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REVIEW ARTICLE

Ventilation/perfusion lung scintigraphy: what is still needed? A review considering technetium-99m-labeled macro-aggregates of albumin

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Abstract Lung perfusion scintigraphy (LPS) with technetium-99m-labeled macro-aggregates of albumin (Tc-99m-MAA) is well established in the diagnostic of pulmonary embolism (PE). In the last decade, it was shown that single-photon emission computer tomography (SPECT) acquisition of LPS overcame static scintigraphy. Furthermore, there are rare indications for LPS, such as preoperative quantification of regional lung function prior to lung resection or transplantation, optimization of lung cancer radiation therapy, quantification of right–left shunt, planning of intra-arterial chemotherapy, and several rare indications in pediatrics. Moreover, LPS with Tc-99m-MAA is a safe method with low radiation exposure. PE can also be diagnosed by spiral computer tomography (CT), ultrasound, magnetic resonance angiography, or pulmonary angiography (PA, former gold standard). The present review considers all these methods, especially spiral CT, and compares them with LPS with respect to sensitivity and specificity and gives an overview of established and newer publications. It shows that LPS with Tc-99m-MAA represents a diagnostic method of continuing value for PE. In comparison with spiral CT and/or PA, LPS is not to be defeated as mentioned also by the most actual Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II reports. This applies in particular to chronic or recurring embolisms, whereas currently spiral CT may be of greater value for major or life-threatening embolisms. At present, LPS cannot be replaced by other methods in some applications, such as pediatrics or in the quantification of regional pulmonary function in a preoperative context or prior to radiation therapy. LPS still has a place in the diagnostics of PE and is irreplaceable in several rare indications as described earlier.

Keywords Lung perfusion scintigraphy · Tc-99m-MAA · SPECT · Pulmonary embolism · Lung resection

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Pharmacokinetic basis for lung perfusion scintigraphy with Tc-99m-labeled macro-albumin aggregates

Lung perfusion scintigraphy (LPS) with macro-aggregates of albumin (MAAs) depends on the principle that particles >10 μm in diameter in the bloodstream are trapped in the lung at first passage [1, 2], causing temporary "micro-embolisms" [3, 4] whose number is in direct proportion to the local rate of blood flow [5]. Following their rapid accumulation in the lung (98% within 1–2 min [6, 7]), MAAs are mechanically and enzymically degraded, and phagocytosed in the liver [8].

For scintigraphic imaging, the MAAs are today labeled with the nuclide technetium-99m (Tc-99m). Following elimination from the lung (half-time for residence 1–24 h [3, 6, 7, 9–11]) the radioactivity is excreted, via the liver and kidneys, in the urine [7, 8, 11].

The perialveolar capillaries have an average diameter of ~8 μm (range 7–10 μm [12]) and the arterioles ~25 μm (15–35 μm [2, 12]). The ideal particle size for good image quality has been stated to be 20–50 μm [2] or 15–40 μm [13]. Today, a range of 25–60 μm is preferred; smaller particles are degraded very rapidly, whereas those in excess of ~60 μm can block the capillary tree at higher levels and thus potentially cause hemodynamic disturbance. Typical Tc-99m-MAA preparations have a size range of 5–100 μm [3], with 80–90% of the particles within the range 10–75 μm [6–9, 14]. Tc-99m-labeled microspheres of human serum albumin are hardly used today, on account of their considerably slower metabolic removal and the consequent safety disadvantage that they bring especially for patients with pulmonary hypertension and for children.

The number of microembolisms caused by MAAs is determined by the ratio between the number of particles injected and the numbers of lung arterioles and capillaries. An adult has some 2.8×10^9 capillaries and 3.0×10^8 arterioles [12]. Therefore, a typical injection with 3×10^5 Tc-99m-MAA particles will—depending on the exact distribution of particle sizes, and varying according to local blood flow rate—temporarily block every millionth capillary and every thousandth arteriole [1]; the latter will not be blocked by particles less than 20 μm in size. Good imaging has been estimated to require at least 60 000 [15] or 100 000 [16, 17] particles in adults, whereas for safety reasons not more than 700 000 particles should be injected [3, 16, 17]. Thus, even if the maximum number of particles is injected, all measuring >20 μm, not more than 0.23% of the arterioles in humans with normal lung function will be blocked (for abnormal cases see "Safety aspects of TC-99M-MAA lung perfusion scintigraphy" section).

Static Tc-99m-MAA lung perfusion scintigraphy in the diagnosis of pulmonary embolism

Pulmonary embolism

Pulmonary embolism (PE) is a major health problem, with an annual incidence of 0.5–1.0 per thousand in the industrialized world [18]; it is more common still among hospital patients [19, 20], where it is the third most common cause of death [13]. The so-called massive embolisms are associated with blockage of ≥70% of the terminal pulmonary vessels and are usually fatal [21]. Some 50–60% of PE cases are caused by deep-vein thrombosis [21].

Pulmonary embolism is frequently clinically asymptomatic in the early stages, until 30% or more of the arterial tree is occluded [22]. It is thus frequently overlooked [13, 18]; a meta-analysis of 12 autopsy studies revealed a high percentage (>50%) of unrecognized, clinically relevant PEs [19]. The mortality rate of unrecognized PE is ~30% [19], but this can be reduced to 2–8% by timely discovery and anticoagulant therapy [23, 24]. The prevalence of PE in patients clinically suspected of having it was found to be 27% [25].

Although it is recognized that several small PEs often herald a large one, such a diagnosis must be reliable, as superfluous anticoagulation can also be dangerous, owing to the suppression of normal coagulation [26].

Initial diagnostic measures for suspected PE

All methods for the diagnosis of PE—imaging and non-imaging—have their characteristic strengths and weaknesses [27]. A "decision tree" of complementary methods is therefore recommended [27, 28]. Clinical symptoms such as acute chest pain, coughing, anxiety, hemoptysis, and tachypnea are unspecific and variable [3, 21, 29], as are instrumental methods such as electrocardiography and chest X-ray [30, 31] and arterial blood gas analysis [32]. A recently developed, relatively reliable marker for PE is the D-dimer, a degradation product of fibrin [33]. Although other factors can lead to a positive D-dimer finding, a negative one allows PE to be *excluded* with high reliability [30, 32–37]. Many authors have therefore proposed that a positive D-dimer result be a requirement for subsequent investigation by an imaging method [18, 27, 30] such as lung scintigraphy [17, 38], spiral computer tomography (CT), ultrasound of the lower leg veins (positive for 70% of PE patients [39]), ultrasound of the thorax (diagnostic accuracy 84% [40]), multidetector row CT [41] echocardiography, or invasive pulmonary angiography (PA). In particular, the accuracy of thoracic ultrasound is heavily contested. As a matter of fact, thoracic ultrasound turned out to be highly unspecific and is mainly used in countries with a lack of imaging departments. A recent study concluded that a combination of negative spiral CT and normal ultrasonography images suffices to exclude PE in emergency contexts [42]. The recently published PIOPED II study [43] found the sensitivity of CT angiography to be 83% with a specificity of 96%, whereas the sensitivity of CT angiography combined with venography was 90% with specificity 95%.

Lung scintigraphy in the diagnostic decision tree

The position of a V/Q lung scintigraphy (LS) within the diagnostic decision tree is currently as follows:

— LS is generally regarded as a method of first choice, if there are clinical signs of PE, as an exclusion criterion [44, 45].
— LS is conducted as a method of first choice if D-dimer elevation has been found [46]; this accords with the recommendations of the European Cardiological Society [18].
— For patients who have already been examined by V/Q scintigraphy, this should be repeated, to ensure the reproducibility of the results [21, 30].
— Certain factors in the patient's earlier findings, clinical symptoms, and/or the pre-test probability [47] are also indications for V/Q LS. If the result of a thorax X-ray was normal, if the clinical pre-test probability was low or middling [48–50], or if the patient is clinically stable, then V/Q LS should be performed first, to allow possible exclusion of PE. If the clinical pre-test probability is high, then spiral CT can be used, as long as the patient is not allergic to the contrast medium [50], has no renal failure, hyperthyroidism or a pacer inducing metal artifacts, and if female, is not pregnant. For patients whose condition is unstable, especially if there is suspicion of a massive PE, echocardiography is recommended on account of the possible hemodynamic consequences [18]; if its result is unclear, then spiral CT or PA should be performed [45, 51].
— LS and spiral CT can be placed sequentially in the decision tree because the integrative-complementary application of these procedures represents a meaningful approach to combining the diagnostic certainty of these two methods: for example, spiral CT following an indeterminate scintigraphic result (middling probability of PE) instead of the invasive PA [28, 52, 53], or following any non-negative scintigraphic result [54]. A prospective study of 779 patients following an abnormal scintigraphy result showed better results from a combination of LS and spiral CT than from either method alone [54].
— LS and spiral CT are considered as options of equal value [55, 56] and are recommended following the establishment of the clinical pre-test probability [27, 57] or an elevated D-dimer level [27, 28, 58, 59].

In clinical routine today, clinicians still have limited knowledge of equipment being used during LPS and spiral CT leading to different decisions about the method of choice in diagnostic imaging of suspected acute PE [60]. In the United States as well as European countries, there is no coherence between the primary diagnostic modality of choice and other factors including hospital size, type, and availability of diagnostic methods [61].

Diagnostic accuracy of static Tc-99m-MAA lung perfusion scintigraphy

In 1990 the PIOPED group published a set of criteria for the determination of the probability of PE on the basis of pre-test probability and the results of V/Q scintigraphy [62]. These criteria were found to provide the most reliable diagnosis of PE when compared with the "gold standard" PA, and the "modified PIOPED criteria" of 1993 [14, 63–65] are still used [17, 66–69]. They allow the probability of PE to be assigned to one of the classes "normal" (in which the prevalence of PE is effectively 0%), "low" (LP; prevalence <20%), "intermediate" (IP; prevalence 20–79%), and "high" (HP, prevalence ≥80%).

Unfortunately, PA is still regarded as the gold standard but this is no longer true [70–72]. Sensitivity of PA may be as low as 70% [71] and this is a reason for the huge number of false-positive results in the PIOPED I study [62]. Therefore, we would like to replace the "gold standard" by the "former gold standard". We summarize here the diagnostic value of these probability classes and discuss them in relation to other, more recent studies. Only a few studies have employed the former gold standard PA as a reference, as this invasive method is ethically unjustified in patients with less than a high probability of PE; therefore, it is used for HP patients only, and clinical course (occurrence of thromboembolic events) is used for the others.

Normal

This can be established on the basis of a normal LPS result only (without a ventilation measurement). Its especial value lies in its high negative predictive value (NPV) of 96–100% [1, 62, 67, 68, 73–75]. The incidence rate of venous thrombo-embolic events (VTEs) after a normal scintigraphic result was correspondingly low (Table 1): 0.3% according to the meta-analysis by van Beek et al. [69], whereas fatal VTEs were very rare (0.15%).

High probability

Various studies have shown that the result "HP" has an overall positive predictive value (PPV) for PE of 88%, which combined with the clinical pre-test probability rises to >95% (Table 2). Therefore, a scintigraphic HP result can be regarded as a sufficient criterion for the initiation of anticoagulation therapy [1, 18, 45, 51]. Of the patients investigated, 4% to 19% were in the HP category [23, 29, 62, 67, 76–80].

Table 1 Studies of the clinical course of patients with normal V/Q lung scintigraphy

Number of patients	Type of study	Observation period (months)	Proportion of patients with non-fatal VTE (%)	Proportion of patients with fatal VTE (%)	References
131	Prospective	12	4	–	[62]
68	Retrospective	2–97	–	–	[35]
586	Prospective	3	0.7	–	[157]
113	Prospective	6	–	–	[81]
188	Prospective	3	–	–	[158]
46	Retrospective	≥6	–	–	[73]
693	Meta-analysis	≥3	0.3	0.15	[69]
27	Prospective	6	–	–	[75]
161	Prospective	3	–	–	[46]
>7000	7 literature studies 1996–2003	Various	0.9	Various	[56]

VTE venous thrombo-embolic events

Table 2 Positive predictive value of a finding "high probability of PE"

Positive predictive value (%)	Standard	References
86	PA	[159]
89.5	PA	[160]
88	PA, clinical course	[62]
96[a]		
98[a]	PA, clinical course	[77]
83.3	PA	[77]
92[a]	PA, clinical course	[161]
96[a]	PA, clinical course	[82]
96[a]	PA	[29]
94[a]	PA, clinical course	[75]
100[a]	PA	[132]

PE pulmonary embolism, *PA* pulmonary angiography
[a] Including consideration of the pre-test probability

Low probability

Results of several studies are shown in Table 3. In summary, the NPV of a PIOPED LP result combined with a low pre-test probability is ca. 96–99% [62, 77, 81], compared with 84–88% when clinical information is not included [62, 82]. With the modified PIOPED criteria, independently of the pre-test probability, a further improvement was gained: only 0.5–5.5% of patients with an LP result experienced PE [77, 78]. LP was found for ~30–80% of the patients investigated [62, 76, 79, 83].

Intermediate probability (indeterminate)

Here V/Q scintigraphy does not strengthen a positive or a negative diagnosis of PE. The frequency of IP assignments varies greatly (up to 51% [2], generally 10–30% [29, 75, 76, 78, 79, 84]) according to patient pre-selection (e.g., reason for investigation, experience of the physician); the use of the modified PIOPED criteria reduced the frequency of such assignments [16, 17, 21, 65, 66, 77]. If IP is found, then clarification by (duplex) sonography of the leg veins is recommended. If deep vein thrombosis is discovered, anticoagulation therapy should be instituted at once [48]; if sonography reveals nothing then a confirmatory invasive PA should be considered [28, 85], although in practice this is not frequently performed [86, 87]. There is controversy as to whether spiral CT can usefully be conducted to clarify an IP finding [68, 88]. Especially in the case of pre-existing lung disease, which often constitutes the background for an IP result, spiral CT is only of restricted diagnostic value [89].

Agreement with static LPS

The correspondence among raters is variously stated as 70–94% [90, 91]. It can be improved by the use of anatomical lung segment sketches and by specific training of raters [92].

Tc-99m-MAA lung perfusion scintigraphy with SPECT

A comparison of LPS with other imaging methods (s uch as multidetector CT) should take account of recent technical developments in LPS, such as single-photon emission computer tomography (SPECT). Most comparative studies have so far failed to do this [93–95]. In comparison with static LPS, SPECT allows the fully automated generation of three-dimensional image data sets, without requiring additional acquisition time [95, 96]. This gives better image quality and improved diagnostic certainty, and correspondingly a higher degree of agreement among raters [34, 67, 96]. It is expected that SPECT will replace static LPS [95]. Promising results with improved sensitivity have been published (Table 4).

It was recently shown [95] that SPECT V/Q scintigraphy afforded comparable specificity (91%) and diagnostic accuracy (94%) as multidetector spiral CT (98%

Table 3 Presence of PE (% of patients) following a finding "low probability of PE"

Standard or type of comparison	Number of lung perfusion patients	Proportion of these patients with PE (%)	References
Retrospective	–	–	[162]
Retrospective	–	–	[163]
Retrospective	–	3.6	[160]
PA or clinical course	–	4 (low pre-test probability) 12–16.3 (without pre-test probability)	[62]
PA or clinical course	133	5.5	[77]
Clinical course	508[a]	4	[78]
PA and/or clinical course	1000	0.5	[77]
PA and/or clinical course	170	10	[75]

PE pulmonary embolism, *PA* pulmonary angiography
[a] Normal plus lung perfusion finding

Table 4 Comparison of the diagnostic predictive value of SPECT and static LS

Type of comparison	No. of patients	Static LS		SPECT		References
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	
Retrospective	985	–	–	–	–	[99]
Prospective	114	80	78	80	96	[96]
Retrospective[a]	103	68	99	92.6	98.6	[94]
Prospective	83	67	85	97	91	[95]

SPECT single-photon emission computer tomography, *LS* lung scintigraphy
[a] Mean of values from three readers with differing experience

and 93%, respectively), but also a higher sensitivity than the latter (97% vs. 86%). It appears that the percentage of IP diagnoses can be reduced by applying SPECT and the modified PIOPED criteria [94–98]; one paper claims a reduction of IP results to only 4% [99]. Other authors believe that the modified PIOPED criteria should be adapted to SPECT [95]. Automated interpretation of SPECT results has been compared with conventional visual assessment; the respective sensitivity, specificity, and accuracy obtained by these methods were 95%/91%, 84%/97%, and 89%/94% [100]. It is important to note that the actual guidelines for LS of the German Society of Nuclear Medicine, recently revised by Schümichen et al. [38], declines the PIOPED criteria for interpretation of positive LPS results, excluding the normal scan. The PIOPED data were obtained by single projection/single breath ventilation scintigraphy with Xe-133. This method as well as the technique of PA is not acceptable today. It should be clarified that ventilation scintigraphy with Xe-133 is obsolete today even by its bad count statistic compared with Tc-99m-Technegas and this is another reason for bad results of PIOPED I study [62]. LPS interpretation should every time be performed in the context with the results of a ventilation scintigraphy using Tc-99m-Technegas or Kr-81m or as a minimal precondition in the knowledge of a recent thorax X-ray. There are some reports about V/Q ratio histogram analyses generated by software algorithms with very reliable results but those software programs are not generally available [96, 100]. SPECT is the method of choice to acquire the images and PIOPED criteria are insufficient for interpretation of positive LPS results [38].

V/Q scintigraphy in patients with concomitant chronic obstructive lung disease

The leading sign of PE in ventilation/perfusion scintigraphy is not the proof of the thrombus itself but the effect of it, e.g., the mismatch between the uptake of the ventilation (preserved) and perfusion (absent) radiotracer. In any area with disturbed ventilation owing to any reason there is the so called hypoxic vasoconstriction leading to an abolished perfusion so that the scintigraphic pattern is the absent uptake of both tracers. Therefore, it is impossible to diagnose PE in those areas by these nuclear medicine methods. But because perfusion is disturbed in these areas anyway it is clinically not so important to proof embolism in these segments.

Lung perfusion scintigraphy in comparison with other diagnostic methods for PE

Spiral CT in comparison with LPS

Spiral CT allows the visual representation of total or partial filling blockage, so that emboli in the pulmonary blood vessels can be located [48]. The proportion of spiral CT examinations that give no result because of technical failure, or give an indeterminate result, is variously reported as 2–10% [49, 68, 101]. Errors can be caused by cardiac [102] or respiratory [49, 103] artifacts, too little contrast medium [70, 102] or anatomical factors such as hilar nodes [31] or peribronchovascular infiltration [49, 103]. First results from the early 1990s [104, 105], admittedly only with acute central PE, indicated a sensitivity of nearly 100% and a specificity of 96%. For segmental emboli, which are frequently overlooked, the early instruments had a lower sensitivity and specificity (diagnostic accuracy 61–79% [70]). The development of a faster scanning method, with resolution into thinner layers, later allowed the observation of smaller pulmonary arteries [102]. In recent years, a new CT generation of up to 64-slice multidetectors has been introduced [70], which allows a slice thickness of 0.7–2.5 mm and thus better spatial resolution [70, 106]. Consequently, there is considerable variation in literature values for sensitivity (53–94%) and specificity (78–100%) have varied, according to the state of development of the equipment used (Table 5) [18, 21, 27, 82, 84, 107]. A meta-analysis has yielded average values of 88% for sensitivity and 92% for specificity [69]. But these results should be interpreted with caution, because no correct references could be used and only follow-up studies can give reliable results (see LPS and spiral CT for the diagnosis of acute and chronic recurrent PE).

By today's standards, spiral CT is not sensitive enough to detect subsegmental PEs (Table 6) [108–110]. The meta-analysis by van Beek et al. [69] showed a sensitivity of only 50–65% for these. A recent study [111] suggested a sensitivity of only 69% if subsegmental emboli were also considered (Table 6). There is much current discussion [70] of the clinical relevance of isolated subsegmental emboli and of whether they should be treated; here, there is a need for long-term studies. Although an isolated subsegmental PE has practically no hemodynamic or clinical relevance for an otherwise healthy and relatively young patient, the hemodynamic effect for an older person with a history of cardiopulmonary disease is clinically important and even fatal [49]. The incidence of isolated subsegmental PEs among patients with suspected LE is quoted as 4–36% [25, 62, 89].

Direct comparative studies of static lung scintigrams and spiral CT results have been conducted. One showed spiral CT to be superior in respect of both sensitivity and specificity (Table 6). However, LS by SPECT was superior in sensitivity and equal in specificity to spiral CT (Table 6).

Table 5 Diagnostic value of spiral CT in PE at segmental level

Comparison/reference/method	Number of patients	Sensitivity (%)	Specificity (%)	Type of comparison/comment	References
Diagnostic value of spiral CT in PE at segmental level					
PA, only central PE	42	100	96	Prospective	[105]
PA, only central PE	10	100	100	Prospective	[104]
PA	20	86	92	Prospective	[164]
Combined with V/Q	25	82	67	–	[108]
PA	33	86	100	Retrospective	[165]
PA, only central PE	75	91	78	Prospective	[102]
Combined PA subgroup ($n = 56$), two readers	149	82–90	93–96	Retrospective	[110]
Combined with V/Q and PA	139	87	95	Prospective[a]	[84]
PA	25	67	100	Prospective	[166]
Multidetector CT	158	90	94	–	[167]
Multidetector CT	94	96	98	–	[93]
Multidetector CT	230	86	–	–	[111]
Accuracy of spiral CT including the segmental level in the analysis					
Gold standard PA	20	63	89	–	[164]
	70	86	92	–	[168]
	26	67	100	–	[166]
	158	90	94	–	[167]
Gold standard PA	230	69	84	–	[111]
	299	70	91	–	[109]

PE pulmonary embolism, *PA* pulmonary angiography
[a] Direct comparison with V/Q lung scintigraphy

Table 6 Comparison of the sensitivity and specificity of LS and spiral CT[a]

Standard	*n*	Comment	V/Q LS		Spiral CT		References
			Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	
C, V	83	P, MD, I	76[a] 97[b]	85[a] 91[b]	86[a]	98[a]	[95]
V	94	P, MD, I	86[a]	88[a]	96[a]	98[a]	[93]
C	179	P	81[a]	74[a]	94[a]	93.6[a]	[101]
C, PA	139	P	65[a]	94[a]	87[a]	94[a]	[84]
C, V/Q, V	123	R	49[a]	74[a]	75[a]	90[a]	[82]
C, V	128	R, I	91[a]	96[a]	81[a]	99[a]	[169]
V	112	P, I	83[b,c] 44[b,d]	65[b,c] 99[b,d]	86[e] 83[f]	82[e] 90[f]	[67]
C, PA	227	R, I, MD	97[a,c] 96[a,d]	90[a,c] 95[a,d]	51	99	[68]

LS lung scintigraphy, *PA* pulmonary angiography, *P* prospective, *R* retrospective, *I* intra-individual, *SD* single detector, *MD* multiple detector, *V* clinical course, *C* combined gold standard

[a] Static, [b] SPECT, [c] intermediate and high probability scans, [d] only high probability scans, [e] indeterminate and positive results, [f] only positive results

Table 7 Studies of the clinical course of patients after a negative result in spiral CT

No. of patients	Follow-up duration (months)	VTE (non-fatal)	VTE (fatal)	References
78	≥6	1	–	[73]
100	6–24	–	–	[112]
215	3	2	1 (0.5%)	[89]
112	3	5 (4.5%)	1 (0.9%)	[170]
993	3	8 (0.8%)	3 (0.3%)	[171]
198	3	2 (1.0%)	–	[81]

VTE venous thrombo-embolic events

The probability of a non-lethal VTE after negative spiral CT is given as 0.5–4.5%, with up to 0.9% for lethal VTEs (Table 7). However, in many of these CT studies other results were taken into consideration in the final determination of the negative CT result—for instance, negative leg-vein sonography [112], and this complicates the assessment of the validity of the method. According to a meta-analysis [69], a negative CT result does not justify withholding anticoagulant therapy, and this method is thus not currently regarded as sufficient to exclude PE [18, 28].

LPS and spiral CT for the diagnosis of acute and chronic recurrent PE

Of special interest are prospective management studies addressing the outcome after a normal LPS, spiral CT or PA with duration of observation ≥3 months, a low clinical probability estimated, a normal D-dimer test result and the knowledge of ultrasonographic results of the legs. From those results can be concluded that recurrent thrombembolic events are an indirect measure of sensitivity of the primarily used diagnostic imaging method. Van Beek et al. [69] found in their meta-analysis recurrent PE after a normal LPS in 0.3% and after a normal spiral CT in 5.5% of patients. Sensitivity of single-slice CT was calculated from follow-up as 69% [111] and 63% [113]. But the aim must be to define a range, within that a percentage of recurrent PE can be expected. For static (planar) V/Q scintigraphy this is expected to be 0% to 0.5%, for single-slice CT and PA this will be 1.0% to 1.5% and for multislice (detector) CT this is expected to be below the latter but it has obviously not been proved yet.

Regarding to chronic recurrent PE, promising data have recently been published by Tunariu et al. from Hammersmith Hospital London (UK) demonstrating that V/Q scintigraphy has a higher sensitivity than PA in detecting chronic recurrent PE [66]. They found a sensitivity of 96% to 97.4% and a specificity of 90% to 95% for V/Q scintigraphy when compared with PA having only 51% and 99%, respectively [68]. This is underlining the greater value of LPS when compared with spiral CT and/or PA, in particular when chronic recurrent PE is suspected in patients suffering from (treatable) pulmonary hypertension.

LPS or spiral CT?

In comparison with spiral CT, static LPS has the advantage that a "normal" finding is a more reliable indicator of the absence of PE. Unlike LPS, spiral CT is at present not recommended as a sole criterion for the exclusion of possible PE [18, 28]. Prospective studies designed to demonstrate unambiguously the value of spiral CT in patient management are still incomplete [51]. An advantage of spiral CT compared with LPS lies in the greater proportion of diagnoses that can be made with confidence, as the proportion of indeterminate (IP) results obtained with the latter method is greater [82, 114]. An overall consideration of the published results leads to the conclusion that the two methods are comparably useful [65]. Technological progress in SPECT LPS and in spiral CT may be expected to allow both methods to find their place in the diagnostic decision tree. The final positioning of spiral CT should be defined take into account the results of the large, prospective, comparative, and multicentre study PIOPED II [115]. Some authors have recommended the complete replacement of LPS by spiral CT [31, 67, 116–118], but these represent somewhat subjective individual opinions. In particular, the recently published data of the PIOPED II study done by Stein et al. [43, 116, 119] are highly important because they are the basis for claiming the leadership of CT angiography and declining LPS. PIOPED II [43] found the sensitivity of CT angiography to be (only) 83% with a specificity of 96%, whereas the sensitivity of CT angiography combined with venography was 90% with specificity 95%. Because the number of slices mainly affects the acquisition time, there are serious doubts whether a further increase in number will able to significantly improve the sensitivity of the method because the lungs do not belong to the category of very fast moving organs. Furthermore, CT angiography has several contra-indications as renal failure, hyperthyroidism, contrast-medium allergy and pregnancy. In addition, metal artifacts induced by pacers will lead to inconclusive CT images. And last but not least, CT angiography has a significant higher radiation exposure compared with LPS, in particular in young women. Therefore, the older and better-established LPS, which is associated with the lower radiation dose, should still occupy an important position in the guidelines as stated by Glassroth [120, 121] in a recently published Editorial in JAMA commentating the latest published study comparing multidetector spiral CT and LPS. If CT is contra-indicated (for example, in cases of contrast-medium allergy or renal failure), then a combined perfusion/ventilation scintigraphy must be performed.

Other imaging procedures for the diagnosis of PE

Magnetic resonance pulmonary angiography (MRPA)

Magnetic resonance cannot yet be regarded as an established method for the diagnosis of PE, as too few consolidated data from large studies are available, such as might justify positioning this method within the diagnostic algorithm [122]. In particular, there is a lack of studies of the clinical course taken by cases where the MR result was inconspicuous; such studies would establish the clinical reliability of a "normal' finding [50]. A meta-analysis of prospective, blinded studies of the detection of PE using the former gold standard PA or an autopsy as reference, published in 2000, showed an average sensitivity of only 77% (ranging from 54.7% to 87.5%) with a specificity of 87% (range: 78.3–93.1%) [123]. MRPA is unsuitable for the detection of subsegmental PEs; the largest study to date showed a sensitivity of only 40% for isolated subsegmental PEs when compared with 84% for segmental PEs [124]. It will require further development of hard- and software [125] before the suitability of this technique for general use can finally be determined, but first results comparing MRPA with LPS and SPECT are encouraging [126].

Vein ultrasound of the lower leg

Duplex sonography of the veins of the leg can reveal deep vein thrombosis as a possible cause of a PE [50]. The sensitivity and specificity of sonography are ~91% and 99%. The sensitivity for thrombus detection in the deep calf veins and the iliac region is only moderate, and is generally lower for asymptomatic patients [28]. If the result of LS is indeterminate, leg-vein sonography offers a valuable complementary method, which is also recommended by many guidelines. If deep leg-vein thrombosis is detected, then anticoagulant therapy should be initiated, irrespective of whether or not PE is present, as the treatment is the same for the two indications [18, 28].

Pulmonary angiography

This invasive method, the "former gold standard" in PE diagnosis, is today only used when findings from other methods are unclear, e.g., when an indeterminate result is obtained by V/Q scintigraphy or spiral CT [28, 50]. However, this is done only relatively rarely [86, 87]. At present, the risk of fatal complications in PA is estimated as lying between 0.1% and 0.5%, and that of serious non-fatal complications as 1.5% [18, 86]. As PA is regarded as a "gold standard" reference, its sensitivity

and specificity can only be inferred indirectly; these are taken to be ~98% and 95–98%, respectively [18]. Studies of the clinical course of a total of 840 cases [127–131] revealed non-fatal VTEs in 1.5% and fatal VTEs in 0.4% of these; such frequencies are similar to those of non-lethal thrombo-embolic events after negative LS. Agreement between two raters of 80–96% was found [39], although some authors state lower values [111]. Even this method is subject to limitations in the detection of peripheral subsegmental emboli, and for these the agreement is only 80–96% [70]. PA gives an indeterminate result in about 3% of cases [86]; however, among cases where LS yields a result "IP" this rises to 30–60% [132], which means that in such cases PA does not always offer an appropriate supportive diagnosis. Unfortunately, PA may not serve as gold standard today [70–72] because its sensitivity may be as low as 70% [71] which generates a clinical significant percentage of false positive findings even in the PIOPED I study.

Transthoracic and transesophageal echocardiography (TTE and TEE)

Unlike LS, these procedures are most often used in cases where there is a hemodynamically relevant, severe PE with more than 30–40% occlusion of the pulmonary blood vessels, usually in the case of clinically unstable patients [18, 28]. The prevalence of LE in echo studies, around 77%, is very high, reflecting the choice of this method in severe PE cases. The particular value of this method consists in its ability to detect the hemodynamic consequences of a severe and extended PE, such as right ventricular strain and pulmonary hypertension [28, 117] and differential diagnosis of other causes such as cardiac tamponade or acute left-heart insufficiency [117]. Pooling of sensitivity and specificity data from eight TTE studies gave values of 68% and 89%, respectively, and the sensitivity of TEE was found to be ~70% [123].

Safety aspects of Tc-99m-MAA lung perfusion scintigraphy

The potential risks associated with the use of Tc-99m-MAA can be classified into those arising from the substance's radioactivity and those arising from the injection of small colloidal particles into the bloodstream, and those that could be exacerbated by pre-existing disorders. We consider these in turn, with particular reference to the issue of risks to children.

The radioactive dosage of Tc-99m-MAA required for LPS is well grounded in experience, and this is reflected in the various guidelines and recommendations [16, 17, 66, 133]. The lungs absorb ~98% of the radioactivity administered [6, 7], with an exposure of 0.066 mGy/MBq, followed by the liver (0.016 mGy/MBq) [134]; all other organs absorb <0.01 mGy/MBq. Thus, the maximum recommended dosage of 200 MBq exposes the lungs to 13.2 mGy radiation. According to ICRP 80 [134] the total exposure for an adult is 0.011 mSv/MBq Tc-99m-MAA, or 2.2 mSv for the highest recommended dosage. This does not represent a significant risk factor, compare, e.g., the natural background radiation in Germany, which varies according to region between 1 mSv/year and 5 mSv/year. For children the recommended Tc-99m-MAA dosages are lower (see the Guidelines of the European Society for Nuclear Medicine [16, 17, 135]); for example, for a 1-year-old patient weighing 10 kg the exposure would be 1.4 mSv and therefore, likewise, does not represent a significant risk. Lactation should be interrupted for 9–12 h following LPS [66, 136].

An issue with labeled MAA could be the risk of accumulation of free radioisotope introduced as a contaminant of the labeled MAA. For Tc-99m, in two studies [137, 138] at most trace amounts of activity were detected in the thyroid, whereas in a third a transient absorption of 0.2% of the applied activity was found there. Even in this worst case, the total exposure of the thyroid is negligible; although it could be reduced still further by thyroid blockage, this does not appear to be necessary.

The effect of particle size has been studied in dogs. No hemodynamic effects were induced by 35-μm particles up to 40 mg/kg body weight, whereas particles sized 80 μm and above showed such effects (raised pulmonary blood pressure, lower pressure in the femoral artery) at 40 mg/kg and even lower dosages for larger particles [2]. Thus, a lower toxic limit of 20 mg/kg may be assumed [2, 139]. A typical dosage for an adult would be 0.007 mg/kg, implying a safety margin of 3000-fold.

The number of particles is of relevance for safety in so far as it determines the fraction of capillaries and arterioles that are temporarily blocked. For the 200 000–700 000 particles used, these fractions are normally negligible (see "Pharmacokinetic basis for lung perfusion scintigraphy with TC-99M-labelled macroalbumin aggregates" section). For additional safety, especially in patients with significant pulmonary hypertension, the lower end of this range has been recommended for use in adults [66]. In children, the number of particles must be reduced according to age and indication and kept as low as possible, especially for right–left shunt quantification (see below and "Other indications for TC-99M-MAA lung perfusion scintigraphy" section) [16].

For patients with certain disorders the particle number should be reduced as far as possible. These disorders include severe pulmonary hypertension or presence of a right–left shunt [3]. Pulmonary hypertension may require a reduction of particle number to 100 000–200 000 [66]; failure to observe this can have serious or even fatal consequences [110, 140–143]. A right–left shunt can introduce MAAs into the systemic circulation [3] and thus, theoretically, into the kidney and brain. A study on monkeys indicated that the safety margin for cerebral micro-embolism in humans is >2000-fold (assuming a 50% shunt); furthermore, no adverse effects have been reported for patients with right–left shunt, where the benefit of a diagnosis with Tc-99m-MAA would appear to outweigh substantially the associated risk.

Other indications for Tc-99m-MAA lung perfusion scintigraphy

Preoperative evaluation of lung function prior to carcinoma resection

Conventional tests reveal only the overall lung function; left/right and regional differences cannot be detected. Scintigraphy is one method that provides functional information at a regional level. LPS is currently regarded as a valuable complement to the measurement of forced expulsion rate (FEV1) and lung ventilation scintigraphy (LVS) [13]. If FEV1 is below 1 l/s lung surgery is contra-indicated anyway and neither LVS nor LPS is needed to predict postoperative lung function. If FEV 1 is at borderline (above 1 but below 2.5 l/s), LVS and LPS are indicated to prove if the remaining lung function after surgery is sufficient, meaning above 1 l/s. The latter cases might not be at risk by LPS but it is recommended to use numbers of particles at the lower end of the range (200 000–700 000). Mismatches between regional ventilation and perfusion occur in ~16.5% of cases; LVS alone leads in these cases to an over- or underestimation of the post-operative lung function to be expected [13]. For this reason current nuclear-medical guidelines [16, 17] state that they will include LPS for pre-operative function evaluation in future versions. Today, the combination of lung function tests and quantitative V/Q LS is routinely used to predict the post-operative lung function of lung-carcinoma patients [144, 145]. Tc-99m-MAA is the method of choice, with exact and reproducible quantification of static lung perfusion [146]. Other methods, such as MR [147, 148] are more costly and have not yet been compared rigorously with this. Consequently, MR does not play a significant role in clinical routine until now [149].

Preoperative evaluation of lung function in lung transplantation

The qualitative determination of parenchymal perfusion anomalies can provide valuable information in the planning of lung transplantation. In one study of 46 patients with advanced cystic fibrosis waiting for a lung transplant, it was shown by Tc-99m-MAA that unilateral perfusion anomalies were associated with a higher mortality risk during the waiting period. Such information can therefore be used to modify the priority of transplantation [150]. Quantitative LPS with Tc-99m-MAA 1–3 months following the transplantation is able to predict rejection of the transplant with higher sensitivity and (especially) specificity than traditional tests of lung function such as FEV1 (83% and 88% vs. 80% and 67% [151]).

Optimization of radiation therapy for lung cancer

In 10% of cases, radiation therapy leads to acute radiation pneumonitis; pulmonary fibrosis can occur later associated with mortality risk [152]. These effects depend on the radiation dosage, fractionation schedule, the lung volume irradiated, and biological factors. Optimization of the radiation therapy plan for lung carcinoma can be supported by a Tc-99m-MAA perfusion test. A quantitative V/Q SPECT LS, giving regional and functional information that morphological methods cannot provide, allows for a better prediction of the effects of radiation upon the pulmonary tissue [152]. The use of perfusion information can help to prevent radiation damage to the remaining functioning lung parenchyma, especially in patients with major perfusion deficiencies [153]. De Jaeger et al. [154] showed that the best predictors of pulmonary function following radiation therapy were variables obtained from Tc-99m-MAA such as "predicted perfusion reduction" and "mean perfusion-weighed lung dosage".

Right–left shunt quantification

In adults, the most common cause of interpulmonary right–left shunt are Osler's and Waldenström's diseases, arteriovenous angioma, pulmonary fibrosis, and sclerodermatitis [13]. It is also found in various end-stage lung diseases (10.3%), especially with primary pulmonary hypertension (19%) [155]. The presence of a shunt influences the surgical procedure to be adopted for lung transplantation [155]. LPS offers the simplest and cheapest procedure for detection and quantification of a right–left shunt and for estimating the consequent right ventricular strain [13]. This indication is planned for

inclusion in the guidelines of the German Society of Nuclear Medicine [17]. The shunt is revealed by extrapulmonary deposition of Tc-99m-MAA particles, mainly in the brain, the liver and the kidneys. Quantification of the shunt is performed by measuring renal activity with known effective renal plasma flow (renal function scintigraphy) [13]. The absence of accumulation in the brain in a static image virtually excludes a significant right–left shunt, and the specificity of a positive result is close to 100% [155].

Pediatric use of Tc-99m-MAA LPS

In children and adolescents, LPS is indicated for worsening of lung function by cystic fibrosis, the clarification of relapsed bronchi in cases of suspected bronchiolectasis, assessment of lung perfusion before and after operation for congenital heart defect or anomalies of the pericardiac blood vessels, right–left shunt quantification, diagnosis and exclusion of possible PE and monitoring lung perfusion after PE. Dosages are given in the relevant guidelines [16, 17, 135].

Conclusions

The clinical studies and reports surveyed in this review have demonstrated that Tc-99m-LPS presents a diagnostic method for PE of continuing value. In comparison with spiral CT and/or PA, LPS is not to be defeated as mentioned also by the most actual PIOPED II reports [156]. This applies in particular to chronic or recurring embolisms, whereas currently spiral CT may be of greater value for major or life-threatening embolisms. Therefore, the most frequent indication in clinical routine is the suspected PE. In this setting, LPS should every time combined with a ventilation scintigraphy using Tc-99m-Technegas or Kr-81 m. SPECT is the method of choice to acquire the images and PIOPED criteria are insufficient for interpretation of positive LPS results. At present, LPS with Tc-99m-MAA cannot be replaced by other methods in applications that do not involve embolism, such as in pediatrics or in the quantification of regional pulmonary function in a pre-operative context or prior to radiation therapy.

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