THE CONCLUSIONS DRAWN FROM VENTILATION/PERFUSION SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) COMPARED TO LUNG PERFUSION SPECT AND A CHEST X-RAY (CXR) IN PATIENTS WITH SUSPECTED PULMONARY THROMBOEMBOLISM

BY

SOFIULLAH ABUBAKAR

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Supervisor: Dr Tessa Kotze

Co – supervisor: Prof Mike D Mann

Nuclear Medicine Division, Department of Radiation Medicine, University of Cape Town

UNIVERSITY OF CAPE TOWN

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DECLARATION

I, *Sofiullah ABUBAKAR*, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Purpose

There are conflicting results from studies on whether the ventilation (V) scintigraphy can be safely omitted or replaced by a chest x-ray. These studies were based on planar ventilation perfusion (V/Q) scintigraphy. We evaluated the value of the V single photon emission computed tomography (SPECT) on the final conclusion drawn from a V/Q SPECT and the possible role of the chest x-ray as a surrogate for the V SPECT.

Methods

Raw data of V/Q SPECT images and chest x-ray acquired within 48 hours over 18 months period were retrieved, reprocessed and reviewed in batches. The V SPECT, Q SPECT and chest x-ray were reviewed separately and in combination. Data on the presence and character of defects and chest x-ray abnormalities were recorded. The V/Q SPECT images were interpreted using the criteria in the EANM guideline and the Q SPECT and chest x-ray images were interpreted using the PISAPED criteria. Agreement between the diagnosis on the V/Q SPECT review and the Q SPECT and chest x-ray review was analysed.

Results

21.1% of the patients were classified as ‘PE present’ on the V/Q SPECT review whereas 48.9% were classified as ‘PE present’ on the Q SPECT and chest x-ray review. Only 5.4% of defects seen on V SPECT had matched chest x-ray lung field opacity.

Conclusion

Our study showed that the omission of a V SPECT led to a high rate of false positive diagnoses and that the ventilation scan cannot be replaced by a chest x-ray.

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LIST OF ABBREVIATIONS

CTPA	Computed tomography pulmonary angiography
CXR	Chest x-ray
GSH	Groote Schuur Hospital
I	International Committee of Medical Journal Editors
PACS	Picture archiving and communication system
PE	Pulmonary thromboembolism
Q	Perfusion
SID	Source image receptor
SPECT	Single photon emission computed tomography
V	Ventilation
V/Q	Ventilation Perfusion

1.0 RESEARCH PROTOCOL

This research protocol was submitted to and approved by the Faculty of Health Sciences, University of Cape Town before the commencement of the study.

Research topic – The conclusions drawn from ventilation/perfusion single photon emission computed tomography (SPECT) compared to lung perfusion SPECT and a chest x-ray (CXR) in patients with suspected pulmonary thromboembolism.

1.1 Background

Acute pulmonary thromboembolism (PE) is the most serious form of venous thromboembolism. The incidence rate of non- cancer associated venous thromboembolism in the UK in a recent study was 107 per 100,000 person years, pulmonary thromboembolism accounting for 45.9% (1). Symptoms, signs and laboratory findings are not sufficiently specific for diagnosis of acute PE which is based on imaging and clinical course. Accurate diagnosis is very important as the main therapeutic option of management of acute PE, long term anticoagulation, is associated with increased risk of bleeding.

Pulmonary angiography is the gold standard in acute PE imaging (2, 3). This is however not widely available largely because the procedure is technically demanding, involves cannulation of the pulmonary vessels for the injection of contrast media and is associated with risks of vascular cannulation(4). Ventilation/perfusion (V/Q) scintigraphy and computed tomography pulmonary angiography (CTPA) are the widely used alternatives to pulmonary angiography in acute PE imaging. Planar V/Q scintigraphy and CTPA have been shown to have similar diagnostic accuracy. V/Q SPECT has a higher diagnostic accuracy compared to planar V/Q scintigraphy (5-7).

V/Q scintigraphy is a non-invasive and relatively simple procedure. Absent or reduced perfusion to a part of the lung is not specific for pulmonary thromboembolus, so ventilation

scintigraphy was added to differentiate other causes of perfusion abnormalities (8, 9). The more demanding for the radiographer and the patient is the ventilation component. In addition, following the low diagnostic yield of planar V/Q scintigraphy and the large number of non-diagnostic scans in the PIOPED I study (2), there have been studies showing that planar perfusion only scintigraphy performs as well as planar V/Q scintigraphy with lower rate of non-diagnostic scans (3, 10-12).

Miniati et al in their review based on the result of the PISAPED study suggested that Q scintigraphy combined with a chest x-ray should be sufficient for diagnosis and a V scan should only be obtained in select cases (10). Their recommendation is based on planar images and there is limited literature on the additional value of V SPECT or chest x-ray on Q SPECT. A literature search on 28 February 2016 using the key words 'ventilation perfusion SPECT' of PubMed, web of science and Scopus databases revealed no publication comparing Q SPECT with V/Q SPECT and one publication that compared V/Q SPECT to Q SPECT/CT (13). This project seeks to evaluate the extent to which the final conclusion on a V/Q SPECT is influenced by the V SPECT and if the chest x-ray can act as a substitute for a V SPECT.

1.2 Literature review

Acute pulmonary thromboembolism (PE) is the most serious form of venous thromboembolism (VTE) (14, 15). The incidence of acute PE in the United Kingdom is about 50 per 100,000 person years (1). A slightly higher annual incidence of 69 per 100,000 persons was reported in the United States (16). The crude mortality rate in patients diagnosed with pulmonary embolism was 17.4% from presentation up to 3 months in the international cooperative pulmonary embolism study(17).

Clinical presentation of acute PE ranges from completely asymptomatic to sudden death (18). Patients may present with instantaneous onset pleuritic chest pain. Other symptoms and signs

are non-specific and include dyspnoea, tachypnoea, syncope, haemoptysis, tachycardia and hypotension (18, 19). Because of the nonspecific presentation, evaluating a patient for pulmonary embolism is based on a high index of suspicion and high pre-test probability using validated clinical prediction rules such as the Wells score (20, 21) where scores are assigned to seven significant variables as summarized in table 1.

Table 1: Wells score

Clinical Characteristic	**Score**
Previous pulmonary embolism or deep vein thrombosis	+ 1.5
Heart rate >100 beats per minute	+ 1.5
Recent surgery or immobilization (within the last 30 d)	+ 1.5
Clinical signs of deep vein thrombosis	+ 3
Alternative diagnosis less likely than pulmonary embolism	+ 3
Haemoptysis	+ 1
Cancer (treated within the last 6 months)	+ 1

Clinical Probability of Pulmonary Embolism	**Score**
Low	0-1
Intermediate	2-6
High	≥6

Measurement of D-dimer, a fibrin degradation product with elevated plasma concentration following fibrinolysis, is an ancillary investigation in acute pulmonary thromboembolism. A negative D-dimer has high negative predictive value in the setting of low clinical pre-test

probability(22). A positive D-dimer however has low specificity as it is elevated in several other conditions including the elderly, pregnant women, malignancy, inflammation and thromboembolism other than PE (23).

Electrocardiography and echocardiography may show features of right ventricular strain in pulmonary thromboembolism but are not sufficiently sensitive or specific for PE(24).

Treatment of acute PE involves anticoagulation for a long duration (14, 25). Thrombolytic therapy is beneficial in cases associated with hypotension(25) and right ventricular dysfunction (26). Both anticoagulation for a long period and thrombolysis are associated with significant increased risk of major haemorrhage and stroke (25, 26). It is therefore important to establish a diagnosis of acute PE in order to avoid unnecessary treatment. Imaging and clinical course are the accepted standard for diagnosis (2, 3, 14). The imaging modalities include pulmonary angiography, CTPA and V/Q scintigraphy (27). Other less commonly used imaging methods are transthoracic echocardiography for assessing the consequences of massive acute PE on the right ventricle and visualization of emboli in the right ventricle(5), transthoracic ultrasonography of the lungs(28) and venous ultrasonography for deep vein thrombosis(29). Pulmonary angiography is the 'gold standard' against which the other imaging techniques are measured (2, 30).The use of pulmonary angiography is limited because of the risks of vascular catheterization and technical demand of the procedure (4, 31).

The main event in acute PE is obstruction in the pulmonary arterial bed with decreased or absent perfusion to the lung tissue distal to the obstruction. There is transient associated hypoventilation in areas of obstruction due to hypocapnia and humoral factors released from platelets involved in the thromboembolic event. Hypoperfusion leads to decreased surfactant formation and subsequent atelectasis (32). Lung parenchymal infarction distal to the obstruction due to inadequate bronchial circulation may also occur. Massive pulmonary

thromboembolism (involving more than 30% of the pulmonary vascular bed) results in increased pulmonary vascular bed resistance, pulmonary hypertension and eventually right heart failure which is often the cause of death in acute PE (14, 33).

Radionuclide imaging of acute PE started with planar perfusion scintigraphy (34, 35). Wagner et al in 1964 described the development and initial evaluation of a new radioisotope scanning procedure for the diagnosis of massive pulmonary embolism in man using macroaggregated albumin labelled with ^{131}I or ^{51}Cr(34). Soon after, Moser et al in an experimental study investigated the reliability and specificity of pulmonary angiography and perfusion photo scanning under experimental conditions They showed a substantial degree of agreement in detecting pulmonary thromboemboli (35).

Lung perfusion follows the segmental anatomy of the lungs. Occlusion of the segmental/ sub segmental pulmonary arteries leads to wedge shaped segmental/ sub segmental perfusion defect with apex located centrally and the base on the pleural surface. More peripherally placed arterial occlusions may give crescentic defects. The diagnosis of acute PE on perfusion scintigraphy is based on segmental/ sub segmental wedge shaped absent or reduced perfusion to part(s) of the lungs. The presence of perfusion defect is not specific for acute PE as it can be seen in other lung disorders including infection, tumours, obstructive airway disease, asthma and congenital pulmonary vascular anomalies (8). To improve specificity, V scintigraphy was combined with Q scintigraphy shortly after the introduction of Q scintigraphy (8). The basis of the combination is that acute PE will usually cause a perfusion defect with a normal ventilation or a perfusion defect which is worse than abnormal ventilation in the same area of the lung (ventilation perfusion mismatch). Conversely, in lung parenchymal disorders, perfusion and ventilation are affected to the same extent (matched) or ventilation abnormality is worse than perfusion abnormality (reverse mismatch). The diagnosis of acute PE on V/Q scintigraphy is

therefore made when there is ventilation-perfusion mismatch that corresponds to the pulmonary vascular anatomy (2, 36).

Currently, planar or SPECT V/Q scintigraphy and CTPA are the most widely used imaging modalities for diagnosis of pulmonary embolism. CTPA became the imaging modality of choice in most centres because of rapidity, easy accessibility and better diagnostic abilities compared to V/Q scintigraphy with detection of alternative diagnosis (30, 37, 38). However, the above conclusions on CTPA were based on comparison of CTPA with planar V/Q scintigraphy. Advances in ventilation radiopharmaceuticals and the introduction of V/Q SPECT imaging have shown that V/Q SPECT has a similar or better diagnostic yield than CTPA with the advantage of lower radiation dose (6, 7, 38-40). CTPA is also associated with over diagnosis of clinically insignificant pulmonary embolism (37).

Lung ventilation scintigraphy has been the more challenging part of the V/Q scintigraphy. Getting a good V scan requires patient cooperation and use of an appropriate ventilation radiopharmaceutical. The ideal ventilation radiopharmaceutical is ^{81m}Kr(41) which is a gas and reflects true ventilation. However, the short physical half-life of the ^{81}Ru – ^{81m}Kr generator, limited availability and high cost limit its use (36, 41). The closest alternative to ^{81m}Kr is aerosolized technetium graphite particles called Technegas (which are about 300times bigger than a Krypton atom). The relatively small particle size (0.005 – 0.2µm) produced by the Technegas generator makes it better than the liquid radioaerosols (41, 42). When Technegas generator is not available, liquid radioaerosols such as ^{99m}Tc-DTPA, ^{99m}Tc-sulfur colloid and ^{99m}Tc-PYP are generated using nebulization chambers. They are larger particles than Technegas and are less suited for ventilation scintigraphy (43).

A few studies have shown that in certain situations, a chest x-ray performs as well as planar V scintigraphy. de Groote et al evaluated the performance of chest x-ray and perfusion (X/Q)

scan versus V/Q scan using planar images. They analysed 389 patients with at least one segmental perfusion defect on perfusion scan. There was an overall agreement of 88% between the X/Q scan and V/Q scan for classifying perfusion defect as matched or mismatched. In a subset of their patients with COPD, the chest x-ray performed poorly in identifying matched defects. They concluded that in patients without COPD, the chest x-ray can reliably replace ventilation scintigraphy in categorizing perfusion defects as matched or mismatched (44).

Similarly, Grimm and colleagues assessed the utility of the ventilation scan in planar V/Q scan in a retrospective study of planar V/Q scan and chest x-ray reports. They studied 500 consecutive patients, 65 of whom had perfusion defects. Seventy point eight percent (70.8%) of the 65 with perfusion defect had no corresponding ventilation defect. The percentage of those with no ventilation defect increased from 70.8% to 95.7% when patients with respiratory disease and abnormal chest x-ray were excluded. In this subset of patients with unmatched perfusion defect, there was statistically significant association between a normal ventilation and a normal chest x-ray. The authors concluded that there may be a sub set of patients (young patients with clear chest radiograph and no respiratory disease) for whom the V scan may be excluded(45).

Using different interpretation criteria, various authors reported that the planar Q scan alone has similar diagnostic validity compared to the planar V/Q scan. Stein et al evaluated the value of planar V/Q scans versus Q perfusion scans alone in acute PE. 98 patients were randomly selected from the PIOPED I studies. The characteristics of these patients were not statistically different from the rest of the 1,389 patients in PIOPED I who had planar V/Q scans. The V/Q scans and Q scans of these 98 patients were independently read using the PIOPED criteria. They found that the diagnostic validity of a high probability or low probability planar ventilation/perfusion scan is similar to that of a high probability or low probability planar

perfusion scan. They also found that the number of those who had intermediate (indeterminate) probability scans is more, though not statistically significant, in patients who had only Q perfusion scans. They therefore suggested that in such patients, a planar V/Q scan may give a more definitive probability (12).

The PISAPED investigators evaluated 890 patients with suspected pulmonary embolism using planar Q only scintigraphy. Scans were interpreted with the PISAPED criteria where emphasis was laid on the conformation of the defect to the pulmonary vascular anatomy. Taking pulmonary angiography as the gold standard, they found a sensitivity of 92% and specificity of 87% for planar perfusion only scintigraphy. They concluded that accurate diagnosis is possible with Q scans alone, without ventilation imaging (3, 10). In the PISAPED study, the chest x-ray was not used as a surrogate for the ventilation scan, scintigraphic diagnosis was based purely on the shape of the perfusion defect (10) .

A recent attempt to replicate the work of the PISAPED investigators by Van Es and co-workers compared planar Q scintigraphy and chest x-ray to CTPA. They found a sensitivity of 60% and specificity of 86% for the Q perfusion and chest x-ray. The positive predictive value for 'PE present' was 71% and negative predictive value for 'PE absent' was 83%. They concluded that a diagnostic strategy of planar Q scintigraphy and chest x-ray using the PISAPED criteria is less safe compared to CTPA (46). In a letter commenting on this study, Miniati identified the mode of interpretation, presumed commencement of anticoagulant/thrombolytic therapy (after the CTPA and before planar perfusion scanning) and sample size as probable factors responsible for the low sensitivity in the study(47).

Similarly, a recent study by Watanabe et al using planar images found a lower sensitivity using the PISAPED criteria for Q only scintigraphy (clinical outcome at 24 weeks was gold standard). They found that adding the V scintigraphy and modifying the PISAPED criteria for the added

V scintigraphy leads to significant improvement in sensitivity (9). Most of the studies (some of which are summarized above) on the value of the ventilation or chest x-ray in V/Q scintigraphy were done with planar ventilation perfusion images.

Over the years, V/Q scanning has evolved from planar scintigraphy to V/Q SPECT scintigraphy. Several studies have shown the superiority of V/Q SPECT over planar V/Q in sensitivity and specificity (48-51). Gutte et al showed a sensitivity and specificity of 100% and 87% for V/Q SPECT compared to 64% and 72% for planar V/Q. The gold standard was a combination of CTPA, V/Q scintigraphy and clinical follow up (51). Similarly, Bajc et al found that V/Q SPECT showed 53% more mismatch points compared to planar V/Q in patients with acute PTE (49). In another study, 102 patients had planar and SPECT V/Q. Sixty two percent (62%) of the scans were non-diagnostic on planar V/Q compared to 4.9% on SPECT V/Q. In this last study, modified PIOPED criteria was used for interpretation of planar images and the EANMMI guideline was used for the SPECT images (52).

In an experimental study by Bajc and co-workers, sixteen anesthetized pigs were artificially embolized with thallium labelled latex material. Imaging of the thallium distribution served as the ‘gold standard’. In a subset of the pigs who had cylindrical embolic material (seven pigs), the ventilation images were not analysable due to ventilation artefacts. However, the planar perfusion images showed a sensitivity and specificity of 71% and 91% compared to 100% sensitivity and specificity for perfusion SPECT images. In the remaining nine pigs, flat 3-tailed embolic latex material was used. The sensitivity and specificity of planar V/Q was 64% and 79% respectively compared to 91% and 87% for SPECT ventilation/perfusion scintigraphy (48). The better diagnostic yield from SPECT is due to its better spatial resolution and ability to better characterize areas of abnormal/normal perfusion which overlap on planar images (53).

Even though there is clear superiority of SPECT lung scintigraphy over planar images, the studies assessing the utility of the ventilation images are mostly based on planar lung scintigraphy. A literature search on 28 February 2016 using the key words 'ventilation perfusion SPECT' of PubMed, web of science and Scopus databases revealed no publication comparing perfusion SPECT with V/Q SPECT and one publication that compared V/Q SPECT to Q SPECT/CT (13). Palmowski and co-workers compared the performance of Q SPECT/CT (low dose unenhanced CT) to V/Q SPECT. Using V/Q SPECT as the gold standard, they found a sensitivity of 95.8%, specificity of 82.6% and false positive of 17.3% for perfusion SPECT/CT. They concluded that V SPECT should be a fixed part of the V/Q SPECT/CT in order to improve specificity and lower the false positive rate. The study was retrospective with no independent gold standard and no documentation of co morbidities especially COPD (13).

The research proposed aims to evaluate the value of the V SPECT on the final conclusion drawn from a V/Q SPECT. It will also evaluate the role of the chest x-ray as a surrogate for the V SPECT.

1.3 Research questions

1. Is the identification of an abnormality the same when perfusion SPECT is reviewed without and with a ventilation SPECT?

2. Is the identification of an abnormality the same when ventilation SPECT is reviewed without and with a perfusion SPECT?

3. Is the final diagnosis on a perfusion only SPECT the same as that on a ventilation perfusion SPECT?

    a. Is there a particular subset of patient where the final diagnosis is the same?

    b. Is there a particular subset of patients where the final diagnosis is different?

4. Is the final diagnosis on a perfusion SPECT + chest X-ray the same as that on a ventilation perfusion SPECT?
    a. Is there a particular subset of patient where the final diagnosis is the same?
    b. Is there a particular subset of patients where the final diagnosis is different?
5. How often do we have a normal ventilation SPECT when the chest X-ray is normal?
6. How often are defects on ventilation SPECT seen as abnormalities on chest X-ray?

1.4 Methods

1.4.1 Patients:

The name, hospital folder number of each patient who had a V/Q SPECT study in the Division/Department of Nuclear Medicine at Groote Schuur Hospital between June 2014 and December 2015 will be retrieved from the Division's clinical database (reference number: R006/2012) with a copy of the request form and the tick sheet completed by the referring physician at the time the study was requested. The raw data of each V/Q SPECT study will be retrieved from the Division's electronic image archive (GSH Hermes archive), matched with the demographic information. The Hospital's PACS will be searched for chest X-rays of these patients. Patients who had a V/Q SPECT for suspected pulmonary embolism and a chest X-ray within 48 hours will be included in this study. It is expected that 200 scans will be available for the study.

All the scans were done for diagnostic purposes as part of the care of each patient in accordance with the guidelines of the European Association of Nuclear Medicine on V/Q scintigraphy (36) for the diagnosis of acute pulmonary thromboembolism in patients with a clinical suspicion of acute pulmonary thromboemboli.

1.4.2 Image acquisition:

The V/Q SPECT images were acquired using Technegas and Tc-99m macro aggregated albumin (IBA molecular) and either a Siemens ecam signature series dual head gamma camera or a Symbia hybrid SPECT-CT system (Siemens Medical Solutions). The V SPECT acquisition was started when a count rate of 2 – 3 kilocounts/second was achieved, with 128 projections (64 per camera head) at 10 seconds per projection. The Q SPECT images, 128 projections at 5 seconds per projection, were acquired immediately after the V SPECT with the patient in the same position. The count rate for the Q SPECT was 10 – 15 kilocounts/second.

Frontal and/or lateral chest x-rays were acquired using the GSH radiology department protocol.

1.4.3 Data collection:

Raw SPECT data will be reprocessed and viewed on a Siemens physicians' work station. Reconstruction will be done using OSEM 2D iterative reconstruction with 4 subsets and 8 iterations. The observer will review separately the V SPECT, Q SPECT, V SPECT with Q SPECT, Q SPECT with chest x-ray, V SPECT with chest x-ray of each patient. Data will be recorded on the relevant data sheets (appendix V, page 67).

The studies will be reviewed in batches with a minimum of one week between batches.

Study	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6
Ventilation	1 – 33	34- 67	68- 101	102 – 135	136-169	170-200
Perfusion	34 - 67	68- 101	102 - 135	136 – 169	170-200	1 – 33
Ventilation with perfusion	68 - 101	102 - 135	136-169	170-200	1-33	34- 67
CXR	102-135	136-169	170-200	1-33	34-67	68-101
Perfusion with CXR	136-169	170-200	1-33	34-67	68-101	102-135
Ventilation with CXR	170-200	1-33	34-67	68-101	102-135	136-169

For example, during the review of batch 1, ventilation scans of patients 1 – 33, perfusion of 34 -67, ventilation/ perfusion of 68 – 101, chest x-ray of 102 – 135, perfusion scan and chest x-ray of 136 – 169 and ventilation scan and chest x-ray of 170 – 200 will be reviewed.

For all SPECT reviews, a pictorial representation of the lung segments in sagittal, coronal and transverse sections will be used to localize involved segments on the ventilation or perfusion scan (appendix IV, page 65).

For the V SPECT, data on the character (absent or reduced), number, location, size and shape of defect(s) will be recorded. The same set of features will be recorded for the Q SPECT.

Similarly, for the V/Q SPECT, the character, number, location, size and shape of the defects will be recorded. In addition, the association of the defects – matched or unmatched and relative sizes will be recorded.

For the chest x-ray, the presence and location of pulmonary oligaemia, central vessel enlargement with abrupt tapering, peripheral consolidation abutting the pleura, atelectasis, small pleural effusion, elevated hemidiaphragm, right ventricular enlargement and lung field opacities will be recorded. In addition, the presence of hyperinflation, pulmonary oedema, hilar nodes, airway compression and massive pleural effusion will be recorded.

The location of abnormalities/opacities on the frontal chest x-ray will be marked on a pictorial representation of a normal chest x-ray during the chest x-ray data collection. The chest x-ray will be reviewed with a radiologist.

Associated chest x-ray opacity will be recorded for the Q SPECT with chest x-ray and V SPECT with chest x-ray series.

The folder number, age, gender and presence of comorbidity will be retrieved from the request form and the clinical information tick sheet and recorded in a separate data sheet.

1.4.4 Interpretation criteria:

The ventilation/ perfusion SPECT will be interpreted using the EANM guideline as detailed below:

Ventilation/ perfusion SPECT

EANM guideline

1. PE present
    a. VQ mismatch of at least one segment or two sub segments that conforms to the pulmonary vascular anatomy
2. PE absent
    a. Normal perfusion pattern

b. Matched perfusion defects of any size, shape or number in the absence of mismatch in any other part of the lung
c. Reverse mismatch defects of any size, shape or number in the absence of mismatch in any other part of the lung
d. Mismatch that does not have a lobar, segmental or sub segmental pattern

3. Non-diagnostic
    a. Multiple VQ abnormalities that do not have patterns described in 1 and 2

There are no parallel criteria for the interpretation of the perfusion SPECT with chest x-ray, so two different interpretation criteria will be used:

A. The PISAPED criteria; and
B. A modified version of the EANM guideline with ventilation SPECT replaced by chest x-ray.

These are detailed below:

A. The PISAPED criteria

PE absent	1. Normal – no perfusion defect of any kind
	2. Near normal – perfusion defects equal or smaller in size and shape to the following CXR abnormalities: cardiomegaly; enlarged aorta, hila and mediastinum; elevated diaphragm; blunting of the costophrenic angle; pleural thickening; intrafissural collection of liquid

	3. Abnormal (PE negative) – single or multiple defects other than wedge shaped with or without matching CXR abnormalities.
PE present	1. Abnormal (PE positive) – single or multiple wedge-shaped perfusion defects with or without matching CXR abnormalities.

B. Modified EANM guideline with ventilation SPECT replaced by chest X-ray

1. PE present
    a. Perfusion defect of at least one segment or two sub segments that conform to the pulmonary vascular anatomy with no associated CXR abnormality
2. PE absent
    a. Normal perfusion pattern
    b. Perfusion/CXR matched defects of any size, shape or number in the absence of mismatch in any other part of the lung
    c. Perfusion/CXR reverse mismatch defects of any size, shape or number in the absence of mismatch in any other part of the lung
    d. Mismatch that does not have a lobar, segmental or sub segmental pattern
3. Non-diagnostic
    a. Multiple VQ abnormalities that do not have patterns described in 1 and 2

1.4.8 Data analysis:

Data will be entered into a data base and analysed for predictive value of a normal/abnormal chest x-ray for a normal/abnormal V SPECT, agreement between the final conclusion on the V/Q SPECT and Q SPECT/chest x-ray, relationship between patient's age/comorbidities and V SPECT, influence of addition of V SPECT on the number of perfusion defects detected and vice versa.

1.5 Study limitations:

A single observer will be involved in interpreting the nuclear medicine scans

1.6 Ethical issues:

The study involves re-evaluation of raw images previously acquired and stored in the Nuclear Medicine database already registered by the Human Research Ethics Committee of the Faculty of Health Sciences with reference number: R006/2012. These studies were performed according to guidelines of the European Association of Nuclear Medicine on ventilation perfusion scintigraphy (36) for the diagnosis of acute pulmonary thromboemboli in patients with clinical suspicion of acute pulmonary thromboemboli.

Patients' details used in the study will only be available to individuals involved in the study and will be properly kept. No patients' detail will be used in the final report. Patients' confidentiality will be maintained throughout the study in compliance with the Helsinki declaration(54).

1.7 Funding:

Images to be analysed have already being acquired and stored as part of establishing the diagnosis of acute PE in patients with clinical suspicion of acute PE. No further images will be

done. There will therefore be no further cost to the patient or hospital for this study. The cost of stationaries, photocopying and printing will be borne by the researcher.

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2.0 PUBLICATION READY MANUSCRIPT - prepared in accordance with ICMJE recommendations*

2.1 TITLE PAGE

Full title: The conclusions drawn from ventilation/perfusion single photon emission computed tomography (SPECT) compared to lung perfusion SPECT and a chest x-ray in patients with suspected pulmonary thromboembolism.

Short title: Comparison of V/Q SPECT and Q SPECT and chest x-ray in acute PE

Authors:

Sofiullah Abubakar[1], MBBS, Donovan Jacobs[2], MBChB, Tessa Kotze[1], FCNP

[1]Nuclear Medicine Division, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa

[2]Radiology Division, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa

Correspondence:

Sofiullah Abubakar

Nuclear Medicine Division

C3/C4, New Main Building, Groote Schuur Hospital

Anzio Road, Observatory

Cape Town 7925

South Africa

Tel: (+27) 21 404 4003; (+27) 61 374 0711

Email: abubakar.yinka@yahoo.com; sofiullah.abubakar@uct.ac.za

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2.2 ABSTRACT

Purpose

There are conflicting results from studies on whether the ventilation (V) scintigraphy can be safely omitted or replaced by a chest x-ray. These studies were based on planar ventilation perfusion (V/Q) scintigraphy. We evaluated the value of the V single photon emission computed tomography (SPECT) on the final conclusion drawn from a V/Q SPECT and the possible role of the chest x-ray as a surrogate for the V SPECT.

Methods

Raw data of V/Q SPECT images and chest x-ray acquired within 48 hours over 18 months period were retrieved, reprocessed and reviewed in batches. The V SPECT, Q SPECT and chest x-ray were reviewed separately and in combination. Data on the presence and character of defects and chest x-ray abnormalities were recorded. The V/Q SPECT images were interpreted using the criteria in the EANM guideline and the Q SPECT and chest x-ray images were interpreted using the PISAPED criteria. Agreement between the diagnosis on the V/Q SPECT review and the Q SPECT and chest x-ray review was analysed.

Results

21.1% of the patients were classified as ‘PE present’ on the V/Q SPECT review whereas 48.9% were classified as ‘PE present’ on the Q SPECT and chest x-ray review. Only 5.4% of defects seen on V SPECT had matched chest x-ray lung field opacity.

Conclusion

Our study showed that the omission of a V SPECT led to a high rate of false positive diagnoses and that the ventilation scan cannot be replaced by a chest x-ray.

Key words: Pulmonary Embolism, Ventilation SPECT, Ventilation Perfusion SPECT, Chest x-ray, Comparison

2.3 MAIN MANUSCRIPT

Research topic – The conclusions drawn from ventilation/perfusion single photon emission computed tomography (SPECT) compared to lung perfusion SPECT and a chest x-ray in patients with suspected pulmonary thromboembolism.

Introduction

Acute pulmonary thromboembolism (PE) is the most serious form of venous thromboembolism(1, 2). The clinical presentation of acute PE is non-specific and ranges from completely asymptomatic to sudden death(3, 4). Accurate diagnosis of acute PE is important as the main options of management, thrombolysis and long-term anticoagulation, are associated with significant risk of major haemorrhage and stroke(5, 6). The gold standard for diagnosis is a combination of imaging findings and clinical course on long term follow up(1, 7, 8).

The main imaging modalities in acute PE include pulmonary angiography, computed tomography pulmonary angiography (CTPA) and ventilation perfusion scintigraphy (V/Q scan)(9). Pulmonary angiography is accepted as the gold standard in acute PE imaging(7, 10) but is not widely used because of the technical demand and associated complications(11, 12).

V/Q scan can be done either as a planar study or single photon computed emission tomography (SPECT) study. Since the advent of SPECT, Ventilation-Perfusion SPECT (V/Q SPECT) has been shown to be superior in sensitivity and specificity compared to planar V/Q scan(13-16). Compared to CTPA, V/Q SPECT has similar or better diagnostic yield with added advantage of lower radiation dose(17-20). A recent service evaluation study by Parekh and colleagues reinforced the utility of the V/Q SPECT in acute PE imaging especially in terms of its high negative predictive value(21).

The diagnosis of acute PE on V/Q scan is based on the presence of perfusion defect that corresponds to the pulmonary vascular anatomy in an area of the lung with normal ventilation

or ventilation defect of smaller magnitude compared to the perfusion defect (ventilation-perfusion mismatch)(7, 22). The PISAPED investigators however reported that accurate diagnosis is possible with a perfusion scan alone without ventilation imaging(8, 23). While some investigators have also reported that the ventilation scintigraphy can be reliably replaced by chest x-ray(24, 25), others could not replicate the diagnostic results of the PISAPED investigators(26, 27). The idea that that the ventilation scan can be omitted or replaced by a chest x-ray is very attractive, given that it is the more demanding part of the study. A high-quality ventilation scan requires a cooperative patient who has the stamina to take enough deep inspirations to move aerosol to the periphery of the lung. It is also the more expensive component of a V/Q scan, particularly when one of the best radiopharmaceuticals, ^{81m}Kr or Technegas, is used.

The original PISAPED study and attempts to replicate it were all based on planar V/Q scan. With the established superiority of the V/Q SPECT over planar V/Q scan(14-16), we evaluated the value of the ventilation SPECT on the final conclusion drawn from a V/Q SPECT and the possible role of the chest x-ray as a surrogate for the ventilation SPECT.

Methods

Patients:

The name and hospital folder number of each patient who had a V/Q SPECT performed for the diagnosis of suspected acute PE in the Division of Nuclear Medicine at Groote Schuur Hospital between 1 June 2014 and 31 December 2015 were retrieved from the Division's clinical database (reference number: R006/2012) with a copy of the request form and the tick sheet completed by the referring physician at the time the study was requested. The raw data of each V/Q SPECT were retrieved from the Division's electronic image archive (GSH Hermes archive) and matched with the demographic information. A chest x-ray acquired after the onset

of symptoms and within 48 hours was required as part of departmental protocol to triage patients with grossly abnormal chest x-ray and normal renal function to CTPA. The Hospital's PACS was searched for chest X-rays of these patients. Patients who had a V/Q SPECT and a chest X-ray within 48 hours were included in the study.

All the scans were done for diagnostic purposes as part of the care of each patient. Scans were acquired in accordance with the guidelines of the European Association of Nuclear Medicine on ventilation perfusion scintigraphy (22) for the diagnosis of acute pulmonary thromboembolism.

Image acquisition:

The V/Q SPECT images were acquired using Technegas generated from technigasplus (Cyclomedica Australia Pty Ltd) and Tc-99m macro aggregated albumin (Pulmocis, IBA molecular) and either a Siemens e.cam signature series dual head gamma camera or a Symbia TruePoint SPECT.CT system (Siemens Medical Solutions). The V SPECT acquisition was started when a count rate of 2 – 3 kilocounts/second was achieved, with 128 projections (64 per camera head) at 10 seconds per projection. The Q SPECT images, 128 projections at 5 seconds per projection, were acquired immediately after the V SPECT with the patient in the same position. The count rate for the Q SPECT was 10 – 15 kilocounts/second.

Posterior-anterior, with or without lateral, chest x-rays were acquired using the GSH radiology department protocol (Appendix 1).

Data collection:

For this analysis, raw SPECT data were reprocessed and viewed on a Siemens physicians' work station (SyngoMI VA1OC, WinNT 5.1, Service pack 3). Reconstruction was done using OSEM 2D iterative reconstruction with 4 subsets and 8 iterations. The observer reviewed separately the V SPECT, Q SPECT, V SPECT with Q SPECT, Q SPECT with chest x-ray and

V SPECT with chest x-ray of each patient. Data were recorded on the relevant data sheets (see appendix 2). The studies were reviewed in batches with at least one week between batches.

For example, during the review of batch 1, ventilation scans of patients 1 – 33, perfusion of 34 -67, ventilation/ perfusion of 68 – 101, chest x-ray of 102 – 135, perfusion scan and chest x-ray of 136 – 169 and ventilation scan and chest x-ray of 170 – 200 were reviewed.

For all SPECT reviews, a pictorial representation of the lung segments in sagittal, coronal and transverse sections was used to localize involved segments on the ventilation or perfusion scan (appendix 3). For the V SPECT, data on the character (absent or reduced), number, location, size and shape of each defect were recorded. The same set of parameters were recorded for the Q SPECT. Similarly, for the V/Q SPECT, the character, number, location, size and shape of the defects were recorded. In addition, the association of the defects – matched or unmatched and relative sizes were recorded.

For the chest x-ray, the presence and location of pulmonary oligaemia, central vessel enlargement with abrupt tapering, peripheral consolidation abutting the pleura, atelectasis, small pleural effusion, elevated hemidiaphragm, right ventricular enlargement and lung field opacities were recorded. In addition, the presence of hyperinflation, pulmonary oedema, hilar nodes, airway compression and massive pleural effusion were also recorded. Chest x-ray opacities associated with a ventilation or perfusion defect were recorded for the Q SPECT with chest x-ray and V SPECT with chest x-ray series.

The folder number, age, gender and presence of comorbidity were retrieved from the request form and the clinical information tick sheet and recorded in a separate data sheet.

Interpretation criteria:

The findings on the combined V/Q SPECT were interpreted using the criteria outlined in the EANM guideline as shown in table 1 below:

The findings on a separate review of the Q SPECT with chest x-ray (without ventilation images) was interpreted using the PISAPED criteria as detailed in table 2.

Data analysis:

Data were entered into multiple Microsoft Excel worksheets and analysed using Microsoft Excel 2013 and Stata 13.0 (StataCorp. 2013. Stata: Release 13. Statistical Software. College Station, TX: StataCorp LP.).

Data were analysed for agreement in identification of perfusion defects when the Q SPECT was reviewed alone and with the V SPECT. The agreement between the final conclusion on the V/Q SPECT and the Q SPECT and chest x-ray was also analysed. The relationship between the presence of a ventilation defect and lung field opacity on chest x-ray was analysed.

Ethical approval:

Study was duly approved by the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town. HREC REF: 508/2016.

RESULTS

A total of 307 patients had V/Q SPECT for the diagnosis of suspected pulmonary embolism in the 18 months period under review (1 June 2014 to 31 December 2015). A chest x-ray acquired within 48hours of the V/Q SPECT was available on the hospital PACS for 205 patients, 66.8% of total number of patients. Of these 205 patients, 6 had missing clinical information leaving a total of 199 patients. A further 19 patients were excluded due to the technical quality of the images (see below) and therefore the final analysis was done on 180 patients.

The gender distribution of patients was 153 (85%) females and 27 (15%) males. The age range was 15 to 78 years with a median of 32 years. Among the 180 patients, 61 had recent surgery

with caesarean section accounting for 48 (79%) of the surgeries and 16 had coexisting malignancy.

Technical quality of images

The 19 patients excluded had one or more poor quality images. On review of the ventilation SPECT images, 14 studies were of poor technical quality due to central deposition of most of the activity, low counts peripherally and excessive movement. Five of these studies were also of poor quality on review of the perfusion SPECT images due to marked inhomogeneity that made identification and localization of perfusion defects impossible. Another 5 studies were excluded on chest x-ray images review due to poor inspiration or under penetration. Hence, a total of 19 studies had poor quality and were excluded.

Perfusion defects

When the Q SPECT images were reviewed alone, a total of 285 perfusion defects were identified. When reviewed with the V SPECT, the number of perfusion defects dropped to 273. Of the 285 perfusion defects identified on Q SPECT only review and the 273 perfusion defects identified on the V/Q SPECT review, 230 perfusion defects were similar in both reviews in terms of location, size and shape. The remaining 55 defects on Q SPECT and 43 defects on V/Q SPECT differed. Hence, in terms of similarities in identification of perfusion defects, 81% of the perfusion defects identified on Q SPECT and 84% of perfusion defects identified on V/Q SPECT were the same. Table 3 is a summary of the perfusion defects and the number of patients with similar/ dissimilar perfusion defects.

A total of 109 out of 180 patients had one or more perfusion defects on Q SPECT review. This number dropped to 105 out of 180 patients when the Q SPECT was reviewed with the V SPECT. Table 4 is a summary of perfusion defect identification in patients.

Ventilation defects

When the V SPECT images were reviewed alone, one or more ventilation defects were identified in 67 patients. There was no ventilation defect in 113 patients. On review of the V/Q SPECT images, one or more ventilation defects were recorded in 71 patients and in 109 patients, no defect was recorded. In 55 patients, one or more ventilation defects were seen in both reviews. Ventilation defects were recorded in 12 patients on only V SPECT review and in 16 patients on only V/Q SPECT review.

The total number of ventilation defects recorded on the V SPECT review was 113 with a range of 1 to 8 and median of 1. On the V/Q SPECT review, the total number of ventilation defects was 125 with a range of 1 to 7 and median of 1.

Diagnosis

A total of 105 patients had one or more perfusion defects on the V/Q SPECT review. Nineteen of these 105 patients had non-wedge-shaped perfusion defects only and were classified as ‘PE absent’ according to the EANM criteria. Of the 86 that had one or more wedge shaped perfusion defects, 1 patient had only non-pleural based defects and therefore also classified as ‘PE absent’. Of the remaining 85 patients with one or more wedge shaped pleural based perfusion defects, 38 had matched ventilation defects or reverse mismatch leaving a total of 47 patients with one or more pleural based ventilation-perfusion mismatched defects (table 5). Using the EANM criteria, 38 of the 47 patients were classified as ‘PE present’ and 9 as ‘non-diagnostic’. Based on the EANM criteria for the interpretation of the V/Q SPECT and including the 75

patients with no perfusion defects, 133 patients (73.9%) were classified as ‘PE absent’, 38 patients (21.1%) were classified as ‘PE present’ and 9 patients (5%) were classified as ‘non-diagnostic’ (table 6).

Using the PISAPED criteria, a total of 109 patients had one or more perfusion defects, 21 had only non-wedge-shaped defects and were therefore classified as ‘PE absent’. The remaining 88 patients had one or more pleural based wedge-shaped perfusion defects (table 5). Hence, including the 71 patients with no perfusion defects, 92 studies (51.1%) were classified as ‘PE absent’ and 88 studies (48.9%) were classified as ‘PE present’ (table 5).

Table 6 is a cross tabulation of the agreement in diagnosis between the EANM criteria for interpretation of the V/Q SPECT and PISAPED criteria for the interpretation of the Q SPECT and chest x-ray.

The final diagnosis using the EANM criteria for interpretation of the V/Q SPECT and PISAPED criteria for the Q SPECT and chest x-ray was the same in 119 patients (66.1%). The final diagnosis was different in 61 patients (33.9%).

Forty-eight patients were classified as ‘PE absent’ on V/Q SPECT interpreted with EANM criteria but as ‘PE present’ on Q SPECT and chest x-ray interpreted with PISAPED criteria. In these 48 patients, the total number of defects seen on the Q SPECT only review was 100 with a range of 1 to 8 defects and a median of 1.5 defects. Each of the 48 patients had one or more pleural based wedge-shaped defect on the Q SPECT review. On the V/Q SPECT review, total number of perfusion defects in these 48 patients was 94 with a range of 0 to 7 defects and median of 1 – 6 patients had no perfusion defect, 19 had one perfusion defect each and 23 had two or more perfusion defects. Eighty of the 94 perfusion defects on V/Q SPECT review had matched/ reverse mismatched ventilation defects. The remaining 14 perfusion defects were single sub-segmental defects in 14 patients and so did not meet the EANM criteria for diagnosis

of PE. Table 7 shows the differences in defect characterization on review of the V/Q SPECT and perfusion SPECT and chest x-ray in these 48 patients.

The 9 patients classified as ‘non-diagnostic’ on V/Q SPECT interpreted with EANM had 2 sub-segmental pleural based wedge-shaped perfusion defects each, one of which was mismatched and the other matched. Using the PISAPED criteria, 6 of these 9 patients were classified as ‘PE present’ on perfusion SPECT chest x-ray and these 6 had 1 to 3 sub-segmental wedge shaped pleural based perfusion defects. The remaining 3 patients classified as ‘PE absent’ on PISAPED criteria had 1 non-wedge sub-segmental perfusion defect each.

Four patients were classified as ‘PE present’ on V/Q SPECT review using the EANM criteria but classified as ‘PE absent’ on perfusion SPECT chest x-ray review. These 4 patients had 2 or more wedge shaped pleural based mismatched defects on V/Q SPECT review. On the perfusion SPECT chest x-ray review, 3 of the patients had 1 non-wedged perfusion defects each and 1 patient had no defect.

Chest x-ray

Eighty six percent of the patients had chest x-ray within 24 hours of the V/Q SPECT after the and after the onset of symptoms. The conclusion on review of the chest x-ray images was ‘normal’ in 37 (21%) patients, ‘abnormal, likely PE’ in 13 (7%) patients, ‘abnormal, unlikely PE’ in 116 (64%) patients and ‘abnormal, consistent with COPD’ in 14 (8%) patients.

When the ventilation SPECT was reviewed with chest x-ray, 111 ventilation defects were recorded. Only 6 (5.4%) of these ventilation defects had associated chest x-ray lung field opacity.

DISCUSSION

The diagnosis of pulmonary embolism on V/Q scintigraphy is based on the concept of ventilation-perfusion mismatch - the presence of a perfusion defect in an area of the lung with normal ventilation or a smaller ventilation. Other causes of lung perfusion defect such as infection, tumours, obstructive airway disease, asthma and congenital pulmonary vascular anomaly are associated with a similar or larger ventilation defect(28). The PISAPED investigators showed that accurate diagnosis is possible with planar perfusion scintigraphy and chest x-ray(8), a conclusion that couldn't be replicated by others(26, 27). These studies are based on planar images. Since SPECT images are more sensitive in the identification and characterisation of defects, we investigated whether using SPECT images will support the findings of the PISAPED investigators. We found that omission of the ventilation SPECT led to a high rate of false positive scans.

In the identification and characterization of defects on V/Q scintigraphy, the intra and inter observer agreement is good, more so in experienced observers (29, 30). A similar trend was found in this study as over 80% of the perfusion defects were identified and characterized in the same way by a single observer who reviewed the V/Q SPECT and the Q SPECT at two different time points. There was a decrease in the number of perfusion defects and the number of patients with defects when the Q SPECT was reviewed with the V SPECT. This may be related to a combination of intra observer variability and the added confidence in excluding the presence of a perfusion defect when the Q SPECT was reviewed with the V SPECT. The agreement in the identification of ventilation defects when the V SPECT was reviewed alone or with the Q SPECT was similar.

In this study, 21.1% of the patients were classified as 'PE present' on V/Q SPECT using the EANM criteria. This is in keeping with prevalence of 19% to 33% of positive scans among patients investigated for acute PE reported in previous papers(7, 19, 26, 31). Using the PISAPED criteria for the perfusion SPECT and chest x-ray review, 48.9% of patients in this

study were classified as ‘PE present’. This is slightly higher than the prevalence reported in the PISAPED study where it was 44.4%(8) and by Watanabe and colleagues where it was 40.3%(27). The higher prevalence in our study may be due to detection of more perfusion defects on SPECT compared to planar perfusion scintigraphy which was used in the PISAPED study and by Watanabe and colleagues.

Forty-eight patients classified as ‘PE present’ when the Q SPECT and chest x-ray was interpreted with the PISAPED criteria were classified as ‘PE absent’ on V/Q SPECT interpreted with EANM criteria. This difference may be accounted for by differences in identification of perfusion defects on the 2 separate reviews of the perfusion images, the addition of the ventilation SPECT or the interpretation criteria.

Of the 48 patients classified as ‘PE present’ on the Q SPECT chest x-ray (PISAPED) review but as ‘PE absent’ on V/Q SPECT (EANM) review, 6 can be attributed to differences in identification of perfusion defects as these 6 had no perfusion defect on V/Q SPECT review. The interpretation criteria also played a role as 5 of the 6 patients had only one sub-segmental defect each and were classified as ‘PE absent’ on the V/Q SPECT.

In 19 of the 48 patients, the difference in diagnoses can be attributed to the interpretation criteria and the addition of the ventilation images. In these 19 patients, 10 had single sub-segmental defects and will therefore be classified as ‘PE absent’ according to the EANM criteria but as ‘PE present’ according to the PISAPED criteria. Nine patients had 1 matched segmental perfusion defect each and hence in these 9 patients, the difference is due to the addition of the V SPECT. The difference in the remaining 23 of the 48 patients can be attributed to the addition of the ventilation SPECT as all perfusion defects that would have been classified as ‘PE present’ in PISAPED had matched ventilation defects.

Overall, the difference in conclusion in 32 (66.7%) of the 48 patients can be attributed to the addition of a ventilation scan, in 10 patients (20.8%) to the interpretation criteria and in 6 patients (12.5%) to a combination of differences in interpretation criteria and perfusion defect identification in the two separate reviews.

With the established sensitivity and specificity of the V/Q SPECT(17, 19), this study showed that the omission of a ventilation scan led to 32 more patients being classified as 'PE present'. Using the EANM criteria as standard, of the 133 patients classified as 'PE absent', 32 patients had false positive scans – a false positive rate of 24%. These patients are at risk of being given unnecessary treatment with attendant adverse effects.

As for the identification of ventilation defects on a chest x-ray, only 5.4% of the ventilation defects were seen as lung field opacity on chest x-ray. This is not unexpected because physiologic derangement precedes anatomic abnormality and ventilation scan is physiologic whereas the chest x-ray is anatomic. Even with more sensitive anatomic imaging modalities, a normal area may have an abnormality on ventilation scan as reported by Palmowski and colleagues who showed ventilation defects in anatomically normal areas of the lung on CT(32).

To our knowledge, this is the first study comparing V/Q SPECT to perfusion SPECT and chest x-ray. Palmowski and colleagues compared V/Q SPECT to perfusion SPECT- CT scan. The rate of false positive finding attributable to the addition of the ventilation in their study was 17.3%. We found a higher false positive rate of 24%. This difference may be due to differences in interpretation as the CT scan was used as a replacement for ventilation SPECT in their study while in our study, the chest x-ray findings were ancillary findings and not a replacement as outlined in the PISAPED study.

There was a preponderance of females of child bearing age in our study population, 85% of patients. This differed from the PISAPED study where 52% of patients were females(8). There

is no consensus on the age adjusted male to female ratio in the incidence of pulmonary embolism with some studies showing a higher female preponderance and others a higher male preponderance(33-36). The incidence rate is however higher in females during child bearing years(33). The pattern of referral in our centre may be due to a higher index of suspicion in females in this age group and a lower threshold to investigate for acute PE. The significance of the higher female ratio on the findings in this study is uncertain.

Limitations of this study include review of the V/Q SPECT images by a single observer, non-availability of an independent gold standard and absence of long term follow up with clinical review of diagnosis of PE present/ absent. Other limitations include the retrospective nature of the study and use of chest x-ray images acquired within 48 hours. However, 86% of the patients had chest x-ray within 24hours of the V/Q SPECT

Conclusion

Our study showed that the omission of a ventilation SPECT and the use of PISAPED criteria in the diagnosis of acute PE on perfusion SPECT and chest x-ray led to a high rate of false positive diagnoses and that the ventilation SPECT cannot be replaced by a chest x-ray.

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2.5 TABLES

Table 1: EANM guideline for V/Q SPECT interpretation

1. PE present	a. V/Q mismatch of at least one segment or two sub segments that conform to the pulmonary vascular anatomy*
2. PE absent	a. Normal perfusion pattern b. Matched perfusion defects of any size, shape or number in the absence of mismatch in any other part of the lung c. Reverse mismatch defects of any size, shape or number in the absence of mismatch in any other part of the lung d. Mismatch that does not have a lobar, segmental or sub segmental pattern
3. Non-diagnostic	a. Multiple V/Q abnormalities that do not have patterns described in 1 and 2

*A V/Q mismatch that conforms to the pulmonary vascular anatomy is defined as a wedge shaped, pleural based perfusion defect with normal ventilation in the same area of the lung or a ventilation defect of lesser magnitude compared to the perfusion defect.

Table 2: The PISAPED criteria for interpretation of V/Q SPECT and chest x-ray

PE absent	1. Normal – no perfusion defect of any kind
	2. Near normal – perfusion defects equal or smaller in size and shape to the following CXR abnormalities: cardiomegaly; enlarged aorta, hila and mediastinum; elevated diaphragm; blunting of the costophrenic angle; pleural thickening; intrafissural collection of liquid
	3. Abnormal (PE negative) – single or multiple defects other than wedge shaped with or without matching CXR abnormalities.
PE present	1. Abnormal (PE positive) – single or multiple wedge-shaped perfusion defects with or without matching CXR abnormalities.

Table 3: summary of perfusion defects

	Number of perfusion defects	Total number of patients with defects	Similar defects	Number of patients with similar defects	Dissimilar defects	Number of patients with dissimilar defects	Minimum number of defects	Maximum number of defects	Median number of defects
Q SPECT	285	109	230	96*	55	36*	1	14	2
V/Q SPECT	273	105	230		43	26*	1	12	2

*Numbers of patients with defects add up to greater than 109 on perfusion SPECT review because 23 patients had both similar and dissimilar defects. On the V/Q SPECT review, it adds up to greater than 105 because 17patients had both similar and dissimilar defect

Table 4: patients and perfusion defects

	Total Number of patient without defects	No defect on both reviews	No defect on one review	Total Number of patients with defects	Defects on both reviews
Q SPECT	71	62	9	109	96
V/Q SPECT	75		13	105	

Table 5: characterization of perfusion defects.

PERFUSION DEFECTS	VENTILATION PERFUSION SPECT	PERFUSION SPECT
1) Defects (number of patients)	273(105)	285(109)
a) Non-wedge shaped only (patients)	23(19)	28(21)
b) One or more wedge shaped (patients)	250(86)	257(88)
i) Non-pleural based only (patients)	2(1)	0(0)
ii) One or more pleural based (patients)	248(85)	257(88)
(1) Matched/ reverse mismatched defects only (patients)	112(38)	
(2) One or more mismatched (patients)	136(47)	

Table 6: Final diagnoses cross tabulation

	PISAPED		
EANM	PE present	PE absent	Total
PE present	34	4	38
PE absent	48	85	133
Non-diagnostic	6	3	9
Total	88	92	180

Table 7 – Defect characterization in patients classified as ‘PE absent’ on EANM criteria for VQ SPECT review but ‘PE present’ on PISAPED criteria for perfusion SPECT and chest x-ray review.

Number of patients	Number of Q defects on V/Q	Shape of Q defect on V/Q SPECT	Size of Q defects on V/Q SPECT	Associated V defect	Number of Q defects on Q SPECT	Shape of defect Q on Q SPECT	Size of defect Q on Q SPECT
6	0	-	-	-	6	W 6 NW 0	SS 5 S 1
19	19	W 15 NW 4	SS 10 S 9	MIS 6 M 13	25	W 22 NW 3	SS 14 S 11
23	75	W 52 NW 23	SS 37 S 38	MIS 8 M 67	69	W 61 NW 8	SS 27 S 42

Q=perfusion, W=wedge shaped, NW=non-wedge shaped, MIS=mismatched, M=matched and reverse mismatched, SS=sub-segment, S=segment and larger

3.0 APPENDICES

3.1 Appendix I: Ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

13 July 2016

HREC REF: 508/2016

Dr T Kotze

Division of Nuclear Medicine
Department of Radiation Medicine
C3/4
NGSH

Dear Dr Kotze

PROJECT TITLE: THE CONCLUSIONS DRAWN FROM VENTILATION / PERFUSION SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) COMPARED TO LUNG PERFUSION SPECT AND A CHEST X-RAY (CXR) IN PATIENTS WITH SUSPECTED PULMONARY THROMBOEMBOLISM (MMeD-candidate- Dr S Abubakar)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 July 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr Sofiullah Abubakar will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

pp TJB Urges)

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

3.2 APPENDIX II: GSH Radiology Chest x-ray protocol

GSH CHEST X-RAY PROTOCOL: PA CHEST X-RAY

SID	180cm
AREA COVERED	Lung fields, apices, costophrenic angles, heart
SIZE AND ORIENTATION OF CASSETTE	35 X 43cm; Landscape but may be portrait depending on patient size.
POSITIONING	Patient facing the cassette/ detector with the chin extended and centred to the middle of the top of the cassette. Feet placed slightly apart so the patient can remain steady. Clear the scapulae off the lung fields by rotating the shoulders forward and pressed downward to make contact with the cassette. This is achieved by placing the dorsal aspects of the hands behind and below the hips with the elbows brought forward or by allowing the arms to encircle the cassette. **Expose on inspiration.**
CENTRING POINT	Midsagittal plane at the level of T4/ inferior border of the scapula, perpendicular to the image receptor.
COLLIMATION	open to show the lung apices superiorly and the costophrenic angles inferiorly. Open to show the lung fields laterally.
EXPOSURE	100kVp; 4mAs

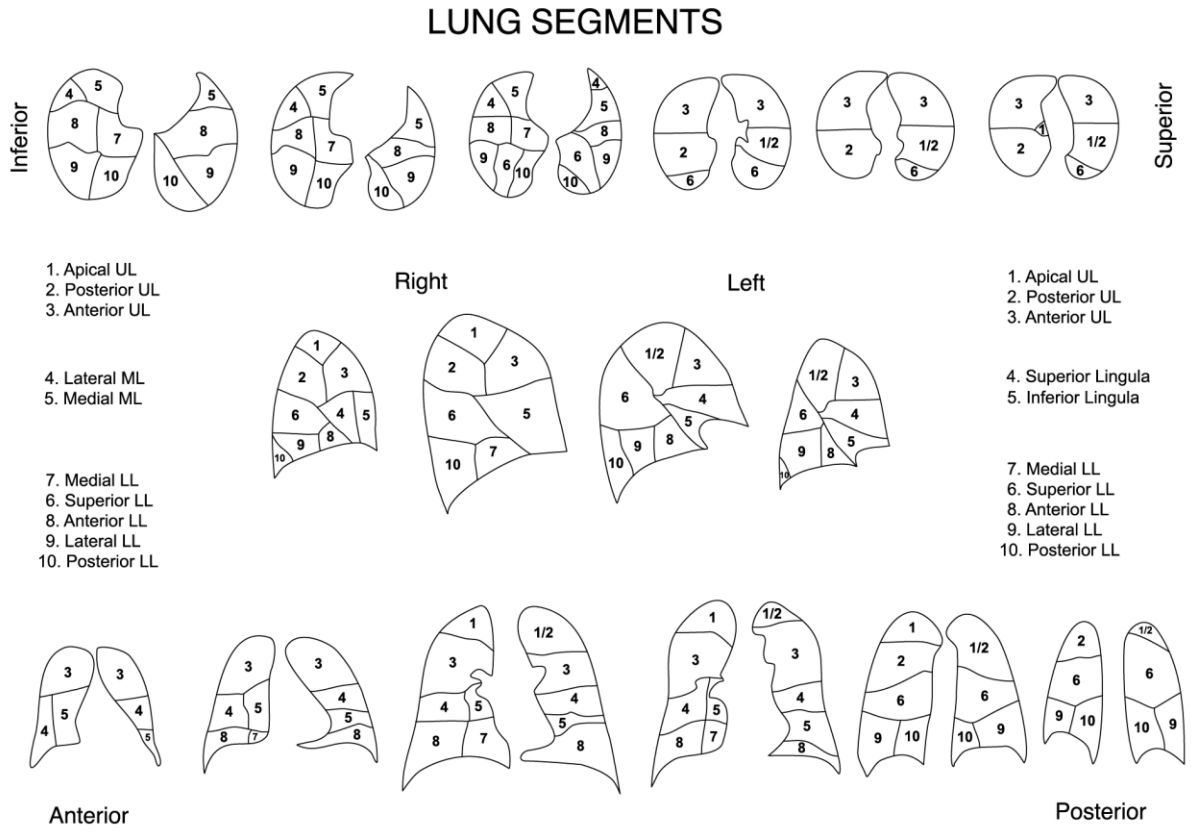
3.3 APPENDIX III: Reprocessed images review

BATCH REVIEW OF IMAGES

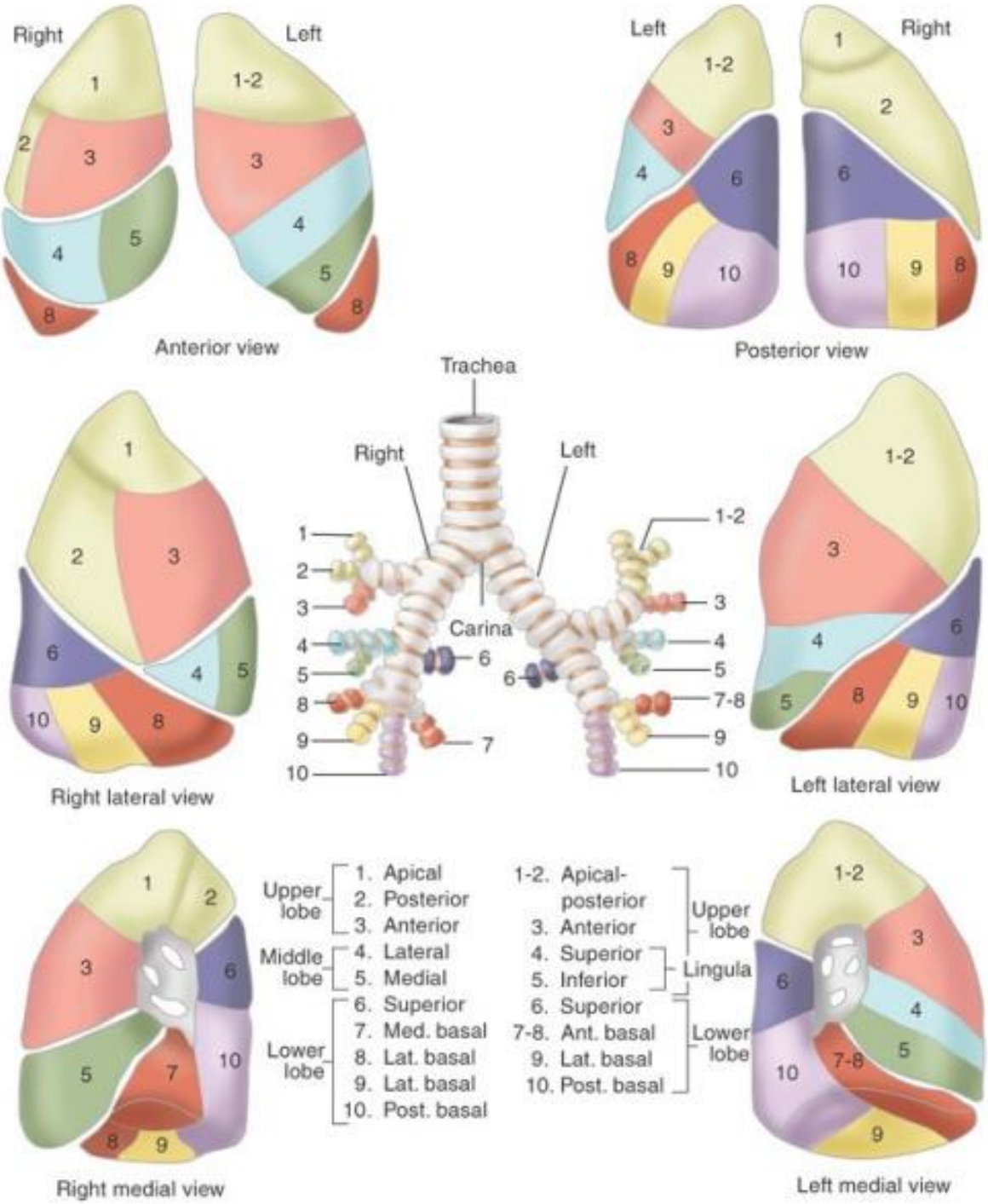
Study	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**	**Batch 5**	**Batch 6**
Ventilation	1 – 33	34- 67	68- 101	102 – 135	136-169	170-200
Perfusion	34 - 67	68- 101	102 - 135	136 – 169	170-200	1 – 33
Ventilation with perfusion	68 - 101	102 - 135	136-169	170-200	1-33	34- 67
CXR	102-135	136-169	170-200	1-33	34-67	68-101
Perfusion with CXR	136-169	170-200	1-33	34-67	68-101	102-135
Ventilation with CXR	170-200	1-33	34-67	68-101	102-135	136-169

3.4 APPENDIX IV: Lung Segments

PICTORAL REPRESENTATION OF LUNG SEGMENTS



Source: Adapted and modified from Bajc M, Neilly JB, Miniati M, Schuemichen C, Meignan M, Jonson B. EANM guidelines for ventilation/perfusion scintigraphy: Part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography. Eur J Nucl Med Mol Imaging. 2009;36(8):1356-70.



Source: www. Anatomychartee.us

3.5 APPENDIX V: Data sheets

DATA SHEET 1

Study: Perfusion ☐

Ventilation ☐

Date _____

Study serial number _____

Folder number _____

Technical quality: Adequate ☐

Inadequate ☐

Adequate – normal sinogram, intravenous injection, no clumping of MAA, counts

Inadequate; why? _____

Is it normal? Yes ☐ No ☐

If No, what is the abnormality?

Inhomogeneous ☐

Central deposition of activity ☐

Big heart impression ☐

Abnormal V or Q gradient ☐

Others (specify) _____

Number of defects _____

Number	Character	Location	size	Shape	Pleural based	Segmental

Location – lung segments = (right lung-R1 – R10; left lung- L1 –L10); right lobes – RUL, RML, RLL; left lobes- LUL, LLL (see appendix 1)

Size – 25%, 50% or 75% sub segmental, segmental, lobar, whole lung

Shape – wedge shaped, crescentic, non-wedge shaped; character – reduced V or Q/ absent V or Q

Pleural based – yes/no; Segmental – yes/no

DATA SHEET 2

Ventilation Perfusion images

Date _____

Study serial number _____

Folder number _____

Is there a perfusion defect? Yes ☐ No ☐

Number	Character	Location	size	shape	Pleural based	Segmental	Associated V defect	Size of V defect	Shape of V defect	Pleural based	Segmental

Associated ventilation defect = Yes /No

Size of the associated ventilation defect= Same/Bigger/Smaller

Are there other ventilation defects? Yes ☐ No ☐

Number	character	Location	size	shape	Pleural based	Segmental

DATA SHEET 3 (CHEST X-RAY DATA SHEET)

Study ID	
Folder no	
Date	

Technical quality	Readable	Unreadable
Inspiration		
Rotation		
Penetration		

Features of PE			Location					
	Yes	No	RUZ	RMZ	RLZ	LUZ	LMZ	LLZ
Pulmonary oligaemia								
Central vessel enlargement with abrupt tapering								
Peripheral consolidation abutting the pleura								
Atelectasis								
Small pleural effusion								
Elevated hemidiaphragm								
Right ventricular enlargement								

Increased lung field density/opacity			Location					
	Yes	No	RUZ	RMZ	RLZ	LUZ	LMZ	LLZ
Lobar consolidation								
Broncho pneumonic								
Interstitial changes								
Nodular infiltration								
Fibrosis								
Tumour								

Other lung field abnormalities			Location	
	Yes	No	Right	Left
Hyperinflation				
Perihilar nodes				
Airway compression				
Pneumothorax				
Pulmonary oedema				
Massive pleural effusion				

	Yes	No		Yes	No
Tracheal deviation			Soft tissue changes		
Mediastinal deviation			Spine abnormality		
Cardiomegaly			Other bony abnormality		

	Normal	Abnormal, likely PE	Abnormal, unlikely PE	Abnormal, consistent with COPD	unreadable
Diagnosis					

DATA SHEET 4

Study: Perfusion + Chest X-ray ☐

Ventilation + Chest X-ray ☐

Date _____

Study serial number _____

Folder number _____

Is there a defect? Yes ☐ No ☐

Number	character	Location	size	shape	Pleural based	segmental	Associated lung opacity	Size of opacity	Cause of opacity

Associated lung field opacity = yes/no

Size of the associated lung opacity = same/ bigger/ smaller

Are there other lung field opacities? Yes ☐ No ☐

Number	Location	Size	Cause [b]

DATA SHEET 5

Patient's data

Date _____

Study serial number _____

Folder number _____

Age _____

Gender _____

Co morbidity (ies) _____