAH/PVOD (ratio)</td>
<td>7/4 (1.7)</td>
<td>63/52 (1.21)</td>
<td>0.81</td>
</tr>
<tr>
<td>Age at diagnosis, yrs (mean±SD)</td>
<td>42 ± 20</td>
<td>53 ± 18</td>
<td>0.06</td>
</tr>
<tr>
<td>Gender, female/male (ratio)</td>
<td>8/3 (2.6)</td>
<td>53/62 (0.8)</td>
<td>0.16</td>
</tr>
<tr>
<td>NYHA FC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2 (18.8%)</td>
<td>11 (9%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>9 (81.2%)</td>
<td>89 (78%)</td>
<td>0.33</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>15 (13%)</td>
<td></td>
</tr>
<tr>
<td>6MWD, m (mean±SD)</td>
<td>271±178</td>
<td>264±169</td>
<td>0.89</td>
</tr>
<tr>
<td>mPAP, mmHg (mean±SD)</td>
<td>49±10</td>
<td>52±13</td>
<td>0.45</td>
</tr>
<tr>
<td>CI, L/min/m² (mean±SD)</td>
<td>2.93±0.8</td>
<td>2.51±0.8</td>
<td>0.03</td>
</tr>
<tr>
<td>PVR, mmHg/L/min (mean±SD)</td>
<td>8.3±4</td>
<td>12.1±8</td>
<td>0.06</td>
</tr>
<tr>
<td>SvO₂, % (mean±SD)</td>
<td>63±9</td>
<td>61±10</td>
<td>0.36</td>
</tr>
<tr>
<td>DLCO, % pred (mean±SD)</td>
<td>51.7±28.6</td>
<td>46.9±24.8</td>
<td>0.27</td>
</tr>
<tr>
<td>BMPR2 status (%)</td>
<td>0/6 (0%)</td>
<td>4/66 (6%)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

% pred: percent of predicted value; 6MWD: 6-minute walk distance; CI: cardiac index; CO: cardiac output; DLCO: diffusion capacity of carbon monoxide; SvO₂: mixed venous oxygen saturation; mPAP: mean pulmonary artery pressure; NYHA FC: New York Heart Association functional class; PVR: pulmonary vascular resistance.
**FIGURE 1** Comparative evaluation of V/Q lung scans between idiopathic PAH and PVOD patients.

In perfusion (idiopathic PAH *versus* PVOD patients): normal perfusion [51 (72.9%) *versus* 46 (82.1%), *p*=0.30]; non-systematized defects [14 (20%) *versus* 6 (10.7%), *p*=0.24]; segmental or subsegmental defects [5 (7.1%) *versus* 4 (7.1%), *p*=0.72].

In ventilation (idiopathic PAH and PVOD patients): normal ventilation [59 (84.3%) *versus* 48 (85.7%), *p*=0.97], non-systematized defects [10 (14.3%) *versus* 7 (12.5%), *p*=0.97] and segmental or subsegmental defects [1 (1.4%) *versus* 1 (1.7%), *p*=0.58].
FIGURE 2 Review of a patient with confirmed PVOD and normal V/Q lung scan

A. V/Q lung scan with normal ventilation and perfusion; B. HRCT with typical PVOD findings: septal lines and centrilobular ground-glass opacities; C histological sample: arrow heads – preseptal veins with intimal fibrosis. (Hematoxylin-Eosin)

LPO: left posterior oblique view; RPO: right posterior oblique view; POST: posterior view.

FIGURE 3 Review of a patient with confirmed PVOD and non-matched perfusion defects

A. V/Q lung scan with multiple non-matched perfusion defects: right superior lobe, right basal pyramid, culmen and left inferior lobe; B, C multiple histological samples from the same patient: narrow straight arrow – repermeabilised old thrombus, arrow head – fibrosed vein, wide arrow – focal lesion of pulmonary haemangiomatosis. (Hematoxylin-Eosin)

LPO: left posterior oblique view; RPO: right posterior oblique view; POST: posterior view.
CONFLICT OF INTEREST: none declared
REFERENCES