Imaging Pulmonary embolism:
what are the issues and how should it be done?

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Up to now, there has been an increasing trend to use CT pulmonary angiography (CTPA) as the first line imaging test for suspected pulmonary embolism (PE), in lieu of the ventilation/perfusion (V/Q) scan. There are several reasons behind this change, including:

1. the perception that the V/Q scan is non-diagnostic in most cases
2. the perception that CTPA (especially on newer machines) is as accurate, if not more accurate, than V/Q scintigraphy
3. the view that CTPA is easily performed and is a safe alternative to V/Q scintigraphy
4. Clinicians' preference for a binary (yes/no) report rather than a probability
5. The ability of CT to assess for other pathologies, e.g. coronary artery disease, aortic dissection, pneumonia, other pleural or pericardial disease etc
6. The increasing dissemination of CT scanners into most hospitals and the lack of access to Nuclear Medicine departments in many institutions, especially in smaller hospitals and outside of routine working hours in many parts of the world.

Let's address each one of these statements in turn:

1. Is the V/Q scan non-diagnostic in most cases?

This statement is quoted widely in the literature and is based on the original PIOPED (Prospective Investigation of Pulmonary Embolism Detection) study. This was a large (n=933 patients) multicentre trial done in the US in the 1980's which was published in JAMA in 1990 (1). Abnormal scans were reported using probabilities (low, intermediate, high) based on certain diagnostic criteria. Of those patients with high-probability scans, 88% had PE but only a minority of patients with PE had high-probability scans (sensitivity, 41%; specificity, 97%). Of those with an intermediate probability scan, 33% had pulmonary embolism and PE was seen in 12% of patients with low-probability scans. The overall accuracy of the V/Q scan was significantly improved by the addition of clinical assessment. It should also be noted that a normal scan was highly reliable in excluding PE. The interpretative criteria were modified in 1993 resulting in some improvement in overall accuracy (2).

It is important to note that the PIOPED study was done with planar imaging and the ventilation agent used was Xe-133. Only single view planar ventilation images were performed which makes the assessment of ventilation-perfusion mismatch difficult. Using the modified interpretative criteria and Technegas, a superior ventilation agent allowing multiple view planar studies (or SPECT), a large prospective study from Newcastle's John Hunter Hospital demonstrated that the non-diagnostic (moderate probability) rate could be reduced to 10% (3). More recently, SPECT has being used for V/Q scintigraphy due to its better sensitivity, specificity and interobserver reproducibility, its better ability to image all segments and its ability to eliminate shine-through from underlying segments. Several studies using SPECT have shown that the non-diagnostic rate is very low being quoted at less than 5%. (4-5)

In summary, the use of better ventilation agents (Technegas) and SPECT has dramatically reduced the non-diagnostic rate to less than 5%.

2. Is CTPA more accurate than VQ scintigraphy?

Initial reports of the use of CTPA for the detection of PE in the early and mid 1990's indicated a high diagnostic accuracy and sensitivities approaching 100%. This was achieved by excluding technically suboptimal studies and assessing only the large proximal arteries. Several subsequent studies had less impressive results in unselected populations. In 2006, the PIOPED II investigators published the results of the largest trial to date investigating the diagnostic accuracy of CTPA, in the New England Journal of Medicine (6). This was a multi-centre study which compared the diagnostic performance of CTPA (using 4-16 slices) to a composite gold standard which included pulmonary angiography, planar V/Q scintigraphy (with Xe-133 often used as the ventilation agent) and clinical follow-up. The overall sensitivity of CTPA in this series was 83%. In other words, CTPA failed to detect emboli in one in every six patients. The sensitivity varied significantly between enrolling sites ranging from 58% to 95%. The addition of CT venography to the study protocol increased the sensitivity to 90%, at the expense of increased radiation exposure to the pelvis and abdomen. Of 824 CTPA studies performed, 6.2% of studies were inconclusive due to poor image quality (most commonly due to respiratory motion artifact). If technically suboptimal studies are included, the overall sensitivity falls further to 78%. As with the original PIOPED study, clinical probabilities were added to scan interpretations to improve accuracy. In patients with a discordance between the clinical probability and the CTPA result, there were significant false positive and false negative rates. Specifically, in patients with a high clinical probability, 40% of negative CTPA

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results were false negative and in patients with a low clinical probability, 42% of positive CTPA results were false positive. The PIOPED II study also demonstrated that while CTPA can usually detect large central clots, it is less accurate with the detection of smaller peripheral PE. The positive predictive values quoted in this paper were 97% (lobar PE), 68% (segmental PE) and 25% (subsegmental PE). In patients with any cardiorespiratory impairment in particular, the detection of PE of any size is important as they can be clinically significant in such patients.

Although the literature is limited, the sensitivity of V/Q SPECT appears to be superior to CTPA. In a comparative study of 83 patients from Germany with suspected PE, the sensitivity for 4 slice CTPA was 86% compared with 97% for V/Q SPECT (7). It is of note that the CTPA sensitivity quoted in this series is comparable to the results from the PIOPED II study.

It should also be noted that CTPA is limited in assessing clot resolution and in all patients with proven PE, serial V/Q scans should be done to assess for reperfusion and exclusion of recurrent emboli, if suspected.

In summary, CTPA has a sensitivity in the order of 83% based on the PIOPED II trial. One of the concluding statements of PIOPED II is "a false negative rate of 17% for CTPA alone indicates the need for additional information to rule out pulmonary embolism". The sensitivity of V/Q SPECT appears to be much higher.

3. Is CTPA easily performed and a safe alternative to VQ scintigraphy?

While V/Q scintigraphy is safe with side effects virtually unheard of, the same cannot be said for CTPA. Safety concerns relate mainly to the use of contrast and the radiation dose delivered.

Of the 7284 subjects originally screened in the PIOPED II study, 23% were excluded due to either co-existant renal impairment or significant contrast allergy (6). Neither of these precludes the use of V/Q scanning. While contrast reactions (such as rash, thyrotoxicosis, urticaria and renal impairment) are usually mild and uncommon with the use of non-ionic contrast media (reported incidence in the order of 3%), serious side effects (including bronchospasm, severe urticaria, anaphylaxis and death) do occur (in about 0.5% patients). In diabetic patients, the use of metformin is also known to increase the likelihood of renal impairment after contrast administration.

There is also an increasing concern regarding the use of CTPA in premenopausal women due to the significant breast radiation doses delivered (in the order of 10-60mGy/breast) (8,9). Breast cancer is a relatively common malignancy and it has been estimated that a dose of 60mGy to the breast will further increase this risk, with a relative risk of 1.68 reported (9). As CT scanner technology improves and the number of slices increases, the breast radiation dose is further increased (10). While there are various strategies that can be used to reduce this dose, each can affect the overall technical quality of the CTPA study.

It is also worth noting that for good quality CTPA studies, a breath hold of about 10 seconds is required. This may be difficult to achieve in some patients, especially in sick and dyspnoeic patients.

In summary, there are safety concerns with CTPA regarding the use of contrast media (with the risk of contrast allergy and renal impairment) and the breast radiation dose delivered (increasing the risk of breast cancer, particularly in premenopausal women). There are no significant safety concerns with V/Q scintigraphy.

4. Do clinicians only want a binary (yes/no) report rather than a probability?

In view of the significant morbidity and mortality of PE (30% untreated), its accurate diagnosis is essential. While a perfectly accurate imaging test would be desirable, it is evident that such a test does not exist. While V/Q scintigraphy is sensitive (especially when done with SPECT –reportedly 97%), it lacks specificity, as other conditions (eg focal lesions, vasculitis, radiation therapy) can also cause ventilation-perfusion mismatch. PIOPED II has shown that CTPA is less sensitive (83%) and hence clots are missed in one in six patients. While there is some evidence to suggest that patients with a negative CTPA have a good outcome even if PE are missed, it is important to note that PIOPED II demonstrates that it is not only small clots that were missed and even small clots may be clinically significant, particularly in patients with cardiorespiratory impairment. PIOPED II also shows that there are high false negative and positive rates if the scan result and clinical likelihood are discordant. This is also important as unnecessary anticoagulation also has a morbidity, with a bleeding risk in the order of 6% reported.

Recently, and particularly since the introduction of SPECT imaging, several centres have assessed binary reporting of V/Q scans, most commonly defining positive as ≥ 0.5 mismatched segments. Using this approach, sensitivities of over 95% and specificities of over 90% have been reported (7,11)

It is important that imaging specialists and clinicians understand the strengths and weaknesses of the various tests. While a yes/no result would be desirable, the

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key question is how accurate is that answer. It is evident from PIOPED II that CTPA is hampered by a suboptimal sensitivity and there is a high false negative and false positive rate when the clinical likelihood and scan results are discordant. It is important that clinicians and imaging specialists are aware of these limitations, given the increasing tendency to rely solely on CTPA when PE is suspected.

5. Is the ability of CT to assess for other pathologies a reason to use it in preference to V/Q scintigraphy?

There is no question that CTPA can be used to assess both the pulmonary vasculature as well as the lung parenchyma and nearby structures. In the United States, multislice CT (typically 64 slice) is being increasingly used to exclude PE, coronary artery disease and aortic dissection (the so-called "triple rule out"). CT scanning can also reveal other conditions which can mimic PE, including pneumonia, pneumothorax and other pleural or pericardial diseases. While several studies have shown that other pathologies can be demonstrated in many cases (quoted as anywhere from 11%-85% patients) (12), it is important to determine whether these are ancillary and unrelated or are actually the cause of the patient's current clinical presentation.
It is important to understand that there is no imaging test that can answer all questions and the ability of CTPA to detect conditions other than PE may be at the expense of a lower sensitivity for PE detection. It should also be noted that because of its ability to assess both the pulmonary ventilation and perfusion, V/Q scintigraphy can diagnose other lung conditions such as asthma, COPD, focal lesions and pleural effusions.

6. Should CT be used because it is more readily available?

While ready access to Nuclear Medicine services is available at many centres, this is not the case universally and in some countries and at some institutions, access is limited, especially outside of routine working hours. Increasingly, CT scanning is becoming more readily accessible and these local factors may impact on which test is ordered to assess for suspected PE. It should be emphasised that any imaging studies selected should be those that are the most accurate in the specific clinical situation and are as safe as practicable. With PE, if access is not readily available, there is the option to commence anticoagulation and perform the confirmatory imaging test the next day when access is more readily available. The selection of the appropriate test may vary according to the specific clinical circumstances. For instance, premenopausal women with no prior lung disease should almost certainly have V/Q scintigraphy performed due to concerns of breast radiation exposure (and the potential risk of contrast allergy with CTPA). An older patient with possible PE or aortic dissection and known fibrotic lung disease may be better assessed by CTPA due to the ability of CTPA to detect dissection and the limitations that V/Q scanning will have with co-existent underlying parenchymal lung disease.
In summary, while local factors may determine which test is selected, it is important for the treatment and safety of individual patients that the most appropriate imaging test is selected in each clinical circumstance. The option of commencing treatment and then obtaining the most appropriate imaging test when it is available should be considered at sites where access to imaging is limited.

In Summary:
How can V/Q scintigraphy be optimized?

While much of this discussion has addressed the strengths and weaknesses of CTPA, it is important to ensure that V/Q scintigraphy is performed optimally in patients with suspected PE. Although limited, the literature consistently shows that compared with planar imaging, V/Q SPECT:

a) has a higher sensitivity in the detection of PE (7,13,14)
b) is more specific (4,15)
c) is more reproducible (14,15)
d) reduces the number of inconclusive results (4,5)
e) takes no longer than planar imaging (10-15 minutes for each SPECT typically)
f) can generate planar images if desired (16)
g) can generate new displays, e.g. quotient images (13)
h) offers potential for further enhancements, eg with image fusion and quantitation (17,18)

Although many clinicians and imaging specialists will have expected that CTPA would have performed better than the results of PIOPED II investigators indicate, it is inevitable that CTPA technology will continue to improve. It is therefore important for the survival of the V/Q scan that the test is optimised. For the reasons stated above, it is clear that SPECT is superior to planar imaging and it is recommended that SPECT (using Technegas as the ventilation agent) should be routinely performed when possible.

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