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PULMONARY EMBOLISM
VALIDATION OF DIAGNOSTIC IMAGING
METHODS IN THE CLINICAL SETTING

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ABSTRACT

Pulmonary embolism (PE) is an elusive diagnosis and none of the existing imaging modalities have a 100% diagnostic specificity or sensitivity. Pulmonary arteriography (PA) is the most specific test although the improvement of computed tomography technique has made this a commonly used method. Lung scintigraphy often gives ambiguous results. Fibrin split products (D-dimer) are released into the blood in PE and elevated levels can be measured. However, D-dimer levels are elevated in venous thromboembolic (VTE) disease as well as in a number of other conditions. The aims of this thesis were to evaluate different radiological methods including pulmonary arteriography, lung scintigraphy and spiral computed tomography for the diagnosis of acute pulmonary embolism and to study if a clinical probability protocol or a simple blood test such as D-dimer could improve the diagnostic accuracy.

Study I investigated the complication rate of PA in 707 patients. The overall complication rate was 1.6%, which is lower than previously reported.

Study II assessed the interobserver variations in PA in 170 patients and compared the consensus results to a final outcome diagnosis. The mean interobserver agreement was 89%, higher for central vessel emboli, lower for peripheral locations.

Study III investigated if the use of a combination of a clinical and scintigraphic protocol in relation to the final outcome could improve the diagnosis in patients with clinical suspicion of acute PE. A low combined probability yielded a negative predictive value (NPV) of 98%. The positive predictive value (PPV) was 100% if the combined probability was high.

Study IV compared the diagnostic accuracy of contrast medium enhanced spiral computed tomography of the pulmonary arteries (s-CTPA) and a latex agglutination D-dimer assay in patients with suspected acute PE by using PA and clinical follow up as reference method. s-CTPA had 95% NPV and 94% PPV. If a cut off level of 0.25 mg/L was used the corresponding figures for D-dimer were 92% and 63%.

Study V investigated if 441 patients with a negative s-CTPA and without DVT symptoms, venous studies or anticoagulant treatment had a new episode of PE during three months follow up. Only 0.9% of the patients had proven PE during the follow up period.

To conclude, the results of our studies show that PA is a safe method with good interobserver agreement and low complication rate. By applying a model of combined clinical and scintigraphic probabilities for PE, the diagnosis is ruled in when the combined probability is high, and ruled out when the combined probability is low. However, nearly half of the patients will still have an uncertain diagnosis if lung scintigraphy is used as diagnostic method.

A low cut-off level of D-dimer can be used as a screening test to rule out PE, but can not confirm the diagnosis. s-CTPA has a high diagnostic accuracy when compared to PA. The overall results indicate that a negative s-CTPA result safely can rule out the existence of clinically significant, acute PE.

LIST OF PUBLICATIONS

The thesis is based on the following five papers, referred to in the text by their roman numerals

I Pulmonary Angiography: A safe procedure with modern contrast media and technique.

Tage Nilsson, Anders Carlsson, Klas Måre
Eur. Radiol. 1998;8:86-89.

II Validity of pulmonary cine arteriography for the diagnosis of pulmonary embolism.

Tage Nilsson, Johan Turén, Åke Billström, Klas Måre, Anders Carlsson, Ulf Nyman
Eur. Radiol. 1998;9:276-280.

III Value of structured clinical and scintigraphic protocols in acute pulmonary embolism.

Tage Nilsson, Klas Måre, Anders Carlsson
J Intern Med 2001;250:213-218

IV A comparison of spiral computed tomography and latex agglutination D-dimer assay in acute pulmonary embolism using pulmonary arteriography as Gold Standard.

Tage Nilsson, Mårten Söderberg, Gunilla Lundqvist, Kerstin Cederlund, Flemming Larsen, Elsbeth Rasmussen, Bertil Svane, Johan Brohult, Hans Johnsson
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V Negative spiral CT in acute pulmonary embolism.

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LIST OF ABBREVIATIONS

CXR	Chest x-ray
DSA	Digital subtraction angiography
DVT	Deep venous thrombosis
ELISA	Enzyme-linked immunosorbent assay
MRA	Magnetic resonance angiography
NPV	Negative predictive value
PA	Pulmonary arteriography
PE	Pulmonary embolism
PPV	Positive predictive value
s-CTPA	Spiral computed tomography of the pulmonary arteries
V/Q	Ventilation/perfusion
VTE	Venous thrombembolism

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Venous thromboembolic disease

Venous thromboembolic disease (VTE) is a condition most often manifested either as deep venous thrombosis (DVT) or pulmonary embolism (PE). DVT is a common disorder and the incidence increases with age. The most dangerous complication of DVT is PE. It is often overlooked by the attending physician and the symptoms and signs are unspecific (1). The severity ranges from clinically unimportant, incidental cases, to life threatening massive embolism with high immediate mortality. PE may occur without previous symptoms from the legs, especially after surgery or trauma. In the long term PE may end up in a chronic state with pulmonary hypertension that is associated with disabling dyspnoea and right ventricular failure when left untreated.

1.1.2 Historical highlights

The clinical entity known as PE as a consequence of DVT was first described by Wiseman in 1676 (2). However, as early as 2650 B.C. the Chinese physician Huan-Ti wrote that blood coagulating in the blood-vessels caused the entire circulation to cease (3). The modern apprehension of venous thromboembolic disease is attributed to the German pathologist Rudolf Virchow who in 1856 wrote about his observations (4). Virchow described different types of thrombus formation and he also described in a very clear-sighted way, the pathogenetic factors behind venous thrombi also known as the triad of Virchow;

- a) changes in the vessel wall
- b) changes of the bloods ability to coagulate
- c) changes of the blood flow characteristics

Virchow also wrote about the causal relation between thrombus and what he described as "embolie": The thrombus is under constant growth and becomes gradually more extended. This growing thrombus is the real threat; parts of the thrombus may be torn off and follow the bloodstream to the pulmonary arteries where they occlude the main arteries, causing asphyxia.

The facts that injuries of the vessel wall and changes in the bloodstream conditions could cause venous thrombosis were more or less evident, but the fact that changes in the bloods ability to coagulate also was important, was first clarified in 1965 when the Norwegian Egeberg described familiar occurrence of venous thrombosis caused by antithrombin deficiency (5).

The need for thrombosis prophylaxis became evident for the surgeons after Azam in 1864 (6) and von Strauch in 1894 (7) reported thrombosis and PE as post traumatic complications.

Efficient drug therapy became possible when Erik Jorpes in Stockholm (8) clarified the chemical nature of heparin. The development of vitamin K-antagonists such as warfarin and the use of warfarin and heparin in combination are milestones in the treatment of PE. Surgical treatment and the use of different percutaneous intravascular interventions are other important development steps that today gives the physician different alternatives to treat this potential lethal disease.

1.1.3 Epidemiology and predisposing factors

The estimated rate of PE in population-based studies varies between 0.2 and 0.5 per 1000 in the general population in the Western World (9,10). The number of clinically silent non-fatal cases cannot be determined and the use of death certificates with a diagnosis of PE is extremely inaccurate (11,12). Absolute criteria for differentiation between fatal and non-fatal PE is missing and thus the presence of co-morbid conditions are important. Patients without preexisting co-morbid conditions can survive PE that occludes half of the pulmonary circulation but on the other hand, for patients with limited cardio-pulmonary reserve even minor emboli may be fatal (13).

Venous thrombembolism is a multifactorial condition with interactions between inherited and acquired risk factors. The main primary and secondary risk factors are summarized in Table 1 (14). The presence or absence of risk factors for VTE is essential in the evaluation of the likelihood of PE. Moreover, it should be recognized that the risk of PE increases with the number of risk factors present. However, PE does occur frequently in individuals without any risk factors (15).

Table 1 Risk factors for venous thrombembolism

Primary	
Antithrombin deficiency	Protein C deficiency
Congenital dysfibrinogenemia	Factor V Leiden (APC-R)
Thrombomodulin	Plasminogen deficiency
Hyperhomocysteinemia	Dysplasminogenemia
Anticardiolipin antibodies	Protein S deficiency
Excessive plasminogen activator inhibitor	Factor XII deficiency
Prothrombin 20210A mutation	
Secondary	
Trauma/fractures	Surgery
Stroke	Immobilisation
Advanced age	Malignancy
Central venous catheters	Obesity
Chronic venous insufficiency	Heart failure
Smoking	Long distance travel
Pregnancy/puerperium	Oral contraceptives
Crohn's disease	Lupus anticoagulant
Nephrotic syndrome	Prosthetic surfaces
Hyperviscosity (polycythemia, Waldenström's macroglobulinemia)	
Platelet abnormalities	

1.2 DIAGNOSIS OF PULMONARY EMBOLISM

1.2.1 Clinical evaluation of acute pulmonary embolism

Evaluating the likelihood of PE is mandatory in the interpretation of diagnostic test results and selection of an appropriate diagnostic strategy. However, the signs and symptoms are unspecific and this is due to that the pulmonary system has limited possible presentations, and it is the site of many diseases. The signs and symptoms also vary depending on the patients constitution i.e. patients with compromised cardiopulmonary function will present with more profound findings than young and healthier patients. The degree and extent of vessel occlusion is another important factor influencing the patient status.

A number of studies on pulmonary embolic disease based on clinical and imaging data have been published. Two large prospective studies were PIOPED and PISA-PED. (1,16). Signs and symptoms from these two studies are summarized in Table 2 as reported by Stein (17) and Miniati (18).

Dyspnoea, tachypnoea or pleuritic chest pain can be found in as many as 97% of the patients with PE. However, the same combinations of clinical characteristics may occur with nearly the same frequency among patients in whom PE is excluded. Miniati described three symptoms: sudden onset of dyspnoea, pleuritic chest pain, and fainting as significant for the presence of pulmonary embolism, particularly when combined with specific findings on ECG and chest radiography.

The signs are no more specific than the symptoms. Since both the signs and the symptoms of PE are so unspecific, the clinical suspicion can only be used as an indicator for further testing.

Table 2. Frequency of signs and symptoms in suspected PE

	PE (n=219)	No PE (n=546)
Symptoms		
Dyspnoea	80%	59%
Chest pain (pleuritic)	52%	43%
Chest pain (substernal)	12%	8%
Cough	20%	25%
Haemoptysis	11%	7%
Syncope	19%	11%
Signs		
Tachypnoea (≥ 20 /min)	70%	68%
Tachycardia (>100 /min)	26%	23%
Signs of DVT	15%	10%
Fever ($>38.5^\circ\text{C}$)	7%	17%
Cyanosis	11%	9%

1.2.2 D-dimer in pulmonary embolism

More than three decades ago the discovery that fibrin split products were released into the blood in PE gave hope that a simple blood test could establish or exclude the diagnosis (19). Cross-linked fibrin is degraded by plasmin into a class of products referred to as D-dimers. However, D-dimer levels are elevated in VTE disease as well as in a number of other conditions such as renal failure, trauma, myocardial infarction, pregnancy, pneumonia or malignancy and are detected by enzyme-linked immunosorbent assays (ELISA) or agglutination techniques. The D-dimer concentration also increases with age. The specificity of the test is therefore low but the negative predictive value is reported in several studies to be more than 90% for excluding PE (20). A number of studies using different latex agglutination D-dimer assays have been published with sensitivities and specificities ranging between 70-90% (21). Whole blood assays have a slightly better performance (22), and ELISA have the highest sensitivities (90-100%), but relatively low specificity (30-40%) (23). The specificity of all D-dimer assays is low since these degradation products are produced whenever there is active intra- or extra vascular fibrin formation and fibrinolysis in the body. The specificity is especially low among inpatients and in the elderly since these patients often are found with a variety of confounding conditions.

1.3 DIAGNOSTIC IMAGING OF PULMONARY EMBOLISM

1.3.1 Chest X-ray

Chest radiography (CXR) is performed in almost all patients suspected of pulmonary embolism and in most of the patients the findings are abnormal. In a subset of the PIOPED study, ninety-two percent of patients with acute pulmonary embolism had abnormal findings (24). The most frequent radiographic abnormalities were atelectasis and pulmonary parenchymal consolidation, either or both of which occurred in 69% of the patients with PE and in 58% of those without. Oligemia, a prominent central pulmonary artery, pleural-based opacities, and elevated diaphragm were found to be poor predictors of PE (25). The main value of CXR is to exclude differential diagnoses such as pneumothorax, pneumonia or rib fractures and to aid in the interpretation of other imaging studies, such as lung scintigraphy.

1.3.2 Pulmonary arteriography

Werner Forssmann was the first to describe right-sided heart catheterization in 1929, which he performed first on himself and later in dogs (26).

Selective pulmonary arteriography (PA) was not performed until 25 years later. Since then, several advances have been made, such as the catheter introduction technique by Seldinger, the development of rapid imaging equipment (film-changers), digital subtraction angiography (DSA), the introduction of the pigtail catheter, the application of safer contrast agents and guide-wire materials.

Selective PA is considered the most specific test for pulmonary embolism. Apprehensions that the procedure is expensive, invasive and thus associated with both fatal and

nonfatal complications, and requires experienced investigators, has more or less limited its use to patients presenting with a non-conclusive lung scan. However, PA has obvious advantages. In hospitals using PA it is available twenty-four hours a day. It allows visualization of the venous system and provides hemodynamic data and the opportunity for treatment in the same clinical setting. The complication rate is low with modern low- and isoosmolar contrast media and technique (27) and there are no absolute contraindications. Care must be taken to patients with pulmonary hypertension, right ventricular overload and limited cardio pulmonary reserve (28).

There are two accepted criteria for the diagnosis of pulmonary embolism; an intraluminal filling defect or a complete obstruction of the vessel with outlining of the end of the embolus (trailing edge) (29).

Pulmonary arteriography has for decades been accepted as the "gold standard" despite variations in interobserver agreement, especially in subsegmental vessels. Though conventional cut film has a higher spatial resolution, the dynamic sequence and temporal resolution in cine technique allows a more precise detection of small emboli, because of their movement during systole and diastole. In addition, motion artefacts are eliminated to a large extent.

The difficulties in interpretation are caused mostly because of low flow in combination with tortuous vessels.

Positive arteriograms with only subsegmental emboli result in a lower grade of interobserver agreement. The interobserver agreement for subsegmental emboli in the PIOPED study was 66% with a prevalence of 5,6% subsegmental emboli compared to our study (30) with an interobserver agreement of 63% and a prevalence of 11,7% subsegmental emboli.

The diagnostic accuracy of PA and s-CTPA was studied by Baile in an experimental porcine model (31). In that study both methods were compared by using a methacrylate cast of pulmonary vessels as an independent gold standard and showed that there was no statistically significant difference between s-CTPA and PA for detection of subsegmental sized PE.



Figure 1. Pulmonary arteriography with selective injection in the right pulmonary artery. Intraluminal filling defects are clearly seen. (Arrows)

1.3.3 Ventilation-perfusion (V/Q) lung scintigraphy

Lung scintigraphy has been widely used as the first line imaging method since the 1960's for the diagnosis of acute PE. It is noninvasive and it has been evaluated in extensive clinical trials. The need for more specific diagnosis of pulmonary embolism, not only detecting perfusion defects, was provided for when ventilation scintigraphy was introduced in 1970. This was based on the expectation, mostly theoretical, that regions of the lung excluded from perfusion by emboli maintained normal ventilation, thus giving rise to mismatched patterns of perfusion and ventilation (32).

During the following years there was an expanding diagnostic activity of acute pulmonary embolism, with little scientific support, by demonstrating ventilated perfusion defects. In 1977, Robin (33) questioned the diagnostic capability of the method. He believed that the only use of lung scintigraphy was for excluding pulmonary embolism. In his opinion, PE was overdiagnosed and overtreated. At that time, a number of diagnostic schemes were used and opinion varied regarding the overall reliability, usefulness, and interpretation of lung scintigraphy for the diagnosis of acute pulmonary embolism (34).

In an effort to address many of the uncertainties of ventilation/perfusion (V/Q) lung scintigraphy, a large prospective, multicenter study (PIOPED) was performed in North America during 1985-1986 (1). The purpose of PIOPED was to determine the sensitivity and specificity of V/Q lung scintigraphy for acute pulmonary embolism. PIOPED resulted in a sophisticated classification that has been revised to try to improve the predictive values of lung scintigraphy (35,36,37). Other studies after PIOPED have been performed in order to sharpen the diagnostic value of lung scintigraphy (38,39). The general outcome of these surveys is that the method is encumbered with a considerable portion of inconclusive results at the present state. However, a normal perfusion scan excludes acute PE with a negative predictive value (NPV) of up to 98% (1).

V/Q lung scintigraphy technique

Lung scintigraphy consists of two components: perfusion and ventilation imaging. Six to eight views are regarded state of the art: anterior, posterior, left lateral, left anterior oblique, right lateral, right anterior oblique as the most commonly used. Perfusion scanning of PE is based on blocking pulmonary capillaries by radioactive particles (size 15-40 μm , biological half-life 1.5-3 h). $^{99\text{m}}$ Tc-labelled macroaggregates of albumin (MAA) are injected intravenously with the patient supine. Ventilation imaging may be performed with a variety of agents, including $^{81\text{m}}$ Krypton, $^{99\text{m}}$ Tc-diethylene triamine penta-acetic acid (DTPA) aerosols, 133 Xenon and $^{99\text{m}}$ Tc-labelled carbon particles (Technegas). Lung scintigraphy can also be performed by SPECT (Single Photon Emission Computed Tomography) that may reveal perfusion defects, their size and configuration in a better way. However, this method has not been validated in prospective studies against a "Gold Standard" and will therefore not be discussed in this thesis.

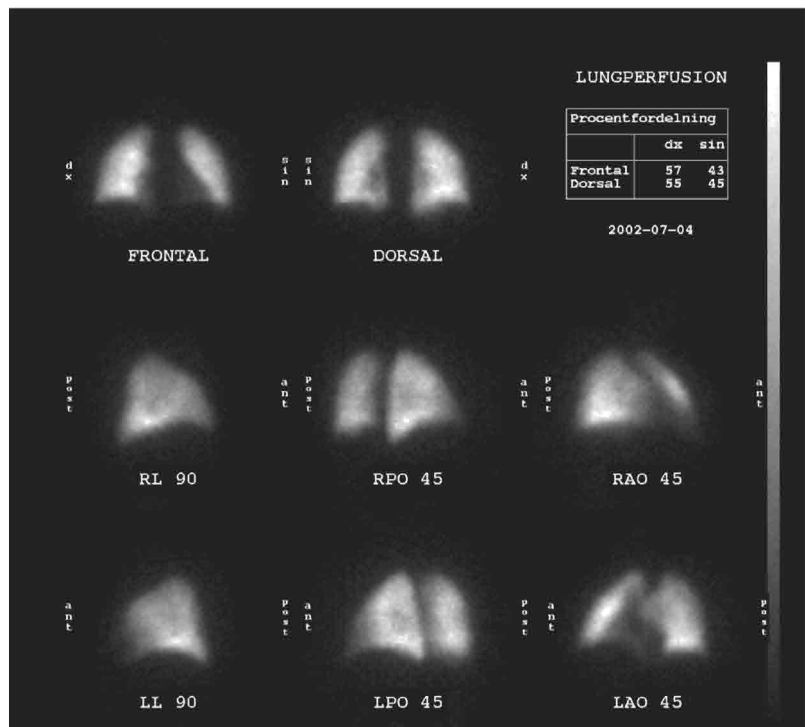


Figure 2a. Normal, homogenous perfusion of both lungs.

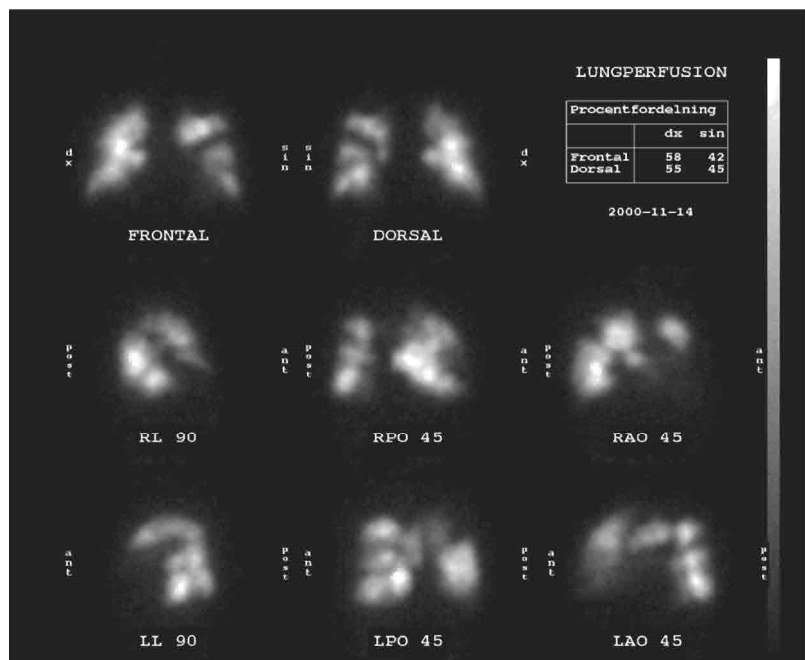


Figure 2b. Large perfusion defects in both lungs. The probability of pulmonary embolism is high.

1.3.4 Spiral computed tomography of the pulmonary arteries (s-CTPA)

The diagnosis of pulmonary embolism using conventional CT scanners was initially made incidentally, visualizing large central emboli. Technical improvement has now resulted in spiral CT technique with continuous rotation of the X-ray tube with simultaneous continuous table feed. This allows for the acquisition of a volume data set in a single breath hold. Other advantages are short scanning times, reduced volume of contrast medium together with higher opacification of the pulmonary arteries during the whole acquisition period, reduced X-ray exposure, thinner sections, detection of other pathological conditions in the lung parenchyma, pleura or lung arteries, and a wider range of post processing possibilities with higher quality opening the new field of CT angiography (40,41). s-CTPA enables the direct visualization of PE within the pulmonary arteries as low attenuation filling defects within the vessel, partly or completely surrounded by opacified blood, or as a complete filling defect which leaves the distal vessel totally unopacified (42). The value of indirect signs of PE, such as pleural-based densities, linear densities or plate-like atelectasis, central or peripheral dilatation of pulmonary arteries, and pleural effusions of variable sizes, is less clear (42). The first report where s-CTPA was used in the diagnosis of pulmonary embolism was published in 1992 (43). In this selected group of 42 patients with central PE the sensitivity and specificity were 100% and 96% respectively. Most studies thereafter have been performed to establish the sensitivity and specificity to detect PE. The reported sensitivity and specificity of s-CTPA has ranged from 53% to 100% and from 81% to 100% respectively (44). The variations of sensitivity and specificity for diagnosing PE reflect the methodological problems and differences in study populations. There are also differences in what reference method s-CTPA is compared to. PA is still regarded as "Gold standard" but this method also has false negative and positive findings. The shortcoming of diagnosing subsegmental emboli with PA was the same as for s-CTPA in an experimental porcine model (31). Hence, small subsegmental emboli seem to be a diagnostic problem, whatever imaging method is used. The risk of withholding anticoagulation from patients with suspected pulmonary embolism, no symptoms or signs of DVT, and negative s-CTPA findings, has been evaluated in a few studies (45,46), and the risk is below 1% to develop a new VTE episode.

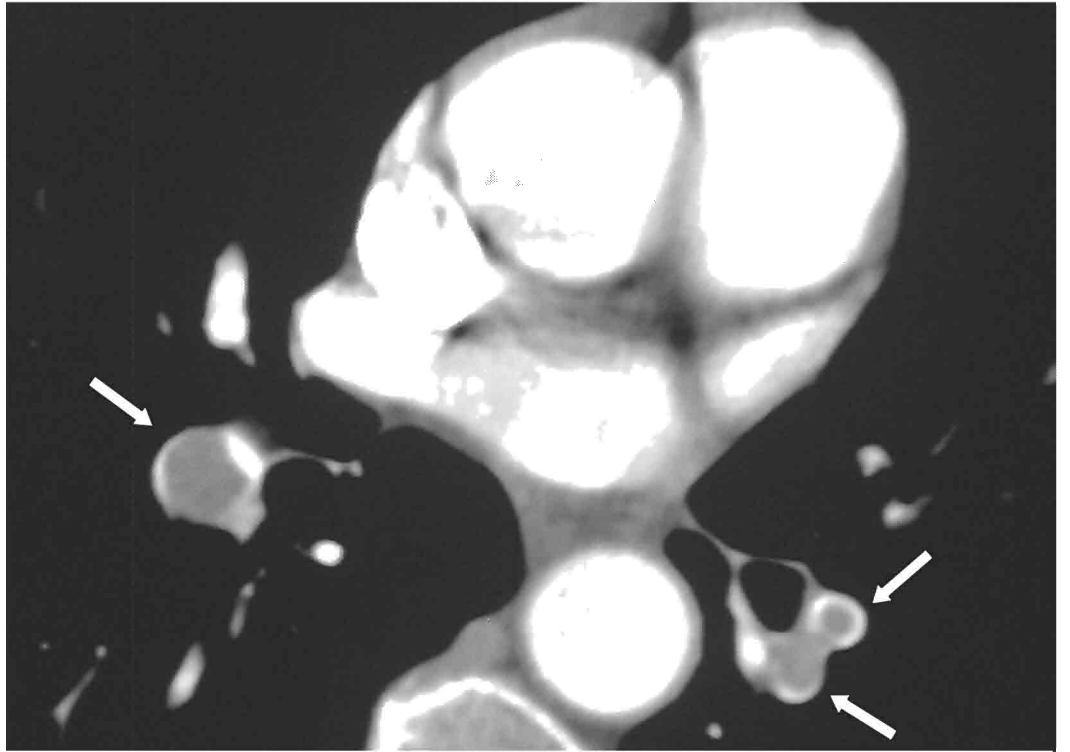


Figure 3. Same patient as in figure 1. s-CTPA. Low attenuation filling defects within the vessels to the lower lobes, partly surrounded by opacified blood. (Arrows).

1.3.5 Magnetic resonance angiography (MRA)

Conventional techniques in magnetic resonance imaging are unable to distinguish segmental and subsegmental pulmonary vessels, because of the peculiar composition of lung tissue. New faster techniques, however, have made it possible to evaluate the pulmonary arteries. Improved methods are being introduced that allow almost simultaneous imaging of ventilation and perfusion of the lung. Thus, magnetic resonance imaging is increasingly applied for diagnosis of a rising number of chest disorders. An advantage with MRA in comparison with CT and PA is that MRA contrast agents are used in low osmolar concentrations, resulting in fewer adverse events and does not involve ionising radiation.

Although the new techniques of MRA seem very promising and accurate, the studies published on this subject report varying sensitivity and specificity with different techniques and expertise of the radiologist.

Reitner et al compared gadolinium enhanced MRA with s-CTPA for the detection of small (4-5mm) PE, with a methacrylate cast of the porcine pulmonary vasculature used as the diagnostic standard (47). The mean sensitivity (and 95% confidence intervals) for s-CTPA and MRA, respectively, were 76% (68%-82%) and 82% (75%-88%) ($P>.05$); the mean positive predictive values, 92% (85%-96%) and 94% (88%-97%) ($P>.05$). In this porcine model, PE were usually seen as parenchymal perfusion defects (98%) with MRA and as occlusive emboli (100%) with s-CTPA.

In a recently published study by Oudkerk (48) in 118 patients using PA as reference method, the sensitivity of MRA for isolated subsegmental, segmental, and central or lobar PE was 40%, 84%, and 100% respectively. However, even though subgroups contained small numbers, this study indicates that with increasing availability of magnetic resonance imaging systems, MRA could become an important test in the future diagnostic strategy for pulmonary embolism.

2 AIMS

The aims of this thesis were to evaluate pulmonary arteriography, lung scintigraphy and spiral computed tomography for the diagnosis of acute pulmonary embolism and to study if a clinical probability score or a simple blood test such as D-dimer could improve the diagnostic accuracy.

In the different papers the specific aims were:

- I. To study the complication rate of pulmonary arteriography.
- II. To study the interobserver variability in PA and compare the consensus results to a final outcome diagnosis.
- III. To study the value of a combined clinical and scintigraphic probability protocol in patients with clinical suspicion of acute PE.
- IV. To compare the diagnostic accuracy of contrast medium enhanced s-CTPA and the latex agglutination D-dimer assay in patients with suspected acute PE by using PA and clinical follow up as reference method.
- V. To retrospectively evaluate the clinical outcome of non-anticoagulated patients with clinically suspected acute PE without symptoms or signs of deep venous thrombosis following a negative contrast medium enhanced s-CTPA.

3 MATERIAL AND METHODS

3.1 PATIENTS (I-V)

Study I: During a five year period (1990-1994) 728 patients, (298 men and 430 women) underwent PA due to clinical suspicion of PE. There were 293 at Danderyd Hospital and 435 at Huddinge University Hospital. The mean age of the patients was 59 years, range 18-93. Seven hundred and seven reports were available for analysis.

Study II and III: Between September 1991 and February 1994, one hundred and seventy of 269 consecutive patients with a clinical suspicion of acute PE, underwent PA with cine technique and ventilation/perfusion lung scintigraphy (60 male, mean age 60 ± 15 years, 110 female, mean age 59 ± 17 years). Patients who met the inclusion criteria in this study underwent PA, regardless of the scintigraphic findings. Reasons for exclusion of 99 patients (33 male and 60 female, mean age 64 ± 17 years) were as follows; other disease than PE (n=15), refused to participate (n=23), too ill to participate (n=5), angiographic suite not available (n=41), contraindication to PA (n=4), and study protocol criteria not fulfilled (n=11).

Study IV: This study was performed at Karolinska sjukhuset and Södersjukhuset, Stockholm, Sweden, between March 1999 and May 2001. Ninety of 139 patients with suspicion of acute PE were evaluated with PA and s-CTPA. PA or s-CTPA could not be performed within stipulated time, i.e. 24 hours, in 32 patients and if the investigations were not fulfilled according to study protocol in another 17 patients. Mean age of the 90 patients were 54 years (range 34-73) and there were 42 men and 48 women. D-dimer levels were measured in 84 of these patients.

Study V: During a two-year period (1998-1999) 739 of 751 patients underwent s-CTPA with acceptable diagnostic quality for clinically suspected acute PE. PE was diagnosed in 158 patients. Of the remaining 581 patients with a negative s-CTPA, 45 patients were lost to follow-up. Eighty-eight patients were excluded because of anticoagulation treatment (cardiac disorder n=32, chronic VTE or acute symptomatic DVT n=31, PE diagnosed at pulmonary angiography n=1, thrombus prophylaxis during diagnostic work-up or other reasons than VTE n=24) and seven patients undergoing lower extremity venous studies because of symptoms of DVT. Thus, 441 patients with a negative s-CTPA and no DVT symptoms, venous studies or anticoagulant treatment constituted the follow-up cohort. There were 287 females, mean age 58 years (range 21-96) and 154 males, mean age 61 years (range 21-86).

3.2 METHODS (I-V)

3.2.1 Pulmonary arteriography (I)

PA was performed with the same technique at both hospitals. No premedication was given, unless there was known hypersensitivity to contrast media. In such cases 50 mg cortison (Prednisolon®, Pharmacia, Sweden) was given orally on the day before and on the day of the angiography, when 2 mg antihistamin i.m. (Tavegyl®, Sandoz, Sweden) also were added. Most of the patients were given heparin 5000 IE as an i.v bolus at the emergency ward because of the suspicion of PE. In cases of long delay before the PA, additional heparin (500 IE/kg/24 h) was given as an infusion and this was not discontinued until the PA had proven an absence of embolus. If serum creatinine levels exceeded 200 $\mu\text{mol/l}$, fluid infusions (Rehydrex®, Pharmacia, Sweden) 100-150 ml/h, and diuretics (Furix®, Nycomed, Norway), 20-40 mg i.v, were given before and after the examination. All patients had ECG-monitoring during the procedure.

Catheterization using Seldinger technique via the common femoral vein was performed in all patients. A 7-F sheath was introduced and contrast medium was manually injected, in order to rule out thrombi in the iliac veins or inferior vena cava.

During 1990 to -92 a left ventricle 145° standard angled pigtail catheter with twelve side holes (Cordis, Holland) was used to catheterize the pulmonary arteries. Later a specially designed pulmonary angiography catheter, Helleman (Cordis, Holland) was introduced. This is a braided 7-F, polyurethane, 120° angled pigtail catheter with 12 oval side holes. The distance between the angle and the pigtail is shorter (60 mm), and the diameter of the pigtail itself is smaller (14 mm) than the original standard catheter. Only non-ionic monomeric, low osmolar contrast media were used, either iopamidol (Iopamiro®, Astra Tech, Sweden) 370 mg I/ml or iohexol (Omnipaque®, Nycomed, Sweden) 350 mg I/ml. Standard volumes for each injection were 40 ml during 2 seconds selectively in each pulmonary artery, but the volume could be reduced (usually to 20 ml during 2 seconds) if there was an elevated (>80 mm Hg) systolic pressure in the pulmonary artery and/or slow pulmonary circulation during test injection

Selective injections into the main right and left pulmonary artery were obtained unless PE was found in the first examined lung. Pressure recordings from the right chamber or main pulmonary trunk were available in 53% of the patients.

The angiographic technique included both bi- and single plane filming with cineangiography or DSA, 25 and 12,5 f/s respectively. At least two oblique projections of each lung were performed. Only direct criteria of pulmonary embolism were used.

3.2.2 Pulmonary arteriography (II and III)

All studies were carried out within 24 hours from the patient's arrival to the emergency ward. All patients had a prior chest x-ray, and a lung perfusion scan was performed before or after PA. PA was performed with Seldinger technique via the common femoral vein and pigtail catheters (Cordis, Holland) measuring 2,3 mm in outer diameter (OD). A non-ionic, monomeric contrast medium, iopamidol (Iopamiro®, Astra Tech, Sweden) 370 mg I/ml was injected, using a standard volume of 40 ml during two seconds. This could be altered depending on the pulmonary artery blood pressure and/or flow rate evaluated by a manual test injection of contrast medium. At least two oblique projections of each lung together with an additional AP-projection were performed. A Siemens single plane Angioscope with a 30 cm image intensifier and cine filming with

25 frames/sec were used. Only direct criteria of PE were used, i.e. an intraluminal filling defect or an occlusion with a concave border of the end of the contrast medium column, indicating a trailing edge of an embolus.

The quality of the angiograms was assessed and classified into three categories; good, when subsegmental branches were visible with adequate diagnostic quality in both lungs; fair, when distal branches were not adequately visible; and poor, when only the main and lobar arteries were possible to evaluate.

Three thoracic radiologists reviewed the arteriograms independently and with no other data available. Each of the readers had to decide whether PE was present or not and if so, to give an exact description of the localisation of the embolus. If there was any disagreement about the diagnosis, all arteriograms were reviewed on a separate reading session with all the observers participating.

3.2.3 Pulmonary arteriography (IV)

All examinations were performed at a Siemens High Cor or Philips Integris digital, single plane angiographic equipment at 12.5 or 25 frames per second. PA was performed with standard Seldinger technique using the femoral approach. At least two oblique projections of each lung were performed. A standard dose of 40 mL Visipaque, 320 mg I/ml (Amersham Health, Lidingö, Sweden) or Iomeron 350 mg I/ml (Astra Tech, Mölndal, Sweden) was injected during two seconds. This could be altered depending on the pulmonary artery blood pressure and/or flow rate evaluated by a manual test injection of contrast medium.

The interpretations of the arteriograms were carried out in the same way as for s-CTPA by two experienced vascular radiologists who also were blinded to the clinical and laboratory data. The diagnostic criterion for PA was an intraluminal filling defect or an occlusion with a concave border at the end of the contrast medium column, indicating a trailing edge of an embolus.

3.2.4 Lung scintigraphy (II and III)

Perfusion and ventilation scintigraphy was performed with a parallel-hole, low energy, all-purpose collimator on a gamma camera (General Electric 400 AT, USA).

Perfusion lung scintigraphy was performed after intravenous injection of 75 MBq ^{99m}Tc macro-aggregated albumin (Solco Nuclear, Switzerland). Registrations were made with the patient in the supine position in 8 standard projections (anterior, posterior, left and right anterior oblique, left and right posterior oblique and 2 laterals). Anterior and posterior projections were registered with 800 000 counts per view, and the remaining projections were registered with 400 000 counts per view.

Ventilation scintigraphy was performed only when the perfusion scan was considered abnormal. This decision was left to one of two nuclear medicine physicians in charge. Of 170 patients, the ventilation was not performed in 35 cases. For those who underwent ventilation scintigraphy, ^{99m}Tc technegas (Tetley Technologies, Australia) was used, and registrations were made in selected projections according to the findings of perfusion imaging. If performed on the same day as perfusion scintigraphy, the count rate at ventilation scintigraphy had to reach three times or more the activity of the remaining ^{99m}Tc macro-aggregated albumin. Most ventilation scintigrams were however performed the day after the perfusion scintigraphy.

The scintigrams were evaluated by a physician experienced in nuclear medicine who also had access to the chest x-rays, but was blinded to the clinical information and the results of angiography.

Immediately after scrutinizing the scintigraphy according to the modified PIOPED criteria (49), the reader made a subjective personal probability estimate as a mark on a visual analogue scale (VAS). Later this mark was measured by means of a ruler and expressed as percent probability. The estimate was based solely on the personal experience and opinion of the reader. The result of the estimation was subsequently divided into four likelihood groups, 0, 1-25% (low), 26-75% (intermediate) and 76-100% (high) probability.

3.2.5 Spiral CT (IV)

All examinations were performed with either a Siemens Somatom Plus unit (Siemens, Erlangen, Germany) or a GE Advantage (GE Medical Systems, USA). The s-CTPA was performed in cranio-caudal direction during inspiration from the top of the aortic arch to the top of the lowest hemidiaphragm with 3 mm collimation and a table speed of 3-5 mm/sec (pitch of 1.3-1.7). A standard dose of 120-150 ml Omnipaque, 240 or 300 mg I/ml (Amersham Health AB, Lidingö, Sweden) was delivered in an antecubital vein at 4mL/sec, 15-20 sec before the start of the scanning. The tube current was 200-210 mA, the exposure time (rotation time) 0,8-1 second and the tube voltage 120 kV. The images were reconstructed with a standard frequency algorithm.

The images were printed on 35x43 cm transparent film, with 20 images on each film using a window width of 500-600 HU and a window level of 60-100 HU. All examinations were also evaluated in cine mode on a workstation at individual window settings. Interpretations of the s-CTPA scans were carried out by two experienced chest radiologists, blinded to all other data, initially by means of individual reading and then by means of consensus reading. The diagnostic criterion for acute PE was a low-attenuation area that completely or partially filled the lumen of a normal-sized or slightly enlarged vessel.

3.2.6 Spiral CT (V)

All examinations were performed with a Siemens Somatom Plus unit (Siemens, Erlangen, Germany). The s-CTPA was performed in cranio-caudal direction during inspiration from the top of the aortic arch to the top of the diaphragm with 3 mm collimation and a table speed of 4-5 mm/sec (pitch of 1.3-1.7). A standard dose of 120 mL Omnipaque, 240 mg I/mL (Amersham Health AB, Lidingö, Sweden) was delivered in an antecubital vein at 4mL/sec, 15 sec before the start of the scanning. The tube current was 210 mA, the exposure time (rotation time) 1 second and the tube voltage 120 kV. The images were reconstructed with a standard frequency algorithm, defined for the actual unit as AB 7557S.

The images were printed on 35x43 cm transparent film, with 20 images on each film using a window width 600 HU and window level 100 HU. All examinations were also evaluated in cine mode on a workstation at individual window settings. A specialist in thoracic radiology reviewed all examinations a second time, before the final report was written.

3.2.7 Protocols (I)

A standardized protocol was used, on which all observations in the angiography suite were noted, i.e. blood pressure, ECG-changes, volumes, flow rate, puncture site, in-lab complications. In search for complications after the patient had left the radiology department, all available patient records were reviewed for signs of any complications following the procedure.

3.2.8 Protocols (II and III)

After admittance to the emergency ward all patients with a clinical suspicion of PE were screened for their probability of having PE by one of three physicians engaged in this project. The patients were evaluated according to a protocol (table 3) including data about previous history, special risk factors for thromboembolic disease, current symptoms and physical findings. The ECG's were scrutinized for signs of right ventricular overload. It was up to the physician's discretion to judge the clinical relevance of each positive item of the clinical protocol. The physician finally estimated the probability of PE by a visual analogue scale (VAS). The VAS was a 100 mm long continuous line marked with 0% probability at its left margin and 100% at its right margin.

The clinical probability was subsequently divided in three categories, i.e., low (1-25%), intermediate (26-75%) and high (76-100%).

All studies included a chest radiograph performed less than 24 h before the perfusion lung scintigraphy and PA, using upright posterior-anterior and lateral projections or when necessary, a portable radiogram.

3.2.9 Final outcome (II and III)

In order to establish a "final outcome diagnosis", a committee of experts including two radiologists, one nuclear physician and three internists analysed all available data during one session (i.e. patient records including follow up data at six months, lung scan results, radiographic examinations including PA, clinical, laboratory, and autopsy findings) and decided whether the patient did or did not have PE at the time of the hospital episode.

3.2.10 D-dimer assay (IV)

Blood samples were obtained on arrival to the emergency ward. Citrate plasma samples were frozen and stored at a temperature of -70°C. A quantitative rapid latex D-dimer assay was later used for batch assessment (Tinaquant®, Boehringer-Mannheim, Germany). D-dimer concentrations were analysed, using the manufacturers recommended cut off level of 0.5 mg/L as well as a tentative cut off level of 0.25 mg/L, to study the diagnostic outcome in comparison to PA.

3.2.11 Protocols (IV)

The patients were evaluated on admission by the physician on call and by one of the primary investigators. Patients, aged between 18 and 79, were eligible for the study if they met the inclusion criteria according to the study protocol, which were symptoms or signs of acute PE possible to investigate during daytime. An electrocardiogram, a chest radiogram and in some cases arterial blood gas analysis were performed prior to the study investigations.

3.2.12 Protocols (V)

All CT reports not read as positive for PE were considered negative as long as the diagnostic quality was regarded as acceptable. Examinations regarded as non-diagnostic due to poor quality were excluded. Patients, whose CT reports were considered negative, were subjected to a retrospective follow-up. A patient questionnaire was sent out to those who were registered as being alive according to the national population registry, and a telephone interview was performed if the questionnaire was not answered. The questionnaire included questions about seeking medical attention anywhere outside Karolinska Hospital within 90 days of the CT examination and if the patient had been treated for venous thrombembolism ("blood clots") with "blood thinners" such as warfarin, during this period. All medical and diagnostic records at the Karolinska Hospital were reviewed and if the patient for any reason had visited any other hospital or health-care centre, the medical record was sent for and reviewed. All death certificates and autopsy reports were also reviewed.

Patients given anticoagulation during the hospitalization and/or follow-up period including short periods of low molecular weight heparin and unfractionated heparin (UH) were excluded and the reasons for anticoagulation were analyzed.

Table 3. Clinical protocol for estimating the likelihood of pulmonary embolism in 170 patients.

History of thromboembolic risk factors registered.
Venous thromboembolic disease in the family
History of venous thromboembolic disease
Surgery or trauma the latest 3 months
Immobilisation for other reasons
Congestive heart failure
Paralysis
Treatment with oestrogen
Malignancy
Alcohol abuse
Chronic obstructive pulmonary disease
Pregnancy
Coagulation defect/disease
Infectious disease
Varicose veins

Current symptoms registered.
Dyspnoea/reduced physical performance
Non specific chest pain
Chest pain with relation to breathing
Anxiety
Fever
Cough
Haemoptysis
Dizziness
Abdominal pain
Symptoms of thrombosis in extremities
Syncope

Findings on physical examination registered
Affected general condition
Respiratory rate above 20 per minute
Heart rate above 90 per minute
Body temperature more than 37.5° C
Clinical suspicion of venous thrombosis in extremities
Filled jugular veins
Accent. pulmonary component of the second heart sound
Tricuspid regurgitation

4 MAIN RESULTS

The principal findings were:

Study I: Of 707 PA studied, there were 137 patients with PE (95 at Huddinge and 42 at Danderyd), 22% and 14% of all angiograms respectively. No deaths occurred. One case of major non-fatal complication (bleeding in the groin requiring surgery) was reported. Moderate/minor complications (i.e. transient angina and cardiac failure, minor haematomas, urticaria) occurred in ten patients (1.4%).

Study II: Fifty-one out of 170 PA were interpreted as positive for PE. Two pulmonary emboli were missed when compared to the diagnosis as stated by the final outcome committee. No arteriograms were considered as non diagnostic. Mean interobserver agreement for lobar vessel emboli were 100%, segmental vessel 93% and subsegmental vessel 63%. The mean interobserver agreement for all vessels was 89%.

Study III: When the scintigraphic and clinical probability judgements were congruent, a combined probability of 1-25% (i.e. low probability) had a negative predictive value of 98%. When the combined probability was 26-75% (i.e. intermediate) half of the cases had PE. With a combined probability of 76-100% (i.e. high) the positive predictive value was 100%.

Study IV: All PA and s-CTPA investigations had an acceptable diagnostic quality in a consensus reading. Thirty-three patients had a positive PA (37%). Three patients had false negative and two patients had false positive s-CTPA findings resulting in 91% sensitivity, 96% specificity, 94% positive predictive value (PPV) and 95% negative predictive value (NPV). The sensitivity and specificity for D-dimer below 0.5 mg/L were 79% and 88% respectively. The PPV and NPV were 81% and 87%. When a cut off level of 0.25 mg/L was used the corresponding figures were 91%, 65%, 63% and 92%.

Study V: The follow up cohort included 441 patients with a negative s-CTPA and no DVT symptoms, venous studies or anticoagulant treatment. Four of these patients (0.9%; 95% confidence limit 0.3-2.3%) had proven PE during the 3-months follow up period. Two of the PE episodes contributed to the patient's death. Both patients had end stage malignant disease.

5 STATISTICS

5.1 STUDY II

In order to evaluate hypotheses of variables in contingency tables, the chi-square test was used or, in case of small expected frequencies, Fischer's Exact Test. The Spearman rank correlation coefficient was used in order to test hypothesis about independence between variables. The kappa statistic was used in order to compare the individual observers rating and the consensus interpretation. This value is a chance corrected proportional agreement rate with a maximum of 1,0 with perfect agreement and zero when agreement is no better than chance (50). In addition to that, standard descriptive statistic methods were used to characterize the data. All analyses were carried out by use of the SAS system version 6 (SAS Institute Inc., Cary, NC), and the 5% level of significance was considered.

5.2 STUDY III

In order to evaluate hypotheses of variables in contingency tables, the chi-square test was used or, in the case of small expected frequencies, Fisher's Exact Test. In addition to that, descriptive statistics were used to characterize the data. All analyses were carried out by use of the SAS system, version 6.12 (Statistical Analysis System; SAS Institute) and the 5, 1 and 0.1% levels of significance were considered. In the case of a statistically significant result the probability value (p-value) has been given.

5.3 STUDY I, IV AND V

Standard descriptive and graphical methods were used to characterize the data. To calculate sensitivity, specificity, NPV and PPV the following formulae were used:

		Pulmonary arteriography		
		PE+	PE-	
Test-method	PE+	a	b	a+b
	PE-	c	d	c+d
		a+c	b+d	a+b+c+d

Sensitivity: $a/(a+c)$

Specificity: $a/(b+d)$

PPV: $a/(a+b)$

NPV: $d/(c+d)$

6 DISCUSSION

The diagnosis of acute pulmonary embolism (PE) remains a clinical dilemma, despite all efforts in searching for the perfect diagnostic tool. PE is associated with a multitude of clinical and routine laboratory abnormalities, none of which are absolutely diagnostic, either alone or together. The patients are often looked upon as a homogenous population although they better should fall into two broad subpopulations: In a previously healthy and otherwise normal outpatient population, the prevalence of PE is low and probably overestimated by clinicians, whereas in chronically ill and hospitalized patients, PE is probably underdiagnosed (33).

A missed diagnosis of PE may be fatal to the patient since the mortality rate of untreated disease has been estimated to be 30% (51). It is of particular interest to establish a correct diagnosis of PE in patients with underlying cardiopulmonary disease where even subsegmental emboli may be dangerous. Hull et al showed that 8% of patients with a low-probability lung-scan, regarded as often connected to subsegmental emboli (52), and limited cardiopulmonary reserve, who did not receive anticoagulants, died within days of entry compared to 0,14% of patients with good cardiopulmonary reserve and a non diagnostic lung scan (53).

On the other hand, a false positive diagnosis may result in side effects from the anticoagulation treatment. Based on an overview of 24 studies the average annual frequencies of fatal, major, and major or minor bleeding during warfarin therapy were reported to be 0,6%, 3,0%, and 9,6% respectively. Bleeding during high-dose heparin therapy is common, with an average risk of approximately 2% per day of treatment (54). Nevertheless, numerous PE cases may go unrecognized and hence untreated, with serious outcomes. As modern medicine improves the longevity of patients with malignancy and cardiac and respiratory disease, PE may become an even more common clinical problem.

6.1 CLINICAL EVALUATION OF ACUTE PULMONARY EMBOLISM

PE has a wide range of clinical signs and symptoms and a reasonable clinical suspicion is required to avoid missing the diagnosis. Every study that documents the low diagnostic rate of PE comments upon the lack of specificity of the symptoms and signs of the disease. Symptoms are not rare in PE: they are simply nonspecific (55).

The use of standardized pretest clinical assessment prior to V/Q scanning has been validated and a simplified clinical model has been developed (56,57). The conclusion from these and other studies using standardised pretest assessment is that the discriminative sharpness is not yet sufficient in excluding VTE. A combination with other non-invasive diagnostic methods may enhance the possibility to exclude VTE.

The disadvantage with clinical judgement alone is that only experienced physician's achieve high diagnostic accuracy. The physicians' judgement may also be affected by variables that are not in a protocol, i.e. if the patient has visited the emergency ward earlier with a suspicion of PE, other colleagues' influence and other reasons. However, in study III the clinical judgement alone yielded high diagnostic accuracy in the groups with low or high probability, i.e. 91% and 81% correct diagnoses respectively, comprising 100 out of the 170 patients.

The conclusion from this study and others evaluating the clinical judgement alone, must be that the most important issue for the clinician is to think of the diagnosis and

raise the question if there is a reasonable possibility that the patient may suffer from PE or not. If so, the clinical judgement must be combined with diagnostic imaging methods.

6.2 PULMONARY ARTERIOGRAPHY

A tremendous effort has been spent on finding non-invasive diagnostic tests for pulmonary embolism in order to avoid pulmonary arteriography because of its invasive nature and thus associated with complications. However, later studies have shown that PA performed with non-ionic, low osmolar contrast medium (58) and modern angiographic technique has reduced the complication rate. We reported 0,1% major, 1,4% moderate/minor complications and no death among 707 PA in study I. Furthermore there are no absolute contraindications.

Despite the term "gold standard" for PA, the mean interobserver agreement varies depending on the size of the vessels. In study II we showed that of all 170 arteriograms at least one reader disagreed with the others in 28 cases (16%). In patients with PE in lobar vessels the interobserver agreement was 100%, with PE in segmental arteries the corresponding figure was 93% and in subsegmental arteries it was 63%.

The individual results of the three observers showed a good to very good agreement with the consensus interpretation. At six-month's follow-up, one of 119 patients in our study with a negative angiogram had suffered from a fatal recurrent PE. The consensus interpretation classified the arteriogram as negative but this was altered by the final outcome committee. The autopsy showed PE. Though conventional cut film has a higher spatial resolution, it is in our opinion that the dynamic sequence and temporal resolution in cine technique allows a more precise detection of small emboli, because of their movement during systole and diastole. In addition, motion artefacts are eliminated to a large extent.

The difficulties in interpretation were caused mostly because of low flow in combination with tortuous vessels.

In our study there were no arteriograms regarded as non diagnostic compared to 3% in the PIOPED study (1), 5% reported by Dalen et al (59), and 7% reported by van Beek et al using conventional cut film (60).

In the study by van Beek a comparison was made between PA using conventional cut film and intra-arterial DSA. DSA did substantially better which may reflect the fact that DSA gives 8 or more frames per second and gives a cine-image review. The image quality was better with DSA although two percent of the angiograms were inadequate. In the PIOPED study 380 patients with a negative angiogram were followed for one year and PE occurred in six patients (1,6%). Two of these were fatal. Other studies have shown that a negative angiogram rules out clinically significant emboli (61,62). Thus, PA is a safe method with low complication rate. The diagnostic accuracy is high when validated against the best possible "Gold Standard", a final outcome committee.

6.3 SPIRAL COMPUTED TOMOGRAPHY

Since the introduction of contrast medium enhanced spiral computed tomography of the pulmonary arteries (s-CTPA) in the diagnosis of acute PE, most studies have been performed to establish the sensitivity and specificity to detect PE. The reported sensitivity and specificity of s-CTPA has ranged from 53% - 100% and from 81% - 100% respectively (63). In a recent literature review the average sensitivity and specificity to detect

PE was 88% and 96% respectively (45). Both PA and s-CTPA are able to detect clots in central, lobar and segmental arteries with high accuracy and good interobserver agreement, but both methods are also afflicted with diagnostic difficulties regarding subsegmental PE (45,64). The question is, however, if this is of importance with respect to clinical outcome. The major strength with our study V compared to most other s-CTPA management studies is that it includes only patients with no coexisting symptoms and/or signs of DVT and none of them had undergone lower extremity venous studies. Notwithstanding, the prevalence of VTE episodes during the 3-months follow-up period was only 0.9% (95% CL 0.3-2.3%). This is well within the upper 95% confidence limit of 4% for the 3-months VTE risk accepted in similar outcome studies of PE (65). Though PE contributed to the death of two patients in our study (0.5%; 95% CL 0.06-1.6%) both had end-stage malignant disease. The cause of death was based on clinical judgement in 65% of the patients and in this cohort additional cases of PE can not be excluded. However, the autopsy frequency of 35% in the present report is more than the average number of autopsies in s-CTPA management studies. The hidden number of PE among deaths not subjected to autopsy is a source of error that in a similar way also affect management studies following negative pulmonary angiography and normal lung scintigraphy (45).

In summary, the present study V as well as three other studies (45,66,67) indicate that most patients with a clinical suspicion of acute PE and without symptoms of DVT, can be safely left without long-term anticoagulation following a negative result of s-CTPA. The introduction of multidetector spiral computed tomography (MSCT) in the late 1990s is another important technical improvement. These scanners are up to eight times faster than conventional single-section spiral CT scanners, allowing greater anatomic coverage and better longitudinal resolution during a single breath hold (68). Remy-Jardin showed that the proportion of examinations interpretable down to the subsegmental arteries was significantly higher with MSCT than s-CTPA. The frequency of examinations devoid of motion artefacts was also significantly higher with MSCT. This was particularly noticeable in the subgroup of patients with underlying respiratory disease (69). The improved image quality of CT angiograms that can be obtained with multislice CT will probably benefit particularly the patients with impaired respiratory function.

However, further management studies are warranted before any consequences can be drawn regarding the accuracy of a negative s-CTPA in critically ill patients, those with limited cardiopulmonary reserve and/or when a high clinical suspicion persists. In the meantime it would be judicious that such risk patients underwent additional testing in order to exclude VTE.

6.4 LUNG SCINTIGRAPHY

The ventilation-perfusion lung scintigraphy results in a large number of inconclusive results because: 1) only a minority of patients with suspected pulmonary embolism present with a high probability V/Q scan (31/170 or 18% in study III); 2) the high probability V/Q scan is very specific for pulmonary embolism (98% in study III) but lacks sensitivity (55% in study III). 3) Consequently, a large proportion of patients with proven pulmonary embolism (45% in study III) do have V/Q abnormalities other than those of high probability V/Q scan category. In patients with pre-existing chronic obstructive pulmonary diseases (COPD), the lung perfusion may be compromised due to reactive vasoconstriction from air-way obstruction resulting in perfusion defects. In

these cases the interpretation of the lung scan renders more difficulties. Several other disorders leading to perfusion defects and normal ventilation mimicking acute PE has been described (70,71).

The problem with V/Q lung scintigraphy is that it does not directly visualize thrombembolism but rather reflects its effects on perfusion and ventilation. This problem causes the need for probability criteria, which in turn causes confusing results and high interobserver disagreement (34). It is noteworthy that when the lung scintigrams in study III were read by three skilled observers at two different occasions, according to the revised PIOPED criteria, the prevalence for PE in the high probability category varied between 67-97% (72).

From our knowledge of V/Q lung scintigraphy today we can summarize as follows:

- a) A normal perfusion lung scan excludes clinically important PE, even though there are some case reports with false negative results.
- b) The clinical probability for PE affects the diagnostic value of the scintigraphic probability.
- c) A combined high clinical and high scintigraphic probability yields a PPV above 90%.
- d) A combined low clinical and low scintigraphic probability yields a PPV less than 10%.
- e) The interobserver disagreement is high, especially in other categories than normal or high probability scans.
- f) The number of inconclusive results varies between 30-80% depending on definitions, patient selection and diagnostic criteria.

6.5 D-DIMER

A number of studies using different latex agglutination D-dimer assays have been published with sensitivities and specificities ranging between 70-90% (73). Whole blood assays have a slightly better performance (22), and enzyme-linked immunosorbent assays (ELISA) have the highest sensitivities (90-100%) but relatively low specificity (30-40%) (23). The specificity of all D-dimer assays is low because these degradation products are produced whenever there is active intra- or extra vascular fibrin formation and fibrinolysis in the body. The specificity is especially low among inpatients and in the elderly because these patients are often found with a variety of confounding conditions. If D-dimer assays are to be used in the workup of acute PE the diagnostic level must be determined and compared with a gold standard, which still is PA. However, most studies are using different non-invasive diagnostic algorithms and different D-dimer assays are seldom used for comparison in the same patient. Therefore we chose to compare two cut off levels for D-dimer concentration. The lower one achieved the same sensitivity as s-CTPA at a cost of low specificity. The higher one lost substantially in sensitivity, but resulted in a higher specificity.

Recent studies using PA as reference method indicate that the D-dimer sensitivity may depend on the thrombus burden, i.e. the tests have poor NPV in subsegmental emboli, but segmental or massive PE can safely be excluded by a negative D-dimer result (20). However, our study could only partially confirm this finding: in seven patients with normal D-dimer levels, two had bilateral, lobar artery PE.

In our study the pretest clinical suspicion for acute PE was high, although no patient was hemodynamically unstable. s-CTPA had a NPV of 95% and the corresponding figure for the latex D-dimer assay using 0.25 mg/L as cut off level, was 92%. Using 0.5

mg/L as cut off level, the NPV was 87%. These results implicate, that the rapid, latex D-dimer agglutination method is a valuable screening method for ruling out significant PE in most cases, when suspected in stable outpatients.

In conclusion we found that in hemodynamically stable patients suspected of having acute PE, there is good agreement between PA and s-CTPA. In hemodynamically stable patients, s-CTPA has high sensitivity and specificity. A negative s-CTPA should safely rule out the existence of clinically important PE. A negative latex agglutination D-dimer test using a cut-off level of 0.25 mg/L, would rule out clinically significant PE with almost the same certainty.

7 CONCLUSIONS AND FINAL REMARKS

The general purpose of this thesis was to evaluate pulmonary arteriography, lung scintigraphy and spiral computed tomography for the diagnosis of acute pulmonary embolism and to study if a clinical probability score or a simple blood test such as D-dimer could improve the diagnostic accuracy.

This thesis supports the following conclusions regarding the diagnosis of acute pulmonary embolism:

- Pulmonary arteriography is a safe and accurate method when compared to final outcome analysis, and thus will continue to be regarded as the "Gold Standard".
- Lung scintigraphy excludes clinical important PE if the perfusion is normal. The method's diagnostic value is enhanced when the clinical probability is added to evaluation of a pathological scintigram.
- Clinical evaluation is fairly accurate to discriminate subgroups of patients with low or high probability of PE.
- Measuring D-dimer levels in the blood using latex agglutination assays is a valuable screening method for excluding PE. A D-dimer concentration in plasma below 0.25 mg/L, would rule out clinically significant PE with almost the same certainty as s-CTPA. Patients with a D-dimer result exceeding 0.25 mg/L should have a s-CTPA for ruling out or confirm the diagnosis, when suspected.
- Spiral computed tomography of the pulmonary arteries is an accurate method in ruling out or confirm acute pulmonary embolism.

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