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Safe Pulmonary Scintigraphy in the Era of COVID-19

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One of the major effects of the COVID-19 pandemic within nuclear medicine was to halt performance of lung ventilation studies, due to concern regarding spread of contaminated secretions into the ambient air. A number of variant protocols for performing lung scintigraphy emerged in the medical literature which minimized or eliminated the ventilation component, due to the persistent need to provide this critical diagnostic service without compromising the safety of staff and patients. We have summarized and reviewed these protocols, many of which are based on concepts developed earlier in the history of lung scintigraphy. It is possible that some of these interim remedies may gain traction and earn a more permanent place in the ongoing practice of nuclear medicine.
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Introduction

As the COVID-19 pandemic evolved, and populations across the world were successively overrun by the virus, practitioners struggled to maintain healthcare in a manner safe for patients and medical workers alike.[1-3] In the realm of nuclear medicine, one area that raised concern was performance of ventilation scintigraphy, an integral component of standard nuclear medicine protocols for the determination of pulmonary embolism, due to apprehension regarding spread of contaminated secretions into the ambient air.[4,5] Nonetheless, the need for a diagnostic test to exclude pulmonary embolism (PE) remained acute both because symptoms of PE and COVID-19 pneumonia overlap,[6-8] and because of an association between COVID-19 infection and thromboembolic disease.[9-11] Widespread relinquishing of scintigraphy in favor of Computed Tomographic Pulmonary Angiography (CTPA) or other radiographic techniques was constrained, at least in part, by variably increased demand on the computed tomography (CT) scanner, heightened decontamination protocols,[12] and inability to use intravenous contrast in some COVID-19 patients.[13,14]

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The purpose of this article is to survey the origin and implementation of several archetypal approaches to performance of lung scintigraphy during the COVID-19 pandemic, and to consider their potential impact on the future practice of lung scintigraphy.

Conceptual Basis of Lung Scintigraphy

In the development of nuclear medicine techniques for the evaluation of PE, perfusion scintigraphy was introduced as the initial method of assessing embolism in 1964;[15] while sensitive, it was noted to be of low specificity.[16] Presence of perfusion defects was insufficient to establish PE because they may be secondary, due to reflex vasoconstriction and provoked by regional hypoxia, rather than primary, as in the case of vascular embolism. This reflex is beneficial in that it prevents shunting blood through poorly oxygenated regions of lung thereby maintaining adequate oxygen concentration in pulmonary veins and the systemic arterial circulation.

The current method of lung scintigraphy for the diagnosis of PE therefore developed into an unusual examination that requires documentation of 2 disparate physiologic processes, pulmonary perfusion and ventilation, which are then contrasted to arrive at a final diagnosis.[17-19] Perfusion scintigraphy, absent ventilation, can never achieve high specificity for PE. Although other schemata have been proposed, standard protocols for interpretation of lung scintigraphy promulgated

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Table 1 Criteria of Lung Scan Interpretation According to SNMMI/Modified PIOPED II Criteria[20]

High LR	≥ 2 Large Mismatched (V/Q) Segmental Defects
Normal	No perfusion defects
Very low LR	Nonsegmental Q defect < CXR lesion 1-3 small segmental defects Solitary matched defect in mid or upper lung Stripe sign Solitary large pleural effusion ≥ 2 matched V/Q defects with regionally normal CXR
Nondiagnostic (intermediate)	All other findings

Legend: LR – likelihood ratio; Q – perfusion; V – ventilation; CXR – chest radiograph.

Table 2 Criteria of Lung Scan Interpretation Modified From EANM*,[21]

PE	V/Q mismatch of at least one segment or two subsegments that conforms to the pulmonary vascular anatomy (wedge-shaped defects with the base projecting to the lung periphery).
No PE	Normal perfusion pattern in keeping with the anatomic boundaries of the lungs. Matched or reversed-mismatched V/Q defects of any size, shape or number in the absence of mismatch. Mismatch that does not have a lobar, segmental or subsegmental pattern
Nondiagnostic for PE	Multiple V/Q abnormalities not typical of specific diseases.

Legend: PE – pulmonary embolism; Q – perfusion; V – ventilation.
*SPECT imaging preferred to planar scintigraphy. "Tomographic imaging has higher sensitivity and specificity for PE compared with planar imaging."

by the Society of Nuclear Medicine and Molecular Imaging[20] and the European Association of Nuclear Medicine[21] both rely on a combination of perfusion and ventilation scintigraphy as critical components of the diagnostic process (Tables 1 and 2).

Challenge to Performing Ventilation During Covid-19 Pandemic

As a general rule, studies that cause aerosol or droplet formation were deferred during the COVID-19 pandemic, in order to not disperse potentially infectious patient secretions into the environment.[22] These concerns were often magnified due to concurrent issues such as insufficient capacity to test for infection,[23] uncertain understanding of how the disease was spread,[24] and basic lack of personal protective supplies such as masks and gloves.[25]

Indeed, escape of radiopharmaceutical from ventilation scintigraphy delivery systems has been frequently investigated over 3 decades, demonstrating presence of a variable degree of leakage from the aerosol device or patient airways into the examination room.[26-30] A similar phenomenon has also been noted with the newest ventilation radiopharmaceutical, ^{99m}Tc-labeled carbon particles (Technegas), where activity was noted to persist in the imaging room air for over one hour following administration.[31,32] Patient coughing,[5] poor mouth seal,[32] and incomplete nose closure[32,33] have all been considered possible avenues of dispersal of patient secretions into the air.

A Plethora of Postpandemic Proposals

The potential spread of droplets or aerosolized secretions from the patient's airways into the environment challenged nuclear medicine practitioners to expeditiously develop protocols for evaluating presence of PE while mitigating risk associated with ventilation scintigraphy. A number of suggestions regarding how to proceed with lung scintigraphy during the COVID-19 era were therefore presented in the nuclear medicine literature, which attempt to address the tension between potential spread of infection when ventilation scintigraphy is performed and the sub-optimal specificity of scintigraphy for detecting PE when ventilation is omitted.[34] These reveal the determination on the part of nuclear medicine physicians to remain clinically relevant without compromising the safety of staff and patients. Interestingly, solutions to this novel problem often leverage concepts and techniques developed earlier in the history of nuclear medicine (Table 3) which will be referenced in the sections below.

Strategy A. Scintigraphy Should Not be Performed; Patients Should be Referred Outside of Nuclear Medicine

Advocates of this position hold the core belief that there is no value to perfusion scintigraphy alone, due to the low predictive value of a positive test, and they also believe that performance of ventilation scintigraphy during the COVID-19 pandemic entails unjustifiable risk to staff and other patients. This opinion was enunciated during the first pandemic wave in early 2020[35-37] and is certainly defensible in a situation of high prevalence of infection, unscreened patients, difficulty in procuring personal protective equipment (PPE), and absent caregiver immunity. In their view, any diagnostic information or other advantage derived from ventilation

Table 3 Prior (Pre-COVID) Models of Scintigraphy for the Diagnosis of Thromboembolic Disease That Do Not Utilize Ventilation Scintigraphy and Their Application in the COVID-19 Era. After Zuckier[34]

Authors	Year	Population	Modality	Concept	COVID-19 Application
Miniati et al[56] Bajc et al[58]	1996 2013	General General	Perfusion Planar Perfusion SPECT	Perfusion scintigraphy combined with pretest clinical probability	Das et al,[49] Lu et al[50]
Sostman et al[43] Lu et al[44] Mazurek et al[45]	2008 2014 2015	General Oncology* Elderly#	Perfusion Planar+CXR Perfusion SPECT-CT Perfusion SPECT-CT	Radiographic information used to evaluate airspace disease	Burger et al,[47] Das et al,[49] Voo et al,[48] Lu et al[50]
Sheen et al[60]	2018	Pregnancy∼	Perfusion Planar	Perfusion scintigraphy used as an initial screening test	Zuckier et al,[62] Lu et al,[50] D.G.N. / B.D.N.[65]

*Population with high pretest probability of PE.
#Moderate pretest probability of PE.
∼Low pretest probability of PE.

scintigraphy that could not be obtained from complimentary examinations does not outweigh excess risk to healthcare workers and other patients in performing the study.

Patients who would otherwise be evaluated by ventilation and perfusion (V/Q) scintigraphy would instead be referred for non-nuclear medicine examinations such as CTPA or Doppler ultrasonography of the lower extremities which do not generate aerosol or droplets. These alternatives may not be optimal, or even feasible. Doppler ultrasonography for the detection of deep vein thrombosis has a low sensitivity for the diagnosis of PE.[38] Many patients referred to nuclear medicine are precluded from receiving intravenous contrast due to allergy or renal dysfunction; one of the manifestations of COVID-19 infection is azotemia.[13,14] Finally, the long-term effect of “closing shop” on subsequent resumption of normal operations remains unknown.[34]

Strategy B. Scintigraphy With Ventilation Should be Performed on All Patients

Several groups strongly endorsed performing full ventilation-perfusion studies with use of appropriate PPE during the period of the COVID-19 pandemic, an especially cogent approach in areas of low disease prevalence.[39-41] While appearing diametrically opposed to the prior position that ventilation scintigraphy should not be performed, in actuality the two opinions closely align with respect to the inadequacy of performing perfusion scintigraphy without ventilation. They differ in whether safe ventilation scintigraphy can be achieved. As more has been learned about the infectivity of COVID-19, availability of polymerase chain reaction (PCR) tests to detect COVD-19 has increased, PPE has become more available, and the medical staff have been vaccinated, consensus has now cautiously moved towards performing full V/Q examinations in many situations,[42] such as in patients with negative PCR tests or those with recent evidence of immunity. Differences in circumstances, and in the local tolerance for risk, will affect a physician’s willingness to proceed with ventilation at any given juncture.

Strategy C. Improve Specificity of Perfusion Scintigraphy by Performing Radiographic Imaging

In the past, several groups have used radiographic information as a replacement or surrogate for ventilation. Sostman evaluated a combination of perfusion scintigraphy and chest radiography, employing modified PIOPED II criteria. Sensitivity and specificity were 85% and 93%, respectively, though 21% of the studies were nondiagnostic.[43] Using hybrid imaging, several groups have exploited the CT component of SPECT-CT, mining the radiographic information present to identify regions of lung that are hypoventilated, thereby serving much in the same, though less effective, manner as ventilation scintigraphy.[44-46] CT is less comprehensive than ventilation scintigraphy in identifying some nonembolic causes of decreased ventilation such as bronchospasm. Prior to COVID-19, Lu et al.[44] performed perfusion SPECT-CT in a cohort of 106 oncology patients, using the CT findings to identify areas of abnormal lung ventilation such as pneumonia, emphysema, and COPD. For the diagnosis of PE, sensitivity of 91% and specificity of 94% were achieved against a composite gold standard including CTPA, Doppler ultrasound, D-dimer and 3-month follow-up. A similar finding was noted by Mazurek who studied 84 eligible subjects amongst 109 consecutive patients suspected of having PE using CT to evaluate the lungs; PE was confirmed in 26 individuals. In this study, most patients had a moderate pre-test clinical probability of PE. Perfusion SPECT-CT was noted to have a sensitivity of 100% and a specificity of 83%, based on 6-month follow-up.[45] In a similar manner, Yildirim and Genc have retrospectively reviewed their experience for evaluation of PE in 305 patients, finding a 92% sensitivity and 76% specificity for perfusion-only SPECT-CT, recommending this test as the first-line diagnostic approach followed by ventilation SPECT-CT on the following day when perfusion defects are present.[46] The concept of staged studies will be further elucidated in strategy E, below.

During the COVID-19 pandemic, several groups have reported using perfusion SPECT-CT, without ventilation, as a definitive examination for detection of PE.[47-50] Of 6

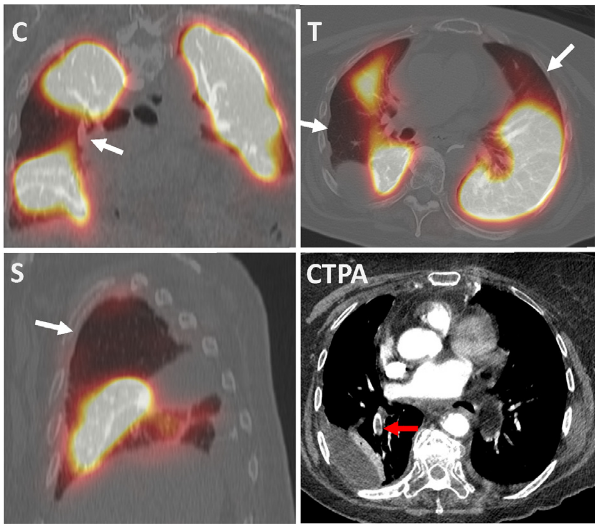

Figure 1 Elderly female with renal cell carcinoma with pleural, pulmonary and mediastinal nodal metastases, currently responding to chemotherapy treatment who presented with increasing exertional dyspnea and pleuritic chest pain. Large bilateral segmental perfusion defects (white arrows) noted on coronal (C), sagittal (S), and transverse (T) SPECT images, without regional abnormalities noted on the underlying CT scan, were interpreted as positive for acute PE. Patient was placed on apixaban and CTPA several days later (right lower panel) confirmed massive pulmonary emboli (red arrow). Images kindly provided by Dr. Heiko Schöder, Memorial Sloan Kettering Cancer Center, New York, NY.

patients with proven diagnosis of PE studied by Das and colleagues, perfusion SPECT-CT was positive in only 4, a surprisingly low fraction.[49] In the era of COVID-19, an additional benefit afforded by the CT component is the ability to screen the lungs for stigmata of infection.[50] An illustrative patient in whom perfusion SPECT-CT was performed is displayed in Fig. 1.

Chief criticism of relying on perfusion SPECT-CT in this manner is that while sensitive, it remains insufficiently specific to warrant long term anticoagulation, an intervention which entails a degree of risk.[51-53] By performing these studies in cancer center populations with elevated pretest prevalence of PE, several groups[44,49,50] were able to ensure a sufficiently high positive predictive value in their cohort, in effect co-opting 2 methods of increasing predictive value. This concept is discussed further in strategy D, below.

Strategy D. Leverage Pretest Probability to Improve Predictive Value of a Positive and Negative Test

In any clinical circumstance, many factors enter into the choice of which diagnostic test should be performed. The key operative metric in the diagnostic realm is positive or negative predictive value.[54] This informs the clinicians of the likelihood of whether a positive or negative test result, viewed in the context of a particular patient, is true positive or true negative. Sufficiently high predictive value of a test grants the physician confidence to make difficult decisions (such as committing to long-term anticoagulation) based on the cost-benefit of therapy. Only with near certainty in the diagnosis of PE would a clinician be willing to recommend a therapy with inherent risk.

The fundamental elements that determine predictive values are sensitivity and specificity of the test, as well the pretest (or *a priori*) probability of disease in a particular patient; this relationship is governed by Bayes' Theorem.[55] As a pragmatic matter, a high pretest probability will give the positive predictive value of an examination an additional boost.

In the pre-COVID-19 era, several authors have published results where they achieve adequate positive and negative predictive value of disease based on combining perfusion scintigraphy results with pretest probability.[56-59] An early iteration of this approach was described in the PISA-PED study which combined clinical assessment with planar perfusion scintigraphy.[56] Probability of PE was determined in 890 consecutive patients based on pretest probability (judged as very likely, possible or unlikely) and results of planar perfusion scintigraphy (described as normal, near-normal, abnormal compatible with PE or abnormal not compatible with PE). Pulmonary angiography and clinical/scintigraphic follow-up were performed in all patients with abnormal scans, yielding a sensitivity of 92% and specificity of 87%. Updating this concept, Bajc retrospectively studied the diagnostic performance of perfusion SPECT scored using a trinary categorization of PE, no PE, or disorder other than PE, in combination with clinical findings in 152 patients.[58] The combination of clinical pretest probability and SPECT perfusion was compared to ground truth as determined by the referring physician, achieving a sensitivity of 90% and specificity of 95%.

In the period of COVID-19, this strategy has been utilized in the performance of perfusion SPECT-CT on oncology patients, a high-risk group, to boost the predictive value of a positive result to an actionable level of certainty, as we earlier noted with respect to studies by Das[49] and Lu.[50]

Strategy E. Staged Examinations With Perfusion Scintigraphy First – The Inverted Q/V Lung Scan

We have noted that the historic function of ventilation scintigraphy is to adjudicate perfusion defects, that is to determine if they are reflexive and secondary to hypoventilation, or primary abnormalities due to a vascular insult. In the typical population of patients seen at lung scintigraphy, only a small fraction of patients will have perfusion defects. For this reason, under given circumstances, it may be reasonable to start with the perfusion study, and only if a defect is identified subsequently elucidate its etiology by performing ventilation scintigraphy or another technique.

Sheen et al reported on such a protocol in use at Montefiore Medical Center for evaluation of PE in pregnant women, a population with generally minimal underlying lung parenchymal disease. Perfusion scintigraphy was performed first, based on an observed low prevalence of segmental defects in the population coupled with a desire to reduce their radiation exposure.[60] In this protocol, the screening perfusion examination was typically performed with a reduced amount of activity, both to minimize exposure, and to facilitate subsequent performance of ventilation scintigraphy using a larger dosage of inhaled radiopharmaceutical, if required. The perfusion study, in essence, served as a screening examination and only if abnormal would a ventilation study, or other examination, be necessary for a final diagnosis. A retrospective analysis of this method in 225 patients demonstrated that over 85% of pregnant women studied by low-dose perfusion scintigraphy did not manifest segmental defects, thereby excluding PE and obviating the need for further evaluation; only the remaining 15% of patients, with segmental perfusion defects, were referred for alternate testing, frequently completion of the ventilation scan. A similar frequency was seen by Abele and Sunner[61] who studied pregnant patients by perfusion SPECT and found that only 13 of 74 subjects (18%) were indeterminate for PE and required further imaging (in their case by CTPA).

Yildirim suggested a similar approach in all patients who present for the scintigraphic evaluation of pulmonary embolism. Perfusion SPECT-CT is performed initially while ventilation SPECT-CT is acquired on a subsequent day only when the perfusion SPECT-CT study demonstrates defects; in their experience, these were seen in only 85 of 305 (28%) studies.[46]

In order to minimize use of ventilation scintigraphy during the COVID-19 period, we introduced a similar staged protocol for all referred patients in whom the chest radiograph was relatively clear without confluent opacities, in essence using planar perfusion scintigraphy as a screening examination (Fig. 2).[62] Patients with confluent parenchymal opacities were studied by other means due to anticipated defects on their perfusion study. When less than a single segmental perfusion defect was noted, the patient was deemed free of PE. Only patients with one or more segmental perfusion defects required further imaging (such as CTPA or completion ventilation scintigraphy under vigilant COVID-precautions) to arrive at a definite diagnosis. In our experience, 42 (79%) of 53 patients, irrespective of whether infected with COVID-19 or not, had less than one segmental defect on perfusion scintigraphy and were deemed free of PE; only 21% required further follow up. An analysis of the 42 subjects with negative perfusion studies demonstrated a very low mortality prior to hospital discharge (1 patient with COVID-19 infection and respiratory failure expired during dialysis). In 6 instances where follow up examinations were performed at the behest of the referring physicians, absence of abnormalities was confirmed.[63] An illustrative patient studied by this technique is displayed in Fig. 3. Lu et al.[50] used a similar strategy to initially screen patients by planar perfusion scintigraphy which they followed up with perfusion SPECT-CT, if defects were noted. Other groups have expressed a similar sentiment to change the order of ventilation and perfusion imaging during the COVID-19 period.[64,65]

The low prevalence of segmental defects in patients with relatively clear chest radiographs begs the question as to why an "inverted" perfusion ventilation protocol has not been more commonly proposed or performed, except in rare

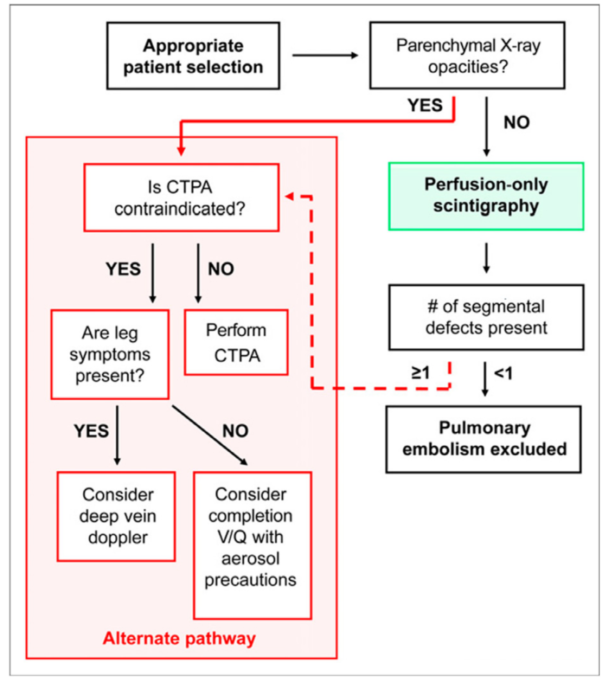

Figure 2 Novel diagnostic algorithm for evaluation of pulmonary embolism, which minimizes performance of ventilation studies. Green box represents perfusion scintigraphy, whereas red box encloses alternate diagnostic examinations that are performed due to prior radiographic opacity (red solid arrow) or indeterminate scintigraphy (red dotted arrow). Originally published in the Journal of Nuclear Medicine.[62] © SNMMI.

exceptions.[66] This may be because of a desire to improve the stochastic properties of the perfusion images by making them sufficiently high-count, or due to the difficulty in ventilating sufficient counts to overwhelm the initial perfusion study.[64,67] The advent of improved ventilation radiopharmaceutical agents[68] may serve to remedy this latter difficulty.

Making Sense of the Spectrum

As noted above, a range of algorithms has been presented regarding how to perform ventilation scintigraphy in the time of COVID-19, including some which combine multiple strategies, such as Lu and Macapinlac[50] or Yildirim and Genc.[46] Some algorithms and opinions appear diametrically opposed to others.

A closer look at the context and circumstances associated with these seemingly contradictory proposals reveals a basically consistent underlying understanding. It is important to remember that each opinion put forward reflects a reaction to the pandemic at a specific and unique location and time. Issues such as disease prevalence, availability of PPE, and availability of diagnostic testing vary between locales. A further dimension in the evaluation of PE is the *a priori* prevalence of disease in the population of patients studied which changes the predictive value of the examination. While it can be tempting to construe differences between authors as *bona fide* conceptual disagreements, it may be more likely that variation in approaches is due to situational differences and/or differences in the institutional tolerance for risk.

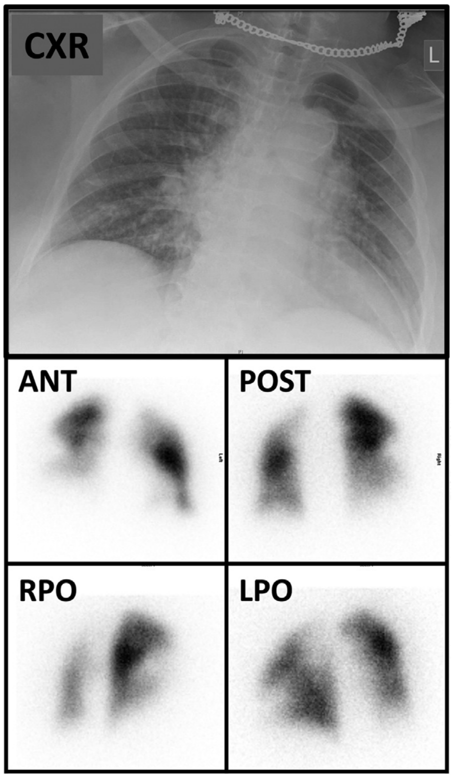

Figure 3 Postmenopausal woman with chronic kidney disease and obstructive sleep apnea admitted with shortness of breath, found to have acute deep vein thrombosis on Doppler ultrasound of the legs. The patient tested negative for COVID-19 by PCR examination. Upper panel: Chest radiograph (CXR), demonstrates scattered patchy densities throughout the lungs. Lower panel: On planar scintigraphy, multiple bilateral wedge-shaped perfusion defects are seen and pulmonary emboli cannot be excluded (anterior, posterior, right posterior oblique and left posterior oblique projections illustrated, as labeled). Based on these findings, and the presence of thrombi in the legs on Doppler study, the patient was treated with Apixaban and discharged home.

Conclusion

The solutions to reduce ventilation scintigraphy proposed during the recent COVID-19 pandemic had their origins in earlier concepts. It is important for nuclear medicine practitioners to be familiar with prior protocols published in the literature to afford them of options when needed. There are a range of approaches available and they should be carefully titrated against the particular situation at hand. We need to constantly weigh variables such as prevalence of COVID-19, availability of protective measures, and immunity of staff, to tailor and modify protocols as indicated.

Following the profound disruption caused by the COVID-19 pandemic, some of the temporary remedies that we have enacted, including reducing the necessity of ventilation scintigraphy through any of the several techniques that we have reviewed, may gain traction and permanently alter the ongoing practice of nuclear medicine.

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