A review of medical imaging in the evaluation of PE and CTEPH

Michael Tong[1,2], Janelle Wheat[2], Geoffrey M. Currie[2*]

Pakistan Journal of Nuclear Medicine
Volume 10(1):1–11

ABSTRACT

Introduction: The diagnostic approach to patients with suspected pulmonary embolism (PE) and its clinical complication of chronic thromboembolic pulmonary hypertension (CTEPH) is usually a combination of clinical and pretest probability assessments, and definitive diagnostic imaging. Diagnostic studies and imaging procedures, such as ventilation and perfusion scintigraphy (V/Q), computed tomography (CT), pulmonary angiography, and CT pulmonary angiogram (CTPA), play an important role and have proven to be excellent complements in accurately confirming or ruling out the presence of PE and CTEPH. The purpose of this review is to compare and aggregate the available data from PE and CTEPH diagnosis studies carried out using the imaging techniques of CTPA, single-photon emission CT (SPECT) V/Q, and planar V/Q.

Methods: A systemic review was conducted with participants who were limited to patients with or suspected with PE or CTEPH. No age limitations, geographic, and gender differentiations were imposed. Pooled sensitivity and specificity performances, positive and negative likelihood ratio (LR), the I-square (I^2) value of heterogeneity SROC curves, and the area under the curve were generated. The Q* value was calculated to define the point where sensitivity and specificity are equal.

Results: Twenty-six studies totalling 5,637 patients were reviewed. The majority of the studies included the comparison of techniques within or between the different imaging modalities. For PE, the patient pool for CTPA was 904, for SPECT V/Q was 3717, and for planar V/Q was 1016, with sensitivity of 84%, 94%, and 85%, respectively, and corresponding specificity of 94%, 99%, and 85%, respectively. For CTEPH, the patient pool for CTPA was 488 for patient-based and 2,538 vessels for vessel-based, and for V/Q was 530, with sensitivity of 76%, 95%, and 98%, respectively, and corresponding specificity of 95%, 96%, and 93%, respectively.

Conclusion: This review demonstrated superior sensitivity and specificity of V/Q SPECT over CTPA and planar V/Q for the diagnosis of PE. Likewise, for CTEPH, V/Q demonstrated superior sensitivity and specificity, although in a select subgroup of CTPA patients assessed on a per vessel basis, performance was improved. Wherever available, V/Q SPECT should be used as the first line imaging tool for PE and CTEPH.

Keywords: Lung scan, ventilation, perfusion, pulmonary hypertension, CTPA, VQ.

Received: 09 January 2020 **Accepted:** 29 May 2020
Type of Article: REVIEW ARTICLE
https://doi.org/10.24911/PJNMed.175-1578555253

Correspondence to: Geoffrey M. Currie
*School of Dentistry and Health Sciences. Charles Sturt University, Wagga, Australia.
Email: gcurrie@csu.edu.au
Full list of author information is available at the end of the article.

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) has generally been accepted to be one of the late complications of pulmonary embolism (PE). An international registry reported a 75% incidence rate of CTEPH patients having a clinical history of PE [1]. The diagnostic approach to patients with suspected PE is usually a combination of clinical and pretest probability assessments, and definitive diagnostic imaging of computed tomography (CT) pulmonary angiography (CTPA) or lung ventilation and perfusion scintigraphy (V/Q).

The pathogenesis of CTEPH is complex and not completely understood [2,3]. CTEPH represents one of the most prevalent forms of pulmonary hypertension (PH) and is the result of acute and nonresolving thromboembolisms of the pulmonary arteries, and is the fibrous organization of these blood clots [4]. Embolic clinical occurrences, such as acute PE, can be clinically silent but may be the trigger, followed by progressive pulmonary vascular remodelling (small vessel vasculopathy), resulting in elevated pulmonary vascular resistance, and subsequently right ventricle failure [5]. Progression of the disease can include secondary events, such as histopathologic changes in the pulmonary microvascular circulation [6]. Several studies have suggested the association with underlying hypercoagulable states. Two observational studies reported elevated levels of factor VII (interpreted as > 230 IU/dl) in patients with CTEPH when compared to healthy subjects, with those above the 90th percentile having a higher risk of recurrent venous thromboembolism (VTE) [7]. The prothrombotic marker in antiphospholipid antibodies has most commonly been associated with an occurrence rate of up to 20% of CTEPH patients [7–9]. Other associated medical conditions include myeloproliferative syndromes, recurrent VTE, ventriculoatrial shunts

and splenectomy [7]. Postulated risk factors include underlying hematological and immune disorders [10], insufficient anticoagulation [11,12], history of PE with systolic pulmonary artery pressure (PAP) >50 mmHg, and significant pulmonary vascular obstructions observed during PE diagnosis [13,14].

CTEPH has been shown to manifest from acute symptomatic PE within 2 years [12]. The incidence rate of CTEPH after the initial episode of acute PE is between 1% and 4% [13,15]. Improved therapy for PE has also improved the clinical outcomes of patients with CTEPH [12]. If left untreated, progressive right ventricular dysfunctions may result in fatal right heart failure. The mortality rate of CTEPH has been reported to be 4%–20% [16–19]. Severe CTEPH, which is not treated, has been found to have a 5-year survival rate of only 30% [20]. Early and accurate diagnosis is crucial in CTEPH. The purpose of this review is to aggregate and evaluate the available data from PE and CTEPH diagnosis studies carried out using the imaging techniques of CTPA, SPECT V/Q, and planar V/Q by conducting a structured literature review with a SROC analysis.

Methods

The electronic databases of Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Ovid SP) 1946–14 January 2018, and EMBASE were searched by employing the search terms (pulmonary embol* or pulmonary chronic thromboembol* or PH), (ventilation), (PE or embolism), (CTEPH), (V/Q or VP), (perfusion), (CT or CTPA), (SPECT or planar or scintigraphy), (diagnosis or diagnostic), (cost-effectiveness adj), (benefit) or (advantage), and (study or studies or trial). An asterisk* was placed within the search to look for any additional phrases that has the searched word as a prefix, including the word itself. Free text and medical subject headings were both entered during the search. No restrictions were imposed on publication status.

Studies were included if they involved the evaluation of diagnostic imaging tests or strategies with the objective of confirming or excluding PE or CTEPH, and that the reference method includes lung scintigraphy (or V/Q). In cases where the studies had multiple publications, the most recent publication was used. Editorials, case reports and series, and abstracts were excluded. All study designs, such as diagnostic cross-sectional studies and cohort studies on lung ventilation and perfusion, were included. The study participants were limited to patients with or suspected with PE or CTEPH. No age limitations, geographic, and gender differentiations were imposed. All relevant and potentially eligible studies were retrieved and reviewed in full manuscripts. Animal studies, editorials, author replies, letters, comments, and conference proceedings were excluded. Studies with clearly nonrelevant data or without specificity and sensitivity reports, and studies with duplicate patient data from different publications were also excluded upon further review.

Studies with CT imaging techniques were included, regardless of the technique or the slices used. Data on true-positive, true-negative, false-positive, and false-negative were either extracted directly (if given) or inferred from the reported values for specificity, sensitivity, and both positive and negative predictive values from the studies in this literature review. These data were inputted into the metaDisc software (version 1.4) [21], generating the pooled sensitivity and specificity performances of each imaging technique, as well as the positive and negative likelihood ratio (LR). The pooled data were analyzed with 95% confidence intervals (CI), with the I-square (I^2) value used in investigating statistical heterogeneity between the included studies. Symmetrical SROC curves were also generated for all three imaging techniques of CTPA, SPECT V/Q, and planar V/Q, with the study size weighted least squares estimation method. In this review, the area under the curve (AUC) was used as a figure of merit which summarizes the diagnostic performance [22] of the various imaging techniques as a single number, with a perfect test having an AUC close to 1 and poor tests having an AUCs close to 0.5. The AUC was computed within the metaDisc software by numeric integration of the curve equation by the trapezoidal method. The Q* value was also used as a performance evaluation figure, defined by the point where sensitivity and specificity are equal, which is the point closest to the ideal top-left corner of the receiver operating characteristic (ROC) space.

In assessing the quality of the studies in this review, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) methodology [23] was employed to overcome the lack of homogeneity in the quality factors used in the reviewed studies due to differences in the study designs. The quality assessment was carried out based on the four domains of patient selection, index test, reference standard, and flow and timing, with each domain assessed in terms of risk of bias and judged as 'low', 'high', or 'unclear'. The first three domains were also assessed in terms of concerns regarding applicability. The generic signaling questions used to help judge risk of bias were also used in this review.

Results

Data identification

There were 1,195 potentially eligible studies identified by searching the electronic databases of CENTRAL, MEDLINE (Ovid SP), and EMBASE. No start date limitation was enforced. The last searched date was 14 January 2018. To ensure a comprehensive search and to maximize the results, no language limitation was used. After initial screening through the titles and abstracts, 742 studies were excluded as they do not meet the defined inclusion

criteria. A total of 235 articles were obtained in full text versions for further detailed screening. The references of these retrieved articles were then scrutinized for potential relevant articles, leading to an additional retrieval of 55 articles which were obtained in full text. In total, 290 full text articles were retrieved. After evaluating the articles in full, 264 of these articles were excluded for having not entirely met the inclusion criteria. Three otherwise suitable provided relevant results for CTPA and SPECT V/Q but were excluded, as there was no definite gold reference standard and, therefore, not possible to extract the sensitivity and specificity of either imaging technique.

Of the included 26 studies, there were 17 that were carried out prospectively, while 9 were a retrospective analysis. Most studies only recruited patients above the age of 18 and excluded pregnant patients. Renal deficiency and contrast media allergy were the general exclusion factors in the studies carrying out CTPA. Two studies excluded patients with previous history of PE, while one study explicitly only excluded patients who had PE within the past one month. Other exclusion criteria included hypotension, hemodynamic instability, respiratory deficiency, mental illness and dementia, patients in circulatory shock, clotting disorder, and life expectancy below a period of three months. Further information on the various imaging techniques employed in the included studies are presented in Table 1.

Pulmonary embolism

All included studies had either confirmation of PE or the diagnosis of PE as the primary objective. The majority of the studies included the comparison of techniques

Table 1. *Studies and data included in the review.*

STUDY	DESIGN	DIAGNOSIS	PREVIOUS PE	CLINICAL EXCLUSIONS	VENTILATION
Dournes [24]	Prospective	CTEPH	Unclear	Contraindication to iodine-based contrast agent injection	Technegas
Skarlovnik [25]	Retrospective	PE	Yes	Patients <18; Pregnancy	Technegas
Bajc [26]	Retrospective	PA	Yes	None	Technegas
Meng [27]	Prospective	PE	Unclear	Unclear	Technegas
Sugiura [28]	Prospective	CTEPH	Unclear	None	CT only
He [29]	Prospective	PE	Yes	Pregnancy; Patients currently experiencing circulatory shock; Hypotension; Renal failure; Hemodynamic instability	Technegas
He [30]	Prospective	CTEPH	Unclear	Unclear	Technegas
Le Duc-Pennec [31]	Prospective	PE	No	Pregnancy; Life expectancy <3 months; Patients <18	^{81m}Kr
Ley [32]	Prospective	CTEPH	Unclear	None	CT only
Thieme [33]	Prospective	PE	Yes	Pregnancy	Technegas
Ling [34]	Retrospective	PE	Yes	None	Unclear
Gutte [35]	Prospective	PE	Yes	Renal impairment	^{81m}Kr
Miles [36]	Prospective	PE	Yes	Patients <50	Technegas
Reichelt [37]	Prospective	CTEPH	Unclear	Serum creatinine >1.5 mg/dl	CT only
Wang [38]	Prospective	PE	Yes	Unclear	Technegas
Bajc [39]	Retrospective	PE	Unclear	None	Technegas
Bartalena [40]	Retrospective	CTEPH	Unclear	None	Technegas
Weinmann [41]	Prospective	PE	No	Patients <18; Pregnancy	Technegas
Tunariu [42]	Retrospective	CTEPH	Unclear	None	^{81m}Kr
Katsouda [43]	Prospective	PE	Yes	Respiratory disorder; Clotting disorders; Hypotension; Respiratory impairment; Pregnancy	Unclear
Macdonald [44]	Prospective	PE	Yes	Patients <18; Mental illness, dementia; Pregnancy; Renal failure	Technegas
Reinartz [45]	Retrospective	PE	Yes	Hemodynamic instability	Diethylenetriamine-pentaacetic acid (DTPA)
Stone [46]	Prospective	PE	Yes	Patients <18; Pregnancy	Technegas
Pitton [47]	Prospective	CTEPH	Unclear	Unclear	CT only
Lemb [48]	Retrospective	PE	Yes	Unclear	Technegas
Worsley [49]	Retrospective	CTEPH	Unclear	None	^{133}Xe

within or between the different imaging modalities. The total number of patients in the included studies was 5,637. Patient pool for CTPA was 904, with 43% (392) true-positive; 3% (25) false-positive; 43% (390) true-negative; 9% (78) false-negative; and 2% (18) nondiagnostic. Patient pool for SPECT V/Q was 3,717, with 28% (1,022) true-positive; 1% (33) false-positive; 67% (2,470) true-negative; 2% (62) false-negative; and 0.5% (19) nondiagnostic. Patient pool for planar V/Q was 1,016, with 38% (385) true-positive; 9% (88) false-positive; 44% (449) true-negative; 8% (82) false-negative; and 1% (12] nondiagnostic. Table 2 describes the efficacy between the three imaging techniques. Three studies reported anomalously low sensitivity values: 57% [43] and 44% [44] for planar V/Q, and 57% [46] for CTPA. Results of these studies were excluded in the ROC analysis. One study [27] was a non-English publication with no English translated version. As a result, retrieval of information and data was limited and the results were similarly excluded from the ROC analysis.

For PE, the pooled sensitivity of CTPA was 84% (95% CI, 80%–87%), with a moderately high statistical heterogeneity in the sensitivity estimates (I^2: 70.5%) attributed to variability between studies, analyzed on a per-patient-based analysis. The pooled specificity of CTPA was 94% (95% CI, 91%–96%), with a low statistical heterogeneity in the specificity estimates (I^2: 12.0%), analyzed on a per-patient-based analysis. The pooled positive LR of CTPA was 12.35 (8.15–18.70), with a low statistical heterogeneity I^2 of 5.1%. The pooled negative LR of CTPA was 0.16 (0.10–0.26), with a low statistical heterogeneity I^2 of 54.9%.

The pooled sensitivity of SPECT V/Q for PE was 94% (95% CI, 93%–96%), with a high statistical heterogeneity in the sensitivity estimates (I^2: 88.4%) attributed to variability between studies, analyzed on a per-patient-based analysis. The pooled specificity of SPECT V/Q was 99% (95% CI, 98%–99%), with a relatively high statistical heterogeneity in the specificity estimates (I^2: 79.3%), analyzed on a per-patient-based analysis. The pooled positive

Table 2. *Subgroup comparison of imaging techniques efficacy (Diagnosis of PE).*

AUTHOR	NO. OF PATIENTS	SENSITIVITY	SPECIFICITY	NONDIAGNOSTIC	TRUE-POSITIVE RESULTS	FALSE-POSITIVE RESULTS	TRUE-NEGATIVE RESULTS	FALSE-NEGATIVE RESULTS
CTPA								
He [29]	544	82	93	16	259	14	197	58
Wang [38]	77	97	97	2	36	1	37	1
Katsouda [43]	63	93	86	0	39	3	18	3
Macdonald [44]	112	83	90	0	22	5	77	8
Reinartz [45]	83	86	98	0	32	1	45	5
Stone [46]	25	57	94	0	4	1	17	3
V/Q (SPECT)								
Skarlovnik [25]	49	100	98	0	9	1	39	0
Meng [27]	111	86	94	0	–	–	–	–
Bajc [26]	152	90	95	0	53	5	88	6
Le Duc-Pennec [31]	243	55	87	0	45	4	191	3
Ling [34]	106	98	98	0	26	0	78	2
Thieme [33]	15	86	88	0	6	1	7	1
Miles [36]	87	83	98	0	19	1	63	4
Bajc [39]	1785	99	99	19	601	6	1153	6
Weinmann [41]	95	79	83	0	56	4	20	15
Reinartz [45]	83	97	91	0	36	4	42	1
Lemb [48]	991	96	97	0	171	7	789	24
V/Q (planar)								
Skarlovnik [25]	98	83	98	7	5	2	83	1
He [29]	544	86	83	0	276	42	181	45
Gutte [35]	36	64	72	0	7	7	18	4
Wang [38]	80	89	92	5	33	3	35	4
Katsouda [43]	63	57	43	0	24	12	9	18
Macdonald [44]	112	44	99	0	12	15	84	1
Reinartz [45]	83	76	85	0	28	7	39	9

LR of SPECT V/Q was 30.56 (11.89–78.56), with a high statistical heterogeneity I^2 of 86.3%. The pooled negative LR of SPECT V/Q was 0.08 (0.04–0.19), with a high statistical heterogeneity I^2 of 89.4%.

The pooled sensitivity of planar V/Q for PE was 85% (95% CI, 81%–88%), with a low statistical heterogeneity in the sensitivity estimates (I^2: 33.5%) attributed to variability between studies, analyzed on a per-patient-based analysis. The pooled specificity of SPECT V/Q was 85% (95% CI, 82%–89%), with a high statistical heterogeneity in the specificity estimates (I^2: 82.2%), analyzed on a per-patient-based analysis. The pooled positive LR of CTPA was 5.89 (3.2 to 10.86), with a moderately high statistical heterogeneity I^2 of 71%. The pooled negative LR of CTPA was 0.22 (0.14–0.36), with a moderate statistical heterogeneity I^2 of 54.8%.

The ROC AUC for CTPA, SPECT V/Q, and planar V/Q in PE were 0.96, 0.98, and 0.89, respectively. In addition, the Q* values for CTPA, SPECT V/Q, and planar V/Q are 0.91, 0.94, and 0.82, respectively. From the extracted data, the performance of planar V/Q evidently lags behind that of both CTPA and SPECT V/Q.

CTEPH

Studies listed in Tables 3 and 4 had either confirmation of, or the diagnosis of, CTEPH as the primary objective, and are patient-based. The results from all V/Q scintigraphy studies in Table 3 are similar; however, the specificity from Worsley et al.'s (49) study was relatively low at 86%. The absence of the availability of true-positive, false-positive, true-negative, and false-negative was prohibitive of detailed analysis of LR, I^2, UAC, or Q for V/Q in CETEPH. For CTEPH, the patient pool for V/Q was 530, with a sensitivity of 98% and specificity of 93%.

The total number of patients in the included CTPA studies from Table 4 was 488, with 28% (136) true-positive; 3% (14) false-positive; 60% (294) true-negative; and 9% (44) false-negative. The pooled sensitivity of CTPA for CTEPH was moderately low at 76% (95% CI, 69%–82%), with a high statistical heterogeneity in the sensitivity estimates (I^2: 93.8%) attributed to variability between studies, analyzed on a per-patient-based analysis. The pooled specificity of CTPA was 95% (95% CI, 92%–97%), with a low statistical heterogeneity in the specificity estimates (I^2: 78.1%), analyzed on a per-patient-based analysis. The pooled positive LR of CTPA was 13.78 (6.10–31.14), with a statistical heterogeneity I^2 of 56.2%. The pooled negative LR of CTPA was 0.11 (0.02–0.68), with a statistical heterogeneity I^2 of 92.5%.

Studies listed in Table 5 had either confirmation of or the diagnosis of CTEPH as the primary objective, and are vessel-based. The total number of vessels in the included studies was 2,538, with 36.8% (933) true-positive; 2.7%

Table 3. *Subgroup analysis: efficacy of V/Q in the diagnosis of CTEPH (patient-based).*

AUTHOR	NO. OF PATIENTS	SENSITIVITY	SPECIFICITY	ACCURACY
He [29]	114	100%	93.7%	96.5%
Tunariu [42]	227	96.2%	94.6%	95.2%
Worsley [49]	75	100%	86%	91%
He [30]	114	100%	93.7%	96.5%

Table 4. *Subgroup analysis: efficacy of CTPA in the diagnosis of CTEPH (patient-based).*

AUTHOR	NO. OF PATIENTS	SENSITIVITY	SPECIFICITY	ACCURACY	TRUE-POSITIVE RESULTS	FALSE-POSITIVE RESULTS	TRUE-NEGATIVE RESULTS	FALSE-NEGATIVE RESULTS
Dournes [24]	40	100%	88%	–	14	3	23	0
He [30]	114	92.2%	95%	92.5%	47	3	60	4
Bartalena [40]	107	95%	90%	–	35	7	63	2
Tunariu [42]	227	51.3%	99.3%	82.8%	40	1	148	38

Table 5. *Subgroup analysis: efficacy of CTPA in the diagnosis of CTEPH (vessel-based).*

AUTHOR	NO. OF PATIENTS	TOTAL NO. OF VESSELS	STANDARD PAP[A]	MEAN PAP[A]	GOLD STANDARD	TRUE-POSITIVE RESULTS	FALSE-POSITIVE RESULTS	TRUE-NEGATIVE RESULTS	FALSE-NEGATIVE RESULTS
Sugiura [28]	16	1,175	696 ± 274	42.2 ± 9.9	DSA	218	44	903	29
Ley [32]	13	639	Unclear	42 ± 10	DSA	360	1	258	0
Reichelt [37]	13	724	763 ± 345	46 ± 8	DSA, V/Q	355	23	329	18
Pitton [47]	Unclear	994	Unclear	Unclear	DSA	–	–	–	–

[a]Pulmonary artery pressure.

(68) false-positive; 58.7% (1,490) true-negative; and 1.8% [47] false-negative.

The pooled sensitivity of CTPA for vessel-based CTEPH was 95% (95% CI, 94%–96%), with a high statistical heterogeneity in the sensitivity estimates (I^2: 96.3%) attributed to variability between studies. The pooled specificity of CTPA was 96% (95% CI, 94%–97%), with moderately low statistical heterogeneity in the specificity estimates (I^2: 89.9%). The pooled positive LR of CTPA was 23.67 (11.21–49.96), with a statistical heterogeneity I^2 of 84.1%. The pooled negative LR of CTPA was 0.05 (0.01–0.16), with a statistical heterogeneity I^2 of 91.2%. One study [47] was a non-English publication with no English translated version. As a result, the retrieval of information and data was limited and the results were excluded from the ROC analysis.

The AUCs for patient-based and vessel-based CTPA are 0.98 and 0.99, respectively. In addition, the Q* values for patient-based and vessel-based CTPA are 0.93 and 0.97, respectively. The extracted data showed significant heterogeneity across the studies for both analyses. This review only selected and analyzed papers which fell under the inclusion criteria stated earlier. The results of QUADAS-2 for the above analyzed studies are tabulated in Table 6.

Discussion

V/Q lung scan was the initial preferred and recommended imaging technique in the clinical evaluation of PE from the late 1960s to the early 1990s. Data from a prospective investigation of PE diagnosis (PIOPED) showed that the rate of low and/or intermediate probability with V/Q scans was as high as 65% [50], thus limiting subsequent utilization of V/Q scans in the clinical evaluation of PE. The introduction of CTPA (Figure 1), with its faster scan times, 24/7 availability, and offer of clear anatomical information, brought about a change from the 1990s, overtaking V/Q scans as the preferred imaging technique in the detection of PE [51,52]. The other potential advantage of having the CT component is the added possibility of other incidental clinical discoveries, although such outcomes were not mentioned in the reviewed studies. There

Table 6. QUADAS-2 evaluation summary.

STUDY	DOMAIN 1: PATIENT SELECTION		DOMAIN 2: INDEX TEST		DOMAIN 3: REFERENCE TEST		DOMAIN 4: FLOW AND TIMING
	RISK OF BIAS	APPLICABILITY CONCERNS	RISK OF BIAS	APPLICABILITY CONCERNS	RISK OF BIAS	APPLICABILITY CONCERNS	RISK OF BIAS
Dournes [24]	Unclear	Low	Low	Low	Low	Low	High
Skarlovnik [25]	Low	Low	Low	Low	High	Low	High
Bajc [26]	Low	Low	Low	Low	High	Low	High
Meng [27]	Low	Low	Unclear	Low	Unclear	Low	Unclear
Sugiura [28]	Low	Low	Low	Low	Low	Low	Low
He [29]	Low	Low	Low	Low	High	Low	Low
He [30]	Low	Low	Low	Low	Low	Low	High
Le Duc-Pennec [31]	Low	Low	Low	Low	High	Low	Low
Ley [32]	Unclear	Low	Low	Low	Low	Low	High
Thieme [33]	Low	Low	Low	Low	High	Low	High
Ling [34]	Low	Low	Low	Low	High	Low	High
Gutte [35]	Low	Low	Low	Low	High	Low	Low
Miles [36]	Low	Low	Low	Low	High	Low	High
Reichelt [37]	Low	Low	Low	Low	Low	Low	High
Wang [38]	Low	Low	Low	Low	High	Low	Low
Bajc [39]	Low	Low	Low	Low	High	Low	High
Bartalena [40]	Low	Low	Low	Low	Low	Low	High
Weinmann [41]	Low	Low	Low	Low	High	Low	High
Tunariu [42]	Low	Low	Low	Low	Low	Low	Low
Katsouda [43]	Low	Low	Low	Low	High	Low	High
Macdonald [44]	Low	Low	Low	Low	High	Low	Low
Reinartz [45]	Unclear	Low	Low	Low	High	Low	Low
Stone [46]	Low	Low	Low	Low	High	Low	Low
Pitton [47]	Low	Low	Unclear	Low	Unclear	Low	Unclear
Lemb [48]	Unclear	Low	Low	Low	High	Low	Low
Worsley [49]	Low	Low	Low	High	Low	Low	Low

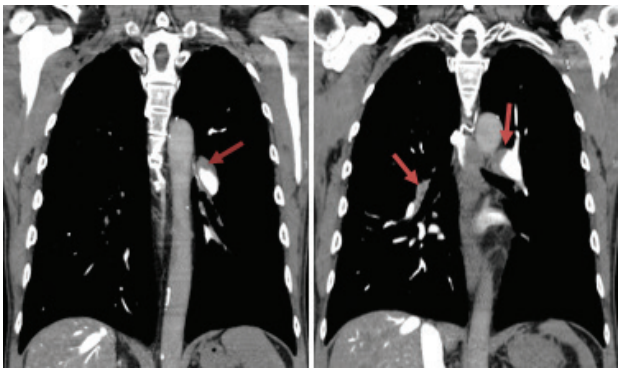

Figure 1. *CTEPH defects in CTPA. Long eccentric, wall adherent, and hypodense filling defects demonstrated in the enlarged left and right pulmonary arteries.*

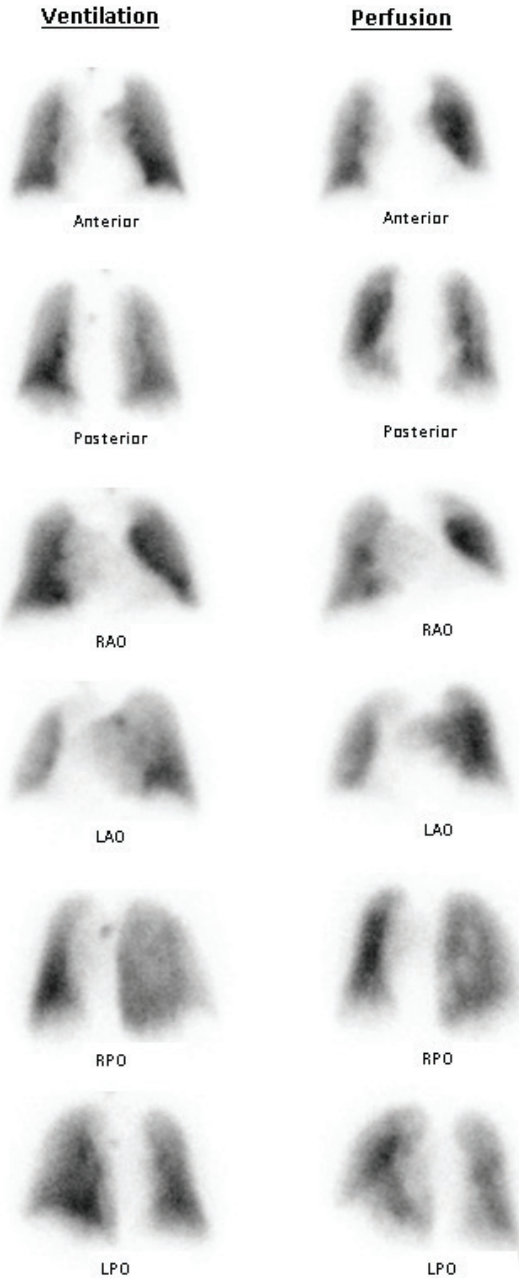

Figure 2. *Abnormal planar V/Q (CTEPH positive) classified as high probability. Moderate and large-sized defects in the inferior lingual, lateral basal segment of the left lower lobe, as well as in the lateral and posterior basal segment of the right lower lobe.*

are, however, concerns about higher radiation doses and contrast contraindications [53].

CTEPH is a rare chronic condition with a cumulative incidence rate of 0.57% in all patients with acute PE after more than three months of curative anticoagulation treatment [54]. The widely proposed etiological theory is that CTEPH is a complication of acute PE following VTE [55]. A recent large international study revealed that 75% of CTEPH patients had a history of acute PE [1]. Several studies have reported the incidence rate of CTEPH subsequent to acute PE, in the range of 0.4%–6.2%, with a 3.4% pooled incidence (95% CI sensitivity, 2.1–4.4) [12,13]. It was also determined that CTEPH can develop long after an episode of acute PE, up to years, with no new clinical symptoms suggestive of its manifestation [12,56]. Imaging modalities, such as CTPA and V/Q scintigraphy, have been the preferred diagnostic tools for diagnosing CTEPH. This review shows a high sensitivity and a moderate specificity for V/Q scintigraphy in the assessment of CTEPH. The sensitivity of V/Q in the diagnosis of CTEPH was, however, noted to be lower in Tunariu's [42] study when compared with other studies, and is believed to be due to the inclusion of patients with subsegmental PE, and because the study was conducted with older technology. For CTPA, there is a moderate sensitivity and high specificity in the patient-based analysis. On the vessel basis, CTPA recorded similarly high sensitivity and specificity in diagnosing CTEPH.

One of the weaknesses of this review is the absence of an analysis on the radiation dose delivered per diagnosis. Given the comparable diagnostic performances of both CTPA and V/Q, the considerably higher radiation doses from CTPA should be taken into account in the physician's imaging choice in the diagnosis of PE or CTEPH. It may be worth customizing certain clinical conditions to fit a particular imaging technique, such as SPECT V/Q for pregnant women and young children in minimizing radiation dose exposure, while critically ill patients, obese, and those with significant underlying pulmonary conditions, such as chronic obstructive pulmonary disease, may be more suitable for CTPA.

Another weakness of this review is the absence of reference to a gold standard diagnostic imaging modality in the diagnosis of PE and CTEPH. Some of the studies actually used some form of composite evaluation, where the imaging studies themselves play a significant part as a reference standard. CTEPH studies with digital subtraction angiography (DSA) or V/Q as gold standards affects the reliability of the pooled data. The absence of a single gold standard diagnostic imaging modality also resulted in the exclusion of several shortlisted studies. In addition, the limited number of relevant CTEPH studies reduced the statistical power of the analysis. Data were extracted from different CT techniques, thus leading to potential bias.

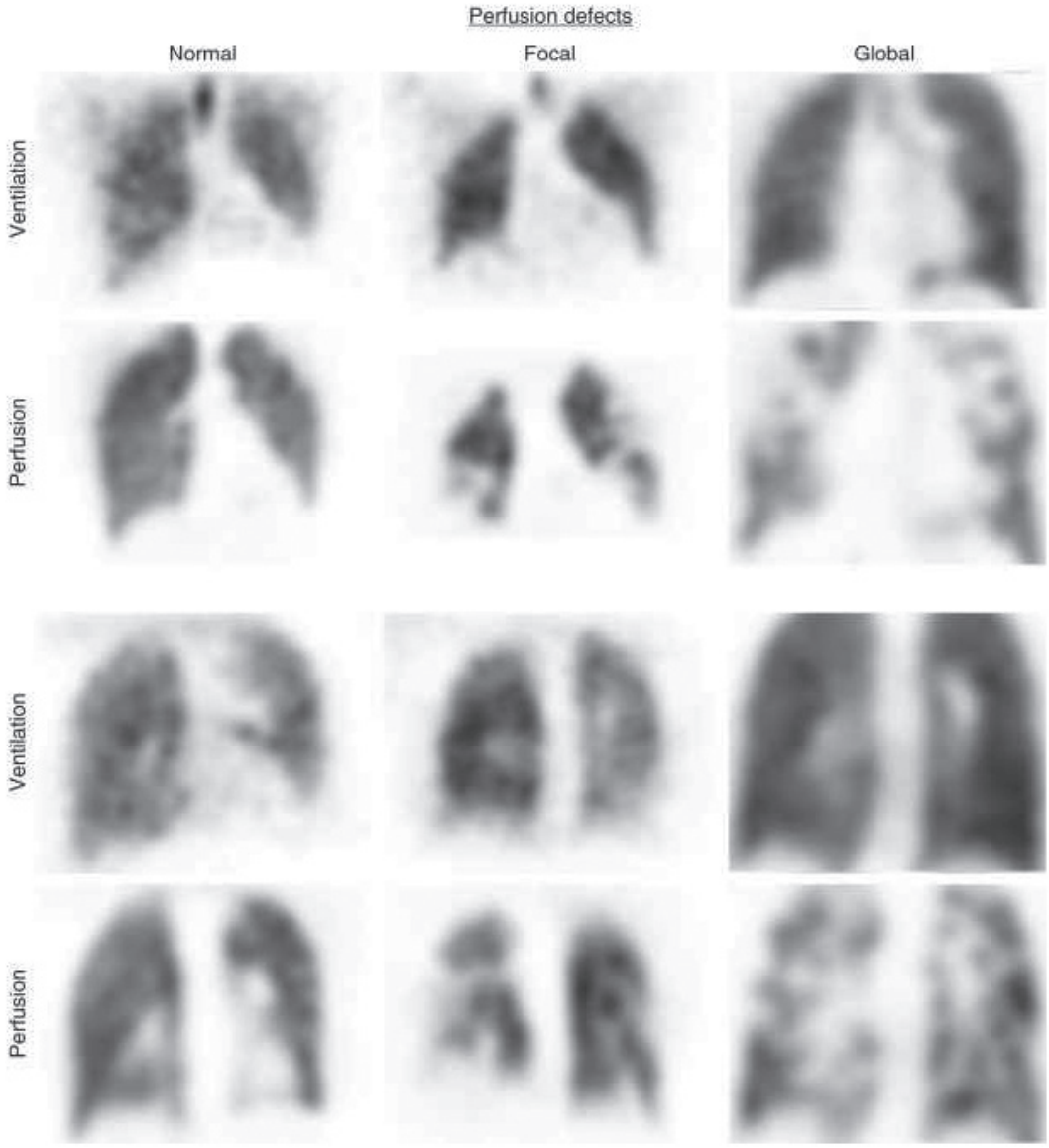

Figure 3. *SPECT V/Q images of normal (left) and perfusion defect consistent with CTEPH in patients with supporting clinical evidence [57].*

The reviewed studies also applied different diagnostic and interpretation criteria (e.g., PIOPED 1, PIOPED II, PISAPED). The ventilating agents used in the SPECT V/Q were also different, ranging from Technegas to 99m-Tc DTPA aerosol to ^{81m}Krypton (^{81m}K); each with different performance capabilities and limitations.

Meta-analysis can also help identify and design potential future investigations of subset hypotheses [58].The role of meta-analysis in scientific studies has been reported to detect biasness, as well as the effect of diversity across various types of studies on the effectiveness of various techniques and interventions in the respective settings [59]. This study had employed the QUADAS-2 methodology in systematically assessing the risks of bias, as well as the applicability of the studies. At the same time, when underlying biases and study diversity are not addressed adequately, such integration of data from different studies will add to the overall variability, potentially resulting in factitious and inconclusive results [59]. An additional limitation of the pooling of statistics is that it does not enhance the quality of the original studies [59].

Current guidelines recommend V/Q (Figure 2 and 3) as the first choice of imaging tool in suspected CTEPH to screen for the presence of thromboembolic disease. Nonetheless, there are wide variations in the selection of imaging tests in diagnosing CTEPH, and the choice of imaging modality often comes down to expertise, and thus preference and availability. A normal lung perfusion result essentially rules out the clinical diagnosis of PE and CTEPH as early manifestations of CTEPH, recurrent or occlusive PE of all types, will demonstrate perfusion defect even if anticoagulant treatments are withheld [60].

Conclusion

This review demonstrated superior sensitivity and specificity of V/Q SPECT over CTPA and planar V/Q for the

diagnosis of PE. Likewise, for CTEPH, V/Q demonstrated superior sensitivity and specificity, although in a select subgroup of CTPA patients assessed on a per vessel basis, performance was improved. Wherever available, V/Q SPECT should be used as the first line imaging tool for PE and CTEPH.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Not Applicable.

Ethical approval

Not Applicable.

Author details

Michael Tong[1,2], Janelle Wheat[2], Geoffrey M Currie[2]

1. Department of Diagnostic Imaging, NUHS Tower Block, National University Hospital, Singapore, Australia
2. School of Dentistry and Health Sciences, Charles Sturt University, Wagga, Australia

References

1. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124(18):1973–81. https://doi.org/10.1161/CIRCULATIONAHA.110.015008
2. Lang IM, Pesavento R, Bonderman D, Yuan JX. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J. 2013;41(2):462–8. https://doi.org/10.1183/09031936.00049312
3. Jaïs X, D'Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol. 2008;52(25):2127–34.
4. Frachon I, Jaïs X, Leroyer C, Jobic Y, Huchot E, Simonneau G, et al. [Diagnosis and care of postembolic pulmonary hypertension: the role of the pneumologist]. Rev Pneumol Clin. 2008;64(6):316–24. https://doi.org/10.1016/j.pneumo.2008.09.009
5. Galiè N, Kim NH. Pulmonary microvascular disease in chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc. 2006;3(7):571–6. https://doi.org/10.1513/pats.200605-113LR
6. Moser KM, Bloor CM. Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest. 1993;103(3):685–92. https://doi.org/10.1378/chest.103.3.685
7. Bonderman D, Turecek PL, Jakowitsch J, Weltermann A, Adlbrecht C, Schneider B, et al. High prevalence of elevated clotting factor VIII in chronic thromboembolic pulmonary hypertension. Thromb Haemost. 2003;90(3):372–6. https://doi.org/10.1160/TH03-02-0067
8. Wolf M, Boyer-Neumann C, Parent F, Eschwege V, Jaillet H, Meyer D, et al. Thrombotic risk factors in pulmonary hypertension. Eur Respir J. 2000;15(2):395–9. https://doi.org/10.1034/j.1399-3003.2000.15b28.x
9. Auger WR, Permpikul P, Moser KM. Lupus anticoagulant, heparin use, and thrombocytopenia in patients with chronic thromboembolic pulmonary hypertension: a preliminary report. Am J Med. 1995;99(4):392–6. https://doi.org/10.1016/S0002-9343(99)80187-9
10. Blauwet LA, Edwards WD, Tazelaar HD, McGregor CG. Surgical pathology of pulmonary thromboendarterectomy: a study of 54 cases from 1990 to 2001. Hum Pathol. 2003;34(12):1290–8. https://doi.org/10.1016/j.humpath.2003.07.003
11. Lang IM, Dorfmüller P, VonkNoordegraaf A. The pathobiology of chronic thromboembolic pulmonary hypertension. Ann Am Thorac Soc. 2016;13(3 Suppl 3):S215–21. https://doi.org/10.1513/AnnalsATS.201509-620AS
12. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med. 2004;350(22):2257–64. https://doi.org/10.1056/NEJMoa032274
13. Becattini C, Agnelli G, Pesavento R, Silingardi M, Poggio R, Taliani MR, et al. Incidence of chronic thromboembolic pulmonary hypertension after a first episode of pulmonary embolism. Chest. 2006;130(1):172–5. https://doi.org/10.1378/chest.130.1.172
14. Lang I, Kerr K. Risk factors for chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc. 2006;3(7):568–70. https://doi.org/10.1513/pats.200605-108LR
15. Dentali F, Donadini M, Gianni M, Bertolini A, Squizzato A, Venco A, et al. Incidence of chronic pulmonary hypertension in patients with previous pulmonary embolism. Thromb Res. 2009;124(3):256–8. https://doi.org/10.1016/j.thromres.2009.01.003
16. Jamieson SW, Kapelanski DP. Pulmonary endarterectomy. Curr Probl Surg. 2000;37(3):165–252. https://doi.org/10.1016/S0011-3840(00)80005-2
17. Daily PO, Auger WR. Historical perspective: surgery for chronic thromboembolic disease. Semin Thorac Cardiovasc Surg. 1999;11(2):143–51. https://doi.org/10.1016/S1043-0679(99)70007-9
18. Lewczuk J, Piszko P, Jagas J, Porada A, Wójciak S, Sobkowicz B, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest. 2001;119(3):818–23. https://doi.org/10.1378/chest.119.3.818
19. Riedel M, Stanek V, Widimsky J, Prerovsky I. Longterm follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. Chest. 1982;81(2):151–8. https://doi.org/10.1378/chest.81.2.151
20. Nishimura R, Tanabe N, Sugiura T, Shigeta A, Jujo T, Sekine A, et al. Improved survival in medically treated chronic thromboembolic pulmonary hypertension. Circ J. 2013;77(8):2110–7. https://doi.org/10.1253/circj.CJ-12-1391
21. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Med Res Methodol. 2006;6(12):31. https://doi.org/10.1186/1471-2288-6-31
22. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve.

Radiology. 1982;143(1):29–36. https://doi.org/10.1148/radiology.143.1.7063747
23. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al.; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529–36. https://doi.org/10.7326/0003-4819-155-8-201110180-00009
24. Dournes G, Verdier D, Montaudon M, Bullier E, Rivière A, Dromer C, et al. Dual-energy CT perfusion and angiography in chronic thromboembolic pulmonary hypertension: diagnostic accuracy and concordance with radionuclide scintigraphy. Eur Radiol. 2014;24(1):42–51. https://doi.org/10.1007/s00330-013-2975-y
25. Skarlovnik A, Hrastnik D, Fettich J, Grmek M. Lung scintigraphy in the diagnosis of pulmonary embolism: current methods and interpretation criteria in clinical practice. Radiol Oncol. 2014;48(2):113–9. https://doi.org/10.2478/raon-2013-0060
26. Bajc M, Miniati M, Jögi J, Stein PD. Perfusion SPECT in patients with suspected pulmonary embolism. Eur J Nucl Med Mol Imaging. 2013;40(9):1432–7. https://doi.org/10.1007/s00259-013-2425-8
27. Meng JJ, Zhang LJ, Wang Q, Fang W, Dai HJ, Yan J, et al. [A comparison of ventilation/perfusion single photon emission CT and CT pulmonary angiography for diagnosis of pulmonary embolism]. Zhonghua Jie He He Hu Xi Za Zhi. 2013;36(3):177–81.
28. Sugiura T, Tanabe N, Matsuura Y, Shigeta A, Kawata N, Jujo T, et al. Role of 320-slice CT imaging in the diagnostic workup of patients with chronic thromboembolic pulmonary hypertension. Chest. 2013;143(4):1070–7. https://doi.org/10.1378/chest.12-0407
29. He J, Fang W, Lv B, He JG, Xiong CM, Liu ZH, et al. Diagnosis of chronic thromboembolic pulmonary hypertension: comparison of ventilation/perfusion scanning and multidetector computed tomography pulmonary angiography with pulmonary angiography. Nucl Med Commun. 2012;33(5):459–63. https://doi.org/10.1097/MNM.0b013e32835085d9
30. He J, Wang F, Dai HJ, Li M, Wang Q, Yao Z, et al. Chinese multi-center study of lung scintigraphy and CT pulmonary angiography for the diagnosis of pulmonary embolism. Int J Cardiovasc Imaging. 2012;28(7):1799–805. https://doi.org/10.1007/s10554-012-0013-9
31. Le Duc-Pennec A, Le Roux PY, Cornily JC, Jaffrelot M, Delluc A, de Saint-Martin L, et al. Diagnostic accuracy of single-photon emission tomography ventilation/perfusion lung scan in the diagnosis of pulmonary embolism. Chest. 2012;141(2):381–7. https://doi.org/10.1378/chest.11-0090
32. Ley S, Ley-Zaporozhan J, Pitton MB, Schneider J, Wirth GM, Mayer E, et al. Diagnostic performance of state-of-the-art imaging techniques for morphological assessment of vascular abnormalities in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Eur Radiol. 2012;22(3):607–16. https://doi.org/10.1007/s00330-011-2290-4
33. Thieme SF, Graute V, Nikolaou K, Maxien D, Reiser MF, Hacker M, et al. Dual energy CT lung perfusion imaging-correlation with SPECT/CT. Eur J Radiol. 2012;81(2):360–5. https://doi.org/10.1016/j.ejrad.2010.11.037
34. Ling IT, Naqvi HA, Siew TK, Loh NK, Ryan GF. SPECT ventilation perfusion scanning with the addition of low-dose CT for the investigation of suspected pulmonary embolism. Intern Med J. 2012;42(11):1257–61. https://doi.org/10.1111/j.1445-5994.2012.02939.x
35. Gutte H, Mortensen J, Jensen CV, von der Recke P, Petersen CL, Kristoffersen US, et al. Comparison of V/Q SPECT and planar V/Q lung scintigraphy in diagnosing acute pulmonary embolism. Nucl Med Commun. 2010;31(1):82–6. https://doi.org/10.1097/MNM.0b013e3283336747
36. Miles S, Rogers KM, Thomas P, Soans B, Attia J, Abel C, et al. A comparison of single-photon emission CT lung scintigraphy and CT pulmonary angiography for the diagnosis of pulmonary embolism. Chest. 2009;136(6):1546–53. https://doi.org/10.1378/chest.09-0361
37. Reichelt A, Hoeper MM, Galanski M, Keberle M. Chronic thromboembolic pulmonary hypertension: evaluation with 64-detector row CT versus digital substraction angiography. Eur J Radiol. 2009;71(1):49–54. https://doi.org/10.1016/j.ejrad.2008.03.016
38. Wang F, Fang W, Lv B, Lu JG, Xiong CM, Ni XH, et al. Comparison of lung scintigraphy with multi-slice spiral computed tomography in the diagnosis of pulmonary embolism. Clin Nucl Med. 2009;34(7):424–7. https://doi.org/10.1097/RLU.0b013e3181a7cfea
39. Bajc M, Olsson B, Palmer J, Jonson B. Ventilation/Perfusion SPECT for diagnostics of pulmonary embolism in clinical practice. J Intern Med. 2008;264(4):379–87. https://doi.org/10.1111/j.1365-2796.2008.01980.x
40. Bartalena T, Oboldi D, Guidalotti PL, Rinaldi MF, Bertaccini P, Napoli G, et al. Lung perfusion in patients with pulmonary hypertension: comparison between MDCT pulmonary angiography with minIP reconstructions and 99mTc-MAA perfusion scan. Invest Radiol. 2008;43(6):368–73. https://doi.org/10.1097/RLI.0b013e31816901e2
41. Weinmann P, Moretti JL, Brauner MQ. Usefulness of tomographic versus planar lung scintigraphy in susoected pulmonary embolism in a daily practice. Open Med Imaging J. 2008;2(1):49–55. https://doi.org/10.2174/1874347100802010049
42. Tunariu N, Gibbs SJ, Win Z, Gin-Sing W, Graham A, Gishen P, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med. 2007;48(5):680–4. https://doi.org/10.2967/jnumed.106.039438
43. Katsouda E, Mystakidou K, Rapti A, Argentos S, Kelekis NL, Mastorakou R, et al. Evaluation of spiral computed tomography versus ventilation/perfusion scanning in patients clinically suspected of pulmonary embolism. In Vivo. 2005;19(5):873–8.
44. Macdonald WB, Patrikeos AP, Thompson RI, Adler BD, van der Schaaf AA. Diagnosis of pulmonary embolism: ventilation perfusion scintigraphy versus helical computed tomography pulmonary angiography. Australas Radiol. 2005;49(1):32–8. https://doi.org/10.1111/j.1440-1673.2005.01390.x
45. Reinartz P, Wildberger JE, Schaefer W, Nowak B, Mahnken AH, Buell U. Tomographic imaging in the diagnosis of pulmonary embolism: a comparison between V/Q lung scintigraphy in SPECT technique and multislice spiral CT. J Nucl Med. 2004;45(9):1501–8.
46. Stone E, Roach P, Bernard E, Briggs G, Havryk A, Faulder K, et al. Use of computed tomography pulmonary angiography in the diagnosis of pulmonary embolismin patients with an intermediate probability ventilation/perfusion scan. Intern Med J. 2003;33(3):74–8. https://doi.org/10.1046/j.1445-5994.2003.00345.x
47. Pitton MB, Kemmerich G, Herber S, Schweden F, Mayer E, Thelen M. [Chronic thromboembolic pulmonary hypertension: diagnostic impact of Multislice-CT and selective

Pulmonary-DSA]. Rofo. 2002;174(4):474–9. https://doi.org/10.1055/s-2002-25117
48. Lemb M, Pohlabeln H. Pulmonary thromboembolism: a retrospective study on the examination of 991 patients by ventilation/perfusion SPECT using Technegas. Nucl Med (Stuttg). 2001;40(6):179–86. https://doi.org/10.1055/s-0038-1625760
49. Worsley DF, Palevsky HI, Alavi A. Ventilation-perfusion lung scanning in the evaluation of pulmonary hypertension. J Nucl Med. 1994;35(5):793–6.
50. PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA. 1990;263(20):2753–9. https://doi.org/10.1001/jama.263.20.2753
51. Perrier A, Howarth N, Didier D, Loubeyre P, Unger PF, de Moerloose P, et al. Performance of helical computed tomography in unselected outpatients with suspected pulmonary embolism. Ann Intern Med. 2001;135(2):88–97. https://doi.org/10.7326/0003-4819-135-2-200107170-00008
52. Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, et al.; PIOPED II Investigators. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006;354(22):2317–27. https://doi.org/10.1056/NEJMoa052367
53. Onyedika C, Glaser JE, Freeman LM. Pulmonary embolism: role of ventilation-perfusion scintigraphy. Semin Nucl Med. 2013;43(2):82–7. https://doi.org/10.1053/j.semnuclmed.2012.11.002
54. Tanabe N, Sugiura T, Tatsumi K. Recent progress in the diagnosis and management of chronic thromboembolic pulmonary hypertension. Respir Investig. 2013;51(3):134–46. https://doi.org/10.1016/j.resinv.2013.02.005
55. Lang IM, Madani M. Update on chronic thromboembolic pulmonary hypertension. Circulation. 2014;130(6):508–18. https://doi.org/10.1161/CIRCULATIONAHA.114.009309
56. Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, et al. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation. 2014;129(1):57–65.
57. Chan K, Ioannidis S, Coghlan JG, Hall M, Schreiber BE. Pulmonary arterial hypertension with abnormal V/Q single-photon emission computed tomography. JACC Cardiovasc Imaging. 2018;11(10):1487–93. https://doi.org/10.1016/j.jcmg.2017.07.026
58. Bangdiwala SI, Bhargava A, O'Connor DP, Robinson TN, Michie S, Murray DM, et al. Statistical methodologies to pool across multiple intervention studies. Transl Behav Med. 2016;6(2):228–35. https://doi.org/10.1007/s13142-016-0386-8
59. Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. J Eval Clin Pract. 2008;14(5):951–7. https://doi.org/10.1111/j.1365-2753.2008.00986.x
60. van Beek EJ, Kuyer PM, Schenk BE, Brandjes DP, ten Cate JW, Büller HR. A normal perfusion lung scan in patients with clinically suspected pulmonary embolism. Frequency and clinical validity. Chest. 1995;108(1):170–3. https://doi.org/10.1378/chest.108.1.170