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## Volume 11 - Issue 1, 2011 - Cardiac Imaging

### Diagnosing Pulmonary Embolism: Clinical Problem or Methodological issue?

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The clinical spectrum of pulmonary embolism (PE) ranges from asymptomatic to sudden death. PE may be clinically silent (Moser et al. 1994) or may present as unexplained breathlessness, chest pain (central or pleuritic), cough, haemoptysis, syncope, palpitations, tachypnoea, tachycardia (heart rate >100), cyanosis, fever, hypotension (Systolic BP < 100 mmHg), right heart failure, pulmonary hypertension and leg swelling. However, these clinical features are common in patients who subsequently are diagnosed not to have PE (Miniati et al. 1999).

While certain symptoms and signs are more commonly observed in PE than other conditions, it is not possible to confirm a diagnosis of PE on clinical features alone. The diagnosis of PE must be confirmed or disproved on the basis of a conclusive imaging test, due to the inherently high mortality if left untreated. Treatment is also associated with significant risks. Because diagnosis cannot be established solely on the basis of clinical observations or on the outcome of simple investigations such as the ECG, chest x-ray or blood chemistry, imaging tests are required to confirm or refute a diagnosis of PE. A number of imaging tests have been employed for this purpose.

1. Conventional pulmonary angiography (PA), previously regarded as the gold standard.
2. Ventilation and perfusion scintigraphy (V/PSCAN) was for a long time the principal diagnostic method of choice.
3. Multidetector computer tomography (MDCT), frequently cited as the primary diagnostic method for PE diagnosis.
4. Magnetic resonance pulmonary angiography is still at an early stage of development.

#### What is the New Reference Standard?

A study by Baile, showed that PA had a sensitivity of only 87 percent and positive predictive value of 88 percent (Baile et al. 2000). They concluded that PA as the gold standard can be misleading. Interpretation is complicated by wide inter-observer variability (Schoepf and Costello 2004; Stein et al. 1999). PA is now rarely used in routine clinical practice. Nevertheless, in special cases, PA has a role in centres with highly qualified angiographers. For clinical routine V/P<sub>SCAN</sub> and MDCT are used. Planar technique for V/P<sub>SCAN</sub> is still frequently used, however, several studies show the inferiority of this technique compared to tomographic V/P studies based upon single photon computer tomography (V/P<sub>SPECT</sub>) (Gutierrez et al. 2009). Subject to availability, V/P<sub>SPECT</sub> is generally feasible in nuclear medicine departments. In accordance with EANM guidelines, there is no reason to adhere to the obsolete planar technique (Bajc et al. 2009a, b). In this article the comparison of available methods focuses on the need for immediate diagnosis of PE in all patients, enabling rational, efficient therapy at optimal cost.

#### Principle of PE diagnosis with V/P<sub>SCAN</sub>

V/P<sub>SCAN</sub> is based on the fact that emboli affecting individual pulmonary arteries cause characteristic lobar, segmental or subsegmental peripheral wedge shape perfusion defects due to the distinctive pulmonary arterial segmental anatomy. Within segment(s) affected by PE, ventilation is usually preserved. This pattern of preserved ventilation and absent perfusion, known as V/P mismatch, provides the basis for PE diagnosis.

The ventilation scan maps regional ventilation and helps define lung borders, thereby facilitating the recognition of peripheral perfusion defects. The ventilation scan may also provide additional information about cardiopulmonary disorders, others than PE. For example, in COPD, the distribution of ventilation is uneven and in aerosol studies focal deposition is often observed in central or peripheral airways. Pneumonias cause regional ventilation defects, usually more extensive than the associated perfusion defects. Combined ventilation and perfusion studies increase specificity for PE diagnosis and allow recognition of alternative pathology. It is therefore recommended that in PE diagnosis, a combined one-day protocol is used (Bajc et al. 2009a, b).

#### Comparison V/P<sub>SPECT</sub> vs MDCT

The absence of a satisfactory gold standard for PE diagnosis poses difficulties for the assessment of sensitivity, specificity and accuracy of all diagnostic methods. The best available standard is adequate follow-up of the patient for recurrence of PE or alternative diagnoses. The most rigorous study of MDCT in PE diagnosis is the PIOPE II study, which showed an overall sensitivity for PE of 78 percent when non-diagnostic studies were included (Stein et al. 2006). This led to the observation that the false negative rate of 22 percent for MDCT indicates the need for

additional information to rule out PE.

In the PIOPED II study the positive predictive value for a PE within a lobar pulmonary artery was 97 percent but fell to 68 and 25 percent at the segmental and sub segmental level, respectively. Freeman stated that the results from the PIOPED II study "do not clearly support the superiority of CT pulmonary angiography over V/P<sub>SCAN</sub> for the diagnosis of PE" (Freeman and Haramati 2009). A recent study by Bajc et al. and a prospective study by Gutte et al. show that V/P<sub>SPECT</sub> has higher sensitivity, and specificity and less non-diagnostic findings than MDCT (Bajc et al. 2008; Gutte et al. 2009).

#### Clinical Utility

PIOPED II as well as the study by Gutte et al. illustrate the limited clinical utility of MDCT (Gutte et al. 2009; Stein et al. 2006). In 50 percent of eligible cases, MDCT could not be performed because of kidney failure, critical illness, recent myocardial infarction, ventilator support and allergy to the contrast agent. Furthermore, six percent of performed MDCT studies were of insufficient quality for conclusive interpretation. In about one percent complications like allergy, contrast extravasation and increased creatinine level were observed. By contrast, V/P<sub>SPECT</sub> has no contraindications and was performed in 99 percent of patients referred in the study of Bajc et al. (Bajc et al. 2008). No complications were identified, and technically suboptimal studies are very rare. MDCT is available in nearly all medical centres and community hospitals. Service is often available around the clock, seven days a week. V/P<sub>SCAN</sub> is available in far fewer hospitals and seldom on a 24 hours basis. Obviously the difference in availability affects the choice between MDCT and scintigraphy.

#### Radiation Dose in V/P<sub>SPECT</sub> and MDCT

Based on data from ICRP reports (ICRP 1988) the effective dose for V/P<sub>SPECT</sub> with the recommended protocol is about 35 - 40 percent of the dose from MDCT. According to Hurwitz, the dose to the female breast for V/P<sub>SPECT</sub> is only four percent of the dose from MDCT even when this is administered with full dose saving methods (Hurwitz et al. 2009). This may have particular importance in pregnant women with proliferating breast tissue. During the first trimester of pregnancy the foetal dose of MDCT is greater than or equivalent to that of V/P<sub>SCAN</sub> (Hurwitz et al. 2006). The advantage of V/P<sub>SPECT</sub> increases after the 1st trimester.

Follow up of PE using imaging is essential to assess the effect of therapy, differentiate between new and old PE, where there is a suspicion of PE recurrence and explain physical incapacity after PE. The demands for follow up are only met with V/P<sub>SPECT</sub>. Obviously, the same method should be used for diagnosis and for follow up.

#### Discussion

V/P<sub>SPECT</sub> has no contraindications, a lower radiation burden, a lower rate of non-diagnostic reports and a higher negative predictive value than MDCT. Chronic PE can only be diagnosed by V/P<sub>SCAN</sub> (Tunariu et al. 2007). An ever greater requirement on health services is to provide cost effective patient care. The method for diagnosis of PE should be fast. V/P<sub>SPECT</sub> can be done in one hour, out of which camera time is only 20 minutes (Palmer et al. 2001). It empowers the clinician to choose the appropriate care regime. V/P<sub>SPECT</sub> allows quantification of PE extension which is essential in order to determine whether home treatment, which is much cheaper and more advantageous for the patient, is appropriate. As PE is present in only 20 to 30 percent of patients with clinically suspected PE, it is particularly important that a negative finding excludes PE. MDCT does not provide this assurance. (Perrier and Bounameaux 2006, Freeman and Haramati 2009).

For follow up and for research, it is essential that a method should be harmless, and capable of both detecting all embolised areas and of quantifying PE extension. The EANM guidelines conclude that only V/P<sub>SPECT</sub> satisfies these conditions. A common argument in favour of MDCT is that it allows diagnosis of diseases other than PE. However, this applies equally to V/P<sub>SPECT</sub>. Furthermore, in the presence of conditions and diseases other than PE, MDCT becomes frequently non-diagnostic. Altered haemodynamics, as in pregnancy, leads to grave difficulties. Conditions like extended pneumonia may lead to similar problems while V/P<sub>SPECT</sub> remains diagnostic for PE (Bajc 2005). As long as V/P<sub>SPECT</sub> is not generally available, MDCT and V/P<sub>SPECT</sub> are both indispensable imaging techniques to study patients with suspected PE.

Diagnosis of PE is a major clinical problem. The crucial dilemma is that the ideal method of diagnosis, i.e. V/P<sub>SPECT</sub> is often not available. Bearing in mind its superiority from a clinical point of view and its cost/effectiveness, V/P<sub>SPECT</sub> should be the method of choice for the detection of PE (Bajc et al. 2010). Accordingly, it is our duty to encourage the adoption of V/P<sub>SPECT</sub> as widely as possible. However, in its absence, MDCT is likely to continue to be used as a diagnostic tool for want of the superior alternative. From that point of view, diagnosis of PE is also a very important methodological issue.

Published on : Mon, 28 Feb 2011