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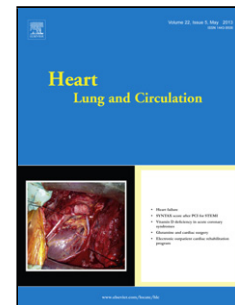
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**Grossly Abnormal Ventilation/Perfusion SPECT Study in Idiopathic Pulmonary Arterial Hypertension Without Thromboembolism**

Short title: V/Q SPECT and pulmonary hypertension

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**Abstract**

Pulmonary hypertension is a serious condition with multiple underlying aetiology which require different treatment strategies. We present a case of severe idiopathic pulmonary arterial hypertension in a 20-year-old patient with ongoing breathlessness. She was initially diagnosed with asthma and panic attacks in community care. As the symptoms became progressively worse, she was referred for pulmonary hypertension clinic assessment.

Ventilation/perfusion single-photon emission computed tomography (V/Q SPECT) showed grossly abnormal perfusion defects which were mismatched to the ventilation scan, suggestive of chronic thromboembolic disease. However, corroborating computed tomographic (CT) pulmonary angiogram and invasive pulmonary angiography showed no thromboembolic disease. Histological examination of the pulmonary arteries post-mortem showed changes consistent with idiopathic pulmonary arterial hypertension. This case highlighted the clinical challenges in interpreting the investigation results and phenotyping pulmonary hypertension. V/Q SPECT might have a role in visualising the extent of vasculopathies in pulmonary arterial hypertension.

**Key words:** Pulmonary hypertension; Thromboembolism; Ventilation/perfusion; SPECT

## Case reports

A 20-year-old Caucasian female was referred to the Pulmonary Hypertension Service for investigation of an 8-year history of progressive breathlessness with exertional syncope on several occasions. She reported exertional central chest pain and felt pre-syncopal with effort approximately once a week. There were no symptoms of connective tissue disease, history of anorexigen use or thrombotic events.

On assessment, she was comfortable at rest but became breathless when walking inclines. Oxygen saturation was 98%, blood pressure 121/88 mmHg, heart rate 91. There was a marked parasternal heave and loud P2, and raised jugular venous pressure at 13cm. Six-minute walk distance was 377 metres with no associated oxygen desaturation.

Echocardiography showed preserved left ventricular function with normal left atrial size.

The right atrium and ventricle were severely dilated with overall preserved systolic function, and a dilated pulmonary trunk at 4.9 cm. Pulmonary function test showed normal spirometry with forced vital capacity 99.7% of predicted and diffusion of carbon monoxide at 78.8% predicted. Haemoglobin level was within normal range (154 g/l). NT-proBNP (brain natriuretic peptide) was raised at 224 pmol/l (normal < 40 pmol/l). Serology for anti-nuclear antibodies (anti-ANA) and antibodies to extractable nuclear antigens were negative.

Initial right heart catheterisation (RHC) in December 2014 showed a mean pulmonary arterial pressure (mPAP) of 108 mmHg, pulmonary arterial wedge pressure (PAWP) was 10 mmHg, cardiac output was 3.2 l/min giving a pulmonary vascular resistance (PVR) of 30.6 Wood Units. Mixed venous oxygen saturation was 66%, with systemic oxygen saturation of 98%.

Single-photon emission computed tomography (SPECT) ventilation perfusion (V/Q) scan was performed on the same day, and showed extensive mismatched segmental and subsegmental perfusion defects in both lungs involving all zones with widespread heterogeneous and patchy perfusion defects (Figure 1). Computed tomography pulmonary angiogram (CTPA) performed on the next day demonstrated markedly dilated pulmonary outflow trunk measures 4.6 cm in transverse diameter, consistent with severe pulmonary hypertension. However, there were no filling defects suggestive of pulmonary embolism (Figure 2). She was treated with warfarin, sildenafil and, 3 weeks later, with macitentan. After 4 months on oral treatments there was modest improvement in the 6-minute walk distance to 395 metres. Right heart catheterisation showed a reduction of mPAP to 92 mmHg, mixed venous oxygen saturations improved to 74%, and cardiac output had improved to 5.48 l/minutes hence PVR halved to 15 Wood Units. Conventional pulmonary angiography, performed at the same time of the RHC, showed no thromboembolic disease (Figure 3). After 8 months on therapy, the 6-minute walking distance was 422 metres. Repeat RHC at 8 months showing no further haemodynamic improvements and intravenous epoprostanol was recommended. Sildenafil was replaced by titrating doses of riociguat as the patient preferred to explore all oral treatment options prior to intravenous treatments. At 12 months the patient agreed to intravenous therapy, however, before treatment was commenced she was admitted with a febrile illness and raised C-reactive protein of 109 mg/dL. Small nodules were seen on CT scan suggestive of lower respiratory tract infection and she had equivocal *mycoplasma pneumonia* serology. Despite treatment with antibiotics she died in December 2015. Examination of the lungs at post-mortem showed no evidence of thromboembolic disease in the pulmonary vessels. Histology showed features of severe pulmonary hypertension with vasculopathy, peri-arterial fibrosis and inflammatory

infiltrates. (Supplementary Figure S1) These changes are consistent with the diagnosis of idiopathic pulmonary arterial hypertension.

## Discussion

Pulmonary hypertension is a severe condition with poor prognosis. Current guidelines emphasise the central role of the V/Q scan in diagnosing chronic thromboembolic pulmonary hypertension. [1] The advent of V/Q SPECT offers 97.4% sensitivity compared to 51% for CTPA in detection of chronic thromboembolic disease[2], and more accurate differentiation from other interstitial lung pathologies such as chronic obstructive pulmonary disease compared to planar V/Q imaging.[3] It has been recognised that patients with pulmonary hypertension may have 'patchy' perfusion on V/Q imaging that is distinct from the typical segmental mismatch suggestive of thromboembolism .[4] We have also found an increasing number of cases where the perfusion abnormalities satisfy current criteria for thromboembolic disease but subsequent corroborating investigations such as CTPA and invasive pulmonary angiograms did not show evidence of thromboembolism.[5] The majority of such cases demonstrated diffuse patchy perfusion mismatches especially on the peripheral segments. [5] It is possible that this widespread perfusion abnormality reflects the degree of vasculopathies in group I pulmonary arterial hypertension, as the radiolabelled microaggregated albumin need to pass through more tortuous and diseased vessels during the perfusion scan. The extent of mismatch, as demonstrated in the current case where segmental arteries are also affected, might also give an insight into the severity of disease. Indeed, there have been attempts to quantify the perfusion defects and correlate them with the severity of pulmonary hypertension.[6] In cases with grossly abnormal V/Q SPECT but otherwise no thromboembolism demonstrable on other

investigations, more aggressive treatment at initial stage might be beneficial in order to halt the rapid disease progression, although this would need to be tested in prospective clinical trials.

**Consent:** Obtained

**Conflict of interests:** None

ACCEPTED MANUSCRIPT



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**Figure legends**

**Figure 1.** V/Q SPECT scan (99mTc-macroaggregated albumin for perfusion, and 81mKr for ventilation) showing global perfusion defects and mismatches with ventilation on various coronal sections.



**Figure 2.** Computed tomographic pulmonary angiogram showing dilated pulmonary trunks consistent with severe pulmonary hypertension. A) Left pulmonary artery on axial section; B) right pulmonary artery on axial section; C) segmental pulmonary arteries on coronal section; D) dilated pulmonary trunk on coronal section.



**Figure 3.** Invasive pulmonary angiogram showing no obvious thromboembolic disease on a) right upper lobe pulmonary artery, b) right lower lobe pulmonary artery and c) left lower lobe pulmonary artery

