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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. 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. Nonetheless, the need for a diagnostic test to exclude pulmonary embolism (PE) remained acute both because symptoms of PE and COVID-19 pneumonia overlap, and because of an association between COVID-19 infection and thromboembolic disease. 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, and inability to use intravenous contrast in some COVID-19 patients.

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, while sensitive, it was noted to be of low specificitiy. 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. 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...
by the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine 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. These concerns were often magnified due to concurrent issues such as insufficient capacity to test for infection, uncertain understanding of how the disease was spread, and basic lack of personal protective supplies such as masks and gloves.

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. A similar phenomenon has also been noted with the newest ventilation radiopharmaceutical, 99mTc-labeled carbon particles (Technegas), where activity was noted to persist in the imaging room air for over one hour following administration. Patient coughing, poor mouth seal, and incomplete nose closure 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. 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 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 Zuckier44

| Authors          | Year | Population | Modality | Concept                                      | COVID-19 Application            |
|------------------|------|------------|----------|----------------------------------------------|----------------------------------|
| Miniati et al56  | 1996 | General    | Perfusion Planar SPECT-CT | Perfusion scintigraphy combined with pretest clinical probability |
| Bajc et al58     | 2013 | General    | Perfusion Planar SPECT-CT | Das et al,49                     |
| Sostman et al43  | 2008 | General    | Perfusion Planar + CXR SPECT-CT | Radiographic information used to evaluate airspace disease |
| Lu et al44       | 2014 | Oncology*  | Perfusion Planar SPECT-CT | Burger et al,47                   |
| Mazurek et al45  | 2015 | Elderly#   | Perfusion Planar SPECT-CT | Das et al,49, Voo et al,48, Lu et al50 |
| Sheen et al60    | 2018 | Pregnancy~ | Perfusion Planar PPE SPECT-CT | Zuckier et al,52, 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 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 nondiembolic causes of decreased ventilation such as bronchospasm. Prior to COVID-19, Lu et al.43 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.43 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.77-80 Of 6
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. 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. An early iteration of this approach was described in the PISA-PED study which combined clinical assessment with planar perfusion scintigraphy. 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. 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 and Lu.

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. 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.

Safe Pulmonary Scintigraphy in the Era of COVID-19

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. 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, 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. 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. 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. An illustrative patient studied by this technique is displayed in Fig. 3. Lu et al. 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.

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 exceptions. 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. The advent of improved ventilation radiopharmaceutical agents 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 or Yildirim and Genc. 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.
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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