LUNG REVIEW

DIAGNOSIS OF PULMONARY EMBOLISM: A CONTINUING DILEMMA.

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Basic considerations:

The vast majority of pulmonary emboli are thromboemboli originating from deep veins. Fat, air, or tumor emboli are rare [1]. Fat emboli are reported with long bone fractures and liposuction while air emboli occur with cardiac and neurosurgeries. Renal cell carcinoma with invasion reaching inferior vena cava is a clinical setting that may lead to tumor emboli. Data indicate that 90% of pulmonary thromboemboli originate from the lower extremities and pelvis. The remainder come from thrombi that occur in the right side of the heart or in bronchial or cervical veins. Embolization and symptomatology are proportional to how proximal is the vein that contains the thrombus. The vast majority of pulmonary thromboemboli originating from thrombi of the lower extremities come more frequently from the thigh and pelvis (75%) than from smaller veins of the calf and feet [2,3]. The risk of pulmonary embolus is also directly related to the presence of a residual clot at the site of a venous thrombus [4].

One of three events can happen during the natural history of venous thrombi. First, the red thrombus grows explosively and obstructs the vein completely. This can happen even within a few minutes. Second, partial venous obstruction may occur. Blood flow therefore continues over the thrombus surface. Under this circumstance, thrombus growth tends to occur by the progressive layering of platelets and fibrin on the clot surface, pathologically seen as the lines of Zahn. Third, probably the most common scenario, a small thrombus is swept away before it reaches an appreciable size. It lodges in the pulmonary vasculature without symptoms.

Unless fibrinolytic resolution is prompt, organization of the thrombus begins within hours of formation. What was a thrombus is slowly replaced by granulation tissue. This process anchors the thrombus to the venous wall. The dynamic battle between fibrinolysis and thrombus formation is fought out over a period of 7–10 days, at the end of which time either complete resolution has occurred or an endothelialized residual is present. At any time during this period, a portion or all of the thrombus can detach as an embolus. This risk is highest early, before significant dissolution or organization occurs [3].

Pulmonary embolism is potentially fatal and the most common pathological condition involving the lungs of hospitalized patients. The majority of fatal emboli are not recognized or suspected prior to death. The best solution to the problem of embolism is to prevent it. However, prevention requires identification of those at risk (table 1).

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Pulmonary thromboemboli occur more commonly in the lower lobes because of the preferential blood flow to these regions. This also applies to the right lung because of the straighter course of the pulmonary artery.

Table (1): Risk factors for pulmonary thromboembolism.

1. Recent surgery specially operations on the abdomen and pelvis
2. Trauma
3. Neoplasms
4. Prior history of thromboembolic disease
5. Venous stasis
5. Hypercoagulability states
7. Immobilization
8. Infection adjacent to veins
9. Heart disease particularly myocardial infarction and congestive heart failure
10. Following cerebrovascular accidents
11. Pregnancy
12. Certain drugs such as oral contraceptives, estrogens
13. Polycythemia
14. Bleeding
15. Vascular spasm
16. Intimal injury
17. Obesity
18. Old age
19. Varicose veins

Immediately after acute embolism, there is a decrease of perfusion distal to the occluded vessel along with a transient decrease of ventilation to the affected segment. The blood flow is diverted to the other portions of the lung and pulmonary artery pressure may increase, although cardiac output usually remains stable. The resultant tissue ischemia disturbs certain metabolic functions of the lung such as the production of surfactant. Reduction of the surfactant concentration reduces the alveolar surface tension and may cause the atelectasis that often accompanies embolism. If the embolus completely occludes an artery or an arteriole and the collateral bronchial circulation is insufficient to sustain tissue viability, infarction occurs over 24–48 h. Pulmonary infarction with coagulative necrosis results in an area of radiographic opacity that requires an average of 20 days to resolve but occurs in less than 10%–15% of patients with pulmonary embolism. There is significant inflammatory component in pulmonary infarcts which is the basis behind the significant FDG uptake in recent lung infarcts as reported recently and can cause false positive interpretation for lung malignancy [5]. More frequently, incomplete infarction with hemorrhage but without necrosis occurs. This type of injury resolves quickly and produces only transient radiographic opacities. Infarction always involves the pleural surface of the lung (peripheral) and more frequently involves the lower lobes than other sites.

The regional decrease in ventilation is due to local bronchoconstriction with a tendency for redistribution of ventilation away from the hypoperfused segment. This probably occurs due to decreased regional alveolar and airway carbon dioxide tension, which is the usual stimulus for bronchodilation. The ventilation of the hypoperfused areas returns to normal within several hours after acute embolism [6, 7]. This concept is the pathophysiological basis for the scintigraphic interpretation of ventilation and perfusion scans, which show segmental perfusion defects with preserved ventilation as a typical scintigraphic pattern for pulmonary embolism. Those showing only regions of matched perfusion and ventilation defects carry a low probability of pulmonary embolism if no chest X-ray abnormalities are noted at the same sites, since this pattern is more likely associated with nonembolic conditions and is more typical of parenchymal lung

disease. Because patients with pulmonary emboli usually arrive at the hospital after normalization of the ventilation at the site of pulmonary emboli, the mismatching pattern is typical of pulmonary emboli. However in patients may have their V/Q scans within a short time after presentation and matching abnormalities may be associated with pulmonary emboli. This has to be borne in mind, and the duration of symptoms should be a factor in decision-making regarding the management of pulmonary embolism. Normally, the lower zones of the lungs are better perfused and ventilated because of the effect of gravity. This gradient is more pronounced in perfusion than in ventilation. This physiological fact will usually cause the perfusion to appear less than the ventilation in the lung apices on scintigraphy. This should not be confused with a mismatching pattern. ^{99m}Tc Macro aggregated albumin (MAA) is injected for perfusion imaging while the patient is in the supine position to minimize the gradient. Injection while the patient is taking a deep breath also helps.

An increase in the resistance of the pulmonary arterial circulation, due primarily to mechanical blockage by numerous small emboli in the pulmonary vasculature and also to humorally mediated vasoconstriction, may follow pulmonary emboli. These hemodynamic consequences may include increased pulmonary arterial resistance with elevated pulmonary arterial and right ventricular systolic pressures and hypoxemia. Normal pulmonary artery systolic pressure at rest is 18 to 25 mm Hg, with a mean pulmonary pressure ranging from 12 to 16 mm Hg. This low pressure is due to the large cross-sectional area of the pulmonary circulation, which results in low resistance. An increase in pulmonary vascular resistance or pulmonary blood flow results in pulmonary hypertension. It is defined as a pulmonary artery systolic pressure higher than 30 mm Hg or a pulmonary artery mean pressure higher than 20 mm Hg.

Pulmonary hypertension may have no cause (primary) which is rare or may follow cardiac or pulmonary disorders (secondary). Pathphysiologically, three predominant mechanisms may be involved in the pathogenesis of secondary pulmonary hypertension, (1) hypoxic vasoconstriction, (2) decreased area of the pulmonary vascular bed, and (3) volume/pressure overload.

When pulmonary hypertension occurs it indicates that at least 25% obstruction of pulmonary vascular tree as assessed by angiography [8]. The higher the degree of obstruction the more severe the abnormalities of the cardiopulmonary hemodynamics become. When over 50% of the pulmonary vasculature is included (massive pulmonary embolism), acute pulmonary hypertension and /or right ventricular failure (cor pulmonale) occurs [8].

Pulmonary emboli may, spontaneously or with treatment, fragment into smaller portions that travel distally and block smaller arterioles. This may create new, smaller perfusion defects that are more peripherally located in comparison to the original defect caused by the original embolus. This pattern should not be mistaken for recurrent pulmonary emboli on a follow-up scan. If this pattern is the only interval change with no other defects seen in areas other than those in the vicinity of the distribution of the original embolus, it does not suggest recurrent emboli [7].

Resolution of pulmonary thromboembolus may start within hours. It can be seen on perfusion scans as early as 24 h and is progressively noted up to 3 months, with insignificant change after 6 months. This is the basis of the recommendation that follow up ventilation and perfusion scans is performed three months after the initial incident for evaluation of resolution and

function as a baseline for future incidents to differentiate between acute and unresolved old emboli. This resolution is dependent on the age of the patient, with complete resolution in young age-groups and less complete and less significant resolution in older age-groups [9]. Other factors include age of the thromboembolus or length of time between formation of the embolus and the institution of proper anticoagulation. This is the basis behind the relatively recent trend of starting anticoagulant therapy in most patients with pulmonary emboli who have no contraindication for anticoagulation immediately when a pulmonary thromboembolus is suspected before finishing the workup for the condition. Anticoagulant therapy may then be stopped if the condition is excluded.

Pulmonary thromboemboli recur in up to 50% of patients [10], although the incidence in treated PIOPED patients was only 8.3% [11]. The vast majority of deaths among pulmonary embolism patients are due to recurrent emboli. In the PIOPED study population, it was found that nine of ten people who died had a recurrent pulmonary embolus [12]. Recurrence has been reported to occur at the same site as the original thromboembolus [13].

Diagnosis of pulmonary emboli:

The clinical diagnosis of pulmonary thromboembolism is difficult and unreliable, due to the nonspecificity of its symptoms and signs as well as the laboratory and chest X-ray findings [14,15]. Chest x-ray however must be obtained since it may show many parynchymal diseases [16] and must be available for lung scan interpretation. Pulmonary embolism may also be asymptomatic. In a study using spiral CT 24% of pulmonary emboli were asymptomatic among patients with moderately to severely injured patients [17]. Furthermore the presentation is commonly more difficult and atypical in older age group compared to younger patients [18, 19]. Accordingly only 24% of fatal emboli were diagnosed antemortem [20]. Data indicate that the mortality of pulmonary embolism is more than 30% if untreated. Promptly diagnosed and treated, emboli have a mortality of 2.5%–8% [9, 12, 21]. The mortality of PE was found to vary among patients with or without cardiac disease. Paraskos et al [22] reported survival rates at a mean follow up period of 29 months of 19% among patients with prior congestive heart failure and 86% for those with no prior congestive heart failure. Pulmonary angiography is the most accurate modality for the diagnosis of pulmonary emboli with an accuracy of 96% [23]. However, angiography is invasive and is not suitable as a screening imaging modality for the disease.

Scintigraphic diagnosis:

Scintigraphy remains the most cost-effective noninvasive screening modality. The major advantages include its ability to provide regional and quantitative information useful for the diagnosis, as well as for mapping to guide selective angiography if needed for the diagnosis, after noninvasive methods including Doppler and Duplex studies for deep venous thrombosis have been exhausted. Additionally it determines the disease severity and monitors its progress [24].

Several agents have been used for ventilation (Table 2). Every agent has certain advantages and limitations. Xenon 133 is useful in evaluating obstructive airway disease. Crypton 81, Tc99m DTPA and Technegas provides ability to perform ventilation studies after the perfusion particularly Crypton-81. Tc99m Macroaggregated albumin is used for perfusion. For proper interpretation of lung perfusion/ventilation study chest X ray must be available and should be obtained within 12 hours of the time of the scans. Technegas is ventilation

aerosol agent that gained popularity recently. It is ultrafine labeled carbon particles produced by heating 99mTc-pertechnetate to very high temperatures of approximately 2500^{o} C in the presence of 100% argon gas. An ash material is produced that acts like a gas with good peripheral deposition because the particles are so small, with a median size of 0.05 to 0.15 um. Technegas has a half-clearance time of 4-6 hours. Another agent, pertechnegas, which is a vapor of pertechnetate, is prepared similarly but in the presence of 2 to 5% oxygen, has a shorter clearance time, and shows excellent deposition in the lungs.

Table (2): Patterns of perfusion defects associated with higher probability of pulmonary emboli

Size	Moderate and large Larger than that of corresponding chest X-ray densities
Location	Pleural based defects
Lower lobes	
Shape	Wedge-shaped
Type	Segmental
Relation to ventilation pattern	Mismatching
Number	Multiple

Normal perfusion study (Figure 1) rules out any clinically significant pulmonary emboli. Since the ventilation and perfusion lung scans lack specificity (Table 4), probabilities are used for the interpretation of abnormal studies. Based on the pathophysiological changes and scintigraphic observations, several scintigraphic features of perfusion abnormalities are known to affect the probability of a scan for pulmonary emboli (Table 5). One of the important features is the size of segmental perfusion defects. A small defect occupies up to 25% of the segment, a moderate defect between 25% and 75%, while a large defect takes up 75% or more. Using these features, several retrospective and prospective studies were conducted to refine the interpretation of ventilation and perfusion scans and assess their value in managing patients suspected of having embolic disease [25-26].

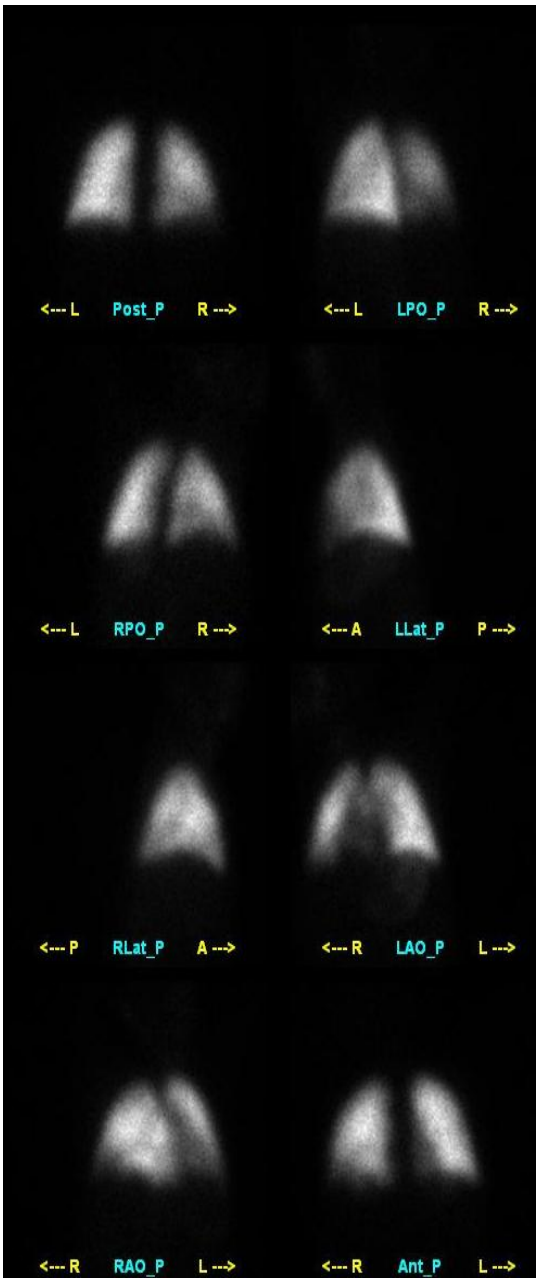

Figure (1): Tc99m MAA perfusion study showing no segmental or subsegmental perfusion defects indicating normal perfusion ruling out the possibility of any clinically significant pulmonary emboli

Table (3): Summary of major ventilation agents

Agent	**Advantages and limitations**
Aerosols	
Tc99m-DTPA aerosol	Lung half clearance time = 58 minutes Pre or post perfusion Multiple projections
Technegas	Multiple projections Good peripheral deposition
Gases:	
Xenon-133	Ability to obtain single breath, equilibrium and washout images Very sensitive for obstructive airway disease Only posterior view is possible in most patients Low energy of 81 keV Pre-perfusion acquisition
Krypton-81m	Expensive - available only in some areas Energy: 190 keV Half life: 13 seconds Multiple views Pre or post perfusion

Table (4): Characteristics of Tc-99m- Macro-aggregated albumin (Tc99m-MAA)

• Size	10-90 Microns (mostly 20 to 50)
• Minimum number of particles to be used in adults	100,000 unless pulmonary hypertension or right to left shunt is present
• Ideal number of particles	200,000 - 500,000
• Biologic half life	4 - 8 hours
• Injection	Care should be taken not to cause particle aggregates that can produce hot spots
• Safety	Particles block <1/1000 of the capillaries and pre-capillary arterioles

Table (5): Causes of abnormal perfusion lung scan

Emphysema
Pneumonia
Abscess
Granulomatous disease (Sarcoidosis, Tuberculosis)
Pulmonary fibrosis
Bronchial obstruction
Acute and chronic Asthma
Mucus plug
Foreign body
Rib fractures (Reduced lung excursion)
Congenital hypoplasia or absence of the pulmonary arteries
Peripheral pulmonary artery stenosis
Thromboembolic disease
Extrinsic vessel compression (Tumor, inflammation)
Left ventricular failure
Mitral valve disease
Venoocclusive disease
Prior lung resection
Radiation

The most popular retrospective study is that by Biello et al. [25], which compared the ventilation and perfusion scans and chest X-rays with angiography to produce a set of criteria for interpreting ventilation and perfusion studies. The most recent and largest prospective study is the PIOPED [11]. Despite its shortcomings, which originated mainly from the use of a pre-established nonstandard set of criteria for interpretation of ventilation and perfusion scans, the PIOPED provided a wealth of information. The study established the value of normal and high probability scans in excluding and diagnosing pulmonary embolism.

It validated the segment equivalent concept and clarified the use of Bayesian analysis utilizing the clinical pre-scan and scan probabilities to figure the post-scan or diagnostic probability. The study showed clearly that when the clinical odds agree with the scan probability in the low and high probability categories, pulmonary embolism can be ruled out or confirmed with a high degree of certainty.

Based on the modifications of PIOPED criteria and the other validated criteria, a simplified set is shown in table 6. Small perfusion defects indicate low probability of pulmonary emboli as well as matching perfusion and ventilation defects regardless of size with no matching x ray abnormalities. Non segemental defects also indicate low probability. When perfusion defects

Table (6): Criteria for interpretation of ventilation/Perfusion lung scans

Category	Pattern on V/Q images
Normal	No perfusion defects. Allow for impressions explained by enlarged heart or other hilar structures as seen on chest x-ray.
Near normal	heterogenous uptake with no definite segmental or subsegmental perfusion defects
Low	- Non segmental perfusion defects other than those explained by cardiomegaly or other prominent hilar structures - Matching V/Q defects with no corresponding CXR abnormalities - Any number of only small defects regardless of ventilation and CXR patterns - Perfusion defect substantially smaller than CXR abnormality - Stripe sign
Intermediate	-Perfusion defect matching chest x-ray abnormality and of the same approximate size. -Single moderate up to less than 2 segmental mismatching defects with no corresponding chest x-ray abnormalities. -Difficult to categorize as low or high.
High	- Two or more large mismatching defects or their equivalent (4 moderate or 1 large plus 2 moderate defects) with no corresponding CXR abnormalities. - Perfusion defect substantially larger than CXR abnormality

** 1.5 in patients with no prior cardiopulmonary disease can be considered high probability.*

match the X ray abnormalities it may indicate low, intermediate or high probability based on the relative size of perfusion compared to the x ray densities. When the perfusion defect is of the same approximate size of the matching x ray density (Figure 2) it indicates intermediate probability (approximately 25%). However, Worley et al suggested that when the perfusion defect matches the chest X-ray density in the upper or intermediate lung zones it indicates low probability while if it is in the lower zones it indicates intermediate probability [27]. Other studies however did not support this categorization and it is debatable [28]. Size of pleural effusion also was interpreted as low probability if large and intermediate if small by Worsley, et al [29] but this was not proved by Goldberg et al [30].

The minimum number of mismatching perfusion defects is two segment equivalent defects to make high probability interpretation (Figure 3). However a study analyzing PIOPED data indicated that defects equivalent of 1.5 segments are indicating high probability among patients with no prior cardiopulmonary diseases [31].

Till further development, proper utilization of V/Q scans along with the DVT tests and Spiral CT solves most diagnostic problems and decreases the need for angiograms

Other diagnostic modalities:

Noninvasive DVT studies are useful in decision making in equivocal cases. Positive DVT studies increases probability to up to 93%.

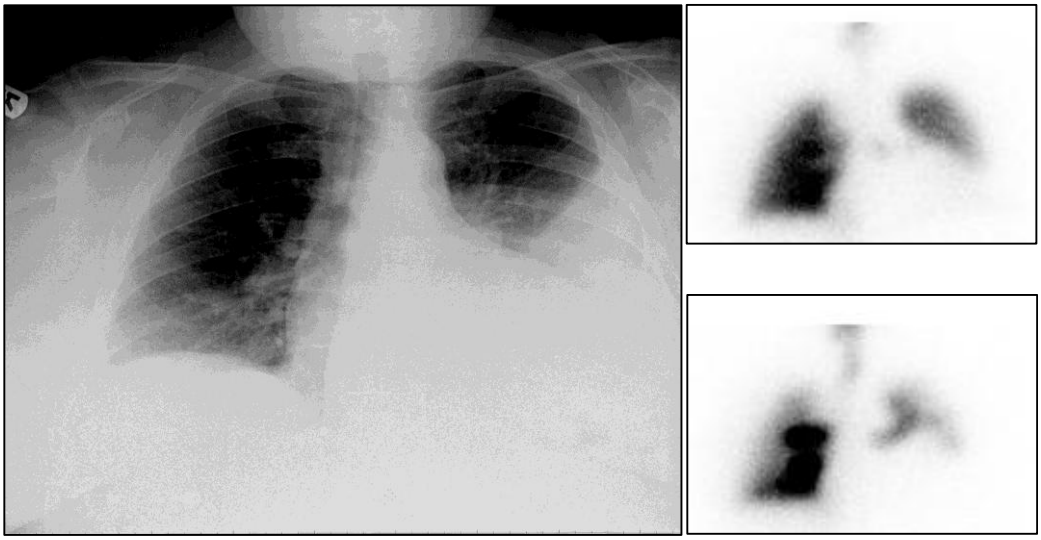

Figure (2): Representative images of a tc99m MAA perfusion scan (a) and Tc99m DTPA arerosol ventilation scan (b) showing perfusion defect matching the ventilation abnormality and is od the same approximate size as the chest X ray density. This pattern indicates intermediate probability of pulmonary emboli.

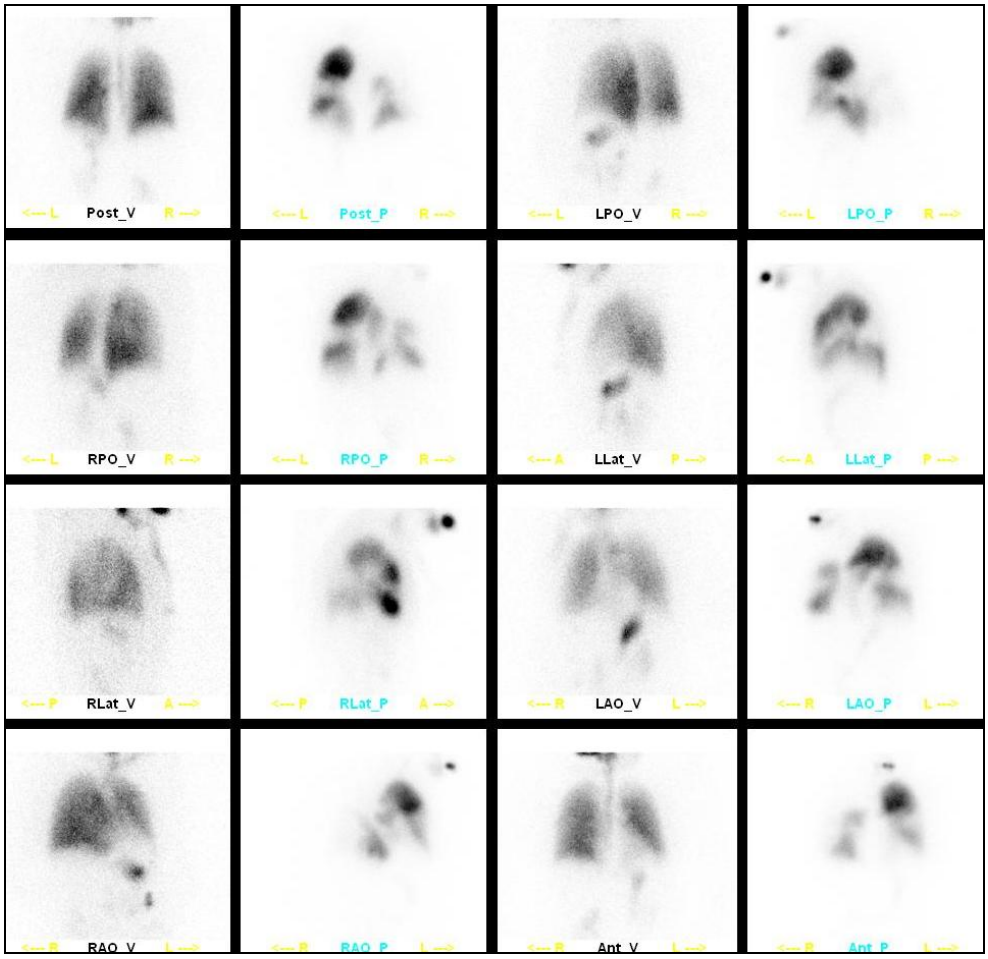

Figure (3): Ventilation and perfusion lung scans showing mulitiple large and medium sized defects equivalent to more than two segments and are mismatching with the ventilation pattern. The chest X ray (not shown) is normal. The pattern indicates high probability of pulmoonary emboli.

Furthermore incorporating DVT studies in algorithms for managing patients suspected of having pulmonary thromboembolism decreases angiograms by 50%. Normal study with low probability V/Q and low clinical probability is associated with a 1%-2% 3 more risk of venous thrombo-embolism in patients left without anticoagulants [32].

Spiral CT is another complementary modality that can help with non diagnostic studies in minimizing the number of patients undergoing pulmonary angiography. It is useful in detecting central emboli but data are controversial for peripheral emboli [33, 34, 35, 37] Several studies have shown that this modality can not be reliable to withhold the anticoagulant therapy based on a negative spiral CT and it needs to be explored further before being accepted as a replacement for V/Q scans [38]. It was found that it has no added value in patients with high probability V/Q scans and has a comparable diagnostic value with SPECT V/Q scans [36]. Spiral CT also as a single study is not cost effective [39]

MRI pulmonary angiography will play a greater role [40]. In a recent experimental study reversible PE was induced by inflating a non-detachable silicon balloon in the left pulmonary artery of five New Zealand White rabbits. MR V/Q scans were obtained prior to, during, and after balloon deflation. High-resolution contrast-enhanced MR pulmonary angiography was also used to confirm the occlusion of the pulmonary artery. Similar to radionuclide ventilation/perfusion technique, acute PE produced a mismatched defect in the MR V/Q scan. MRA verified the occlusive filling defect in the left pulmonary artery. The study suggests that high-resolution MRA and MR V/Q imaging of the lung is feasible and allows comprehensive assessment of pulmonary embolism in one imaging session [41].

REFERENCES

1. Frieman DG, Suyemoto J, Wessler S (1965) Fequency of pulmonary thromboembolism in man. N Engl J Med 272:1278–1280
2. McLachlin J, Patterson JC (1961) Some basic observations on venous thrombosis and pulmonary embolism. Surg Gynecol Obstet 93:1–8
3. Moser KM (1990) Venous thromboembolism: state-of-the-art. Am Rev Respir Dis 141:235–249
4. Palevsky HI, Alavi A (1991) Noninvasive strategy for management of patients suspected of pulmonary embolism. Semin Nucl Med 21:325–331
5. Kamel E, Mckee T, Calcagni M, Schmidt S, Markl S, Bischof Delaloye A (2005): Occult lung infarction may induce false interpretation of F19 FDG PET in primary staging of pulmonary malignancies. Eur J Nucl Med Mol Imaging; 32: 641-646
6. Dass H, Hcekscher T, Anthonisen NR (1967) Regional pulmonary gas exchange in patients with pulmonary embolism. Clin Sci 33:355–364
7. Smith R, Alderson PO (1987) Ventilation perfusion scintigraphy in pulmonary embolism in pulmonary nuclear medicine. In: Loken MK (ed) Pulmonary nuclear medicine. Appleton and Lange, Norwalk, Connecticut, pp 51–79
8. Wolfe MW, Skibo LK, Goldhaber SZ (1993): Pulmonary embolic disease: diagnosis, pathophysiologic aspects and treatment with thrombolytic therapy. Curr Probl Cardiol; XVIII: 587-633.
9. National Heart, Lung and Blood Institute (1970) Urokinase pulmonary embolism trial – phase I results. JAMA 214:2163–2172

10. Elgazzar AH, Jobalia R, Subramanian P, Ryan J, Hughes JA (1994) Multiple ventilation and perfusion (V/Q) scans in patients with and without pulmonary emboli (PE). J Nucl Med 35:239

11. PIOPED investigators (1990) Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA 263:2753–2759

12. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, Schwartz JS, Thompson BT, Popovich J Jr, Hobbins TE, et al. (1992) The clinical course of pulmonary embolism. N Engl J Med 326:1240–1245

13. Schober B (1980) Do pulmonary emboli lodge preferentially in prior foci? J Nucl Med 21:659–661

14. Hoffman JM, Lee A, Grafton S, Bellamy P, Hawkins RA, Webner M (1994) Clinical signs and symptoms in pulmonary embolism. A reassessment. Clin Nucl Med., 19:803–808.

15. Stein PD, Terrin ML, Hales CA, Palevsky HI, Saltzman HA, Thompson BT, Weg JG.(1991) Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest; 100:598-603.

16. Coche E , Verschuren F, Hainaut P, Goncette L (2004) Pulmonary embolism findings on chest radiographs and multislice spiral CT. Eur Radiol; 14:1241-1248.

17. Schultz DJ, Brasel KJ, Washington L, Goodman LR, Quickel RR, Lipchik RJ, Clever T, Weigelt J. (2004) Incidence of Asymptomatic Pulmonary Embolism in Moderately to Severely Injured Trauma Patients. J Trauma; 56:727-731.

18. Timmons S, Kingston M, Hussain M, Kelly H, Liston R, (2003): Pulmonary embolism: differences in presentation between older and younger patients. Age Ageing; 32: 601-605.

19. Berman AR, Arnsten JH (2003) Diagnosis and treatment of pulmonary embolism in the elderly. Clin Geriatr Med; 19: 157-175.

20. Elgazzar AH (1997) Scintigraphic diagnosis of pulmonary embolism: unraveling the confusion seven years after PIOPED. Nucl Med Ann; pp 69–101.

21. Elgazzar AH, Khadada M: Respiratory system. In Elgazzar AH, the pathophysiologic basis of Nuclear Medicine. Springer, Berlin, New York, 2006

22. Paraskos JA, Adelstein SJ, Smith RE, Rickman FD, Grossman W, Dexter L, Dalen JE. (1973) Late prognosis of acute pulmonary embolism. N Eng J Med; 239:55-58.

23. Stein PD, Athanasoulis C, Alavi A, Greenspan RH, Hales CA, Saltzman HA, Vreim CE, Terrin ML, Weg JG. (1992) Complications and validity of pulmonary angiography in acute pulmonary embolism. Circulation; 85: 462-468.

24. Kawamoro M, Ogura Y, Honda N, Satoh K, Suga K, Mori Y, Imai T, Inoue T, Narabayashi I (2002) Present diagnostic strategies for acute pulmonary thromboembolism; results of a questaionaire in a retrospective trial conducted by the respiratory nuclear medicine working group of the Japanese Society of Nuclear Medicine. Ann Nucl Med; 16:549-555.

25. Biello DR, Mattar AG, McKnight RC, Siegel BA (1979) Ventilation-perfusion studies in suspected pulmonary embolism. AJR 133:1033–1037.

26. Hull RD, Hirsh J, Carter CJ, Jay RM, Dodd PE, Ockelford PA, Coates G, Gill GJ, Turpie AG, Doyle DJ, Buller HR, Raskob GE (1983): Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. Ann Intern Med. 98:891-899.

27. Worsley DF, Kim CK, Alavi A, Palevsky HI (1993) Detailed analysis of patients with matched ventilation-perfusion defects and chest radiographic opacities. J Nucl Med; 34:185-1-3.

28. Goldberg SN, Palmer EL, Scott JA, Fisher R (1994) Pulmonary embolism: prediction of the usefulness of initial ventilation-perfusion scanning with chest radiographic findings. Radiology; 193:801-805.

29. Worsley DF,Alavi A(1995): Comparative analysis of the results of the PIOPED study. J Nucl Med; 36: 2380-2387.

30. Goldberg SN, Richardson DD, Palmer EL, Scott JA (1996): Pleural effusion and ventilation/perfusion scan interpretation for acute pulmonary embolus J Nucl Med; 37:1310-1313.

31. Stein PD, Coleman ER, Gottscalk A, saltzman H, Terrin ML, Weg JG (1991) Diagnostic utility of ventilation/perfusion lung scans in acute pulmonary embolism is not diminished by pre-existing cardiac or pulmonary disease. Chest; 100: 604-606.

32. Perrier A (2001) Pulmonary embolism: from clinical presentation to clinical probability assessment Semin Vasc Med.; 1:147-154.

33. Schoepf UJ, Goldhaber SZ, Costello P (2004) Spiral computed tomography for acute pulmpnary embolism. Circulation; 109: 2160-2167.

34. Radan L, Mor M, Gips S, Schlang-Eisenberg D, Lurie Y, Dickstein K, Bitterman H, Ben-Haim S (2004) The added value of spiral computed tomographic angiography after lung scintigraphy for the diagnosis of pulmonary embolism. Clin Nucl Med; 29:255-261

35. Aviram G, Levy G, Fishman JE, Blank A, Graif M (2004): Pitfalls in the diagnosis of acute pulmonary embolism on spiral computed tomography. Curr probl diagn radiolol; 33:74-84.

36. Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, Buell U (2004) Tomographic Imaging in the Diagnosis of Pulmonary Embolism: A Comparison Between V/Q Lung Scintigraphy in SPECT Technique and Multislice Spiral CT. J Nucl Med; 45:1501-1508.

37. Ranji SR, Shojania KG, Trowbridge RL, Auerbach AD. Impact of reliance on CT pulmonary angiography on diagnosis of pulmonary embolism: a Bayesian analysis. J Hosp Med;1:81-87, 2006

38. Velmahos GC, Toutouzas KG, Vassiliu P, Rhee P, Wilcox A, Hanks SE, Chan LS, Tillou A, Demetriades D. (2004) Can we rely on computed tomographic scanning to diagnose pulmonary embolism in critically ill surgical patients?J Trauma; 56:518-525

39. Perrier A, Nendaz MR, Sarasin FP, Howarth NM Bounameaux H (2003) Cost effectiveness analysis of diagnostic strategies for suspected pulmonary embolism including helical computed tomography. Am J Respiratory Crit Care Med; 167: 39-44.

40. KanneJP, Lalani TA (2004): Role of computed tomography and Magnetic resonance imaging for deep venous thrombosis and pulmonary embolism; Circulation; 109(1), 115-121.(Supplement).

41. Altes TA, Mai VM, Munger TM, Brookeman JR, Hagspiel KD (2005):Pulmonary Embolism: Comprehensive Evaluation with MR Ventilation and Perfusion Scanning with Hyperpolarized Helium-3, Arterial Spin Tagging, and Contrast-enhanced MRA.J Vasc Interv Radiol. 16:999-1005.