

Original article

Feasibility, safety and clinical utility of angiography in patients with suspected pulmonary embolism

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Abstract. The purpose of our study was to assess feasibility, safety and clinical utility of selective pulmonary angiography in patients with suspected pulmonary embolism and a nondiagnostic lung scan. The design was a prospective, descriptive study. The subjects were consecutive patients with clinically suspected pulmonary embolism and a nondiagnostic lung scintigram in whom pulmonary angiography was considered. Angiography was withheld in cases of manifest heart failure, renal failure, mean pulmonary artery pressure above 40 mmHg, or if there were compelling clinical reasons. All patients were followed-up for 6 months. The outcome measures were successful angiography, morbidity, mortality and recurrent pulmonary embolism in patients with normal angiogram in whom anticoagulants were withheld during 6 months of follow-up. Of 487 patients, 196 (40%) had nondiagnostic lung scan findings. In 46 patients (23%) pulmonary angiography was withheld. Pulmonary embolism was excluded in 105 patients (70%), and proven in 40 (27%) patients. In 5 (3%) patients the angiogram was inadequate for interpretation. No fatal complications were encountered [95% confidence interval (CI) 0–2.4%]. Nonfatal complications occurred in 3 patients (2%; 95% CI 0.4–6.0%); all recovered spontaneously. None of 105 patients with a normal angiogram returned with thromboembolism during follow-up (0%; 95% CI 0–3.4%). Pulmonary angiography is safe, rules out pulmonary embolism in two thirds of patients with a nondiagnostic lung scan and can be performed in almost 80% of these patients. It is safe to withhold long-term anticoagulants if a normal angiogram is obtained in this subgroup of patients with clinically suspected pulmonary embolism.

Key words: Pulmonary embolism – Angiography – Utility – Safety

Introduction

Several studies have shown that of all patients with clinically suspected pulmonary embolism who undergo lung scintigraphy, approximately 50% ultimately require pulmonary angiography to have this diagnosis confirmed or rejected [1–5]. The existing reluctance among physicians to perform angiography is understandable in view of the fear of complications [6–8], the inability to perform the procedure in a considerable number of patients [9] and the unavailability of equipment and experience in many hospitals. Therefore, noninvasive diagnostic tests would be preferred and are being investigated [5, 10]. However, no optimal diagnostic strategy is currently available which omits the need for angiography [3, 11, 12].

Although the introduction of safer contrast media and improvements in the radiological techniques have enhanced the safety of pulmonary angiography [8, 13], in our hospitals we had limited experience, with less than 10% of patients with nondiagnostic lung scan results being referred for angiography before the start of this study [14].

Several questions surround the implementation and routine use of pulmonary angiography in patients with clinically suspected pulmonary embolism and nondiagnostic lung scan findings such as its feasibility, complication rate, prevalence of pulmonary embolism and the clinical validity of a normal angiogram. The present report addresses these questions.

Materials and methods

Patients

From 1 April 1991 to 1 April 1994, all consecutive patients who presented to two large teaching hospitals with clinically suspected pulmonary embolism were eligible for the study. Reasons for exclusion were: age younger than 18 years, confirmed pregnancy, known al-

lergy to iodine-containing contrast media, patients on respiratory support or if patients received full-dose anticoagulants for more than 48 h. Within 24 h of inclusion all patients underwent perfusion lung scintigraphy, using technetium-99m-labelled macro aggregates of albumin (Sorin Biomedica SpA, Vercelli, Italy), which was followed by ventilation scintigraphy, using $^{81\text{m}}\text{Krypton}$ gas (Cygne bv, Eindhoven, The Netherlands), if perfusion defects were seen. A classification of normal, high probability (defined as one or more segmental perfusion defects with locally normal ventilation) or nondiagnostic was used [1, 2, 15]. In all patients with nondiagnostic lung scan findings, compression ultrasonography and pulmonary angiography was intended to be performed within 24 h of obtaining the initial perfusion lung scan, i.e. within 48 h of inclusion into the study.

Written informed consent was obtained from all patients and the study was approved by the respective Institutional Review Boards of both hospitals.

Compression ultrasonography

In all patients compression ultrasonography was performed according to a previously described technique [16]. The presence of deep vein thrombosis was considered proven if the proximal leg veins showed noncompressibility. The calf veins were not included in the examination. The results were only taken into consideration in patients in whom pulmonary angiography could not be obtained and for diagnostic purposes during follow-up.

Pulmonary angiography technique

Selective pulmonary angiography was performed using a modified Seldinger approach. Patients were monitored by automated pulse/blood pressure recording at 1-min intervals, and electrocardiography if required. After local anaesthetic of the groin, the femoral vein was identified, and a 6.7-F braided, multiple side-holed Grollman-type pigtail catheter was introduced. Using an angled type guide wire with a flexible 3-cm tip (Terumo's, Hertogenbosch, the Netherlands), the catheter was positioned selectively in the pulmonary artery or, if required, a lobar branch according to the areas of absent perfusion on the lung scan. Subsequently, the mean pulmonary artery pressure (PAP) was measured to identify patients with pulmonary hypertension. If a mean PAP of greater than 40 mmHg existed, no contrast was injected for fear of complications [7].

Using only low-osmolar contrast media (iohexol, Omnipaque 300, Nycomed, Haarlem, the Netherlands; or ioxaglate, Hexabrix 320, Guerbet, Gorinchem, the Netherlands), 40 ml of contrast medium was injected in 2 s at a pressure of 600 pounds per square inch (42 kg/cm²) with a linear rise of 0.5 s. The amount of contrast medium was reduced to 30 ml in 2 s if the catheter was positioned in a lobar branch.

The patient was initially placed in a neutral anteroposterior position. The second series was obtained with

the X-ray tube tilted to obtain oblique views. The series were obtained with three images per second for 2 s, followed by 2 images per second for 2 s, followed by one image per second for 5 s. Initially, this was done using conventional films, but later the images were obtained using a digital subtraction technique with the aid of a Siemens Polytron Plus system (Siemens, Den Haag, the Netherlands), which allowed digital processing of X-ray images.

Criteria for the interpretation of the angiogram have been described previously [1, 2, 17]. Only a filling defect in at least two projections or an acute cutoff of branches with a diameter greater than 2 mm were accepted as proof of pulmonary embolism. All angiograms were read immediately by an experienced radiologist.

Follow-up

All patients were followed-up for a minimum of 6 months. After 3 months, the patient visited the outpatient clinic, and after 6 months, a telephone call was made to the patient by a physician. Therapeutic decisions were based on the results of the pulmonary angiogram, i.e. in patients with normal results anticoagulants were withheld or withdrawn, whereas patients with angiographically diagnosed pulmonary emboli were treated with heparin for a minimum of 7 days, followed by oral anticoagulants for a minimum of 3 months. In patients in whom angiography could not be performed and in whom compression ultrasonography was normal, the management was based on clinical grounds.

In patients with recurrent clinical signs of pulmonary embolism, an objective diagnosis was sought, using lung scintigraphy, ultrasonography of the leg veins and/or angiography. In patients who died during follow-up, pulmonary embolism was classified as the main cause of death, contributing to the death of the patient, or classified as unlikely to be related to death. This classification was based on clinical grounds, new diagnostic findings, postmortem investigations and/or the conclusion of the attending physician.

Analysis

The main outcome measures of the study were feasibility of performing angiography, mortality and morbidity as a direct result of angiography (the latter defined as bleeding complications requiring blood transfusion, heart rhythm disorders requiring therapeutic intervention, perforation or extravasation of contrast medium and allergic reactions to contrast media). Furthermore, the clinical outcome at follow-up was assessed with regard to thromboembolic complications (fatal and nonfatal).

Results

A total of 487 consecutive patients were included in the study: 278 females and 209 males with a mean age of 56.9 ± 17.8 years (range 18–92 years). Lung scintigraphy was normal in 138 (28 %) patients, whereas a high-probability lung scan was obtained in 153 (31 %) patients. The remaining 196 (41 %) patients with a nondiagnostic-lung-scan result are the focus of this analysis.

Of these 196 patients in whom pulmonary angiography was intended to be performed, 150 were able to undergo the procedure. In 46 (23 %) patients angiography was not feasible for reasons that are described in Table 1. Eight patients refused to undergo the procedure and 1 patient died of a myocardial infarction prior to angiography, which was considered to be too high a risk in the remaining patients, due to manifest right-sided heart failure, myocarditis, pulmonary hypertension and other conditions. Ultrasonography showed proximal deep vein thrombosis in 4 of these patients.

In the 150 patients who underwent pulmonary angiography, no mortality was encountered (0 %; 95 % CI 0–2.4 %). One major complication was seen in a patient who suffered a dissection of the pulmonary artery (pulmonary emboli were also demonstrated, and the patient was treated with heparin, which was commenced 4 h after angiography followed by 3 months of oral anticoagulants without further complications), whereas minor complications were seen in 2 patients, in whom a limited extravasation of contrast media occurred, for an overall morbidity rate of 2.0 % (95 % CI 0.4–6.0 %).

Pulmonary angiography showed pulmonary embolism in 40 (27 %) patients, and these patients were subsequently treated with heparin and long-term oral anticoagulants. In 105 (70 %) patients anticoagulants were withheld after a normal angiogram was obtained. Finally, the angiogram was inadequate for interpretation in the remaining 5 (3 %) patients. None of the patients with a normal angiogram showed abnormal findings on compression ultrasonography, whereas 4 of the 40 patients with proven pulmonary embolism showed non-compressibility of proximal deep leg veins.

During 6 months of follow-up, 19 patients, in whom a normal pulmonary angiogram was obtained, died. These patients are described briefly in Table 2. Although post-mortem investigations were performed in only 3 patients, none of the patients were thought to have died as a result of pulmonary embolism. Furthermore, no patients in whom anticoagulants were withheld on the basis of a normal angiogram presented with clinical signs or symptoms suggesting pulmonary embolism.

Discussion

Lung scintigraphy is unable to adequately diagnose or exclude pulmonary embolism in approximately 40 % of all patients who are suspected of this disorder. At present, pulmonary angiography, the gold standard for the diagnosis of pulmonary embolism, would be required in these patients. This study showed that despite limited

Table 1. Reasons for failure to perform pulmonary angiography

Reason	n
Manifest heart failure	12
Refused by patient	8
Pulmonary hypertension (mean PAP > 40 mmHg)	7
Severe dyspnea	6
Thrombocytopenia (less than $20 \times 10^9/l$)	4
Cardiac contraindications ^a	4
Renal failure	3
Sickle cell crisis	1
Died before angiography could be performed	1
Total	46

^a Cardiomyopathy (1), myocarditis (1), suspected myocardial infarction (1) and severe multiple heart valve disease (1)

Table 2. Patients with clinically suspected pulmonary embolism and a normal angiogram in whom anticoagulants were withheld who died during 6 months of follow-up. AIDS acquired immunodeficiency syndrome

	Age (years)	Days after angiography	Diagnosis
M	44	2	AIDS, <i>Pneumocystis carini</i> and toxoplasmosis ^a
M	22	30	Wilms' tumour (locally inoperable), untreatable pleuritis ^a
F	52	45	Chest wall sarcoma ^a
F	77	46	Metastatic vulva carcinoma ^a
M	70	48	Lung fibrosis; pulmonary hypertension ^a
F	39	75	Idiopathic pulmonary hypertension (mean PAP of 40 mm Hg); postmortem investigation: no pulmonary embolism
M	77	76	Emphysema; progressive respiratory failure ^a
F	69	85	Progressive respiratory failure ^a
F	52	86	Metastatic oesophagus carcinoma ^a
M	37	88	AIDS; postmortem investigation: no pulmonary embolism
F	64	90	Pericarditis carcinomatosa ^a
M	64	96	Emphysema; progressive respiratory failure ^a
F	45	100	Breast carcinoma; pleuritis carcinomatosa ^a
M	39	109	Metastatic Kaposi sarcoma, AIDS ^a
M	45	114	Septicaemia, AIDS ^a
M	64	115	Metastatic bronchus carcinoma ^a
M	73	125	Emphysema; postmortem investigation: no pulmonary embolism
M	59	143	Multiple myeloma, septicaemia ^a
F	45	180	Fibrosing alveolitis ^{a, b}

^a No postmortem investigation performed and compression ultrasonography normal at time of inclusion in study

^b Pathology proven by open lung biopsy

experience before the start of the investigation, pulmonary angiography may be safely introduced and incorporated in a management strategy for pulmonary embolism. The observed complication rate is comparable to that reported previously [2, 6–8]. The low rate in the present study may in part be explained by careful patient selection [8, 13, 18], which in turn implies that angiography may not be feasible in up to 23 % of patients. Hence, this study emphasizes the safety of pulmonary angiography.

A physician who is faced with a patient with symptoms suggesting pulmonary embolism and a nondiagnostic lung scan result could decide to treat the patient with anticoagulants. However, it should be realized that only approximately one third of such patients have pulmonary emboli. This would mean that 70 % of these patients, or almost 30 % of the entire population of patients with suspected pulmonary embolism, would be at risk for developing bleeding complications unnecessarily [19]. Because severe bleeding complications tend to occur early [20] and may involve over 10 % of patients before they are discharged [21], a definitive diagnostic strategy should be preferred.

Pulmonary angiography is generally regarded as the gold standard for the diagnosis of pulmonary embolism. In a previous study in 180 patients in whom anticoagulants were withheld following normal pulmonary angiography, no patients returned with recurrent emboli [22]. Nevertheless, its application in patients with nondiagnostic lung scans may be more cumbersome. This is due largely to the fact that subsegmental emboli may be more difficult to visualize, resulting in more inadequate investigations [9], whereas recognition of small peripheral emboli is also more difficult [23]. Two recent studies followed patients with normal angiographic findings in whom anticoagulants were withheld [24, 25]. The reported incidence of recurrent pulmonary embolism varied between 0 and 1.6 % during a follow-up period of 3 and 12 months, respectively. Variations in the technique of performing pulmonary angiography may be partly to blame. In our study we showed that it should be discouraged to withhold anticoagulant therapy in patients with clinically suspected pulmonary embolism and a nondiagnostic lung scan. However, it is safe to withhold anticoagulants in such patients once a normal selective pulmonary angiogram has been obtained. This underscores the validity of pulmonary angiography as the reference standard for the exclusion of pulmonary embolism.

In conclusion, although the feasibility of pulmonary angiography in patients with suspected pulmonary embolism was limited to 77 %, safe implementation in an institution that was not previously using angiography routinely was achieved. The prevalence of pulmonary embolism in patients undergoing pulmonary angiography was 27 %, making it a clinically useful addition to lung scintigraphy. Finally, it is a safe approach to withhold anticoagulants in patients with clinical symptoms suggesting pulmonary embolism, a nondiagnostic lung scan result and a normal pulmonary angiogram.

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References

- Hull RD, Hirsh J, Carter CJ et al. (1985) Diagnostic value of ventilation–perfusion lung scanning in patients with suspected pulmonary embolism. *Chest* 88: 819–828
- PIOPED (1990) Value of the ventilation–perfusion scan in acute pulmonary embolism: results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED). *JAMA* 263: 2753–2759
- Stein PD, Hull RD, Saltman HA, Pineo G (1993) Strategy for diagnosis of patients with suspected acute pulmonary embolism. *Chest* 103: 1553–1559
- McBride K, LaMorte WW, Menzoian JO (1986) Can ventilation–perfusion scans accurately diagnose acute pulmonary embolism? *Arch Surg* 121: 754–757
- Morrell NW, Seed WA (1992) Diagnosing pulmonary embolism. *Br Med J* 304: 1126–1127
- Dalen JE, Brooks HL, Johnson LW et al. (1971) Pulmonary angiography in acute pulmonary embolism: indications, techniques, and results in 367 patients. *Am Heart J* 81: 175–185
- Mills SR, Jackson DC, Older RA et al. (1980) The incidence, etiologies, and avoidance of complications of pulmonary angiography in a large series. *Radiology* 136: 295–299
- Stein PD, Athanasoulis C, Alavi A et al. (1992) Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation* 85: 462–468
- Hull R, Hirsh J, Carter C et al. (1983) Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. *Ann Intern Med* 98: 891–899
- Hull RD, Raskob GE, Ginsberg JS et al. (1994) A non-invasive strategy for the treatment of patients with suspected pulmonary embolism. *Arch Intern Med* 154: 289–297
- Kelley MA, Carson JL, Palevsky HI, Schwartz JS (1991) Diagnosing pulmonary embolism: new facts and strategies. *Ann Intern Med* 114: 300–306
- Oudkerk M, Beek EJR van, Putten WLJ van, Büller HR (1993) Cost-effectiveness analysis of various strategies in the diagnostic management of pulmonary embolism. *Arch Intern Med* 153: 947–954
- Nicod P, Peterson K, Levine M et al. (1987) Pulmonary angiography in severe chronic pulmonary hypertension. *Ann Intern Med* 107: 565–568
- Beek EJR van, Büller HR, Brandjes DPM, Rutten GCFM, Cate JW den (1994) Diagnosis of clinically suspected pulmonary embolism: a survey of current practice in a teaching hospital. *Neth J Med* 44: 50–55
- Hull RD, Raskob GE (1991) Low-probability lung scan findings: a need for change. *Ann Intern Med* 114: 142–143
- Lensing AWA, Prandoni P, Brandjes DPM et al. (1989) Accurate detection of deep-vein thrombosis by real-time B-mode ultrasonography. *N Engl J Med* 320: 342–345
- Bookstein JJ (1969) Segmental arteriography in pulmonary embolism. *Radiology* 93: 1007–1012
- Perlmutter LM, Braun SD, Newman GE, Oke JE, Dunnick NR (1987) Pulmonary arteriography in the high-risk patient. *Radiology* 162: 187–189
- Levine MN, Hirsh J, Landefeld S, Raskob G (1992) Hemorrhagic complications of anticoagulant treatment. *Chest* 102: 352S–363S

20. Fihn SD, McDonnell M, Martin D et al. (1993) Risk factors for complications of chronic anticoagulation. A multicenter study. *Ann Intern Med* 118: 511–520
21. Landefeld CS, McGuire E III, Rosenblatt MW (1990) A bleeding risk index for estimating the probability of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med* 89: 569–578
22. Novelline RA, Baltarowich OH, Athanasoulis CA et al. (1978) The clinical course of patients with suspected pulmonary embolism and a negative pulmonary arteriogram. *Radiology* 126: 561–567
23. Quinn MF, Lundell CJ, Klotz TA et al. (1987) Reliability of selective pulmonary arteriography in the diagnosis of pulmonary embolism. *Am J Radiol* 149: 469–471
24. Van Rooij WJJ, Heeten GJ den, Sluzewski M (1995) Pulmonary embolism: diagnosis in 211 patients with use of selective pulmonary digital subtraction angiography with a flow-directed catheter. *Radiology* 195: 793–797
25. Henry JW, Relyea B, Stein PD (1995) Continuing risk of thromboemboli among patients with normal pulmonary angiograms. *Chest* 107: 1375–1378

Book review

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Kucharczyk J., Moseley M., Barkovich J.: Magnetic Resonance Neuroimaging. Boca Raton, Ann Arbor, London, Tokyo: CRC Press, 1994, 496 pages, £ 95.00. ISBN 0-8493-4719-X

In the introduction, the editors (Kucharczyk J, Moseley M, and Barkovich AJ, from the University of California, San Francisco) of *Magnetic Resonance Neuroimaging* state that the purpose of this book is “to integrate both clinical and research applications of MR technology”. They have attempted to achieve this by covering 11 topics in the field of neuroimaging. Most authors of the chapters are recognized authorities and should have a good overview of the commissioned topic. Each chapter aims to cover clinical background, current MR applications, and future research goals.

The title of this book is misleading, since this book is not intended to simply describe imaging findings in neurological disorders but to bridge the gap between fundamental research and clinical management, using a variety of MR techniques (not only imaging). Readers looking for a more comprehensive overview of MR imaging in Neurology will not be well served, as the choice and coverage of the topics is not intended to be complete. Moreover, other techniques, especially MR spectroscopy, deservedly receive ample attention. A more appropriate title would have been *The Role of Magnetic Resonance in Neurosciences*. This type of book will need to find its readers amongst neuroscientist, since the major focus is on understanding the pathophysiology of the diseases, where MR techniques serve as a tool to unravel mechanisms and monitor treatment. Strategies for future research are indicated, which sometimes are overly optimistic (“intra-uterine spectroscopy of brain development in mice”).

The quality of the chapters is variable, both in focus and in writing. While some are written with great emphasis on technical background, such as the ones on principles and techniques, contrast media, and MR angiography, others are more clinically orientated, such as the ones on brain development and inborn errors of metabolism. Both types of focus have their charm, but the lack of balance between the two in this book implies that some chapters contain redundant information for more technically oriented readers (MR physicists), while other chapters contain redundant information

for the more clinically orientated reader. For instance, I do not think it is necessary for a dedicated audience such as the editors would like to address to explain the basic principles of MR (even though this chapter is well written). Some chapters, like the one on functional imaging and MR angiography, focus techniques, indicating applications for such techniques to illustrate the value of that particular technique. Other chapters focus diseases and disease mechanisms, illustrating how MR can be used to understand pathophysiology. Still other chapters are written for non-academic radiologists, simply describing imaging findings in a variety of disorders, as in the chapter on neurodegenerative disorders.

Several chapters are very up-to-date, providing frontline concepts and beautiful illustrations. The chapters on brain development, inborn errors of metabolism, and metabolic encephalopathy manage to focus on relevant brain processes. The illustrations are overall of good quality, with the exceptions of the chapters on neurodegenerative disorders and intracerebral hemorrhage. Unfortunately, parts of illustrations are sometimes spread out over several pages, making it difficult to obtain an overview; others are upside down, or black-and-white reproductions of full-color originals. Most chapters provide a wealth of references, which is very useful, and the majority is up-to-date, with the exception of the chapter on neurodegenerative disorders, where only 4 of 138 references were published after 1990.

The editors have chosen an arbitrary selection of topics for this book, with no attempt to cover the whole area of neurosciences. The reasons for this selection remain unspecified, but the absence of chapters on major topics such as CSF flow and hydrocephalus, brain tumours, and inflammatory diseases, lead to the opinion that this book is a not more than a random illustration of the role of MR. The insights obtained with MR are sometimes intriguing but mainly of interest to academic workers, many of whom will then require even more detailed information than what is presented. The readership for this book is probably limited (e.g. Ph.D students and basic neuroscientists), and I wonder whether they are prepared to pay £ 95.– per copy.

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