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A/Prof C Rajasoorya, Editor
Singapore Medical Journal
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Cover Picture:
2-D Echo picture showing the typical 'windsock' appearance of an aneurysm of the sinus of valsalva.
*(Refer to page 473-476)*

Editorial

# Non-Invasive Tests for Acute Pulmonary Embolism: What are the Real Advances?

**T K Lim**

Results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) were published in 1990[1]. This is a benchmark study which sets the standards for the formal validation of diagnostic tests in acute pulmonary embolism (PE)[1,2]. Following publication of this study, radionuclide ventilation-perfusion lung (V/Q) scans became widely adopted as the first line tests for patients suspected of PE. However, in the past decade, because of the limitations associated with radionuclide lung scanning and advances in imaging techniques, a number of new non-invasive tests for the diagnosis of PE have been developed. One of these new tests, spiral computer tomographic (CT) pulmonary angiography, is the subject of two articles in this issue of the SMJ[3,4].

The main limitation of V/Q scans is the high proportion of non-diagnostic studies. In the original PIOPED series, 39% of patients were reported as having intermediate probability for PE and 73% either intermediate or low probability[1]. Even low probability lung scans may be considered non-diagnostic since, in the PIOPED study, the incidence of PE in this group of patients was 13.5%[1]. Wong et al reported an incidence of 14% for V/Q scans with intermediate probability of PE[3]. This relatively low incidence of non-diagnostic lung scans may have resulted from variations in patient selection or more likely, revised V/Q scan reporting criteria used by radiologists who avoid giving equivocal comments. This is because failure to deliver a definitive result would lead, in most patients, to further testing. In clinically stable patients with non-diagnostic lung scans, non-invasive examination of the lower limbs either with ultrasound or impedance plethysmography to confirm deep vein thrombosis is the standard approach[5]. Thus, in the patients described by Wong et al, ultrasound examination of the leg was the most common second line test[3]. Urgent pulmonary angiography is usually recommended in hypotensive or hypoxic patients with uncertain diagnosis[5]. Pulmonary angiography may also be needed for a definitive diagnosis following negative leg examination[5]. In the case series from the Singapore General Hospital, pulmonary angiography was performed only in one patient following a non-diagnostic lung scan[3]. By contrast, the pulmonary vasculature was imaged by spiral CT in 25 patients[3]. Spiral CT examination of the pulmonary arteries has also been evaluated as an alternative to V/Q scans in the initial work up of suspected acute PE[6-9]. The ascendancy of spiral CT as a first choice imaging technique to detect PE is illustrated in the report by Lingamanaicker et al, who used it as the definitive test for their patients[4].

The new non-invasive tests for the diagnosis of acute PE which have undergone evaluation in recent years include plasma D-dimer assay, magnetic resonance imaging, echocardiography and spiral (helical) CT. However, none of these studies match the rigorous standards of the

**Respiratory Medicine**
**National University Hospital**
**Singapore 119074**

T K Lim, MBBS, MMed, FRCP
Head
Tel: (65) 772 4367
Fax: (65) 779 4112
Email: mdclimtk@nus.edu.sg

PIOPED project. Thus, precise and confident recommendations for the use of these techniques in the routine diagnosis of acute PE cannot be made at the moment[5]. Nevertheless, while we await the completion of large, prospective multi-centre trials, many of these tests have entered the realm of everyday clinical practice in the "real world". The test which has generated the most interest and which is likely to yield the best added value is the spiral CT.

The reported sensitivity of spiral CT for PE, which ranges from 53% to 100%, and the specificity, which ranges from 81% to 100%, have been derived mostly from small single centre studies[5,9]. As a result, experts who performed systematic analyses and clinical guidelines committees have failed to endorse the use of spiral CT in the initial work up of patients suspected of acute PE[5,9]. The role of spiral CT has also been evaluated in decision models comparing cost-effectiveness of different diagnostic and management strategies for suspected acute PE. However, these computer generated models do not produce consistent results regarding the role of spiral CT[10-12].

One important advantage of the spiral CT over that of the standard tests such as lung scan and leg examination is that CT examination is a polyvalent diagnostic technique while the other two tests have been designed to detect only thrombo-embolic disease. The versatility of the spiral CT examination is underestimated in studies which only ask the question "does the patient have acute PE?" rather than "why is the patient sick?" Two-thirds to three-quarters of patients suspected of acute PE actually have an anternative diagnosis. So that, while it is important to make an accurate diagnosis of PE, it is equally, if not even more important, to make a specific alternative diagnosis in the majority of patients who do not have acute PE. Recent prospective studies which examined the overall diagnostic yield in patients suspected of PE showed consistently that spiral CT, when used as first choice test in comparison with lung scanning, gives a higher proportion of definitive diagnosis[13-15]. However, because of its variable sensitivity for PE, the spiral CT should not be the only test employed[16]. The best outcome is achieved when the spiral CT is used in conjunction with other non-invasive tests in a systematic sequential manner[17].

*Even low probability lung scans may be considered non-diagnostic since, in the PIOPED study, the incidence of PE in this group of patients was 13.5%.*

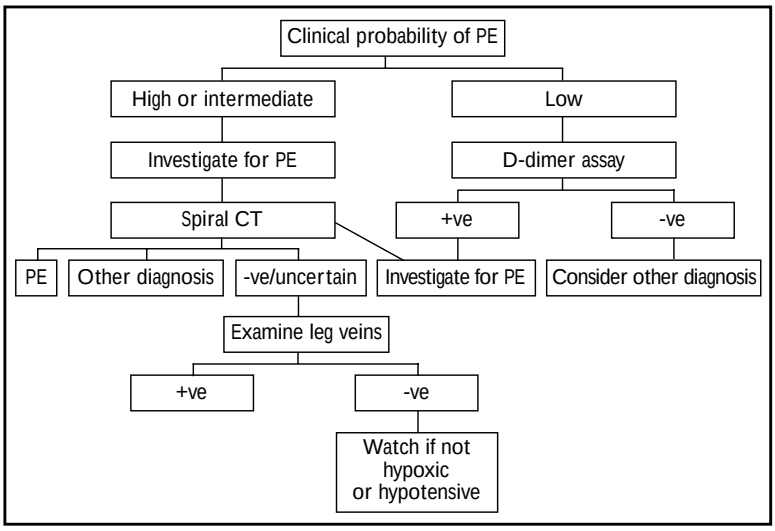
Results of echocardiographic examination were described in five out of six patients by Lingamanaicker et al[4]. In the context of suspected acute PE, echocardiography cannot be recommended as a primary diagnostic test[5]. It is insensitive in the detection of blood clots in the pulmonary artery and right heart dysfunction is common to many conditions which can be confused with acute PE. Evidence of right heart dysfunction seemed to have provided the indication for thrombolytic therapy in at least four of their patients (all six patients either received or were offered thrombolytic therapy). While thrombolytic agents are recommended treatment for patients with massive acute PE who present with shock, this was not the case in the patients described by Lingamanaicker et al[4]. The role of thrombolytic therapy in haemodynamically stable patients with acute PE and right ventricular dysfunction is debatable[5]. Several retrospective studies report conflicting results and, in the light of recent evidence showing higher rates of severe bleeding with thrombolysis, expert reviewers are calling for large-scale prospective studies[18,19].

Another non-invasive test for acute PE which is under evaluation is the plasma D-dimer assay[20]. Several studies have shown that further work up for PE can be avoided safely in low risk patients with a negative D-dimer assay[21-24]. Rapid, bedside D-dimer assays which are also reliable

and validated should be available in the near future. Low-risk patients can be identified with either a measurement of alveolar dead space (which requires a calculation based upon arterial blood and end tidal breath analysis) or even simpler, a PE risk model from basic clinical information[21-24].

With further advances, we can anticipate that, in the near future, the standard approach for patients suspected of acute PE will be a series of sequential non-invasive tests guided by an estimate of clinical pre-test probability and along the lines of the algorithm outlined in Fig. 1. SMJ

**Fig. 1** Suspected pulmonary embolism.




*The versatility of the spiral CT examination is underestimated in studies which only ask the question "does the patient have acute PE?" rather than "why is the patient sick?*

## REFERENCES


1. PIOPED Investigators. Value of the ventilation-perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). JAMA 1990; 263:2753-9.
2. Miniati M, Pistolesi M, Marini C, Di Ricco G, Formichi B, Prediletto R, Allescia G, Tonelli L, Sostman HD, Giuntini C. Value of perfusion lung scan in the diagnosis of pulmonary embolism: results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Am J Respir Crit Care Med 1996; 154:1387-93.
3. Wong WY, Ng DCE, Ang ES, Goh ASW, Sundram FX. Intermediate probability lung scans (IPLS): retrospective review of 82 cases. Singapore Med J 2001; 42(10):450-4.
4. Lingamanaicker J, Mukherjee JJ, Fock KM, Khoo TK. The role of spiral computed tomogram in the diagnosis of pulmonary embolism. Singapore Med J 2001; 42(10):455-9.
5. American Thoracic Society. The diagnostic approach to acute venous thromboembolism clinical practice guideline. Am J Respir Crit Care Med 1999; 160:1043-66.
6. Remy-Jardin M, Remy J, Deschildre F, Artaud D, Beregi JP, Hossein-Foucher C, Marchandise X, Duhamel A. Diagnosis of pulmonary embolism with spiral CT: comparison with pulmonary angiography and scintigraphy. Radiology. 1996; 200:699-706.
7. Kim KI, Muller NL, Mayo JR. Clinically suspected pulmonary embolism: utility of spiral CT. Radiology. 1999; 210:693-7.
8. Holbert JM, Costello P, Federle MP. Role of spiral computed tomography in the diagnosis of pulmonary embolism. Ann Emerg Med. 1999; 33:520-8.
9. Bates SM, Ginsberg JS. Helical computer tomography and the diagnosis of pulmonary embolism. Ann Intern Med 2000; 132:240-2.
10. van Erkel AR, van den Hout WB, Pattynama PM. International differences in health care costs in Europe and the United States: Do these affect the cost-effectiveness of diagnostic strategies for pulmonary embolism? Eur Radiol 1999; 9:1926-31.
11. Hull RD, Pineo GF, Stein PD, Mah AF, Butcher MS. Cost-effectiveness of currently accepted strategies for pulmonary embolism diagnosis. Semin Thromb Hemost 2001; 27:15-23.
12. Paterson D, Schwartzman I, K Strategies incorporating spiral CT for the diagnosis of acute pulmonary embolism: a cost-effectiveness analysis. Chest 2001; 119:1791-800.
13. Mayo JR, Remy-Jardin M, Muller NL, Remy J, Worsley DF, Hossein-Foucher C, Kwong JS, Brown MJ. Pulmonary embolism: prospective comparison of spiral CT with ventilation-perfusion scintigraphy. Radiology 1997; 205:447-52.
14. Cross JJ, Kemp PM, Walsh CG, Flower CD, Dixon AK. A randomised trial of spiral CT and ventilation perfusion scintigraphy for the diagnosis of pulmonary embolism. Clin Radiol 1998; 53:177-82.

15. Wille KM, Ball JA, Nath H. Safety of helical chest CT in the evaluation of acute pulmonary embolism in a randomised prospective outcome based trial. Am J Respir Crit Care Med 2000; 161:D14.
16. Perrier A, Howarth N, Didier D, Loubeyre P, Unger P-F, de Moerloose P, Solsman D, Junod AM, Bounameaux H. Performance of helical computer tomography in unselected out patients with suspected pulmonary embolism. Ann Int Med 2001; 135:88-97.
17. Lorut C, Ghossains M, Horellou MH, Achkar A, Fretault J, Laaban JP. A noninvasive diagnostic strategy including spiral computed tomography in patients with suspected pulmonary embolism. Am J Respir Crit Care Med 2000; 162:1413-8.
18. Hamel E, Pacouret G, Vincentelli D, Forissier JF, Peycher P, Pottier JM, Charbonnier B. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. Chest 2001; 120:120-5.
19. Davidson BL, Lensing AW. Should echocardiography of the right ventricle help determine who receives thrombolysis for pulmonary embolism? Chest 2001; 120:6-8.
20. Quinn DA, Fogel RB, Smith CD, Laposata M, Taylor Thompson B, Johnson SM, Waltman AC, Hales CA. D-dimers in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med 1999; 159:1445-9.
21. Kline JA, Israel EG, Michelson EA, O Neil BJ, Plewa MC, Portelli DC. Diagnostic accuracy of a bedside D-dimer assay and alveolar dead-space measurement for rapid exclusion of pulmonary embolism: a multicenter study. JAMA 2001; (14)285:761-8.
22. Rodger MA, Jones G, Rasuli P, Raymond F, Djunaedi H, Bredeson CN, Wells PS. Steady-state end-tidal alveolar dead space fraction and D-dimer: bedside tests to exclude pulmonary embolism. Chest 2001; 120:115-9.
23. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, Forgie M, Kovacs G, Ward J, Kovacs MJ. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. Ann Int Med 2001; 135:98-107.
24. Cocci F, Monti S, Bauleo C, Dainelli A, Scoscia E, Catapano G, Marini C, Di Ricci G, Pistolesi M, Miniati M. Value of combined D-dimer test and clinical probability in the exclusion of pulmonary embolism in inpatients. Am J Respir Crit Care Med 2000; 161D44.

## ERRATUM

In the article "MRI of the Hypothalamus and Pituitary gland in Patients with Hyperprolactinaemia Following Radiotherapy for Nasopharyngeal Carcinoma" published in Vol 42 issue 9 September 2001, the order of authors should be K Y Lau, W M Sze, A W M Lee, T K Yau, W T Fung, P O Chan.

We are sorry for the error.

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