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REVIEW ARTICLE

Critical review of SPECT imaging in pulmonary embolism

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Abstract Outcome studies have shown that pulmonary embolism can be safely excluded in patients with negative ventilation/perfusion (V/Q) single-photon emission computed tomography (SPECT). The effective radiation dose of V/Q SPECT is much less than with computed tomographic (CT) pulmonary angiography, which would make it preferable to CT angiography in many young female patients. The accuracy of V/Q SPECT, however, is difficult to assess, because most published investigations are limited by incorporation bias or partial verification bias, as well as other limitations in study design and reporting. Consequently, the accuracy of V/Q SPECT relative to planar V/Q scintigraphy or CT angiography has not been definitively determined. There is need for a prospective investigation of the accuracy of V/Q SPECT with consecutive patients, blinded interpretations, and an independent reference standard, or independent composite reference standard.

Keywords Pulmonary embolism · Venous thromboembolism · Single-photon emission computed tomography

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Since the publication of the prospective investigation of pulmonary embolism diagnosis (PIOPED) in 1990 [1], there has been a decline in the use of ventilation/perfusion (V/Q) planar scintigraphy [2] and widespread adoption of computed tomographic (CT) pulmonary angiography for the diagnosis of acute pulmonary embolism (PE) [2]. The development of tomographic radionuclide imaging presents diagnostic possibilities that were not available at the time of publication of the PIOPED. In 2009, together with colleagues, we reviewed the use of single-photon emission computed tomography (SPECT) in acute PE [3]. Numerous observations with SPECT in the 5 years since then prompted us to conduct the present review of its potential role in evaluating patients with PE. One aim of this review is to present data that will allow physicians to make informed choices regarding the use of SPECT in patients with suspected PE.

We searched PubMed using the following search terms: SPECT PE matched with accuracy (20 results), sensitivity (34 results), specificity (39 results); SPECT pulmonary embolism matched with accuracy (35 results), sensitivity (78 results), specificity (80 results); single-photon emission computed tomography pulmonary embolism matched with accuracy (30 results), sensitivity (71 results), specificity (72 results); single-photon emission computed tomography pulmonary embolism (174 results); SPECT pulmonary embolism (197 results). We also checked the references of relevant studies to identify additional investigations. The inclusion criteria were: studies in all languages related to the accuracy of SPECT that included >10 patients suspected of having acute PE and showed or allowed the reader to calculate sensitivity, specificity, and results of clinical follow-up. We identified 21 such articles and 2 preliminary articles with fewer patients that were of interest. Some addressed more than one topic.

Guideline recommendations for use of V/Q SPECT

According to the European Association of Nuclear Medicine Guidelines of 2009, V/Q SPECT should be strongly preferred over planar V/Q imaging, since it allows an accurate diagnosis of PE even in the presence of comorbid conditions such as chronic obstructive pulmonary disease and pneumonia [4]. In the USA, however, the Society of Nuclear Medicine, in 2012, acknowledged SPECT and allowed its use, but did not prefer it [5]. They indicated that (1) the criteria for interpretation of SPECT and SPECT in combination with low-dose CT need to be established, (2) no data from comparison of SPECT and planar imaging in a multi-institutional setting are, as yet, available, and (3) the utility of breathing maneuvers or respiratory gating with SPECT needs to be established [5].

Interpretation of V/Q SPECT

The European Association of Nuclear Medicine recommends the following criteria for interpretation of V/Q SPECT [4]:

No PE:

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

PE present:

- V/Q mismatch of at least one segment or two subsegments that conforms to the pulmonary vascular anatomy.

Non-diagnostic:

- Multiple V/Q abnormalities not typical of specific diseases.

The guidelines emphasize that the shape of a mismatch should be pleural based and conform to subsegmental and segmental vascular anatomy [4, 6].

The Society of Nuclear Medicine (USA) [5] examined the interpretation of V/Q using: the PIOPED criteria (1), the modified PIOPED criteria [7], the modified PIOPED criteria using perfusion scans combined with the chest radiograph [8], and the prospective investigative study of pulmonary embolism diagnosis (PISA-PED) criteria, also using perfusion scans combined with the chest radiograph [8]. All of these criteria emphasize, as do the European Association of Nuclear Medicine guidelines, that PE presents segmental defects. The Society of Nuclear Medicine guidelines did not distinguish between criteria for interpretation of planar V/Q and V/Q SPECT, beyond stating that SPECT criteria need to be established [5].

Radiation dose of perfusion SPECT and ventilation/perfusion SPECT compared with multidetector CT

An ideal administered activity of ^{99m}Tc-MAA (macroaggregated albumin) for a perfusion SPECT is 100-120 MBq when used in combination with ventilation SPECT [4]. The effective dose of ^{99m}Tc-MAA has been reported as 0.011–0.017 mSv/MBq [4, 5] based on data from the International Commission on Radiological Protection (ICRP) [9]. With an administered activity of 120 MBq, the effective dose of a perfusion SPECT would be 1.32–2.04 mSv. The administered activity may range from 40 [4, 5] to 150 MBq [5].

An ideal administered activity for a ventilation SPECT in combination with a perfusion SPECT is 25–30 MBq [4]. Using ^{99m} Tc DTPA (diethylene triamine pentaacetic acid) with an administered activity of 30 MBq, at 0.006–0.0071 mSv/MBq the effective dose would be 0.18–0.21 mSv [4, 5].

A ventilation SPECT using ^{99m}Tc-Technegas with an administered activity of 30 MBq at 0.015 mSv/MBq would result in an effective dose of 0.45 mSv [4]. The biological half-life of ^{99m} Tc DTPA is 80 ± 20 min in healthy non-smokers [10], whereas the biological half-life of ^{99m}Tc-Technegas is 135 h [11].

The administered activity of ^{81m} Kr ranges from 40 to 400 MBq and the effective dose is 0.000027–0.0007 mSv/MBq [4, 5]. The administered activity of ^{133}Xe is 200-750 MBq and the effective dose is 0.00071 mSv/MBq.

Ventilation/perfusion SPECT delivers a lower radiation dose, particularly to the female breast, than CT imaging. The effective dose for V/Q SPECT is about 35–40 % of the dose from multidetector CT pulmonary angiography [9, 12]. The dose to the female breast is only 4 % of the dose from multidetector CT [13]. Eliminating the ventilation scan by using only perfusion SPECT further reduces the radiation dose.

Regarding multidetector CT angiography, the average effective dose for 4- to 16-detector CT is 5.4 mSv based on computed rather than measured dose data [12]. On the other hand, Hurwitz et al. reported a measured effective dose of 19.9 ± 1.38 mSv with 64-detector CT [14]. Dose-saving protocols with automatic current modulation and lower tube voltage are promising [15], as is the use of alternative image reconstruction algorithms [16]. Breast doses were decreased from 62 mGy to 33 mGy with bismuth shields, but the effects of increased noise on the diagnosis of PE were not assessed [13].

In a 2012 study of dual-energy CT lung perfusion imaging and SPECT/CT, the mean equivalent dose of perfusion SPECT in combination with low-dose CT imaging and planar ventilation scintigraphy was 2.8 mSv [17]. The mean equivalent dose of dual-energy CT lung perfusion imaging was 3.88 mSv or 4.08 mSv depending on which dual-source CT system was used [17].

Study designs and comparisons used in investigations of SPECT for diagnosis of PE

Many comparisons of SPECT alone and in combination with low-dose CT (SPECT/CT) have been made with various imaging modalities. We addressed the following topics: (1) V/Q SPECT using multidetector CT angiography as the reference standard, (2) V/Q SPECT using composite reference standards, (3) V/Q SPECT compared with planar V/Q scintigraphy, (4) V/Q SPECT/CT accuracy, (5) V/Q SPECT/CT compared with multidetector CT angiography, (6) perfusion SPECT/CT plus planar ventilation scintigraphy compared with dual-energy CT imaging, (7) perfusion SPECT accuracy, (8) perfusion SPECT/CT compared with V/Q SPECT/CT, (9) perfusion SPECT/CT compared with planar V/Q scintigraphy, (10) outcome after SPECT diagnosis, (11) V/Q SPECT for follow-up after acute PE, (12) SPECT after administration of ^{99m}Tc-labeled anti D-dimer monoclonal Fab' fragments or ^{99m}Tc-apcitide.

It is difficult to draw firm conclusions about the diagnostic accuracy of SPECT largely because of design-related biases [18, 19]. The intuitive conclusions would be that SPECT enhances sensitivity for detecting perfusion defects, facilitates evaluation of regional V/Q matching or mismatching, and is further aided by combination with low-dose CT imaging. However, despite continued research and publication in this area over the past 5 years, it has not been proven that these expectations are correct. The sensitivity and specificity of SPECT determined from investigations that used planar scintigraphy or SPECT itself as a component of the reference standard are most likely overestimated as a result of incorporation bias [18, 19]. Incorporation bias was present in the design of 80 % of the investigations that we reviewed. On the other hand, sensitivity is likely to be overestimated and specificity to be reduced in the presence of partial verification bias, defined as a design in which the gold standard test (CT angiography or conventional angiography) is more likely to be obtained if the test under examination (SPECT or planar imaging) is abnormal, and only a small portion of patients with a negative test under examination are verified by the gold standard test [18, 19]. Partial verification bias was present in 15 % of the studies we reviewed. Other biases [18] also occurred, including differential verification bias (15 % of studies), imperfect gold standard (40 % of studies), disease spectrum bias (30 % of studies), and test result bias (35 % of studies). In calculating the proportion of investigations with design bias, we included two substudies as separate investigations, because their methods differed from those used in their primary investigations. In addition, considering the Standards of Reporting of Diagnostic Accuracy [20], we identified numerous limitations in describing the study design and reporting the results. This contributed to difficulty in detecting the potential for bias of these studies (internal validity) and assessing the applicability of their results (external validity) [20].

V/Q SPECT

V/Q SPECT using multidetector CT angiography as reference standard

An independent reference test without partial verification bias or incorporation bias was available in only two investigations that we identified (Table 1) [21, 22]. With CT pulmonary angiography as the reference test as part of a larger investigation and $\geq$2 mismatches required for the diagnosis of PE, V/Q SPECT showed a sensitivity of 25 out of 30 (83 %) and a specificity of 61 out of 86 (71 %) [21]. Also with CT pulmonary angiography as the reference test as part of a larger investigation, and $\geq$1 segmental mismatches required for the diagnosis of PE, V/Q SPECT showed a sensitivity of 19 out of 22 (86 %) and specificity of 56 out of 57 (98 %) [22]. Arguably, CT angiography may have failed to identify some PE that SPECT appeared to show.

Among 100 high-risk patients who required both V/Q SPECT and CT angiography due to an initial indeterminate or negative imaging test despite a high pre-test probability, the agreement between these tests was evaluated [23]. Pulmonary embolism was diagnosed by clinical findings as well as the results of V/Q SPECT and CT angiography. There was no significant agreement between V/Q SPECT and CT angiography when positive, negative, and indeterminate results were included ($K = 0.18$, SE $= 0.09$, $p = 0.051$). However, in the presence of a positive finding on either test, there was substantial agreement between the two ($K = 0.62$, SE $= 0.27$, $p = 0.02$). Single-photon emission tomography was diagnostic in 28 out of 30 (93 %) patients in whom CT angiography was indeterminate. Computed tomographic angiography was diagnostic in 10 out of 12 (83 %) patients in whom V/Q SPECT was indeterminate. Ventilation/perfusion SPECT often provides a diagnosis in the presence of an indeterminate CT angiogram in patients with high clinical suspicion of PE, and CT angiography often provides a diagnosis when SPECT is indeterminate [23]. These data suggest that in difficult cases the two modalities can be complementary.

Table 1 Sensitivity and specificity of V/Q SPECT or perfusion SPECT in patients with suspected pulmonary embolism

References	Reference standard	SPECT criteria	Prospective (yes/no)	Consecutive (yes/No)	Ventilation agent	SPECT sensitivity (n/N) (%)	SPECT specificity (n/N) (%)
Investigations of V/Q SPECT							
Bajc [21]	CT angio	PE $\geq$ 2 segmental or subseg mismatches	N	Y	Technegas	25/30 (83)	61/86 (71)
Miles [22]	CT angio	$\geq$1 Mismatch of $\geq$0.5 of a lung segment	Y	N	Technegas	19/22 (86)	56/57 (98)
Weinmann [24]	CT angio, leg US, clinical, conventional pulmonary angiography, SPECT if single subseg on CT angio	$\geq$1 Segmental or subseg mismatch	Y	Y	Technegas	15/19 (79)[a]	62/75 (83)[a]
Palla [25]	Conventional angiogram if planar V/Q or planar Q abnormal. No PE if V/Q normal or angio negative	$\geq$1 Segmental mismatch	Y	N	^{133}Xe	14/14 (100[b]	0/6 (0)[b]
Gutte [27]	CT angio, V/Q SPECT, leg ultrasound, clinical, and follow-up	$\geq$1 Mismatch	Y	Y	^{81m} Kr	28/29 (97)	42/48 (88)
Bajc [21]	V/Q SPECT, CT angio, clinical, and laboratory	PE $\geq$2 segmental or subseg mismatches	N	Y	Technegas	601/607 (99)	1153/1159 (99)
Reinartz [29]	Consensus reading of V/Q SPECT, V/Q planar, clinical, and other radiological tests	$\geq$1 Segmental or $\geq$1 subseg mismatch	N		Technegas	63/71 (89) Senior reader	32/32 (100) Senior reader
Reinartz [30]	Consensus including V/Q SPECT, CT angio, clinical, and follow-up	$\geq$1 Segmental or $\geq$1 subseg mismatch	N	N	Technegas	36/37 (97)	42/46 (91)
Bajc [28]	V/Q SPECT, V/Q planar, CT angio, clinical, and laboratory	PE $\geq$2 seg or subseg mismatch No PE = 0 mismatch	Y	N	^{99m}Tc DTPA	13/13 (100) Reader A	37/40(93) Reader A
Miles [22]	CTPA, V/Q planar, clinical information, and follow-up	$\geq$1 Mismatch of $\geq$0.5 of a lung segment	Y	N	Technegas	19/23 (83)	63/64 (98)
Lemb [33]	SPECT defects improved, normalized, or new = PE; SPECT unchanged = No PE	PE $\geq$1 mismatch No PE, 0 mismatch	N	N	Technegas	42/44 (96)	38/39 (97)
Le Duc-Pennec [26]	Planar V/Q scan, CT angio, leg ultrasound and clinical	Revised PIOPED criteria	Y	Y	^{81m} Kr	27/49 (55)	174/200 (87)
Gutte [34]	CT angio, V/Q SPECT, V/Q planar, clinical, leg US, and follow-up	$\geq$1 Mismatch (>0.5 segment)	Y	Y	^{81m}Kr	10/10 (100)	20/23 (87)
Meng [35]	Consensus including V/Q planar, V/Q SPECT, CT angio, clinical, and follow-up.	$\geq$1 Segmental or $\geq$2 subseg mismatches	Y		Technegas	69/80 (86)	29/31(94)
Collart [31]	D-dimer, leg ultrasound, V/Q scan, CT angio, and follow-up	$\geq$1 Wedge-shaped mismatch	Y	Y	^{81m}Kr	12/15 (80)	49/51 (96)
Reinartz [32]	Consensus including SPECT, CT angio, clinical, D-dimer, and follow-up	$\geq$1 Mismatch (>0.5 segment)	N	N	Technegas	20/22 (91)	30/31 (97)
Investigation of perfusion SPECT							

Table 1 continued

References	Reference standard	SPECT criteria	Prospective (yes/no)	Consecutive (yes/No)	Ventilation agent	SPECT sensitivity (n/N) (%)	SPECT specificity (n/N) (%)
Bajc [36]	V/Q SPECT, CT angio, leg US, clinical, and laboratory	≥1 Wedge-shaped perfusion defect	N	N	None	53/59 (90)	88/93 (95)

Ref reference, *V/Q* ventilation/perfusion, *SPECT* single-photon emission computed tomography, *CT* computed tomography, *angio* angiography, *PPV* positive predictive value, *yr* year, *US* ultrasound, *subseg* subsegmental, *PE* pulmonary embolism, *DTPA* diethylenetriaminepentaacetate

[a] Included patients had non-diagnostic planar V/Q scan

[b] Included patients had abnormal planar V/Q scan

Weinmann et al. performed an investigation that included only patients who had non-diagnostic planar V/Q scans and required SPECT to confirm the reference standard diagnosis if CT angiography showed only a single subsegmental defect [24]. The sensitivity of SPECT was 15 out of 19 (79 %) and the specificity was 62 out of 75 (83 %) (Table 1)

Palla et al. obtained conventional pulmonary angiograms in 20 patients with abnormal planar perfusion scans. The sensitivity of SPECT, based on the angiograms, was 14 out of 14 (100 %), but specificity was 0 out of 6 (0 %) [25]. The study design contributed to the low specificity. When comparing individual lung segments, the sensitivity of SPECT was 56 out of 62 (90 %) and the specificity 75 out of 118 (64 %) (Table 1)

V/Q SPECT using composite reference standards

Most investigations of the sensitivity and specificity of V/Q SPECT included the index test (SPECT) or planar V/Q results in the composite reference standard [21, 22, 24–36] (Table 1). This would introduce incorporation bias [18, 37], which can be expected to result in an overestimation of the diagnostic accuracy [18, 38].

Across all investigations, the sensitivity of V/Q SPECT ranged from 55 to 100 % [21, 22, 24–36] (Table 1). The specificity ranged from 71 to 100 % [21, 22, 24, 26–36] except in a single investigation of six patients without PE, in which the specificity was 0 out of 6 (0 %) [25]. The agents used for V SPECT differed (Table 1) and the diagnostic criteria for interpretation of SPECT also differed among investigations (Table 1). Le Roux et al. [39], in a subset of patients reported by Le Duc-Pennec et al. [26], showed the best performance of SPECT with a diagnostic cutoff of ≥1 segmental or ≥2 subsegmental mismatches [sensitivity: 45 out of 49 (92 %), specificity: 182 out of 200 (91 %)].

V/Q SPECT compared with planar V/Q scintigraphy

It is general opinion that V/Q SPECT shows a superior diagnostic performance compared with planar V/Q scintigraphy [3]. V/Q SPECT correctly diagnosed or excluded PE in 77 of 94 patients who had a non-diagnostic planar V/Q scan [24]. The sensitivity of V/Q SPECT was higher than that of planar V/Q in every investigation [23, 28–31, 34, 35] (Table 2). The specificity of SPECT CT in some investigations was higher than that of planar V/Q [30, 31, 34], but it was sometimes the same or nearly the same [29, 35] and in some investigations V/Q SPECT showed a lower specificity than planar V/Q [23, 28] (Table 2). Reinartz et al. used planar images reconstructed from SPECT data [29, 30]. Some differences have been observed between reconstructed images and true planar images [40].

Table 2 Comparison of V/Q SPECT or perfusion SPECT with planar V/Q

References	Reference standard	SPECT criteria	Planar V/Q criteria	Ventilation agent	Planar V/Q method	SPECT sensitivity n/N (%)	SPECT specificity n/N (%)	Planar V/Q sensitivity n/N (%)	Planar V/Q specificity n/N (%)
V/Q SPECT									
Gutte [34]	CT angio, V/Q SPECT, V/Q planar clinical, leg US, and follow-up	≥1 Mismatch (>0.5 segment)	≥1 Mismatch (>0.5 segment)	^{81m}Kr	6-view	10/10 (100)	20/23 (87)	7/11(64)	18/25 (72)
Palla [25]	Conventional angiogram. No PE if V/Q normal or angiogram neg or perfusion defect not in area of PE on angiogram	≥1 Segmental mismatch	McNeil Criteria	^{133}Xe	6-view conventional (V only if no CXR abnormality matching Q)	14/14 (100)	0/6(0)	11/14 (79)	2/6 (33)
Reinartz [29]	Consensus reading of V/Q SPECT, V/Q planar, clinical, and other radiological tests	≥ 1 Segmental or subseg mismatch	≥ 1 Segmental or subseg mismatch	Technegas	8-view reconstructed from SPECT	63/71 (89) Senior reader	32/32 (100) Senior reader)	43/71 (61) Senior reader	32/32 (100) Senior reader)
Reinartz [30]	Consensus including V/Q SPECT, CT angio, clinical, and follow-up	≥1 Segmental or subseg mismatch	≥1 Segmental or subseg mismatch	Technegas	8-view reconstructed from SPECT	36/37 (97)	42/46 (91)	28/37 (76)	39/46 (85)
Bajc [28]	V/Q SPECT, V/Q planar, CT angio, clinical, and laboratory	PE ≥ 2 segmental or subseg mismatch No PE = 0 mismatch	PE ≥ 2 segmental or subseg mismatch No PE = 0 mismatch	^{99m}-Tc DTPA	^{99m}-Tc DTPA	13/13(100) Reader A	37/40(93) Reader A	11/13(85) Reader A	40/40(100) Reader A
Meng [35]	Consensus including V/Q planar, V/Q SPECT, CT angio, clinical, and follow-up.	≥1 Segmental or ≥2 subseg mismatches	Updated PIOPED II criteria	Technegas		69/80 (86)	29/31(94)	61/80 (76)	29/31 (93)
Perfusion SPECT									
Collart [31]	D-Dimer, leg US, V/Q scan, CT angio, and follow-up	≥1 Wedge- shaped mismatch	≥1 Wedge-shaped mismatch	^{81m}Kr	6-view conventional	12/15 (80)	49/51 (96)	12/15 (80)	40/51(78)

Other abbreviations as in Table 1

CXR chest X-ray

V/Q SPECT combined with low-dose CT imaging (V/Q SPECT/CT)

V/Q SPECT/CT accuracy

Ling et al. reported a sensitivity of 26 out of 28 (93 %) and a specificity of 78 out of 78 (100 %) with V/Q SPECT/CT [41] (Table 3). The reference standard was the final physician diagnosis including findings on V/Q/SPECT/CT providing that no better alternative diagnosis was shown for a positive or negative diagnosis after 6 months [41].

Low-dose CT imaging combined with V/Q SPECT appears to increase the specificity of V/Q SPECT. In 77 patients, the sensitivity of V/Q SPECT alone was 28 out of 29 (97 %) and the specificity was 42 out of 48 (88 %) [27]. Among 81 patients with V/Q SPECT/CT, the sensitivity did not change, 30 out of 31 (97 %), but the specificity increased to 50 out of 50 (100 %). The reference standard included all imaging studies.

V/Q SPECT/CT compared with multidetector CT angiography

Ventilation/perfusion SPECT combined with low-dose CT imaging (V/Q SPECT/CT) appears to be more sensitive than multidetector CT angiography. Ventilation/perfusion SPECT combined with low-dose CT imaging was compared with 16-detector CT angiography in 81 patients [27]. The diagnosis of PE was based on all imaging studies (including SPECT and CT angiography), all clinical information, and follow-up. Six of the original 100 patients were excluded because of poor quality CT angiograms, eight because of poor quality SPECT images, and five because the diagnosis of PE was uncertain (no reference standard). In the remaining 81 patients, V/Q SPECT combined with low-dose CT showed a sensitivity of 30 of out of 31 (97 %) and a specificity of 50 out of 50 (100 %). Multidetector CT angiography showed a sensitivity of 21 out of 31(68 %) and a specificity of 50 out of 50 (100 %) [27].

It has been suggested that in some instances, there may be a dissociation between intraluminal filling defects shown on CT pulmonary angiography and perfusion defects in the same region [42]. CT angiography showed intravascular clots in 30 out of 34 (88 %) patients with lobar, segmental, or subsegmental perfusion defects on deep-inspiratory breath-hold perfusion SPECT [42]. In each of the four patients who did not show PE on CT angiography, SPECT showed one segmental and one or two subsegmental perfusion defects. In the 30 patients with PE shown on CT angiography, SPECT/CT fusion images showed that 69 out of 166 (42 %) perfusion defects were in lung territories that did not show PE on CT angiography. Four of these perfusion defects were lobar, 20 segmental, and 45 subsegmental. However, 97 out of 166 (58 %) perfusion defects were in lung territories with identifiable PE. Without further investigation it is not possible to determine whether SPECT was falsely positive or CT angiography was falsely negative.

Again, as a result of methodological limitations, the question of whether the V/Q approach of showing the pathophysiological effects of pulmonary vessel occlusion is superior, inferior, or complementary to that of showing the anatomy and pathology by CT angiography has not been answered by these investigations, either individually or collectively.

Perfusion SPECT/CT plus planar ventilation scintigraphy compared with dual-energy CT imaging

Dual-energy CT of pulmonary iodine distribution after intravenous administration of contrast material for CT pulmonary angiography has shown the ability to visualize perfusion defects resulting from PE [17]. In 15 patients, dual-energy CT imaging was found to show higher sensitivity and specificity than perfusion SPECT/CT plus planar ventilation scans [17]. Diagnosis of PE was by consensus opinion based on the perfusion SPECT images and dual-energy CT as standard of reference. In one of seven patients with PE, the CT diagnosis was made on the basis of a dual-energy perfusion map showing a triangular perfusion defect. The other six showed intraluminal filling defects. Dual-energy CT imaging had a sensitivity of seven out of seven (100 %) and specificity of eight out of eight (100 %). Perfusion SPECT/CT plus planar ventilation scintigraphy had a sensitivity of six out of seven (85.7 %) and a specificity of seven out of eight (87.5 %).

Perfusion SPECT

Perfusion SPECT accuracy

Bajc et al. suggested that perfusion SPECT (without ventilation SPECT) might be a valid alternative to V/Q SPECT or multidetector CT angiography in critically ill patients [36]. Its sensitivity was 53 out of 59 (90 %) and its specificity was 88 out of 93 (95 %). The reference standard for PE included V/Q SPECT which introduces incorporation bias [18, 37].

Perfusion SPECT/CT

Perfusion SPECT/CT compared with V/Q SPECT/CT

Perfusion SPECT/CT has been shown to be less specific than V/Q SPECT/CT [27]. The specificity of perfusion

Table 3 Sensitivity and specificity of V/Q SPECT/CT or perfusion SPECT/CT in patients with suspected pulmonary embolism

References	Reference Standard	SPECT criteria	Prospective (Yes/No)	Consecutive (Yes/No)	Ventilation agent	SPECT/CT sensitivity n/N (%)	SPECT/CT specificity n/N (%)
Investigations of V/Q SPECT/CT							
Ling [41]	V/Q SPECT providing no better alternative diagnosis after 6 months	≥2 Mismatch regardless of size or ≥1 mismatch >50 % of segment	N	N	Not specified	26/28 (93)	78/78 (100)
Gutte [27]	CT angio, V/Q SPECT, lower extremity US, ECG, clinical, D-dimer, echocardiography, and follow-up[b]	≥1 Mismatch	Y	Y	^{81m} Kr	30/31 (97)	50/50 (100)
Thieme [17]	Q SPECT/CT, dual-energy CT, V planar	≥1 Wedge-shaped mismatch (lobar, segmental, subseg)	Y	N	Technegas	6/7 (86)	7/8 (88)
Investigations of Perfusion SPECT/CT							
Lu [43]	Clinical, D-dimer, leg US, ECG, CT angio, and follow-up[a]	≥1 Wedge-shaped mismatch >50 % of segment	N	N	^{99m}Tc DTPA (planar)	20/22 (91)	79/84 (94)
Gutte [27]	CT angio, V/Q SPECT, lower extremity US, ECG, clinical, D-dimer, echocardiography, and follow-up[b]	≥1 Mismatch	Y	Y	Not applicable	26/28 (93)	21/41 (51)

Abbreviations as in Table 1

[a] Not all patients had all components of the composite reference standard

[b] All patients had VQ SPECT. Not specified which patients had other tests

SPECT/CT was 21 out of 41 (51 %), whereas the specificity of V/Q SPECT/CT was 50 out of 50 (100 %) [27]. The sensitivity of perfusion SPECT/CT, 26 out of 28 (93 %), was only slightly lower than that of V/Q SPECT/CT, 30 out of 31 (97 %).

Perfusion SPECT/CT compared with planar V/Q scintigraphy

Perfusion SPECT/CT was found to be more sensitive than planar V/Q scans in 106 patients with cancer and a high risk of PE [43]. The diagnosis of PE was based on clinical findings, lower extremity Doppler studies, CT angiography when available, and follow-up. The sensitivity of perfusion SPECT/CT was 20 out of 22 (91 %). Instead, the sensitivity of planar V/Q was 11 out of 22 (50 %) with the modified PIOPED criteria and 19 out of 22 (86 %) with the PISA-PED criteria. The specificity of perfusion SPECT/CT was 7 out of 84 (94 %). The specificity of planar V/Q was 77 out of 78 (98 %) with the PIOPED criteria and 79 out of 84 (93 %) with the PISA-PED criteria. These data confirm previous results indicating that the PISA-PED criteria perform better than the modified PIOPED criteria for the interpretation of planar perfusion imaging. There was no substantial increase in the accuracy for perfusion SPECT/CT compared with planar imaging when the PISA-PED criteria were used for interpretation of the planar perfusion scans [43].

Outcome after SPECT diagnosis

Outcome studies following a negative V/Q SPECT or Q SPECT showed negative predictive values for PE that ranged from 98.5 to 99.9 % (Table 4) [21, 44, 45]. This was comparable to results of outcome studies following planar V/Q scans in which normal, very low-probability, and low-probability readings were interpreted as negative [46]. These outcomes were also comparable to outcomes following normal planar perfusion scans [47], conventional pulmonary angiograms [48], CT angiography [49], and outcome in patients in whom clinical prediction rules combined with measurement of D-dimer indicated no PE [50, 51]. All of these showed negative predictive values that ranged from 98.4 to 99.8 %. Outcome studies provide an appropriate measurement for clinical management, even though outcome does not equate to accuracy [52]. When evaluating tests for conditions that may resolve spontaneously, outcome studies tend to overestimate the accuracy of testing.

V/Q SPECT for follow-up after acute PE

Follow-up with V/Q SPECT has been useful for showing resolution of PE. Among 23 patients with PE followed with serial V/Q SPECT, the extent of resolution was 54 % at 2 weeks, 79 % at 3 months, and 82 % at 6 months [53]. The proportion of patients who show complete resolution has been shown to depend on the severity of the initial perfusion defect [54]. In those with minor PE (<20 % perfusion defect), complete resolution of perfusion defects occurred in 45 out of 86 patients (52 %) after 8.2 ± 7.4 months. In patients with medium PE (20–50 % perfusion defect), complete resolution of perfusion defects occurred in 29 out of 99 patients (29 %) after 6.2 ± 5.9 months. In patients with major PE (>50 % perfusion defect), complete resolution occurred in 2 out of 42 (5 %) after 6.5 ± 0.7 months [54].

Recurrent PE occurred in 37 out of 227 patients (16 %) [54]. Most of these patients, i.e., 32 out of 37 (92 %), showed residual perfusion defects on the second V/Q SPECT [54]. With planar perfusion scans, the rate of resolution of perfusion defects among 70 patients treated with anticoagulants in the Urokinase-Pulmonary Embolism Trial was 7 % at 24 h, 16 % at 2 days, and 75 % at 3 months; thereafter, the rate increased only slightly [55]. Among patients with no prior cardiopulmonary disease, ≥90 % resolution was shown at 1 year in 29 out of 32 (91 %). However, among patients who had prior cardiopulmonary disease, ≥90 % resolution was shown at 1 year in only 13 out of 18 (72 %) [55].

Table 4 Outcome results with negative V/Q SPECT or Q/SPECT in patients with suspected pulmonary embolism

References	Test	SPECT criteria for no PE	Ventilation agent	Follow-up duration (months)	SPECT negative predictive value Follow-up n/N (%)
Corbus [45]	V/Q SPECT or Q SPECT	Normal or low-probability by revised PIOPED criteria	^{99m}Tc- DTPA	3	677/678 (99.9)[a]
Leblanc [44]	V/Q SPECT	No segmental or subseg mismatch	Technegas	3	399/405 (98.5)
Bajc [21]	V/Q SPECT	≤1 Mismatch	Technegas	6	1153/1159 (99.5)

Abbreviations as in Table 1

[a] 9 patients with negative CT angiograms in addition to low-probability V/Q SPECT were excluded

SPECT after administration of ^{99m}Tc-labeled anti D-dimer monoclonal Fab' fragments or ^{99m}Tc-apcitide

Radiolabeled antibody fragments that bind to the D-dimer regions of fibrin render fibrin-rich thromboemboli visible by scintigraphy [56, 57]. The method appears to be safe and suggests a promising level of accuracy. Based on CT pulmonary angiography as a reference standard, SPECT with ^{99m}Tc-labeled anti-D-dimer monoclonal Fab' fragments had a sensitivity of 16 out of 21 (76.2 %) and a specificity of 19 out of 21 (90.5 %) [57].

A synthetic ^{99m}Tc-labeled peptide, ^{99m}Tc-apcitide, formerly known as ^{99m}Tc- P280 [58] and showing high affinity and specificity for the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor on activated platelets, was investigated for its potential usefulness for imaging PE and deep vein thrombosis (DVT) [59]. Using ^{99m}Tc-apcitide with SPECT, PE was identified in four out of six (67 %) patients with PE [59]. It was also identified in seven out of nine (78 %) patients with DVT. The test was negative in four patients who had the onset of clinical symptoms and the diagnosis of DVT and/or PE more than 40 days before scintigraphy, suggesting that the peptide does not bind to thrombi when thrombogenesis is not active. Others in a preliminary investigation with ^{99m}Tc-apcitide identified one out of three segmental PE and none of the three subsegmental PE cases, resulting in an overall sensitivity of one in six (17 %) [60]. However, ^{99m}Tc-apcitide appeared more promising for the detection of DVT [60].

Conclusion

Trends in the reported aggregate data seem to show that SPECT V/Q is more sensitive, but not more specific, than planar V/Q and that combining low-dose CT with V/Q SPECT appears to increase its specificity. In general, a holistic approach to diagnosis has been employed in investigations of the accuracy of V/Q SPECT. In investigations of diagnostic accuracy, when the reference standard is based on information that includes the index test (V/Q SPECT) or planar V/Q, as is the case with a holistic approach, the problem of incorporation bias is introduced. In investigations that used CT angiography as an independent reference test, when there were discordant results, it was not possible to determine whether SPECT was falsely positive or angiography was falsely negative. Accordingly, the accuracy of V/Q SPECT is difficult to assess conclusively.

Our conclusions upon review of the available evidence are the following:

1. Outcome studies showed that PE can be safely excluded in patients with a negative V/Q SPECT. The negative predictive value of a negative SPECT is similar to that of a negative CT angiogram or of clinical prediction rules (including D-dimer) that indicate a low likelihood of PE.
2. The effective radiation dose for V/Q SPECT is about 35–40 % of the dose from multidetector CT pulmonary angiography and the dose to the female breast is only about 4 % that of CT. This, of course, is a major benefit of SPECT that would indicate its use in preference to CT in many young female patients.
3. Perfusion SPECT (without ventilation SPECT) might be a valid alternative to V/Q SPECT or multidetector CT angiography in critically ill patients.
4. Published studies do not establish the accuracy of V/Q SPECT relative to that of planar V/Q or CT angiography.

There is a need for a prospective investigation of the accuracy of V/Q SPECT with consecutive patients, blinded interpretations, and an independent reference standard or independent composite reference standard.

Conflict of interest The authors, Paul D. Stein, MD, H. Dirk Sostman, MD, and Fadi Matta, MD, have no conflicts of interest.

Ethical standard This article does not contain any studies with human or animal subjects performed by any of the authors.

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