CANM ACMN
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CANM GUIDELINES FOR VENTILATION/PERFUSION (V/P SPECT) IN PULMONARY EMBOLISM

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CANM Guidelines for Ventilation/Perfusion (V/P SPECT) in Pulmonary Embolism
Executive Summary

1. Diagnostic approach for PE.

Generally, predictive models based on clinical data for PE are poor.

D-dimer has high NPV but low specificity for PE, and is not needed if the pretest probability for PE is other than low.

V/P SPECT has at least the same or better accuracy for PE as CTPA, but much lower radiation dose especially regarding breast exposure. Also, there have been little or no reported adverse reactions.

2. Methodology

V/P SPECT should be used instead of planar acquisition when available. Multidetector gamma-cameras with large FOV are preferred for V/P SPECT. A one-day ventilation and perfusion protocol where the ventilation precedes the perfusion is the norm.

For ventilation, ^{99m}Tc-Technegas is the best radio-aerosol, particularly in patients with COPD. Liquid aerosols produced in nebulizers such as ^{99m}Tc-DTPA are inferior for SPECT and should not be used unless Technegas is not available.

Lung perfusion is performed using ^{99m}Tc-macroaggregated albumin (MAA). Suggested administered doses and acquisition parameters are presented in **table 1** of attached document. Appropriate iterative reconstruction and display of transverse, sagittal and coronal projections are essential for interpretation.

3. Interpretation criteria and reporting

Interpretation in probabilistic terms is not appropriate and must be avoided. Accordingly, all exams should be interpreted as either "PE present" or "PE absent" or other similar clear affirmative terms. **Affirmative diagnosis of PE** requires the presence of vascular type mismatches. **PE is considered excluded** if perfusion is normal, if there are only matched defects, non-vascular type mismatches or reverse mismatches. See document for explanations.

Findings other than PE may be clinically pertinent, especially if symptoms include dyspnea or desaturation.

All PEs should have a final control 3 months after diagnosis to assess final reperfusion and to benefit from the availability of a baseline exam in case of recurrent symptoms.

4. Other considerations

In the **pediatric population and during pregnancy**, one should consider V/P SPECT as the first investigation for suspected PE due to better sensitivity, lower radiation, and no adverse reactions. As ventilation co-morbidities are unlikely, a perfusion-only study might suffice, with an optional ventilation study the next day if needed. However, V/P SPECT should be used in pregnant women with co-morbidities or a history of smoking.

Due to a higher sensitivity and no adverse reactions, V/P SPECT should be the first investigation for the assessment of **Chronic PE**.

Although we do not recommend performing **SPECT-CT** on a regular basis, it could be appropriate in more challenging and selected cases.

Recommandations de l'ACMN pour les études de ventilation et de perfusion (V/P SPECT) dans l'embolie pulmonaire
Résumé

1. Approche diagnostique

De façon générale, les modèles pour établir la probabilité clinique d'embolie pulmonaire (EP) sont médiocres.

Les D-dimères ont une valeur prédictive négative (VPN) élevée mais ne sont pas spécifiques d'EP et sont par ailleurs non-contributoires à moins d'une faible probabilité clinique pré-test.

La scintitomographie pulmonaire (V/P SPECT) a une exactitude diagnostique au moins égale ou supérieure à l'angio-tomodensitométrie (Angio-TDM) et offre un taux de radiation nettement plus bas, en particulier au niveau des seins, et ne cause virtuellement aucune réaction adverse.

2. Méthodologie

Lorsque disponible, l'acquisition en mode tomographique (SPECT) à l'aide d'une caméra scintigraphique multi-détecteurs à large champs devrait toujours être favorisée à la méthode planaire.

Le protocole standard consiste à réaliser une étude ventilatoire suivie d'une étude perfusionnelle pendant la même session.

Pour la ventilation, le meilleur agent est le ^{99m}Tc-Technegas, à plus forte raison chez les sujets atteints de maladie pulmonaire obstructive chronique (MPOC). Les radio-aérosols liquides administrés par nébulisateur tel le ^{99m}Tc-DTPA sont clairement inférieurs en mode SPECT et ne devraient être utilisés que si le Technegas n'est pas disponible. La perfusion est évaluée avec des macro-aggrégats d'albumine (^{99m}Tc-MAA). Les doses recommandées ainsi que les paramètres d'acquisition sont énumérés au Tableau 1 du document ci-joint. Une méthode de reconstruction itérative des données et un affichage des coupes transverses, coronales et sagittales sont nécessaires pour une bonne interprétation.

3. Critères d'interprétation et compte-rendu

Une interprétation en matière de probabilité d'EP est inadéquate et doit être évitée à tout prix. Conséquemment, tous les résultats d'examens doivent être rapportés en matière d'embolie pulmonaire "présente" ou "absente", ou autre terminologie équivalente. **Un diagnostic affirmatif d'EP** requiert la présence de déficits perfusionnels non-congruents (mismatches) de type vasculaire. **L'embolie pulmonaire est éliminée** lorsque la perfusion est normale, s'il n'y a que des déficits congruents ou non-congruents mais de type non-vasculaires ainsi qu'en présence de déficits ventilatoires non-congruents (reverse mismatches). Voir le document accompagnateur pour les détails.

Outre la présence d'embolies pulmonaires, d'autres trouvailles sont à l'occasion pertinentes en particulier si les signes et symptômes incluent désaturation ou dyspnée.

Un suivi scintigraphique (V/P SPECT) de contrôle devrait être obtenu 3 mois après un diagnostic initial d'EP, pour établir le degré final de reperfusion et à titre d'examen de référence en cas de suspicion d'une récidive.

4. Considérations additionnelles

Chez la population pédiatrique et pendant la grossesse, la scintitomographie pulmonaire devrait être utilisée comme examen de première ligne en raison d'une meilleure sensibilité, moins d'exposition à la radiation et absence de réactions adverses. Les co-morbidités étant peu fréquentes chez ces populations, l'investigation peut se limiter à une étude perfusionnelle, avec l'option de procéder à une étude ventilatoire le lendemain si nécessaire. Cependant, une évaluation complète (V/P SPECT) est requise chez les patientes enceintes avec co-morbidités ou histoire de tabagisme.

La scintitomographie pulmonaire est aussi l'examen de choix en première ligne dans l'embolie pulmonaire chronique, grâce à sa meilleure sensibilité et à l'absence de réactions adverses.

Bien qu'une évaluation hybride de type SPECT-CT ne soit pas recommandée de façon routinière, ceci peut être utile pour certains cas plus complexes ou face à un diagnostic difficile.

CANM Endorsement of the 2009 EANM Guidelines for Ventilation / Perfusion Scintigraphy

1) Diagnostic approach to pulmonary embolism (PE)

Key Points:

1. **Predictive models for PE are generally inaccurate**
2. **D-dimer has high sensitivity but low specificity for PE**
3. **Negative D-dimer has a high NPV**
4. **High quantitative value of D-Dimer increases likelihood for PE**
5. **D-dimer is not needed if pretest probability for PE other than low**
6. **V/P SPECT has at least the same or better accuracy for PE as MDCT**
7. **Availability is the main determinant of use for MDCT vs V/P SPECT**
8. **Fetal dose is roughly equivalent for both V/P SPECT and MD-CTPA**
9. **Breast dose is much higher with MD-CTPA as compared to V/P SPECT**
10. **V/P SPECT carries less risk of allergic reaction associated with contrast agent injection**
11. **99% of patients referred for V/P can undergo the exam.**

Referral criteria and assessment of clinical probability

For the diagnosis of PE the patient's clinical factors are non-specific. The clinical probability of PE can be accomplished empirically or by means of a prediction rule. Wells model is most frequently used. PISA model may be a more precise predictor of PE. Combining clinical probability with objective testing for PE can rule in or out PE. The measurement of D-dimer is widely used in the investigative work-up of patients with suspected venous thromboembolism. D-dimer features a low specificity (40%). Accordingly, a negative quantitative D-dimer test has a high negative predictive value for venous thromboembolism. High quantitative value of D-Dimer increases likelihood for PE

CANM endorses Fig. 1 and 2 - **Clinical algorithms for investigation of patients with suspected PE** as published in *Eur J Nucl Med Mol Imaging* (2009) 36:1528–1538.

Imaging studies in PE

The diagnosis of PE relies upon imaging tests, notably V/P scan and MDCT. In many clinical studies, including recent ones, comparisons between V/P scan and MDCT have been based upon obsolete scintigraphic techniques and interpretation criteria. The lack of a satisfactory gold standard for the diagnosis of PE poses difficulties for the assessment of sensitivity, specificity and accuracy of all diagnostic methods for PE. V/P SPECT has at least the same or equal accuracy for PE as MDCT. Additional diagnoses found on V/P SPECT include COPD, left heart failure and pneumonia. MDCT provides valuable information about diagnoses other than PE, such as aortic aneurysm, tumour, pleural effusion and pneumonia. A high number of patients are ineligible for MDCT due to kidney failure, allergy, ventilator support, recent MI and critical illness. 99% of patients referred for V/P can undergo the exam. CTPA is more readily available on a 24/7 basis and thus may be used more often.

Radiation Doses

The effective radiation dose from V/P SPECT is 1.2–2 mSv. The absorbed dose to the female breast is estimated as 0.8 mGy. During the first trimester, the estimated dose for perfusion study (50 MBq) gives a fetal absorbed dose of 0.1–0.2 mGy [47].

For MDCT during the first trimester the absorbed fetal dose was estimated as 0.24–0.66 mGy and significantly higher later during gestation. Recent studies have shown that MDCT is often technically suboptimal during pregnancy. The rate of nondiagnostic MDCT studies was 27.5% during pregnancy, versus 7.5% in nonpregnant women.

Based upon data from ICRP reports, the effective dose for V/P SPECT with the recommended protocol is about 35–40% of the dose from MDCT. The dose to the female breast for V/P SPECT is only 4% of the dose from MDCT. During the first trimester of pregnancy the fetal dose from MDCT is greater than or equivalent to that of V/P SCAN. The advantage of V/P SPECT increases after the first trimester.

Follow-up

V/P SPECT is ideally suited for use in the follow-up of PE because small and large emboli are recognized so that regression or progression of thrombotic disease can be studied in detail. Furthermore, the low radiation exposure allows repeated studies. It can be applied **in all patients.** Using the same method for diagnosis and for follow-up has great advantages. Perfusion-only scintigraphy may be chosen for control during the initial phase of treatment

CANM endorses Fig. 3 - **Algorithms for diagnostic imaging for acute PE suspected** as published in *Eur J Nucl Med Mol Imaging* (2009) 36:1528–1538.

2) Methodology

Introduction

Planar ventilation/perfusion technique with probabilistic interpretation suffered disrepute since the PIOPED I study showed that 65% of scans were nondiagnostic for PE. Consequently, it has become an inferior technique for most clinicians and should be replaced by more advanced nuclear medicine imaging using SPECT acquisition whenever available. The following recommendations regarding the choice of radiopharmaceuticals and imaging strategies for V/P studies are based on the 2009 EANM guidelines, updated with the more recent literature.

Radiopharmaceuticals

Ventilation

^{81m}Kr (krypton) is currently the only gas appropriate for V/P SPECT. However, because of high costs and limited distribution, it is not readily available in Canada. The best widely available agent for ventilation is ^{99m}Tc-Technegas, an aerosol of carbon nanoparticles (5-200 nm) generated in a high temperature furnace (Technegas Generator, Cyclomedica). Because of the very small particle size, this agent is distributed in the lungs almost like a gas and deposited in alveoli by diffusion, where they remain stable, thus providing the best possible images for ventilation SPECT. In practice, between 400-900 MBq (10-25 mCi) of $^{99m}TcO_4$ in 0.15ml NS is vaporized in a graphite crucible at 2750 °C in an argon atmosphere. The resulting ^{99m}Tc-Technegas is inhaled as soon as possible (<5 minutes) by the patient in a supine position, over the course of 2 to 5 inspirations. Activity over the lungs should be monitored, and administered activity should be around 30-50 MBq (0.8-1.4 mCi).

Liquid aerosols produced in nebulizers, such as ^{99m}Tc-DTPA, are inferior for SPECT, and should not be used unless technegas is not available. Overall, technegas remains the best radio-aerosol, particularly in patients with obstructive lung disease. Another advantage is that only a few breaths are sufficient to achieve an adequate amount of activity in the lungs, reducing time and personnel exposure to radiation.

Perfusion

Lung perfusion is performed using ^{99m}Tc-macroaggregated albumin (MAA). These albumin particles average 10–90 um in size, which allows them to lodge in the pulmonary capillaries and properly define lung perfusion. Normally, about 400,000 particles are injected, but a reduction to between 100,000 and 200,000 is recommended in patients with severe pulmonary hypertension or after a single lung transplantation. A minimum of 60,000 particles is needed to obtain a uniform distribution.

The suspension containing ^{99m}Tc-MAA should be gently shaken immediately before use and then administered by slow i.v. bolus injection over several respiratory cycles while the supine patient breathes at normal tidal volumes. Withdrawal of blood into the syringe must be avoided to prevent aggregation artefacts. The administered dose is typically between 120–240 MBq (3-6 mCi) but actually depends on the count rate of the ventilation agent. The activity ratio between perfusion and ventilation should be at least 4:1. The EANM guidelines recommend doses at the low end of the range to keep radiation exposure low (< 2.5 mSv).

Equipment and imaging protocols

A one-day ventilation and perfusion protocol where the ventilation precedes the perfusion is the norm. Ventilation is essential to maximize specificity and may help recognize alternate pathologies. A perfusion only protocol might be considered during pregnancy (with an optional day-after ventilation study if needed) or in the context of massive PE.

Planar acquisition should not be used anymore, unless SPECT is not feasible for some reason. In this case, six to eight projections are recommended for both ventilation and perfusion. The recommended matrix size is 256×256 in combination with a LEHR collimator, and acquisition time should be long enough to yield 500–1,000 kcounts per view.

Multidetector dual or triple head γ-cameras with large FOV are preferred for V/P SPECT. LEHR parallel collimators with 128 x 128 matrix size represents a good combination, but LEAP collimators with a 64 x 64 matrix are also adequate especially if one aims for lower doses and/or shorter acquisition times. It is important that the patient remains in the same supine position, carefully maintained between ventilation and perfusion acquisitions. A total acquisition time of 20–30 minutes (excluding dead time) is usually sufficient to complete both the ventilation and the perfusion SPECT scans. Ranges of acceptable doses and acquisition parameters are shown in Table 1 below. Ultimately the doses to be administered should be determined by each institution on the basis of the image quality obtained in a reasonable time, which is influenced by factors such as camera sensitivity, collimator choice, acquisition matrix size, processing parameters and local radiation protection guidelines. The added benefit of SPECT-CT is still debated, but the SPECT part acquisition parameters are similar, if there is a need to acquire CT data in selected cases.

Table 1: Suggested doses and acquisition parameters for V/P SPECT

Parameter	Value range
Administered dose Ventilation	30 - 50 MBq
Administered dose Perfusion	120 - 240 MBq
Collimator and Matrix size	LEHR (128 x 128), LEAP (64 x 64)
# steps / 360°	64 - 128 (32 - 64 / detector)
Step time for Ventilation	10 - 25 seconds
Step time for Perfusion	5 - 15 seconds
P/V activity (count rate) ratio	at least 4:1

Reconstruction and display

Transverse, sagittal and coronal projections are generated using an OSEM (ordered-subset expectation maximization) or equivalent iterative reconstruction algorithm. The number of iterations, subsets and other parameters may vary according to the manufacturer's software used to this end, but overly noisy images should be avoided as they do not promote reproducible interpretations. A 3D post reconstruction filter is usually applied, and the final images can be reviewed in each of the orthogonal planes, preferably on a workstation with dedicated software. Pseudo-planar images can be generated using an angular summing technique and other methods. More advanced data processing can also be performed. Defect contrast on perfusion SPECT can be further enhanced by subtracting the background activity remaining from the preceding ventilation scan. Further, by examining the pixel-based V/P ratio, quotient images can be generated from the SPECT data. These parametric images can facilitate reporting and improve the demonstration of defect location and extent.

3) Interpretation criteria and reporting

- **Basic criteria**
- **Affirmative or negative w/r to PE**
- **Other possible diagnoses**
- **Follow-up recommendations**

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Interpretation

Interpretation in probabilistic terms is not appropriate with VQ SPECT and should be abandoned. All images should be interpreted as either “PE present” or “PE absent” or other similar clear affirmative terms. A small number of “non-diagnostic or equivocal studies” is inevitable for various reasons but should not exceed 5% of the case load.

Affirmative diagnosis of PE requires the presence of vascular type mismatches. Vascular type perfusion defects have the following characteristics: moderate to severe defects, with clear borders, which are pleural based, wider at pleura than centrally, with an orientation compatible with pulmonary vascular anatomy. At the sub-segmental level, the shape is usually triangular.

PE present: PE is diagnosed if there is at least one lobar or segmental vascular type mismatched defect (perfusion defect with preserved ventilation), or two sub-segmental vascular mismatches, regardless of other findings.

PE absent: PE is considered excluded if perfusion is normal, if there are only matched defects (regardless of morphology), non-vascular type mismatches or reverse mismatches (perfusion preserved but ventilation absent).

A frequent cause of non-vascular mismatches is physiologically compressed lung. Typical locations are posterior para-mediastinal lung, costophrenic angles, the top of the great fissures and shallow posterior lung surfaces in cases of gravity dependant atelectasis. Other causes include penetration of ventilation agent in emphysema bullae or cystic space in severe fibrosis.

False positives interpretation may occur mainly in extrinsic vascular compression, pulmonary vein stenosis and rare cases of vasculitis.

The interpretation of an isolated vascular-type defect that is matched on ventilation and congruent with a radiographic opacity of similar size remains controversial because an isolated pulmonary infarct is a possibility (albeit not a frequent one). If symptoms are not acute (more than a few days), partial reperfusion of embolic disease can give atypical perfusion patterns. In difficult cases, consultation with the clinician is suggested.

Other diagnoses
Other findings than PE may be clinically pertinent, especially if symptoms include dyspnea or desaturation.

- Cardiac failure: redistribution of perfusion to superior and anterior portions of the lungs (inversion of the normal gradient) associated with preserved normal ventilation gradient is highly suggestive of early cardiac failure and can be observed earlier than on chest X-ray. This redistribution of perfusion is often lost with more advanced failure and typical X-ray change of edema.
- COPD: The magnitude of changes observed on VQ SPECT correlates with COPD severity, which can be underestimated clinically. Changes are typically more severe on ventilation, which include varying degrees of heterogeneity, ventilation defects and aerosol deposition at various bronchi levels indicating turbulence.
- Reverse mismatch: indicates failure of the physiological pulmonary vasoconstriction in the presence of a ventilation defect. May contribute to hypoxemia because of right-to-left shunt effect. Frequent association with pneumonia and may also be seen in atelectasis, mucous plug or other causes of bronchi obstruction.

Follow up
All PEs should have a final control 3 months after diagnosis to assess final reperfusion and benefit from the availability of a baseline exam in case of recurrent symptoms. Once a diagnosis of PE is made, a follow up exam is necessary to evaluate the degree of reperfusion. This has 2 purposes. First, incomplete reperfusion of a moderate to extensive PE is associated with the development of chronic pulmonary hypertension. Second, if there is a suspicion of new PE on follow up, it may be impossible to distinguish new PE from unresolved prior PE.
If PE is extensive, routine early control 7-10 days after diagnosis is advisable since a substantial part of reperfusion may occur in the first week. If there is early suspicion of new PE, this early control may be invaluable for correct diagnosis in this group.

Interpretation of new defects on control VQ SPECT has some known pitfalls. Sometimes, a partially occluding proximal defect may dissolve in several distal severe defects. Although those defects may seem impressive, they are not new. Also, clots located close to branching arteries may dissolve proximally and part of the clot may be drawn in the adjacent artery.

4) Additional considerations

CHART 1: ACUTE PE

	V/P SPECT	V/P SPECT/ low dose CT
SENS	93-97	93-97
SPEC	91-96	98
NPV	97-99	97-99
Inconclusive	1-3	~ 1
Nephrotoxicity	none	none
Mortality	none	none
Allergy	none	none

COMMENT: low dose non-contrast CT improves specificity and reduces inconclusive findings in selected patients. SPECT/CT is not recommended as a routine procedure in the diagnosis of PE.

CHART 2: RADIATION EXPOSURE

V/P SPECT	V/P SPECT/ low dose CT	CTPA (4 to 16 slice)	CTPA (64 slice)
~ 2.1 mSv	~ 3.1 mSv	~ 5.4 mSv	~ 20 mSv

COMMENT: exposure from CTPA is difficult to assess as many variables influence exposure: these include patient BMI, mAs, pitch, and radiation reduction protocols to name a few. As the number of slices increase with CTPA exposure does increase.

CHART 3: CHRONIC PE

	SENS	SPEC
CTPA	51	
V/P SPECT	93-97	90

CHART 4: PREGNANCY

	CTPA	V/P SPECT
Breast Exposure	10-70 mGy	less than 1.5 mGy
Fetal Exposure	less than 1.0 mGy	less than 1.0 mGy
Adverse reactions	Possible	None

Conclusions

In situations of Acute PE, Chronic PE, Pregnancy, Pediatrics, and the COPD population one can consider V/P SPECT, with or without low dose CT, as a first line investigation due to high sensitivity and specificity, low radiation, and no adverse reactions.

In situations of Pregnancy and Pediatrics due to the low likelihood of ventilation co-morbidities one could consider Perfusion only SPECT as a first line investigation. If co-morbidities exist then a full V/P SPECT should be performed. Also, V/P SPECT is not influenced by vascular volume changes during pregnancy as is CTPA.

In situations of COPD up to 31% of patients may have PE and up to 10% may die. Even those patients who have abnormal Chest X ray can still undergo V/P SPECT and in selected patients, V/P SPECT with low dose non-contrast CT could be considered. Technegas is considered the agent of choice in this population as there is less central airway deposition, better peripheral penetration, and it does not wash out as quickly as traditional aerosols.

List of Acronyms Used In The Present Document

COPD	Chronic Obstructive Pulmonary Disease
EANM	European Association of Nuclear Medicine
FOV	Field of View
ICRP	International Commission on Radiological Protection
LEAP	Low Energy All-Purpose
LEHR	Low Energy High Resolution
MDCT	Multi-Detector Computed Tomography
MD-CTPA	Multirow-Detector Computed Tomographic Pulmonary Angiography
OSEM	Ordered-Subset Expectation Maximization
PE	Pulmonary Embolism
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
SPECT	Single Photon Emission Computed Tomography
SPECT-CT	Single Photon Emission Computed Tomography--X-ray Computed Tomography
V/P SPECT	Ventilation/Perfusion Single Photon Emission Computed Tomography

REFERENCES:

1: Prospective evaluation of the negative predictive value of VQ SPECT using 99mTc-Technegas: Nucl Med Commun Aug:28(8):667-72

2: Ventilation/Perfusion SPECT for the diagnosis of pulmonary embolism in clinical practice; J Intern Med 2008 Oct:264(4)379-87

3: Radiation Dosimetry and Safety Issues in the investigation of Pulmonary Embolism: Seminars in Nuclear medicine: 40(6): November 2010:442-454

4: ventilation/Perfusion SPECT lung scintigraphy and computed tomography pulmonary angiography in patients with clinical suspicion of pulmonary embolism: Rev Esp Med Nucl Imagen Mol 2016 Jul-Aug; 35(4):215-20

5: Identifying the heterogeneity of COPD by V/P SPECT: a new tool for improving the diagnosis of parenchymal defect and grading the severity of small airways disease: DOVEPRESS 26 May 2017 Volume 2017:12 pages 1579-1587

6: Overview of the Novel and Improved Pulmonary Ventilation-Perfusion Imaging Applications in the Era of SPECT/CT: AJR December 2016; Volume 207 (6) 1307-1315

7: V/Q Scanning Using SPECT and SPECT/CT J Nucl Med September 1,2013 vol 54 no. 9 1588-1596

8: SPECT in Acute Pulmonary Embolism J Nucl Med December 2009 vol 50 no 12 1999-2007

LINKS TO EANM 2009 GUIDELINES FOR VENTILATION/PERFUSION SCINTIGRAPHY

https://eanm.org/publications/guidelines/gl_pulm_embolism_part1.pdf

https://eanm.org/publications/guidelines/gl_pulm_embolism_part2.pdf