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ORIGINAL ARTICLE

Is the lung scan alive and well? Facts and controversies in defining the role of lung scintigraphy for the diagnosis of pulmonary embolism in the era of MDCT

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Abstract
Purpose The last decade has seen a changing pattern of utilization of multidetector CT (MDCT) versus lung perfusion scintigraphy in the investigation of pulmonary venous thromboembolism (VTE). In response to this the International Atomic Energy Agency (IAEA) determined that the subject required an overview.
Method The IAEA has invited a group of five specialists in the relevant fields to review the current status and optimum role of scintigraphy, to explore some of the facts and controversies surrounding the use of both modalities and to make recommendations about the continued role of nuclear medicine for the investigation of pulmonary embolism. This paper identifies the relative merits of each technique, highlights benefits, focuses on complementary roles and seeks a nonadversarial symbiosis.
Conclusion The consultants reached a consensus that the continued use of scintigraphy for diagnosis of thromboembolic disease is recommended, particularly in scenarios where scintigraphy confers specific benefits and is complementary to MDCT.

Keywords V/Q · Pulmonary embolism · MDCT · CTPA

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Introduction

It is generally accepted that the efficacy and continued technical improvements in multidetector computed tomography (MDCT) technology have produced a significant rise in its use for the diagnosis of acute pulmonary thromboembolism (PTE) [1]. The ascendancy of CT pulmonary angiography (CTPA) has coincided with a corresponding reduction in the utilization of lung scintigraphy [2] to the extent that some recent publications have suggested that ventilation-perfusion (V/Q) scanning has firmly become a second-line test [3, 4]. However, it is not clear if this approach threatens to cause atrophy and eventual redundancy of a robust technique which has so far shown specific clinical advantages. The International Atomic Energy Agency Consultants Group was tasked with identifying related issues requiring clarification and examining the potential future for lung scintigraphy in the diagnosis of

pulmonary embolism (PE). In this article we review nonimaging tests and then consider the current status of the two principal imaging modalities, contrasting benefits and highlighting controversies.

Background

PTE, which most often results from deep vein thrombosis (DVT) in a lower extremity, is a common and potentially fatal disease that can be treated efficiently if correctly diagnosed within a short time of presentation [5]. The estimated incidence of venous thrombosis is approximately 1 in 1,000 per year, and the fatality from PTE can be as high as 10% within the first hour [6]. The incidence rises with age, approaching approximately 1 in 100 in the very old. The overall mortality in untreated patients with PE is 30%, rising to 58% in haemodynamically unstable patients [7]. Conversely, the fatality during anticoagulation therapy has been reduced to 0.4% in patients presenting with DVT and 1.5% in those presenting with PTE [8].

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

Clinical diagnosis

The clinical diagnosis of PTE is considered unreliable, as symptoms and signs (dyspnoea, tachypnoea, tachycardia, pleuritic chest pain, cough and haemoptysis) are variable and can be encountered in many other cardiorespiratory conditions [9, 10].

Pretest probability scoring

A number of systems have been developed to aid clinicians in establishing the likelihood of pulmonary thromboembolic disease (see further below). Implementation and utilization of these systems, that affect the accuracy of further diagnostic tests [11], is variable across clinical practice. The necessity of employing these scoring systems is explored further below.

Laboratory tests

Arterial blood gases Hypoxaemia and respiratory alkalosis are common findings in PTE. This was confirmed in both the PIOPED ("Prospective Investigation of Pulmonary Embolism Diagnosis") [12] and the PISA-PED ("Prospective Investigation Study of Acute Pulmonary Embolism Diagnosis") [13] trials. However, PISA-PED found that hypoxaemia and respiratory alkalosis were present in 75% of patients who did not have PTE, thus making them nonspecific for this condition.

ECG findings Nonspecific ST segment changes were found by the PIOPED study in 70% of patients with PTE. PISA-PED found signs of right ventricular overload (T inversion in precordial leads, S1Q3T3, transient right bundle branch block) in 50% of patients with proven PTE, but only in 12% of those who did not have PTE.

D-dimer Measurement of D-dimer, which is a degradation product of crosslinked fibrin, is highly sensitive but nonspecific for thromboembolism. Elevated levels are also found in any condition in which fibrin is formed and degraded by plasmin, such as advanced age, trauma, infection and inflammation, pregnancy, postoperative states, and cancer [14]. This makes it of high negative predictive value (NPV) in ruling out PTE in patients with low clinical probability, but of low positive predictive value (PPV) in confirming the presence of the disease. However, its effective use depends on establishing a reliable and fast methodology. Although a threshold of 500 ng/ml is accepted as the upper range of normal, hospitals are advised to establish their own reference values. A number of additional approaches have improved the diagnostic process, and one of them is the combination of a clinical decision rule using Wells score (see below) and the D-dimer test [15]. Several studies have shown that PTE can be safely ruled out without the need for additional imaging in patients with low clinical probability and normal D-dimer test (less than 500 ng/ml), a condition occurring in 20–40% of patients suspected of having PE.

Imaging investigations

The chest radiograph

A preliminary chest radiograph remains important in all patients for exclusion of alternative readily diagnosable conditions (pulmonary oedema, pneumonia, trauma, pneumothorax, etc.) and to aid in interpretation of subsequent tests.

The chest radiograph also has a potentially important but often overlooked role in the choice of subsequent imaging tests (i.e. scintigraphy or MDCT). It has been shown that the presence of any abnormality on the initial chest radiograph decreases the utility of scintigraphy [16]. Conversely, a normal chest radiograph strongly indicates that scintigraphy will have a high likelihood of confirming or refuting the diagnosis of PE. In some diagnostic

algorithms it also defines the requirements for ventilation scintigraphy and is pivotal in the interpretation of the perfusion scintigram (see below).

Lung scintigraphy

Scintigraphic imaging of lung perfusion for diagnosing PTE has been employed for well over four decades, based on the intravenous injection of radiolabelled macroaggregates of human serum albumin (MAA), that is, particles large enough to impact in the terminal arterioles and other precapillary vessels [17, 18]. The underlying rationale is that, provided that such scanning agent is evenly distributed within the blood, its distribution within the lungs mirrors distribution of blood flow. Therefore, areas of the lungs where blood flow originating from the pulmonary artery is arrested because of embolization show up as "cold" areas in the scan (perfusion defects).

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 truly normal perfusion scan virtually excludes the diagnosis of PTE for all practical purposes [19]. The sensitivity and NPV of this noninvasive imaging technique for detecting PE are therefore extremely high. Instead, specificity is rather low, as there are several pathophysiological conditions possibly causing focal defects in a lung perfusion scan. In addition to acute embolism, lung perfusion scintigraphy can in fact be abnormal in a variety of conditions, the most relevant of which is prior, unresolved PE that can affect as many as 35% of patients with acute PTE [20]. Other conditions associated with the appearance of focal defects in a perfusion lung scan include compression or invasion of pulmonary vessels by tumours or granulomata, emphysema (especially in bullous disease), interstitial fibrosis, bronchiectasis, pneumonic consolidation and atelectasis, localized bronchial obstruction, vasculitis, arteriovenous fistulae, etc. [21–23].

Most of these changes in diseases that primarily affect air flow in the alveolar space are due to intrapulmonary adaptation mechanisms whereby blood flow is diverted from poorly ventilated to better ventilated spaces in order to optimize the V/Q ratio, and therefore to maximize respiratory gas exchanges. Conversely, within a few hours of blood flow obstruction other intrapulmonary adaptation mechanisms start diverting air flow from unperfused to perfused lung zones [12, 24–28], thus avoiding ventilation of areas where respiratory gas exchanges cannot occur [29]. While early after embolization these mechanisms may be linked to local bronchoconstriction caused by hypocapnia [30–33], reduced production of surfactant distal to embolization (with ensuing shrinkage of the alveolar space in the unperfused region) is the most important mechanism taking place more slowly, within 18–24 h [34–36]. Nevertheless, the contribution of additional compensatory factors (besides hypocapnia and reduced local production of surfactant) capable of shifting ventilation away from unperfused areas of the lung cannot be excluded. Taken altogether, such compensatory factors are very efficient, as complete or incomplete infarct has been observed in almost 70% of the patients with PTE [37].

In an attempt to increase specificity of perfusion lung scintigraphy, adding a ventilation scan was then proposed as an aid to identify areas of the lung with impaired ventilation [38], under the assumption that all areas with reduced perfusion *and* ventilation (matching defects) would indicate some preexisting parenchymal condition (thus making PTE unlikely), whereas embolism would be indicated by underperfused but normally ventilated areas (V/Q mismatch pattern). Nevertheless, this approach still did not represent a univocal solution to the diagnostic problem, as also shown by a retrospective study indicating a frequency of only 30% of in-vita successful diagnosis of PTE, based on correlation of clinical data with autopsy findings [39]. Therefore, combined assessment of ventilation and perfusion did not increase per se the diagnostic capability of scintigraphy [40].

The two most widely applied procedures developed with the purpose of enhancing diagnostic accuracy of the scintigraphic approach in PTE have initially been formalized as clinical investigation trials, the so-called PIOPED [41] and the PISA-PED [13] protocols. In the PIOPED protocol, results of the V/Q scan are correlated with the chest radiography findings to classify patients into categories with either high, intermediate, or low probability of PTE. Instead, the PISA-PED protocol correlates the results of perfusion lung scintigraphy alone (where shape and distribution – segmental or non-segmental – of the perfusion defects are considered) with the chest radiography findings to categorize patients as either with or without PTE. In addition to its important role in the pretest clinical evaluation of patients with suspected PE according to the Pisa scoring system (see section below on the necessity of pretest probability), chest radiography is thus confirmed to play a pivotal role also in the PISA-PED protocol for interpreting the perfusion lung scan; in particular, while in the prescintigraphy phase chest radiography mainly serves to raise the suspicion of PTE because of positive findings (amputation of hilar artery, focal oligaemia, pleural-based consolidation), in the interpretation phase of a scan with perfusion defects it helps to exclude embolism (by detecting intrathoracic, extrapulmonary abnormalities causing absence/displacement of lung parenchyma).

Although the PIOPED criteria did succeed in increasing specificity of the V/Q scan in the diagnosis of PTE

(reaching 97% in the presence of underperfused, normally ventilated areas), this result was achieved at the expense of sensitivity (only 41% of patients with documented PTE had a high probability scan). In particular, the pattern of matching V/Q defects did not invariably exclude PTE, while underperfused but normally ventilated areas did not invariably represent embolism. An additional major limitation of the original PIOPED protocol was that as many as 44% of the patients were classified as "intermediate probability" of PE (neither confirming nor excluding PTE), i.e. the protocol was nondiagnostic. This feature contributed to further complicate rather than unequivocally solve the clinical dilemma in a subgroup of patients, one-third of whom actually had PE. Moreover, even experienced observers may underestimate or overestimate the percentage of perfusion defects [42, 43]. These limitations led the PIOPED investigators to revise the original interpretation criteria for easier application and also for better integration with the clinical pretest probability of PTE [44–47] (Table 1). Such modified criteria resulted in increased sensitivity as compared to the original criteria (83% versus 41%), with virtually unchanged specificity (96% versus 97%).

On the other hand, the PISA-PED protocol includes perfusion lung scintigraphy alone (i.e. without the ventilation scan) in a diagnostic algorithm that starts with evaluation of the clinical probability of disease, assessed according to the pretest Pisa scoring system [48]. In this protocol, the diagnostic relevance of the scintigraphic findings relies mostly on the shape and type of segmental or nonsegmental distribution of the perfusion defects, but also takes into account possible chest radiographic abnormalities (Table 2). Moreover, it must be underlined that the PISA-PED approach does not employ chest radiography as a surrogate for the ventilation scan, e.g. to diagnose PE only in regions of the lung where perfusion is absent and the radiographic appearance is normal, as is suggested in the so-called modified PIOPED approach [49]. When compared to the original PIOPED protocol, the PISA-PED approach has two main advantages: (1) scintigraphy either confirms or excludes the clinical suspicion of PE (thus virtually eliminating nondiagnostic examinations), and (2) the sensitivity of lung scintigraphy is greatly increased (86% versus 41%), yet with minor reduction of specificity (from 97% to 93%). Such advantages are maintained also versus the revised PIOPED protocol, although to a lesser extent [43, 44].

As a general trend, most nuclear medicine centres in the US adopt the PIOPED criteria, whereas most centres in Europe and elsewhere in the world tend to employ perfusion lung scintigraphy alone (whether or not fully formalized as in the PISA-PED protocol). Such latter operational choice is supported both by practical considerations (e.g. reduced radiation exposure, easier handling of acutely ill patients often in discomfort) and by considering that even a subgroup analysis of the PIOPED data indicated that the ventilation scan was not essential [49]. This conclusion (whose pathophysiological roots lie in the adaptation mechanisms mentioned above, whereby air flow is diverted from underperfused to normally perfused lung zones in order to optimize respiratory gas exchanges [50], is further supported by a retrospective analysis in which one of the PISA-PED investigators re-read the perfusion scans and chest radiographs from the PIOPED I study, showing higher sensitivity than when including the ventilation scan in the analysis [13]. Furthermore, reliability of the perfusion scan alone has been confirmed also by a recent retrospective analysis of data from the PIOPED II study, whereby such perfusion scans were re-read according to the PISA-PED criteria [51, 52] as well as according to the modified

Table 1 Modified PIOPED II scintigraphic criteria for the diagnosis of PE

Category	Findings
PE present (high probability)	Two or more segments of V/Q mismatch
PE absent (normal perfusion or very low probability)	Nonsegmental perfusion abnormalities: enlargement of the heart or hilum, elevated hemidiaphragm, costophrenic angle effusion, and linear atelectasis with no other perfusion defect in either lung
	Perfusion defect smaller than corresponding radiographic lesion
	Two or more matched V/Q defects with regionally normal chest radiograph and some areas of normal perfusion elsewhere in the lungs
	1–3 small segmental perfusion defects (<25% of segment)
	Solitary triple-matched defect (defined as a matched V/Q defect with associated matching opacity on chest radiograph) in the mid or upper lung zone confined to a single segment
	Stripe sign (a stripe of perfused lung tissue between a perfusion defect and the adjacent pleural surface; best seen on a tangential view)
	Pleural effusion of one-third or more of the pleural cavity with no other perfusion defect in either lung
Nondiagnostic (low or intermediate probability)	All other findings

Reproduced from reference [47].

PIOPED criteria [49]. In this analysis, sensitivities and specificities of the diagnostic scans were similar for the two reading methods, as follows: 84.9% sensitivity for modified PIOPED versus 80.4% for PISA-PED, 92.7% specificity for modified PIOPED versus 96.6% for PISA-PED. It must be emphasized, however, that there were 20.6% non-diagnostic scans with the PIOPED reading criteria (which were therefore excluded from the computation of sensitivity and specificity), versus 0% with the PISA-PED criteria.

SPECT imaging for lung scintigraphy

Traditional interpretation of the lung V/Q scan is based on two-dimensional planar image acquisition [53]. With the use of single photon emission computed tomography (SPECT) acquisition, the V/Q scan has undergone a transition to three-dimensional volumetric imaging. This has been reported to demonstrate improvements in diagnostic sensitivity, specificity and interobserver agreement [54, 55]. In addition, SPECT has other advantages such as the ability to analyse data objectively, or to incorporate both functional and anatomical information by using image fusion [56]. Despite these benefits, the transition from planar to SPECT imaging poses a challenge for nuclear medicine specialists, since they have to adjust to the increased ability of tomographic images to resolve regional impairment due to removal of partial voluming and shine-through effect. Nevertheless, SPECT has a higher spatial resolution, so it can detect abnormalities particularly at the subsegmental level and in the lung bases, where the segments are tightly packed. It has been suggested that SPECT is suitable for the diagnosis of postoperative PTE [57].

V/Q SPECT is based on the fundamental principle that the number of photons originating from an area of lung is proportional to the relative distribution of the agent being imaged. Consequently, perfusion images provide information on the relative topographic distribution of cardiac output, whereas ventilation images provide similar information on alveolar ventilation. Objective analysis of SPECT images has a high diagnostic accuracy in patients with suspected PTE and also has the potential to reduce the number of nondiagnostic scans. It may be useful for quantifying V/Q mismatch in other pulmonary disorders [55]. Planar-like images have been generated from the SPECT data without increasing scan time and radiation dose by two methods. One method sums projections over a limited angular range (resulting in angular summed images), while another uses reconstructed SPECT data projected through an attenuation map to generate count-rich reprojected planar images [58]. Angular images result in a perceived decreased likelihood of PTE compared with true planar images. In contrast, while reprojected biplanar images result in an increased number of matched defects compared with true planar scans, there is no change in the clinical interpretation [58]. Caution should be exercised when interpreting SPECT derived angular summed planar images in isolation.

SPECT not only improves the diagnostic accuracy of V/Q, but also facilitates the application of advanced image-processing techniques. Because of the 3-D properties of the SPECT data, the analysis of lung scans can be automated and objectified. Algorithm-produced images have been reported to be easy to read and well suited to the demonstration of PTE [59].

Evolution of MDCT

For the last two decades, MDCT has benefited from virtually continuous technical development. This technical improvement is set to continue and is moving in different directions. The first is the increasing number of rows of detectors, with a parallel increase in volume coverage in one rotation time and a decrease in the time necessary to acquire the entire chest. At the RSNA 2007 (Radiological Society of North America), some companies presented MDCT with 320 slices or 264 slices per rotation covering 160 mm and 80 mm with submillimetric slices (0.5–0.625 mm) in one rotation, respectively. Using this new technology, it is possible to image the pulmonary arteries of

Table 2 Reading of perfusion lung scintigraphy according to the PISA-PED protocol

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

Reproduced from reference [13].

the entire chest in a short breath-hold of a few seconds and consequently reduce the amount of contrast medium necessary to highlight the pulmonary arteries. The gantry rotation has decreased also to 270 ms or less for some MDCT systems, and effectively freezes cardiac motion during acquisition. It also enables better delineation of juxtacardiac pulmonary arteries and possible assessment of coronary arteries within the same CT acquisition. The use of ECG-gated synchronization is an alternative for this purpose and has already been used in patients with atypical chest pain in the context of a triple rule-out protocol [60–62]. In this situation, MDCT has the potential to play a role in the emergency room for the triage of patients with suspicion of PTE, coronary artery disease, or aortic dissection. Other investigators have explored the ability to diagnose PTE also assessing its secondary cardiac effects within the same CT acquisition using retrospective ECG-synchronization and dedicated reconstructions [63, 64]. It appears possible that retrospective ECG-synchronized MDCT facilitates detection of right ventricular dysfunction, depending on the location of the pulmonary embolus [64].

A second direction of development is the possibility of producing dual-energy images by using double-tube technology or by two superimposed coats of detectors with the property of capturing images with two different energies during the x-ray tube rotation. In this context, it has been demonstrated that the use of low-dose energy images can reduce the amount of contrast medium needed to highlight the pulmonary arteries [65]. Other teams of investigators have demonstrated, in preliminary studies, that it is possible to provide anatomical and functional imaging with the demonstration of perfusion defects in patients with proven PTE [66, 67].

Another possible way to facilitate PTE assessment with MDCT is the introduction of computer-assisted detection (CAD) for PTE [68]. The different CAD systems already tested show a wide range of sensitivities and specificities, with a mean false-positive rate in the detection of emboli in the pulmonary arteries ranging from 0.93 to 24 per case [68]. Although this technique requires refinement, it promises to help the radiologist in daily practice to detect incidental PTE or overlooked peripheral emboli.

Worldwide CT availability

A global audit of CT distribution is difficult, but a relatively recent publication by the Organisation for Economic Cooperation and Development (OECD) provides data for member states (see Table 3). Although the data in this OECD census table is for the year 2005, it clearly demonstrates the wide disparity in CT availability also in countries considered to be developed. The difference across less wealthy parts of the world is likely to be considerably greater. This has a direct influence on access to CTPA, which must compete for availability of CT resource with other pressing diagnostic protocols.

Table 3 CT scanners per million of population arranged in decreasing order (OECD census 2005)

Country	Scanners per 10^6 population
Japan	92.6
Australia	45.3
USA	32.2
Belgium	31.6
Austria	29.4
Luxembourg	28.6
Italy	27.7
Portugal	26.2
Greece	25.8
EU average	20.6
Germany	15.4
Finland	14.7
Denmark	13.8
Spain	13.5
Czech Republic	12.3
Ireland	10.7
France	9.8
Poland	7.9
United Kingdom	7.5
Hungary	7.1

Furthermore, international experience shows a wide heterogeneity of distribution of the different generations of CT scanners. In 2004, 75% of MDCT scanners in Belgium were 16 slice or greater. In Japan in 2005, 25% of all scanners were MDCT (Tomio Inoue, personal communication, IAEA 2008). This heterogeneity should encourage caution when comparing diagnostic accuracy and imparted radiation dose.

Magnetic resonance imaging

Although MRI has been used to reliably detect central (truncal to segmental) pulmonary emboli [69], it has not been widely embraced clinically for reasons of access and poorer sensitivity and specificity for more peripheral emboli. Nevertheless, the group acknowledge the theoretical advantage of combined pulmonary angiography, venography and lung perfusion offered by MRI [70]. Future large-scale studies are awaited in this regard.

Changing pattern of imaging modality utilization

Many centres anecdotally report a significant reduction in lung scintigraphy examinations, but this appears to differ appreciably between countries. Contemporary comparative data is relatively scarce, but some evidence exists regarding an overall declining trend for the frequency of use lung

scintigraphy, an examination that is mostly performed to diagnose PTE. This pattern is exemplified in Tables 4 and 5 for some European countries. A similar trend is also occurring in the USA, where the annual number of lung scans reached a peak of about 1.1 million in the years 1997–1999, declining however to about 67% of that figure in the year 2005 (source: The Society of Nuclear Medicine, Reston, VA).

It would appear that rates for scintigraphy remain more buoyant in countries where nuclear medicine remains separate from radiology. In countries such as Germany and the UK, where radiologists perform both scintigraphy and CT, the impact of MDCT has been felt more acutely. In the example from the Yokohama City University Hospital shown in Fig. 1a, the influence of MDCT appears even greater, possibly reflecting the greater availability and utilization of CT in Japan (authors' own data, Tomio Inoue). Nevertheless, it should be pointed out that, even in the same geographical area there are widely heterogeneous patterns of utilization, as shown in Fig. 1b that depicts the corresponding pattern occurring in the nearby hospital affiliated to the same Yokohama City University, where perfusion lung scintigraphy actually seems to have shown a new surge of utilization after the initial enthusiasm for the new imaging technique MDCT pulmonary angiography. Such diverging patterns might be linked to differences in cultural attitude, different experience of each local team, and/or to other local factors.

Lung scintigraphy versus MDCT?

In the past, the sequence of imaging investigations depended on the clinical scenario, the probability of PTE, the condition of the patient, the availability of diagnostic tests, the risks of iodinated contrast material, radiation exposure, and cost. Now, however, there is a perception that the referring clinician and the radiologist may have a tendency to move directly to MDCT for all scenarios without full knowledge or consideration of all these issues [71]. To help consider if this is due to acknowledgement of the accuracy of MDCT or clinical expediency (as perhaps witnessed by the falling prevalence of positive MDCT studies [2]), it was considered valuable to tabulate the recognized relative benefits and drawbacks of CTPA versus lung scintigraphy (either the perfusion alone or V/Q scans). Some of the issues raised in Table 6 are discussed in detail below.

Table 4 Sample of European lung scintigraphy activity

	France	Germany	Italy	Spain	UK
Perfusion lung scans					
2005	71,748	123,128	57,610	36,145	85,858
2007	63,222	77,918	59,302	38,718	67,601
Ventilation lung scans					
2005	64,857	34,001	6,331	20,860	67,611
2007	61,168	42,614	7,985	20,190	47,871

(source: Anthony Stevens, Medical Options Inc., London, UK)

Table 5 Overall percentage changes in lung scintigraphy in the year 2007 versus 2005 (same 40 centres per country)

	France	Germany	Italy	Spain	UK	Europe
Perfusion lung scans	−6.4	−19.4	+0.1	−7.2	−15.2	−10.4
Ventilation lung scans	−1.4	−0.6	+10.9	−6.7	−17.8	−7.1

(source: Anthony Stevens, Medical Options Inc., London, UK)

Is pretest probability scoring essential?

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 PTE, 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 for the round-the-clock availability of a team of specialists, each possessing specific competence in the different medical fields involved with PE.

Recognizing the importance of such a multidisciplinary approach, virtually all major hospitals have developed sequential diagnostic algorithms for patients with suspected acute PE. The first step in such algorithms is almost invariably represented by accurate clinical history, physical examination and some basic instrumental evaluations (such as ECG, arterial blood gas analysis, etc.). While each institution may have developed its own internal guidelines for approaching this clinical condition, as mentioned above there are at least three internationally recognized systems that have been developed with the purpose of assessing, before employing more complex imaging procedures, the probability that a given patient with suspected acute PE actually has the disease (pretest probability). These systems, commonly employed to assess the predictive value for PTE of the physicians' estimates of clinical probability for such disease (sometimes with minor variations adopted locally), are generally known as the "Hamilton" [72], the "Pisa" [48], and the "Geneva" [73] scores, respectively. All three scores rely on a set of relatively simple data that can be obtained clinically and/or with first-line instrumental evaluation, as summarized in Table 7.

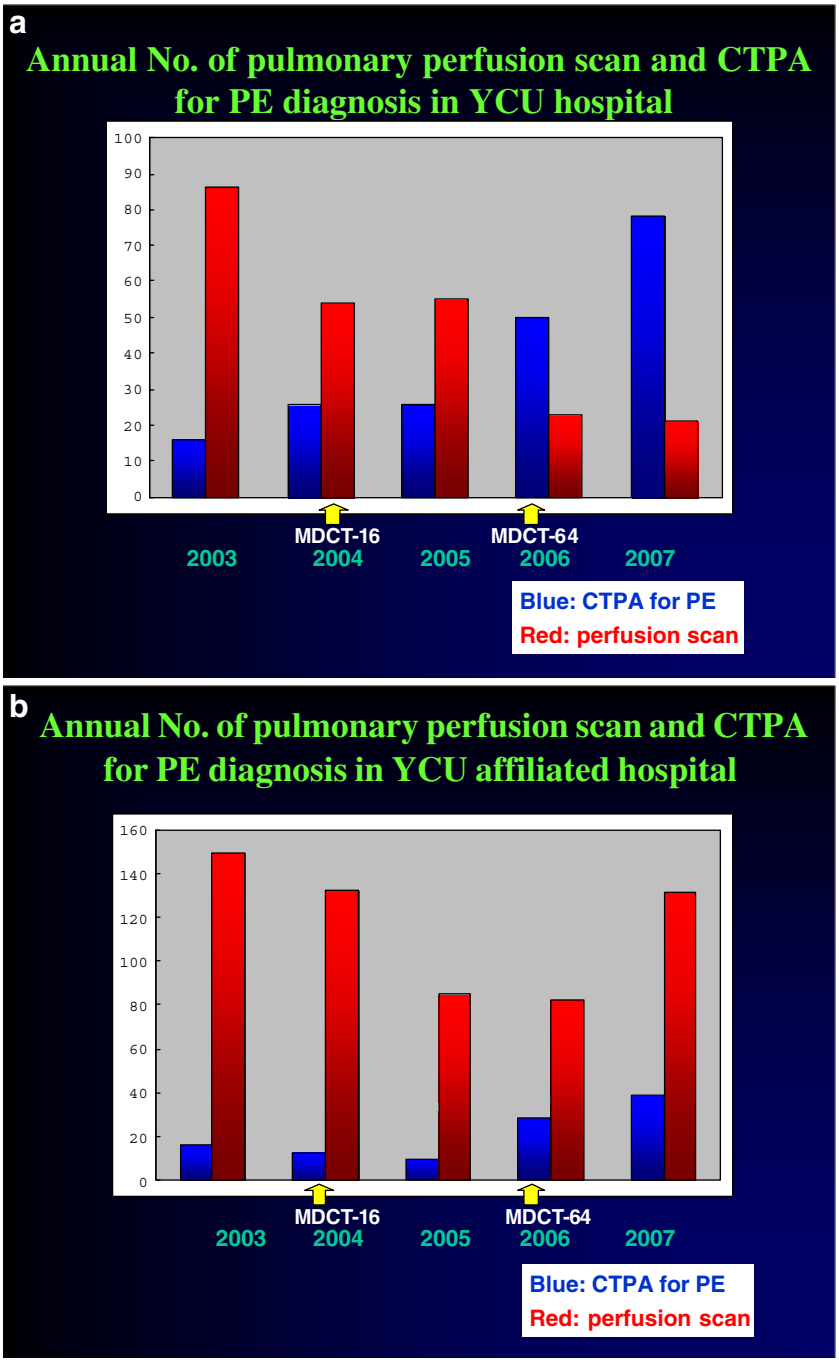

Fig. 1 Annual numbers of pulmonary perfusion scans and CT pulmonary angiograms for diagnosis of PTE, respectively in the Yokohama City University Hospital (**a**) and in the Yokohama City University affiliated hospital (**b**). Introduction points of MDCT are shown by arrows, respectively for the 16-slice MDCT (in 2004) and for the 64-slice MDCT (in 2006) (courtesy of Prof. Tomio Inoue)

While some contributing signs and symptoms are considered in one only of the three scores (e.g. malignancy in the Hamilton score, ECG signs of right ventricular overload in the Pisa score, and older age in the Geneva score), there are several overlapping factors, perhaps with different weight. In particular, DVT (past and/or present) is considered both in the Hamilton and in the Geneva score, the possibility of an alternative diagnosis (either a formal component of the score or mentioned among the interpretation criteria) is considered both in the Hamilton score and in the Pisa score as are symptoms of acute PE (either haemoptysis or other symptoms), chest radiographic abnormalities (although differently identified) are considered both in the Pisa score and in the Geneva score, and so on. For the Hamilton and the Geneva scores, this preliminary phase in the diagnostic approach to patients with suspected acute PE also includes, even without formal specific mention, some ancillary evaluations that are important towards ascertaining the presence of DVT, such as the circulating levels of fibrinogen and D-dimer, as well as

Table 6 Relative strengths and weaknesses of MDCT pulmonary angiography and lung scintigraphy in the evaluation of PTE

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	

Doppler ultrasound examination of venous circulation in the lower limbs.

Despite some non-negligible differences in the contributing factors, all three scores perform comparably well in their ability to correctly identify patients with either a low or a high probability of acute PE (see Table 8). In particular, the proportion of patients initially classified pretest as low-probability for PTE who are eventually diagnosed as not being affected by the disease ranges between about 90% and 97%. On the other hand, the proportion of patients initially classified pretest as high-probability who are eventually diagnosed as actually having the disease ranges

Table 7 Comparative summary of signs and symptoms contributing to form the Hamilton [73], the Pisa [48], and the Geneva [74] scores, respectively. Numerical scores are indicated in parentheses

	Hamilton	Pisa	Geneva
Signs and symptoms of DVT	Yes (3.0)	No	No
PE as or more likely than an alternative diagnosis	Yes (3.0)	No	No
Tachycardia	Yes[a] (1.5)	No	Yes[b] (2)
Immobilization or surgery	Yes (1.5)	No	Yes (2)
Previous DVT or PE	Yes (1.5)	No	Yes (2)
Haemoptysis	Yes (1.0)	No	No
Malignancy	Yes (1.0)	No	No
Older age	No	No	Yes (2)
Hypocapnia	No	No	Yes (2)
Hypoxaemia	No	No	Yes (2)
Chest radiography	No	Yes[c]	Yes[d] (2+2)
Symptoms of PE	No	Yes[e]	No
ECG	No	Yes	No
Low probability	<2	None of the above or alternative diagnosis	≤5
Intermediate probability	2 to 6	One or more symptoms alone or with ECG indicating acute right ventricular overload	5 to 8
High probability	>6	One or more symptom *and* one or more chest radiographic abnormalities	≥9

[a] Defined as heart rate >100.
[b] Not specifically defined.
[c] One of: amputation of hilar artery, focal oligaemia, pleural-based consolidation.
[d] Either plate-like atelectasis and/or hemidiaphragm elevation.
[e] One of: sudden onset dyspnea, chest pain, fainting.

between about 78% and 97%. Finally, all three scoring systems share similar degrees of uncertainty in identifying acute PE in patients classified pretest as intermediate-probability, as the proportion of these patients eventually diagnosed with the disease ranges between about 30% and 40%.

Nevertheless, 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". In fact, this is the patient population that requires further testing to either confirm or rule out actual occurrence of the disease. Furthermore, the system should be designed so as to perform equally well in patients presenting to the emergency room as outpatients and in patients who are already hospitalized. In this regard, the Pisa score classifies the smallest fraction of patients as intermediate probability for acute PE, i.e. 22.1% compared with 32.5% for the Hamilton score and 44.3% for the Geneva score (see Table 8). It should also be noted that neither the Hamilton nor the Geneva score take into account the three more frequent symptoms of PE: sudden onset dyspnoea, chest pain, and fainting [13].

The above issues explain why the Pisa score is has an especially high predictive accuracy, while it has also been emphasized that, at variance with the Hamilton and the Geneva scores (that are more accurate for outpatients than for inpatients), the Pisa score performs equally well for inpatients as for outpatients [74]. This is readily apparent from the last two rows of Table 8, which show that the Hamilton and the Geneva scores perform well in patients with low probability (who are frequent among outpatients), but poorly in patients with high probability (who are more frequent among inpatients).

It can therefore be concluded that, although clinical assessment alone cannot definitely confirm or rule out acute PTE, it has nevertheless an important role in stratifying patients' probability of having the disease. This topic is clarified in the discussion of posttest probability. Therefore, each institution should adopt well-defined internal guidelines for clinical assessment of the pretest probability of acute PE. Such guidelines, possibly adapted locally based on availability of the various diagnostic facilities/procedures, can be derived from any of the three validated systems discussed above, as also from alternative models taking into account a number of additional diagnostic/prognostic factors [75, 76]. Whatever is the scoring system adopted for assessing the pretest probability of acute PE in patients suspected of having this condition, such preliminary evaluation should form the beginning of a multistep procedure leading to diagnosis and treatment of the disease by a multidisciplinary team of experts.

Modality selection bias

Several reports of decision-analysis algorithms have advocated the use of conventional pulmonary angiography to confirm or exclude the diagnosis of PTE after a V/Q lung scan. However, as many as 80% of patients never receive a definitive diagnosis after lung scan since physicians often are reluctant to refer the patients for pulmonary angiography, and as many as 34% of patients also receive anticoagulants without having a confirmatory diagnosis of PTE [77]. These findings appear to be consistent across many health-care systems and countries [78]. In a study from Boston by Khorasani et al. [79], 14% of patients were treated for acute PTE solely on the basis of clinical findings, although the overall frequency of major bleeding among patients starting anticoagulant therapy has been reported to be 6% (which is much greater than the 1.5% of major complications from pulmonary angiography) [80]. Rosen et al. [78] used a utility analysis to explore physicians' attitudes toward the misdiagnosis of PTE. A utility is a quantitative measure of the strength of an individual's preference for a specific outcome. It is assumed that the decision alternative with the highest expected utility should be preferred to the other alternatives. Their study demonstrated that the utility of providing inappropriate

Table 8 Performance of the three pretest scoring systems in classifying patients as low, intermediate and high probability, respectively, of acute PE, and final classification of patients after full diagnostic testing

	Hamilton	Pisa	Geneva
Patient population (*n*)	1,239	750	986
Overall patients with acute PE	215 (17.3%)	305 (40.7%)	266 (27.0%)
Low probability	734 (59.3%)	350 (46.7%)	486 (49.3%)
Intermediate probability	403 (32.5%)	166 (22.1%)	437 (44.3%)
High probability	102 (8.2%)	234 (31.2%)	63 (6.4%)
Low probability without PE	712 (97.0%)	340 (97.1%)	437 (89.9%)
Intermediate probability with PE	113 (28.0%)	68 (41.0%)	166 (38.0%)
High probability with PE	80 (78.4%)	227 (97.0%)	51 (80.9%)

treatment of PTE is not considered to be as bad as missing a case of PTE. There may be several reasons why physicians' practice and perceptions could be at odds with suggested practice guidelines as derived from decision-analysis models. One bias affecting clinician decision making may be attributed to the concept of "availability", in which recent or compelling experiences are remembered more strongly than remote or less compelling experiences [81]. A second explanation may relate to physicians' attitudes toward iatrogenic complications. A third factor that may influence physicians' responses relates to framing bias [82].

CTPA now appears to be a safe alternative to lung scintigraphy for excluding PTE, but also detects more emboli than scintigraphy. Therein lies a potential problem, since many of these additional diagnoses by CTPA recommended by biased general clinicians or radiologists may be clinically insignificant (see below) and lead to potentially dangerous and costly treatment with an attendant increase in radiation exposure [83]. Further well-controlled studies are required to determine whether all pulmonary emboli detected by CTPA should be managed with anticoagulant therapy.

Clinical dilemma of potential over-diagnosis of non-clinically relevant PTE by MDCT pulmonary angiography

The advent of MDCT pulmonary angiography has contributed to major advances in the diagnosis of PTE. Using this technology, an exquisite depiction of peripheral pulmonary arteries has been reached [84–86] with a parallel increase in detection of incidental clots. To date, the frequency of emboli discovered by the recent generation of MDCT scanners has been reported only in a few studies [87–89]. Storto et al. [87] found incidental PTE in 3.4% of 581 patients assessed by four-slice CT, with an inpatient prevalence of 4% and outpatient prevalence of 0.9%. In this series, the proximal extent of emboli involved main pulmonary arteries in five patients, and a segmental artery in ten patients. Thirteen patients showed multiple filling defects, whereas isolated emboli were identified within segmental arteries in five patients and lobar arteries in two. None of the patients showed isolated subsegmental pulmonary emboli. However, subsegmental filling defects were observed in combination with larger emboli in eight patients. In this study, 70% of patients with incidental PTE had malignancy. Ritchie et al. [88] studied prospectively 547 inpatients with a 4- and 16-slice CT scanner, and discovered a 5.6% rate of incidental pulmonary arterial clots. The proximal level of thrombus was seen at a segmental and subsegmental level in 13 (46%) and 5 (17%) of the 28 positive scans. Unsuspected emboli were not detected in any of the patients aged below 50 years, whereas incidental filling defects were present in almost 17% of those aged over 80 years. In this series, approximately 32% of incidental PTE were not identified prospectively by the original reporting radiologists. All of those were found in segmental or subsegmental vessels. Engelke et al. [89] reviewed retrospectively CT images performed on 4- and 16-slice CT scanners from 1,869 consecutive patients, and found incidental PTEs in 4.3% of all patients undergoing MDCT over an 11-month period, with no mention of the distribution level of those emboli. In this patient cohort, the diagnosis of unsuspected PTE was frequently missed (39 out of 56 cases, 69.4%) despite routine double reading by at least one board-certified and one trainee radiologist.

A question often raised over the past few years concerns the clinical relevance of such peripheral emboli discovered incidentally. Several authors consider that tiny clots originating from calf veins do not require anticoagulation [90, 91]. However, occlusion of a few subsegmental branches perfusing the most "normal" part of the lung parenchyma has been reported to lead to respiratory failure in patients with preexisting chronic obstructive pulmonary disease [92]. It is speculated that one important function of the lung is to prevent small emboli from entering the arterial circulation. Such emboli may form even in healthy individuals, although this notion has never been substantiated [93]. Controversy also exists about the treatment of small emboli and whether this will result in improved clinical outcome [94–96]. It is assumed that the presence of such emboli may indicate current DVT that potentially heralds more severe embolic events [97, 98]. In this situation, there is a need to search occult DVT by compression ultrasonography or CT venography which may dictate the subsequent therapy. A burden of small peripheral emboli is also thought to have prognostic relevance in individuals with cardiopulmonary disease and for the development of irreversible pulmonary hypertension in patients with chronic thromboembolic disease [99]. One clinically controlled study [100] has been conducted in which the recurrence and mortality rates among anticoagulation-treated patients with proved PTE were compared with those among nontreated patients with proved PTE. Nielsen et al. [100] studied 87 ambulatory patients with proved DVT and no symptoms of PTE. Occult PTE occurred in 49% of these patients. One-half of them were treated with anticoagulation, and one-half were given the nonsteroidal antiinflammatory agent, phenylbutazone. At the 3-month follow-up, 19 patients in each group had developed progressive venous thromboembolism, documented by venography, V/Q scanning, or clinical evaluation. Thus, anticoagulation did not appear to alter disease progression. One patient who was undergoing anticoagula-

tion therapy died. There were no deaths among the 43 control patients, despite progressive venous thromboembolism in 19 of them.

Currently, there is no straightforward recommendation for the treatment of subsegmental PE. Recently, Goodman [95, 101] defined four groups of patients in whom the risks of anticoagulation may outweigh the benefits: (1) patients with symptomatic isolated subsegmental PTE, no DVT and adequate cardiopulmonary reserve; (2) patients with asymptomatic PTE, no DVT and adequate cardiopulmonary reserve; (3) patients with indeterminate MDCT scan, no DVT, adequate cardiopulmonary reserve and low or moderate clinical probability of PTE; and (4) patients with isolated subsegmental PTE or indeterminate MDCT, no DVT or contraindications to anticoagulation.

Based on the scarce published literature, there is no definitive and unequivocal answer to the clinical relevance and treatment of incidental PTE discovered by MDCT. From a diagnostic point of view, the discovery of incidental subsegmental PTE should influence the clinician to search for occult malignancy and DVT in patients. From a therapeutic viewpoint, there is a need for prospective and controlled studies to confront the important question of anticoagulation therapy in patients with non-clinically relevant PTE identified by MDCT.

Specific clinical scenarios

It has been suggested that there are defined clinical scenarios where MDCT pulmonary angiography may be disadvantageous. Although frequently cited [83], there is often a lack of clarity as to how the clinician and radiologist should proceed in these situations. It is worth examining these scenarios briefly and the evidence that supports these concerns.

Patients with significant renal impairment

Contrast-induced nephropathy, arbitrarily defined as a 25–50% rise in serum creatinine, is unfortunately not a rare sequel to CT angiography and can occasionally lead to acute renal failure constituting the third most common hospital acquired cause [102]. This event is considerably more likely to happen in patients with preexisting renal impairment. Predisposing factors include increasing age, diabetes, congestive heart failure, and dehydration. Preexisting renal impairment is a strong predisposing factor, and the risk of contrast-related nephropathy rises as the estimated glomerular filtration rate (eGFR) falls. Although pharmacological prophylaxis including *N*-acetylcysteine and methylxanthines have been used to variable effect, adequate hydration and avoidance of large volumes of contrast medium seem to have the most predictable effects. In someone with an eGFR<20 ml/min, alternative strategies for investigation which avoid the use of contrast medium should be strongly considered.

Investigation of PTE in pregnancy

There has been considerable debate on the relative merits of CTPA versus scintigraphy for the exclusion of PTE in the gravid patient [103]. Much of this debate centres around the interpretation of radiation dosimetry (both to the fetus in particular and to the maternal breast) and the hardware and protocols used for CTPA (which are continually being modified). In many centres, the relatively low incidence of lung comorbidity in pregnancy allows perfusion scintigraphy to be performed using "half-dose" (40 MBq ^{99m}Tc-MAA) without the need for a ventilation scan. Some authors have highlighted the relatively high dose to the breast from CTPA, which can range from 10 to 35 mGy [104]. Whereas, it has been estimated that the average breast exposure from half-dose perfusion scintigraphy can be up to 150 times lower than that of CTPA [105]. Conversely, it is accepted that scintigraphy imparts a higher dose to the fetus (640–800 μGy) than CTPA (3–131 μGy), and this notion must be given due consideration [106].

Unfortunately (or fortunately), no conclusive data yet exist to firmly prove or disprove the risks of carcinogenesis to breast tissue or the fetus from diagnostic tests. Some authors, however, persuasively argue that the risk to the fetus may have been over-emphasized, since the estimated incidence of radiation-induced childhood malignancy after half-dose scintigraphy is thought to be in the order of 1 in 560,000, compared to 1 in 1,000,000 from CTPA [105]. When taken in context of the estimated 14% increased risk against the background rate of malignancy in maternal breast tissue per 10 mGy it would appear that there are reasonable grounds to utilize scintigraphy in the pregnant patient.

Follow-up of acute PTE

The most feared long-term consequence of untreated or poorly treated acute PE is chronic thromboembolic pulmonary hypertension, a severely debilitating and potentially fatal condition [107–109]. On the other hand, 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 [110]. 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. These considerations emphasize the clinical relevance of adequate follow-up after the diagnosis and primary therapy of acute PTE, both in the short term and in the long term. 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, see Table 6) 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.

Therefore, whatever is the diagnostic imaging modality that has ascertained the occurrence of acute PE (i.e. either 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 [111]. 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 PTE (i.e. at 1 and 4 weeks), then at 3, 6 and 12 months [112–117].

On the other hand, 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 [109, 118], even in patients without a clinically obvious episode of acute PTE [119]. In this regard, a recent comparative study by Tunariu et al. has clearly demonstrated the superior diagnostic performance of V/Q scintigraphy versus MDCT pulmonary angiography in identifying chronic pulmonary thromboembolic disease as a treatable cause of pulmonary hypertension [120]. Exquisite sensitivity of lung scintigraphy (ranging between 97.4% and 96.2% whether or not considering an intermediate-probability scan as indicative of chronic thromboembolic pulmonary hypertension, compared to 51.3% for MDCT) results in a very high NPV (98.5–97.9% versus 79.7% for MDCT), its specificity being marginally lower than that of MDCT pulmonary angiography (90–94.6% versus 99.3%).

Previous anaphylaxis to intravenous contrast agents

Although the precise mechanism of anaphylaxis to iodinated contrast agents is not clearly understood, histamine release certainly plays a part in the symptomatology. Although the phenomenon is universally feared, it is exceptional using modern contrast media. Lethal reaction is rare, and in one large series of 67,000 patients no deaths were encountered [121]. However, it is recognized that contrast agent anaphylaxis can be profound and unpredictable. In the scenario of a previous reaction, there is no good evidence that pharmacological prophylaxis will avoid a second event, although it may modify some of the histamine-mediated symptoms [122]. In this respect, scintigraphy remains a useful and efficacious alternative for the exclusion of PTE.

Discussion

The data available to this IAEA consultants group would suggest that utilization of scintigraphy for PTE investigation is declining, although not perhaps at the rapid rate previously suspected. International variations exist which may depend upon the clinical discipline that supervises and performs nuclear medicine procedures. MDCT technology continues to develop at an impressive rate, perhaps adding to the impression that it is a continuously updated "product" and therefore more appealing to referring clinician bias. On the other hand, it is clear that the technological status of scintigraphy is not static, and the effect of SPECT and direct thrombus imaging may yield further diagnostic benefits.

The several distinct advantages of MDCT including high specificity, availability and the superior ability to supply alternative diagnoses have come at the expense of an increased radiation burden. The effect of a low clinical threshold for utilization which promotes indiscriminate and repeated use, particularly in younger patients, has yet to be felt. Although the statistical data may be difficult to gather, it is intuitive that the lower radiation dose and higher sensitivity of scintigraphy in younger patients can only be beneficial.

As with CT, scintigraphy offers specific advantages in a number of scenarios, particularly where high NPV and low radiation dose are of parallel importance, such as in the young pregnant patient. Its routine use in patients who are young, have no preexisting lung pathology, and have a normal chest radiograph should not be demeaned. It remains one of the best tests yet established for the follow-up of PTE after diagnosis and shows significant advantage in the investigation of the aetiology of pulmonary hypertension. In randomized direct comparison studies, MDCT has been found to be not inferior to scintigraphy, and CT has been shown to identify more cases of embolic disease [83]. However, as highlighted above, it is not yet clear if all emboli thus identified require treatment by anticoagulation.

Conclusion

There is considerable international variability in the diagnostic approach to investigating PTE based on cost, modality availability, training and cultural approach to radiation exposure. It is, however, necessary for everyone (referring physician, nuclear medicine specialist and radi-

ologist alike) to be judicious in the use of imaging technology. It is the clinical community's responsibility to ensure that population exposure to ionizing radiation is kept as low as possible and commensurate with accurate diagnosis. Despite the great technical advances in MDCT, the IAEA Group consider that lung scintigraphy is not redundant and has instead a clearly defined role. The Group feel it is important to re-emphasize the radiation-sparing nature of scintigraphy in certain patient groups.

It is also considered mandatory, for intelligent direction of diagnosis and treatment of PTE to utilize pretest scoring. It is also helpful to be reminded that in the clinical rush to adopt new technologies we "do not throw one of our babies out with the bath-water".

Recommendations

- Proper pretest clinical probability scoring is important irrespective of the modality used. It will aid interpretation and also help focus referrals, thereby promoting sensible utilization of imaging.
- Lung scintigraphy has a high NPV and should be employed particularly where low radiation dose is desirable. Lung scintigraphy should be used preferentially in certain clinical scenarios:
  - Outpatient with low clinical probability plus normal chest radiograph
  - Patient with high clinical probability plus normal chest radiograph
  - Patient with prior contrast anaphylaxis and strong allergic history
  - Patient with renal failure
  - Patient with myeloma and paraproteinaemia
  - Juvenile and young female with normal chest radiograph
  - Pregnancy
  - Follow-up
  - Investigation of aetiology of pulmonary hypertension

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