

**Title: A case series of outcomes in isolated subsegmental pulmonary embolism on ventilation-perfusion imaging**

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## **Abstract**

### **Objectives**

The risk of recurrent venous thromboembolic disease and the management for patients with isolated subsegmental pulmonary embolism (SSPE) remains unclear. We sought to assess the long term clinical outcome of patients with isolated SSPE demonstrated by isolated subsegmental mismatch (SSM) found on ventilation/perfusion (V/Q) scans.

### **Methods**

We performed a retrospective observational study of 1,300 consecutive patients with suspected PE who underwent index ventilation-perfusion (V/Q) single-photon emission computed tomography (SPECT) between 2012 and 2013. Forty (3%) patients were found to have isolated SSPE identified on V/Q scan. 19 out of 40 patients with isolated SSPE on V/Q scan underwent further investigation with CT pulmonary angiogram (CTPA) within 48 hours.

### **Results**

Amongst 19 patients who had corroborating CT pulmonary angiogram performed concurrently, 94.7% of the SSPEs identified on V/Q were not detectable on CTPA. 10 out of 40 (25%) of patients were anticoagulated. In a median follow up of  $3.28 \pm 0.55$  years, all-cause mortality occurred in 2 patients, recurrence of suspected venous thromboembolism (VTE) occurred in 12 out of 40 patients (30%) but none had confirmed recurrent thromboembolism on further imaging. In the 40 patients with SSPE on V/Q there was no difference in the risk of recurrence of suspected VTE or mortality between patients treated with anticoagulation and not treated (HR 2.04, 95% CI 0.75-7.28)

### **Conclusions**

In this case series, a large proportion of isolated SSPE on V/Q imaging were not identified on corroborating CTPA performed within 48 hours. In patients with isolated SSPE (identified

by isolated SSM on V/Q SPECT) we found no difference in risk of recurrent suspected VTE or all-cause mortality in those treated with anticoagulation and those not treated.

## **Introduction**

Pulmonary embolism (PE) is common cause of mortality and accurate diagnosis is essential to guide anticoagulation therapy. There is currently no randomised controlled trial evidence regarding the effectiveness and safety of using anticoagulation treatment versus no intervention for isolated subsegmental pulmonary embolism (SSPE). A recent Cochrane review concluded that further research is required before informed evidence based practice decisions can be made. [1]

V/Q scans have an important role for investigation in suspected PE. European Association of Nuclear Medicine (EANM) guidelines have set a cut off of at least 1 segmental or 2 sub-segmental mismatches (SSM) for a V/Q based diagnosis of PE, therefore a single sub-segmental pulmonary embolism (SSPE) on V/Q is not diagnostic of PE.[2]

Previous studies have identified that SSPE accounts for 9 to 16% of all PE detected on CT pulmonary angiogram (CTPA), with an overall incidence of 3% amongst patients with suspected PE.[3, 4] CTPA has good specificity in diagnosing PE, however ventilation/perfusion (V/Q) scans may offer higher sensitivity. [5] The future risk of thrombosis in SSPE, the requirement for anticoagulation and role of further confirmatory imaging remains unclear. In this case series we sought to study this small yet important subset of patients referred for V/Q imaging and address controversy surrounding this topic.

## **Methods**

### **Patient cohort**

We performed a retrospective observational study of consecutive patients with suspected PE who underwent V/Q imaging in 2012 and 2013 at the Royal Free Hospital. Of the 1,300 consecutive patients, 40 patients had single sub-segmental mismatches (SSM) in the clinical reports. No V/Q scans were excluded due to inconclusive findings. Patient demographics and follow up investigations such as CTPA performed within 48 hours of the index V/Q SPECT were recorded. The reason for request of CTPA in these patients was based on

clinical suspicion for clarification of diagnosis and to guide the need for anticoagulation. A previous study showed that SSPE identified on CTPA had significant clinical risk and outcome compared to patients with proximal PE.[3] Anticoagulation status of the patients was obtained from electronic health records. Recurrent presentation to hospital for suspected thromboembolism, and all-cause mortality were recorded. The study was undertaken in accordance with the principles of the Declaration of Helsinki.

### **V/Q SPECT**

All V/Q SPECT scans were undertaken using either a dual head (Siemens Symbia, Germany) or triple-head (Philips Irix, Netherlands) gamma camera equipped with low energy, high resolution, parallel-hole collimators. Perfusion studies were performed with  $^{99m}\text{Tc}$ -macroaggregated albumin (200 MBq, CIS Bio International, Ireland). Ventilation studies were performed during tidal inhalation of  $^{81m}\text{Kr}$  (190keV; Sandwell and West Birmingham NHS Trust). All scans were reported by two independent nuclear medicine physicians experienced in V/Q imaging. CTPA were reported by one radiologist. Scans were not retrospectively re-analysed. Observers were not blinded to pre-test clinical history and all scans were reported in accordance with European Association of Nuclear Medicine (EANM) guidelines.

### **Statistical analysis**

Categorical variables were analysed with Chi-Square test. Continuous variables were presented as mean $\pm$ SD and analysed with linear regression. Co-proportion analysis was used for outcome data. Statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL).

### **Results**

A total of 40 patients (mean age  $56.0 \pm 19.6$ ) with isolated single-subsegmental mismatch on V/Q scan were identified. 19 patients had corroborating CTPA within 24 hours but SSPE was identified on CTPA in only one patient (5.2%). Given that SSPE was detectable on CTPA, this patient was treated with anticoagulation for 6 months. The remaining 21 patients were not followed up immediately with CTPA as they were low clinical suspicion of significant thromboembolism, or already received long term anticoagulation (4 patients) for an alternative indication of atrial fibrillation. Patients were followed up for a median of  $3.28 \pm 0.55$  years and none were lost to follow up. Recurrent presentation for suspected PE occurred in 12 out of 40 (30%) of the patients, of which 4 received anticoagulation following index presentation and 8 were not anticoagulated ( $p=0.34$ ). None had PE or SSPE demonstrated on further V/Q or CTPA imaging, and none were clinically treated with further anticoagulation. Median time to recurrent presentation was  $121.0 \pm 361.2$  days. Out of the 40 patients, 10 were anticoagulated following the index SSPE found on V/Q SPECT (Table 2). The anticoagulation status of the patients did not affect future presentation for suspected thromboembolism, with hazard ratio (HR) 2.04 (95% CI 0.75-7.28). This remained the same after excluding patients on long-term anticoagulation for other reasons, HR 1.82 (95% CI 0.37-9.04). All-cause mortality occurred in 2 patients. Both occurred over 1 year following the index V/Q SPECT and one was anticoagulated ( $p=0.44$ ). In both cases thromboembolism was not the primary cause of death.

## Discussion

In this study we found a low the incidence of 3% (40/1300) isolated SSPE on V/Q SPECT imaging. However, 95% (18/19) of the SSPE were not detectable in corroborating CTPA performed simultaneously, which might reflect the higher sensitivity of V/Q SPECT in detecting SSPEs. CTPA is not an ideal method to diagnose PE and might lead to many false positives, with a study finding up to 42% false positive in patients with low clinical suspicion.[6] European Association of Nuclear Medicine guidelines state that at least 1

segmental or 2 sub-segmental mismatches is required for a V/Q based diagnosis of PE [7]. Further studies have shown that V/Q SPECT is better than V/Q planar for diagnosis in indeterminate scans.[8] Some studies have demonstrated safe outcomes for exclusion of PE on V/Q SPECT in accordance with EANM guidelines. [2] Other studies have found an increased risk of recurrent venous thromboembolism in patients with small sub-segmental PE on V/Q scans, however they did not study isolated SSPE. [9, 10]

The strength of this study is long-term follow up of patients with SSPE on V/Q with or without anticoagulation. However, this study follows the limitation of a retrospective observational study design. There may be an inherent index test bias in patients selected for CTPA following V/Q SPECT.

Sub-segmental PE is complex problem in clinical practice and its management is currently dependent on the global clinical assessment of the patient. A prospective study is underway to investigate the safety of withholding anticoagulation in patients with sub-segmental PE (without cancer), who have negative serial bilateral lower extremity ultrasound tests and are followed over a 3-month period (ClinicalTrials.gov: NCT01455818). During the long term follow up in our study, 12 out 40 (30%) patients represented with suspected PE within a median time of 121 days, although PE was not confirmed on imaging in these recurrent presentations. Presentation with suspected recurrent VTE is a further important clinical issue and can lead to complexity in clinical decisions regarding anticoagulation. We found that those who were not anticoagulated had similar risk of recurrent presentation with suspected VTE and all-cause mortality as those were anticoagulated. Further evidence regarding anticoagulation in SSPE patients is awaited, and the role of imaging in informing clinical decision making also requires further study.

## **Conclusion**

Our case series highlights a complex clinical issue of initial diagnosis and management of SSPE and its follow up. In our centre of 1,300 consecutive patients with suspected PE who underwent index V/Q SPECT, 40 (3%) of patients were found to have isolated SSPE identified as single SSM. Nineteen out of forty patients underwent subsequent CTPA for diagnostic clarification, and 18/19 (94.7%) were negative for SSPE on CTPA. We found that in all patients with isolated SSPE on V/Q there was no difference in risk of recurrent suspected PE or all-cause mortality between those treated for SSPE with a 6 month course of anticoagulation and those not treated, and this was also found when adjusting for patients already on long term anticoagulation for other indications. Further larger studies are needed to assess the risk of recurrent VTE following diagnosis of SSPE, and prospective studies are needed to determine the safety of withholding anticoagulation in patients with SSPE.

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