Ventilation Scintigraphy With Radiolabeled Carbon Nanoparticulate Aerosol (Technegas)

State-of-the-Art Review and Diagnostic Applications to Pulmonary Embolism During COVID-19 Pandemic

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Abstract: Invented and first approved for clinical use in Australia 36 years ago, Technegas is the technology that enabled ventilation scintigraphy with 99mTc-labeled carbon nanoparticles (99mTc-CNP). The US Food and Drug Administration (FDA) has considered this technology for more than 30 years but only now is getting close to approving it. Meanwhile, more than 4.4 million patients benefited from this technology in 64 countries worldwide. The primary application of 99mTc-CNP ventilation imaging is the diagnostic evaluation for suspicion of pulmonary embolism using ventilation-perfusion quotient (V/Q) imaging. Because of 99mTc-CNP's long pulmonary residence, tomographic imaging emerged as the preferred V/Q methodology. The FDA-approved ventilation imaging agents are primarily suitable for planar imaging, which is less sensitive. After the FDA approval of Technegas, the US practice will likely shift to tomographic V/Q. The 99mTc-CNP use is of particular interest in the COVID-19 pandemic because it offers an option of a dry radioaerosol that takes approximately only 3 to 5 tidal breaths, allowing the shortest exposure to and contact with possibly infected patients.

Key Words: aerosols, computed tomography, lung diagnostic imaging, lung physiology, multimodal imaging, nuclear medicine, PET, pulmonary embolism, pulmonary ventilation, radionuclide imaging, SPECT, ventilation-perfusion scintigraphy, X-ray

The nuclear medicine techniques for interrogating airway functionality are fundamental to understanding pulmonary physiology and are integral to assessing various pulmonary diseases.1 One of the most optimal and increasingly popular diagnostic techniques uses 99mTc-labeled carbon nanoparticles (99mTc-CNP) produced and aerosolized using a Technegas generator (Cyclomedica Australia, Sydney, Australia). Such an aerosol is genetically called a “pseudogas,” which Burch et al defined as near-monodisperse submicronic particles that diffuse in a gas-like manner without aggregation. Dr Burch invented this technology while working in the Nuclear Medicine Department of the Royal Canberra Hospital as a physicist in the early 1980s and at the John Curtin School of Medical Research as a faculty at the Australian National University in Canberra, Australia. He later joined an Australian commercial medical devices developer, Mr Ian Tetley (the Chairman of Tetley Technologies), who managed the successful commercialization of the generator and its disposable patient administration kit, which was first approved under the brand name Technegas in 1986 for clinical use in Australia, then receiving authorization for marketing in the European Union in 1996, followed in 2003 by the marketing approval in Canada, and at this time the device was approved for clinical use in 64 countries around the globe.

The first attempt to introduce a commercial pseudogas generator in the United States was in the early 1990s. The generator was initially demonstrated at the US Food and Drug Administration (FDA) in 1992, designed to produce a pseudogas with particle sizes substantially smaller than generated by the original protocol used with the current Technegas generator, which had a much faster pulmonary clearance rate. This 99mTc-CNP aerosol variation was named “pertechnegas,” and it was produced using the identical Technegas generator, but the standard high-purity (>99.9%) argon was substituted with the mixture of 97% argon and 3% oxygen.2 The manufacturer selected pertechnegas because they believed that a radiopharmaceutical with rapid body clearance would be more likely to gain a speedy FDA approval. The US nuclear medicine physicians primarily used planar imaging and were already used to ventilation agents with rapid washout (noble gases and liquid aerosols). However, this attempt never progressed to the formal new drug application submission to the FDA predominantly because all supporting clinical data were available for Technegas but not for pertechnegas.

The second interaction with the FDA began in 2001, and it was about the Technegas generator using the standard aerosol production methodology. After more than 20 years of FDA scrutiny, Technegas remains not approved in the United States despite untainted experience in 64 countries worldwide (no attributable serious adverse events ever recorded). It took the FDA until 2004 to designate this technology a “combination product,” assigning the drug (ie, 99mTc-CNP) to the drug-focused FDA branch while the other components (the Patient Administration Kit and the Technegas Generator) to the device-focused branch. In consultation with the FDA, the manufacturer set up the first phase 3 trial that ultimately concluded in 2007. However, the manufacturer and the FDA could
not resolve their differences regarding the data adequacy to support the technology's effectiveness, leading eventually to the company's new drug application withdrawal in early 2009.

The third cycle of manufacturer-FDA interactions was initiated in the latter part of 2009. The new phase 3 trial was designed with guidance from the FDA. The design complexity explains the decade-long trial. On September 18, 2020, after the independent expert review panel unanimously voted to affirm that the study met its primary efficacy endpoint, the FDA deemed the trial completed (ie, successfully proving its objectives). US nuclear medicine professionals were flabbergasted to learn in June 2021 that despite the successful phase 3 trial and untainted clinical safety, the FDA issued a “Complete Response Letter” that conveyed nonapproval and further guidance. It is customary for the FDA and a company not to disclose specifics of what additional data are needed for approval. Regardless of what the FDA asked for, it is superfluous given the impecable experience of more than 4.4 million patients worldwide in 64 countries using it without significant adverse effects. For example, a recent review spanning 2007–2016 of the British Nuclear Medicine Society’s national database of Adverse Reactions (also known as Adverse Event in the US FDA parlance) amounted to a single patient who complained of “tingling” that was self-limiting and inconsequential.4 Rojas-Burke5 wrote with clairvoyance in the 1991 news article: “When, if ever, will the device that has won near-ubiquitous use in Australia gain approval for lung ventilation studies in the US?” More than 30 years later, the nuclear medicine community and the patients in the United States are still awaiting the FDA’s approval with bated breath.

Since the beginning of the COVID-19 global pandemic, many US nuclear medicine physicians and technologists have collectively written 4 petitions to the FDA, emphasizing the safety advantages of 99mTc-CNP during the pandemic times.6,7 Liquid aerosols were well known to facilitate the spread of the virus. Many health care institutions in the United States prohibited their use, including nuclear medicine ventilation scanning with nebulized radiopharmaceuticals. The only alternative for ventilation scanning, 133Xe, initially did not guarantee that delivery equipment was protected against viral contamination and potential for transmission. Later equipment modifications successfully mitigated this concern; however, 133Xe use requires a negative pressure room that is not readily available in facilities accustomed to radioaerosols. The vast majority of the US physicians were experiencing in interpreting ventilation-perfusion quotient (V/Q) scintigraphy and learned to rely on ventilation imaging for differential vascular causes for perfusion defects from others due to airway diseases. Nuclear medicine physicians and technologists concerned with possibly harmful consequences to patients from the inaccessibility of ventilation studies urged the FDA to promptly approve 99mTc-CNP, as a dry aerosol would not have a basis for the same concerns as the liquid aerosols. In many countries (including the authors’ institutions in France and Germany), 99mTc-CNP V/Q scan acquisition continued unabated throughout the pandemic because, in the best medical judgment of physicians, the risk of misdiagnosing pulmonary embolism (PE) without ventilation part of the scan is greater than the risk of COVID-19 transmission.7–10 This concern was recently substantiated by the retrospective study from France that showed the critical importance of ventilation imaging for the accurate interpretation of perfusion defects in patients with COVID-19.10 Paraphrasing the proverbial saying about Americans to the topic, US FDA will always do the right thing—after exhausting all the alternatives.11 The above narration supports the conclusion that all the alternatives will be soon exhausted in response to whatever FDA asks for in the nonapproval letter. It is opportune time for the following comprehensive and practical information on why and how best to incorporate 99mTc-CNP aerosol ventilation imaging into US nuclear medicine practices, especially during the COVID-19 pandemic.

STATE-OF-THE-ART

Ventilation Agents’ Essentials

Ventilation scintigraphy can be performed after inhaling radioactive isotopes in the form of either a noble gas or a radioaerosol.13 Xe is the only radioactive noble gas available in the United States. It is still commonly used in V/Q scanning, a close second to 99mTc-labeled aerosols (43% vs 57%, respectively).12 The long physical half-life (5.3 days) and low gamma photon energy are sub-optimal for gamma camera imaging. Limitations include poor image quality, and only 1 view of the lungs can usually be obtained on a single breath and equilibrium phases. However, additional obliques could be done during a more extended washout series. In contrast, 81mKr gas offers high-quality imaging and the option of performing simultaneous dual-isotope image acquisition of ventilation and perfusion.81mKr also has the advantage of low-radiation absorbed dose (especially important for children and pregnant women) because of its short physical half-life of 13 seconds. However, the critical limitations of 81mKr are its high cost and low availability of the 81Rb generator.13

Two types of radioaerosols are used in ventilation imaging—liquid and dry. A liquid variety is produced using a nebulizer, whereas a dry kind can be generated by vaporizing a carbon crucible at high temperatures. The size of the particles has a predominant influence on their aerodynamic properties that determine their distribution and deposition within airways and alveoli. The main mechanisms of particle deposition are inertial impaction, sedimentation, and diffusion.14 Inertial impaction occurs when particles are too large to keep their trajectory despite changes in the direction of the airflow and consequently collide with the walls of the respiratory tract, which contributes to the heterogeneous distribution and intense depositions of certain aerosols in central airways (also known as “hot spots” or “clumping”). This phenomenon worsens with the increasing size of particles and the airflow velocity in the respiratory tract. Hence, with their high airflow velocity, the proximal airways are the primary deposition site of larger particles, such as 99mTc-DTPA-diethylenetriamine pentaacetate (DTPA) in normal saline nebulized to form larger liquid droplets that range in size from 0.5 to 2 μm.15 On the contrary, 99mTc-CNP can be made much smaller, as detailed in the following section, allowing them to diffuse through the Brownian motion (ie, random molecular collisions) and deposit by sedimentation according to the forces of gravity in the most distal airways where the airflow velocity is the lowest.

99mTc-CNP Physical Properties

99mTc-CNP nanoparticles are hydrophobic primary hexagonally structured CNPs (Fig. 1A) whose size ranges from 5 to 60 nm.16,17 Primary nanoparticles are structured with graphite planes oriented parallel to the technetium surface to form nanoparticles with a thickness of 5 nm and a mean diameter of 20.9 ± 7.2 nm.18,19 Primary CNPs can agglomerate into larger secondary aggregates, whose size is approximately 100 to 200 nm.17–20 The primary 99mTc-CNP nanoparticles are as much as 100 times smaller, and their aggregates are 5 times smaller than 500- to 2000-nm 99mTc-DTPA aerosol droplets.21

Because of the nano size of its particles, 99mTc-CNP undergoes the Brownian diffusion comparable to that of gas molecules.22 This permits deep penetration of particles to the nonconducting (ie, terminal) airways. Ventilation studies with 99mTc-CNP and 81mKr have provided nearly identical information.23–25 A normal 99mTc-CNP planar lung ventilation scintigraphy is shown in Figure 1B. The very limited formation of larger particles offers the greatest advantage over 99mTc-DTPA droplets. There is also less impaction of particles in the airways, leading to lesser “hot spot” (also known as “clumping”) formation, especially in patients with obstructive airway diseases.26
**99mTc-CNP Aerosol Generation**

99mTc-CNP production is a straightforward process requiring the following components: 99mTc pertechnetate in saline, a Technegas generator, a graphite crucible, brass contacts inlaid with carbon to ensure good electrical conductivity, and a high-purity argon gas bottle. More detailed and illustrated descriptions of the components are available from either the manufacturer’s manual or the excellent recent review by Currie and Bailey.27 In a facility with an available 99Mo/99mTc generator, 99mTc pertechnetate is eluted with 5 mL of 0.9% NaCl, or it can be supplied from a central radiopharmacy. Using a syringe with a needle, up to 0.14 mL of 99mTc eluate (200–900 MBq) is introduced in a graphite crucible prehumidified with 99% ethanol and placed between the generator electrodes.28 The Technegas generator operation is standardized for all process parameters, including heating temperature and duration. After loading the crucible, there are 2 stages in the 99mTc-labeled CNP production, called “simmer” and “burn.”

**Simmer Stage**

The simmer stage reduces the 99mTc valency in the eluate from 99mTc7+ to the metallic form 99mTc. For this purpose, the graphite crucible is heated for 6 minutes at 70°C. The simmer stage can be performed immediately after loading the crucible. As the crucible volume is limited, several simmering sessions can be conducted to increase the aerosol activity if the radioactive concentration of the 99mTc eluate is low. In this case, the crucible can be reloaded from the third minute of the simmer stage. However, Lloyd et al20 have shown that increasing the number of simmers increases the median size of the 99mTc-labeled CNPs. The whole chamber is purged during this stage with pure argon, replacing the original room air.

**Burn Stage**

After the simmer cycle, the crucible is heated to 2750°C ± 100°C for 15 seconds in the high-purity argon atmosphere. The 99mTc and carbon vaporize and condense during this burn stage to form the aerosolized 99mTc-CNP.18 This pseudogas is captured in the 6-L chamber of the Technegas generator and ready for administration. 99mTc-CNP aerosol can be administered to a patient for up to 10 minutes after generation. But the longer the administration delay, the higher are the chances of compromising the image quality because of the particle size growth through coagulation (also known as agglomeration).20,28

**99mTc-CNP Administration**

During the COVID-19 pandemic, the administration rehearsal is essential for assessing patients’ compliance with various options before 99mTc-CNP administration to limit the potential risk of radioaerosol and viral contamination. A manual valve controls inhalation, and commercial PAL filters trap the exhaled radioactive particles during expiration. Patients with preexisting lung diseases (eg, asthma, emphysema, etc) should use their bronchodilators and other pulmonary medications to achieve optimal aerosol distribution. The ventilation procedure is best rehearsed immediately before the actual 99mTc-CNP administration. The rehearsal session is the time for selecting the optimal mouthpiece option or the mask and testing those selections for compliance.13 To allow a homogeneous diffusion of 99mTc-CNP aerosol to the alveoli, the patient would usually inhale slowly and hold their breath for 5 to 10 seconds at maximum inspiration. Generally, the flute or snorkel mouthpieces (Figs. 2A, B)

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**FIGURE 1.** A, Transmission electron microscopy (TEM) view of primary 99mTc-labeled CNPs. TEM shows primary hexagonal particles (red hexagon and red arrows) agglomerated in clusters. The blue circle indicates the layered structure of some of the primary particles. B, Lung ventilation planar scintigraphy after administration of 99mTc-Technegas. Images show the homogenous distribution of 99mTc-Technegas within the lungs.
tend to get better patient compliance than a mask (Fig. 2C). Using a nose clip with mouthpieces (Fig. 2D) is recommended for the best seal. Immediately after radioaerosol generation, the chamber contains no oxygen but only argon and $^{99m}$Tc-CNP. The patient may become uncomfortable after initial inhalations for a brief period and could rarely cough.

By loading the crucible with 250 to 700 MBq of $^{99m}$Tc pertechnetate eluate, 2 to 5 inhalation cycles are required to attain a count rate between 2000 and 5000 counts per second, which are equivalent to approximately 30 to 80 MBq (0.8–2 mCi) of a radioaerosol deposited within the lungs.\(^{29-32}\) It is crucial to stop radioaerosol delivery by turning it off when its activity approaches the higher end of the desired range, or the $^{99m}$Tc-labeled macroaggregated albumin ($^{99m}$Tc-MAA) maximum of 6 mCi will not be enough to override the ventilation activity immediately after. Hence, the deposited radioactivity is optimally monitored during the ventilation procedure. A gamma camera readily monitors the chest radioactivity when ventilation is performed on an imaging table with the detector positioned behind the patient. Those concerned with the possibility of contaminating the gamma camera detector in the prior method reported using a collimated Geiger-Müller monitor.\(^{26}\) The variation of the second approach is using a calibrated contamination monitor (Fig. 2D).

**Imaging Protocols**

The traditional sequence starts with a $^{99m}$Tc-CNP ventilation scan and is immediately followed by the $^{99m}$Tc-MAA perfusion scan. A patient is administered both radiopharmaceuticals in the same supine position. Some sites in Europe use a mobile negative pressure dome (eg, vent-medis Inc, Salzgitter, Germany) positioned directly above the patient during ventilation to capture leaked radioaerosol. Immediately after the ventilation imaging, the patient is intravenously administered 150 to 220 MBq (4–6 mCi) of $^{99m}$Tc-MAA. This administered activity is chosen to achieve a perfusion image count rate at least 3 to 4 times the ventilation image count rate, that is, the required minimum for background count rate override. The achieved count rates of ventilation and perfusion can be assessed on the camera monitor. This way, it can be checked directly in real time whether the minimum required activity ratio has been achieved. A German multicenter study showed that in routine V/Q SPECT practice with $^{99m}$Tc-CNP performed before the perfusion, approximately a quarter of examinations failed to meet the minimum required 3 times' count rate in the following perfusion imaging.\(^{33}\) This highlights the importance of routinely checking the quality of the whole V/Q or Q/V study in meeting this minimum count rate override requirement.

**Planar Imaging**

The images are acquired with a large field-of-view single or multiheaded gamma camera. The complete planar set of projections consists of 8 views, usually starting from the anterior and posterior projections on a dual-detector gamma camera and turning the detectors 45 degrees for 4 acquisitions. The recommendation is to obtain at least 6 views: the anterior, posterior, both posterior obliques, and either both laterals or both anterior obliques. The ventilation set of images is traditionally acquired first and followed immediately by perfusion imaging. Such a protocol allows straightforward quality control to ensure that the second set in a sequence fulfills the minimum count rate override of 3 times the first set. This can be accomplished by displaying counts per minute on the anterior and posterior projections for interpreters' visual inspection. A minimum of 20 kilocounts per ventilation view is recommended, typically taking approximately 1 minute per projection. It is customary to obtain ventilation and perfusion images in all projections for the same acquisition time. However, some choose to increase the acquisition time for the first set of images (ventilation in the above example) by a factor of 3 to equalize the image quality between the sets.
V/Q SPECT/CT

The use of $^{99m}$Tc-CNP facilitates the transition from planar to SPECT imaging. Protocols generally include the acquisition of projections at 120 to 128 angular positions over 360°. In one approach, each stop is acquired for 10 to 12 seconds for the ventilation and 4 to 5 seconds for the perfusion portions of the examination. Acquisition times should be selected to compensate for the perfusion and ventilation activity ratio substantially. Images should be acquired using a 128 × 128 matrix (pixel size, 4.8 mm) with a low-energy high-resolution collimator. Iterative reconstructions (OSEM, 4 iterations, 8 subsets) incorporating collimator response modeling and scatter compensation are recommended. SPECT acquisition can be combined with an unenhanced low-dose CT for attenuation correction and correlation of V/Q and CT findings. Attenuation correction is beneficial for quantification. Careful attention should be paid to the risk of misregistration between CT and SPECT images in the inferior areas of the lungs, which may cause overcorrection or undercorrection and could cause false-positive defects. To reduce SPECT and CT misregistration, shallow breathing or holding the breath at incomplete expiration or midinspiration during the CT acquisition is recommended.

A survey of practices in Australia, Canada, and France conducted in 2014 showed that tomographic techniques largely replaced planar V/Q imaging. Improved sensitivity of tomographic over planar V/Q imaging raised concern for PE overdiagnosis. The definition of PE overdiagnosis is a correct (true positive) diagnosis in an asymptomatic person that does not produce a net benefit (or results in net harm from complications of unnecessary treatment, ie, overtreatment) for that person. In the context of V/Q techniques, overdiagnosis means detection of a true-positive finding, typically of a subsegmental defect, on a tomographic technique that does not produce a net benefit or causes net harm from adverse effects of anti-coagulation (overtreatment) that would have passed undetected and untreated on the planar scan. This concern held back the transition from planar to tomographic V/Q imaging in the United States. However, a recent prospective study showed that withholding anti-coagulation from patients with even a single subsegmental defect increased the rate of subsequent PE. This argues in favor of converting to the more sensitive tomographic scintigraphy.

V/Q PET/CT With $^{68}$Ga-Labeled Radiopharmaceuticals

PET/CT is a superior technology to either SPECT/CT or planar image acquisition, offering higher sensitivity and resolution and better integration with respiratory gating technology. Therefore, it is an exciting opportunity to consider V/Q PET/CT. Lung ventilation imaging is obtained after inhaling $^{68}$Ga-labeled CNPs, termed “Galligas.” Galligas is prepared using the original Technegas generator and substituting $^{68}$Ga for $^{99m}$Tc in the carbon crucible of the synthesis unit. Blanc-Beguin et al demonstrated that the previously described methodology used in a routine clinical manner produces $^{99m}$Tc-labeled and $^{68}$Ga-labeled CNPs of similar shape and size. Perfusion imaging is then obtained after injection of $^{68}$Ga-MAA. The first pilot studies of the V/Q PET/CT for diagnosing PE were promising and warrant further investigations. Other emerging applications for V/Q PET/CT are lung cancer radiotherapy planning and preoperative regional lung function assessment.

Interpretation Criteria

The hallmark of PE on V/Q imaging is the mismatched perfusion defect, that is, an area with decreased to absent perfusion but preserved ventilation. Figure 3 shows an example of acute PE on V/Q SPECT/CT. Importantly, the interpretation criteria for planar versus SPECT or SPECT/CT V/Q approaches are significantly different. This review details the latter and defers a comprehensive discussion of planar V/Q criteria to a recent review by Metter et al.

In short, interpretational systems for planar V/Q imaging are either probabilistic or definitive. The PIOPED probabilistic criteria have the advantage of being validated in extensive multicenter studies. An interpreter discerns a probability of PE based on the observed patterns and associated radiographic characteristics, which is complex enough to cause high interobserver disagreement. Furthermore, probabilistic terminology to report the results is often confusing. It was demonstrated that the misunderstanding of probabilistic categories by the ordering physicians frequently leads to inappropriate management. On the other hand, the definitive approach, for example, the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED) system, is
considered the ventilation portion of the SPECT/CT methodology retrospectively compared it with the PISA-PED’s original criteria. Investigators adopted their criteria to the Q + CXR paradigm and found the Q + CXR PIOPED II modified approach superior to the original PIOPED II and avoid doing ventilation. But these results did not noticeably reduce the utilization of ventilation imaging in the United States. This suggests that diagnostic accuracy for the PE indication is not the only factor determining the ventilation scintigraphy’s continued usage, and interrogating patients’ ventilatory patterns is even a more compelling reason.

In addition, a later study using SPECT/CT technology and performed prospectively showed that omitting the ventilation component significantly reduced the specificity for PE. The authors considered the ventilation portion of the SPECT/CT methodology “mandatory” for evaluating PE to maintain high specificity. More recent studies confirmed that reliance on the low-dose CT and skipping the ventilation SPECT would significantly increase the rate of false-positive results. Whereas V/Q SPECT/CT has similar sensitivity to V/Q SPECT, the addition of CT often reveals the underlying nonvascular causes for the matched defects.

The advantages of tomographic V/Q imaging over planar are its ability to eliminate activities overlap, improve visualization of the medial-basal segment, and better characterize defects’ size, shape, and location. Expectedly, V/Q SPECT is more sensitive for identifying small, subtle, and deep perfusion defects than planar imaging. V/Q SPECT Q and V/Q improve lung scintigraphy’s diagnostic accuracy and significantly decrease the proportion of nondiagnostic (also known as indeterminate) studies to less than 5% of cases. Although prospective clinical outcome studies on tomographic V/Q imaging are still lacking, the technique has been widely implemented in the routine practice of countries where 99mTc-CNP is available. Interpretive positivity threshold of 1 segmental or 2 subsegmental mismatched defects (European Association of Nuclear Medicine criteria) is accepted worldwide. A defect is usually considered segmental if it involves greater than 75% of the size of the segment. However, the definitive criteria for “PE present” based on a single “segmental” defect are based on a defect that is greater than 50% of a corresponding anatomical segment’s size. However, ambiguity remains about the size of a small “subsegmental” defect that should not be considered in the diagnostic criteria for a positive examination. The V/Q SPECT threshold for a positive test (ie, 1 segment or 2 subsegments) is lower than the planar study (ie, 2 segments segmental equivalents). Accurately recognizing false-positive defects in V/Q SPECT is paramount. The addition of a low-dose CT improves the SPECT quality through attenuation correction. It reduces the probability of false-positive findings caused by readily identifiable on CT pleural effusions, emphysema, or pneumonia. The “fissure sign” is also better identified by correlating with CT.

The recommendations of North American nuclear medicine organizations cautioned about the risks of ventilation imaging with some variation. The American College of Nuclear Medicine guidance stated: “Avoid use of ventilation scintigraphy, especially based on aerosolized liquids, since they may hasten transmission of SARS-CoV-2.” Guidance of the Society of Nuclear Medicine and Molecular Imaging has evolved in response to the pandemic-related circumstantial changes. The first iteration recommended skipping ventilation altogether and performing the perfusion-only study. The second Society of Nuclear Medicine and Molecular Imaging iteration suggested a slight easing of the restrictive approach. The final recommendation was most liberal by stating that “ventilation scans can be increasingly incorporated as a routine part of the workup of suspected pulmonary embolism.”

The British Society of Nuclear Medicine offered a multifactorial algorithm that favored V/Q SPECT in most instances while limiting to perfusion-only scans or CT pulmonary angiography in COVID-19–positive patients. Still, some British Society of Nuclear Medicine members expressed strong opposition to ventilation scans in favor of Q SPECT/CT, which echoes the view of some American

![FIGURE 4](image_url). The “fissure sign” on a normal V/Q SPECT/CT study performed in the traditional sequence. The oblique fissure on the sagittal CT reconstruction is annotated with red arrows. The SPECT images show a corresponding decrease in activity that appears more conspicuous on perfusion than on ventilation images. The same finding displays a wedge-shaped appearance on the axial perfusion slice (red arrowheads) that could lead an unaware reader to a false-positive interpretation.
FIGURE 5. A, Example of a positive SPECT/CT scan for PE performed during the COVID-19 era using the reverse-order sequence (Q/V SPECT/CT). The perfusion SPECT/CT was obtained first and revealed a segmental defect in the right upper and middle lobes that had no correlating CT findings. The ventilation imaging was then obtained using higher-activity Technegas settings and administered under real-time monitoring to ensure more than 3:1 count rate override. A, Slice-by-slice comparison of ventilation and perfusion SPECT shows mismatched right upper and the middle lobe defects. Notice how the perfusion images are noisier than ventilation in this reverse-order imaging sequence because of the deposited activity differences. B, The same patient’s images are shown in traditional ventilation first and perfusion second sequence of representative SPECT and perfusion SPECT/CT fusion slices. The addition of CT provided better anatomical delineation and confirmed the diagnosis of PE by demonstrating the absence of underlying structural CT abnormalities. The MIPs of SPECT data in the right posterior oblique view show the void of perfusion in the region with normal ventilation. The bottom left perfusion MIP includes the outline of the ventilation MIP (the green dotted line).
The 99mTc-CNP is an excellent imaging option for assessing pulmonary airways and offers unique advantages during the COVID-19 pandemic. It also provides the flexibility of either the traditional sequence of V/Q imaging or the reverse sequence of Q/V imaging that can reduce the overall utilization of ventilation studies, hence lessening the staff exposure time and the risk of getting infected. The nuclear medicine community will continue with intense but exciting clinical research that should bring us closer to the best imaging protocol that should depend on individual patient circumstances, considering all of the options that include planar, SPECT, SPECT/CT, or the recently developed PET/CT imaging.

REFERENCES
1. Tulchinsky M, Fotos JS, Wechalekar K, et al. Applications of ventilation-perfusion scintigraphy in surgical management of chronic obstructive lung disease and cancer. Semin Nucl Med. 2017;47:671–679.
2. Burch WM, Tetley IJ, Gras JL. Technetium-99 m ‘pseudogas’ for diagnostic studies in the lung. Clin Phys Physiol Meas. 1984;5:79–85.
3. Isawa T, Teshima T, Anazawa Y, et al. Inhalation of pertechnegas: similar clearance from the lungs to that of inhaled pertechnetate aerosol. Nucl Med Commun. 1995;16:741–746.
4. Kennedy-Dixon TG, Gossell-Williams M, Cooper M, et al. Evaluation of radiopharmaceutical adverse reaction reports to the British Nuclear Medicine Society from 2007 to 2016. J Nucl Med. 2017;58:2010–2012.
5. Rojas-Burke J. High hopes for Technegas. J Nucl Med. 1991;32:24N–25N, 30N.
6. Tulchinsky M. The U.S. nuclear medicine physicians & technologists are petitionioning the FDA: “approve Technegas® now!”. Available at: https://www.linkedin.com/pulse/us-nuclear-medicine-physicians-technologists-fda-now-mark-tulchinsky/. Accessed May 25, 2022.
7. Gross LJ, Tulchinsky M. Petition to the FDA for the expedient approval for Technegas®. 2020. Available at: https://www.linkedin.com/pulse/petition-fda-expedient-approval-technegas-lucasm-gross/?trackingId=bgX5IagqTq6ZUvVxCrKmgg%3D%3D. Accessed May 25, 2022.
8. Le Roux PY, Le Gal G, Salaun PY. Lung scintigraphy for pulmonary embolism diagnosis during the COVID-19 pandemic: does the benefit-risk ratio really justify omitting the ventilation study? Eur J Nucl Mol Med Imaging. 2020;47:2498–2501.
9. Krause BJ, Bartenstein P, Freudenberg LS, et al. Coronavirus SARS-CoV-2: Empfehlungen für die nuklearmedizinische Versorgung in nuklearmedizinischen Kliniken/Abteilungen mit Therapiestation und Praxen, Instituten sowie Ordinationen. Nuklearmedizin. 2020;59:e1–e4.
10. Le Roux PY, Bonnefoy PB, Bhaloua A, et al. Lung scintigraphy for pulmonary embolism diagnosis in COVID-19 patients: a multicenter study. J Nucl Med. 2022;63:1070–1074.
11. Americans will always do the right thing—after exhausting all the alternatives. Quote Investigator. 2012. Available at: https://quoteinvestigator.com/2012/11/11/exhaust-alternatives/. Accessed May 31, 2022.
12. Opanowski A, Gross LJ, Tulchinsky M. Radiopharmaceutical options for the ventilation part of ventilation-perfusion scintigraphy performed for the indication of pulmonary embolism: US practice survey. Clin Nucl Med. 2015;40:553–558.

13. Bajc M, Schumichen C, Gruning T, et al. EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond. Eur J Nucl Med Mol Imaging. 2017;44:2429–2451.

14. Carvalho TC, Peters JI, Williams RO 3rd. Influence of particle size on regional lung deposition—what evidence is there? Int J Pharm. 2011;406:1–10.

15. Sanchez-Crespo A. Lung scintigraphy in the assessment of aerosol deposition and clearance. Semin Nucl Med. 2019;49:47–57.

16. Burch WM. Evidence for the long-term biological distribution of Technegas particles. Nucl Med Commun. 1993;14:559–561.

17. Lamb M, Oei TH, Eifert H, et al. Technegas: a study of particle structure, size and distribution. Eur J Nucl Med. 1993;20:576–579.

18. Senden TJ, Moock KH, Gerald JF, et al. The physical and chemical nature of Technegas(R). Mol Imaging Biol. 2021;23:62–69.

19. Carvalho TC, Peters JI, Williams RO 3rd. Influence of particle size on regional lung function: generation of normal mean and standard deviation 3-D maps. Front Med (Lausanne). 2020;7:143.

20. Le Roux PY, Hicks RJ, Siva S, et al. PET/CT lung ventilation and perfusion scanning using Galligas and gallium-68-MAA. Semin Nucl Med. 2019;49:71–81.

21. Moller H, Felten K, Seitz J, et al. A generator for the production of radiolabelled ultrafine carbonaceous particles for deposition and clearance studies in the respiratory tract. Aerosol Sci. 2006;37:631–644.

22. Cook G, Clarke SE. An evaluation of Technegas as a ventilation agent compared with krypton-81 m in the scintigraphic diagnosis of pulmonary embolism. J Nucl Med. 1992;33:770–774.

23. Peltier P, de Faucom P, Chetanneau A, et al. Comparison of technetium-99 m aerosol and krypton-81 m in ventilation studies for the diagnosis of pulmonary embolism. Nucl Med Commun. 1990;11:631–638.

24. James JM, Lloyd JJ, Leahy BC, et al. 99mTc-technegas and krypton-81 m ventilation scintigraphy: a comparison in known respiratory disease. Br J Radiol. 1992;65:1075–1082.

25. Hartmann U, Hagen PJ, Stokkel MP, et al. Technegas versus (81m)Kr for ventilation part of ventilation/perfusion scintigraphy performed for the indication of pulmonary embolism. Eur J Nucl Med. 1997;38:1327–1333.

26. Jogi J, Jonson B, Ekberg M, et al. Ventilation-perfusion SPECT with 99mTc-Galligas and (81m)Kr: a study of krypton-81 m in ventilation studies for the diagnosis of pulmonary embolism. Nucl Med Commun. 1995;16:476–480.

27. Gray HW, McKillop JH, Bessert RG. Lung scan reports: interpretation by clinicians. Nucl Med Commun. 1993;14:989–994.

28. Bulteau D, Tulchinsky M, Freeman LM. Current status of ventilation-perfusion scintigraphy for suspected pulmonary embolism. J Am J Roentgenol. 2017;208:489–494.

29. Perrier A, Desmarais S, Miron MJ, et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet. 1999;353:190–195.

30. Anderson DR, Kahn SR, Rodger MA, et al. Computed tomographic pulmonary angiography vs ventilation/perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA. 2007;298:2747–2753.

31. Wells PS, Ginsberg JS, Anderson DR, et al. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med. 1998;129:997–1005.

32. Opanowski A, Gross LJ, Tulchinsky M. Radiopharmaceutical options for the ventilation part of ventilation-perfusion scintigraphy performed for the indication of pulmonary embolism: US practice survey. Clin Nucl Med. 2015;40:553–558.

33. Freiman LM, Glaser JE, Haramati LB, et al. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). J Nucl Med. 2008;49:1741–1748.

34. Glaser JE, Chamarthy M, Haramati LB, et al. Successful and safe implementation of a trinary interpretation and reporting strategy for V/Q lung scintigraphy. J Nucl Med. 2011;52:1508–1512.

35. Sostman HD, Miniati M, Gottschalk A, et al. Sensitivity and specificity of perfusion scintigraphy combined with chest radiography for acute pulmonary embolism in PIOPED II. J Nucl Med. 1998;39:1082–1091.

36. Gutte H, Mortensen J, Jensen CV, et al. Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-dose CT: head-to-head comparison with multidetector CT angiography. J Nucl Med. 2009;50:1987–1992.

37. Gutte H, Mortensen J, Kjaer A. Detection of pulmonary embolism: comparison of methods. J Nucl Med. 2010;51:824–8224.

38. Le Roux PY, Robin P, Dellac A, et al. Additional value of combining low-dose computed tomography to V/Q SPECT on a hybrid SPECT-CT camera for pulmonary embolism diagnosis. Nucl Med Commun. 2015;36:922–930.

39. Palmowski K, Oltmanns U, Kreuter M, et al. Diagnosis of pulmonary embolism: conventional ventilation/perfusion SPECT is superior to the combination of perfusion SPECT and nonenhanced CT. Respir Med. 2014;88:291–297.

40. Tanuja M, Maimanah M, Sara U. Diagnosis of pulmonary embolism: a comparison between ventilation/perfusion CT and perfusion-only SPECT/CT. Med J Malaysia. 2020;75:490–493.

41. Le Roux PY, Robin P, Salaun PY. New developments and future challenges of nuclear medicine and molecular imaging for pulmonary embolism. Thromb Res. 2018;163:236–241.

42. Mazurek A, Dziuk M, Witkowska-Patena E, et al. The utility of hybrid SPECT/CT lung perfusion scintigraphy in pulmonary embolism diagnosis. Respiration. 2015;90:393–401.

43. Miles S, Rogers KM, Thomas P, et al. A comparison of single-photon emission CT lung scintigraphy and CT pulmonary angiography for the diagnosis of pulmonary embolism. Chest. 2009;136:1546–1553.

44. Le Duc-Pennecc A, Le Roux PY, Comly JC, et al. Diagnostic accuracy of single-photon emission tomography ventilation/perfusion lung scan in the diagnosis of pulmonary embolism. Chest. 2012;141:381–387.
62. Le Roux PY, Robin P, Tromeur C, et al. Ventilation/perfusion SPECT for the diagnosis of pulmonary embolism: a systematic review. *J Thromb Haemost*. 2020;18:2910–2920.

63. Bajc M, Neilly JB, Miniati M, et al. EANM guidelines for ventilation/perfusion scintigraphy: part 2. Algorithms and clinical considerations for diagnosis of pulmonary emboli with V/P(SPECT) and MDCT. *Eur J Nucl Med Mol Imaging*. 2009;36:1528–1538.

64. Le Roux PY, Robin P, Delluc A, et al. V/Q SPECT interpretation for pulmonary embolism diagnosis: which criteria to use? *J Nucl Med*. 2013;54:1077–1081.

65. Howarth DM, Booker JA, Voutnis DD. Diagnosis of pulmonary embolus using ventilation/perfusion lung scintigraphy: more than 0.5 segment of ventilation/perfusion mismatch is sufficient. *Intern Med J*. 2006;36:281–288.

66. Schembri GP, Roach PJ, Bailey DL, et al. Artifacts and anatomical variants affecting ventilation and perfusion lung imaging. *Semin Nucl Med*. 2015;45:373–391.

67. Tulchinsky M, Osmany S. The American College of Nuclear Medicine guidance on operating procedures for a nuclear medicine facility during COVID-19 pandemic. *Clin Nucl Med*. 2021;46:571–574.

68. Society of Nuclear Medicine and Molecular Imaging. SNMMI statement: COVID-19 and ventilation/perfusion (V/Q) lung studies. Available at: https://www.snmmi.org/NewsPublications/NewsDetail.aspx?ItemNumber=36714. Accessed May 25, 2022.

69. SNMMI statement: COVID-19 and ventilation/perfusion (V/Q) lung studies. *J Nucl Med Technol*. 2021;49:12A.

70. Buscombe JR, Notghi A, Crosdale J, et al. COVID-19: guidance for infection prevention and control in nuclear medicine. *Nucl Med Commun*. 2020;41:499–504.

71. Voo S, Dizdarevic S. Single photon emission computed tomography lung perfusion imaging during the COVID-19 pandemic: does nuclear medicine need to reconsider its guidelines? *Nucl Med Commun*. 2020;41:991–993.

72. Lu Y, Macapinlac HA. Perfusion SPECT/CT to diagnose pulmonary embolism during COVID-19 pandemic. *Eur J Nucl Med Mol Imaging*. 2020;47:2064–2065.

73. Zuckier LS, Moadel RM, Haramati LB, et al. Diagnostic evaluation of pulmonary embolism during the COVID-19 pandemic. *J Nucl Med*. 2020;61:630–631.

74. Boone SL, Zuckier LS. Ventilation-perfusion scans after the COVID-19 pandemic: point-ventilation studies are dispensable. *AJR Am J Roentgenol*. 2022;218:29–30.

75. Zuckier LS. To everything there is a season: taxonomy of approaches to the performance of lung scintigraphy in the era of COVID-19. *Eur J Nucl Med Mol Imaging*. 2021;48:666–669.

76. Konstantinides SV, Meyer G, Becattini C, et al. ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Respir J*. 2019;54:1901647.

77. Palmar JC, Barnett CA, Reich SB, et al. Reverse ventilation-perfusion mismatch. *Clin Nucl Med*. 1984;9:6–9.

78. Zuckier I, Heyman S, Ozdemir S. Reversed ventilation-perfusion mismatch involving a pediatric patient in congestive heart failure. *J Nucl Med*. 1997;38:1681–1683.

79. Wartski M, Zerbib E, Regnard JF, et al. Reverse ventilation-perfusion mismatch in lung cancer suggests intrapulmonary functional shunting. *J Nucl Med*. 1998;39:1986–1989.

80. Carvalho P, Lavender JP. The incidence and etiology of the ventilation/perfusion reverse mismatch defect. *Clin Nucl Med*. 1989;14:571–576.

81. Shih WJ, Bognar B. Reverse mismatched ventilation-perfusion pulmonary imaging with accumulation of technetium-99m-DTPA in a mucous plug in a main bronchus: a case report. *J Nucl Med Technol*. 1999;27:303–305.

82. Lavelle WC, Patel VK. Ventilation-perfusion scans after the COVID-19 pandemic: counterpoint-ventilation studies are here to stay. *AJR Am J Roentgenol*. 2021;218:31–32.

83. Suh M. In the COVID-19 era, is it OK to perform a perfusion-only SPECT/CT for the diagnosis of pulmonary embolism? *Nucl Med Mol Imaging*. 2022;56:67–70.