Planar Ventilation-Perfusion Imaging for Pulmonary Embolism: The Case for “Outcomes” Medicine

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Single-photon emission computed tomography (SPECT) has been a significant advancement in scintigraphy, impacting many areas of diagnosis. It has begun to find use in ventilation-perfusion (V/Q) scintigraphy. However, its utility has been limited in the United States because of a lack of an optimal and Food and Drug Administration-approved SPECT ventilatory agent. Although SPECT V/Q can show more and smaller mismatches than planar studies, there is persistent debate regarding the clinical significance of these smaller pulmonary emboli (PE); they may be neither clinically significant nor require treatment. Available data suggest that planar V/Q, SPECT V/Q, and computed tomographic pulmonary angiography (CTPA) have similar false-negative rates and thus have a similar impact on outcomes. In most cases, emergency department physicians are the first to encounter patients who may have PE and they frequently use an imaging study as part of the evaluation. We discuss the rational for triaging patients to different imaging modalities with the use of chest radiography and the strengths and weaknesses of each modality. Detailed anatomy is an advantage of CTPA, breast radiation dose is reduced with scintigraphy, and imaging is quicker and more detailed with SPECT. We also review planar and SPECT V/Q and CTPA from the differing vantage points of diagnostic accuracy vs patient outcomes. Whatever modality their patients require, physicians can be confident that they are all similarly efficacious at diagnosing clinically relevant emboli.

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Singl-photon emission computed tomography (SPECT) has remarkably advanced radionuclide imaging. Some examinations, such as modern myocardial perfusion imaging, cannot be performed without it and SPECT has enhanced others, including skeletal scintigraphy and infection imaging. Many investigators have campaigned heavily for its use in ventilation-perfusion (V/Q) scintigraphy. It was no accident that we very recently devoted a complete issue of Seminars in Nuclear Medicine to the subject.1

Almost all the interest in SPECT V/Q has been outside the United States, primarily because of the unavailability of Technegas (Cyclomedica Corporation, Sydney, Australia) here. This agent is generally regarded as the best-available ventilatory agent with excellent dispersion of radiolabeled particles to the peripheral airways. It is produced in Australia and with the exception of the United States has had considerable worldwide distribution for 2 decades.2,3 U.S. Food and Drug Administration approval has been elusive, although new attempts to achieve this are underway. In the interim, some American companies have developed particulate ventilatory agents, for example, Swirler (Amici Corporation, Spring City, PA), which has enjoyed reasonable success for planar imaging but may not be optimal for SPECT. As described by Roach et al,4 a superior ventilation agent is required to support SPECT methodology. Interestingly, many medical centers continue to use xenon-133 gas for ventilatory studies. However, SPECT is impossible with the rapidly cleared gaseous agent.

Champions of SPECT V/Q methodology have been extremely critical of colleagues who continue to solely rely upon planar imaging; they cite comparative data claiming superiority of SPECT over planar imaging5 and produce data showing that more V/Q mismatches are evident on SPECT. As pointed out by Bailey et al,6 these comparative data may be flawed because the planar images used for comparison are derived from the SPECT acquisitions by the use of an angular summed method and are therefore not “true” acquired planar images. These reconstructed planar images are inherently blurred. Bailey et al’s reprojection method of reconstructing
planar images from SPECT data appears to provide planar images with greater accuracy. Nevertheless, it is reasonable to accept that small peripheral pulmonary emboli (PE) can be better seen with SPECT. This speaks to the practice of “accuracy” medicine; the belief that seeing more information on imaging inherently improves patient care. This had been called into question for PE imaging and diagnosis, because the current standard of care almost always mandates anticoagulation (with its attendant risks), regardless of the size of the PE. This is why “outcomes” rather than “accuracy” is preferable with diagnosis and management of PE.

A burgeoning body of evidence suggests that smaller PE probably do not need treatment in most patients, most of whom are otherwise healthy. Increasing imaging with high-resolution technologies, such as multidetector computed tomography (CT) and SPECT, leads to greater detection of clinically inconsequential small, peripheral PE that may be treated. The low false-negative (FN) rate of 1%-1.5% for planar imaging is similar to that of the high-resolution technologies and provides important “outcomes” justification to avoid unnecessary anticoagulation therapy. Evidence supporting overdiagnosis of PE will be presented later in this discussion.

Overuse of Both V/Q and Computed Tomographic Pulmonary Angiography (CTPA)

Emergency department (ED) physicians generally are the first clinicians to examine patients with signs or symptoms suggestive of PE. They are under great pressure to triage rapidly and decide whether to discharge or hospitalize patients. In cases of suspected PE, use of either V/Q (or increasingly so) CTPA represents an attractive triage method. Most patients presenting to the ED have minimal risk factors. However, even with a low subjective or objective clinical probability, ED physicians are reluctant to discharge patients with this potentially fatal disease and often request a diagnostic imaging study to improve their level of confidence. A recent report showed that the likelihood of a positive CTPA in these very low-risk patients is <1% and when negative D-dimer levels were accompanied by low clinical suspicion, the incidence of positive CTPAs was zero.

Evidence of Overdiagnosis of PE

The 2006 Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II report evaluated the role of CTPA as a diagnostic study for PE with the use of a composite reference standard, including the Wells score (Table 1) and additional imaging. CTPA did not perform well when its results were discordant with the clinical probability. The negative predictive value (NPV) of CTPA was 60% when the clinical probability of PE was high and the positive predictive value (PPV) of CTPA was 58% when the clinical probability was low. This latter number was comparable with the 56% PPV for V/Q when the clinical probability was low. Overall, the sensitivity of CTPA in diagnosing PE was 83%

In an accompanying editorial to the PIOPED II study, Perrier and Bounameaux express disappointment over the 17% FN results. They concluded that multidetector CTPA still misses small peripheral subsegmental clots better detected by V/Q or classic pulmonary angiography. They further point to results of outcome studies in which many small PE were not treated, presumably on the basis of FN studies. They boldly suggest “that most such thrombi do not need to be treated and therefore do not need to be detected.”

Additional evidence supporting favorable outcomes in patients with undetected and, therefore, untreated PE was presented in a 2006 report by Engelke et al, in which they addressed FN contrast chest CTs. They reexamined 1912 multidetector CT scans of the chest (including pulmonary CT angiography, thoracic CT aortography, thin collimation mediastinal CTs performed for esophageal disease, and standard chest CT) and correlated with clinical data and outcomes. A total of 65.5% of patients found to have PE on this review had initially FN examination reports. Because small, unsuspected PE may go undetected at initial imaging examination, the authors believed that these patients may do well in the short-term without anticoagulation.

Carrier et al in a meta-analysis of 22 clinical trials similarly found an increased detection rate of subsegmental PE with the change from single to multidetector CT without a change in subsequent thromboembolism rate within 3 months. They concluded that subsegmental PE may not be clinically relevant.

In 2007, Anderson et al published the results of the first randomized trial of CTPA versus V/Q in patients with suspected PE. The entry criteria for this large study were either a Wells score of >4.5 or a positive D-dimer. Six hundred nine-
ty-four patients were randomized to CTPA and 712 to V/Q. The authors found that 17.7% (123/694) in the CT group and 11.7% (83/712) in the V/Q group were diagnosed with PE. Although CTPA diagnosed 51% more PE, the outcomes were comparable. The FN rates (on the basis of a 3-month follow up for development of PE) were 0.4% for CTPA and 0.7% for V/Q. A total of 0.3% of the V/Q patients developed deep-vein thrombosis (DVT).

In an editorial accompanying Anderson’s study, Glassroth echoes the prior theme by asking if imaging of PE may be “too much of a good thing.” As part of his argument, he mentions the thoughts of Dr Larry Goodman expressed in an oft-quoted 2005 editorial in Radiology. Goodman refers to Gurney’s work, which emphasized that healthy patients often pass asymptomatic clots from the legs to the lungs, which are trapped by the lung capillary bed and lysed by intrinsic fibrinolysis, protecting the systemic circulation. Goodman presents 3 circumstances in which the benefit-to-risk ratio of not treating PE to using anticoagulant therapy favor treatment. He lists these as:

- patients with small PE and inadequate cardiopulmonary reserve;
- patients with small PE and coexistent acute DVT; and
- patients who have recurrent small PE possibly because of thrombophilia to prevent chronic PE and pulmonary artery hypertension

Egermayer and Town have also emphasized an important difference between PE and DVT when deciding to anticoagulate, namely that the pulmonary arteries possess an intense fibrinolytic environment that will dissolve even untreated emboli. Peripheral veins lack this ability. When combined with their risk of future embolization, this forms the basis for more aggressive therapy for DVT.

Epidemiologic evidence also supports overdiagnosis of PE. Burge et al retrospectively studied the records of 24,871,131 New York State inpatients in a 10-year period from 1994 to 2004 (the introduction and first 10 years of CTPA usage to diagnose PE). They showed a doubling in number of PEs diagnosed. Despite this increased detection rate, there was no significant increase in the death rate from PE. Wiener et al recently reviewed PE trends, mortality, case fatality, and presumed complications of anticoagulation using the Nationwide Inpatient Sample and Cause of Death Databases. Their data similarly supported the hypothesis that CT is associated with overdiagnosis of PE with an 81% increase in the diagnosis of PE with the advent of CT, accompanied by minimal change in mortality, a decreasing case fatality rate, and an increase in presumed complication of anticoagulation.

Sheh et al presented data from New York’s Montefiore Medical Center on 2087 patients with PE. Among patients diagnosed using either CT or V/Q, the odds of death for those with PE diagnosed by CT were only approximately one-half that of those diagnosed with planar V/Q studies. This finding suggests that CT diagnoses a less-severe spectrum of PE disease. These data further strengthen the idea that increased detection and treatment has no impact on PE-related mortality but may lead to complications of over anticoagulation. To carry this further, it supports the concept that the large number of small PE detected by SPECT and not by planar imaging likewise falls into this “overdiagnosis” category and have no impact whatsoever on patient outcome.

Why V/Q Instead of CTPA?

There has been attention in both the medical literature and the lay press about the increase in population radiation exposure from medical imaging, with a large proportion related to CT. Breast radiation in young women (who represent a very significant proportion of patients studied for suspected PE) is a concern with regard to chest CTPA, and the lung remains susceptible to carcinogenic effects of radiation into old age. In fact, when dose-reduction strategies are not employed, exposures as high as 20-60 mSv have been reported for chest CTPA; a dose range to which an increase in the lifetime risk of cancer has been attributed. The comparison to a dose of 0.22-0.28 mSv from V/Q scintigraphy prompted our development of a hospital-wide algorithm to use V/Q instead of CTPA whenever possible.

Improvement in Interpreting V/Q Studies

Proponents of SPECT certainly will point to cross-sectional imaging’s greater capability of detecting smaller lesions. We agree with this argument but, once again, it deals with accuracy rather than outcome. With the aforementioned similar NPV for planar V/Q and CTPA, the case for the adequacy of planar imaging remains convincing. Although CTPA and SPECT V/Q derive from differing sources, both are tomographic imaging modalities, and it is logical to extrapolate the points about CTPA regarding overdetection of PE to SPECT V/Q.

In the 2 decades since the original PIOPED report, there have been remarkable improvements in both performance and interpretation of planar V/Q imaging (Table 2). A very fortuitous aspect of the original PIOPED study was that use of newly introduced computer technology allowed establishment of a database, which has facilitated further retrospective review and clearer understanding of mistakes that were made. It also has allowed us to appreciate several ancillary findings that have greatly enhanced our ability to interpret V/Q scans. It is well worth reviewing the pros and cons of the original PIOPED criteria to better understand how V/Q scintigraphy has witnessed a rebirth and a new partnership with CTPA in studying PE.

The Problems with the PIOPED Study

One important problem with the initial 1990 PIOPED study was that 68% of the subjects studied were inpatients. The patients had a much greater incidence of un-
derlying cardiopulmonary disease (with associated chest radiographic abnormalities) than a similar-sized outpatient population. Chest radiograph abnormalities make interpretation of V/Q scans more difficult. In retrospect, the PIOPED population was a suboptimal group to be imaged with V/Q scanning. This flaw in the study design resulted in an unacceptable 44% of scans being interpreted as indeterminate/intermediate probability. This factor was the most major in the loss of confidence in V/Q scans’ clinical utility.

A second problem was the misclassification of the single segmental mismatch (SSM) as “low-probability.” Biello et al.,36 in their retrospective comparison of V/Q with catheter pulmonary angiography, had originally placed this in his “intermediate” category. As it turned out, 36% of these SSM cases had PE. This finding was placed back into the “intermediate” category in the follow-up modified PI-OPED report published in 1993.37,38

Finally, the changed association of a low-probability result from Biello et al’s PPV for PE of <10% to the PI-OPED’s <20% was very damaging. This was an apparent effort to reduce the number of intermediate interpretations. This failed, as evidenced by the 44% intermediate interpretations that resulted. A clinician deciding whether to anticoagulate a patient can usually accept a 10% possibility of missing a small PE because this allows an acceptable benefit-to-risk ratio when weighed against possible complications of anticoagulant therapy. However, a change to a 20% chance of misdiagnosis was generally considered unacceptable.

### The Good Thing About PIOPED

The computer database generated by the PIOPED study has been used to greatly enhance our understanding and interpretation of the V/Q study.35

### Impact on Underlying Cardiopulmonary Disease on Interpretation

In Stein et al’s30 retrospective review of PIOPED data, an SSM in patients with no previous evidence of cardiopulmonary disease was associated with PE in 86% of cases and could therefore be categorized as a high-probability study. In patients with previous cardiopulmonary disease, 3.5 segmental mismatches were required to achieve the same 86% PPV. We have used a negative chest x-ray as being reflective of no significant underlying cardiopulmonary disease, which has allowed us to place a well-defined SSM in the high-probability/PE present category.
Impact of Objective Clinical Assessment (Pre-Test Probability)

In a separate publication, Stein et al. showed how use of pretest probability could further enhance lung scan interpretation. The PIOPED study showed an 87% PPV for a high-probability study, which increased to 96% PPV when combined with a high pretest probability. Similarly, PIOPED's low-probability 14% PPV decreased to 4% when combined with a low pretest probability. In addition, the 86% PPV of an SSM in a patient with no previous cardiopulmonary disease increased to 100% when combined with a high pretest probability.

Location of Radiographic Infiltrates (the “Triple Match”)

When matched V/Q defects were combined with a corresponding radiographic infiltrate (“triple match”), PIOPED classified them as intermediate. Worsley et al. reviewed all of these “triple matches” and determined that if they occurred in the upper- or midlung fields, the prevalence of PE was 11% and 12%, respectively. This determination as allowed reclassification of these as low-probability. By contrast, such findings in the lower lung fields had a 33% prevalence of PE and must, therefore, remain in the intermediate category.

Size of Pleural Effusions

PE’s are commonly associated with small rather than large pleural effusions. In an older study of 534 patients with matching effusions and perfusion loss, only 3.7% had PE. Gottschalk and Stein in a retrospective PIOPED analysis found only 10% of patients with large effusions and matching V/Q abnormalities had PE. They proposed that such large effusions with matching V/Q defects and no other mismatches could be called low-probability studies.

The “Stripe Sign”

As originally described by Sostman and Gottschalk, the presence of a peripheral parenchymal stripe around a perfusion defect has proven to be an extremely useful and accurate finding for excluding the presence of a PE. The same authors reviewed the significance of this finding in the PIOPED population and found that its presence was associated with a 93% NPV for PE.

Ventilation Worse Than Perfusion (“Reverse Mismatch”)

Although described separately from the PIOPED study, we have found this observation to be extremely helpful in lung scan interpretation. One year before PIOPED, Carvalho and Lavender found that in 11.7% of their V/Q studies (46 of 392), ventilation defects exceeded perfusion defects. They called these ventilation/perfusion “reverse mismatch” defects. None of these patients had PE; bronchial obstruction and chronic obstructive pulmonary disease were the most common causes. This was subsequently confirmed in another study.

Several other findings, such as the segmental contour sign, loss of perfusion in an entire lung, and perfusion defects worse than radiographic findings, have been reviewed in a prior issue of Seminars. Additional improvements, such as the resolution of our gamma cameras, have also contributed to improved diagnosis. A summary of the improvements in V/Q interpretations since the PIOPED I study is presented in Table 2.

A Safe, Simple, and Accurate Algorithm to Study Patients With Suspected PE

In late 2006, a joint decision was made between 3 hospital departments (Emergency Medicine, Nuclear Medicine, and Radiology) at Montefiore Medical Center to reduce the number of CTPAs being performed for suspected PE. The Nuclear Medicine service took the lead in holding educational sessions with the support of our chest radiologists and emergency department physicians. After drawing upon lessons learned from the 1990 PIOPED report, it was decided that chest radiography could serve as an appropriate triage tool in stable patients to determine whether CTPA or V/Q was appropriate. A normal or near-normal chest x-ray would triage to V/Q, whereas a positive x-ray showing infiltrates, significant chronic lung disease, or pleural fluid would be tracked to CTPA. By using this algorithm, we achieved our goal of reducing overall radiation exposure. Comparing 2006 and 2007, we found that the number of CTPAs decreased 25% whereas V/Q studies increased by 61%. The ratio of CTPA to V/Q was 1.7:1 in 2006 and decreased to 0.8:1 in 2007 (Table 3). Most importantly, the FN rates (based on 3-month follow-up) were 1.1% for CTPA and 1.2% for V/Q. All patients categorized as normal, low, or very-low-probability who returned with evidence of either DVT or PE were considered as FN cases.

This successful change in practice patterns with good clinical outcomes was achieved with planar imaging alone. The one report in which investigators addressed “outcomes” analysis of SPECT V/Q demonstrated an FN rate of 1.5%, com-

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<th>Year</th>
<th>Imaging</th>
<th>2006</th>
<th>2007</th>
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<td>Ratio of CTPA:</td>
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Note. Data in parentheses are percentages.

CTPA, CT pulmonary angiography; PE, pulmonary embolism; V/Q, ventilation-perfusion.

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parable with that of planar V/Q and CTPA. Thus, there are considerable data to support continued use of planar V/Q imaging.

The Language of Lung Scan Interpretation

The language of lung scan interpretation has long been a source of confusion both among requesting clinicians and the interpreters. This confusion was nicely documented by Scotland’s Dr Harry Gray almost 2 decades ago. He conducted separate surveys for both physician groups. Biello’s original formulation associated low-probability interpretations with a <10% likelihood of PE. PIOPED, unfortunately, expanded this to a <20% likelihood of PE. Gray’s survey of clinicians showed an astonishingly mistaken belief that low-probability interpretations could go as high as 50%. Even more surprising were the survey results for those interpreting the V/Q scans, which revealed that low-probability interpretations were erroneously thought to extend as high as a 50% possibility that PE was present. Gray proposed replacing probability-based interpretations with a “percent likelihood” interpretive scheme.

The very low FN rate achieved using our algorithm is quite similar to that achieved by Anderson et al’s prospective randomized study where they used objective clinical assessment (ie, Well’s Score) rather than the chest x-ray. Their FN rates for PE were 0.4% for CTPA and 0.7% for V/Q. An additional 0.3% in the V/Q group that developed subsequent DVTs was found to be statistically insignificant in their large series of cases.

To further address the interpretative language issue and following the analysis of our initial comparative data, we decided to abandon the “probability” categorization at our institution. In March of 2009, a memo was sent out to ED physicians, diagnostic radiology physicians, and nuclear medicine staff detailing a new V/Q interpretation scheme that would be implemented. The radiology and nuclear medicine residents are the first to interpret these studies on evenings and weekends. Normal, low and very-low-probability studies were changed to a simple “No evidence of PE,” intermediate/indeterminate studies became “non-diagnostic,” whereas positive studies were called “PE present.” This made V/Q interpretation similar to that of CTPA and readily understandable to everyone.

In the more than 2 years that this new language has been in place, the results have mirrored that of the “probability era” interpretations. The FN rate has been 1.5%. It has been fully accepted by the clinical services. In addition, the radiology and nuclear medicine residents who initially interpret evening and weekend studies have universally found it a much easier system to use. It should also be noted that significant disparities between resident interpretations and those of the attending nuclear medicine physician have been <1%.

Conclusion: Planar Imaging Is “Good Enough”

Current practical barriers to implementation of SPECT V/Q include the current lack of an optimal ventilatory agent in the United States. Secondarily to this, most U.S. nuclear medicine physicians and radiologists are unfamiliar with SPECT V/Q interpretation on a practical basis and U.S. technologists generally lack sufficient experience to perform such studies. This is obviously not the case with CTPA and is often much less so with traditional V/Q. If Technegas becomes available in the United States, then these circumstances certainly would change through new experience and training. It should be mentioned that a benefit of SPECT V/Q is time saved; when the sample protocols outlined in Miles et al are used, traditional 8-view planar V/Q requires 53 minutes of acquisition time, whereas SPECT requires 25. Once SPECT V/Q becomes more widespread, this would clearly be helpful in busy emergency rooms. It would allow for more direct comparison and complementary information to CTPA and may even allow for hybrid imaging if needed, without the risk of intravenous contrast.

In revisiting some points made by Freeman et al in 1968 in one of the earliest correlative papers between V/Q and catheter angiography, we see that, since then, not much has changed. Lung scanning and angiography are complementary and should not be considered competitive modalities; we have shown here that both play important roles in concert even today. Lung scanning helped bridge the diagnostic gap between clinical suspicion and pulmonary angiography; this is still true. Catheter angiography was more helpful in cases of preexisting cardiopulmonary disease causing localized perfusion defects; CTPA now primarily fills this role. Anatomic imaging is still the only way to obtain precise location of thrombi. Localized peripheral embolic defects are still better detected with scintigraphy, but even improvement with SPECT may not confer any additional benefits. Serial scans are safe to perform at regular intervals to follow disease progression, which is still true today and is what we routinely recommend to referring clinicians.

Therefore, before traditional V/Q scanning is unfairly discounted in a quest for “prettier pictures” or some perceived clinical detection benefit, it is clear that the information presented here makes a case for the continued usefulness of planar V/Q imaging for several reasons. First, the FN rates among CTPA, planar V/Q, and SPECT V/Q are all comparable, which indicates comparative detection ability of all 3 examinations if performed properly, without loss of patient safety. Second, there is abundant literature showing that the additional detected abnormalities by SPECT V/Q may lead to overtreatment of clinically inconsequential findings. Third, V/Q planar imaging has stood the test of time, is considered a basic clinical skill in nuclear medicine, and has undergone decades of refinement since the earliest forms of lung scintigraphy for PE were first described in the 1960s. SPECT V/Q will require more analysis and experience before it can be used in a similar fashion to more commonly used meth-
ods. Until then, clinicians can therefore be confident that when selecting planar V/Q scans from available imaging modalities, their patients will be safely evaluated and those who need treatment will be detected appropriately.

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