PULMONARY EMBOLISM DIAGNOSIS: A CLINICAL COMPARISON BETWEEN CONVENTIONAL PLANAR AND SPECT V/Q IMAGING using Krypton 81m – with CTPA as the gold standard

by

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Thesis Presented in Partial Fulfilment of the Requirements for the Degree Of Master Of Science in Medical Sciences (Nuclear Medicine) at the Stellenbosch University, South Africa

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March 2010

DECLARATION

I, **Patrick Sitati Ngoya**, declare that the entirety of the work contained herein is my own, original work, that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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ABSTRACT

Single photon emission computed tomography (SPECT) with a superior contrast resolution has been shown to be more sensitive and specific with a lower non-diagnostic rate than planar imaging in many nuclear medicine studies but it is still not being routinely implemented in V/Q studies at many centres including Tygerberg Hospital. There are many studies on V/Q SPECT using Technegas as a ventilation agent but very limited studies available on ^{81m} Kr gas.

Aim: To clinically compare conventional planar and SPECT V/Q imaging using ^{81m}Kr gas in the diagnosis of pulmonary embolism, with CTPA as the gold standard.

Patients and Methods: All patients referred with clinical suspicion of pulmonary embolism were assessed. The inclusion criteria were normal chest radiograph, normal renal function and no contrast allergy. Exclusion criteria were age below 18 years old, pregnancy, abnormal chest radiograph, abnormal serum creatinine/urea levels and unstable patients. A Well's score was assigned to each enrolled patient.

Perfusion scintigraphy was performed after intravenous injection 125 MBq of ^{99m}Tc MAA. Ventilation scintigraphy was performed with ^{81m}Kr gas. On a dual head camera, SPECT was done before planar acquisition, while perfusion was done before ventilation imaging in the same position. Planar V/Q images consisted of 6 standard views. All V/Q SPECT images were reconstructed using ordered-subset expectation-maximization (OSEM) algorithm and a post-reconstruction 3D Butterworth filters were applied. V/Q Planar and V/Q SPECT images were later evaluated and reviewed separately and reported based on recent EANM guidelines blinded to the CTPA results.

All patients underwent multi-slice CTPA examinations on a 40-detector row scanner. The images were later assessed and reported blinded to the V/Q results.

Statistical analysis was done using the Fisher exact test for comparison of categorical variables and the one-way ANOVA for continuous variables ($p<0.05$ was significant).

Results: A total of 104 consecutive patients were referred with clinical suspicion of pulmonary embolism. Seventy-nine patients were excluded from this study mostly due to abnormal serum creatinine/urea levels. Only 25 patients were included in this study, with a mean age of 48 ± 19 years, and 64% being females. When compared to CTPA as gold standard, the prevalence of PE was 16% [5% – 37% at 95% CI], sensitivity 75% [21% – 99% at 95% CI], specificity 90% [68% – 98% at 95% CI], positive predictive value 60% [17% – 93% at 95% CI], negative predictive value 95% [73% – 100% at 95% CI] and diagnostic accuracy 88% [69% – 97%at 95% CI] for both V/Q Planar and SPECT. V/Q Planar showed a lower reader confidence i.e. could only clearly resolve 72% of cases compared to V/Q SPECT, which could precisely interpret all cases, showed more and better delineated mismatch vs match and segmental vs non-segmental defects. All patients who were scored as PE unlikely on Wells' score (≤4) had PE ruled out on CTPA (p=0.04581) as well as 89% of patients on V/Q SPECT and V/Q Planar.

Conclusion: Based on this study, V/Q Planar and V/Q SPECT have a similar diagnostic performance in patients with a normal or near normal chest X-rays.

OPSOMMING

Enkelfoton emissie rekenaartomografie (EFERT) met beter kontrasresolusie is bewys om meer sensitief en spesifiek met ‘n laer nie-diagnostiese opbrengs as planare beelding in verskeie kerngeneeskunde ondersoeke te wees. In Tygerberg Hospitaal, soos in verskeie ander sentra, word dit egter steeds nie roetineweg vir ventilasie-perfusiestudies (V/Q) geïmplementeer nie. Daar is verskeie EFERT V/Q studies met Technegas as ventilasie agens, maar beperkte studies met ^{81m} Kr gas beskikbaar.

Doel: Om konvensionele planare en EFERT V/Q beelding vir die diagnose van pulmonale embolisme met mekaar te vergelyk, met rekenaartomografie pulmonale angiografie (RTPA) as goue standaard.

Pasiënte en Metodes: Alle pasiënte wat met ‘n kliniese vermoede van pulmonale embolisme verwys is, is geevalueer. Die insluitingskriteria was ’n normale borskas X-straal, normale nierfunksie en geen kontrasallergie nie. Uitsluitingskriteria was pasiënte jonger as 18 jaar, swanger pasiënte, abnormale borskas X-straal, abnormale serum kreatinien / ureumvlakke en onstabiele pasiënte. ’n Wells telling is vir elke pasiënt wat in die studie ingesluit is, bepaal.

Perfusiebeelding is uitgevoer na die intraveneuse toediening van 125 MBq ^{99m}Tc MAA. Ventilasiestudies is gedoen met ^{81m}Kr gas. Die V/Q EFERT studies is voor die planare beelding met ’n dubbelkop gammakamera uitgevoer. Perfusiebeelding is voor die ventilasie in dieselfde posisie verkry. V/Q planare beelding het bestaan uit 6 standaard beelde. Alle V/Q EFERT is met “ordered-subset expectation-maximization” (OSEM) algoritmes verwerk, en post-rekonstruksie 3D Butterworth filters is toegepas. V/Q planare en V/Q EFERT beelding is later afsonderlik en sonder RTPA inligting volgens onlangse EANM riglyne evalueer en gerapporteer.

‘n Veelsnit RTPA met ‘n 40 snit skandeerder is op alle pasiënte uitgevoer. Die beelde is later beoordeel en gerapporteer sonder inagneming van die V/Q beeldingsresultate

Statistiese verwerking is gedoen met die Fisher presisietoets vir vergelyking van kategoriese veranderlikes en die eenrigting ANOVA vir kontinue veranderlikes ($p<0.05$ is statisties betekenisvol).

Resultate: ‘n Totaal van 104 opeenvolgende pasiënte met ‘n kliniese vermoede van pulmonale embolisme is verwys. Nege-en-sewentig pasiënte is uitgesluit, in die meeste gevalle as gevolg van abnormale serum kreatinienvlakke. Slegs 25 pasiënte is ingesluit, met ’n gemiddelde ouderdom van 48 ± 19 jaar, en 64% vroue. In vergelyking met RTPA as goudstandaard, was die prevalensie van PE 16% [5% – 37% met 95% VI], sensitiwiteit 75% [21% – 99% met 95% VI], spesifisiteit 90% [68% – 98% met 95% VI], positiewe voorspellingswaarde 60% [17% – 93% met 95% VI], negatiewe voorspellingswaarde 95% [73% – 100% met 95% VI] en diagnostiese akkuraatheid van 88% [69% – 97% met 95% VI] vir beide planare en EFERT V/Q beelde. V/Q planare beelde het ‘n laer lesersvertroue getoon, nl. dat slegs 72% van gevalle opgelos kon word relatief tot V/Q EFERT beelde, wat in alle gevalle presies geïnterpreteer kon word, met meer en beter omskrewe nie-ooreenstemmende teenoor ooreenstemmende en segmentele teenoor nie-segmentele defekte. In alle pasiënte met ‘n Wells puntetelling van ≤ 4 is PE met die RTPA uitgeskakel ($p=0.04581$), terwyl dit in 89% van pasiënte met V/Q EFERT en planare beelde uitgeskakel is.

Gevolgtrekking: Gebaseer op hierdie studie het V/Q planare en EFERT beelding ‘n ooreenstemmende diagnostiese prestasie in pasiënte met ’n normale of naby normale borskas X-straal.

DEDICATION

In memory of

Dr. Marie Grobbelaar

CONTENTS

DEFINITION OF TERMS

Pulmonary embolism (PE) = refers only to thrombotic emboli and not non-thrombotic emboli (includes fat, air, amniotic fluid).

Mismatch defect = As seen on a V/Q scan, a perfusion defect that ventilates normally. Segmental if it is in a whole segment, sub-segmental if less than 50% of a segment.

Match defect = As seen on a V/Q scan, a perfusion defect that corresponds to a ventilation defect.

Non-segmental defect = As seen on a V/Q scan, it is not pleural based and does not conform to known subsegmental or segmental vascular anatomy.

Reverse match defect = As seen on a V/Q scan, a defect that is worse (larger in size) on the ventilation image or chest radiograph compared to a corresponding area on the perfusion image in keeping with lung parenchymal disease.

PE diagnosis = As seen on a V/Q scan, at least one segmental or two subsegmental mismatch perfusion defect(s) that ventilate(s) normally conforming to the pulmonary vascular anatomy (according to the recent EANM guidelines).

LIST OF ABBREVATIONS

(In alphabetical order)

^{0}C = degrees Centigrade

^{81}Rb = Rubidium 81

^{81m}Kr = metastable Krypton 81

^{133}Xe = Xenon 133

^{99m}Tc = metastable Technetium 99

2D = 2 dimensional

3D = 3 dimensional

µm = micrometres

ANT = anterior

BMI =Body mass index

bpm = beats per minute

COPD = Chronic obstructive pulmonary disease

CT = Computed Tomography

CTPA = Computed Tomographic Pulmonary Angiography

CTV = Computed Tomographic Venography

DSPA =Digital subtraction pulmonary angiography

DTPA = diethylenetriaminepentaacetic acid

DVT = Deep venous thrombosis

EANM = European Association of Nuclear Medicine

ECG = Electrocardiography

ECHO = Echocardiography

Gd- MRA = gadolinium-enhanced Magnetic Resonance Angiography

HU = Hounsfield unit

IAEA = International Atomic Energy Agency

kcps = kilocounts per second

kcts = kilocounts

keV = kiloelectronVolts

kV = kiloVolts

LAO= Left Anterior Oblique

LEHR = Low Energy High Resolution

LLAT = Left Lateral

LPO = Left Posterior Oblique

mA = milliAmperes

MAA = macroaggregates of albumin

MBq = MegaBequerels

mCi = milliCurie

mGy = milliGrays

MIP = maximum intensity projection

mg = milligram

ml = millilitres

mm = millimetres

mmHg = millimetres of Mercury

MR = Magnetic Resonance

MRA= Magnetic Resonance Angiography

MRV = Magnetic Resonance Venography

mSv = milliSiverts

ng = nanogram

nm = nanometre

NPV = Negative predictive value

P = Perfusion

PE = Pulmonary embolism

PERF = Perfusion

PTE = pulmonary thromboembolism

PIOPED = Prospective investigation of pulmonary embolism diagnosis

PISA-PED = Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis

POST = Posterior

PPV = Positive predictive value

Q = Perfusion

rad = Unit for radiation absorbed dose

RAO = Right Anterior Oblique

RLAT = Right Lateral

RPO = Right Posterior Oblique

s = seconds

SLE = Systemic Lupus Erythematosus

SNM = Society of Nuclear Medicine

SPECT = Single Photon Emission Computed Tomography

SPECT/CT = Single Photon Emission Computed Tomography with (low dose) X-ray Computed Tomography

™ = Trademark

USS = Ultrasonography

V = Ventilation

Vent = Ventilation

VTE = Venous thromboembolism

V/Q = Ventilation/ Perfusion

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ACKNOWLEDGEMENT

All the patients that are an important part of this study, without whom this study would not have been feasible.

My research supervisor Dr Nisaar A Korowlay for the overall guidance, teachings and experience bestowed.

My co-researcher and consultant radiologist, Dr Marie Grobbelaar.

The entire members of staff of the Nuclear Medicine and the Radiology departments of Tygerberg Hospital for their cooperation and assistance.

The Professor and Head of the Nuclear Medicine department, Prof Annare Ellmann, for approving this study as well as for sound knowledge, advice and supervision. All consultant nuclear physicians in particular Dr J Warwick, our radio pharmacist – Prof S Rubow. All past and present registrars as well as fellows during my time.

The Professor and Head of the Radiology department, Prof Jan Lotz, for eye-opening radiology teaching sessions and meetings. All consultant radiologists, registrars and radiographers who performed CTPAs.

Mr. Thomas Hilton, Mrs. Jennifer Cockrell who guided me through the technical aspects of the V/Q acquisition. To all Radiographers – Ms Aleta Du Toit, Ms Elrina Beetge, Mr Marclan Tarental, Ms Azalea Africander, Ms Caroline Lackay, Ms.Chamandra Kammies, Ms Valencia Marcus, Ms Olivia Sanders, Ms Yolanda Issel, Ms Blanche Theron, Mrs Yolanda P. Armino, Mr Pravin Meyer, Mr Marlin Vergotine and all Radiography students, who performed the V/Q scans.

Members of the Nursing staff – Mrs M Hofstander, Mrs A VanGraan, Mrs C Daries and Ms M Hess.

The in-house Physicists, Mrs. Monique DuToit, Mr Tumelo Moalosi and Mr Stadium Mohlapholi for performing vital quality control tests on the gamma cameras and instrumentation. Chief Technical Officers Mr Marius Ramashidza and Mrs L Nolan for the help provided on Hermes network.

Mrs Cynthia Roets, Mrs Marlene Govin, Mrs Marlise Van Niekerk, Mrs Petro Joerdens, Ms Charmaine Fluks, Ms R Smith and Mrs A Keown for their assistance.

Ms T Nyangintsimbi and her colleagues, at the Chemical Pathology department of the Tygerberg Hospital, for expedient laboratory results.

Prof M Kidd and Prof DG Nel of the Centre of Statistical Studies of the University of Stellenbosch, for statistical analysis and consultation.

The International Atomic Energy Agency (IAEA) under the auspices of the Bugando Medical Centre's Bugando Cancer Project for providing me with the fellowship training opportunity.

Finally, my family and friends for the well wishes and support.

INTRODUCTION

Pulmonary embolism is an important cause of morbidity and mortality. The diagnosis of pulmonary embolism remains problematic because clinical symptoms and signs are mimicked by other disorders. Pulmonary imaging procedures lack certainty, and patient co-morbidities may limit the utility of certain tests. The availability of a simple, accurate, non-invasive diagnostic test would be very beneficial to assist with the diagnosis of pulmonary embolism.[1,2]

Ventilation/Perfusion (V/Q) scintigraphy is able to visualize pulmonary emboli indirectly. Multi-detector Computed Tomography Pulmonary Angiography (CTPA) visualizes pulmonary emboli directly but no reliably safe gold standard is available. Difficulties arise in expressing the results of both V/Q scintigraphy and CT in terms of sensitivity, specificity and accuracy.[3]

Since time immemorial, the management of patients with non-diagnostic V/Q scans has been problematic. The incidence of pulmonary embolism was too low to recommend the empiric treatment of all patients. However, not treating any patient having a non-diagnostic lung scan with anticoagulants would be fraught with risk. Although high probability and normal V/Q scan reports are very useful findings to rule in or out pulmonary embolism respectively, most patients (44% in the PIOPED study) undergoing V/Q scanning had non-diagnostic results (intermediate or indeterminate probability) in whom the incidence of pulmonary embolism may vary from 10% to 30%.[4,5]

Over the years, mortality from acute PE has declined as increasingly safe methods of investigation have become more widely available.[6] The question is whether clinicians really know how to investigate patients with pulmonary embolism? Clinicians in the UK were assessed using a clinical questionnaire based on British Thoracic Society (BTS) guidelines by McQueen et al.[7] It came to light that, the majority of the doctors did not agree that a negative CTPA or lung scintigraphy excluded PE and thus a need to identify methods to improve this situation.[7]

Computed tomography (CT) scans account for the largest population radiation dose in medical diagnostic studies. High and accumulative radiation doses may initiate or promote carcinogenesis. There is a need for radiation dose reduction by seeking alternative and accurate imaging strategies.[8]

Single photon emission computed tomography (SPECT) has replaced planar imaging in many areas of nuclear medicine. Given its superior contrast resolution and improved anatomical detail, SPECT (and more recently SPECT/CT) is used in lieu of planar imaging for cardiac and brain scanning and as an adjunct to planar scintigraphy in many other areas, such as bone, infection and tumor imaging. Given the improvements in sensitivity and diagnostic accuracy that have generally accompanied the transition from two-dimensional planar to three-dimensional (3D) imaging, it is surprising that only a limited number of centers routinely utilize the SPECT technique with V/Q scintigraphy, one of the most commonly performed diagnostic studies in nuclear medicine.[9]

LITERATURE REVIEW

The Lungs – Anatomy and Physiology

The airway of the respiratory tract starts at the nostrils and passes the pharynx and then through the trachea. The trachea divides into right and left main stem bronchi to enter each lung; these in turn divide to form lobar bronchi which further divide into bronchioles and then finally alveoli. In the lungs, there are three lobar divisions on the right i.e. upper-, middle- and lower- lobes and two lobar divisions on the left i.e. upper- and lower- lobes. The lobes are further divided into broncho-pulmonary segments. The knowledge of such broncho-pulmonary segments (Figure 1 and Figure 2) is vital for interpretation of radionuclide images. Each broncho-pulmonary segment is made up of alveoli as the terminal respiratory units. An alveolus has an average diameter of 150μm and an adult human has about 700 million alveoli with a surface area of $80m^2$. Apart from the direct pathway, air can get to the alveoli through indirect pathways such as the pores of Kohn and canals of Lambert. These indirect pathways allow collateral ventilation and prevent collapse of an obstructed broncho-pulmonary segment or segments. The lungs are lined on the outside by a visceral membrane while the thoracic cavity is lined on the inside by a parietal membrane forming the pleural cavity in between, containing serous fluid – a lubricant during breathing.[10,11]

The main pulmonary arteries carry de-oxygenated blood from the right ventricle of the heart and divide in each lung to follow the broncho-pulmonary segmental airway pattern while the pulmonary vein carries oxygenated blood to the left atrium, which is then pumped to the systemic circulation via the left ventricle and the aorta.[11]

The pulmonary artery branches into distribution arteries of diameter ranging from 60 to 100μm. These arteries branch into precapillary arterioles with diameters of 25 to 35μm which terminate in alveoli capillary units of average diameter 8μm – large enough to allow passage of red blood cells (7μm) without deforming them. There are about 280 billion arterial capillaries and approximately 500 to 1000 capillaries surrounding each alveolus. Deoxygenated blood carried by arterial capillaries rapidly exchanges its carbon dioxide for inhaled oxygen at the alveoli membranes; carbon dioxide released is exhaled.[11]

Lungs also receive blood from the aorta via the bronchial arteries which follow the bronchial tree to finally anastomose at the capillary level with the pulmonary circulation. The bronchial circulation supplies about 5 to 6% of the lung blood supply.[10,11]

Ventilation and perfusion vary with gravity and position. In the upright position, both ventilation and perfusion increase progressively from apices to bases due to a progressive increase in intra-pleural pressure and gravitational blood supply

respectively – such a gradient is more prominent for perfusion than ventilation. In the supine position, both ventilation and perfusion have a relatively uniform distribution throughout the lungs.[10]

Acute changes in perfusion such as local ischaemia and hypoxia, affect ventilation by causing a reflex bronchoconstriction which leads to a shift in ventilation from hypoperfused areas – this phenomenon rarely occurs in humans. Commonly, lung parenchyma remains viable in PE despite loss of pulmonary artery blood supply due to the alternative bronchial arterial system. Therefore, normal alveolar spaces will remain aerated without infarcting. This is the basis of the V/Q mismatch in PE. However, abnormalities in ventilation commonly cause redistribution of perfusion away from hypoventilated regions.[10]

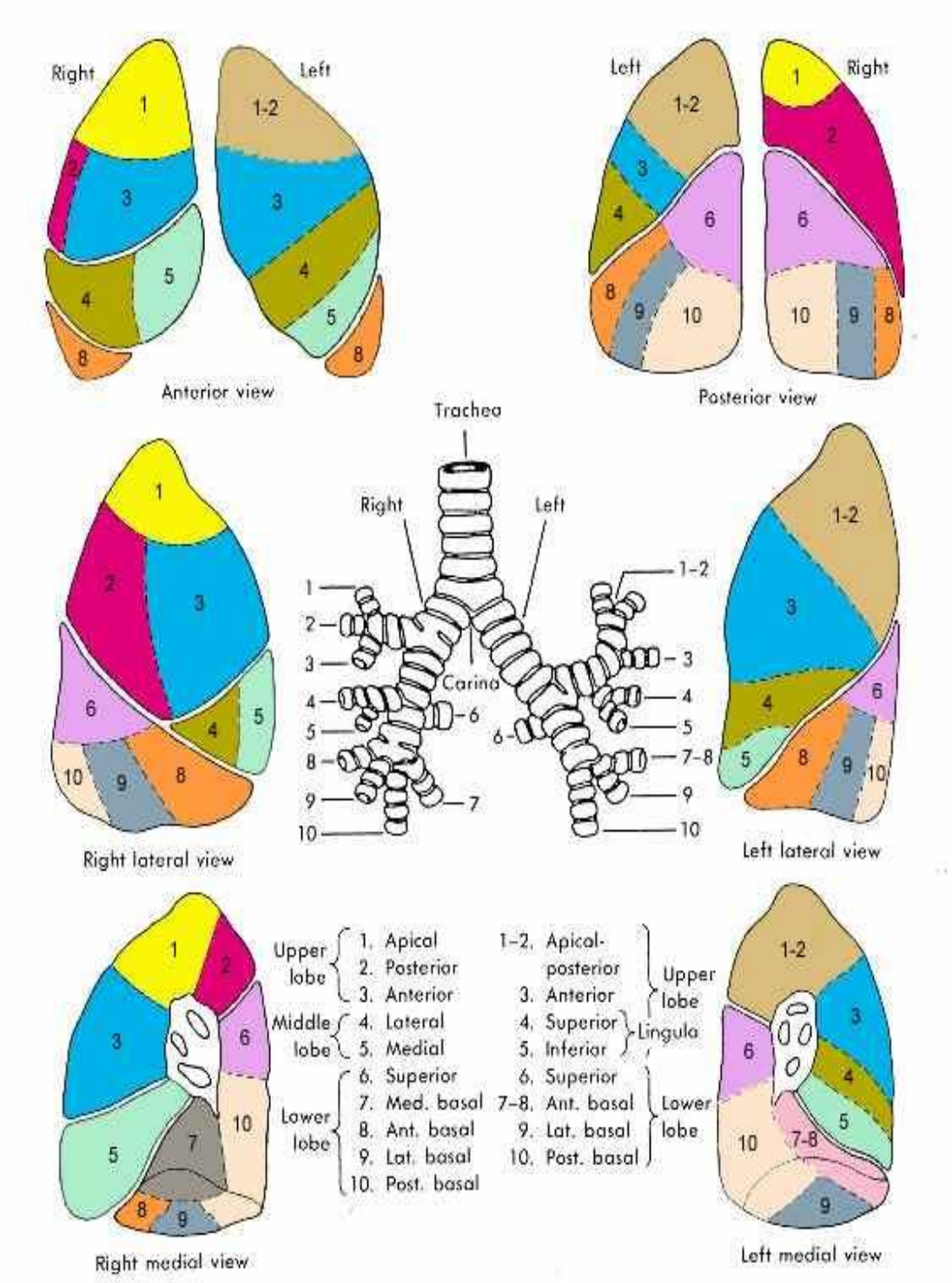


Figure 1 Broncho-pulmonary segments of the lungs (from www.nucmedinfo.com)

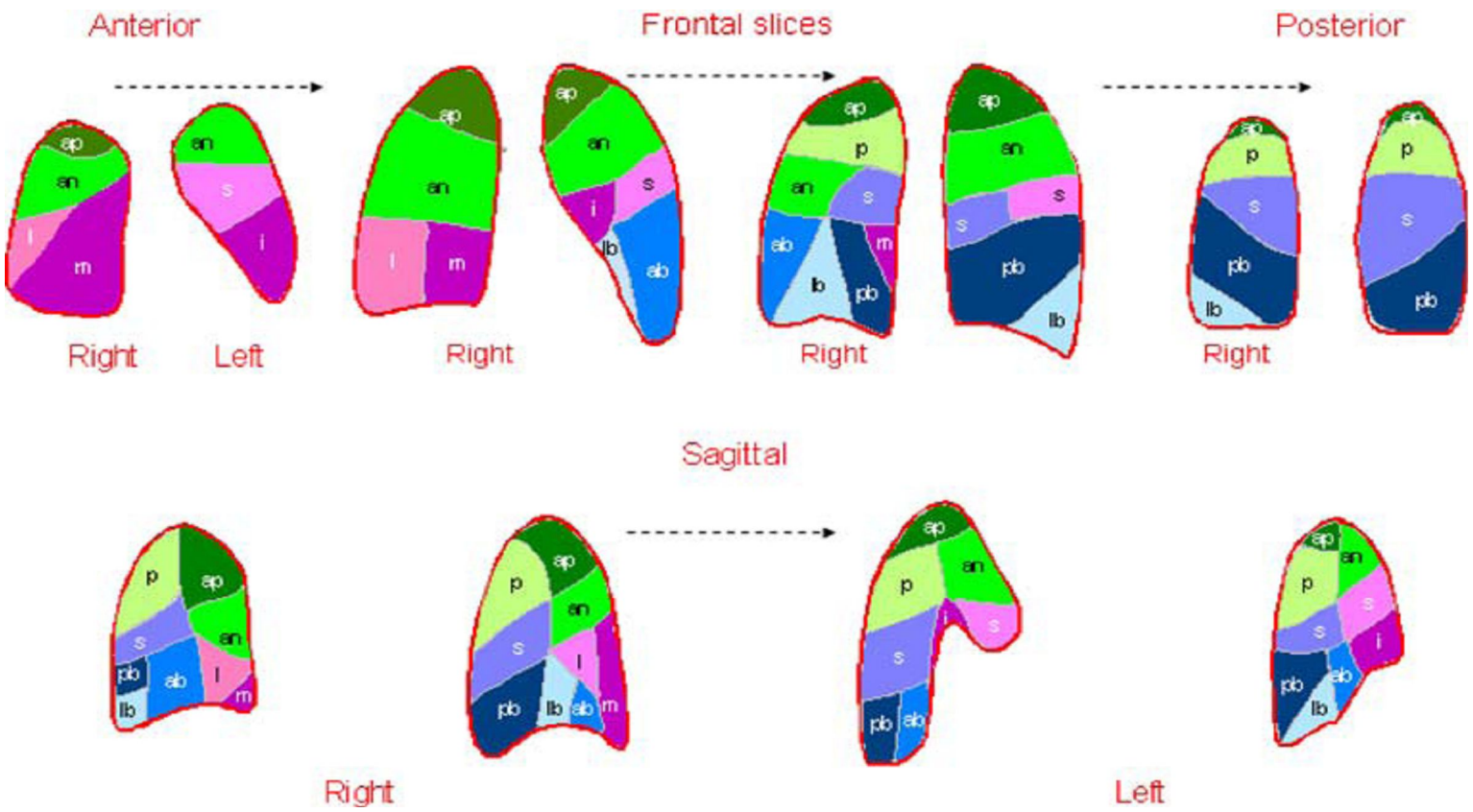


Figure 2 Broncho-pulmonary segmental map of the lungs on SPECT as frontal or coronal slices from anterior to posterior (*above*) and sagittal slices from right to left periphery (*below*). Key to segments: an=anterior; ap=apical; p=posterior; l=lateral; m=medial; s=superior (and superior lingula on the left lung); i=inferior lingula; ab=anterior basal; mb=medial basal; lb=lateral basal; pb=posterior basal. (from EANM guidelines for ventilation/perfusion scintigraphy part 1 *Eur J Nucl Med Mol Imaging* 2009; 36:1359)

PULMONARY EMBOLISM

Acute pulmonary embolism (PE) is characterised by partial or complete obstruction of central or peripheral arteries of the lungs by emboli. Not only the disease itself but also the anticoagulant treatment of PE may entail substantial morbidity.[12] There is a need for prompt and accurate diagnosis. However, the clinical diagnosis of PE has proven to be difficult, since clinical signs and symptoms are often non-specific.[13] In fact, in only up to one-third of patients clinically suspected of having PE is the diagnosis subsequently established.[14]

Epidemiology of PE

Acute PE is the third most common cause of death after cardiovascular diseases and malignancies and also the third most-common cause of cardiovascular death after myocardial ischemia and stroke.[15] PE is the leading cause of maternal death in pregnancy.[16,17]

PE is a common disorder, with an estimated annual incidence of 23 to 69 per 100,000 in a community.[18,19] The incidence of PE rises with age, approaching approximately 1 in 100 in the very old. In the absence of risk factors, PE is rare in children under 15 years of age (<5 per 100,000).[20]

The fatality from PE can be as high as 10% within the first hour.[21] Untreated PE is associated with a mortality rate of 15 to 30% across all age groups[22] rising to 58% in haemodynamically unstable patients.[1]

Conversely, the fatality during anticoagulation therapy has been reduced to 0.4% in patients presenting with deep venous thrombosis (DVT) and 1.5% in those presenting with PE of thrombotic origin.[23]

Natural History of PE

Pulmonary embolism usually arises from deep vein thrombosis of the lower extremities.[24] Further evidence that DVT and PE are distinct manifestations of the same disease process referred to as venous thromboembolism (VTE), comes from the observation that in the majority of patients with PE, DVT can be diagnosed using sensitive methods. In patients with proven leg vein DVT, 40% have asymptomatic PE.[25] Mortality is higher for PE than for DVT.[20]

Usually, deep vein thrombosis originates in leg veins of the calf and propagates to the proximal leg veins.[24] Patients with deep vein thrombosis involving the proximal leg veins are considered at greatest risk for developing pulmonary embolism (as opposed to those with isolated calf vein thrombosis). It is hypothesized that isolated calf vein thrombosis may be a clinically self-limiting condition and patients become at risk for pulmonary embolism if the thrombus propagates to the proximal venous system.[24,26]

With time, the thrombosis will extend in a contiguous fashion to involve the more proximal venous system of the legs; the popliteal, superficial femoral, and common femoral veins. Less commonly, deep vein thrombosis originates in the iliac veins

and, with time, will spread distally. Iliofemoral or pelvic deep vein thrombosis tends to occur in certain settings such as pregnancy or in the presence of pelvic masses and post surgery in gynaecological, urological or abdominal procedures. The thrombus dislodges from the deep veins, travelling through the inferior vena cava and the right heart to finally lodge in the pulmonary arterial system or paradoxically to the systemic arterial circulation via a patent foramen ovale or atrial septal defect.[24,27-29]

PE may less commonly originate from other venous sources. Particularly, with the chronic use of upper extremity indwelling catheters, pulmonary embolism may arise from the veins in the upper extremities. The de novo development of pulmonary embolism is thought to be uncommon.[24,30,31]

In the International Cooperative Pulmonary Embolism Registry (ICOPER) set up to determine baseline mortality rates and mechanisms of death in pulmonary embolism, the 3-month overall mortality rate was 15% and the factors that were significantly associated with increased mortality were systolic arterial hypotension, congestive heart failure, cancer, tachypnoea, right ventricular hypokinesia, chronic obstructive pulmonary disease (COPD), and age >70 years.[1]

The most feared long-term consequence of untreated or poorly treated acute PE is chronic thrombo-embolic pulmonary hypertension, a severely debilitating and potentially fatal condition.[32-34]

Pathophysiology of PE

Three factors known as the Virchow's triad (Figure 3) contribute to the development of venous thrombosis: hypercoagulability, stasis and endothelial injury. A German physician Rudolf Virchow (1821-1902) coined the two terms, venous thrombosis and pulmonary embolism. Interestingly, Virchow only began to be routinely credited with this triad one hundred years after publication of his work on venous thrombosis. This acknowledgement coincided with the accumulation of experimental evidence for the role these factors play in thrombogenesis.[35]

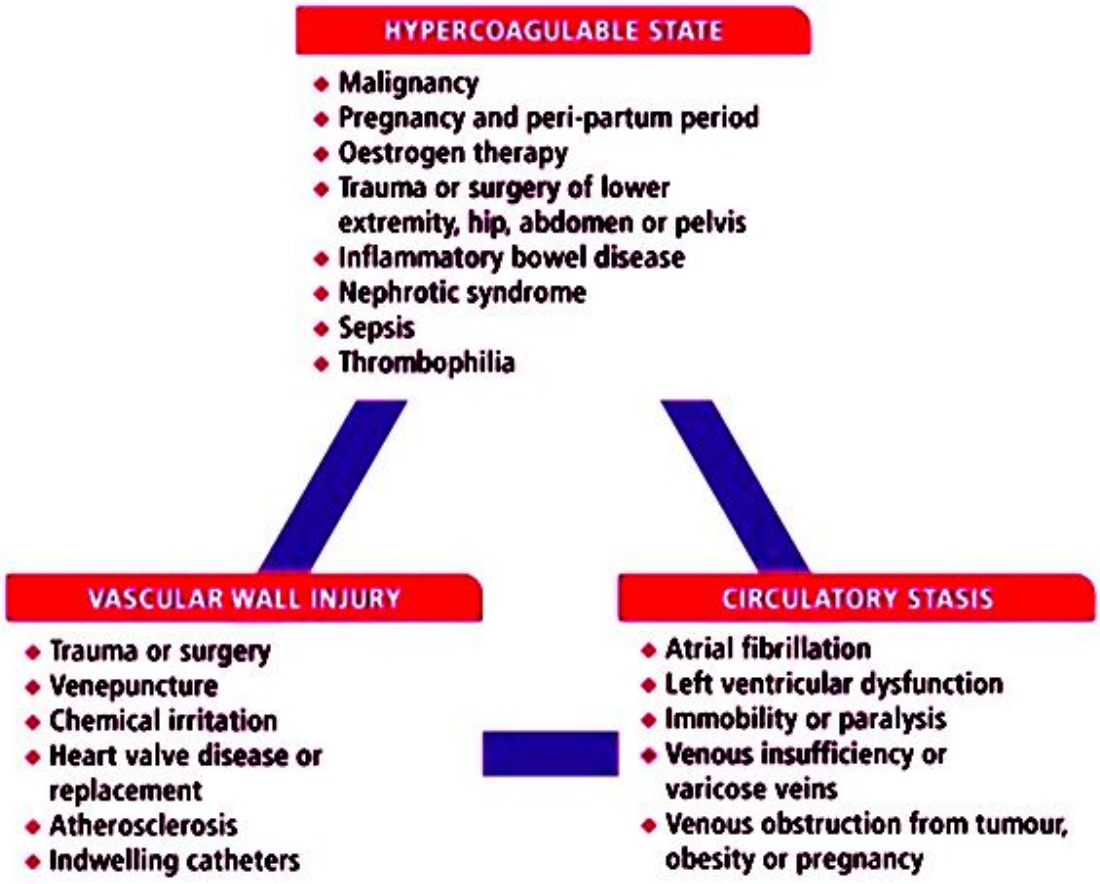


Figure 3 Virchow's triad (from www.thrombosisadviser.com)

Acquired and genetic factors can predispose to venous thromboembolism. Among the acquired factors include long distance flights, obesity, smoking, oral contraceptives, postmenopausal hormone replacement, pregnancy, surgery, trauma and medical conditions such as antiphospholipid antibody syndrome, malignancy, systemic arterial hypertension and chronic obstructive pulmonary disease. Genetic predisposing factors are present in only a minority of patients such as thrombophilia, as well as factor V Leiden and the prothrombin gene mutation (the two most common autosomal dominant genetic mutations).[29,36]

The haemodynamic effects of major PE on the circulation and may include[37];

- Ventilation of unperfused regions will cause increased dead space[38] – this is one reason for dyspnoea. Other reasons for dyspnoea are impaired gaseous exchange, alveolar hyperventilation, increased airway resistance and decreased pulmonary compliance.[37]
- Emboli occluding pulmonary end arteries may lead to haemorrhage, pleuritic pain, pleural effusion and atelectasis. The lung has no pain fibres. Pain with PE indicates involvement of parietal pleura.[37]
- Increased pulmonary vascular resistance and pulmonary hypertension due to a decrease in the number of normal perfusing lung segments, leads to right ventricle strain, right ventricular dysfunction (electromechanical dissociation), hypotension, syncope and sudden death may follow.[37]
- An increase in right atrial pressure can lead to a right to left shunt through a

patent foramen ovale contributing to hypoxaemia. The shunt can also lead to paradoxical emboli, implying that thrombus of venous origin causes infarctions in the aortic distribution, commonly the brain.[39]

Clinical Presentation of PE

The clinical spectrum ranges from asymptomatic to sudden death. The majority of patients with PE present with recognized patterns of symptoms and signs that may include unexplained breathlessness, chest pain (central or pleuritic), cough, haemoptysis, syncope, palpitations, tachypnoea, tachycardia (heart rate >100 beats per minute), cyanosis, fever, hypotension (systolic blood pressure <100 mmHg), right heart failure, pulmonary hypertension and leg swelling.[40]

Clinical syndromes[29] of PE include;

- *Massive PE* – if hemodynamically unstable manifested by systemic hypotension or shock (systolic BP $\leq$ 90mmHg and/or the use of vasopressor therapy). Traditionally, defined by angiographic obstruction of $\geq$50% or obstruction of two lobar arteries.
- *Moderate to large PE* – have right ventricular hypokinesis on Echocardiography but are normotensive.
- *Small to moderate PE* – have normal cardiac function as well as being normotensive.
- *Pulmonary infarction* – not uncommon in PE (complete or incomplete infarct has been observed in 70% of patients with PE at post-mortem)[41] and is very

painful if in proximity to pleural nerves but may be present in any of the above syndromes.

- *Non-thrombotic PE* – may be due to air, fat, amniotic fluid, sepsis, tumor and substance abuse (hair, cotton or talc powder).

Differential diagnoses of pulmonary embolism include acute coronary syndrome, congestive cardiac failure, pericarditis, pneumonia, chronic obstructive airway disease (COPD), pleurisy, primary pulmonary hypertension, costochondritis (Tietze's syndrome), and anxiety disorders.[29]

According to the PIOPED II study, signs and symptoms are similar in both the young and the elderly except that dyspnoea or tachypnoea is less frequent in the elderly, who have no history of cardiopulmonary disease. Typical symptoms and signs may even be absent in patients with severe PE. The haemoptysis/pleuritic pain syndrome, uncomplicated dyspnoea syndrome or circulatory collapse syndrome typical of PE are more common in proximal artery PE (94% of patients) than segmental artery PE (72% of patients).[40]

While certain symptoms and signs are more commonly observed in PE than in other conditions, it is not possible to confirm a diagnosis of PE on clinical features alone. The diagnosis of PE must be confirmed or refuted on the basis of a conclusive imaging test.[42,43]

Diagnosis of Pulmonary Embolism

Prompt and accurate diagnosis of pulmonary embolism has been shown to greatly influence patient outcome. More than 30% of untreated patients with PE will die, compared with less than 10% of treated patients.[15,44] Accordingly, it is important to quickly and accurately diagnosis PE. When evaluating a patient with suspected PE, it is important to remember that PE is only one part of venous thrombo-embolic disease. The other part is the venous thrombus that commonly forms in a lower extremity vein, and subsequently migrates into the pulmonary arterial circulation.

Many tests and algorithms have been suggested for the evaluation of patients with suspected VTE, from the history and physical examination to blood analysis, electrocardiogram, echocardiography, chest radiography, ventilation/perfusion scintigraphy, catheter pulmonary angiography, CT and MR pulmonary angiography, lower-extremity vein sonography, CT venography and MR venography.

The main challenge in the diagnostic work-up of patients with clinically suspected PE is to accurately and rapidly distinguish the 25% of patients (the approximate proportion of patients who test positive for PE in most population groups) who have the disease and require anticoagulant therapy from the 75% who do not have PE.[45]

Over the years, mortality from acute PE has declined as increasingly safe methods of investigation have become more widely available.[7]

NON-IMAGING

Clinical Probability Testing for PE

Clinical acumen is the mainstay for raising the suspicion of acute PE in the early approach to patients, especially if presenting with atypical and/or equivocal symptoms. On the other hand, wise judgement should guide the sequential choice of diagnostic tests required to confirm or exclude the actual occurrence of PE, and should also guide interpretation of the results obtained (mostly consisting of the application of imaging modalities). These considerations emphasize the need for a multidisciplinary approach to the diagnosis of PE. Therefore, the desire for round-the-clock availability of a team of specialists, each possessing specific competence in the different medical fields involved with PE.[45]

The PIOPED II investigators recommended stratification of all patients suspected of having PE according to an objective clinical probability assessment. PIOPED II, which primarily studied the accuracy of CTPA, showed a poor positive predictive value (PPV) of only 58% when the CTPA results and pretest probability was discordant.[40] A conclusion of PIOPED II was that when results of imaging are discordant with pretest probability, further investigation is needed.[40] Interestingly, a similar poor performance (PPV of 56%) was noted when V/Q scintigraphy results were discordant with pretest probability in PIOPED.[4]

Many patients presenting with leg pain or swelling, chest pain or dyspnoea, when investigated, end up being DVT or PE negative and, conversely, many are not investigated when VTE should have been suspected in the first place.[46] Furthermore, many clinical practitioners fail to realize the limitations of imaging tests. It has been suggested that physicians should always take a careful history and physical examination and, in many cases, perform an electrocardiogram and chest x-ray before using these clinical probability tools.[47]

Evidence suggests a strategy that uses clinical probability and the D-dimer test will be most the cost-effective.[48] However, comparative analyses of CTPA and V/Q scanning are lacking. Wells et al[47] performed a comparative analysis of a randomized study where it was deducted that although CTPA is more effective at preventing overall mortality, the CTPA strategy has an incremental cost of more than $27,000 per life year saved compared with V/Q scanning.

An ideal scoring system aimed at assessing the pretest probability of any disease requiring prompt therapeutic intervention (such as acute PE), should be designed so as to keep to a minimum the proportion of patients classified as “intermediate probability”.[45]

The Wells and coworkers model[49] has been used in at least 12 studies, and more than 10,000 patients have been evaluated, including 5 studies with a total of more than 5800 patients in which the authors used the dichotomous scoring system of PE unlikely (score ≤4) or PE likely (score >4) (Table 1). Simply posting the model in the clinic area has proven useful in one centre.[47]

The Wells model seems better suited to rule out rather than to rule in the diagnosis of PE, and its performance is likely to be better in clinical settings where the prevalence of the disease is expected to be low.[47]

Table 1 The Wells and coworkers model[47]

Clinical Variable	Score
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
PE as or more likely than an alternative diagnosis	3
Heart rate greater than 100	1.5
Immobilization or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy (on treatment, treated in the last 6 months or palliative)	1

*Scoring method: A score of >4 indicates the probability of PE is "likely"; ≤4 indicates the probability for PE is "unlikely." Alternatively, a score of <2 is low probability, moderate if score is 2 to 6, and high if score is >6.

Recently, a more precise prediction model (the simplified Pisa model) [50] was introduced which depends on *16 variables* including older age, risk factors, pre-existing cardiopulmonary diseases, relevant clinical symptoms and signs, and the interpretation of the electrocardiogram (Table 2). In contrast to other prediction rules, the model includes variables that are negatively associated with PE. This gives the model greater flexibility, which may explain why it performs equally well in detecting and excluding PE. Instead of using a point-scale score proportional to the regression coefficients, typical of other approaches such as the Wells score as described above, the Geneva score[51] and the Hamilton score[52], the probability of PE is estimated directly from the algebraic sum of the regression coefficients. This allows prediction of the clinical probability as a continuous function and it estimates likelihood ratios for PE precisely.[53]

Table 2 Clinical prediction model for PE (simplified Pisa model)

Predictor	Coefficient
Age 57–67 years	0.80
Age 68–74 years	0.87
Age 75–95 years	1.14
Male sex	0.60
Prior cardiovascular disease	−0.51
Prior pulmonary disease	−0.89
History of venous thromboembolism	0.64
Immobilization (>3 days)	0.42
Sudden onset dyspnoea	2.00
Orthopnoea	−1.51
Chest pain	1.01
Haemoptysis	0.93
Fainting or syncope	0.66
Unilateral leg swelling suggestive of venous thromboembolism	0.80
Fever >38°C	−1.47
Wheezes	−1.20
Crackles	−0.61
ECG signs of acute cor pulmonale	1.96

(from http://www.ifc.cnr.it/pisamodel).

Blood Analysis

i. Plasma D-dimer levels

D-dimer is a specific breakdown product of cross-linked fibrin in blood clots. D-dimer is thus elevated in the setting of deep venous thrombosis and pulmonary embolism.[5,49]

The plasma D-dimer enzyme-linked immunosorbent assay (ELISA) has become recognized as a sensitive screening test for excluding acute pulmonary thromboembolism. Quantitative assay of D-dimer, based on a rapid ELISA method, has a high sensitivity (about 95%) for venous thromboembolism. Other numerous qualitative and quantitative D-dimer assays have been introduced. One quantitative assay, the immuno-turbidimetric assay, has been shown to be equivalent to the ELISA.[54]

A negative D-dimer result is potentially useful in excluding acute pulmonary thromboembolism, with reported negative predictive values of 91–100%.[5,55-57] D-dimer measurement by the Elisa test is very promising since it can exclude nearly 30% of patients with suspected PE without any further investigation on the basis of a D-dimer level less than 500 ng/ml.[58] Venous thromboembolism event rates were less than 0.5%.in follow-up data on patients in whom PE was ruled out on the basis of clinical probability (low probability or PE unlikely) and negative D-dimer testing.[59,60]

On the contrary, a positive D-dimer result is of limited value in hospitalized or critically ill patients, the elderly, pregnancy, infection and inflammation, trauma, neoplasia, and post-operative states, since all are independently associated with elevated D-dimer levels; hence, it cannot be used to triage such patients.[5,55-57]

If patients have a high pretest probability (PE likely) or a positive D-dimer, then imaging, V/Q scan or CTPA is recommended. If the V/Q scan is non-diagnostic, then lower-extremity venous ultrasound is also recommended. In low pretest probability (PE unlikely) patients who have a high-probability V/Q scan, it is important to verify the diagnosis with lower-extremity venous ultrasound, CTPA or pulmonary angiogram.[61]

ii. Brain-type Natriuretic Peptide (BNP)

The potential role of elevated brain-type natriuretic peptides (BNP) in the differentiation of patients suffering from acute pulmonary embolism at risk for adverse clinical outcome has not yet been fully established. High BNP or N-terminal–pro-BNP levels (NT–pro-BNP) distinguish patients with pulmonary embolism at higher risk of adverse events and death. Increased BNP concentrations alone, however, do not justify more invasive treatment regimens. Normal BNP levels might be an indication for outpatient treatment.[62]

iii. Arterial Blood Gases

Hypoxaemia and respiratory alkalosis are common findings in PE. This was confirmed in both the PIOPED and the PISA-PED trials.[4,63] However, the PISA-PED study found that hypoxaemia and respiratory alkalosis were not specific since they were present in 75% of patients who did not have PE.[63]

Electrocardiography (ECG)

Classically seen in PE are sinus tachycardia; new-onset atrial fibrillation or flutter; an S wave in lead I, a Q wave in lead III; inverted T wave in lead III. Often the QRS axis is greater than 90^{o}. More frequent is the T wave inversion in leads V_1 to V_4, right bundle branch block, right axis deviation and, in longstanding cases, P-pulmonale reflecting a right ventricular strain.[29]

IMAGING – (no radiation)

Echocardiography

Echocardiography is easily transportable, can be performed at the bedside which is an added advantage for patients in shock or with severe hypotension and can also diagnose emboli in transit in the right atrium or ventricle. Emboli in transit are classified as type A or type B thrombi. Type A thrombi are long, thin, and extremely mobile, characteristically found in the right atrium and, tend to originate in the peripheral deep venous system. These type A thrombi are generally found in the high risk group manifesting with severe PE and mortality, as such thrombi tend to migrate suddenly to the pulmonary arterial system precipitating an acute deterioration. Type B thrombi are usually smaller, round or oval-shaped, less mobile and arise in the right ventricle and are commonly associated with right ventricle thrombogenetic abnormalities (*namely,* congestive heart failure, pacemaker electrodes, cardiac prostheses). Patients with PE arising from type B thrombi have a good prognosis independent of the treatment type.[64]

Normal echocardiograms are seen in 50% of patients with PE.[29] Nevertheless, echocardiography is important in rapidly triaging patients. *McConnell's sign* demonstrated by right ventricular free wall hypokinesia with normal right ventricular apical motion is specific for PE. The presence of right ventricular dysfunction determines risk stratification, prognosis and planning optimal management.[29]

Echocardiography can also reliably distinguish among other conditions that have radically different treatment regimens, including acute myocardial infarction, pericardial tamponade and aortic dissection.[29]

Leg Venous Ultrasonography

Bilateral compression ultrasonography of the proximal venous system of the legs between the popliteal and common femoral veins is the most common screening procedure used to evaluate patients with suspected PE. With this technique, a 5 or 7.5MHz linear array probe is used to compress the veins at 1-cm intervals between the proximal portion of the common femoral vein to the trifurcation of the popliteal vein distal to the popliteal fossa. The absence of vein compressibility is the most sensitive and specific feature of deep vein thrombosis (DVT). Doppler flow and colour doppler are used to assist with the identification of veins but do not appear to otherwise add to the diagnostic accuracy of the technique.[65]

In the past venography has been regarded as the gold standard for the diagnosis of DVT. It was and is the most reliable test for identifying thrombosis in isolated to calf veins. However, with the advent of ultrasonography, its use is largely of historical interest only. Venography detected the presence of DVT of the lower extremities in 70% to 90% of patients with PE with most thrombi found in the proximal leg veins.[66-68]

With the use of bilateral compression ultrasonography of the proximal venous system, significantly fewer deep vein thrombi are detected in patients with PE than with venography. Only 25% to 50% of patients with PE will be found to have deep vein thrombosis when ultrasonography is used as a screening test.[69-72] Most of these thrombi will be asymptomatic. These lower sensitivity figures likely reflect the limitations of ultrasound as a screening test for DVT in asymptomatic patients. If both thrombo-embolic risk factors and symptoms of DVT are absent, the usefulness of ultrasonography in patients with an indeterminate- or low-probability scan is low.[73] Although thrombo-embolic risk factors or symptoms of DVT are present in nearly 70% of patients with suspected PE, the prevalence of DVT in that group has been reported to be 6% and 8% in two studies.[3,73,74]

Compression ultrasonography is a very accurate test for the diagnosis of proximal DVT of the lower extremities in symptomatic patients presenting with their first suspected episode. In this setting, compression ultrasound has been shown to have a sensitivity and specificity of approximately 97%.[75] Ultrasound is less sensitive and specific as a diagnostic test for DVT isolated to calf veins.[75] Many centres do not routinely image calf veins because of this lack of accuracy, it is time consuming and, the fact that isolated calf clots have a relatively low risk of developing into PE in the absence of their extension into the more proximal venous system.[2] Specialized training and additional procedure time were required for a complete calf vein assessment.[76]

In a search for safe, non-invasive strategies for the investigation of suspected pulmonary embolism, it has been recommended that ultrasonography be performed as an alternative to pulmonary angiography in patients with non-diagnostic V/Q scans to look for evidence of DVT.[58,77,78] Multiple studies have reported that the outcome of patients presenting with symptoms of suspected DVT is excellent as long as ultrasonography at the proximal venous system (popliteal to common femoral vein) remains negative.[78-80] About 1% of patients in whom a diagnosis of PE is excluded and who are not managed with anticoagulant therapy, will subsequently return with DVT or PE in follow-up.[5,81-85] This complication rate is similar to the development of PE in the follow-up of patients with normal pulmonary angiograms.[86]

The performance of ultrasonography as the initial diagnostic test in clinical situations can be argued where pulmonary imaging is relatively contraindicated or problematic to perform. Such settings would include pregnant patients in whom radiation exposure is undesirable or in critically ill patients in whom transport to radiology departments is problematic.

With more recent research advances such as the development of clinical probability scores and D-dimer, the need for serial ultrasonography can be avoided.[82,87-89]

IMAGING – (involving radiation)

Chest Radiography

A chest radiograph remains important in all patients for the exclusion of alternative readily diagnosable conditions (pulmonary edema, pneumonia, fractures, pneumothorax, COPD, lung cancer or pulmonary fibrosis) and to aid in interpretation of subsequent tests.[90]

A routine chest radiograph obtained in both the posterior-anterior and lateral projections is preferred. A portable anterior-posterior chest radiograph is acceptable only if the patient cannot tolerate a routine chest radiographic examination. In patients who have no changes in signs or symptoms, a chest radiograph within 1 day of scintigraphy is adequate. A more recent chest radiograph (preferably within 1 hr) is necessary in patients whose signs and symptoms are changing.[91]

A chest radiograph plays a major role in the choice of subsequent imaging tests (V/Q scintigraphy or CTPA). It has been shown that the presence of any abnormality on the initial chest radiograph decreases the utility of V/Q scintigraphy.[92] Conversely, a normal recent chest radiograph strongly indicates that scintigraphy will have a high likelihood of confirming or refuting the diagnosis of PE. Patients with no underlying cardio-respiratory disease or with (near) normal chest radiographs can safely undergo V/Q scanning because the diagnostic yield will be much higher than in an unselected group

(definite diagnoses are obtained in well above 80%).[93] In some diagnostic algorithms it also defines the requirements for ventilation scintigraphy and is pivotal in the interpretation of the perfusion scintigram. Normal radiographs have been described in at least 12 – 30% of patients with PE.[4,40,90] Radiological signs of PE on a chest x-ray include *Fleischner's sign* – dilatation of the proximal pulmonary artery; *Hampton's hump* – pleural based infiltrates; *Westermark's sign* – decreased vascularity ipsilateral to the PE affected area.[94] Atelectasis, a raised hemidiaphragm, cardiomegaly and pulmonary infarction may also be seen. However, while these chest X-ray findings raise suspicion of PE, they are not diagnostic of PE.[13]

The original PIOPED study had a very high number of inpatients who constituted 68% of the total population. PIOPED II had an inpatient population of 11%. Inpatients are much more likely to have abnormalities on chest radiographs that would potentially interfere with optimal V/Q scan interpretation. Screening patients by chest radiography has significantly cut down the number of intermediate, non-diagnostic interpretations in V/Q scans.[4,40]

Computed Tomography (CT)

In 1982, Sinner and coworkers[95] reported abnormalities within the first (main)

through third (lobar) order pulmonary arteries with central emboli using non-helical (non-spiral) CT in the first series of 21 consecutive patients with clinically suspected PE. During the next decade, most reports on the use of CT for PE described the appearance of PE on non-helical CT scans obtained for other reasons where PE was an incidental finding or on the use of CT for massive or central PE. In 1992, Remy-Jardin and coworkers first reported the use of helical (spiral) CT for the evaluation of central PE in 42 patients, using selective pulmonary angiography as the reference test, demonstrating 100% sensitivity and 96% specificity.[96] As with many first reports, the accuracy estimates may have been high because of the selection of more ideal patients for study (selection bias). Helical CT quickly evolved from being performed on single detector scanners to multi-detector scanners.

For single-detector helical CT, sensitivity and specificity in the detection of PE have been reported to vary from 53% to 91% and from 78% to 97%, respectively.[97]

Catheter Pulmonary Angiography

Using angiography, PE is diagnosed based on direct visualization of endoluminal filling defects, thromboemboli, or abrupt vascular obstruction. Indirect signs, such as delayed opacification or a diminished capillary stain,

are nonspecific. Atelectasis is a common finding; it is shown as crowding of the vessels, usually at the lung bases. Findings in chronic PE include arterial webs, stenoses, irregular occlusions, scalloped mural irregularities, and the pouching defect (a concave edge of thrombus facing the opacified lumen).[98,99]

Since the late 1960s, catheter pulmonary angiography has been considered the most accurate test or gold standard for the evaluation of PE and the reference test to which new diagnostic techniques are compared.[100,101] However, catheter pulmonary angiography is invasive, with a 2% morbidity and small risk of mortality, which have contributed to its under utilization.[102,103] The method is time consuming and labour intensive, and it requires the use of a relatively large amount of contrast material. Currently, conventional or cut-film angiography is rarely used, which have been surpassed by digital subtraction pulmonary angiography (DSPA) which can be performed rapidly and safely with minimal discomfort to the patient.[104]

DSPA is the criterion standard or definitive test in evaluating diseases involving the pulmonary vasculature including PE. The technique allows visualization of all pulmonary arterial branches, catheter-based measurement of pulmonary artery pressure, and may be used for therapeutic interventions e.g. catheter-directed thrombo-fragmentation and embolectomy for PE.[104]

The DSPA technique requires percutaneous venous catheterization, intracardiac catheter manipulation and catheterization of the pulmonary artery.

Ionizing radiation and iodinated contrast agents are used to produce images of the pulmonary arteries and veins. The right common femoral vein is the vessel most commonly used. The jugular or an upper-arm vein may also be used. The injection is preferably made within each of the main pulmonary arterial branches and is positioned so as to allow all of the lobes of one lung to be well opacified. Rapid-sequence images are acquired in multiple antero-posterior and oblique projections. A major concern is the passage of the catheter through the heart with the possible induction of cardiac arrhythmias.[104]

Significant variation in inter-observer agreement related to embolus size has been observed for pulmonary angiography. In the PIOPED study, the interobserver agreement on the presence or absence of subsegmental PE was found to be 66% as compared with 98% and 90% in relation to lobar and segmental PE, respectively. This suggests that subsegmental PE may be difficult to diagnose even using pulmonary angiography, and that subsegmental PE may have been missed. Therefore pulmonary angiography may not be an adequate gold standard for PE diagnosis.[14,86]

Computed Tomography Pulmonary Angiography (CTPA)

Multi-detector Computed Tomography (MDCT) scanners with 4, 8, 16, 32, and 64 detector-rows are now several years old and have solved most of the problems concerning single-slice CT angiography.

The collimation or slice thickness used today is commonly at or near 1-mm, with sub-second gantry rotation speeds of 0.3 to 0.5 seconds resulting in improved spatial and temporal resolution as well as increasing the number of subsegmental (fourth-order pulmonary arterial branches and smaller) arteries that can be evaluated, enhancing the interpretation of the spiral CT scan[105,106] and improving observer agreement.[107] The increased number of detectors means that a greater craniocaudal thickness of the thorax is included in each gantry rotation; hence, more detectors means faster scanning. Scan times range from 18 to 28 seconds on 4-MDCT, 8 to 13 seconds on 16-row MDCT, and 4 to 6 seconds on 64-MDCT. These scan times allow high-resolution imaging of small pulmonary arteries throughout the entire thorax in a single breath-hold even in dyspnoeic patients.[108] Soon scanners with an even greater number of detector row systems will become more widespread and there is even the possibility of a volume CT scanner that would allow imaging of the entire thorax in a single gantry rotation.[109]

During the past decade, many centres have adopted CTPA as the pulmonary imaging procedure of choice for patients with suspected pulmonary embolism.[110] CTPA has an intuitive appeal for clinicians because it provides dichotomous or binary results (either positive or negative), the thrombosis is directly visualized in the pulmonary arterial circulation, permits multi-planar reconstruction, alternative causes for symptoms may be observed and widespread availability especially outside routine hours.[110]

CT is able to depict other conditions better than V/Q scintigraphy, pulmonary angiography, and MR angiography.[109] CT can also demonstrate other conditions that clinically mimic PE, such as acute pneumonia, lung abscess, pneumothorax, pneumomediastinum, pleural or pericardial effusion, aortic dissection, cardiovascular disease, mediastinitis, mediastinal abscess, esophageal rupture, malignancy and interstitial pulmonary fibrosis. In addition, 64-detector scanners have the ability to detect coronary artery disease during the same study, if the appropriate parameters are set. Such disorders have been reported in 11% to 70% of CT examinations performed for suspected acute PE.[112-117]

PIOPED II is the largest and most significant study that assessed the use of MDCT in the diagnosis of PE. Positive predictive values (PPV) were 96% with a concordantly high probability of VTE on clinical assessment, 92% with an intermediate probability on clinical assessment and 58% or non-diagnostic if clinical probability was discordant. Negative predictive values (NPV) in the PIOPED II study were 96% with a concordantly low probability of VTE on clinical assessment, 89% with an intermediate probability on clinical assessment and 60% or non-diagnostic if clinical probability was discordant.[40]

On a per-patient basis, CTPA interobserver agreement for the detection of acute PE is moderate to almost perfect, with kappa values ranging from 0.59 to 0.94.[109]

Computed Tomography Venography (CTV)

Since PE is believed to originate from the lower extremities or pelvis, CT venography is an important adjunctive tool in the protocol of PE evaluation at the time of CTPA.

Investigators have evaluated whether CT venography of the proximal venous system could be performed during CTPA to diagnose deep vein thrombosis and potentially avoid the need to perform ultrasonography. Studies have demonstrated that it is technically feasible to perform CTPA and CT venography during the same procedure. Furthermore, combining the two, modestly increased the diagnostic yield of venous thromboembolism.[117,118]

In PIOPED II, the sensitivity of CTPA for PE was 83% and specificity 96%. In subjects where CTV was also performed, the combined sensitivity for PE and DVT was 90% and the specificity 95%. However, there are concerns about the routine performance of CT venography because of its high contrast load and additional radiation exposure. During the course of PIOPED III, data analyzed from PIOPED II showed that venous phase CT venography and venous ultrasound were diagnostically equivalent.[119]

Magnetic resonance angiography/ venography (MRA/MRV)

Magnetic resonance (MR) has not yet found a routine role in the imaging of patients with suspected PE and is still at an early stage of development. It has

the ability to image vascular structures without ionizing radiation or iodinated contrast but utilizes gadolinium based contrast and can also indicate alternative diagnoses. Currently, gradient-echo and spin-echo MR techniques are used, with faster imaging sequences and gradients that allow imaging the entire chest in a single breath hold. MR may play a role in PE diagnosis in future.[120]

Previous investigations of gadolinium-enhanced MRA(Gd-MRA) showed a sensitivity that ranged from 77% to 100% in studies of 8 to 35 patients with PE and specificity ranged from 95% to 98% among 22 to 83 patients in whom PE was excluded.[121-123] More recently, one study reported sensitivities that differed considerably between readings by teams of experienced radiologists. Among 63 patients with PE, sensitivities were 31% with readings by outside radiologists and 71% with readings by local radiologists. Specificities among 26 patients who did not have PE were 85% and 92%, respectively.[124]

However, there are many pitfalls to MRI which include patient isolation and the examination duration with the need for an extended breath hold potentially limits its use in unstable or critically ill patients. In addition, image degradation resulting from breathing artefacts and areas of atelectasis, perihilar or peribronchial fat have been misinterpreted as PE.[125] There are concerns with regard to nephrogenic systemic fibrosis/ nephrogenic fibrosing dermopathy (NSF/NFD), which occurs rarely in patients with poor renal function who

receive gadolinium-containing contrast material. Therefore, similar to CTPA, gadolinium-enhanced MRA is contraindicated in patients with impaired renal function and also a history of allergy to gadolinium-containing contrast agents or to iodinated contrast media (since patients allergic to iodinated contrast material are sometimes allergic to gadolinium containing contrast media).[126]

The PIOPED III trial was designed to study the accuracy of gadolinium-enhanced MRA in combination with venous phase magnetic resonance venography(MRV) for the diagnosis of acute PE. Although recently completed, the results are not yet available. However, the investigators have published an article describing the methods used in the study. Total scan time for Gd-MRA was 20 minutes while for gadolinium-enhanced MRV was approximately 3 minutes. Gd-MRA diagnostic criteria for acute PE were partially occlusive intra-luminal filling – seen as “railway tracking,” i.e. a small amount of contrast material between the central filling defect and the arterial wall. In cross sectional images, PE are seen as filling defects surrounded by contrast material and/or complete arterial occlusion with termination of the column of contrast material in a meniscus that outlines the trailing edge of the embolus. The diagnostic criteria for acute DVT on Gd-MRV were occlusive – a complete filling defect, i.e., failure to opacify the entire lumen due to a central filling defect (the vessel may enlarge compared with the opposite vein) and/or non-occlusive – a partial filling defect surrounded by opacification.[127]

LUNG SCINTIGRAPHY

A ventilation (V) and perfusion (Q) scan is often referred to as a V/Q scan. It was introduced in 1964 for the evaluation of pulmonary blood flow and has been used as the first-line examination for patients with suspected PE for several decades.[128]

V/Q scintigraphy is a diagnostic radionuclide imaging test that assesses both pulmonary perfusion (arterial flow) using limited capillary blockade as well as ventilation using inhaled inert gases or aerosols by recording their distribution using a gamma camera acquisition either by two-dimensional (2D) planar imaging or three-dimensional (3D) SPECT imaging.[91,129]

Conventional interpretation of V/Q scintigraphy is based on two-dimensional (2D) planar image acquisition.[129] With very few exceptions (such as central, non-obstructing PE causing an evenly distributed reduction in whole lung perfusion, or minimal perfusion defects below the resolution power of scintigraphy), a normal perfusion scan virtually excludes the diagnosis of PE.[101]

The V/Q scan has decreased radiation and the advantage of not requiring iodinated contrast material, unlike CTPA. Therefore, if a patient with suspected PE has a history of an iodinated contrast allergy or renal impairment, V/Q scintigraphy is recommended as an alternate test to CTPA.

V/Q scintigraphy is also recommended when obesity (increased body mass index [BMI]) prevents a patient from either fitting into the CT gantry or is beyond the weight limit for the CT and/or angiography table.[109]

V/Q scanning has been the imaging procedure of choice in patients with suspected PE especially in those with a normal chest radiograph. A normal V/Q scan essentially excludes the diagnosis of PE (1% VTE rate in follow-up), while a high-probability lung scan has an 85% to 90% positive predictive value for PE.[4,68] Unfortunately, most planar V/Q scans fit into a non-diagnostic category, in which the incidence of PE varies from 10% to 30% and further investigation is necessary.[4,5] However, physicians should be not deceived that CTPA is the holy grail because a recent meta-analysis[130] suggests that the sensitivity and the specificity of CTPA is 86% and 93.7%, respectively.

In a retrospective study on PE in pregnant patients, lung scintigraphy proved to be a more reliable imaging technique for the diagnosis or exclusion of PE than did pulmonary CTPA (p=0.0058). This is because of interruption of contrast material by unopacified blood from the inferior vena cava during CTPA. It was recommended that lung scintigraphy should be the technique of choice for imaging of pregnant patients with suspected PE unless the image quality of pulmonary CTPA can be optimized with adapted breathing maneuvers and contrast administration.[17]

V/Q scintigraphy has been shown to have higher sensitivity (94% – 97.4%) than multidetector CT pulmonary angiography (51%) in detecting chronic thrombo-embolic pulmonary disease as a treatable cause of pulmonary hypertension.[131]

The PIOPED II study focused on the accuracy of CTPA rather than comparing its accuracy with V/Q imaging.[40] In fact, the V/Q scan actually represented the most frequently used reference standard required for entry into the study. The overall sensitivity and specificity of CTPA in the 824 patients studied was 83% and 96% respectively, after 6% (51 patients) of the study population were excluded due to technical inadequacy. With the entire study population included, the overall sensitivity and specificity of CTPA declined to 78% and 90%, respectively. The overall positive predictive value (PPV) of 86% and negative predictive value (NPV) of 95% are values comparable to V/Q statistics.[132,133]

One of the major parameters in judging the effectiveness of a diagnostic procedure is examining the rate of false negatives (FN). In patients with suspected PE and negative imaging, a subsequent diagnosis of PE or deep vein thrombosis (DVT) within 3 months constitutes a reasonable FN. Results from two recent studies support the comparable FN rate of V/Q scintigraphy and CTPA. In a large, prospective randomized Canadian study in more than 1,400 patients with high pretest probability and/or positive D-dimer levels,

the FN rates for V/Q scintigraphy and CTPA were similar at 1% and 0.4%, respectively.[81] In another study of over 2,000 patients, the FN rates were statistically equivalent at 1.1% for V/Q scans and 1.2% for CTPA when the chest radiograph was used to guide the choice of procedure.[134]

Anderson et al[81] showed that more emboli were detected by CTPA than by V/Q scintigraphy but questioned the clinical significance of detecting and treating these smaller emboli. Although not proven, it is believed that the pulmonary capillary bed traps small emboli and prevents them from entering the systemic circulation, possibly even in normal individuals.[135] Nielsen et al[136] randomized patients with DVT to either anticoagulation or a non-steroidal anti-inflammatory agent (NSAID). In each group, 50% developed PE and it was concluded that anticoagulant therapy had no effect on disease progression. The burden of clot has prognostic significance and may be a major determinant of whether anticoagulant therapy is appropriate. Patients with underlying cardiopulmonary disease who develop even small PE are at greater risk of developing right heart failure, death and chronic pulmonary hypertension[137] and should be anticoagulated. V/Q studies are sometimes requested in pulmonary hypertension patients to evaluate for chronic PE. If present, chronic PE is treated with anticoagulation to prevent disease progression.[138,139]

Goodman[135,140] recently defined several patient groups where the risks of

anticoagulant therapy may outweigh the benefits. Freeman and Haramati[138] recommended that further prospective, controlled studies are needed to resolve this problem.

A) V/Q Planar

V/Q Planar scintigraphy is a standard investigation for the diagnosis of pulmonary embolism. A V/Q planar scan is comparable to a standard chest X-ray in terms of two-dimensional (2D) imaging.

Although widely used for over 30 years in the assessment of pulmonary embolism (PE), V/Q Planar scintigraphy is hampered by the inherent limitations of 2D imaging. These include significant overlap of anatomical segments, 'shine-through' from underlying lung segments with normal perfusion, and difficulty in visualizing all of the lung segments, especially the medial basal segment of the right lower lobe.[141] For referring clinicians, accurately confirming or excluding PE is essential. The use of probabilistic reporting schema, which is widespread following the PIOPED study, is a significant limitation of planar imaging and has eroded clinician confidence in V/Q scanning, due primarily to the perception that many studies are non-diagnostic.[142]

B) V/Q SPECT

The principles of single photon emission computed tomography (SPECT) imaging are based on emission tomography which provides three dimensional (3D), quantitative images of the radiotracer distribution used to mark physiological, metabolic, or pathological processes. SPECT is comparable to computed tomography (CT) in terms of 3D acquisition. SPECT allows simultaneous imaging of more than one process, e.g. both regional blood flow and ventilation during normal tidal breathing – no breathing manoeuvre required – for the whole lung. Quantitative single photon emission computed tomography (SPECT) requires correction for the image degrading effects due to photon attenuation and scatter.[143]

V/Q Planar vs. V/Q SPECT

Studies performed in animal models and in clinical practice have consistently shown that the use of V/Q SPECT will increase both sensitivity (from 64-71% to 91-100%) and specificity (from 79-91% to 87-100%) compared with planar imaging.[144] In addition, several studies have also shown that V/Q SPECT improves intraobserver and interobserver reproducibility[148,145,146] and results in an extremely high negative predictive value of 98.5% and a low indeterminate rate in one large prospective series.[147] SPECT has also been shown to reduce the number of intermediate or inconclusive results (the Achilles' heel of planar V/Q scintigraphy) to less than 5%.[147]

Only about 50 – 80% of cases can be resolved by planar scintigraphy.[148] In one study by Collart et al[148], a total of 114 consecutive patients with a suspected PE underwent planar and SPECT lung ^{99m}Tc MAA perfusion scans as well as planar ^{81m}Kr ventilation scans. The final diagnosis was obtained by using an algorithm, including D-dimer measurement, leg ultrasonography, a V/Q scan and chest spiral computed tomography, as well as the patient outcome. A planar perfusion scan was considered positive for PE in the presence of one or more wedge shaped defect, while SPECT was considered positive with one or more wedge shaped defect with sharp borders, three-plane visualization, whatever the photopenia. Intraobserver and interobserver reproducibilities were 91% / 94% and 79% / 88% for planar / SPECT images, respectively.[148] The sensitivities for PE diagnosis were similar for planar and SPECT perfusion scans (80%), whereas SPECT had a higher specificity (96% vs 78%; p=0.01). SPECT correctly classified 8/9 intermediate and 31/32 low probability V/Q scans as negative.[148] It was concluded that lung perfusion SPECT is readily performed and reproducible. A negative perfusion SPECT study eliminates the need for a combined V/Q study and most of the `non-diagnostic' V/Q probabilities can be solved with a perfusion image obtained by using tomography.[148]

Bajc et al[146], in a prospective study of 53 patients suspected for PE, evaluated whether the diagnostic information of V/Q SPECT applied in clinical routine might enhance information compared with V/Q planars and streamline data -

processing for the demands of clinical routine. After inhalation of ^{99m}Tc DTPA, planar ventilation imaging was followed by tomography, using a dual-head gamma camera. ^{99m}Tc MAA was injected for perfusion tomography followed by planar imaging. Patients were examined in the supine position, unchanged during V/Q tomography. Two reviewers evaluated V/Q planar and V/Q SPECT images separately and randomly. Mismatch points were calculated on the basis of extension of perfusion defects with preserved ventilation. Patients were followed up clinically for at least 6 months. With V/Q SPECT the number of patients with PE was higher and 53% more mismatch points were found. Ancillary findings were observed by both techniques in half of the patients but more precisely interpreted with V/Q SPECT. V/Q SPECT showed more and better delineated mismatched defects, improved quantification and less interobserver variation compared with V/Q planars. It was concluded that V/Q SPECT is amenable to implementation for clinical routine and suitable even when there is demand for a high patient throughput.[146]

V/Q SPECT not only increases the diagnostic accuracy of the method but also permits the application of advanced image-processing techniques. With the help of these techniques, the detection of matched and mismatched defects can be automated and objectified. In comparison with conventional (visual) image interpretation, the automated analysis leads to significant improvement in detection rate of pathological lesions. As far as sensitivity is concerned,

the computerized procedure proved to be excellent, especially in complex cases with heterogeneous ventilation and perfusion. Yet it could not surpass the accuracy of conventional image interpretation, primarily because of artefacts in the pulmonary recesses. If these artefacts could be overcome, the efficiency of the automated algorithm would be at least equivalent to that of the conventional approach. At present, the best results can be achieved by combining both the automated analysis and conventional evaluation.[149]

The incremental value of tomography (SPECT) over planar studies was evaluated in another study. There was marked improvement in the accuracy of determination of defect size for tomographic studies over the planar equivalents. With planar studies, the accuracy of estimation of defect size was 51% compared with 97% using tomographic studies in the computerized model of PE. Defects in the medial basal segment of the right lower lobe were not identified in planar studies but were easily seen by all observers in the tomographic study. This was especially important in the lung bases, the most common reported site of pulmonary emboli.[150]

A further option in V/Q SPECT is to calculate and display ventilation/perfusion quotient (V/Q quotient) images using standard software. Based upon acquisition in which the patient is examined without movement between ventilation and perfusion imaging, the ventilation background may be subtracted from perfusion tomograms.[151] After normalization of the ventilation

to perfusion count rates, a V/Q quotient is calculated. The V/Q quotient images facilitate diagnosis and quantification of PE extension, particularly in complex cases. Notably, as attenuation is similar for ventilation and perfusion studies, V/Q quotient images make attenuation correction less important.[42]

Palmer et al[151], developed a fast method for V/Q SPECT to improve diagnostic value of lung scintigraphy, using ^{99m}Tc DTPA aerosol and ^{99m}Tc MAA for ventilation and perfusion respectively on 15 patients. Total SPECT acquisition was 20 min. ^{99m}Tc DTPA clearance, calculated from initial and final ventilation SPECT projections was used for correction of the ventilation projection set before iterative reconstruction of V/Q SPECT data. The ventilation background was subtracted from perfusion tomograms. A normalized V/Q quotient was calculated. V/Q SPECT had adequate quality and showed V/Q quotient relationships more clearly than did planar images. Frontal and sagittal slices were superior than planar scintigraphy in characterization of embolized areas. It was deduced that fast, high flying V/Q SPECT is possible, more comprehensive and has higher objectivity in evaluating PE; costs for the procedure seemed low.[151]

Based on the premise that PE results in the lung is altered to a number of distinct functional subpopulations, Harris et al[152] evaluated a novel parameter of V/Q heterogeneity, termed the “weighted median V/Q value” and found it to be the most accurate parameter with respect to PE diagnosis.

Such objective analysis of V/Q SPECT may reduce the number of non-diagnostic scintigraphy results by providing quantitative measures of V/Q mismatch and more likely may be useful in the physiological investigation of other pulmonary diseases. V/Q SPECT has the definite advantages of being better able to quantify the extent of perfusion abnormalities (which may be valuable in guiding treatment decisions) and can assess reperfusion after PE (especially in follow up), something not easily done with CTPA.[141,146]

Harris et al[129], compared interpretation of traditional planar ventilation–perfusion lung scan images with planar images reformatted from SPECT data using two different techniques. V/Q data were acquired from 50 patients referred with suspected pulmonary embolism. In addition to traditional six-view planar images, six-view planar images were also generated from SPECT data using two methodologies: an angular summing technique (angular summed planar images) and a forward projection technique (reprojected planar images). Three experienced nuclear medicine clinicians reviewed the images in a blinded, randomized fashion. Results were analyzed by comparing the two reprojected techniques with the traditional true planar scans, examining for differences in the defects seen (number, type and confidence), and the impact on final clinical interpretation. Compared with true planar scintigraphy, angular summed images demonstrated fewer mismatched defects ($p<0.0001$), while the reprojected planar images had more matched defects ($p=0.013$). In addition, there was a significant change

in the clinical interpretation of the angular summed planar images resulting in clinicians perceiving a decreased likelihood of pulmonary embolism ($p<0.016$). No such difference in interpretation was observed for the reprojected planar images. It was concluded that angular summed planar images result in a perceived decreased likelihood of pulmonary embolism compared with true planar images. In contrast, while reprojected planar images resulted in an increased number of matched defects compared to true planar scans, there was no change in the clinical interpretation.[129]

Based on the available evidence, Roach et al, proposed that V/Q SPECT scans be used as the initial diagnostic test in cases of suspected PE and have considerably less radiation exposure (particularly to the breast) than CTPAs. V/Q SPECT should be performed using state-of-the-art technology. This includes a superior ventilation agent, a modern generation multi-headed gamma camera, and a software display package that allows co-registered ventilation and perfusion scans to be viewed simultaneously in the three orthogonal planes in a synchronized manner. V/Q SPECT is a new paradigm and, as such, probabilistic reporting criteria such as the PIOPED scheme should be discarded. The applicability of PIOPED criteria (derived from a single view ^{133}Xe planar image or multi-view planar perfusion scans) to V/Q SPECT is dubious. Lung scanning has advanced since that time and new and more appropriate reporting schema should be used.[9]

Currently, debate remains regarding the appropriateness of performing V/Q scintigraphy or CTPA as the initial imaging procedure for suspected PE. According to Roach et al[9], direct comparisons of the two techniques are limited and a published prospective study showed that V/Q SPECT was more sensitive, but less specific than multidetector CTPA, with comparable overall accuracy.[145] A multicenter prospective trial is ideal to answer this question, but is difficult for several reasons:

a) Evaluating the clinical effectiveness of rapidly evolving health technologies is problematic. Both CT and V/Q SPECT technology continue to develop and, therefore, any published direct comparison inevitably reports on previous-generation technology.
b) A robust 'gold standard' is lacking for the diagnosis of PE resulting in the V/Q scan and/or CTPA being pivotal in determining the presence or absence of disease[142,146]
c) Ethical concern about subjecting individuals to the radiation exposure from both V/Q SPECT and CTPA, especially in individuals without PE.
d) The time interval between the two studies being performed could result in embolus fragmentation, movement, or lysis, thus affecting the perceived accuracy of each modality.

Given the superiority of V/Q SPECT over planar imaging and the various limitations of CTPA, the use of V/Q SPECT remains limited due to;

a) CTPA is widely available and is often more accessible than V/Q scanning.[141]

b) Reporting specialists may be reluctant to change to SPECT given their familiarity with planar imaging and lack of familiarity with 3D lung anatomy. However, SPECT data can be used to easily generate planar-like images that may be helpful during a transition period to SPECT.[153]

c) The misconception that SPECT imaging takes longer to acquire than traditional planar imaging. With the use of multi-head gamma cameras and modern computing, SPECT acquisition times are often faster than typical planar studies.[9]

d) There may be the belief that SPECT can only be performed with ideal ventilation agents, such as Technegas. Several other satisfactory options are available for ventilation SPECT imaging, including several new generation radioaerosol nebulizers using ^{99m}Tc-DTPA. Inert radioactive gases such as ^{81m}Kr can be used, although often less readily available and relatively expensive. The ongoing use of ^{133}Xe as the primary ventilation agent in many centers in the United States is certainly a factor hampering the development of V/Q SPECT in that country.[9]

These two modalities (V/Q SPECT and CTPA) have complementary roles and it is important that clinicians recognize the strengths and weaknesses of each (Table 3) so that the appropriate test can be selected in individual patients.[9]

Table 3 Strength and weaknesses of CTPA and Lung Scintigraphy in PE[45]

Modality	Strengths	Weaknesses
MDCT pulmonary angiography	High overall accuracy	High relative radiation burden
	High interobserver agreement	Patient safety issues: contrast reactions; renal impairment; injection site trauma
	Provision of alternative diagnoses	Dilemma of "incidental" PTE
	High out-of-hours availability	Higher relative cost
	Rapidity of acquisition	Variable worldwide availability
	Assessment of haemodynamic surrogates for prognosis	Not suitable for follow-up
Lung scintigraphy	High NPV in low pretest probability	Lower overall specificity
	High PPV in high pretest probability	Lower interobserver agreement of intermediate probability scans (PIOPED)
	Relative safety in certain patient groups	Poorer out-of-hours availability in some areas
	Lower radiation dose	Longer acquisition time
	Lower relative cost	Does not provide alternative diagnoses
	Suitable for follow-up	
	Higher worldwide availability	

Radiopharmaceuticals used in Lung Scintigraphy

(i.) Perfusion Imaging Agent

Technetium-99m macroaggregates of albumin (^{99m}Tc MAA) is the radio-pharmaceutical of choice for pulmonary perfusion imaging. Its mechanism of localization is by capillary blockade. In normal circumstances, more than 90% of the particles (>10μm) are mechanically trapped in the lung capillaries within 5 to 10 minutes, depending on the regional pulmonary blood flow. Optimally, between 100,000 and 400,000 particles are required to allow good statistical distribution.[10,11,154,155]

Production of MAA particles is by heat aggregation of human serum albumin (HSA) with a reducing agent (stannous chloride) in buffer (acetate) at 80-90^{0}C for 30 minutes. The particles are then washed with normal saline to remove any free stannous ions, re-suspended in saline and aliqouted in vials to be used later in kits. Commercial kits are available in lyophilized form. Different manufacturers add other inactive ingredients such as sodium acetate, HSA, succinic acid and lactose to facilitate particle dispersion during reconstitution with pertechnetate. The number of particles varies from 1 to 12 million particles per milligram of MAA. The labelling efficiency should be greater than 90%. Microscopic inspection on *hematocytometer* (grid size = 50μm) should be performed to make sure that the MAA particles are not too large (should not exceed 100μm) or clumped. The particle size of MAA generally ranges from 5 to 100μm, with above 60% in the range of 10 to 60μm.[10,11,154,155]

After intravenous injection through a peripheral vein, the ^{99m}Tc MAA particles travel intravascularly to be trapped in the pulmonary bed via the right atrium and ventricle. The number of capillaries occluded is negligible (less than 0.1% of about 280 billion capillaries). ^{99m}Tc MAA has a biological life of 2 to 3 hours. It may begin to breakdown even as early as 30 minutes after injection depending on the kit used. The particles are broken down into smaller particles by mechanical movement of the lung during breathing and/or through enzymatic proteolysis. The broken down particle fragments (<10μm) enter the systemic circulation to be removed by phagocytes of the reticuloendothelial system.[10,11,154,155]

The recommended administered activity in adults (70kg body mass) is between 74 to 148MBq containing 200,000 to 350,000 MAA particles. The lung is the critical organ receiving an absorbed dose of 5mGy for a 111MBq ^{99m}Tc MAA dose. Contraindications to radionuclide particulate lung perfusion scans include severe pulmonary hypertension (can cause a sudden rise in pulmonary pressure and even death) and a history of hypersensitivity reactions to products containing human serum albumin. Caution should also be exercised in patients with known right to left shunts to avoid adverse effects leading to coronary or cerebral microembolization. Hypersensitivity reactions to products containing HSA are possible, thus epinephrine, antihistamines and corticosteroids should be available.[10,11,154,155]

(ii.) Ventilation Imaging Agents

Ventilation imaging agents used in radionuclide lung scans include radioactive inert gases such as Xenon-133 (^{133}Xe) and Krypton-81m (^{81m}Kr), radio-labelled aerosols such as ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) and Technegas.

a) Xenon-133(^{133}Xe)

Xenon-133 gas has a half life of 5.3 days with 81keV principal gamma ray energy. The low energy leads to attenuation of the gamma rays and is the reason for the single projection posterior positioning during ventilation imaging. The patient is asked to inhale ^{133}Xe (10-15mCi or 370-555MBq) gas mixed with air in a closed system. The critical structure is the trachea. ^{133}Xe allows assessment of all phases of regional ventilation using initial single breath, wash-in or equilibrium and washout acquisition. The initial single breath phase represents instant ventilation, wash-in and equilibrium phases are proportional to the aerated lung volume while the washout phase demonstrates regional clearance or areas of air trapping. ^{133}Xe is usually administered by using one of the commercially available delivery and rebreathing units. ^{133}Xe gas is heavier than air, thus, when exhaled it can be released to the environment via an exhaust vent at ground level. A charcoal trap may be used or the study may be performed in a room kept under negative pressure.[10,11,154]

b) Krypton-81m (^{81m}Kr)

Krypton-81m gas has a half life of 13 seconds with 190keV as the principal gamma ray energy. It is eluted from a Rubidium 81 (^{81}Rb) generator which has a half life of 4.6 hours implying that it can be used for 1 day. Unlike ^{133}Xe, ^{81m}Kr is used in a continuous steady-state inhalation technique that is proportional to the regional ventilation rate rather than lung volume. ^{81m}Kr, by virtue of its radio-physical characteristics is often considered a reference gas for ventilation scintigraphy. Its short half-life (13s) enables multiple views and leads to a low radiation exposure. This makes ^{81m}Kr suitable for use in children[156] and pregnancy. The high photon energy (190 keV) allows simultaneous or immediate acquisition of perfusion and ventilation data in multiple and comparable views. Consequently, a short time is required for the procedure and, because ^{81m}Kr has a short half-life and is not readily soluble, the absorbed dose is low and therefore the radiation dose is negligible.[10,120]

c) Radio-labelled Aerosols

An aerosol is a relatively time-stable two-phase system consisting of particles suspended in gas (air). The radio-labelled particles may be liquid, solid or a combination of the two. Deposition depends on size (mainly), shape, density and electric charge of the particle as well as breathing pattern. Aerosols have a mean aerodynamic diameter of

about 0.5μm. The larger the particle size, the more the unwanted central deposition of the aerosol particles which may obscure visualization of adjacent uptake.[10,11,154]

i. Tc-diethylenetriaminepentaacetic acid (DTPA)

Technetium labelled aerosols e.g. ^{99m}Tc DTPA, do not allow dynamic imaging like ^{133}Xe gas but rather map the distribution of aerated lung volume. Radio-labelled aerosols distribution depicts the ventilation during the inhalational phase. The inhaled aerosol is deposited on the broncho-alveolar spaces with slower washout allowing multiple views acquisition in contrast to radioactive gases.[120] Tc-99m DTPA is delivered to the patient via a nebulizer/ aerosol delivery system connected to an oxygen supply flow meter. Air or oxygen is forced through the nebulizer at a certain pressure to produce aerosol droplets that are inhaled while the exhaled air is trapped in a filter attached to the aerosol unit. Central deposition is also common in patients with COPD (chronic obstructive pulmonary disease) owing to turbulent flow in central airways. The biological half life of ^{99m}Tc DTPA in the lungs is 80±20 minutes in healthy non-smokers, 45±8 minutes in healthy passive smokers and 24±9 in healthy smokers due to increased alveolar membrane permeability.[157] ^{99m}Tc DTPA aerosol particles cross the alveolar-capillary membrane and enter the pulmonary circulation to be later cleared by the kidneys. One major downfall in the use of ^{99m}Tc

DTPA aerosols is that only 2 – 10% of the approximately 30mCi (1.11GBq) available in the aerosol generator is actually delivered to the lungs while the rest remains airborne or is exhaled.[10,11,154]

ii. Technegas

Technegas, an aerosol, is technetium-labelled with carbon particles (graphite crucible). A commercially available technegas generator produces very small particles (0.005μm to 0.2 μm) by combustion of ^{99m}Tc eluate at 1500^{0}C - 2500^{0}C in an argon atmosphere. Technegas are hydrophobic particles that tend to grow by aggregation and should be used within 10 minutes of generation. They are cleared by alveolar resorption and have a biological half-life of 135 hours. Among the ^{99m}Tc-labelled aerosols, Technegas is relatively new, considered to behave truly like a gas because of the ultrafine (5 - 150nm) dispersion of the ^{99m}Tc-labelled carbon particles in contrast to ^{99m}Tc DTPA, an aerosol which is affected by central deposition due to large particle size or in COPD. However in comparison with ^{81m}Kr in the Advances in New Technologies Evaluating the Localization of Pulmonary Embolism (ANTELOPE) study, Technegas increased the number of non-diagnostic V/Q lung scan results, leading to a demand for further additional tests to confirm or exclude PE.[120,154] Using Technegas has minimized the problem of artefactual hotspots that might hamper interpretation in patients with COPD, and according to clinical experience is better than the best liquid aerosols.[120]

INTERPRETATION of V/Q Scans

Different criteria have been advocated for the interpretation of V/Q lung scans in patients with suspected PE. For example, in a comparison of observer variability and accuracy of the Hull, PIOPED and Gestalt interpretations of V/Q lung scans, all had good accuracy and inter-observer variability.[158] The Gestalt interpretation is an integration of different sets of criteria and the physician's own experience in interpreting lung scintigrams of patients with suspected pulmonary embolism.[159] The Hull criteria[160] are almost similar to the revised or modified PIOPED criteria (Table 4).

The two most widely applied procedures developed with the purpose of enhancing the diagnostic accuracy of the scintigraphic approach in PE have initially been formalized as clinical investigation trials, the so-called PIOPED[4] and the PISA-PED[63] protocols.

Miniati et al in the PISA-PED study proposed using a combination of perfusion scan only (Table 5), pretest probability and chest radiography findings to evaluate patients with suspected PE.[63] These investigators felt that the finding of wedge-shaped defects on the perfusion scan can make a diagnosis of PE "irrespective of the radiographic findings in the corresponding lung regions".[161] Radiographic findings such as oligaemia and consolidation suggesting infarction help when they can be distinguished from emphysema, congestive failure and more typical pneumonic consolidations. The investigators stated that the chest radiograph is not to be used as a surrogate for the ventilation scan.

Two recent articles by the proponents of this PISAPED methodology claim an 85% PPV and 96% NPV which, when retrospectively applied to the PIOPED II patient population are comparable to the CTPA values in the same study (86% PPV, 95% NPV). The V/Q scan data using modified PIOPED criteria had a 72.4% PPV and 96.5% NPV and the number of non-diagnostic studies fell to zero.[161,162]

The use of the PISA-PED interpretive scheme is of greatest value when used by individuals or a closely integrated team with expertise in clinical evaluation, as well as radiographic and scintigraphic interpretation. Since this type of universal expertise is not always available, the continued use of the ventilation scan is a safer, justifiable approach in most medical centers, although its elimination would reduce cost and radiation exposure.[162]

A wedge-shaped perfusion defect is not always simple to characterize on planar images. Accordingly, there has been one study that advocates a perfusion-only SPECT study as performing better than perfusion-only planar studies and eliminating most “non-diagnostic” or intermediate studies.[148] A perfusion-only study is recommended during pregnancy and patients with suspected massive PE.[42]

In the PIOPED protocol, results of the V/Q scan were correlated with the chest radiography findings to classify patients into categories with either high, intermediate, or low probability of PE.[4]

In the PIOPED study, only 40% of patients with PE had a high probability V/Q scan result, whereas another 40% of patients with PE had an indeterminate result and 14% had a low probability result.[4] According to the PIOPED II study, a high probability scan is sufficient diagnostic evidence of PE to begin anticoagulation therapy and a normal V/Q scan is considered sufficient evidence to exclude PE. However, the frequency of low or intermediate probability scan results can be as high as 50% to 70%, carrying a 10% to 50% probability of PE. This makes it difficult to decide whether or not to begin anticoagulation therapy based on the test result alone.[40]

The original PIOPED study had a high number of inpatients, who constituted 68% of the total population studied. PIOPED II had an inpatient population of 11%. Inpatients are much more likely to have abnormalities on chest radiographs that would potentially interfere with optimal V/Q scan interpretation. Screening patients by chest radiography has significantly cut down the non-diagnostic interpretations.[138]

The use of a number of ancillary scintigraphic findings not used in PIOPED subsequently became available, derived from a retrospective review of PIOPED. Most of these allow a very low probability or PE absent interpretation. These include the stripe sign (activity at the periphery of a perfusion defect), the fissure sign (defects that conform to the oblique or horizontal fissure), segmental contour pattern, large pleural effusions with matched V/Q scintigraphy findings and no other V/Q scan mismatches, radiographic densities with matched V/Q scintigraphy findings in upper

or mid-lung zone, perfusion scan better than abnormal chest radiograph, ventilation defects worse than perfusion defects (reverse mismatch).[138]

A retrospective analysis of the PIOPED criteria found errors, e.g., a moderate single segmental mismatch was erroneously called low probability. In a subsequent publication modifying the original criteria, the single segmental mismatch was correctly placed in the intermediate category. Different significance of findings when correlated with objective clinical assessment (pretest probability), i.e., a single segmental mismatch in a patient with high pretest probability constitutes a high probability V/Q scan interpretation.[138]

Other conditions associated with the appearance of focal defects in a perfusion lung scan include compression or invasion of pulmonary vessels by tumors, mediastinal lymphadenopathy or granulomata, emphysema (especially in bullous disease), interstitial fibrosis, bronchiectasis, pneumonic consolidation and atelectasis, localized bronchial obstruction, vasculitis and, arteriovenous fistulae,[163-165] and post radiation pneumonitis or fibrosis.[42]

Harris et al[166] examined the feasibility and accuracy of fusing ventilation and perfusion data from SPECT V/Q scintigraphy together with computed tomographic pulmonary angiography (CTPA) data. In addition, the findings of the technique were correlated to the final clinical diagnosis. Thirty consecutive in-patients investigated for potential pulmonary embolism were identified retrospectively. Image datasets from these two modalities were co-registered and fused using commercial software.

Accuracy of the fusion process was determined subjectively by correlation between modalities of the anatomical boundaries and co-existent pleuro-parenchymal abnormalities. In all 30 cases, SPECT V/Q images were accurately fused with CTPA images. Nine patients who had positive CTPA performed as an initial investigation had co-localized perfusion defects on the subsequent fused CTPA/ SPECT images. Three of the 11 V/Q scans initially reported as intermediate were reinterpreted as low probability owing to co-localization of defects with parenchymal or pleural pathology. It was suggested that the fusion technique may be clinically useful in patients who have non-diagnostic initial investigations or in whom corroborative imaging is sought.[166]

According to the 2009 EANM guidelines for ventilation/ perfusion scintigraphy[42,43], interpretation of imaging tests such as V/Q Planar and V/Q SPECT should be based upon 3 principles:

1. Basic criteria for reading the images (the so called probabilistic interpretation e.g. PIOPED should be done away with since it was based upon old techniques),
2. Knowledge and experience of the interpreter, according to the principle of "Gestalt"
3. Pretest probability in accordance with the principle of holistic interpretation – this includes the clinical information and laboratory test.

Additionally, for the above principles to be clinically useful, the conclusion should be either positive or negative for PE;

Positive for PE:

- V/Q mismatch of at least one segment or two subsegments that conforms to the pulmonary vascular anatomy i.e. lobar, segmental and subsegmental

Negative for PE:

- Normal perfusion pattern conforming to the anatomic boundaries of the lungs
- Matched or reverse mismatch V/Q defects of any size, shape or number in the absence of mismatch
- Mismatch that does not have a lobar, segmental or subsegmental pattern

Non-diagnostic for PE:

- Multiple V/Q abnormalities not typical of specific diseases

Table 4 Modified PIOPED II criteria for the diagnosis of PE[167, 168]

Revised PIOPED Criteria

Scan Category	Definition
High probability (≥ 80%)	At least two large mismatched segmental perfusion defects or the arithmetic equivalent in moderate or large and moderate defects*
Intermediate probability (20%–79%)	One moderate to two large mismatched segmental perfusion defects or the arithmetic equivalent in moderate or large and moderate defects*; one matched V-P defect with a clear chest radiograph†; difficult to categorize as low or high, or not described as low or high
Low probability (≤ 19%)	Nonsegmental perfusion defects (eg, cardiomegaly, enlarged aorta, enlarged hila, elevated diaphragm); any perfusion defect with a substantially larger abnormality at chest radiography; perfusion defects matched by ventilation abnormality† provided that there are (*a*) normal chest radiographs and (*b*) some areas of normal perfusion in the lungs; any number of small perfusion defects with a normal chest radiograph
Normal	No perfusion defects, perfusion outlines exactly the shape of the lungs seen on the chest radiograph (hilar and aortic impressions may be seen, and the chest radiograph and/or ventilation scan may be abnormal)

* Two large mismatched perfusion defects are borderline for high probability. Individual readers may correctly interpret individual scans with this pattern as showing high probability for PE. In general, it is recommended that more than this degree of mismatch be present for inclusion in the high-probability category.

† Very extensive matched defects can be categorized as indicative of low probability. Single V-P matches are borderline for low probability and thus should be categorized as intermediate in most circumstances by most readers, although individual readers may correctly interpret individual scans with this pattern as showing low probability.

Table 5 PISAPED Protocol for perfusion scintigraphy[63]

Category	Findings
Normal	No perfusion defects of any kind
Near normal	Perfusion defects smaller than or equal in size and shape to extrapulmonary chest radiographic abnormalities such as: cardiomegaly, enlarged aorta, enlarged hila and mediastinum, elevated diaphragm, blunting of the costophrenic angle, pleural thickening, intrafissural effusion collection
Abnormal scan with PE	Single or multiple wedge-shaped defects with or without matching pulmonary chest radiographic abnormalities; wedge-shaped areas of overperfusion usually coexist
Abnormal scan without PE	Single or multiple defects other than wedge-shaped, with or without matching pulmonary chest radiographic abnormalities; wedge-shaped areas of overperfusion are usually not seen

Table 6 Main differences in the modified PIOPED criteria and Hull criteria[158]

PIOPED criteria	Hull criteria
High probability (≥2 segments)	High probability (≥1 segment)
Intermediate probability	Indeterminate probability
Low probability	
Normal perfusion	Normal perfusion

Table 7 Radiation Exposure in adults[169-172]

Radiopharmaceutical	Administered activity (MBq)	Critical organ, dose (mGy/MBq)	Effective dose (mSv/MBq)
^{99m}Tc-MAA	40–120	Lungs, 0.067	0.017
^{99m}Tc-DTPA	20–30	Bladder, 0.047	0.007
Technegas	20–30	Lungs, 0.11	0.015
^{81m}Kr	40–400	Lungs, 0.0068	0.0007

SAFETY in DIAGNOSIS of Pulmonary Embolism (PE)

A key objective of imaging in pulmonary embolism (PE) is to minimize radiation exposure without sacrificing image quality and diagnostic accuracy. The radiation exposure (Table 7) using radio-isotopes is 1.2–2mSv[42] while for CTPA is 13–40mSv.[173]

The increased risk of breast cancer from the radiation exposure with CTPA has become a controversial issue. It is probable that premenopausal women represent a very significant segment of the population that is evaluated for PE. However, dose calculation is very complex because absorption is variable from patient to patient and risk data are extrapolated from studies of individuals exposed to large amounts of radiation (Hiroshima atomic bomb survivors).[174] The linear-non threshold relationship between dose and cancer risk is theoretical and not uniformly decided. Breast radiation estimates made with 4-slice CT vary from 20 to 60 mSv whereas those from V/Q vary, approximately 0.28 to 0.9 mSv.[170,175-177] A recent report by Einstein and coworkers, estimated that 64-slice CTPA delivers a dose of 50 to 80 mSv to the breast.[178] These reports indicate an enormous difference in radiation dose between CTPA and V/Q scans. According to Hurwitz et al, the dose to the female breast for V/Q SPECT is only 4% of the dose from MDCT with full dose-saving means.[179] This may have particular importance in pregnant women with proliferating breast tissue.[180]

The estimated radiation exposure from CTPA suggests that a non-negligible increase in lifetime attributable risk of cancer exists, particularly to the breasts of young women (1 in 143 for a 20-year-old woman and 1 in 284 in a 40-year-old woman, with risk further decreasing with increasing age).[178,181] It is estimated that 0.4% of all cancers in the United States are attributable to the radiation from CT studies including CTPA, but proper large-scale population-based studies are lacking. The American College of Radiology white paper strongly emphasizes that it is the responsibility of the imaging physician to be fully educated concerning the radiation risks associated with each procedure and, in turn, educate the clinician requesting the procedure. Nonetheless, providing diagnostically equivalent options is part of this educational process.[174]

During the first trimester of pregnancy the fetal dose from MDCT is greater than or equivalent to that of V/Q scan. The advantage of V/Q SPECT increases after the first trimester.[182] A 2-day protocol has been suggested in pregnancy. Perfusion-only scans should be performed on day 1, using a reduced dose of ^{99m}Tc MAA. In most patients PE can be excluded on the basis of a normal perfusion pattern. When the perfusion pattern is abnormal but not diagnostic of PE, a ventilation study is performed on day 2, using an activity deposited in the lung of 20–30 MBq.[42]

The latency period for potential cancer induction is estimated to be 10–30 years in the dose ranges used in CTPA.[183] It is an accepted concept among radiation biologists and public health officials that the younger the patient is at the time of exposure, the greater their lifetime risk of developing nonfatal and fatal cancers.

The greater lifetime risk is compounded by the increased biologic susceptibility to radiation induced cancer. Thus, CTPA may not always be the best diagnostic option in young patients or reproductive-age and peri-menopausal women. If CT is indeed justified in this patient population, every effort should be made to reduce the radiation dose, shield the patient, and limit the number of CT examinations performed.[175]

Radiation concerns have also been raised with the use of CT venography for detection of DVT. There is little to be gained by extending CT imaging to the pelvis or lower extremities because isolated pelvic DVT are very rare and ultrasound is very accurate for lower extremity DVT.[47]

Contrast-induced nephropathy is the other safety issue, yet to be evaluated in randomized trials. A meta-analysis suggests that the risk is halved with the low-osmolality contrast agents currently in use and, in PIOPED II, only 1 of 824 patients experienced renal failure.[40] This patient had diabetes, two contrast injections in 24 hours and the renal dysfunction was transient. However, PIOPED II excluded patients with “abnormal creatinine” levels. Data suggest an increase risk for contrast medium-induced nephropathy in pre-existing renal dysfunction, if the serum creatinine pre-exposure is 265μmol/L (3.0mg/dL).[184] In patients presenting to the emergency department with suspected PE, contrast nephropathy (an increase of serum creatinine of 45μmol/L [0.5mg/dL] or a 25% increase within 7 days of CTPA) developed in 4% of patients in one study.[185]

To prevent renal dysfunction in low-risk patients, saline hydration appears to be beneficial. There are conflicting data on the use of *N*-acetylcysteine, but it is recommended in high-risk patients. In those with pre-existing significant dysfunction and diabetics, saline and *N*-acetylcysteine are recommended. Ideally, a V/Q scan would be well suited in these patients.[47]

Contrast allergic reactions may occur after application of larger volumes of contrast media (80–120ml). Mild adverse reactions are encountered after intravenous non-ionic low osmolarity contrast media in up to 3% of patients. Severe and very severe reactions occur much less frequently, with an incidence of 0.22% and 0.04% respectively.[186] In patients with mild allergy, lower extremities ultrasound is recommended. Premedication with steroids has also been recommended if the ultrasound is negative and CTPA is to be performed. However, in most of these cases V/Q scan is recommended first, reserving CTPA for select cases.[47]

TREATMENT of Pulmonary Embolism (PE)

Primary therapy consists of thrombolysis using thrombolytic agents and/or embolectomy (surgery or catheter) which is reserved for high risk patients i.e. those with hemodynamic instability, right ventricular dysfunction, or elevated troponin levels secondary to right ventricular microinfarction and elevated brain natriuretic peptide (BNP) values.[29,62] *Secondary prevention* for recurrent PE consists of anticoagulation with heparin and warfarin or an inferior vena caval filter placement.[29,187]

Adjunctive therapy includes non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief. Opoid analgesics are not recommended because they depress the respiratory function. Dobutamine – a β-adrenoreceptor agonist is effective in treating right heart failure and cardiogenic shock.[29]

Heparin binds and accelerates antithrombin-III enzyme activity which inhibits coagulation factors. Heparin thus prevents additional thrombus formation but does *not* dissolve the already existing thrombus. After 5 to 7 days of intravenous or sub-cutaneous heparin, the residual thrombus begins to stabilize. Heparin can be given in 2 forms, unfractionated heparin or as fragments of unfractionated heparin. The fragments of unfractionated heparin are low-molecular weight heparins which exhibit less binding to plasma proteins, greater bioavailability, better dose response, and causes less heparin-induced thrombocytopenia or osteopenia.[29]

Warfarin, an oral anti-coagulant, is a vitamin K antagonist that prevents γ-carboxylation activation of coagulation factors II, VII, IX and X. Warfarin takes about 5 days to become fully effective. Overlapping warfarin treatment with heparin in the early 5 days is crucial. Warfarin should be avoided in pregnancy due to the risk of embryopathy.[29]

The efficacy of anticoagulation is monitored by using the International Normalised Ratio (INR) levels and the activated partial thromboplastin time. The INR is the ratio of the patient's prothrombin to the control prothrombin multiplied by the international sensitivity index. The INR was introduced by the World Health Organization (WHO) to standardize control of anticoagulant therapy internationally. According to the Prevention of Recurrent Venous Thromboembolism (PREVENT) Trial, the recommended target INR levels for VTE should be between 2.0 to 3.0 since low rates of recurrence have been observed after 6 months of anticoagulation therapy especially if PE is of known origin. The contrary is true for "idiopathic" PE where there are increased rates of recurrence in PE after cessation of anticoagulation therapy at 6 months.[29]

The major life threatening side effect of anticoagulation is haemorrhage, especially with elevated INR levels (should not exceed 5). If haemorrhage occurs, anti coagulants should be withheld and patient given intravenous Vitamin K, cryoprecipitate or fresh frozen plasma infusion. In case of heparin overdosage, protamine sulphate should be used for reversal.[29]

Inferior vena caval filters are indicated if there is active bleeding that obviates anticoagulation or recurrent venous thrombosis unresponsive to anticoagulation. Paradoxically, such filters may provide a nidus for clot formation, may fail by allowing passage of small to medium-sized clots or may be bypassed by thrombi through collateral veins that develop after a PE incident. A common complication of caval thrombosis is marked bilateral lower limb swelling secondary to decreased venous return. Therefore, such filters may double the venous thromboembolism rate in a span of 2 years after placement.[29]

Thrombolysis, according to MAPPET-3 (Management Strategy and Prognosis of Pulmonary Embolism Trial)[33], rapidly reverses right heart failure and decreases the mortality rate and recurrent PE by dissolving both the anatomically obstructing pulmonary arterial thrombus and source of thrombus in the deep lower limb or pelvic veins. Thrombolysis prevents the continued release of neurohumoral factors such as serotonin which exacerbate pulmonary hypertension. The preferred thrombolytic agent is recombinant tissue plasminogen activator (tPA). The major side effect of thrombolysis is intracranial haemorrhage. Contraindications to thrombolysis include intracranial disease, recent surgery or trauma.[29]

Embolectomy can be achieved by open surgery or by catheterization and is indicated in patients with massive PE and those at risk of intracranial haemorrhage with thrombolysis. Pulmonary thromboendarterectomy has been suggested in the management of chronic pulmonary hypertension secondary to previous PE leading

to reduction or remission of pulmonary hypertension.[29]

Primary Prevention or rather prophylaxis against PE is advised in those at increased risk of PE using mechanical (graduated compression stockings and pneumatic compression devices) or pharmacological (anticoagulation) measures. Those at increased risk of PE are patients for major surgical procedures especially in the lower limb, hip, pelvis, thorax and debulking of tumours.[29]

Resolution of PE may be prolonged and it is often problematic for lung scintigraphy or CTPA to distinguish between residual versus recurrent PE. In a systematic review, the percentage of patients with residual thrombi was 87% at 8 days after diagnosis, 68% at 6 weeks, 65% at 3 months, 57% at 6 months, 52% at 11 months. On the basis of such a high percentage of incomplete resolution of PE routine re-imaging should be considered after cessation of anticoagulation therapy in patients with PE to obtain a new baseline if clinically indicated.[188] Resolution of PE may even be more variable. Some have reported rapid resolution of a large PE within hours of the onset of heparin therapy.[189] Fredin and Arborelius[190] noted complete restoration of lung perfusion in patients with PE within 1 week of diagnosis. On the basis of this rapidly changing pattern of perfusion in PE, Coakley[191] recommended that imaging tests for PE diagnosis should be carried out as soon as possible, preferably within 24 hours after onset of symptoms.

Follow up of acute PE. Although decreasing over time from a peak 82.3% at one month, recurring PE per se is still responsible for over 30% of the deaths at 2 years after an acute episode.[192] It should also be noted that the fraction of vascular obstruction (e.g. above or below 50% of pulmonary perfusion) is a significant determinant of overall survival. The most feared long-term consequence of untreated or poorly treated acute PE is chronic thrombo-embolic pulmonary hypertension, a severely debilitating and potentially fatal condition.[32-34] These considerations emphasize the clinical relevance of adequate follow-up after the diagnosis and primary therapy of acute PE, both in the short term and in the long term.[45]

At present, lung perfusion scintigraphy is the imaging procedure of choice for monitoring restoration of pulmonary perfusion after embolism (therefore for monitoring the efficacy of therapy) and for extended follow-up of patients. This technique (which is much more feasible, less expensive, and entails fewer biological risks and lower radiation dosimetry to patients than CT-contrast angiography has proven to mirror improvement in partial pressure of oxygen in arterial blood, which continues up until at least 1 year after the acute episode.[45] Lung scintigraphy should also be considered an integral component of diagnostic screening in all patients with pulmonary hypertension, considering that underlying chronic thromboembolic disease frequently sustains such condition[34,193], even in patients without a clinically obvious episode of acute PE.[194]

Regardless of the diagnostic imaging modality that has ascertained the occurrence of acute PE (either on lung scintigraphy and/or CT angiography), a baseline pulmonary perfusion scan performed at diagnosis or immediately thereafter should be obtained in all patients, to serve as the reference image for subsequent follow-up scans assessing restoration of pulmonary perfusion.[195] Although timing of such imaging follow-up may vary among different clinical practices, the risk of developing chronic thromboembolic pulmonary hypertension is best monitored by sequential perfusion lung scans performed soon after acute PE (i.e. at 1 and 4 weeks), then at 3, 6 and 12 months.[45]

Clinical outcome is considered the ultimate gold standard in judging the clinical utility of testing methods in the diagnosis of venous thromboembolism. As it is impossible to be sure that PE or deep vein thrombosis has not occurred, recurred or persisted, one can only assess the consequences of withholding treatment. Few outcome studies have been performed in patients with spiral CT as the only imaging technique, or in selected patients who have previously undergone V/Q scintigraphy and who have had anticoagulant therapy withheld after negative spiral CT results without additional pulmonary angiography.[111,196,197] In such studies, the incidence of clinically evident recurrent venous thromboembolism during 3–6 months of follow-up was found to range from 0% to 4.8%.[111,196-198] These results are comparable to the results of other studies in patients with a negative pulmonary angiogram that revealed PE within 1 year in 0.6% to 4.2%.[68,199]

PROBLEM STATEMENT

SPECT with a superior contrast resolution has been shown to be more sensitive and specific with a lower non-diagnostic rate than planar imaging in many nuclear medicine studies but it is still not being routinely implemented in V/Q studies at many centres including Tygerberg Hospital.

There are many studies on V/Q SPECT using Technegas as a ventilation agent but very limited studies available on ^{81m} Kr gas.

It is against this background that this study was designed.

OBJECTIVES

To clinically compare conventional planar and SPECT V/Q imaging using ^{81m}Kr gas in the diagnosis of pulmonary embolism, in terms of the sensitivity, specificity and diagnostic accuracy, with CTPA as the gold standard.

To apply the recent 2009 EANM guidelines in planar and SPECT V/Q image interpretation.

To determine the value of the Wells and coworkers model – a simple clinical probability testing tool – in the diagnosis of pulmonary embolism.

PATIENTS & METHODS

A. Study area

The Nuclear Medicine Department of the Tygerberg Hospital, Cape Town, South Africa.

B. Study design

This prospective study was carried out between October 2008 and October 2009.

C. Study population

All patients referred to the Nuclear Medicine Department of the Tygerberg Hospital with clinical suspicion of pulmonary embolism.

D. Sample size

A total of 104 patients were referred to the Nuclear Medicine Department of the Tygerberg Hospital with clinical suspicion of pulmonary embolism. During the initiation of the study, the required sample size was 50 patients as calculated using Power Analysis for ANOVA Designs[200] but only 25 patients were enrolled based on the inclusion and exclusion criteria below.[91]

E. Inclusion criteria

- ✓ Normal (recent i.e. within 24 hours) chest radiograph[$]
- ✓ Normal renal function[#]
- ✓ No contrast allergy[#]

[$]*V/Q scan,* [#]*Contrast enhanced CTPA pre-requisites.*

F. Exclusion criteria

- ✓ Age less than 18 years old
- ✓ Pregnant patients
- ✓ Abnormal chest radiograph
- ✓ Abnormal serum creatinine (≥180μmol/L) / urea (≥10mmol/L) levels
- ✓ Unstable patient (unable to withstand more than 20minutes of imaging)

Note! ^{81m}Kr gas was only available twice a week and thus the study was carried out when ^{81m}Kr gas was available.

G.Sampling method

Consecutive patients were selected using the above inclusion and exclusion criteria and underwent the same study protocol.

STUDY PROTOCOL

Ethical and Medico-Legal Aspects

This study was approved by the Ethics Committee of the Division of Research Development and Support at the University of Stellenbosch. Informed consent (see Appendix) was obtained from all study participants. The information collected during the study was kept confidential – only the research team had access to the study participants' medical records.

Clinical Probability Testing

An independent clinical history was taken by the principal investigator from the patient in addition to the information provided by the referring physician or in the patient's file. Consequently, a score was given to each study participant based on the Wells and co-workers model (Table 1).[47]

Scintigraphic Methods

Most imaging was done on a dual-head gamma cameras – GE (General Electric) Infinia Hawkeye^{TM} (Figure 4) and on some occasions Helix1^{TM}, using a low-energy, high-resolution (LEHR) collimator.

Quality control of the dual-head gamma camera was done before each study by an experienced physicist based on the National Electrical Manufacturers' Association (NEMA) standards.[201,202]

Both V/Q SPECT and V/Q Planar were done on the same dual-head gamma camera, with the patient lying supine position and arms raised above the head (Figure 4 and 5).

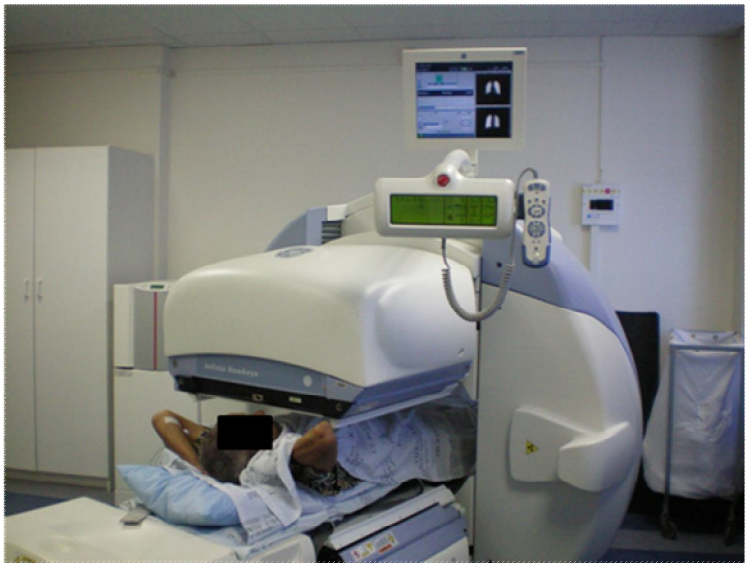


Figure 4 Patient undergoing perfusion scintigraphy on a dual head gamma camera

Figure 5 Patient undergoing ventilation scintigraphy on a dual head gamma camera

Perfusion scintigraphy was performed in a 140keV ± 10% energy window, after intravenous injection of resuspended 125 MBq ^{99m}Tc labelled macro aggregates of albumin (^{99m}Tc MAA) through a saline-flushed large bore (≥ 20G) intravenous catheter with the patient lying in the supine position under tidal breathing. The ^{99m}Tc MAA particles, were resuspended by gently shaking the syringe. The perfusion imaging agent (^{99m}Tc MAA) was injected only once and used for both SPECT perfusion and planar perfusion imaging.

Ventilation scintigraphy was performed in a 190keV ± 10% energy window, with the patient inhaling ^{81m}Kr gas through an air tight mouth mask (Figure 5) via a 3 way tube connected by an inverted Y-connector which was directed cranially, away from patient's chest to decrease background emission. The mouth mask was held in position by a member of the nuclear medicine personnel.^{81m}Kr gas was eluted at 3L/min from a 555 MBq (15mCi) ^{81}Rb generator produced from a cyclotron at iThemba Labs, CapeTown South Africa which was only available twice a week. ^{81m}Kr gas was continuously inhaled by the patient for both SPECT ventilation and planar ventilation imaging.

SPECT was performed before planar acquisition. Perfusion and ventilation SPECT were both acquired in the same position, using a step and shoot technique of 3^0 a step of 10 seconds each (60 projections per head), on a 128 X 128 matrix over 360^0 (120 projections in total). Perfusion SPECT images were acquired before ventilation SPECT images.

Total acquisition time for both perfusion and ventilation SPECT was 20 minutes.

Planar imaging was done immediately after SPECT. Planar images consisted of 6 standard views (ANT, POST, RLAT, LLAT, RPO and LPO) for both perfusion and ventilation. Each view had at least 300,000 counts and acquired on a 256 X 256 matrix. A perfusion image for each standard view was immediately followed by a corresponding standard view for the ventilation, in the same position. Total acquisition time was 30 minutes.

All images acquired were transferred via network to a HERMES workstation for storage and processing.

For accurate interpretation and reporting, Planar ventilation and perfusion images were concatenated into 6 standard pairs of views (a total of 12 images), saved and viewed next to each other in a HERMES workstation in the following order (ANT PERF, ANT VENT; POST PERF, POST VENT, RLAT PERF, RLAT VENT, RPO PERF, RPO VENT, LLAT PERF, LLAT VENT, LPO PERF and LPO VENT).

All SPECT perfusion and ventilation images were reconstructed using ordered-subset expectation-maximization (OSEM) algorithm of 8 iterations and 4 subsets. A post-reconstruction 3D Butterworth filter was applied to the perfusion images (cut off frequency of 0.8 cycles per cm and an order of 9) and ventilation images (cut off frequency of 1.1 cycles per cm and an order of 5).

No correction for photon attenuation or scatter was applied. A set of saved co-registered images of each patient were viewed with a HERMES volume fusion display dual application as maximum intensity projection (MIP) movie, coronal, transverse, and sagittal slices on a HERMES workstation.

Standard reports were routinely issued mainly based on planar scintigraphic findings and modified PIOPED criteria (Table 4) to the referring physician.

V/Q Planar and SPECT images were later evaluated and reviewed separately by an experienced nuclear medicine physician and the principal investigator blinded to clinical data and CTPA findings. The scintigraphic findings of V/Q Planar and SPECT images were later compared with CTPA findings.

Reader confidence in the interpretation of the V/Q Planar and SPECT images was qualitatively assessed as; high (100%) if defects can be clearly defined or low (50%) if defects cannot be clearly defined.

The final interpretation, review and consensus of both V/Q Planar and SPECT was based on recent EANM guidelines for ventilation and perfusion scintigraphy[42,43],

Positive for PE:

- V/Q mismatch of at least one segment or two subsegments that conforms to the pulmonary vascular anatomy i.e. lobar, segmental and subsegmental

Negative for PE:

- Normal perfusion pattern conforming to the anatomic boundaries of the lungs
- Matched or reverse mismatch V/Q defects of any size, shape or number in the absence of mismatch
- Mismatch that does not have a lobar, segmental or subsegmental pattern

Non-diagnostic for PE:

- Multiple V/Q abnormalities not typical of specific diseases

CT Pulmonary Angiography

After V/Q imaging, all study participants were referred for a CT Pulmonary Angiogram (CTPA) on the same day. Multislice spiral CT examinations were done on a 40-detector row scanner (Siemens SOMATOM Sensation) (Figure 6)

Figure 6 CT scanner – Siemens SOMATOM Sensation 40

The patient lying supine and head first in CT scanner, was scanned from superior to inferior thoracic inlet, down to the diaphragm during inspiration. Un-enhanced scout and axial scan (topogram) was first obtained over 0.2s at 100kV, 40mA, slice thickness (0.6mm).

Using an automatic injector / infusion pump connected to a large bore intravenous catheter (≥ 20G) on the upper limb of the patient, a 20ml saline bolus preceded the 80ml of contrast medium (Ultravist 300) at a flow rate of 4mL per second. The contrast medium was followed by a 40ml saline chaser bolus.

After an automatic trigger at 80Hu, and when contrast medium was within the pulmonary artery, CTPA was acquired. Scan parameters were; 100kV, 135 mA, slice thickness (3mm). The entire chest was examined in 10 seconds.

Reconstruction of images was done using CT Angio window ("smooth"; Siemens B25f) and lung window ("very sharp"; Siemens B70f) into the axial slices (0.75mm slice thickness). The images were later assessed and reported on a separate computer workstation by at least two experienced radiologists blinded to the V/Q scan results.

Statistical Analysis

Statistical analysis was done using STATISTICA^{TM} version 7.1, in consultation at the Centre for Statistical Consultations of the University of Stellenbosch. The Fisher exact test was used for comparison of categorical variables. The One-way ANOVA was used for comparison of continuous variables (e.g. age); $p<0.05$ was considered significant.

RESULTS

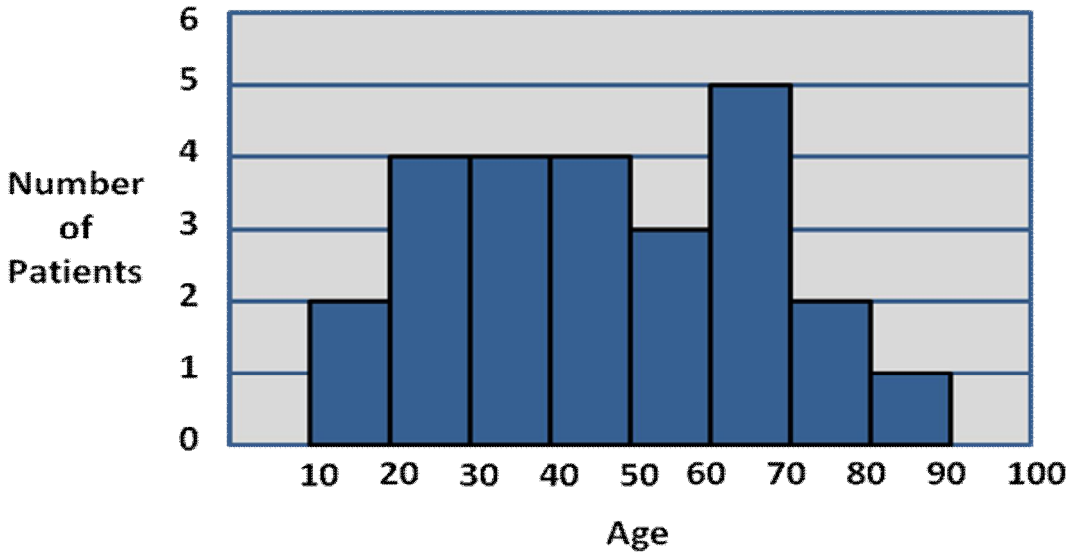
Over a period of 1 year, between October 2008 and October 2009, a total of 104 consecutive patients were referred to our nuclear medicine department with clinical suspicion of pulmonary embolism were assessed. Only 25 patients were included in this study. Seventy nine patients were excluded from this study mostly due to abnormal serum creatinine / urea levels or renal impairment.

Table 8 Characteristics of the study population (n=25);

Characteristic	*Number (Percentage)*
Age ≥ 60 years	8/25 (32%)
Sex (females)	16/25 (64%)
Referral (outpatients)	13/25 (52%)
Shortness of Breath	21/25 (84%)
Chest pain	13/25 (52%)
Underlying cardiovascular disorders	10/25 (40%)
Lower limb swelling and pain	6/25 (24%)
Pulmonary hypertension	5/25 (20%)
Systemic lupus erythematosus (SLE)	4/25 (16%)
Palpitations	3/25 (12%)
Malignancy	3/25 (12%)
Polycythaemia	2/25 (8%)

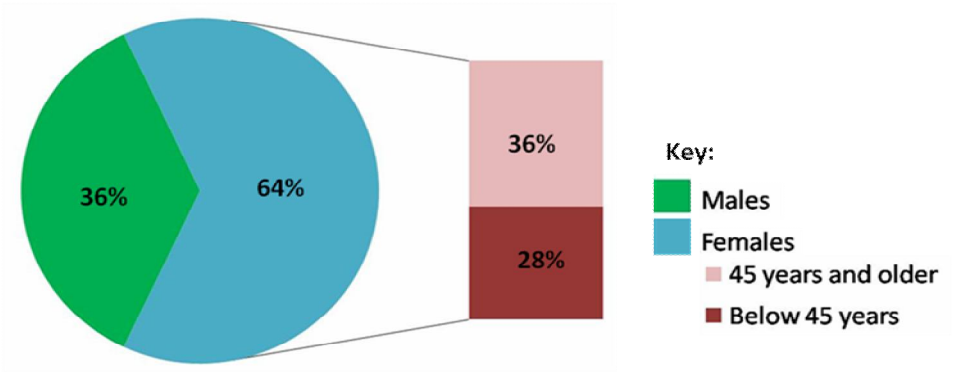
Shortness of breath was the commonest symptom (84%), followed by chest pain (52%). DVT was confirmed in one of the patients with lower limb swelling and pain. Twenty per cent presented with pulmonary hypertension while 16% had SLE.

Table 9A Age against number of patients (n=25);



The youngest patient was 19 years and oldest was 88 years (only one patient over 80 years of age). The commonest age group that was referred for PE was 60 to 70 years. The overall mean age ± std. dev. was 48 ±19 years.

Table 9B Pie Chart of Sex (n=25);



64% (16 out of 25) were females with 28% (7 out of 25) being below the age of 45years.

Table 10 PE Yes or No – V/Q Planar compared to CTPA as gold standard;

CTPA	V/Q Planar		Total
	No	Yes	
No	19	2	21
Yes	1	3	4
Total	20	5	25

Prevalence of PE (4/25) = 16% [5% – 37% at 95% CI]

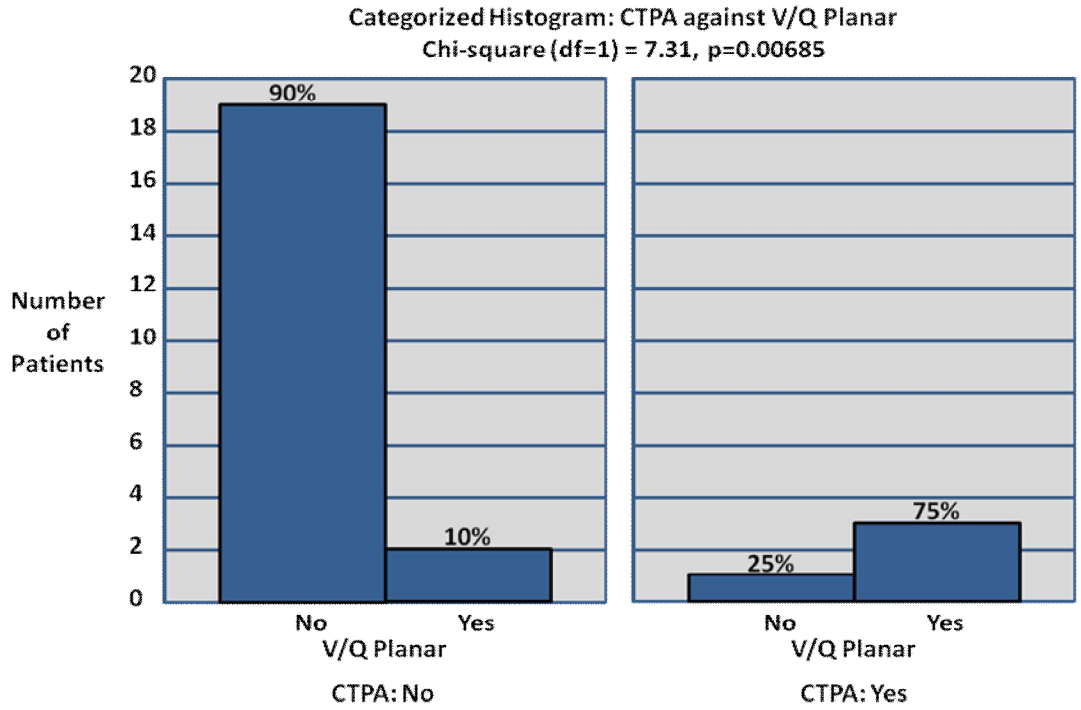
Sensitivity (3 /4) = 75% [21% – 99% at 95% CI]

Specificity (19/21) = 90% [68% – 98% at 95% CI]

Positive predictive value (3/5) = 60% [17% – 93% at 95% CI]

Negative predictive value (19/20) = 95% [73% – 100% at 95% CI]

Diagnostic Accuracy (3+19/25) = 88% [69% – 97%at 95% CI]



When V/Q Planar was compared to CTPA as gold standard, 90% of the PE negative on CTPA group had PE excluded on V/Q Planar.This was statistically significant ($p<0.00685$).

Table 11 PE Yes or No – V/Q SPECT compared to CTPA as gold standard;

CTPA	V/Q SPECT		Total
	No	Yes	
No	19	2	21
Yes	1	3	4
Total	20	5	25

Prevalence of PE (4/25) = 16% [5% – 37% at 95% CI]

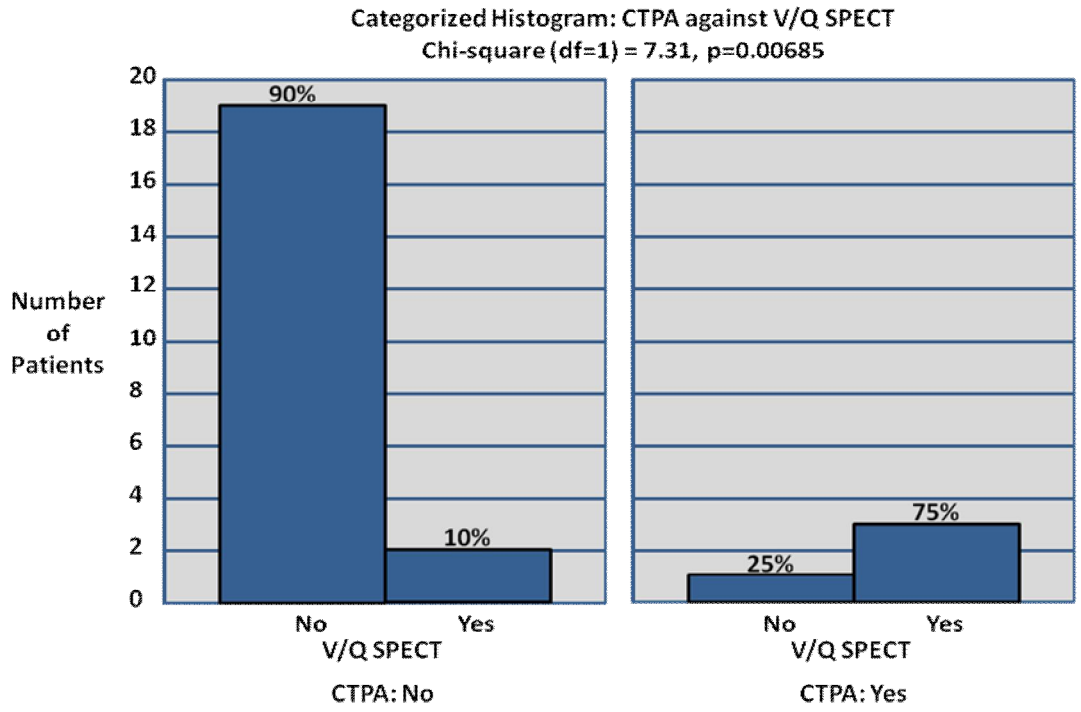
Sensitivity (3 /4) = 75% [21% – 99% at 95% CI]

Specificity (19/21) = 90% [68% – 98% at 95% CI]

Positive predictive value (3/5) = 60% [17% – 93% at 95% CI]

Negative predictive value (19/20) = 95% [73% – 100% at 95% CI]

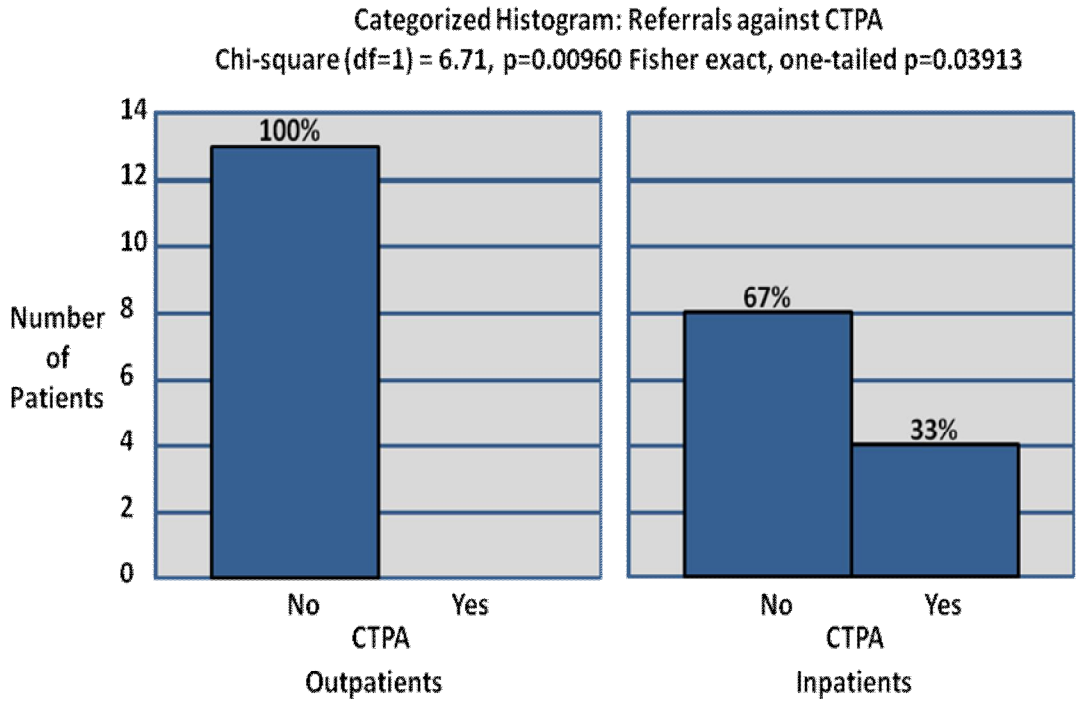
Diagnostic Accuracy (3+19/25) = 88% [69% – 97%at 95% CI]



When V/Q SPECT was compared to CTPA as gold standard, 90% of the PE negative on CTPA group had PE excluded on V/Q SPECT.This was statistically significant ($p<0.00685$).

Table 12 PE Yes or No – CTPA according to referrals;

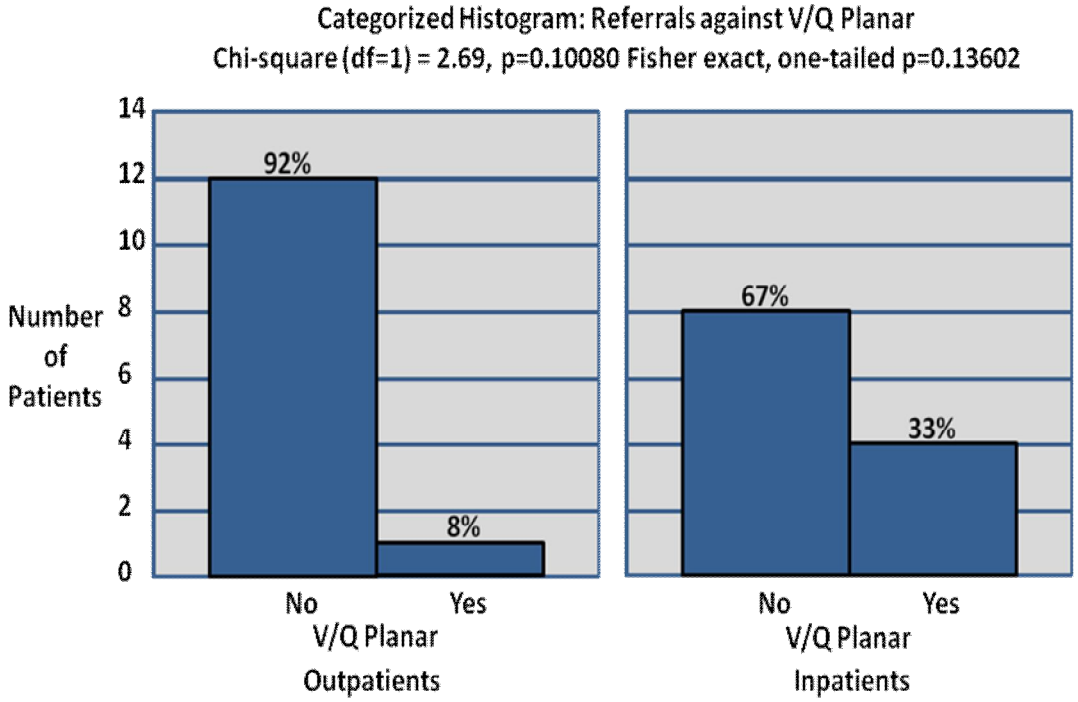
Referrals	CTPA		Total
	No	Yes	
Outpatients	13	0	13
Inpatients	8	4	12
Total	21	4	25



PE was more common amongst inpatients (33%) than outpatients on CTPA. This was statistically significant (p=0.00960).

Table 13 PE Yes or No – V/Q Planar according to referrals;

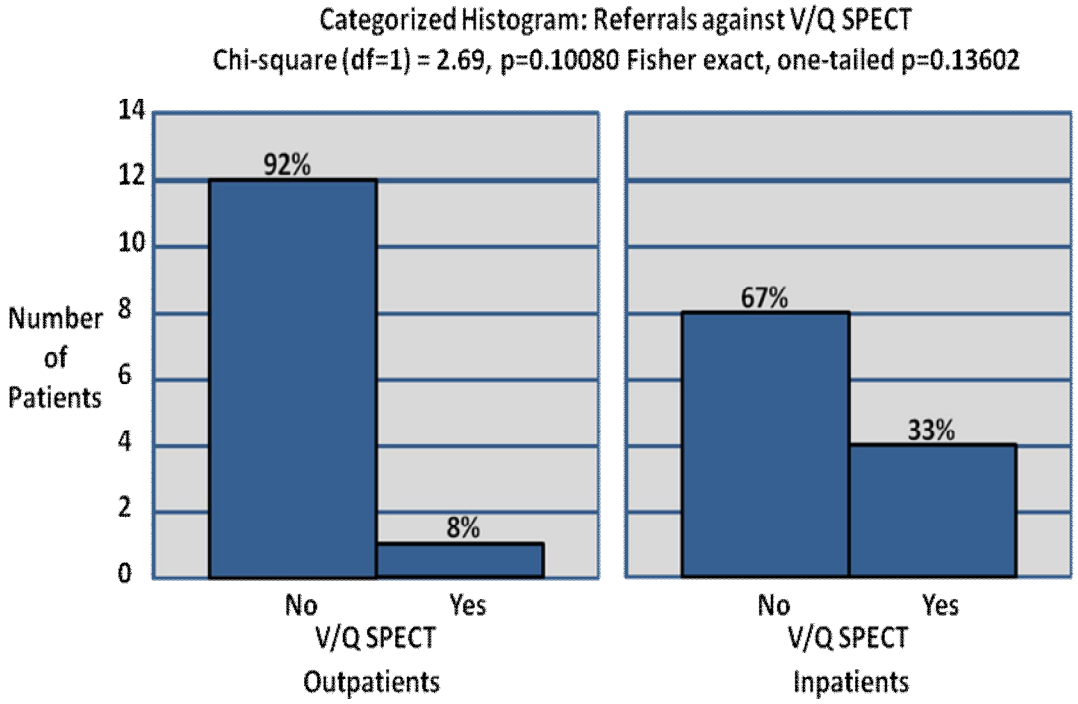
Referrals	V/Q Planar		Total
	No	Yes	
Outpatients	12	1	13
Inpatients	8	4	12
Total	20	5	25



33% of inpatients had PE on V/Q Planar compared to outpatients (8%). This was not statistically significant (p=0.10080).

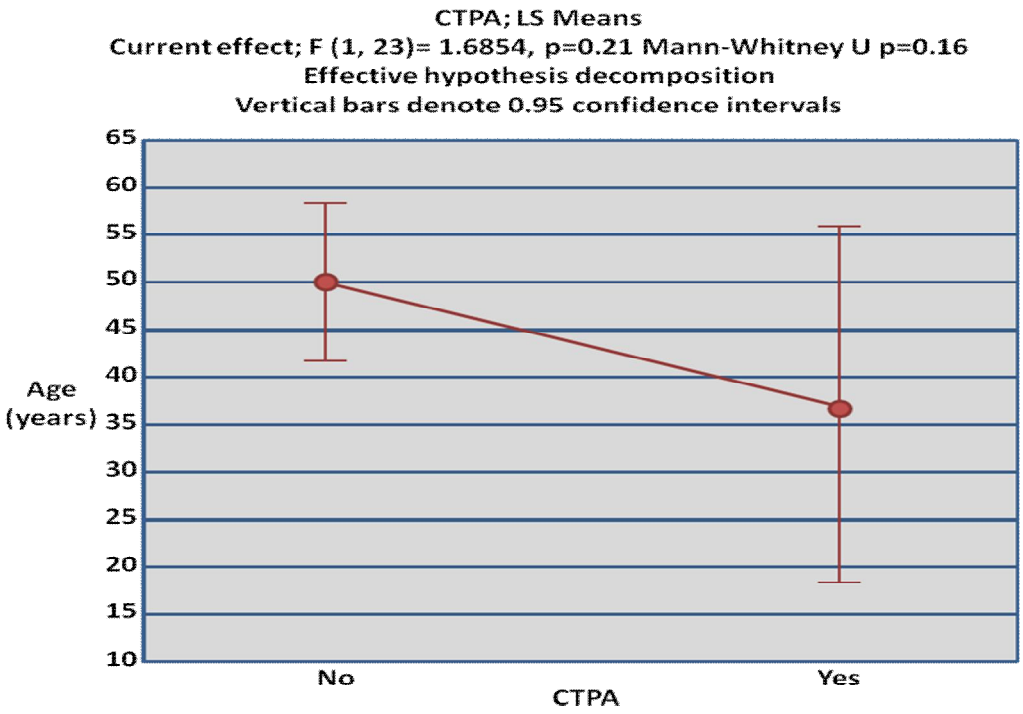
Table 14 PE Yes or No – V/Q SPECT according to referrals;

Referrals	V/Q SPECT		Total
	No	Yes	
Outpatients	12	1	13
Inpatients	8	4	12
Total	20	5	25



33% of inpatients had PE on V/Q SPECT compared to outpatients (8%). This was not statistically significant (p=0.10080).

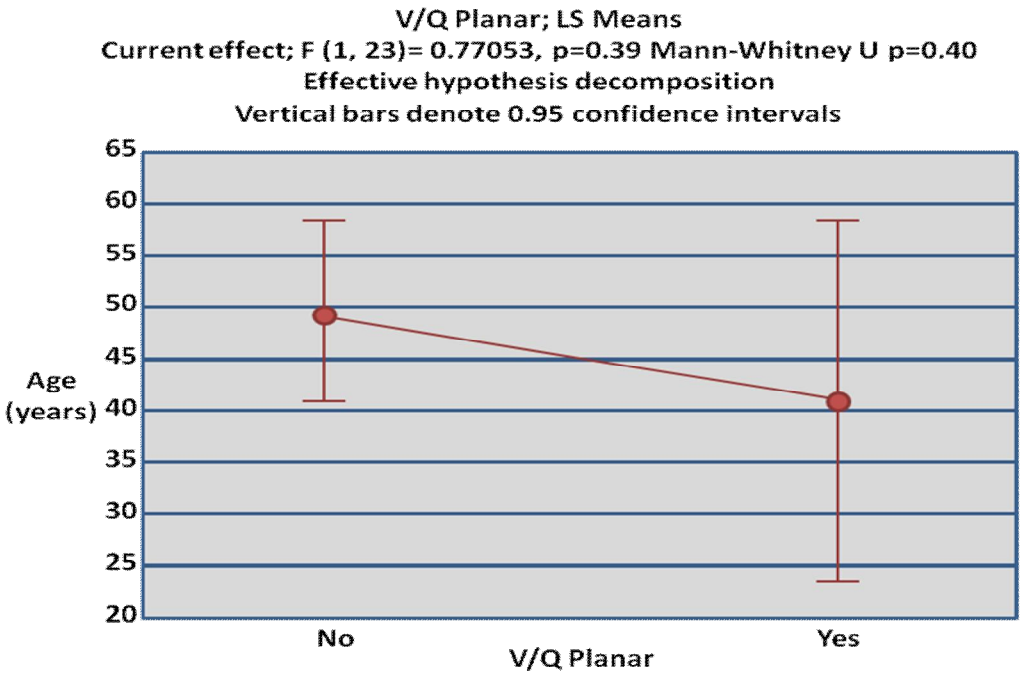
Table 15 PE Yes or No – Least Square Means of CTPA against Age;



Effect	Descriptive Statistics						
	Level of Factor	n	Age Mean	Age Std. Dev.	Age Std. Error	Age -95.00%	Age +95.00%
Total		25	48.04	18.82	3.76	40.27	55.81
CTPA	**No**	21	50.14	19.26	4.20	41.37	58.91
CTPA	**Yes**	4	37.00	12.88	6.44	16.50	57.50

On CTPA, the PE positive group had a lower mean age ± std. dev. (37 ± 13 years) compared to PE negative group (48 ± 19 years). This was not statistically significant (p=0.21).

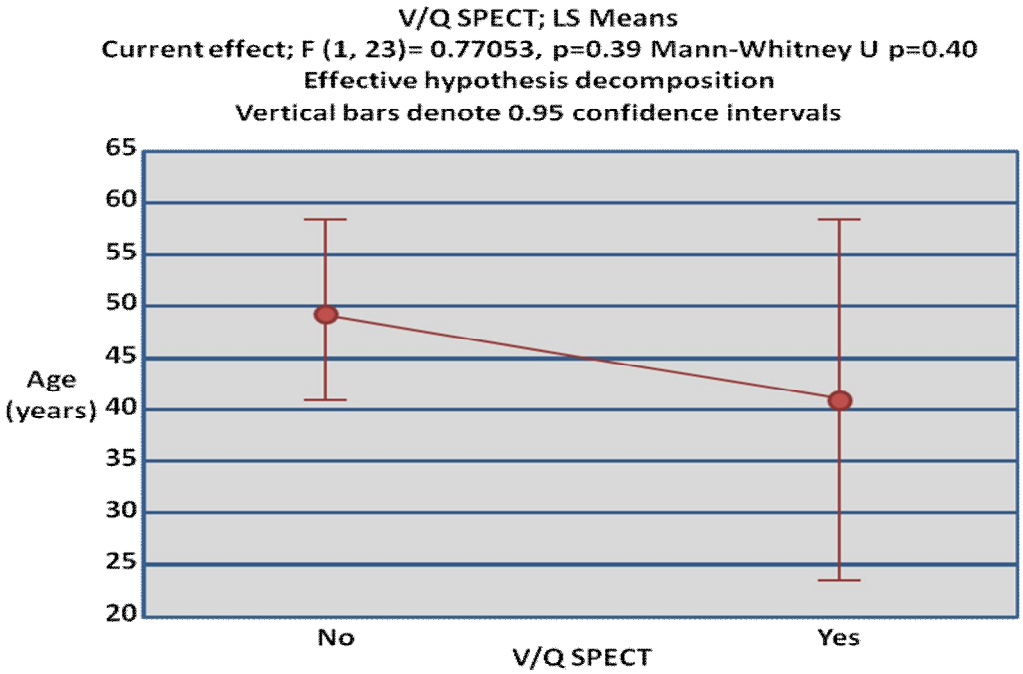
Table 16 PE Yes or No – Least Square Means of V/Q Planar against Age;



Effect	Descriptive Statistics						
	Level of Factor	n	Age Mean	Age Std. Dev.	Age Std. Error	Age -95.00%	Age +95.00%
Total		25	48.04	18.82	3.76	40.27	55.81
V/Q Planar	**No**	20	49.70	18.69	4.18	40.95	58.45
V/Q Planar	**Yes**	5	41.40	19.92	8.91	16.67	66.13

With V/Q Planar, the PE negative group had a higher mean age ± std. dev. (50 ± 19 years) compared to PE positive group (41 ± 20 years). This was not statistically significant (p=0.39).

Table 17 PE Yes or No – Least Square Means of V/Q SPECT against Age;

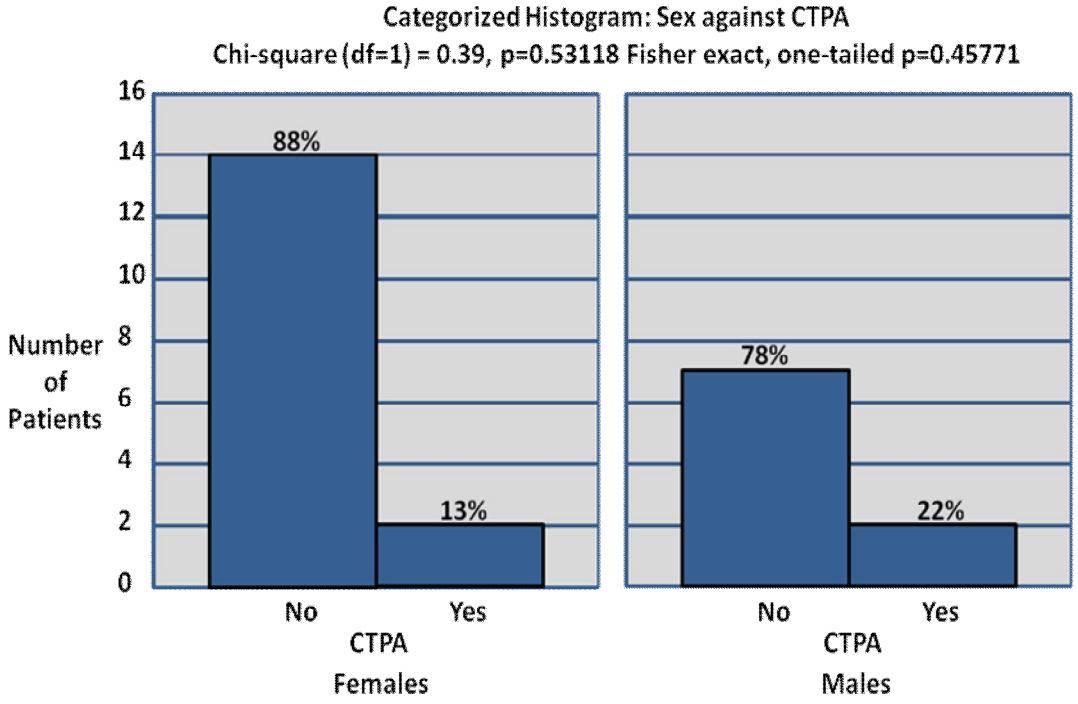


Effect	Descriptive Statistics						
	Level of Factor	n	Age Mean	Age Std. Dev.	Age Std. Error	Age -95.00%	Age +95.00%
Total		25	48.04	18.82	3.76	40.27	55.81
V/Q SPECT	**No**	20	49.70	18.69	4.18	40.95	58.45
V/Q SPECT	**Yes**	5	41.40	19.92	8.91	16.67	66.13

With V/Q SPECT, the PE negative group had a higher mean age ± std. dev. (50 ± 19 years) compared to PE positive group (41 ± 20 years). This was not statistically significant (p=0.39).

Table 18 PE Yes or No – CTPA according to sex;

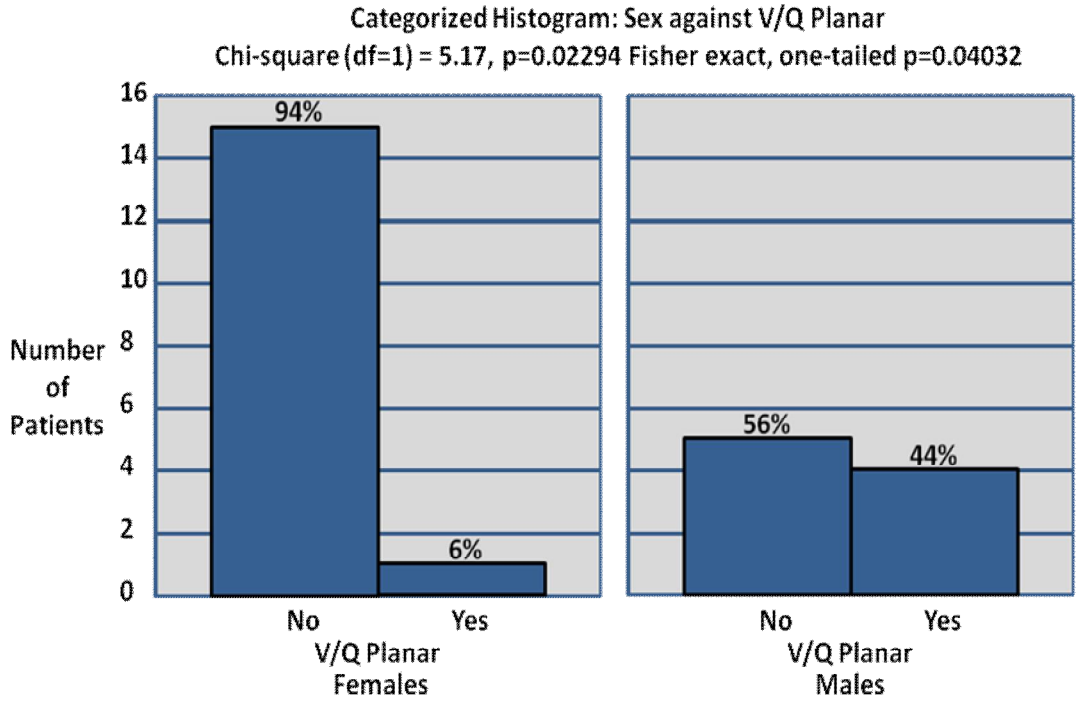
Sex	CTPA		Total
	No	Yes	
Females	14	2	16
Males	7	2	9
Total	21	4	25



On CTPA, 22% of males were PE positive compared to 13% females. This was not statistically significant (p=0.53).

Table 19 PE Yes or No – V/Q Planar according to sex;

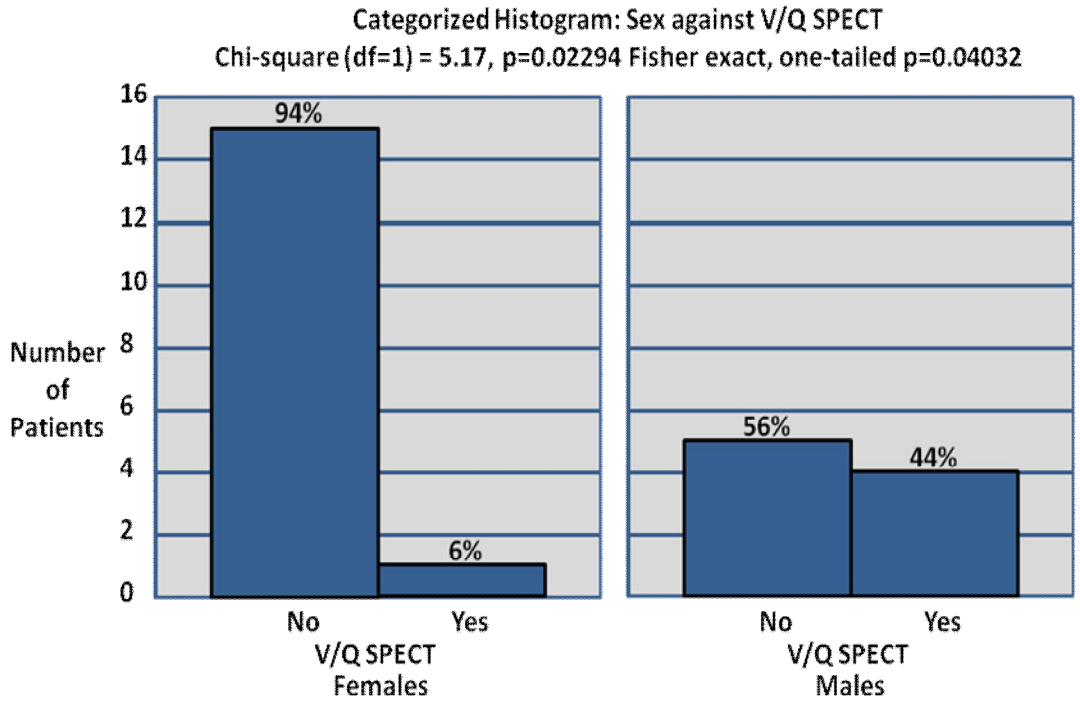
Sex	V/Q Planar		Total
	No	Yes	
Females	15	1	16
Males	5	4	9
Total	20	5	25



On V/Q Planar, 44% of males were PE positive compared to 6% of females. This was statistically significant (p=0.02).

Table 20 PE Yes or No – V/Q SPECT according to sex;

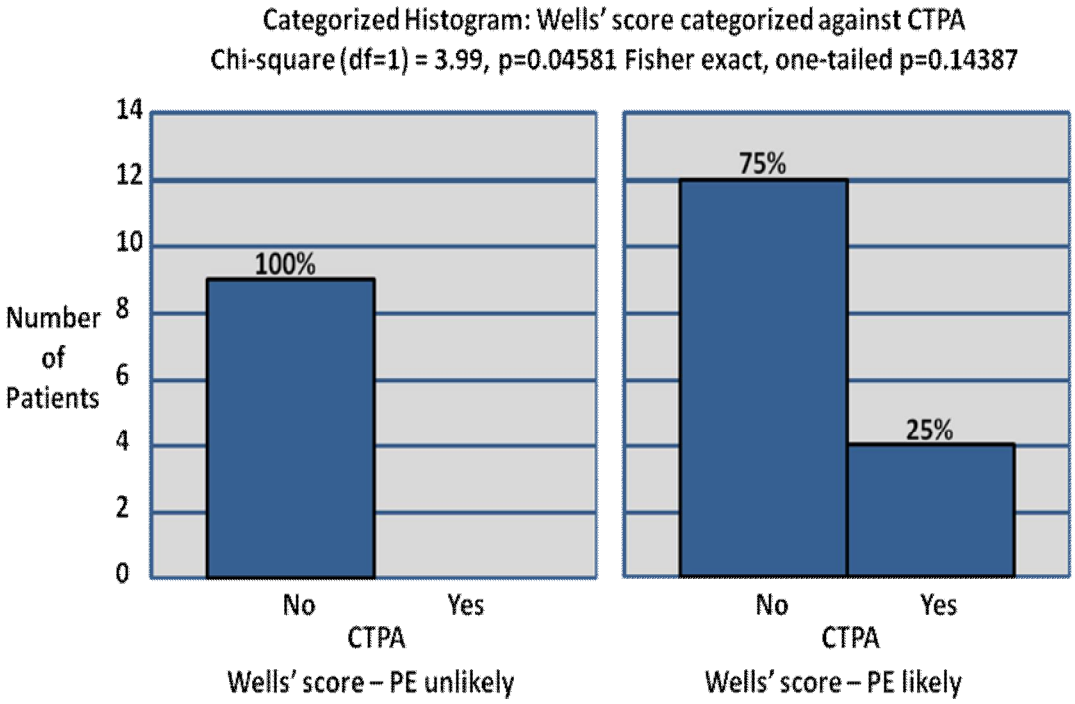
Sex	V/Q SPECT		Total
	No	Yes	
Females	15	1	16
Males	5	4	9
Total	20	5	25



On V/Q SPECT, 44% of males were PE positive compared to 6% of females. This was statistically significant (p=0.02).

Table 21 PE Yes or No – CTPA according to a categorized Wells' score;

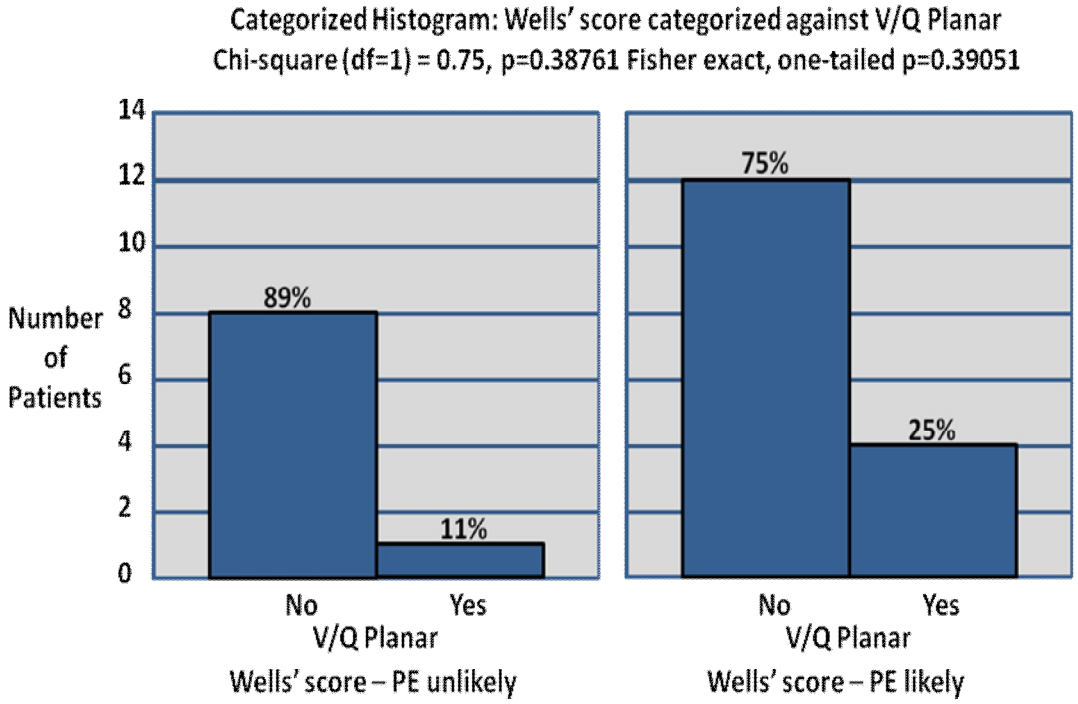
Wells' Score categorized	CTPA		Total
	No	Yes	
PE unlikely (≤4)	9	0	9
PE likely (>4)	12	4	16
Total	21	4	25



Using the Wells' score, all patients who were scored as PE unlikely had PE ruled out on CTPA. Only 25% with a PE likely Well's score (>4) went on to be diagnosed with PE on CTPA. This was statistically significant (p=0.04581).

Table 22 PE Yes or No – V/Q Planar according to a categorized Wells' score;

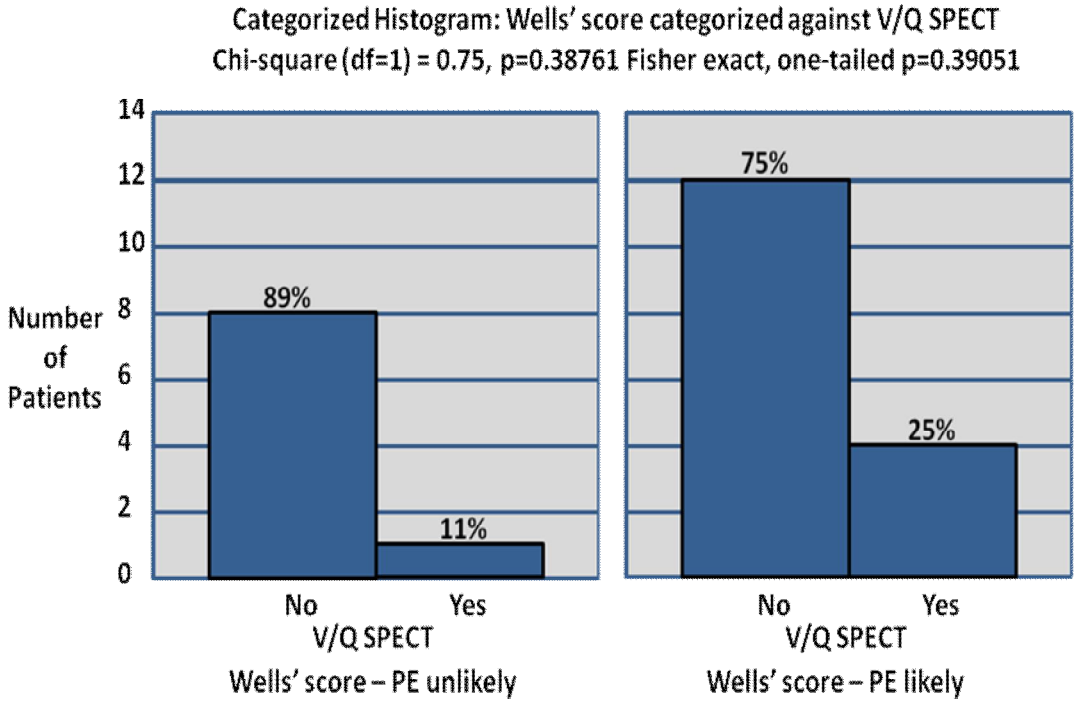
Wells' Score categorized	V/Q Planar		Total
	No	Yes	
PE unlikely (≤4)	8	1	9
PE likely (>4)	12	4	16
Total	20	5	25



Using the Wells' score, 89% of patients who were scored as PE unlikely had PE ruled out on V/Q Planar. Only 25% with a PE likely Well's score (>4) went on to be diagnosed with PE on V/Q Planar. This was not statistically significant (p=0.38761).

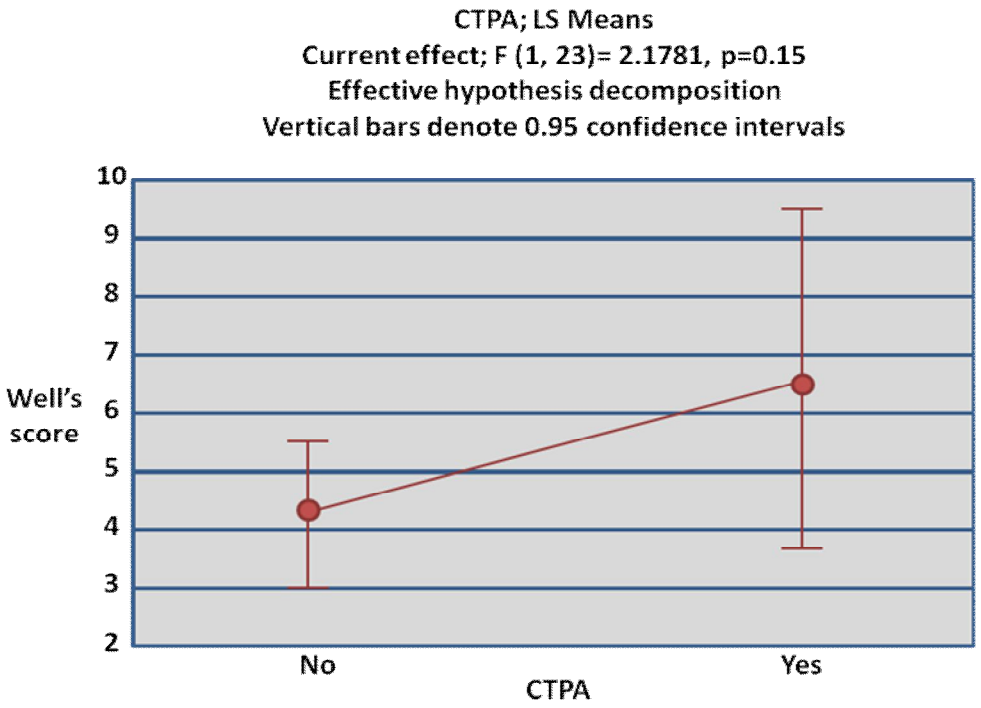
Table 23 PE Yes or No – V/Q SPECT according to a categorized Wells' score;

Wells' Score categorized	V/Q SPECT		Total
	No	Yes	
PE unlikely (≤4)	8	1	9
PE likely (>4)	12	4	16
Total	20	5	25



Using the Wells' score, 89% of patients who were scored as PE unlikely had PE ruled out on V/Q SPECT. Only 25% with a PE likely Well's score (>4) went on to be diagnosed with PE on V/Q SPECT. This was not statistically significant (p=0.38761).

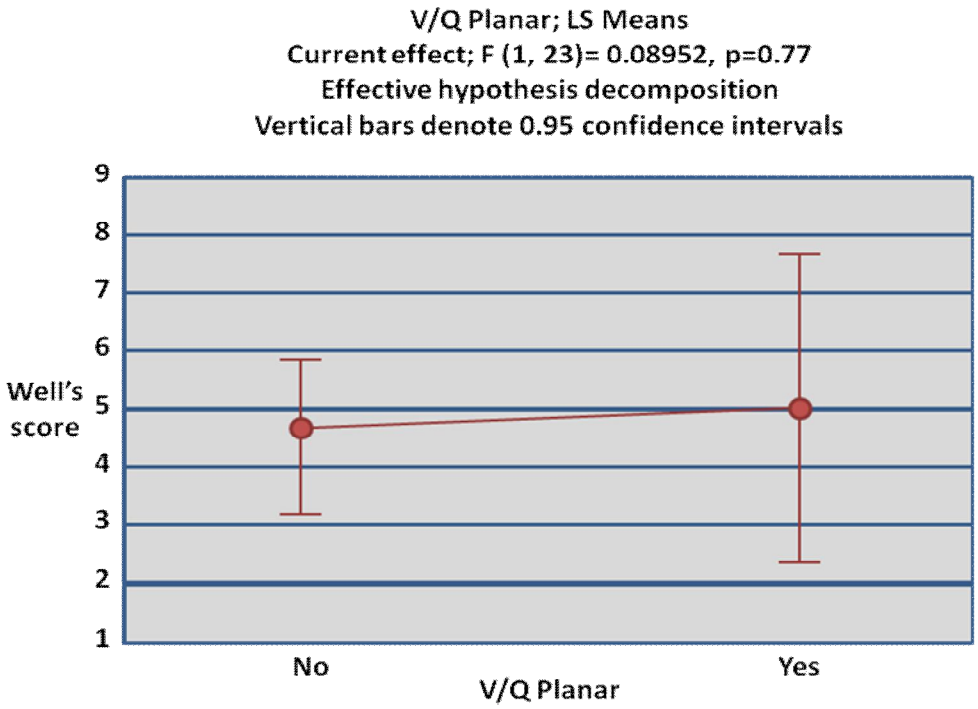
Table 24 PE Yes or No – Least Square Means of CTPA against Wells' score;



Effect		Descriptive Statistics					
	Level of Factor	n	Wells' score Mean	Wells' score Std. Dev.	Wells' score Std. Error	Wells' score -95.00%	Wells' score +95.00%
Total		25	4.66	2.79	0.56	3.51	5.81
CTPA	**No**	21	4.31	2.90	0.63	2.99	5.62
CTPA	**Yes**	4	6.50	0.91	0.46	5.05	7.95

On CTPA, a higher mean Wells' score ± std. dev. (6.5 ± 0.9) increased the likelihood of being PE positive while a lower mean Wells' score ± std. dev (4.3 ± 2.9) tended to be PE negative. This was not statistically significant (p=0.15).

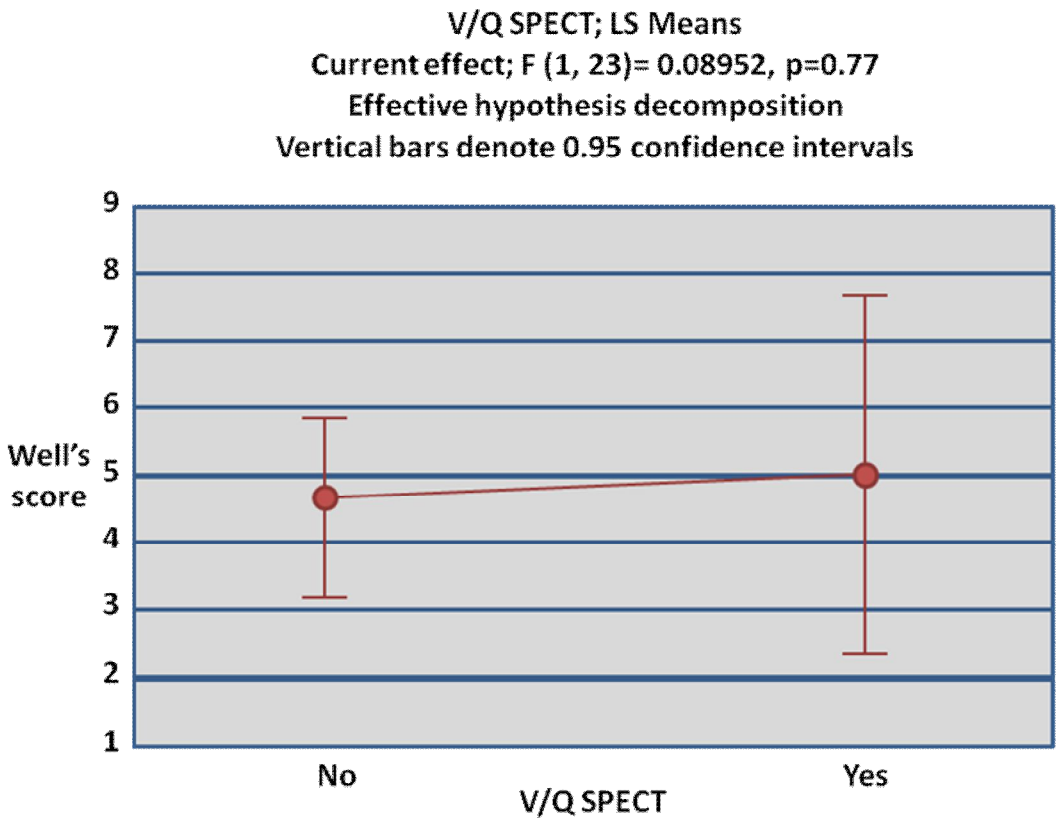
Table 25 PE Yes or No – Least Square Means of V/Q Planar against Wells' score;



Effect		Descriptive Statistics					
	Level of Factor	n	Wells' score Mean	Wells' score Std. Dev.	Wells' score Std. Error	Wells' score -95.00%	Wells' score +95.00%
Total		25	4.66	2.79	0.56	3.51	5.81
V/Q Planar	**No**	20	4.58	2.80	0.62	3.26	5.88
V/Q Planar	**Yes**	5	5.00	3.02	1.35	1.25	8.75

With V/Q Planar, the PE negative group had a lower mean Wells' score ± std. dev. (4.6 ± 2.8) while the PE positive group had a higher mean Wells' score ± std. dev. (5.0 ± 3.0). This was not statistically significant (p=0.77).

Table 26 PE Yes or No – Least Square Means of V/Q SPECT against Wells' score;



Effect		Descriptive Statistics					
	Level of Factor	n	Wells' score Mean	Wells' score Std. Dev.	Wells' score Std. Error	Wells' score -95.00%	Wells' score +95.00%
Total		25	4.66	2.79	0.56	3.51	5.81
V/Q SPECT	**No**	20	4.58	2.80	0.62	3.26	5.88
V/Q SPECT	**Yes**	5	5.00	3.02	1.35	1.25	8.75

With V/Q SPECT, the PE negative group had a lower mean Wells' score ± std. dev. (4.6 ± 2.8) while the PE positive group had a higher mean Wells' score ± std. dev. (5.0 ± 3.0). This was not statistically significant (p=0.77).

Table 27 V/Q Planar and V/Q SPECT according to number, size, type of defects, and reader confidence in interpretation compared CTPA findings (n=25);

ID	V/Q Planar Defects					V/Q SPECT Defects					Comment	CTPA PE (additional findings)
	No.	Size	Type	Reader Confidence	PE	No.	Size	Type	Reader Confidence	PE		
1	0	-	-	100%	No	0	-	-	100%	No	Planar = SPECT	No
2	>3	segmental	mismatch	100%	Yes	>3	segmental	mismatch	100%	Yes	Planar = SPECT	Yes
3	1	segmental	?match	**50%**	No	1	segmental	match	100%	No	Clearly defined on SPECT	No (Pulmonary nodule)
4	0	-	-	100%	No	0	-	-	100%	No	Planar = SPECT	No (Incidental liver lesion)
5	3	2segmental, 1 sub-segmental	match	**50%**	No	3	2segmental, 1sub-segmental	2segmental match, 1 sub-segmental mismatch	100%	No	1 sub-segmental defect match on planar was a mismatch on SPECT	No (Incidental thyroid lesion, kidney cyst)
6	1	sub-segmental	mismatch	100%	No	1	sub-segmental	mismatch	100%	No	Planar = SPECT	No (Degenerative thoracic spine)
7	0	-	-	100%	No	0	-	-	100%	No	Normal	No
8	0	-	-	100%	No	0	-	-	100%	No	Normal	No (Pneumonic changes)
9	>3	segmental	mismatch	100%	Yes	>3	segmental	mismatch	100%	Yes	Planar = SPECT	Yes
10	3	segmental	2 segmental match, 1 non segmental mismatch	**50%**	No	2	segmental	1segmental match, 1 non-segmental mismatch	100%		SPECT detected shine through from the contralateral lung, read as a segmental match defect on Planar	No

Table 27 continued...

ID	V/Q Planar Defects					V/Q SPECT Defects					Comment	CTPA PE (additional findings)
	No.	Size	Type	Reader Confidence	PE	No.	Size	Type	Reader Confidence	PE		
11	>3	segmental	mismatch	**50%**	Yes	>3	segmental	mismatch	100%	Yes	Clearly defined on SPECT	Yes
12	2	2 sub-segmental	mismatch	100%	Yes	2	2 sub-segmental,	mismatch,	100%	Yes	Planar = SPECT Fissure sign noted	No
13	0	-	-	100%	No	0	-	-	100%	No	Planar = SPECT	No
14	3	segmental	2 reverse mismatch,1 non-segmental match	100%	No	3	segmental	2 reverse mismatch, 1 non-segmental match	100%	No	Planar = SPECT	No (Solitary pulmonary nodule, mediastinal lymphadenopathy degenerative thoracic spine)
15	1	segmental	non-segmental match	**50%**	No	2	1 segmental, 1 additional sub-segmental	1 segmental match, 1 additional sub-segmental mismatch	100%	No	SPECT detected shine through from the contralateral lung, read as a non-segmental match defect on Planar. (See Figure 7a and 7b)	No
16	1	segmental	reverse mismatch	100%	No	1	segmental	reverse mismatch	100%	No	Planar = SPECT	No (Pleural effusion, cysts, mediastinal lymphadenopathy)
17	1	sub-segmental	mismatch	**50%**	No	1	sub-segmental	match	100%	No	Matched defect on SPECT-the mismatch on planar was arising from overlying tracheal activity	No (Pleural mass, granulomas)
18	1	sub-segmental	mismatch	100%	No	1	sub-segmental	mismatch	100%	No	Planar = SPECT	No (Nodule, pleural thickening)
19	0	-	-	100%	No	0	-	-	100%	No	Planar = SPECT	No (Degenerative thoracic spine)
20	0	-	-	100%	No	0	-	-	100%	No	Planar = SPECT	No (Pleural effusion)

Table 27 continued...

ID	V/Q Planar Defects					V/Q SPECT Defects					Comment	CTPA PE (additional findings)
	No.	Size	Type	Reader Confidence	PE	No.	Size	Type	Reader Confidence	PE		
21	1	segmental	match	**50%**	No	2	1 segmental, 1 additional segmental	All match	100%	No	Clearly defined on SPECT Fissure sign noted	No (Post infective changes, granulomas, pleural thickening)
22	>3	segmental	mismatch	100%	Yes	>3	segmental	mismatch	100%	Yes	Planar = SPECT (Figure 8a and 8b)	No
23	0	-	-	100%	No	0	-	-	100%	No	Planar = SPECT	No
24	0	-	-	100%	No	0	-	-	100%	No	Planar = SPECT	No (Solitary pulmonary nodule)
25	1	segmental	mismatch	100%	No	1	segmental	mismatch	100%	No	Planar = SPECT (Figure 9a,9b and 9c)	Yes

Both V/Q Planar and SPECT had the same number of PE positive cases based on the recent EANM V/Q scintigraphy guidelines[42,43]. V/Q Planar could not clearly resolve defects in 28% cases (7 out of 25) as shown by the 50% reader confidence compared to V/Q SPECT which could clearly resolve all cases. CTPA detected additional findings in 52% (13 out of 25).

Figure 7a Case One (Below **V/Q Planar** images)

Findings; Left apico-posterior non-segmental match defect – *arrows* (PE negative). PERF=pefusion, vent=ventilation.

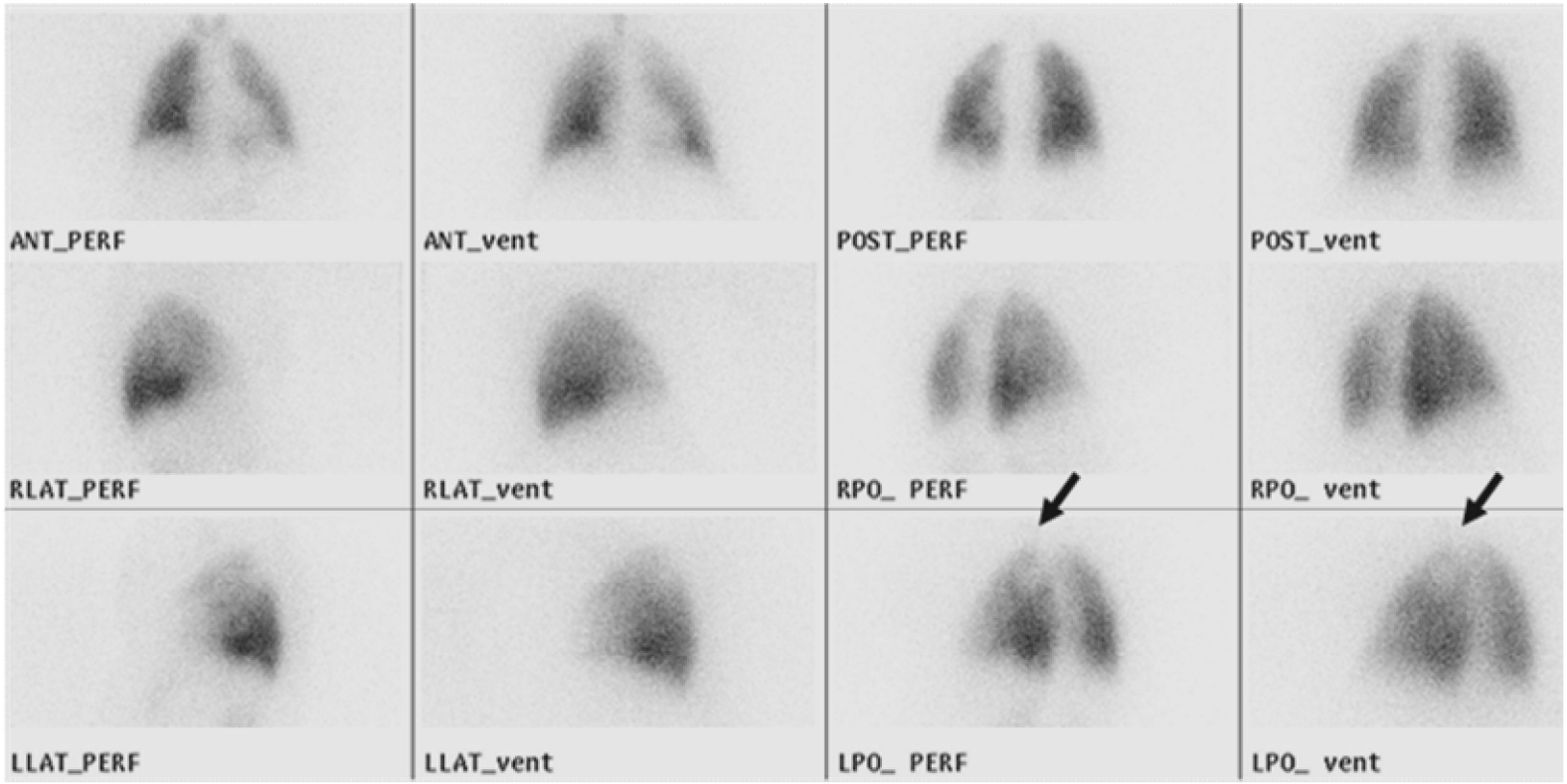
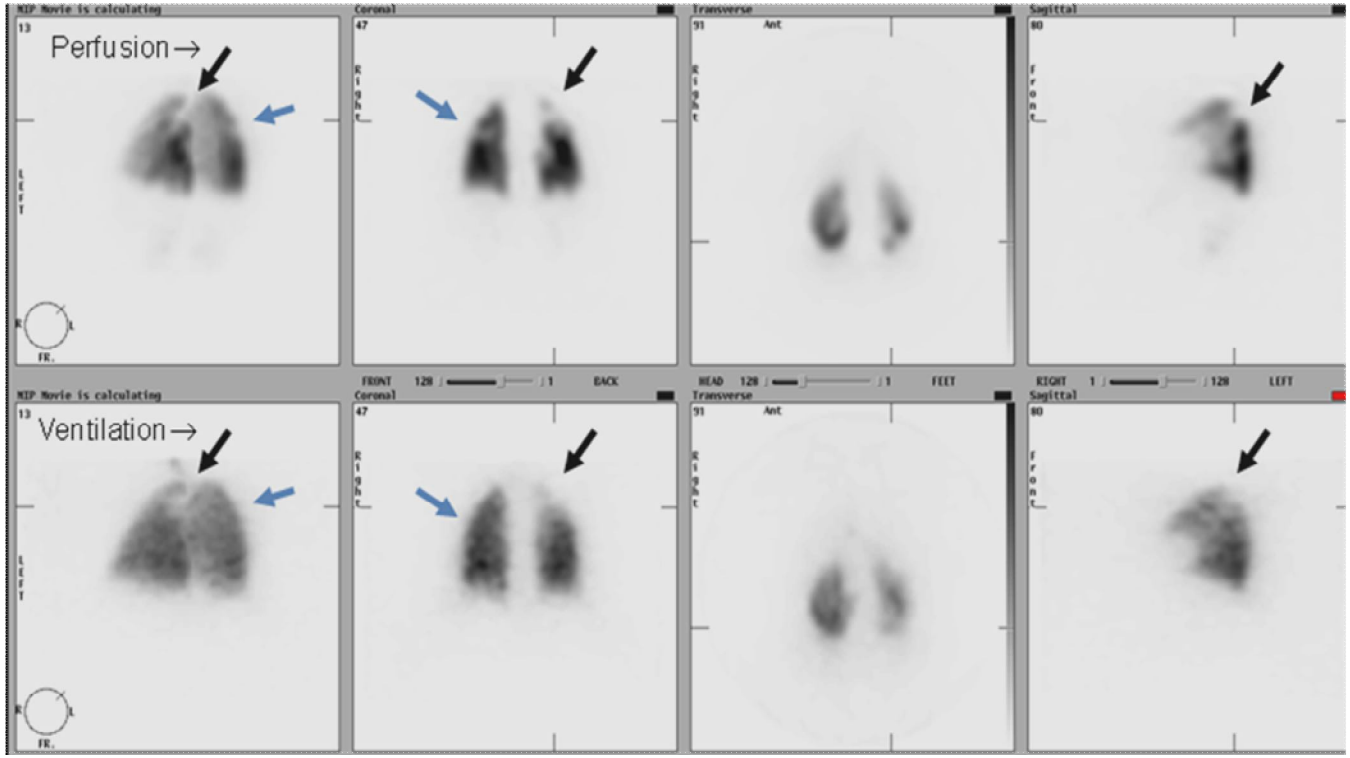


Figure 7b Case One (Below **V/Q SPECT** MIP images)

Findings; Left apico-posterior segmental match defect and an additional single subsegmental V/Q mismatch defect in the superior segment of the right lower lobe – *arrows* (PE negative).



CTPA: Findings; were negative for PE.

Figure 8a Case Two (Below **V/Q Planar** images)

Findings; multiple segmental V/Q mismatch defects in both lungs (PE positive). P=pefusion, vent=ventilation.

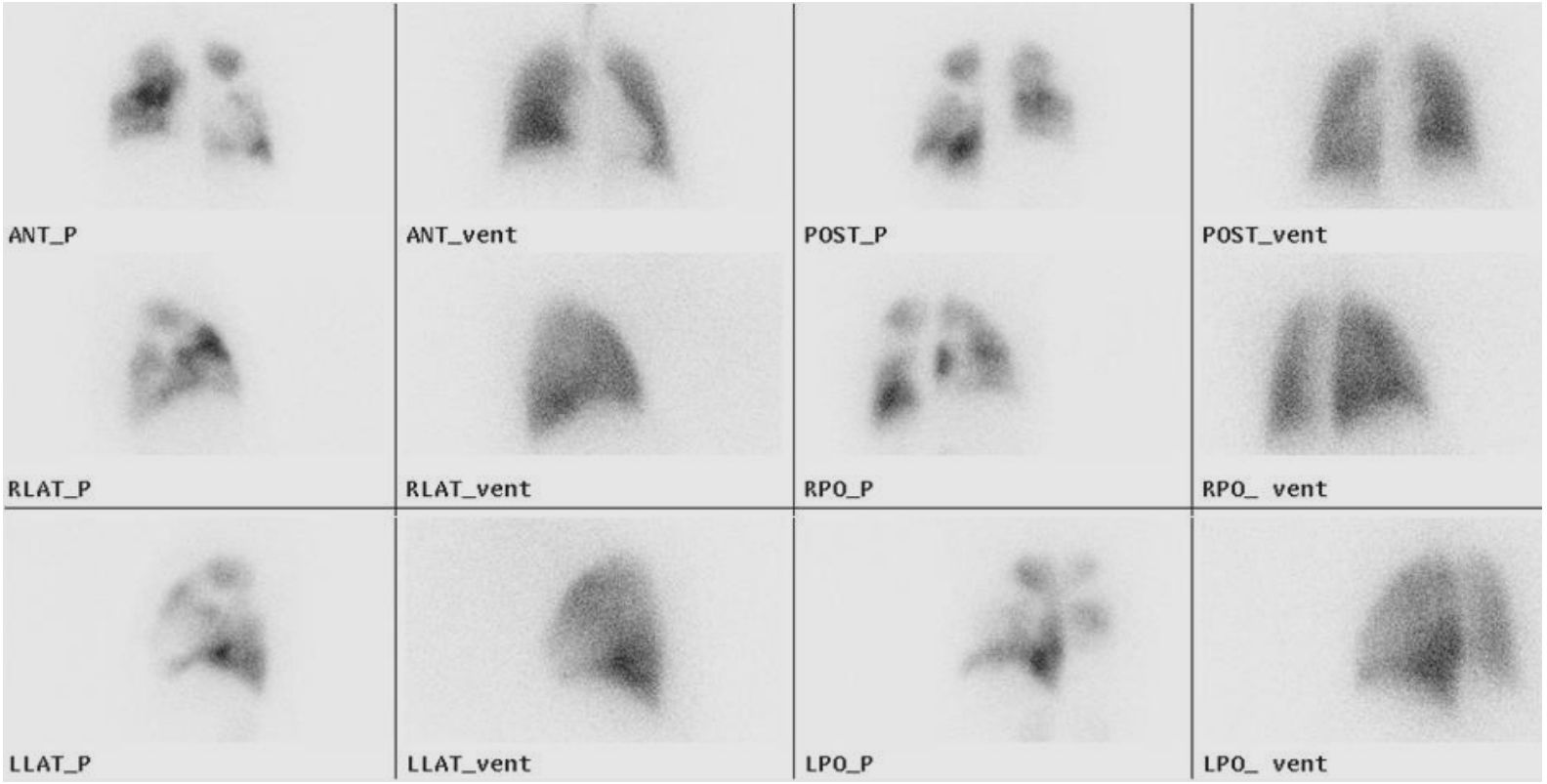
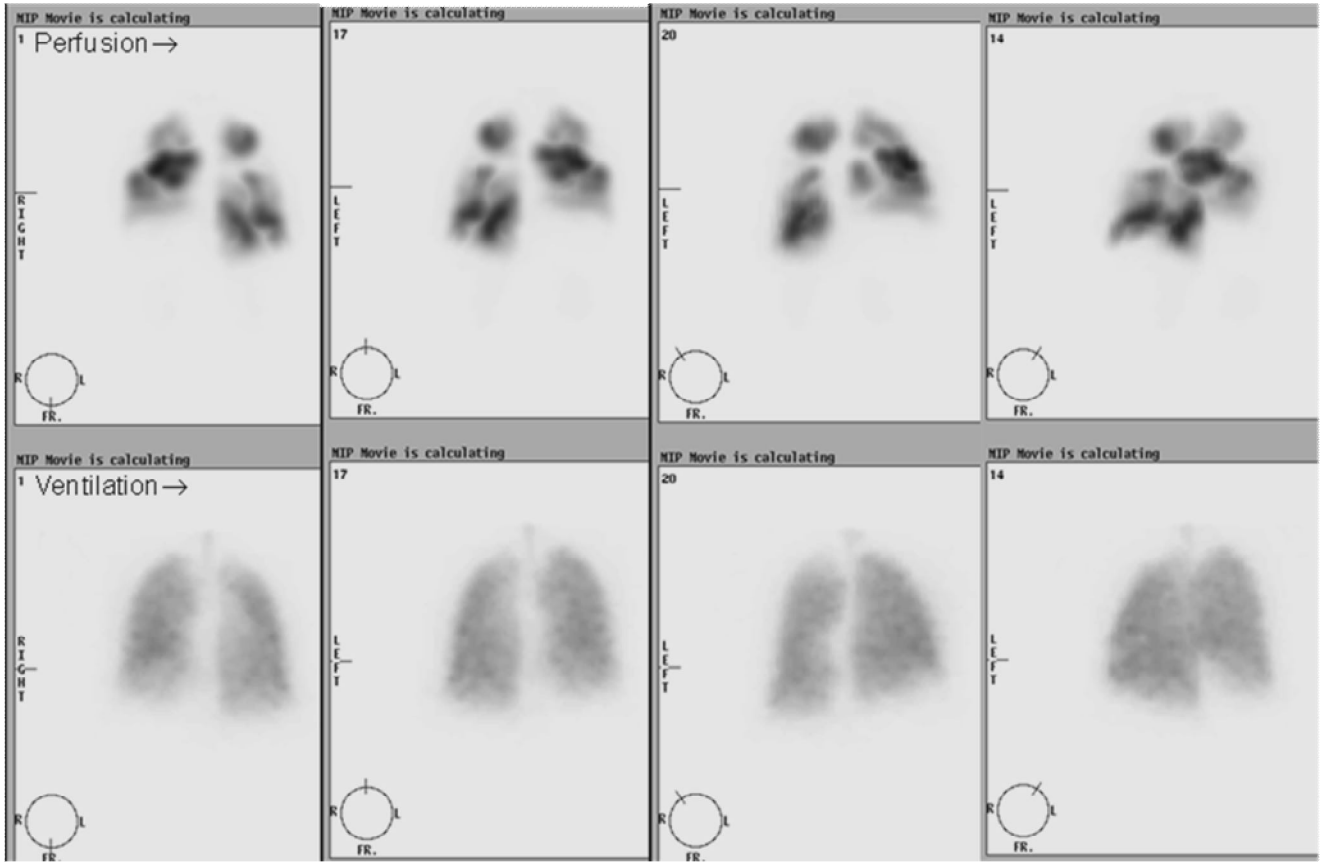


Figure 8b Case Two (Below **V/Q SPECT** MIP images)

Findings; similar to V/Q Planar.



CTPA: Findings; Negative for PE

Figure 9a Case Three (Below **V/Q Planar** images)
Findings; a single subsegmental V/Q mismatch defect in the right posterior basal segment – *arrows* (PE negative). P=pefusion, vent=ventilation.

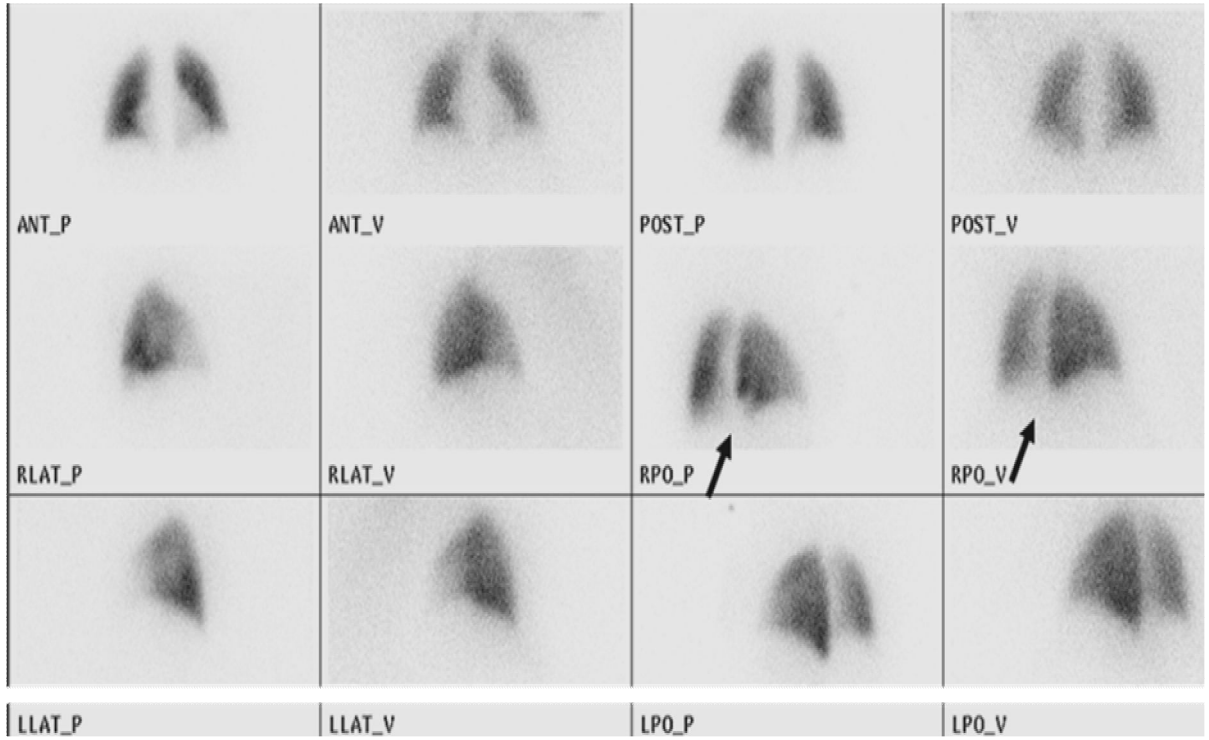


Figure 9b Case Three (Below **V/Q SPECT** images)

Findings; similar to V/Q Planar.

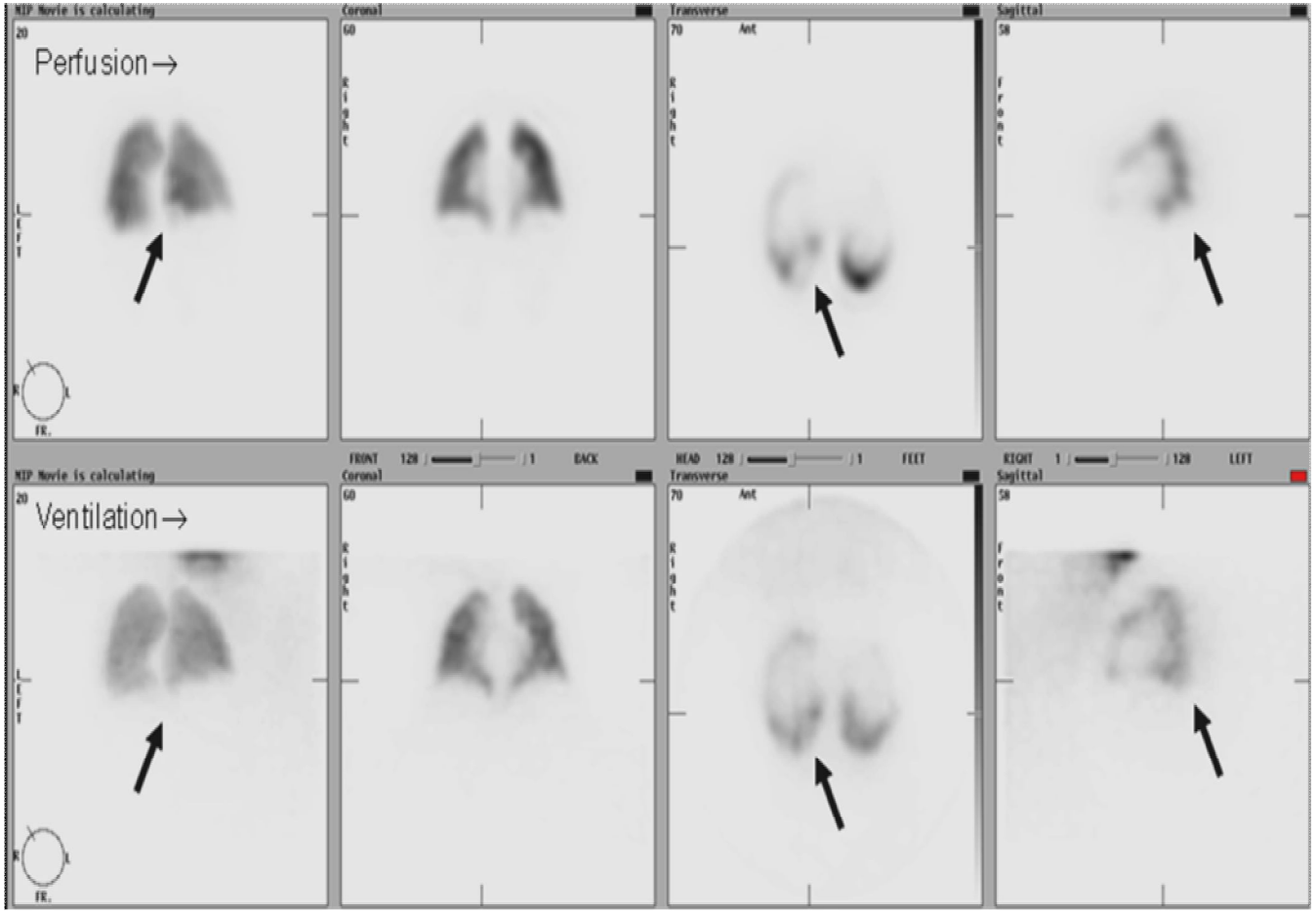


Figure 9c Case Three (Below **CTPA** image)

Findings; Filling defects in the right lower lobe – *arrow* (PE positive).

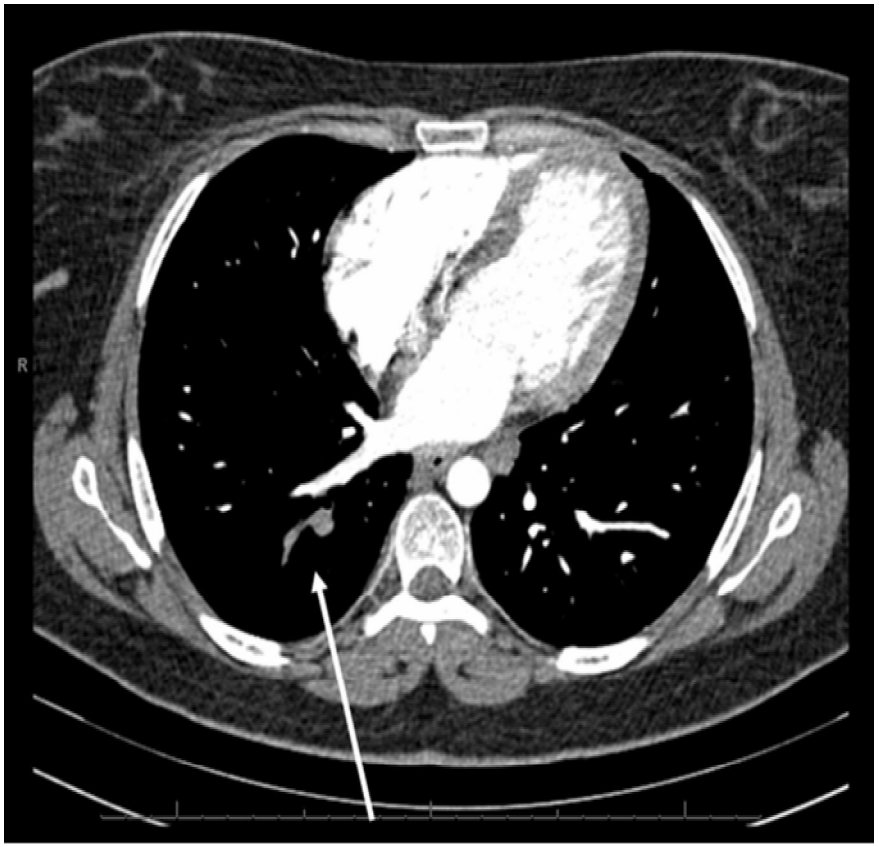
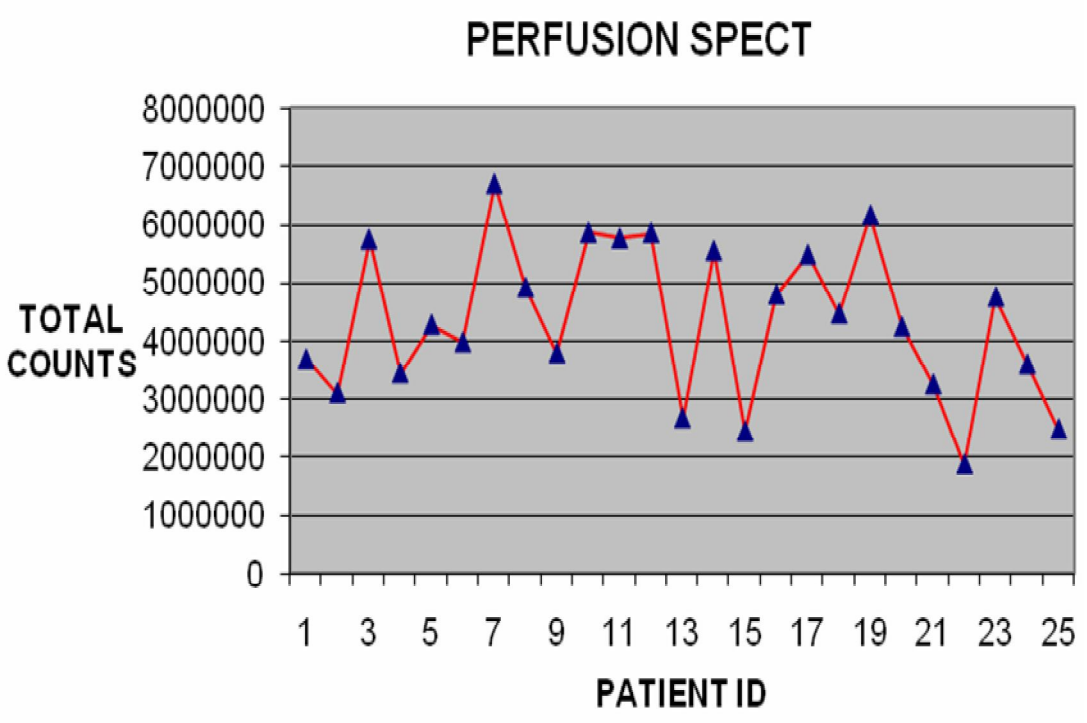
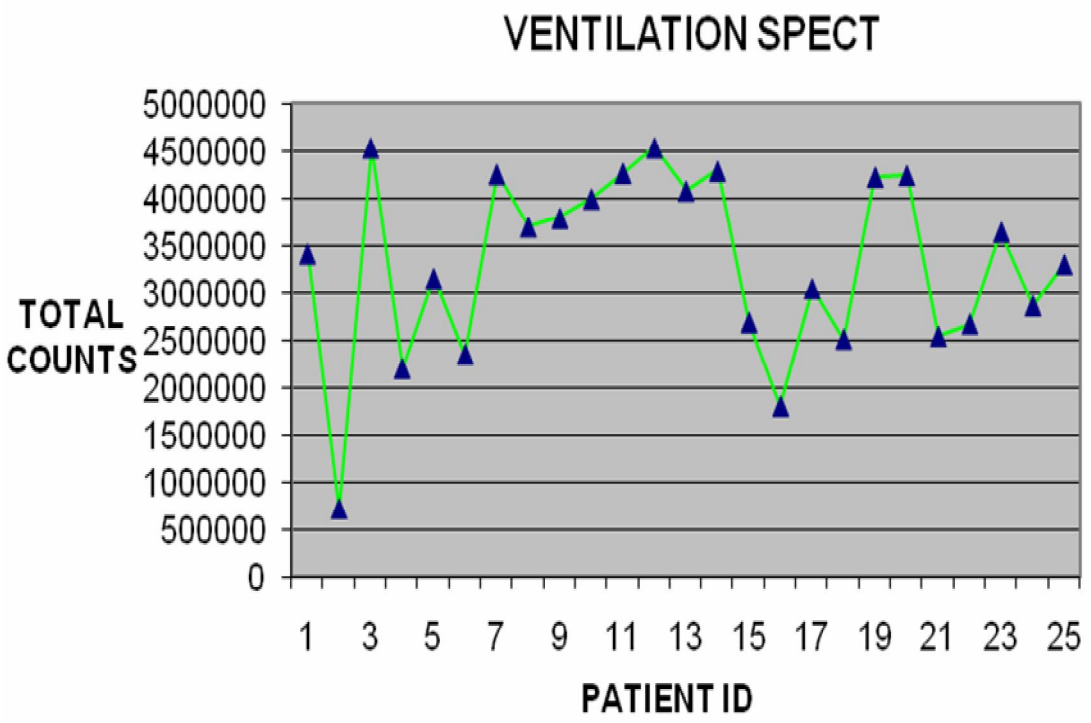


Figure 10 Total counts for each patient on V/Q SPECT;





DISCUSSION

V/Q SPECT which has a superior contrast resolution has been shown to be more sensitive and specific with a lower non-diagnostic rate than V/Q planar imaging in the diagnosis of PE.

This study found that V/Q Planar and V/Q SPECT have a similar performance in terms of sensitivity (75%), specificity (90%), negative predictive value (95%) and diagnostic accuracy (88%), with CTPA as the gold standard (p=0.00658). The similar performances of both V/Q Planar and V/Q SPECT in this study are in contrast to previous studies carried in animal models and in clinical practice which consistently showed that the use of V/Q SPECT will increase both sensitivity (from 64-71% to 91-100%) and specificity (from 79-91% to 87-100%) compared with planar imaging.[144] Our V/Q Planar and V/Q SPECT sensitivities were comparable to those of another study which reported similar planar and SPECT perfusion scans sensitivities (80%) for PE diagnosis.[148]

In this study, the number of patients positive for PE was similar in both V/Q Planar and V/Q SPECT. This is in contrast to a previous study in which PE was more prevalent in V/Q SPECT as well as 53% more mismatch defects were noted on V/Q SPECT than V/Q Planar.[146] On the basis of visual analysis, V/Q SPECT not only detected all defects seen on the V/Q Planar images but also clarified any uncertainties in the V/Q Planar images in this study. In two cases, V/Q SPECT detected additional defects, but did not alter the diagnosis. V/Q Planar in this study

had a lower reader confidence i.e. could clearly resolve only 72% of the cases (18 out of 25) compared to V/Q SPECT (Table 27), which could precisely interpret 100% of the cases. V/Q SPECT showed more and better delineated mismatch vs. match and segmental vs. non-segmental defects quite in agreement to a previous study.[146] In this study, the inferior reader confidence or lack of clarity in V/Q Planar interpretation is in agreement to the fact that only 50 – 80% of cases can be resolved by planar scintigraphy.[148] This study elucidated that despite the similar performance of both V/Q Planar and V/Q SPECT, V/Q SPECT has a better reader confidence. In this study, there was no difference in the diagnosis of PE based on the recent EANM guidelines[42],[43] or the modified PIOPED criteria[167,168] when all the reports were reviewed.

Both V/Q Planar and SPECT had two false positives and one false negative based on CTPA as gold standard. The first false positive case, a young male, had presented with shortness of breath and pulmonary hypertension diagnosed on Echocardiography and had a Wells' PE likely score of >4. Both V/Q Planar and V/Q SPECT imaging noted multiple segmental V/Q mismatch defects (Figure 8a and 8b) but CTPA was negative for PE. V/Q scintigraphy has been shown in a previous study to have a higher sensitivity (94% - 97.4%) than multidetector CT pulmonary angiography (51%) in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension.[131] This case illustrates that V/Q imaging is more sensitive in detecting chronic PE.

The second false positive case had underlying cardiovascular disease (known hypertension and dilated cardiomyopathy) with a Wells' PE unlikely score ≤4. Both V/Q Planar and V/Q SPECT imaging noted two subsegmental V/Q mismatch defects in the left apico-posterior segment and left posterior basal segment but CTPA was negative for PE. Based on the recent EANM guidelines[42,43], this was classified as PE positive.

As for the false negative case, the Wells' score was PE likely (>4) and had a single V/Q mismatch subsegmental defect in the right lower lobe seen on both V/Q planar and SPECT imaging. Based on the recent EANM guidelines[42,43], this was classified as PE negative. In this false negative case, CTPA positively confirmed features of PE in the right lower lobe (Figure 9a, 9b and 9c).

In the original PIOPED study[4], the large number (44%) of non-diagnostic interpretations was related to the fact that 68% of the study population comprised inpatients who were more likely to have underlying cardiopulmonary disease, such as pneumonia, chronic obstructive lung disease and pleural effusions that tend to cause "triple matches". In this study, 48% (12 out of 25 patients) were inpatients and all patients who were enrolled, had a normal or near-normal chest radiograph making interpretation less difficult. PE was more common amongst inpatients (33%) on CTPA (p=0.00960), V/Q Planar and V/Q SPECT compared to outpatients (0% on CTPA [p=0.00960], 8% on V/Q Planar and V/Q SPECT) in this study.

Assessment of the clinical probability can be accomplished empirically or by means of a prediction rule. The latter is preferable over empirical assessment, especially for less experienced clinicians. Clinical probability tests like the Wells' score used in this study can be rapidly obtained by a clinician at the bedside and is reproducible.[47] The Wells and coworkers model[47] seems better suited to rule out rather than to rule in the diagnosis of PE, and its performance is likely to be better in clinical settings. In this study, all patients who were scored as PE unlikely on Wells' score (≤ 4) had PE ruled out on CTPA (p=0.04581) as well as 89% on V/Q SPECT and V/Q Planar. Only 25% with a PE likely on Wells' score (>4) went on to be diagnosed with PE on CTPA (p=0.04581), V/Q Planar and V/Q SPECT.

There is a misconception that SPECT imaging takes longer to acquire than traditional planar imaging. With the use of multi-head gamma cameras and modern computing, SPECT acquisition times are often faster than typical planar studies.[9] Most centers use dual headed detectors to shorten the time of the examination.[138] In this study, the total acquisition time of V/Q SPECT was 20 minutes (10 minutes less than planar acquisition) comparable to other studies done on V/Q SPECT with Technegas.[129,145,147] This time would have been shortened by 50% if the gamma cameras used were capable of simultaneous dual radioisotope energy acquisition of both ventilation and perfusion SPECT. The only concern is down scatter of higher energy ^{81m}Kr gas (190Kev) into the lower energy 99mTc MAA (140keV) which may fill in true defects in perfusion images leading to false negatives. Therefore, in this

study, ventilation and perfusion were acquired separately. It is not unforeseeable in the near future, that gamma cameras with state of art technology may be able to use simultaneous dual radioisotope energy acquisition in V/Q SPECT.

Many studies have been done on V/Q SPECT using Technegas because of limited availability of ^{81m}Kr gas. In this study, perfusion SPECT was performed first followed by ventilation SPECT, and immediately thereafter planar perfusion was followed by planar ventilation imaging according to our study protocol. However, in clinical practice either perfusion or ventilation can be done first with ^{81m}Kr gas. Background emission was cut back in this study by using better, air tight, hand-held mouth masks with a 3 way tube connected by an inverted Y-connector, which was directed cranially, away from the patient's chest to decrease background emission. ^{81m}Kr gas produced good quality interpretable images with sufficient counts (Figure 10).

V/Q SPECT has the definite advantages of being better able to quantify the extent of perfusion abnormalities and can assess reperfusion after PE (especially in follow up), something not easily done with CTPA,[141,146] as well as having a lower radiation dose. V/Q SPECT unlike V/Q Planar permits the application of advanced image-processing techniques. With the help of these techniques, the detection of match and mismatch defects can be automated and objectified. The automated analysis has a significant improvement in the detection rate of pathological lesions especially in complex cases with heterogeneous ventilation and perfusion (e.g. in COPD patients) compared to conventional visual image interpretation.[149] In this study,

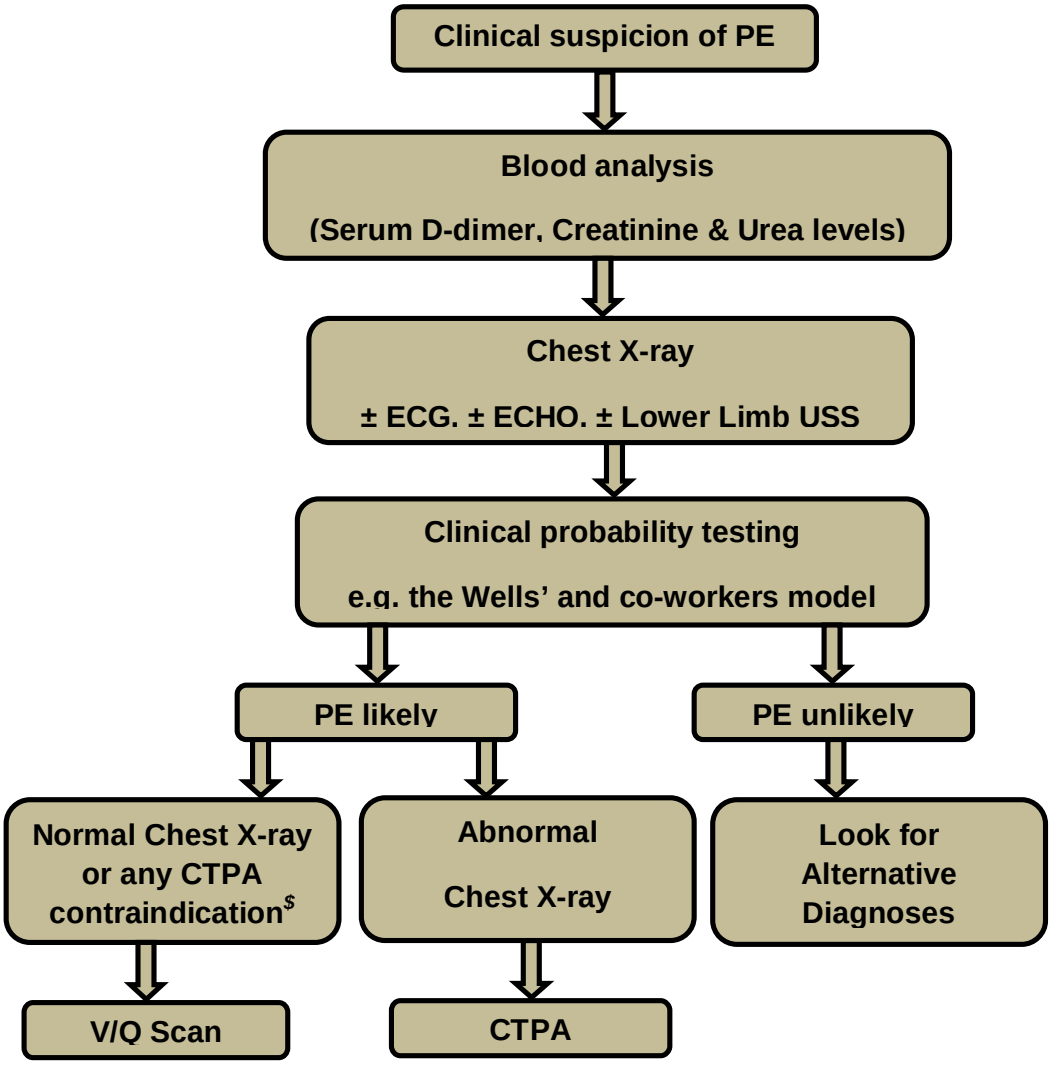
image interpretation was based on conventional visual analysis and the various advanced image-processing options offered by V/Q SPECT such as planar regeneration, correction for photon attenuation or scatter, V/Q Quotient quantification as has been suggested by various studies[151-153] were not explored. Presently, it is not known if such techniques would have added more value to our V/Q SPECT findings.

CTPA detected conditions not visualized on V/Q scintigraphy such as mediastinal lymphadenopathy, solitary pulmonary nodules, pneumonic changes, pleural disease, degenerative thoracic spine changes, incidental thyroid lesion, liver lesion and kidney cyst in 52% (13 out of 25) of the CTPA examinations performed in this study(Table 27). This confirmed that CT is better in depicting other conditions than V/Q scintigraphy[109] and correlates with other studies where other conditions have been reported to have been found in 11% to 70% of CT examinations performed for suspected acute PE.[111-116]

There is a potentially increased risk of breast cancer from the radiation exposure with CTPA, especially with premenopausal women, since they tend to represent a very significant segment of the population that is evaluated for PE[174] as collaborated in this study where 28% (7 out of 25) were premenopausal (less than 45 years of age). Furthermore, there were more males (44% on V/Q Planar and V/Q SPECT (p=0.02), 22% on CTPA) with PE positive compared to females (6% on V/Q Planar and V/Q SPECT (p=0.02), 13% on CTPA) in this study.

A multidisciplinary approach should be used in developing sequential diagnostic algorithms (Figure 11 [based on this study]) for patients with suspected PE.[43] Imaging physicians should be fully educated concerning the radiation risks associated with each diagnostic procedure for PE and, in turn, educate the clinician requesting the procedure.

Figure 11 Diagnostic alogrithm for PE;



$*Some of the CTPA contraindications include abnormal serum creatinine or urea levels, contrast allergy and excess BMI.*

Study Limitations:

Individually, symptoms, signs, or common laboratory tests have limited diagnostic power but jointly, they may provide accurate assessment of the clinical probability of PE. In this study, all patients were assumed to be D-dimer positive due to the fact that the D-dimer levels of each patient by the referring physician were done at different laboratories, hospitals and on different dates, thus impossible to compare.

Comparison of ^{81m}Kr gas with other ventilation imaging agents was not possible due to radiation safety concerns and costs.

Since there is no adequate gold standard, the clinical outcome is considered the ultimate gold standard – although it is argued that clinical outcome can be erroneous in patients with small pulmonary emboli that undergo spontaneous lysis and/or do not recur or if patients are lost on follow up; and only autopsy can provide a definitive diagnosis in patients who die after diagnosis of PE. A normal V/Q scan essentially excludes the diagnosis of PE (1% VTE rate in follow-up).[4,68] In this study, follow up of patientswas not done. It would have been ideal to follow up patients, to determine the VTE rate especially in the PE negative cases. It would have also been ideal to repeat V/Q Planar and/ or V/Q SPECT in the PE positive cases after anticoagulation to ascertain efficacy of therapy, progression of disease (residual vs. new PE). In a way, this would have contributed in risk stratification and prognosis of PE positive patients.

The small study sample based on the strict inclusion and exclusion criteria did not permit statistical analysis of trends.

Advanced image-processing options offered by V/Q SPECT were not explored. Presently, it is not known if such techniques would have added more value to our V/Q SPECT findings.

CONCLUSION

Based on this study, using Krypton 81m gas a ventilation imaging agent, V/Q Planar and V/Q SPECT had a similar diagnostic performance in the diagnosis of PE, in patients with a normal or near normal chest X-rays with CTPA as a gold standard. V/Q SPECT had a better reader confidence than V/Q Planar.

A dichotomous or binary system (PE yes or no) according to the recently published EANM guidelines can be reliably applied in V/Q image interpretation.

A simple clinical probability testing tool such as the Wells and coworkers model can be useful in conjunction with V/Q scintigraphy in the diagnosis of PE.

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