

Review article

Venous thromboembolic disease

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Abstract. The advent of spiral CT has encouraged investigation into the diagnosis of venous thromboembolic disease. It has also exposed the limitations of prior methods of investigation and raised questions as to the significance of small pulmonary emboli. This article discusses this new technique, the clinical detection of venous thromboembolic disease and possible current and future strategies in diagnosis.

Introduction

The frequency of patients presenting with pulmonary embolic disease (PED) associated with deep vein thrombus (DVT), and the occurrence of PED following propagation of calf vein thrombus, provide confirmatory evidence that they are part of the same disease process, venous thromboembolic disease (VTED) [1, 2]. The morbidity and mortality of untreated VTED, coupled with difficulty in clinical diagnosis, is responsible for the large numbers of patients referred for investigation. The difficulty in diagnosis is confirmed by autopsy evidence that, despite heightened clinical awareness and the availability of new tests, there has been no decrease in the incidence of VTED over the last 30 years [3] and that a prior embolic episode, with organized pulmonary artery thrombus, is present in 50% of patients dying from the disease [4].

Difficulty in diagnosis is compounded by differences in the significance of PED in various patient groups and the effects of different sized emboli in these groups [5]. More than 50% of the cross-sectional area of the pulmonary vascular bed must be occluded before a significant change in pulmonary artery pressure and cardiac output occurs in animal studies [6–8]. These data, plus the known physiological effects which follow pneumonectomy or unilateral pulmonary artery occlusion, enable a prediction to be made of the effect of small and large emboli in most patients [9]. The patients in whom PED is most difficult to diagnose are those with an already compromised cardiopulmonary reserve; it is in these patients that small, subsegmental emboli may have the most life-threatening consequences and yet be difficult to confirm. Recent reports on spiral computed tomography and PED have raised questions as to the size of

emboli detected both by this new technique [10, 11] and the “gold standard” test of pulmonary angiography (PA) [12, 13]. The clinical significance of small, difficult to detect, subsegmental emboli is now one of the most important unresolved issues in VTED.

The importance of a correct diagnosis lies not only in preventing further and possibly more significant embolic disease, but also in not submitting patients unnecessarily to the risks of anticoagulant treatment. A broad generalization for risk of haemorrhage in patients treated with continuous intravenous or subcutaneous unfractionated heparin is 5% morbidity and 1% mortality; for treatment with warfarin there is a 0.9% morbidity and 0.1% mortality [14].

Methods of investigation

Deep vein thrombosis

The radiologist now has a well stocked armamentarium for diagnosing VTED. Further help has come from the recent development of the D-dimer blood test and clinical risk stratification. D-dimer, a specific degradation product of cross-linked fibrin, should be elevated in patients with thrombus. D-dimer may be measured in many different ways, the different assays having different sensitivities, specificities and turnaround time [15]. An elevated D-dimer level is of less value because of low specificity; however, a low level, especially in combination with a low clinical suspicion of VTED, may obviate the need for further testing. In a recent report, D-dimer measured by a whole blood agglutination assay technique had a sensitivity of 93% for proximal DVT and 70% for calf DVT, with an overall specificity of 77% and negative predictive value of 98% for proximal DVT [16]. Further studies are required to confirm these findings in a more heterogeneous patient group with co-morbid pathology.

Although there has been little progress in the

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clinical selection of patients for investigation of PED or DVT, a recent report suggests that it is possible to stratify patients into risk groups [17]. The presence of pre-morbid risk factors, such as cancer and recent bedrest, in conjunction with clinical features, such as localized tenderness along the distribution of the deep venous system and calf swelling, was used to divide patients into high probability, moderate and low probability groups. In 529 patients, this model predicted the prevalence of DVT as 85% in the high pre-test probability category, 33% in the moderate and 5% in the low [17].

Ultrasound (US) has a sensitivity of more than 90%, and almost 100% specificity in the diagnosis of femoral and popliteal vein thrombosis, but is less sensitive in assessing calf vein thrombosis [18–20]. The risk in non-treatment of isolated calf vein DVT relates to propagation, with the inherent risk of PED if this occurs. Concerns that post-phlebotic venous insufficiency will develop in calf vein DVT which has not been treated with anticoagulation now appear to be unfounded, provided the pre-symptomatic leg veins are normal [21]. Up to 20% of calf vein thrombus propagates into the popliteal and femoral veins, and propagation occurs prior to embolization [21–23]. In the context of clinical risk stratification, it would therefore seem reasonable to withhold anticoagulant treatment in patients suspected of DVT if the femoral and popliteal veins are normal and the patient has a low pre-test probability of DVT. If the US examination is negative in this patient group then no further investigation or treatment is required. However, if the pre-test probability is intermediate or high and the US examination is negative, then serial scanning of the popliteal fossa to look for propagation is warranted [24]. Clinical confidence in this approach may be strengthened if D-dimer is included in the diagnostic algorithm. A low D-dimer, low pre-test probability and a negative US would then make the risk to the patient of DVT insignificant. In some departments, serial US may be logistically impractical and venography is then an acceptable alternative.

Although currently not feasible due to inadequate resources, magnetic resonance (MR) venography may eventually be the radiological examination of choice. MR has the added advantages of a high degree of accuracy in assessing the pelvic veins and the ability to demonstrate a non-vascular cause for pain in the calf [25]. In comparison with contrast venography, MR venography was 100% specific and 95% sensitive in the detection of pelvic vein thrombosis and 100% sensitive and specific in the detection of DVT in the thigh, while in the calf the sensitivity was 87% with a specificity of 97% [25]. MRI may play a more significant role in VTED when used to assess the presence of PED.

Pulmonary embolic disease

Nuclear medicine is currently the mainstay of diagnosis of PED. Reports from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) have clarified the value of ventilation/perfusion (VQ) scans in the investigation of PED [13, 26]. The majority of patients who are referred for VQ scanning in order to confirm or exclude pulmonary embolism fell into the indeterminate (intermediate) category (39%) or low probability category (34%); only a minority had high (13%) or normal/very low probability (14%) scans. The positive predictive value of a high probability scan was 91%, falling to 74% in patients with a previous episode of PED. The value of prior clinical probability assessment was confirmed, a high clinical pre-test probability proving correct in 68% of cases and a low pre-test probability correct in 91%. Unfortunately, although not surprisingly, the pre-test probability was non-committal in 64% of patients. Combining clinical pre-test probabilities and VQ scans was the most accurate means of predicting the presence of PED; if both were high probability then 96% of patients had PED, and if both were low then only 4% had PED. The contribution of nuclear medicine to the diagnosis of PED as demonstrated by PIOPED was summarised in the final sentence of the report “the scan combined with clinical assessment permitted a non-invasive diagnosis or exclusion of acute pulmonary embolism for a minority of patients” [13]. However, support for nuclear medicine in the investigation of PED has been bolstered by the recent Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISAPED) [27]. This has cast doubt on both the apparent lack of accuracy of nuclear medicine in the diagnosis of PED as reported by PIOPED and the need for ventilation imaging in addition to perfusion scintigraphy. A combination of clinical assessment and perfusion scanning permitted the diagnosis or exclusion of pulmonary embolism in 76% of patients with abnormal perfusion scans and an accuracy of 97%. The authors attribute the success of this method to a marked simplification of perfusion scan criteria resulting in only two categories of abnormal scan: PE+ (abnormal compatible with PE) and PE– (abnormal not compatible with PE).

Unfortunately, the picture in clinical practice remains unclear, with the usefulness of the VQ scan in confirming or excluding the diagnosis of pulmonary embolism depending on the population studied. In the outpatient setting, where the incidence of prior cardiopulmonary disease is low, chest radiographic abnormalities are unusual and the prevalence of PED is low, a high proportion of normal scans and fewer indeterminate scans

would be expected, and this is the case [28]. In contrast, in the PIOPED study 90% of VQ scans were non-diagnostic in patients with chronic obstructive pulmonary disease [13].

Despite PIOPED, many clinicians base their decision to treat or withhold therapy on VQ scans that fall into the intermediate or low categories, and sometimes anticoagulate patients with low probability or normal scans without further investigation [29]. This may reflect a lack of faith in a test giving such a wide range of likelihood of diagnosis, perhaps compounded by inconsistencies in methods of reporting. It has been suggested that VQ scans are reported making use of the PIOPED data by incorporating pre-test and test probability odds [30], for example, "with a low pre-test probability of PE and a low probability VQ scan, the odds of a PE are 20:1 against". Whether this is helpful or a cause for further clinical confusion remains to be seen.

The advent of neural networks may produce consistency of interpretation and reporting in the future [31]. Neural networks are computer programs designed to imitate the human brain. They consist of non-linear computing elements organized in several multiconnected layers. The strengths of these connections vary, depending upon the input to the computer and its value in enabling a correct diagnosis during programming. The computer will enable either a correct diagnosis or "best guess" to be given in the same way as practising radiologists. VQ scanning lends itself to assessment by neural nets due to the limited data required for input. In some settings neural networks have outperformed experienced observers in the interpretation of VQ scans [32].

Until recently, there has been general agreement that patients with intermediate or low probability VQ scans should undergo pulmonary angiography. Despite morbidity rates as low as 1–5% and mortality rates of only 0.1–0.5% [33], PA is seldom performed as a means of further investigating patients with "non-diagnostic" VQ scans. The failure to perform PA in such circumstances may in fact be appropriate, a recent report suggesting that serial leg ultrasound or impedance plethysmography (IPG) is a safe means of investigation for patients with non-diagnostic scans and normal cardiopulmonary reserve [24]. Hull et al prospectively investigated 1564 consecutive patients referred for investigation of PED. Only 12 (1.9%) of 627 patients with normal cardiopulmonary function and non-diagnostic VQ scans, with no evidence of proximal vein thrombosis on serial IPG (although US would now be a better test [22, 34]), developed VTED on follow-up when anticoagulation was withheld. Eight of 145 patients (5.5%) with high probability scans treated with anticoagulation had further episodes of VTED on follow-

up. The exclusion of patients with abnormal cardiopulmonary reserve from the study confirms the need for a non-invasive test in such patients, and in those with an abnormal chest radiograph, resulting in considerable interest in the use of spiral CT and MR [35–37].

The recent development of CT scanners capable of fast data acquisition and volume datasets has encouraged research into the value of CT in the investigation of PED. The initial optimism about sensitivity and specificity has been tempered by more careful analysis of its limitations and reasons for error. All reports stress the need for meticulous scanning technique, with the possible requirement of a test bolus of contrast medium to optimize scan start times, and scanning in a cranio-caudal direction to ensure adequate opacification of upper lobe arteries and avoid partial opacification of pulmonary veins. Knowledge of hilar anatomy and intersegmental nodal sites, with reformatting in cases of doubt, all improve diagnostic accuracy [38]. For details of scanning technique the reader is referred to a recent review [39].

Spiral CT demonstrates thromboemboli in main, lobar and segmental (4th order) vessels with a sensitivity and specificity of more than 90% [40, 41]. The accuracy of diagnosis falls if reliance is placed on the detection of emboli in subsegmental vessels. The reported number of patients presenting with isolated subsegmental emboli ranges from 0 to 36% [10, 11, 42, 43], and up to 75% of these emboli may not be detected by spiral CT scanning [10]. Before discarding spiral CT, the failure to detect subsegmental emboli must be taken in the context of the reliability of the previous "gold standard" test of PA in their detection, the presence of segmental or larger thrombus being detected in more than 90% and subsegmental emboli in only 66% of cases [13]. Isotope studies may be similarly assessed, with the PIOPED data revealing more than 90% reader agreement for high probability and normal VQ scans but only 70% and 75% agreement on low and intermediate probability scans, respectively [13]. The significance of smaller subsegmental emboli has become an important issue, particularly in view of the unchanging mortality from PED and the evidence of a prior embolic event at post-mortem. If it is assumed that subsegmental emboli may give rise to indeterminate or low probability scintigrams, then the study of Hull et al [24] suggests that provided there is no evidence of a thrombus within the proximal deep veins on serial testing then the inability to detect such emboli in patients without cardiopulmonary compromise may be unimportant. However, the importance of such emboli in patients with diminished cardiopulmonary reserve remains to be determined.

Although not infallible in the detection of

emboli, spiral CT has the additional advantage of assessing the pulmonary parenchyma as well as the vasculature of the lung. The importance of this factor was confirmed by a study in which 24 of 42 patients with non-diagnostic VQ scans had abnormalities other than PED which were likely to account for the patient's VQ scan defects [41]. The evidence from this study, coupled with the obvious inherent advantages of spiral CT in patients with an abnormal chest radiography, and the failure of VQ scanning in patients with compromised cardiorespiratory reserve, may in future lead most radiologists and clinicians to use spiral CT in these patient groups.

MRI has also been used as a research tool in the investigation of PED. Difficulties for MRI to overcome before it is of clinical value in PED include cardiac and respiratory motion, and difficulty in differentiating slow flow from thrombus. In addition, there are practical limitations such as the difficulty of placing very ill patients in MR scanners. Nevertheless, many of the difficulties with MRI may be offset by using different pulse sequences, slice thicknesses, imaging planes perpendicular to each other and cardiac gating.

Blood may give rise to a range of signal intensities in cardiac gated MR studies. With a spin echo (SE) sequence, flowing blood ideally produces little signal and appears dark (black blood). However, inflowing blood with previously unexcited protons may produce high signal at the entry slice(s). With gradient echo (GE) sequences, flowing blood produces high signal (white blood), but loss of signal may occur in areas of turbulence and non-uniform flow. Non-thrombosed blood may in either sequence produce signal expected from areas of thrombus [44]. The use of sequences in different planes and double SE acquisition often allows discrimination of thrombus from slow flow. Pre-saturation pulses in SE imaging may remove signal artefact at the entry slice(s). Ultrafast gradient echo techniques with intravenous gadolinium enable single breath-hold MRI of the pulmonary arteries, or imaging during gentle respiration [45, 46].

MRI has been compared with nuclear medicine studies and pulmonary angiography [46–48]. MRI appears reliable in the detection of emboli larger than 3 mm in size and down to the level of segmental vessels, and has a similar sensitivity but significantly greater specificity when compared with VQ scanning as a screening test [48].

The true value of MR pulmonary angiography will only be demonstrated when MR is more readily available and suitable for the majority of patients investigated for PE, *i.e.* those who are ill and have tachypnoea. Once these problems are overcome, the ability to assess both the pulmonary arteries and the venous system of the pelvis and

legs may result in MRI being the first line investigation in future.

D-dimer appears to have a useful role to play in suspected PE as well as in the investigation of DVT [49]. Again, due to low specificity, the potential value of this test is in exclusion of PE rather than in establishing the diagnosis of PE. In an outpatient setting, a normal plasma D-dimer concentration allowed the exclusion of PE in 29% of patients suspected of having PE. Withholding anticoagulation from these patients was associated with only a 1% risk of thromboembolic complications during a 3 month follow-up [49].

Conclusion

The past, present and future practices of investigating patients with suspected pulmonary emboli now seem to be very different. Current recommendations must take into account local availability of equipment and expertise. In the majority of centres, pulmonary angiography is effectively discounted from venous thromboembolic disease investigation and management. Currently, most patients suspected of having pulmonary embolic disease will undergo VQ scanning and may have a sufficiently diagnostic study to enable a treatment decision to be made. In patients with normal cardiopulmonary reserve, if the VQ scan is non-diagnostic, the patients should undergo serial ultrasound examinations of their femoral and popliteal veins. If serial US is impractical for purely logistic reasons, venography may be substituted. Patients suspected of having PED with an abnormal chest radiograph or significant cardiopulmonary compromise could have spiral CT as their first investigation with US examination of their leg veins if negative. However, before spiral CT is included wholeheartedly in the diagnostic algorithm, its accuracy should be tested in multicentre controlled trials, looking particularly at outcome in untreated patients with negative CT scans [50–52]. As spiral CT becomes more readily available and if future reports confirm its usefulness in PED, the value of isotope studies may be further questioned. It is conceivable that, in all but those patients with a low clinical pre-test probability for PED, spiral CT will become the first line of investigation.

In the distant future, patients may forego VQ scanning and spiral CT and move straight to MRI. When MRI of the thorax is negative or equivocal, then they will undergo MRI of the pelvic and leg veins. Those patients not suitable for MRI will probably undergo spiral CT of the chest and, if this is negative, imaging of their leg veins. The role of D-dimer now and in the future is less clear in PED, with D-dimer possibly being used as an

adjunct to VQ scans, particularly in helping decide on the requirement for further imaging.

References

- Kakkar VV, Flanc C, Howe CT, Clarke MB. Natural history of postoperative deep-vein thrombosis. *Lancet* 1969;2:230-2.
- Grant BJB. Noninvasive tests for venous thromboembolism. *Am J Respir Crit Care Med* 1994;149:1044-7.
- Lindblad B, Sternby NH, Bergqvist D. Incidence of venous thromboembolism verified by necropsy over 30 years. *Br Med J* 1991;302:709-11.
- Morgenthaler TI, Ryu JH. Clinical characteristics of fatal pulmonary embolism in a referral hospital. *Mayo Clin Proc* 1995;70:417-24.
- Gorham LW. A study of pulmonary embolism. *Arch Int Med* 1961;108:189-207.
- Haggart GE, Walker AM. The physiology of pulmonary embolism as disclosed by quantitative occlusion of the pulmonary artery. *Arch Surg* 1923;6:764-83.
- Steinberg B, Mundy CS. Experimental pulmonary embolism and infarction. *Arch Pathol* 1936;22:529-42.
- Gibbon JH, Churchill ED. The physiology of massive pulmonary embolism. An experimental study of the changes produced by obstruction to the flow of blood through the pulmonary artery and its lobar branches. *Ann Surg* 1936;104:811-22.
- Brandfonbrener M, Turino GM, Himmelstein A, Fishman AP. Effects of occlusion of one pulmonary artery on pulmonary circulation in man. *Fed. Proc* 1958;17:19.
- Goodman LR, Curtin JJ, Mewissen MW, et al. Detection of pulmonary embolism in patients with unresolved clinical and scintigraphic diagnosis: helical CT *versus* angiography. *AJR* 1995;164:1369-74.
- Van Rossum AB, Pattynama PMT, Ton ERTA, et al. Pulmonary embolism: validation of spiral CT angiography in 149 patients. *Radiology* 1996;201:467-70.
- Quinn MF, Lundell CJ, Klotz TA, et al. Reliability of selective pulmonary arteriography in the diagnosis of pulmonary embolism. *Radiology* 1987;149:469-71.
- The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *J Am Med Assoc* 1990;263:2753-9.
- Levine MN, Raskob G, Landefeld S, Hirsh J. Hemorrhagic complications of anticoagulant treatment. *Chest* 1995;108 (Suppl):276-90.
- Veitl M, Hamwi A, Kurtaran A, et al. Comparison of four rapid D-dimer tests for diagnosis of pulmonary embolism. *Thromb Res* 1996;82:399-407.
- Wells PS, Brill-Edwards P, Stevens P, et al. A novel and rapid whole-blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. *Circulation* 1995;91:2184-7.
- Wells PS, Hirsh J, Anderson DR, et al. Accuracy of clinical assessment of deep-vein thrombosis. *Lancet* 1995;345:1326-30.
- Cronan JJ, Dorfman GS, Scola FH, et al. Deep venous thrombosis: US assessment using vein compression. *Radiology* 1987;162:191-4.
- Lensing AWA, Prandoni P, Brandjes D, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med* 1989;320:342-5.
- Baxter GM, McKechnie S, Duffy P. Colour Doppler ultrasound in deep venous thrombosis: a comparison with venography. *Clin Radiol* 1990;42:32-6.
- Philbrick JT, Becker DM. Calf vein venous thrombosis. A wolf in sheep's clothing. *Arch Intern Med* 1988;148:2131-8.
- Heijboer H, Buller HR, Lensing AWA, et al. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. *N Engl J Med* 1993;329:1365-9.
- Ginsberg JS. Management of venous thromboembolism. *N Engl J Med* 1996;335:1816-28.
- Hull RD, Raskob GE, Ginsberg JS, et al. A noninvasive strategy for the treatment of patients with suspected pulmonary embolism. *Arch Intern Med* 1994;154:289-97.
- Evans AJ, Sostman HD, Knelson MH, et al. Detection of deep venous thrombosis: prospective comparison of MR imaging with contrast venography. *AJR* 1993;161:131-9.
- Gottschalk A, Sostman HD, Coleman RE, et al. Ventilation-perfusion scintigraphy in the PIOPED study. Part II. Evaluation of the scintigraphic criteria and interpretations. *J Nucl Med* 1993;34:1119-26.
- Miniati M, Pistolesi M, Marini C, et al. 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.
- Van Beek EJ, Buller HR, Brandjes DP, et al. Diagnosis of clinically suspected pulmonary embolism: a survey of current practice in a teaching hospital. *Neth J Med* 1994;44:50-5.
- Schluger N, Henschke C, King T, et al. Diagnosis of pulmonary embolism at a large teaching hospital. *J Thorac Imaging* 1994;9:180-4.
- Gray HW. Reporting of lung scans: the future beckons. *Nucl Med Commun* 1993;14:1-3.
- Boone JM. Neural networks at the crossroads. *Radiology* 1993;189:357-9.
- Tourassi GD, Floyd CE, Sostman HD, Coleman RE. Acute pulmonary embolism: artificial neural network approach for diagnosis. *Radiology* 1993;189:555-8.
- Perlmutter LM, Braun SD, Newman GE, et al. Pulmonary arteriography in the high-risk patient. *Radiology* 1987;162:187-9.
- Wells PS, Hirsh J, Anderson DR, et al. Comparison of the accuracy of impedance plethysmography and compression ultrasonography in outpatients with clinically suspected deep vein thrombosis. *Thromb Haemost* 1993;70:404-7.
- Smith R, Ellis K, Alderson PO. Role of chest radiography in predicting the extent of airway disease in patients with suspected pulmonary embolism. *Radiology* 1986;159:391-4.
- Goldberg SN, Palmer EL, Scott JA, Fisher R. Pulmonary embolism: prediction of the usefulness of initial ventilation-perfusion scanning with chest radiographic findings. *Radiology* 1994;193:801-5.
- Gefer WB, Hatabu H, Holland GA, et al. Pulmonary thromboembolism: recent developments in diagnosis with CT and MR imaging. *Radiology* 1995;197:561-74.

38. Remy-Jardin M, Remy J, Cauvain O, et al. Diagnosis of central pulmonary embolism with helical CT: role of two-dimensional multiplanar reformations. *AJR* 1995;165:1131–8.
39. Hansell DM. Spiral computed tomography and pulmonary embolism: current state. *Clin Radiol* 1997;52:575–81.
40. Remy-Jardin M, Remy J, Wattinne L, Giraud F. Central pulmonary thromboembolism: diagnosis with spiral volumetric CT with the single breath-hold technique—comparison with pulmonary angiography. *Radiology* 1992;185:381–7.
41. Van Rossum AB, Treurniet FEE, Kieft GJ, et al. Role of spiral volumetric computed tomographic scanning in the assessment of patients with clinical suspicion of pulmonary embolism and an abnormal ventilation/perfusion lung scan. *Thorax* 1996; 51:23–8.
42. Oser RF, Zuckerman DA, Gutierrez FR, Brink JA. Anatomic distribution of pulmonary emboli at pulmonary angiography: implications for cross-sectional imaging. *Radiology* 1996;199:31–5.
43. Robinson PJA. Ventilation–perfusion lung scanning and spiral computed tomography of the lungs: competing or complementary modalities. *Eur J Nucl Med* 1996;23:1547–53.
44. Miller SW, Holmvang G. Differentiation of slow flow from thrombus in thoracic magnetic resonance imaging, emphasizing phase images. *J Thorac Imaging* 1993;8:98–107.
45. Rubin GD, Herfkens RJ, Pelc NJ, et al. Single breath-hold pulmonary magnetic resonance angiography. *Invest Radiol* 1994;29:766–72.
46. Loubeyre P, Revel D, Douek P, et al. Dynamic contrast-enhanced MR angiography of pulmonary embolism: comparison with pulmonary angiography. *AJR* 1994;162:1035–9.
47. Grist TM, Sostman HD, Macfall JR, et al. Pulmonary angiography with MR imaging: preliminary clinical experience. *Radiology* 1993;189:523–30.
48. Erdman WA, Peshock RM, Redman HC, et al. Pulmonary embolism: comparison of MR images with radionuclide and angiographic studies. *Radiology* 1994;190:499–508.
49. Perrier A, Desmarais S, Goehring C, et al. D-dimer testing for suspected pulmonary embolism in outpatients. *Am J Respir Crit Care Med* 1997;156:492–6.
50. Sostman HD. Opinion response to acute pulmonary embolism: the role of computed tomographic imaging. *J Thorac Imaging* 1997;12:89–92.
51. Mayo JR. Opinion response to acute pulmonary embolism: the role of computed tomographic imaging. *J Thorac Imaging* 1997;12:95–7.
52. Gefter WB, Palevsky HI. Opinion response to acute pulmonary embolism: the role of computed tomographic imaging. *J Thorac Imaging* 1997;12:97–100.