Tomographic ventilation-perfusion lung scintigraphy in cardiopulmonary disease

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"If you think you have things under control,
you are not going fast enough"
-Mario Andretti

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List of publications

This thesis is based on the following papers, which in the text will be referred to by their Roman numerals.

I. **Jögi J**, Palmer J, Jonson B, Bajc M.
Heart failure diagnostics based on ventilation/perfusion single photon emission computed tomography pattern and quantitative perfusion gradients. *Nucl Med Commun*. 2008; 29(8):666-73

II. **Jögi J**, Jonson B, Ekberg M, Bajc M.
Ventilation-perfusion SPECT with 99mTc-DTPA versus Technegas: a head-to-head study in obstructive and nonobstructive disease. *J Nucl Med*. 2010; 51(5): 735-41

III. **Jögi J**, Ekberg M, Jonson B, Bozovic G, Bajc M.
Ventilation/Perfusion SPECT in chronic obstructive pulmonary disease: an evaluation by reference to symptoms, spirometric lung function and emphysema, as assessed with HRCT. *Submitted*.

IV. Begic A*, **Jögi J***, Hadziredzepovic A, Kucukalic-Selimović E, Begovic-Hadzimuratovic S, Bajc M.
Tomographic ventilation/perfusion lung scintigraphy in the monitoring of the effect of treatment in pulmonary embolism: serial follow-up over a 6-month period. *Submitted*.

* These authors contributed equally to the study and are listed in alphabetical order.

Summary

Respiration is essential to life and relies, among other things, on the balance between regional ventilation and perfusion. There are many cardiopulmonary diseases, such as pulmonary embolism (PE), chronic obstructive pulmonary disease (COPD) and left heart failure (LHF), which can affect respiration negatively. The diagnosis of PE, COPD and LHF follows separate diagnostic pathways. The symptoms that cause the patient to seek medical care are overlapping. This results in a diagnostic dilemma that is complicated by the fact that cardiopulmonary diseases often coexist.

Ventilation and perfusion can be imaged with lung scintigraphy. Lung scintigraphy is primarily used to diagnose PE. In recent years, the introduction of 3-dimensional tomographic ventilation-perfusion lung scintigraphy (V/P SPECT) has resulted in an improved accuracy in the diagnosis of PE. Follow-up with V/P SPECT may lead to better individualization of PE treatment, but has not yet been evaluated. Changes in ventilation and perfusion are also found in COPD and LHF. V/P SPECT may have a clinical role in the diagnosis and characterization of COPD and LHF, but this has been insufficiently studied. Therefore, this thesis focuses on the potential role of V/P SPECT in the follow-up of PE and in the diagnosis and classification of LHF and COPD.

In **study I**, we found that V/P SPECT can be used to diagnose LHF with a high positive predictive value. We developed an algorithm to objectively calculate perfusion gradients and found that an inverted gravitational gradient in the lungs is indicative of LHF. It was also shown that LHF was common among patients with suspected PE.

In **study II**, we compared ventilation studies performed with ^{99m}Tc-DTPA and ^{99m}Tc-Technegas, in patients with and without obstructive lung disease. This study showed that ^{99m}Tc-Technegas, due to a more homogeneous distribution with less focal deposition and better peripheral penetration, should be regarded as the preferred radioaerosol in V/P SPECT studies.

Study III indicated an additional value of V/P SPECT in the diagnosis of COPD, compared to HRCT and spirometry. V/P SPECT could also be used to characterize the severity of COPD.

In **study IV**, we found that restoration of regional perfusion after acute PE occurred during the first 3 months of treatment, but not thereafter. Follow-up after an episode of PE, using V/P SPECT, seems important since about 20% of the patients had remaining perfusion defects at 3 months after diagnosis, although all were free from symptoms.

Populärvetenskaplig sammanfattning (Summary in Swedish)

En välfungerande andning med utbyte av syrgas och koldioxid mellan kroppen och omgivningen är en förutsättning för liv. För att detta gasutbyte ska fungera krävs bl. a. att ventilationen, dvs. in- och utflödet av luft i lungorna, står i balans med blodflödet genom lungorna. I lungorna tar blodet emot syrgas som behövs för att cellerna i kroppen ska fungera och samtidigt avges den koldioxid som kroppen bildat i ämnesomsättningen. Det finns många sjukdomstillstånd i hjärta och lungor som kan påverka gasutbytet negativt. Flera av dem är allvarliga och några behöver snabb behandling. Exempel på sådana sjukdomstillstånd är lungembolism (LE), hjärtsvikt och kronisk obstruktiv lungsjukdom (KOL).

Akut LE kan uppträda när man drabbats av en blodpropp i benen. Bitar av det levrade blodet i benen kan då lossna och transporteras till lungorna där det orsakar en avstängning av ett eller flera kärl. LE är ett allvarligt tillstånd som kräver snabb behandling med blodförtunnande mediciner.

Hjärtsvikt kännetecknas av att hjärtat inte längre klarar att tillgodose de krav som kroppen ställer. Patienten drabbas då av andfåddhet, tilltagande trötthet och vätskeansamling i bland annat lungorna. En tidigt insatt behandling förbättrar oftast förloppet för patienten.

KOL är en inflammatorisk sjukdom som främst drabbar luftvägar och lungvävnad. Sjukdomen leder till att luftflödet hindras och till att lungvävnaden förstörs; det bildas emfysem. Rökning är orsaken till KOL i 90 % av fallen. Många har KOL utan att veta om det eftersom besvären kommer smygande. En tidig diagnos är viktig eftersom tidigt insatta åtgärder med rökstopp är den effektivaste behandlingen.

Besvären som dessa olika sjukdomstillstånd orsakar, i form av t ex andfåddhet, tilltagande trötthet, obehag från bröstet och hosta, är gemensamma. Tillvägagångssätten för att ställa diagnoserna LE, hjärtsvikt och KOL skiljer sig dock åt. Detta leder till ett diagnostiskt dilemma som förstärks av det faktum att sjukdomarna ofta förekommer samtidigt.

Fördelningen av ventilationen och blodflödet i lungorna kan avbildas med lungscintigrafi. Lungscintigrafi är en nuklearmedicinsk metod som främst använts för att diagnostisera akut LE. På senare år har introduktionen av 3-dimensionell tomografisk lungscintigrafi (V/P SPECT) lett till en förbättrad diagnostik avseende LE. V/P SPECT skulle också kunna ha en roll i uppföljningen av patienter som drabbats av LE för att möjliggöra en mer individuellt anpassad medicinering. Detta är dock ännu inte studerat. Förändringar i ventilation och lungblodflöde ses också vid hjärtsvikt och KOL. V/P SPECT skulle eventuellt även kunna bidra till en bättre diagnostik och klassificering av dessa tillstånd. Denna avhandling fokuserar således på den möjliga rollen för V/P SPECT vid uppföljning av LE och vid diagnostik och klassificering av hjärtsvikt och KOL.

I **studie I** fann vi att V/P SPECT kan användas för att diagnostisera vänstersidig hjärtsvikt. Finner man en omfördelning av blodflödet till mer högt belägna delar av lungorna talar detta med relativt stor säkerhet för att patienten lider av vänstersidig hjärtsvikt. I studien utvecklade vi också en programvara för att objektivt beräkna denna omfördelning av blodflödet. En annan observation var att förekomsten av hjärtsvikt var så hög som 15 % hos patienter där man egentligen misstänkte ett de led av LE.

För att kunna studera ventilationen är det viktigt att de radioaktiva ämnen som används verkligen avbildar ventilationen på ett tillförlitligt sett. De måste därför följa luftströmmarna ända ut i lungornas minsta delar, alveolerna. Oftast används Technetium (^{99m}Tc) märkta aerosoler som patienten får andas in. Detta är lätthanterligt och ger en låg stråldos till patienten. De vanligaste aerosolerna är ^{99m}Tc-DTPA och ^{99m}Tc-Technegas. Trots att dessa aerosoler skiljer sig åt i sina egenskaper har man ännu inte studerat hur deras förmåga att avspegla ventilation skiljer sig hos en och samma patient. I **studie II** ville vi därför studera detta, både hos patienter med och hos patienter utan KOL. Vi fann att ^{99m}Tc-Technegas, pga en jämnare fördelning och en bättre förmåga att tränga ut i lungornas periferi, är att föredra vid ventilationsstudier med V/P SPECT.

I **studie III** använde vi oss av V/P SPECT för att studera patienter med KOL. Resultaten från V/P SPECT undersökningarna jämfördes med resultaten från spirometri och skiktröntgen (CT) samt relaterades till hur mycket symtom och vilken grad av funktionsnedsättning patienterna hade. Denna studie talar för att V/P SPECT kan bidra vid diagnostiken av KOL och att V/P SPECT också kan användas för att bedöma svårighetsgraden av den obstruktiva lungsjukdomen.

I **studie IV** använde vi V/P SPECT för att följa sjukdomsförloppet för patienter som behandlades för akut LE. Patienterna följdes med upprepade V/P SPECT undersökningar under sex månader för att se hur fort störningarna i blodflödet normaliserades. I denna studie fann vi att den förbättring av lungfunktionen som sker, den sker inom de första tre månaderna. Blodflödesstörningar som kvarstår

efter tre månader förefaller sedan att kvarstå väsentligen oförändrade. Bland de patienter som ingick i studien hade c:a 20% kvarstående defekter i blodflödet tre månader efter diagnos, trots att de alla då var fria från besvär. Kvarstående lungembolier är en riskfaktor för att utveckla förhöjda tryck i lungartärerna. Även om större studier behövs, talar detta för att en objektiv uppföljning med V/P SPECT 3 månader efter akut LE kan vara betydelsefull för att bättre styra den fortsatta handläggningen av patienterna.

Abbreviations

^{81m}Kr	^{81m}Krypton
^{99m}Tc	^{99m}Technetium
^{131}Xe	^{131}Xenon
ATS	American thoracic society
CO_2	Carbon dioxide
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed tomography. In the text used for X-ray computed tomography.
CTPA	CT pulmonary angiography
D_LCO	Diffusion capacity for carbon monoxide
DTPA	Diethylene triamine pentaacetic acid
EF	Ventricular ejection fraction, i.e. stroke volume/end-diastolic volume.
ERS	European respiratory society
FEV_1	Forced expiratory volume in 1 second
$\%FEV_1$	Forced expiratory volume in 1 second as percent of predicted
FVC	Forced vital capacity
FRC	Functional Residual Capacity
GOLD	Global initiative for chronic obstructive lung disease
HRCT	High resolution CT
LHF	Left heart failure
LMWH	Low molecular weight heparin
MMAD	Mass median aerodynamic diameter
O_2	Oxygen
PE	Pulmonary Embolism
PPV	Positive predictive value
SPECT	Single photon emission computed tomography
TLC	Total lung capacity
VC	Vital capacity
V/P	Ventilation/Perfusion

Introduction

Respiration

Respiration could be defined as the processes concerned in gas exchange between an organism and its surroundings.[1] In complex multicellular animals, such as humans, the major goals of respiration are to provide the tissue cells with oxygen (O_2), which they need to live and carry out their functions, and to remove carbon dioxide (CO_2) formed by intracellular metabolic processes.[1]

Functional role of the respiratory system

Because of the distance between the surrounding air and the innermost cells, an effective respiratory system is needed. The basic processes of the respiratory system are usually separated into four key functions:[1]

- ventilation: the movement of air between the outside atmosphere and the lung alveoli.
- pulmonary diffusion: the movement of O_2 and CO_2 across the alveolar-capillary membrane.
- perfusion: the inflow of deoxygenated mixed venous blood from the body to the gas-exchange units by the pulmonary arterial circulation. Then the transport of oxygenated blood from the lungs, through the pulmonary veins and out to the tissue cells of the body.
- regulation of ventilation in accordance with changing metabolic demands.

As the CO_2 level in arterial plasma is controlled by changes in ventilation, this process has an important role in the regulation of acid-base balance and in maintaining constant conditions in the internal environment (homeostasis).[1,2]

In cardiopulmonary disease, respiration may directly or indirectly be

compromised in a variety of ways, by alterations in ventilation, perfusion or disturbances in gas-exchange over the alveolar-capillary membrane.

The anatomy of the lungs

The most important organ in the human respiratory system is the lungs, which occupies a major part of the thoracic cavity. Each lung is surrounded by pleurae and is connected to the mediastinum at the hilum by blood and lymphatic vessels, nerves and main bronchi. Each lung is subdivided into lobes. In the right lung there are the upper, middle and lower lobes, partitioned by the oblique and horizontal fissures. The left lung is subdivided by the oblique fissure into the upper and lower lobes.[3] Each lobe is in turn subdivided into a number of bronchopulmonary segments, which are the independent anatomical and functional units of the lungs.[3,4] Each segment is served by its own segmental artery and vein, and exchange air with the atmosphere by an independent segmental bronchus.[3] The bronchopulmonary segments are clinically important as many pulmonary diseases typically affect the lungs in a segmental manner.[4,5]

After entering the bronchopulmonary segments, the bronchus divides repeatedly up to about 20 times, and gives rise to the bronchioles.[6,7] Bronchioles are <1 mm in diameter and lack cartilage in their walls. Bronchioles divide into terminal respiratory bronchioles, which finally branches into alveolar sacs consisting of several alveoli. The alveoli are surrounded by a capillary network, and these together with the terminal respiratory bronchioles form the basic gas-exchanging units of the lungs. Although ventilation occurs primarily via the bronchial system, alveoli can to some degree be aerated through collateral ventilation if conducting airways have been blocked.

The gas-exchanging units receive mixed venous blood from the right chamber through the pulmonary circulation, whereas the rest of the lung parenchyma, including conducting airways, is supplied from the bronchial circulation.[3] The bronchial arteries originate from the aorta and provide the lung parenchyma with oxygenated blood.

The pulmonary circulation is a low pressure system. In the normal human, the pulmonary arterial pressures are about 25/8 mmHg, with a mean arterial pressure of 15 mmHg.[1] The pulmonary capillary system is the largest capillary bed in the body with a surface area of up to 80 m^2.[7] Under normal resting conditions the blood volume of the lungs is about 9 % of the total blood volume.[1] This proportion can rapidly change due to a range of physiological as well as pathophysiological conditions, such as body position, exercise, bleeding or left heart failure (LHF).

Breathing under normal conditions

Breathing is controlled by the autonomous nervous system that regulates the depth and rate of breathing in response to the body's needs, primarily the plasma CO_2 level. Breathing can also, to a large degree, be voluntarily controlled, e.g. when speaking or holding your breath.[8] In humans, inhalation is driven by the build-up of negative pressures in the most distal airways.

In the normal lung, the air in the alveoli is in continuum with the surrounding atmosphere through the conducting airways. Therefore, when no airflow occurs and the glottis is open, the pressure in the alveoli equals the surrounding atmospheric pressure. Under these conditions, the only force that prevents the elastic lung from collapsing is the slightly negative pressure in the pleural space. During inspiration, when the pleural cage expands, the pleural pressure becomes more negative. Dependent on the elastic forces of the lung, this causes a fall in the alveolar pressure so that it becomes slightly lower than the atmospheric pressure. As a result air flows into the alveoli. The opposite conditions occur during expiration. Then, the alveolar pressure exceeds the atmospheric pressure and forces the air out from the alveoli.

The extensive branching of airways leads to a progressive increase in cross sectional area and hence lowered resistance with every division.[6] In the normal lung, only about 25% of the intrathoracic airway resistance is located in bronchi and bronchioles.[9] Moreover, as the airways from trachea and down only account for about 50% of the total airway resistance, the small airways (< 2 mm) only account for 10-15% of the total airway resistance. Therefore, pathological processes may accumulate for many years in the peripheral conducting airways with very little symptoms or signs of disease. Mead named this "the Lung's quiet zone".[10]

Ventilation and perfusion distribution in the normal lungs

Pleural pressure varies along the direction of gravity.[11-14] This difference in pleural pressure, and hence the transpulmonary pressure, has been regarded the main reason to the observed vertical gradient in lung expansion.[15,16] At functional residual capacity (FRC) the alveoli were found to be less expanded in lower parts of the lungs compared to upper regions.[14-18] This leaves the dependent alveoli more compliant to expand at the beginning of inspiration.[14] Early studies, using radioactive gases, confirmed that ventilation was greater in lower compared to upper lung regions.[14-16,19]

The regional blood flow was also demonstrated to be non-uniform,

following the same vertical distribution as ventilation, with greater perfusion in lower compared to upper regions of the lungs.[20,21]

These observations lead to the formation of the zonal model by West et al. in which the non-uniform distributions of regional ventilation and perfusion are explained by the shared forces of gravity.[22,23] The early studies using radioactive tracers examined relatively large lung regions. Several contemporary as well as subsequent studies, however, have shown that heterogeneity of regional ventilation and perfusion also exists within isogravitational planes, at least at higher spatial resolution.[24-27] Some authors have even expressed the opinion that gravity is not the main determinant of regional blood flow distribution, based on high-resolution animal studies performed with microspheres.[28,29] These differences of opinion have lead to debate.[30,31] Still, gravity is regarded a major determinant of regional ventilation and blood flow. However, other factors, probably related to the anatomy of the pulmonary vascular and bronchial tree, are also important.[30-34]

Nominal units in which the regional perfusion and ventilation are presented vary and this complicates interpretation. When posture is changed, there is a shift of lung tissue to dependent zones in accordance to gravity.[32] As a result, lower lung zones contain higher numbers of lung units. This contributes to an increase in regional blood flow and ventilation per unit lung volume. The change in blood flow per unit lung tissue (i.e. per alveolus) is less pronounced.[21,28,29,32]

Some authors have found that the alveoli are more uniformly expanded at FRC in prone compared to supine position.[18,35-37] This could be a result of the position of the heart, which in prone position does not exert the same pressure on the lung parenchyma as in supine position.

In addition to gravity and the morphological properties of vessels and bronchi, there are functional modifiers of regional ventilation and blood-flow, such as airway pressure and breathing phase.[38] The greatest vertical differences in blood flow per alveolus are seen at total lung capacity (TLC), whereas the greatest gradient in alveolar expansion is found at FRC.[39,40] Hypoxic pulmonary vasoconstriction is a physiological phenomenon that influences regional pulmonary blood flow.[41] As a response to alveolar and local arterial hypoxia, pulmonary arteries constrict and blood flow is redirected to alveoli with higher oxygen content. Hypoxic pulmonary vasoconstriction is important in diseased lungs as well as at high altitudes.

The balance between ventilation and perfusion

The foundation for an efficient pulmonary gas-exchange is the balance between ventilation and perfusion in the lungs. Under normal conditions there is a close relation between regional ventilation and perfusion.[42,43] However, the match is not perfect. Even in normal subjects most studies have reported somewhat greater vertical gradients for perfusion than for ventilation, explained by the greater influence of gravity on blood.[16,20,21,44-46] This results in lower ventilation to perfusion (V/P) ratios in lower parts of the lungs. The V/P ratio for the whole lungs varies in the range of 0.8 to 1.2.

Disturbance in the balance between pulmonary ventilation and perfusion leads to impaired gas exchange and, when severe, hypoxemia. Regional inequalities in V/P ratios can be found in a diversity of cardiopulmonary diseases, such as pulmonary embolism (PE), left heart failure (LHF) and chronic obstructive pulmonary disease (COPD).

Cardiopulmonary diseases that affect pulmonary ventilation and perfusion

Pulmonary embolism

Acute PE is a severe and potentially deadly condition. PE has a historical mortality rate of approximately 30% if untreated.[47] In more recent studies, were most patients have obtained treatment, mortality rates of 8-15% have been reported.[48-50] Even if non fatal, PE leads to chronic thromboembolic pulmonary hypertension in up to 4% of patients at 2-years follow up.[51,52] PE is notorious for its unspecific symptoms and the exact incidence has therefore been difficult to establish. In the Western world the reported incidence of PE ranges from about 50 to 200 cases per 100,000 person years.[53-56] PE is typically caused by migration of dislodged thrombi to the pulmonary circulation from the deep veins of the lower extremities. The occlusive emboli affect individual pulmonary arteries at the lobar, segmental or subsegmental levels.[57] Because each bronchopulmonary segment is supplied by a single end-artery, the blood flow peripheral to the embolus is either reduced or occluded in a segmental manner. As ventilation is usually preserved within lung segments affected by PE, this results in a segmentally elevated V/P ratio, or V/P mismatch. Ventilation of unperfused lung regions in PE will cause increased dead space.[58] Pulmonary blood flow is also redirected away from vessels obstructed by PE to open lung regions which

become over-perfused.[59] Acute PE affecting >30-50% of the pulmonary bed has hemodynamic consequences.[60] Large or multiple emboli might abruptly reduce the cross-sectional area of the pulmonary arterial bed. This can lead to an acute increase in the pulmonary vascular resistance to a level of afterload, which cannot be matched by the right ventricle.[61] Right heart failure, hypotensive syncope, electromechanical dissociation and sudden death may occur.[57] An inverted pressure gradient between the right and left atrium can lead to right-to-left shunt through a patent foramen ovale, which may contribute to hypoxemia and result in paradoxical emboli to the systemic circulation.[62]

There are both inherited and acquired risk factors associated with the development of venous tromboembolism.[63] The inherited risk factors include congenital hypercoagulable states such as deficiencies in antithrombin III, Protein C, Protein S etc. Well known acquired factors are cancer, major surgery, recent immobilization, flight travel, obesity and congestive heart or respiratory failure.[64] It is important, however, to recognize that 26-47% of cases with a first time diagnosis of venous tromboembolism are idiopathic.[55]

Although PE can be asymptomatic, 90% of patients with PE present with symptoms of which dyspnea, tachypnea or chest pain (pleuritic or central) are the most common.[65,66] Other symptoms and signs include cough, palpitations, syncope, oxygen desaturation, hypotension and ECG changes. All these clinical findings are non-specific and common in other diseases than PE. Although laboratory tests such as D-dimer (which measures plasma levels of a derivate of cross-linked fibrin) might sometimes be useful in low-risk patients, the diagnosis and exclusion of PE relies on medical imaging.[61,67] V/P lung scintigraphy and CT pulmonary angiography (CTPA) are the most available and used examinations to diagnose PE today.[68]

Ever since the study by Barritt and Jordan in 1960, it has been known that early diagnosis and treatment of PE are life saving.[47] The benefit of unfractionated or low-molecular-weight heparin (LMWH) followed by oral anticoagulation with vitamin K antagonists are well defined.[61,69,70] The optimal duration of therapy, however, remains a matter of controversy. It is still under debate whether therapy should be pursued for 3-months, 6-months, or even longer after a first incident of unprovoked PE.[61,69-73] The length of oral anticoagulant therapy in an individual patient must balance the estimated risk of recurrence after treatment termination against the risk of iatrogenic bleeding while on anticoagulant therapy.[61] The annual risk of major or fatal bleeding during oral anticoagulant treatment varies from 1.3 to 3.4%.[74,75] The optimal method to assess the individual risk of PE recurrence is at present undefined. The risk of recurrence most likely depends both on whether the acute episode of PE was effectively treated and on the existence of continuous risk factors.[71] Decisions of

prolonged anticoagulant therapy, however, is most often based on the prevalence of continuous risk factors rather than on an objective evaluation of treatment efficiency.[75] This may potentially lead to both under- and overtreatment in individual patients. There could also be potential risk that the development of chronic PE stays undetected if no objective follow-up is performed.

Chronic obstructive pulmonary disease

The American Thoracic Society (ATS), the European Respiratory Society (ERS) and the Global initiative for chronic obstructive lung disease (GOLD) all defines COPD as a preventable and treatable disease characterized by airflow obstruction that is not fully reversible.[76,77] Chronic airflow limitation is caused by a combination of airway obstruction and parenchymal destruction (emphysema). The relative contributions of each component may vary from patient to patient. The airflow limitation is usually progressive.

COPD is a major cause of both morbidity and mortality globally.[78] COPD remains one of the few diseases that still continue to rise in its numbers in many countries, particularly among women.[78,79] In the last 20 years the mortality in COPD has doubled among women. In 2001 COPD was the fifth leading cause of death worldwide and it has been estimated to become the third leading cause of death by the year 2020.[80,81] The estimated prevalence of COPD in the population varies between studies from about 5 to 20%, depending on diagnostic criteria, survey and estimation methods.[77,82-85] Prevalence values based on diagnosed disease and morbidity data underrate the burden since COPD is often not diagnosed until the person is symptomatic.[80] Because of the long pre- and subclinical phase of COPD, patients have time to adapt to their decreased pulmonary capacity. A majority of diagnosed COPD subjects therefore also underestimate the severity of their disease.[86]

Cigarette smoking is the most important risk factor and cause 80-90% of COPD cases.[87] The fact that COPD is prevalent in both developed and developing countries is mainly a result of the tobacco epidemic.[80] In the late 1970's Fletcher et al prospectively showed that tobacco smoking accelerated the age related decline of forced expiratory volume in 1 s (FEV_1), and that smoking cessation halted this rapid decline.[87] It is therefore important to diagnose COPD early as smoking cessation is the only causal intervention for patients at all stages of COPD.[88] Furthermore smoking cessation reduces the risk of hospital admission and lowers the long-term all-cause mortality in COPD patients.[89,90] The second most important risk factor of COPD is occupational exposure to chemicals and harmful dusts and fumes.[91]. However, the risk of developing COPD due

to occupational exposure is greater when the person is a smoker.[77,91] Alpha-1 antitrypsin deficiency is a well documented, but rare, hereditary genetic risk factor most frequently seen in persons of Northern European origin.[92] It is associated with the accelerated development of panlobular emphysema. The increased risk to develop airway obstruction among smoking siblings of patients with COPD indicates that other genetic risk factors contribute to the susceptibility to develop COPD.[93].

Cigarette smoke, as well as other environmental irritants, cause inflammation in the lungs. In patients who develop COPD it is recognized that the inflammatory response is amplified beyond the normal protective level.[77,94,95] Small airways and the surrounding alveoli are the key sites of inflammation. Chronic inflammation leads to structural changes such as fibrosis, airway wall thickening, airway narrowing (obstructive bronchiolitis), alveolar wall destruction (leading to emphysema) and also pulmonary vascular changes with endothelial dysfunction and hyperplasia of intima and vascular smooth muscle.[96]

There is increasing recognition of COPD as a disease with significant systemic manifestations and comorbid conditions.[97,98] Hence, the disease is not restricted to the airways, as airflow limitation and emphysema, but also presents with several extrapulmonary abnormalities.[98] It is still not known if these systemic manifestations are a result of systemic spill-over of the inflammatory events occurring in the lungs, or if the pulmonary manifestations of COPD rather are one form of expression of a systemic inflammatory state with multiple organ involvement. Common comorbidities that complicate the clinical manifestation of COPD are: left heart failure (LHF), arteriosclerotic disease, metabolic syndrome (diabetes, dyslipidemia and hypertension), cancer, pulmonary vascular disease and pulmonary embolism.[98-100] In patients with stable COPD the prevalence of previously unknown concomitant LHF has been reported to be about 20% and even higher in patients with exacerbation.[101-103] The prevalence of PE among COPD patients hospitalized with exacerbation has been reported to be as high as 20-30% but is generally underdiagnosed.[104-106] Differentiation between COPD, LHF and PE is hampered by similarities in symptoms and signs. A diagnostic method that could assess all three diseases would be of value.

In COPD, airway obstruction and emphysema lead to inhomogeneous regional ventilation. Ventilation could regionally be completely absent. Perfusion within the lung becomes abnormal as the lungs attempt to adapt blood flow to ventilation to preserve an efficient gas exchange. V/P defects in emphysema are often more or less matched due to the concurrent destruction of airways and blood vessels of the respiratory units. Matched defects has also been observed in airway obstruction, probably as a result of "protective" hypoxic vasoconstriction.[23] If hypoxic vasoconstriction is incomplete, regions with low V/P ratios, or reverse

mismatch, will appear. Vascular remodelling in COPD may result in regions with elevated V/P ratios. In later stages of COPD, may vascular wall changes and hypoxic vasoconstriction lead to the development of pulmonary hypertension.[107] The regional changes of ventilation and perfusion in different phenotypes of COPD are still not fully understood and needs to be studied further. Studies of V/P patterns might become important in the characterization of COPD.[108]

The diagnosis of COPD should, in accordance to major guidelines, be considered in any patient with a history of exposure to risk factors, particularly in those with symptoms of cough, sputum production and/or dyspnea.[76,77] The presence of non-reversible airflow limitation is assessed with spirometry and the diagnosis of COPD is defined as the finding of a post bronchodilator FEV_1/VC ratio of less than 0.7 (VC measured as either forced or slow vital capacity).[76,77,109] The fix ratio is easy to use but has drawbacks as FEV_1/VC also declines with normal aging. This leads to the overestimation of the ventilatory defect in older people, as well as a risk of underestimation in younger persons. Some authors have instead advocated the use of the lower limit of normal (LLN) values to diagnose COPD, in which the lower 5% of the population is regarded as abnormal.[109,110] However, the LLN method depends on the reference value that is used, and this varies.[110] In the Swedish national guidelines, persons more than 65 years old must instead have a FEV_1/VC ratio of <0.65 to be diagnosed with COPD.[111]

The severity staging of COPD is assessed with FEV_1 alone and commonly classified as mild, moderate, severe or very severe based on specific FEV_1 values in percent of predicted (%FEV_1) (e.g. 80, 50 and 30 %FEV_1). One problem with FEV_1 is that it is a rather insensitive method to detect airway changes in COPD as these mainly occur in small airways. Furthermore, emphysema and other lung disease can be present although FEV_1 is within normal limits.[112,113] The statement that only 15-20% of smokers develop COPD is therefore misleading and studies show that the prevalence of emphysema among long term smokers could be about 2-3 times as high.[112,113] Reversely, in a study by Gelb et al., 35 out of 81 patients with severe fixed airflow obstruction (%FEV_1<50%) had no or only trivial emphysema.[114] Spirometric classification is a predictor of morbidity and mortality when applied to COPD populations, but not in individual patients.[76,78] FEV_1 measures the degree of airflow limitation but gives no information on the underlying pathophysiology. It is therefore accepted that spirometry alone cannot explain the complex clinical consequences of COPD.

High resolution CT (HRCT) can be used to assess the extent, type and localisation of emphysema and also the presence of airway wall thickening in COPD.[115] In this way HRCT can provide morphological information, however, it gives no functional evaluation. Several studies have reported that the correlation between airflow limitation (measured with FEV_1) and the degree of emphysema

or small airway disease (as measured with HRCT) is poor or absent.[114,116] HRCT is today only recommended if the COPD diagnosis is in doubt or if lung volume-reduction surgery is considered.[76,77]

The degree of functional impairment, dyspnea and symptoms can be used to predict prognosis and future mortality risk.[117,118] This can be assessed with different questionnaires such as the modified medical research council questionnaire (MRC) regarding the effect of breathlessness on daily activities and the clinical COPD questionnaire (CCQ) regarding symptoms and functional state.[117,119] Yet, these scales correlate poorly or not at all with spirometric measures of airflow limitation.[117,118,120] When combining the information of body-mass index, degree of obstruction (FEV_1), dyspnea and exercise capacity (6-min walk test) this could better predict mortality in COPD patients than lung function alone.[121]

Hence, COPD is a heterogeneous condition with much systemic comorbidity. Better diagnostic tools to understand and categorize the different phenotypes of COPD are requested.[78]

Left heart failure

Left heart failure is a complex clinical syndrome that can follow upon any cardiac disorder that affects the ability of the left ventricle to function as a pump. In LHF the left ventricle is unable to meet the functional demands of the body. However, LHF is not the same thing as left ventricular dysfunction. LHF is a clinical diagnosis that needs the presence of symptoms, typically dyspnea and fatigue, and signs of pulmonary fluid retention in combination with some objective evidence that these findings are the consequence of a functional or structural abnormality of the heart.[122] Myocardial pathology is the most common reason for LHF. Coronary heart disease is in turn the most common cause of myocardial disease, being the initiating factor in about 2/3 of patients with systolic LHF. Cardiomyopathies, valvular disease, hypertension, tachyarrhythmias, viral infections, alcohol abuse and congenital heart disease are examples of other initiating causes.[122] About two percent of the population in developed countries have heart failure.[122,123] The average age at diagnosis is 76 years.[122,124] The prevalence of LHF is rising because of the aging of the population and the effective treatment of patients suffering from coronary events. Heart failure has a poor prognosis with a mortality rate similar to that of many malignancies.[124,125] However, in Sweden, as well as in other countries, modern heart failure therapy has shown to decrease both morbidity and mortality from LHF.[126] Sometimes even causal treatment can be given. Early detection of LHF is therefore important.

LHF is often separated into systolic or diastolic heart failure depending

on whether the left ventricle has impaired ability to eject or fill with blood.[127] Patients with diastolic LHF have symptoms and/or signs of LHF but a preserved ejection fraction (EF).[128] The distinction between systolic and diastolic heart failure is somewhat arbitrary and many patients with LHF have evidence of both systolic and diastolic dysfunction.[122]

Regional hypoperfusion rather than hypoventilation characterize the pulmonary gas exchange in LHF.[129] Already in the 1960s Friedman and Braunwald, West and others showed that patients with mitral valve disease demonstrated an inversion, or "cephalization" of the normal dependent distribution of blood flow.[130,131] In their studies, redistribution of blood to upper lung zones correlated with an elevated pulmonary venous pressure. The inverted distribution of blood flow has also been demonstrated in patients after myocardial infarction and in patients with other causes of LHF.[132,133] To explain the inverted blood flow distribution in LHF many theories have been suggested, but there is still no consensus. Ventilation is not affected to the same degree as perfusion. This results in an increased dead space in pulmonary congestion. In patients with stable LHF lung function is predominately restrictive. However, in patients with decompensated LHF, airway obstruction caused by oedema and airway hyperresponsiveness is common. Oedema and alveolar flooding can also hinder the diffusion of gases over the alveolar-capillary membrane.

Although largely a clinical diagnosis, symptoms of LHF overlap with those described for PE and COPD. In patients with the most common risk factor, coronary disease, dyspnea only had a positive predictive value of about 25% for systolic LHF.[124] It has also been shown that clinicians frequently disagree in the recognition of physical signs of heart failure, and that these signs have an unpredictable relationship with Chest X-ray (CXR) and measurement of left ventricular performance.[134]

It is more common with COPD among patients with heart failure than the general population. The prevalence of COPD in patients with heart failure has recently been reviewed and varies from 9 to 41% in European cohorts, and from 11 to 52% in North American patients.[135] The review summarises the findings of 43 studies. The risk of venous thromboembolic disease, including PE, is also elevated in LHF. Approximately 15% of patients with LHF, who have symptoms at rest or on less-than-ordinary exertion according to New York Heart Association classification (stage III and IV), develop venous thromboembolism.[64]

Diagnosis of heart failure requires objective evidence of underlying cardiac dysfunction. In general, a diagnosis of LHF will therefore need an examination with echocardiography. Echocardiography is a cornerstone in the diagnosis of heart failure and provides essential information regarding the aetiology of LHF and can determine whether structural or functional abnormalities of

myocardium, heart valves or pericardium are present. Echocardiography can give a numerical estimate of EF, which often is used to categorise patients into systolic or diastolic heart failure.[122,128] EF is strongly dependent on volumes, heart rate, preload and afterload and is therefore not a direct index of contractility.[122] Hemodynamic data such as left atrial pressure, pulmonary artery pressure and left ventricular filling patterns can noninvasively be estimated through Doppler echocardiography.[123] Nevertheless, abnormalities in any of these parameters can be present in the absence of LHF. An entirety normal echographic examination argues against clinical LHF.

B-type natriuretic peptide (BNP) and the N-terminal fragment of pro-BNP (NT-proBNP) are synthesized and released from the heart as a response to increased myocardial wall stress. Plasma level of BNP has been used as a tool in the diagnosis of heart failure.[136] It is associated with reduced EF, acute myocardial infarction, coronary ischemia and ventricular hypertrophy, but also with other conditions such as infection, renal dysfunction and advanced age.[122] Elevated BNP levels can also be found in PE and COPD.[123] Hence, an elevated plasma level of BNP is unspecific but could trigger the consideration of LHF in patients when diagnosis is unknown. In combination with other findings it lends weight to a suspected diagnosis of LHF.[137] A normal level of BNP, in an untreated patient makes LHF an unlikely cause of symptoms.[122]

CXR is today recommended as an essential tool in the diagnostic work-up of LHF. According to guidelines it permits the assessment of pulmonary congestion, pleural fluid accumulation and cardiomegaly.[122,123] Therefore, CXR is commonly used for estimating severity of pulmonary congestion and titrating therapy of chronic congestive heart failure. The sensitivity of CXR for pulmonary congestion, however, is low.[138,139] Even in patients with known elevated pulmonary venous pressure and known pulmonary congestion, CXR can be normal in as many as 50%-60% of cases.[140,141] The interobserver variability is high when assessing heart failure with CXR.[142] Radiological signs of LHF can also be obscured by the simultaneous presence of COPD. Pulmonary congestion can therefore stay undetected.

Objective imaging methods in the diagnosis of PE and cardiopulmonary disease

Lung scintigraphy

Lung scintigraphy gives a physiologic map that evaluates the primary functions of the lungs.[143] It was the first method that made it possible to attain spatial 2-dimensional information of ventilaion and perfusion in vivo.[14,40,144] In lung scintigraphy, tracers which either are radioactive by themselves or labelled with a radioactive compound, are used to localize and quantify the functional distribution of ventilation and perfusion in the lungs. Photons emitted from the radiotracers are then registered outside the body by a gamma-camera. The data from the gamma-camera is then used to reconstruct an image of the regional ventilation and perfusion.

Ventilation imaging

For ventilation imaging there are several alternatives. These include inert gases such as ^{133}Xenon (^{133}Xe) and ^{81m}Krypton (^{81m}Kr), or radiolabelled aerosols such as ^{99m}Technetium (^{99m}Tc)-diethylene triamine pentaacetic acid (DTPA), and ^{99m}Tc-labeled Technegas.[145]

Inert gases

^{133}Xe has historically been the agent used for ventilation studies.[14] The half-life of ^{133}Xe is relatively long (5.3 days). The ^{133}Xe ventilation studies have some shortcomings including poor spatial resolution as a result of the low photon energy (81 keV) and the fact that only a few projections, often only posterior, can be performed with a single dose.[146] ^{133}Xe that is not cleared from the lungs through expiration is cleared to the pulmonary circulation and is then recirculated, and this can introduce errors.[147] All this together, makes ^{133}Xe less than ideal as an agent to image ventilation and impairs its ability to be used for SPECT imaging.[148] The use of ^{133}Xe is no longer recommended according to the guidelines of the European Association of Nuclear Medicine.[57] ^{133}Xe is still commonly used for ventilation studies in the United States.[149]

^{81m}Kr has the ideal gamma-energy of 193 keV and is produced on-site from a Rubidium generator. The generator is expensive and requires to be replaced daily which leads to limited use.[57] As the gamma-energy of ^{81m}Kr is different from that

of ^{99m}Tc, ventilation and perfusion imaging can be performed simultaneously. ^{81m}Kr has a short half-life of 13 s. As a result, ^{81m}Kr disappears faster from the alveoli by decay than by expiration, and therefore needs to be administered continuously during image acquisition.[148] At steady-state, ^{81m}Kr concentration is proportional to regional ventilation and ^{81m}Kr is therefore by many regarded as the ”gold standard” for ventilation studies.[145] The match between regional concentration of ^{81m}Kr and regional ventilation is not perfect, however, in areas with very high or low alveolar ventilation in relation to volume.[150]

Aerosols

Given the limitations of the inert gases, ^{99m}Tc-labeled particle aerosols such as ^{99m}Tc-DTPA and ^{99m}Tc-Technegas have become widely used due to their lower cost, greater availability and high image quality.[68]

A radioaerosol consists of radioactive particles suspended in gas. The depth of aerosol delivery and deposition in the lungs depends on the aerodynamic properties of the particles (mainly their size), the breathing pattern and the anatomy of the airways.[57,151,152] Ultrafine nanoparticles with a diameter of 0.02 µm has a deposition fraction of up to 50%, predominantly in the alveoli by diffusion.[153] The alveolar deposition fraction then decreases with increasing size up to a diameter of 0.45 µm. At this particle size aerosols are especially stable with low alveolar deposition as diffusion and gravitational sedimentation balance each other.[153] At larger diameters sedimentation dominates as the mechanism of deposition. Diffusional deposition occurs and contributes to deposition up to an inhaled particle size of approximately 1 µm.[154] Particles with a diameter of >1-2 µm will be deposited in conducting airways by inertial impaction since large particles are unable to follow the curved streamlines that the air follows when passing through bifurcations. As a result there will be a risk of accumulation of radioactive particles and ”hot spot” formation. Particles with a diameter exceeding 5 µm will impact already in upper airways. Airway obstruction with turbulence may cause impaction even of smaller particles.

As aerosols contain particles of different sizes and somewhat different shapes, the mass median aerodynamic diameter (MMAD) is often used to characterize their properties. MMAD describes the aerodynamic diameter that divides the aerosol particles in half, based on the particles weight. A radio-aerosol should preferably have a MMAD of less than 1.2 µm and the maximum particle size inhaled by the patient should be less than 2 µm.[57,147] The droplet size of liquid aerosols depends on the nebulizer that is used. The best liquid aerosol generators used today can produce an aerosol with a size distribution of 0.5-2 µm.

^{99m}Tc-DTPA is the most commonly used liquid aerosol.[155] ^{99m}Tc has a physical half-life of 6.02 hrs and photopeak energy of 140 keV, which is ideal for gamma-camera imaging. Taplin proposed the use of ^{99m}Tc-DTPA instead of ^{133}Xe already in 1977.[156] ^{99m}Tc-DTPA is soluble in water and is cleared from the lungs to the blood by diffusion through the alveolar-capillary membrane.[157] The mean biological half-life is approximately 70 min in healthy non-smokers.[158] Clearance rate increases when alveolar epithelial integrity is compromised such as in alveolar inflammation (alveolitis) or in smokers.[159,160] The variable biological half-life of ^{99m}Tc-DTPA may interfere with image quality in some patients. A ventilation study with 30 MBq of ^{99m}Tc-DTPA results in a low effective dose of 0.2 mSv to the patient.[161] Because of the relatively larger inhaled particle size and the tendency for the hydrophilic particles to grow as a result of airway humidity, there may be problems with deposition in large airways, particularly in patients with COPD. For PE diagnosis in patients with normal ventilation, ^{99m}Tc-DTPA has been shown to have the same or better diagnostic properties as ^{81m}Kr and ^{133}Xe.[146,162,163]

The use of ^{99m}Tc-Technegas for ventilation studies was first reported in 1986.[164] Technegas is an aerosol containing ultrafine ^{99m}Tc-labelled particles of solid graphite. The aerosol particles are generated by heating a graphite crucible loaded with ^{99m}Tc to 2550°C.[165] The process is performed in an atmosphere of pure Argon. This produces radioaerosol particles with a size range of 0.005 to 0.2 µm.[166] The small particle size makes penetration characteristics gas-like with less impaction in conducting airways.[166-168] ^{99m}Tc-Technegas has therefore often been called a ”pseudo-gas”.[164] In contrast with gases, graphite particles adhere to the walls of the alveoli on inhalation.[164] A few breaths on the part of the patient are sufficient to deliver adequate activity to the lungs.[145] There is no clearance of ^{99m}Tc-Technegas from the lungs during the time it takes to acquire ventilation images and the biological half-life is 135 hrs. ^{99m}Tc-Technegas gives the same diagnostic information as ^{81m}Kr.[147,169,170] The effective radiation dose from 30 MBq of ^{99m}Tc-Technegas is low (0.45 mSv).[161] This would appear to make ^{99m}Tc-Technegas an ideal agent for ventilation scintigraphy and particularly tomographic imaging. ^{99m}Tc-Technegas is at present not approved for use in the United States.

Despite the common use of both ^{99m}Tc-Technegas and ^{99m}Tc-DTPA, they have never been compared in a head-to-head study.

Perfusion imaging

^{99m}Tc-macro-aggregated albumin (MAA) is generally used to assess distribution of pulmonary perfusion.[57,171] Imaging with ^{99m}Tc-MAA is based on the principle of capillary blockade through microembolization. MAA particles are prepared through heat denaturation of human serum albumin.[171] The particles are then labelled with ^{99m}Tc. ^{111}Indium has also been used as a marker, but this is more expensive and not widely available.[172] The ^{99m}Tc-MAA particles are irregularly shaped molecules where 95% of the particles are within a size range of 10-100 µm in commercial kits. No particles should be larger than 150 µm as they can obstruct larger arterioles. Because of their size range, ^{99m}Tc-MAA paricles lodge principally in precapillary arterioles but to some part also in capillaries.[171] Typically, about 400,000 particles are injected, lading to a temporary and safe occlusion of less than 0.1% of the pulmonary capillaries. Patients with known pulmonary hypertension and right-to-left shunts should only be given 100,000-

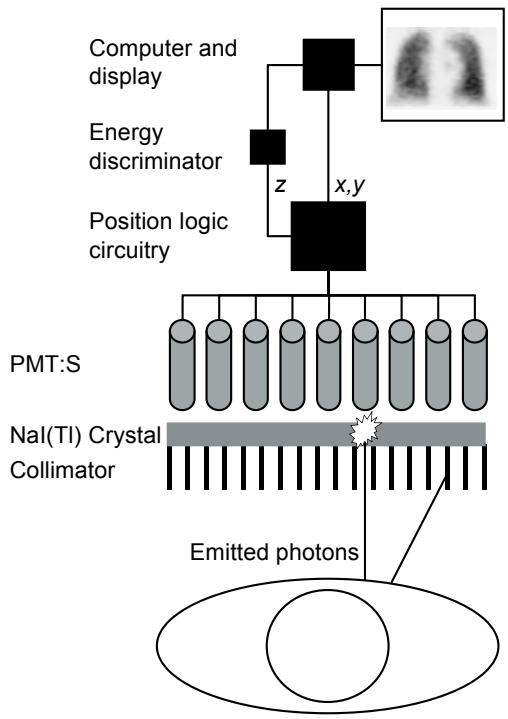

Figure 1. The basic design of a gamma-camera.

200,000 particles. In children the dose should also be smaller and adjusted to weight. ^{99m}Tc-MAA leaves the lungs through breakdown into smaller particles that pass through the capillaries into the systemic circulation. ^{99m}Tc-MAA is injected slowly intravenously and travels to the right heart were venous blood is mixed. The particles then follow the pulmonary arterial blood-flow and are distributed peripherally in proportion to regional perfusion. The distribution of ^{99m}Tc-MAA will be reduced distal to occlusions in pulmonary arteries and the functional consequence of the occlusion can thereby be seen. When performing lungscintigraphy as one-day protocol using ^{99m}Tc first for ventilation and then for perfusion studies, the dose of the perfusion agent must drown the underlying ventilation signal.[155] A ventilation dose of about 30 MBq of ^{99m}Tc-aerosol will therefore require approximately 100-120 MBq of ^{99m}Tc-MAA, which will result in an effective dose of 1.1-1.3 mSv.[161,173]

Gamma-cameras

The gamma-camera is the predominant imaging device in nuclear medicine and was first developed by Hal Anger in the late 1950s. A gamma-camera basically consists of a lead collimator, a crystal (commonly made of thallium-doped sodium iodide [NaI(Tl)]), an array of photomultiplier tubes (PMT), an energy discriminator and a position logic circuitry [Fig 1]. Only photons travelling perpendicular to the crystal surface will pass the apertures of the multi-hole collimator and contribute to the resulting image. Photons travelling in oblique axis to the apertures will hit the lead septa and will therefore not (in about 95% of cases) reach the crystal. Gamma-camera collimators are classified with respect to photon energy and resolution (inversely related to sensitivity). In ^{99m}Tc imaging low-energy (<200 keV) all purpose (LEAP) or high resolution collimators are used. In the crystal, i.e. scintillator, gamma-radiaton energy from absorbed photons is deposited and converted to visible light. The thickness of the crystal determines its spatial resolution and sensitivity (a thin crystal yields high spatial resolution; a thick crystal yields high sensitivity). Behind the crystal is a two-dimensional arrangement of PMTs. The light emitted from the crystal is spread out among the PMTs and amplified to an output signal that is proportional to the incoming light and thereby also to the incident radiation. The position logic circuitry calculates and determines the exact location of a scintillation within the crystal. Scintillations with energy not typical for the used isotope, falls outside the predefined energy window and can thereby be sorted out. The information from the remaining scintillations can then be used to produce images.

Planar lung scintigraphy

Evaluation of ventilation and perfusion with lung scintigraphy was introduced in the 1960s, and was soon accepted in the detection of perfusion defects in PE.[174] Lung scintigraphy visualizes the V/P balance in healthy individuals and the V/P abnormalities in cardiopulmonary disease. When disease causes an equal regional deficiency in both V and P the defect is "matched". When a defect is only observed in perfusion images it is conventionally denoted "mismatched".[175]Gamma-camera images basically represent a two-dimensional (or planar) view of the three-dimensional (3-D) distribution of the radionucleide within the body. Hence, to localize patophysiological processes within the body, projections in various angles must be obtained. In planar lung scintigraphy four to eight projections are commonly used. Two-dimensional lung imaging has some inherent limitations:[149]

- The overlap of anatomical segments complicates accurate localization of defects.
- Regions with normal V or P can "shine-through" regions with lower function and thereby result in an underestimation of V or P loss.
- Difficulties in visualizing all the segments of the lungs.

All these limitations can have an undesirable effect on diagnostic accuracy.[149] Nevertheless, planar lung scintigraphy was for many years the routine clinical procedure in the diagnosis of PE [Fig 2A]. Segmental perfusion defects with preserved ventilation are the key finding in the diagnosis of acute PE.[57] It was widely accepted that a normal lung perfusion pattern nearly excluded PE.[50,57] The reputation of planar lung scintigraphy was hampered in the 1990s after the prospective investigation on pulmonary embolism diagnosis study (PIOPED).[50] In PIOPED, a probabilistic reporting scheme was used to classify all V/P scans, that were not completely normal, as low, intermediate or high probability of PE.[50] ^{133}Xe vas used for ventilation imaging and commonly only in posterior projection. As 73% of the studies were regarded as nondiagnostic (low or intermediate probability) the usefulness of scintigraphy was questioned.[50,176] No aerosol ventilation studies were included in any of the reports critical of the accuracy of lung scintigraphy. Probabilistic reporting has been widespread following PIOPED.

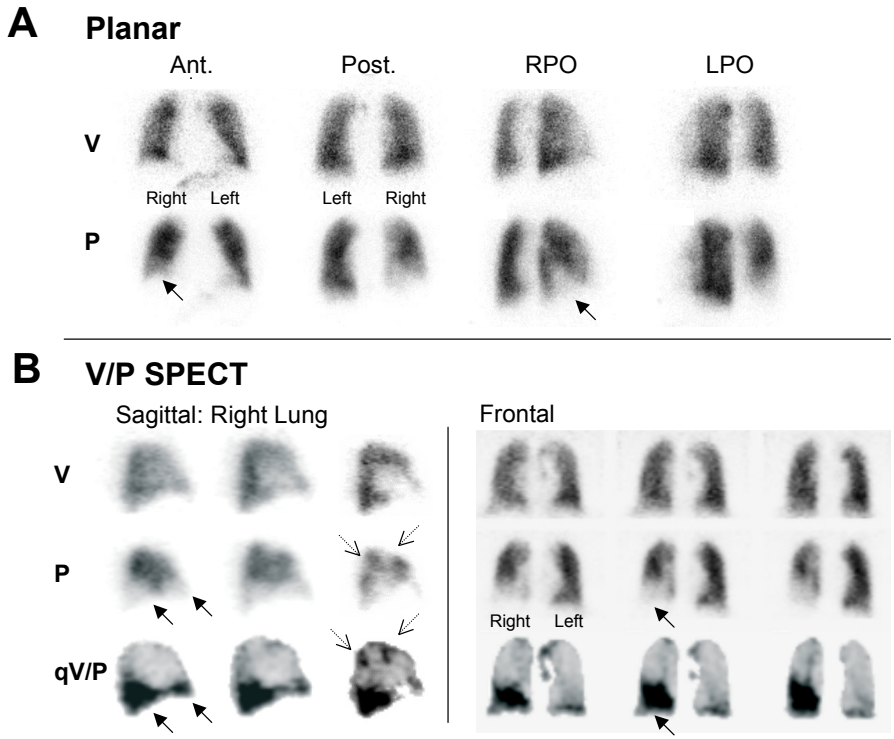

Figure 2. Lung scintigraphy in a patient with pulmonary embolism. (A) In planar images, a perfusion defect of segmental character (arrows) in the basal part of the right lung. Ventilation is preserved. (B) In tomographic images (V/P SPECT), it is found that the defect actually consists of two separate perfusion defects (black arrows). Moreover, subsegmental mismatched perfusion defects are found within upper parts of the right lung (open arrows).
(Ant.=anterior, LPO=left posterior oblique, P=perfusion, post.=posterior, qV/P=ventilation/perfusion quotient, RPO=right posterior oblique, V=ventilation.) *Modified with permission from M. Bajc.*

CTPA in the diagnosis of pulmonary embolism

About the same time as PIOPED, CTPA was introduced in the diagnosis of PE. In some studies CTPA showed a higher specificity compared to planar lung scintigraphy.[177,178] CTPA was soon widespread and generally used. The popularity increased based on arguments that CT also could detect differential

diagnoses when signs of PE were absent. PIOPED II, that studied the assessment of PE with multidetector CTPA, showed that CTPA had a high sensitivity and a high positive predictive value (PPV) for central PE. However, the PPV of CTPA was only 68% for segmental and 25% for subsegmental PE.[178] The accuracy fell further if there were discrepancy between clinical probability and CTPA findings.[179] The 17% false negative rate of multidetector CTPA indicated the need for additional methods to rule out PE.[180] In a recent review of pooled data the sensitivity of spiral CTPA was 83%, when patients with contraindications for CT or poor image quality were excluded.[181] There are safety concerns related to the intravenous contrast.[182] In PIOPED II, 24% of the patients had one or more contraindications to CTPA and more than 45% of the patients in the study were not eligible to be examined with CTPA due to health reasons.[183] In a recent study by Gutte et al 96 out of 196 consecutive patients (49%) had to be excluded due to contraindications to CTPA.[184] Another negative aspect of CTPA is the high radiation exposure of the patient. In the United States, CT scans account for 15% of studies but more than one-half of the collective radiation dose.[185] The average annual effective dose per-capita from medical radiation has approximately doubled in the last 10-15 years.[186] In PE diagnosis, effective doses of 8-20 mSv have generally been reported by the use of 16-array or greater CT scanners.[187-189] CTPA delivers a high radiation dose to breast and lungs as these organs are directly in the path of the radiation beam.[189] The radiation dose to the breast has been estimated to range from 20-70 mSv with current protocols.[187,188,190] One CTPA examination corresponds to the breast dose from 100-400 CXR.[189] Some authors have worked on ways to lower the radiation dose from CTPA but this has not been generally implemented.[187,191] The American College of Radiology has recommended caution in the use of CTPA in women of reproductive age because radiation levels exceed those shown to increase cancer risk.[192] As a comparison, the radiation dose to the breast from modern lung scintigraphy with ^{99m}Tc-aerosol+^{99m}Tc MAA is 0.8 mSv.[161]

Tomographic lung scintigraphy

The progress in nuclear medicine has lead to the development of tomographic 3-D techniques to assess the patients. Single photon emission computed tomography (SPECT) is the tomographic method based on the emitted single photons from radiopharmaceuticals such as some of those previously mentioned. If multiple scintigraphic images are acquired from a multitude of angles around a patient, these images may be used to computationally reconstruct transverse images. In V/P SPECT is the number of projections typically 120

with 3° angular steps between them, thereby covering 360°.[57,145,173,193,194] Because the reconstructed transverse emission images are contiguous, with no gap between them, the reconstructed 3-D array of volume elements (voxels) can be reorganized in any angle yielding coronal, sagittal, transverse or even oblique images.[195] Hence, SPECT compares to planar gamma-camera imaging as CT compares to conventional X-ray imaging. The main advantage with SPECT lies in its improved image contrast achieved by eliminating counts from activity in tissue outside the section of interest.[195] SPECT also results in an improved spatial resolution allowing smaller processes to be imaged.[196] SPECT imaging has because of its ability to image in 3-D since long been standard in many areas of radionucleide imaging, such as in the assessment of ischemic heart disease and degenerative brain disorders, were it has been shown to be superior to planar imaging.[68] SPECT studies of the lungs were first introduced in canine studies in the early 1980s and its probable advantages in the diagnosis of PE was advocated already then.[197-199] SPECT assumes a "static" distribution of radiotracer during the time of image acquisition and V/P SPECT is therefore best performed with a ^{99m}Tc-aerosol in combination with ^{99m}Tc-MAA.[57,67,68] ^{81m}Kr can also be used but needs continuous administration. A multihead gamma-camera is required to perform V/P SPECT in an efficient fashion. Both the administration of ventilation and perfusion radiotracers and imaging is performed in the supine position. Total acquisition time for a V/P SPECT examination is approximately 20 min which is well tolerated by almost all patients.[57,67,111,173] V/P SPECT has no contraindications and can be performed in 99% of patients.[67,200]

Primary diagnosis of PE is the main indication for lung scintigraphy and several studies have therefore compared V/P SPECT with planar imaging in this diagnosis [Fig 2B]. In animal studies it was shown that the tomographic technique improved the specificity and accuracy of lung scintigraphy.[194,199] The first small study comparing V/P SPECT with planar lung scintigraphy in humans was published in 1993.[201] It was concluded that V/P SPECT made it possible to visualize subsegmental defects not visible on planar images and also that it had the ability to more accurately localize defects. In a study of 985 patients with suspected PE it was found that V/P SPECT resulted in a specificity of 92% compared to 52% in PIOPED.[202] The number of indeterminate studies was 4%. A rate of nondiagnostic examinations <5% has been published by many authors since then, and this is a significant observation given the criticism of PIOPED.[67,200,203-205] In a study by Lemb et al. following 991 patients, V/P SPECT had a sensitivity of 96% and a specificity of 97% in the diagnosis of PE.[204] Reinartz et al. were also using ^{99m}Tc-Technegas and found that V/P SPECT had a sensitivity of 97% and a specificity of 92% in 83 patients that were also examined with CTPA. In this study the accuracy of V/P SPECT was similar

to that of CTPA (94% vs. 93%), with a somewhat higher sensitivity for PE with V/P SPECT.[206] Studies comparing V/P SPECT with planar imaging using ^{81m}Kr as the ventilation agent have been performed by Collart et al and Gutte et al including in total 102 patients with suspected PE.[207,208] Collart et al. used planar ^{81m}Kr images and combined these with tomographic and planar perfusion images. They found that the specificity was 96% for SPECT compared to 78% for planar imaging while the sensitivity was similar (80%).[207] In the study by Gutte et al. ^{81m}Kr-ventilation studies were tomographic. V/P SPECT was found to have a sensitivity of 100% and a specificity of 87% compared to 64% and 72% when using planar 2-D imaging.[208] In this study, 8% of the examinations were reported as uninterpretable due to poor technical quality. V/P SPECT can also be used to generate V/P quotient images to facilitate the diagnosis of PE.[173,175] By authors using V/P SPECT, a binary reporting system is implemented and this is also recommended in the guidelines of the European Association of Nuclear Medicine.[67,149,205,209] Hence, there are many studies that have demonstrated the advantage of 3-D V/P SPECT over 2-D planar lung scintigraphy in the primary diagnosis of PE, especially when radioaerosols are used. Globally, the majority of lung scintigraphic examinations are nevertheless still performed using the planar technique.[68] Although V/P SPECT has improved the diagnostic accuracy regarding PE it has not been evaluated for PE follow-up.

V/P SPECT has mostly been used in clinical practice for the investigation of suspected PE. The clinical potential of V/P SPECT for investigation of 3-D ventilation/perfusion changes in other cardiopulmonary diseases such as COPD and LHF has been less explored.[108] V/P SPECT might be useful both in the diagnosis and characterization of COPD and LHF. Functional disturbances in regional ventilation and perfusion have previously been described for both conditions.[210,211] V/P SPECT has in several studies been shown more sensitive than HRCT in detecting early changes of alveolar destruction. [212-214]

Aims

The general aim of this thesis was to evaluate the role of V/P SPECT in the follow-up of patients with PE and in the diagnosis of LHF and COPD

The specific aims for each paper were:

I. To investigate if LHF could be diagnosed using V/P SPECT, and to develop and evaluate objective parameters in terms of perfusion gradients in the diagnosis of LHF.

II. To systematically investigate differences between ventilation studies performed with ^{99m}Tc-DTPA and ^{99m}Tc-Technegas in a head-to-head study.

III. To investigate, in patients with COPD, how lung function imaging and obstructive disease grading performed with V/P SPECT correlate to symptoms, spirometric lung function and degree of emphysema.

IV. To quantitatively follow-up the history of treated PE using V/P SPECT. This could prove helpful in defining an anticoagulant treatment regime for individual patients.

Materials and methods

Study populations

All studies were approved by local ethical review board committees.
Study I was a retrospective study that included 247 consecutive patients examined with V/P SPECT under a two-month period due to clinically suspected PE. Typical symptoms were chest pain, dyspnea, tachycardia, syncope, sudden unexplained tiredness, atrial fibrillation, and confusion. The mean age of the patients was 63 years, 153 of the patients were women and 97 of the patients were outpatients. Patients examined for other indications than suspected PE were not included in the study.

In study II, sixty-five patients were included. Thirty-five of the patients were referred for V/P SPECT examination to evaluate clinically suspected PE (n=29), to evaluate alveolitis (n=3), or to evaluate lung function before surgery or after transplantation (n=3). Their mean age was 57 years, 51% were women, and 5 had known obstructive lung disease. Two of these 35 patients were later excluded because data had not been properly stored for reevaluation. In addition, 30 outpatients with known COPD (mean age 65 years; 63% women) were consecutively recruited from the Department of Respiratory Medicine and Allergology. They had moderate to very severe COPD according to GOLD. COPD classification was performed at the outpatient clinic before the start of the study. The COPD patients were clinically stable and had been free from exacerbation for at least 6 weeks. All patients were under optimized pharmacological treatment.

The COPD patients included in study II were also utilized in study III.

Study IV was a prospective study that comprised of consecutive patients with clinically suspected PE, who were primarily examined with V/P SPECT at the University Hospital of Sarajevo. 83 patients (mean age 54 years, 40% women) were examined with V/P SPECT. All were examined within 12 hours from onset of symptoms. Patients with a negative V/P SPECT (48 out of 83) were left untreated regarding PE and were followed up by telephone interviews

approximately three months after the V/P SPECT examination. V/P SPECT identified PE in 35 patients (87% out-patients), 23 out of these 35 patients were able to take part in the study. As the other 12 patients lived far away from Sarajevo, for logistical reasons they were not included in the study. They were, however, all clinically followed-up during anticoagulant treatment. Clinical follow up was performed by experienced pulmonologists.

V/P SPECT acquisition

In all studies, V/P SPECT was performed as 1-day protocol according to the guidelines of the European Association of Nuclear Medicine, using the protocol of Palmer et al. and Bajc et al.[57,67,173,196] A large field-of-view gamma-camera equipped with a LEAP collimator was used. Acquisition was performed in a 64 x 64 matrix, zoomed to a pixel size of 6.8 mm with 128 projections over 360°. Sixty-four steps, each of 10 s. duration, were used for the ventilation study, and 64 steps of 5 s. duration were used for the perfusion study.

Inhalation of ^{99m}Tc-DTPA (Studies I and II) or ^{99m}Tc-Technegas (Studies I, II, III and IV) was performed in the supine position. Ventilation tomography was then performed. Thereafter, in maintained supine position, ^{99m}Tc-MAA was slowly injected intravenously. Then, perfusion tomography followed. Transversal V/P images were reconstructed using ordered-subsets expectation maximization with 8 subsets and 2 iterations. To account for remains of aerosol in the perfusion study, ventilation counts were subtracted from the perfusion images after ventilation activity had been adjusted for the time difference between acquisitions. In study II, all patients were reexamined for ventilation on a following day, using the radioaerosol not used at the initial examination. In study IV, the included patients were reexamined with V/P SPECT at two weeks, three months and six months after PE diagnosis.

All V/P SPECT examinations performed at the department of Clinical Physiology, Lund, fulfilled the requirements in ISO/IEC 17025.

Preparation and administration of radiotracers

^{99m}Tc-DTPA was prepared using a commercial kit (TechneScan DTPA; Mallinckrodt Medical BV). The ^{99m}Tc-DTPA aerosol was generated and inhaled using an UltraVent nebulizer (Mallinckrodt Medical BV) or a SmartVent aerosol generator system (Diagnostic Imaging Ltd.). The MMAD of the delivered particles from those nebulizers was 1.7 mm or less.

Technegas was delivered from the Technegas generator according to the manufacturer's instructions. The inhaled Technegas particles are all of submicron size.[166] Inhalation of both ^{99m}Tc-DTPA and ^{99m}Tc-Technegas was performed in supine position and the dose was 30 MBq. After ^{99m}Tc-MAA was prepared (Technescan LyoMaa kit; Mallinckrodt Medical BV) it was administered intravenously in a dose of 100-120 MBq.

Spirometry, lung volumes and diffusion capacity for carbon-monoxide

In study III, lung function evaluation including FEV_1, vital capacity (VC), total lung capacity (TLC), residual volume (RV), functional residual capacity (FRC) and diffusion capacity for carbon monoxide (D_LCO) were assessed using a body plethysmograph (MasterScreen Body/Diffusion; Viasys Healthcare). Lung function evaluation was quality controlled according to the American Thoracic Society guidelines and performed in accordance with Swedish Board for Accreditation and Conformity Assessment (SWEDAC) accreditation, fulfilling the requirements in ISO/IEC 17025.[215]

HRCT

In study III, 28 of the 30 patients with COPD were examined with HRCT using a MDCT scanner. Imaging was performed in deep-inspiratory breath hold with the patients in supine position. Transaxial images, 1 mm thick, were reconstructed with the lung algorithm. HRCT images were then visually assessed by an experienced chest radiologist, blinded to V/P SPECT results. The review was performed with focus on emphysema type, its location and extent. The degree of emphysema was scored as a percentage of the total lung volume. Other findings such as bronchiectasis, thickening of bronchial wall and mucus plugs were also identified but not further analyzed.

Symptoms, the effect of breathlessness and functional state in COPD patients

Patients with COPD in study III were evaluated regarding symptoms, dyspnea and functional state with the Medical Research Council (MRC) questionnaire and the clinical COPD questionnaire (CCQ). The MRC dyspnea scale was developed in the 1950s and modified in the 1990s.[117,216] MRC is used to grade the effect of breathlessness on daily activities and it has been related to morbidity and mortality in populations with obstructive lung disease.[117,118]

Degree of breathlessness related to activities according to MRC dyspnea scale:[216]

1. Not troubled by breathlessness except on strenuous exercise
2. Short of breath when hurrying or walking up a slight hill
3. Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace
4. Stops for breath after walking about 100m or after a few minutes on level ground
5. Too breathless to leave the house, or breathless when dressing or undressing

The CCQ has been developed as a simple clinical tool to identify not only the clinical status of the airways but also activity limitation and emotional dysfunction in patients with COPD.[119] CCQ is a 10 items self-administered questionnaire covering symptoms, functional and mental state. Patients are instructed to recall their experiences during the previous week and respond to each question using a 7-point scale witch ranges from 0 = asymptomatic/no limitation to 6 = extremely symptomatic/totally limited. The total sum is then divided by the number of questions so that CCQ varies from very good (0) to extremely poor disease control (6). CCQ was used in study III with permission from the developers.

Perfusion gradients in LHF

In study I, an algorithm for calculation of objective perfusion gradients was developed and applied on the tomographic lung perfusion data. The analysis was made from transversal slices, delineated automatically at a lower count threshold set to 20% of the 90:th volumetric percentile of the filtered slice volume.[173] The

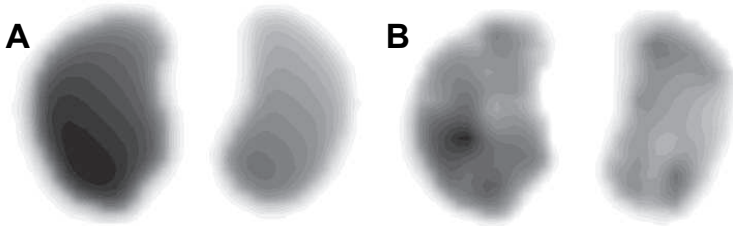

Figure 3. Mathematical phantom used to evaluate the perfusion gradient algorithm. (A) Sample phantom image generated with predefined gradients and added edge effects. (B) Sample phantom as seen in (A), but with random gross structures added.

medial part of each lung was then removed in order to exclude central airways and large vessels. This was accomplished by indenting the lung contour by an amount prescribed by an elliptical formula, the size of which was proportional to the total size of the lung. Voxels in the lung periphery were then excluded to avoid partial volume effects and artefacts due to heart motion and breathing. Accordingly, in each patient, a series of 3-D linear regressions were performed to estimate an optimum distance to retreat from the lung periphery. The principle applied here was that the coefficient of variance for the 3-D fit (SD/number of fitted voxels) is large when the data are in fact non-linear, as at the lung periphery. Peripheral voxels were thus removed until the coefficient of variance for the 3-D perfusion gradient no longer decreased. This resulted in a retreat from the lung contour by 1-3 pixels (described as "approximately 1 cm" in paper I). Perfusion gradients could then be calculated in the 3-D volume. In study I, perfusion gradients were calculated in body-oriented orthogonal planes (x, y, z). Before application to patient data, these procedures were validated using a mathematical phantom with gradients between -4 and +4 %/cm and with lung contours derived from real lungs. Known gradients as well as edge effects, and later also random gross structures, were added to the phantom to resemble partial volume effects and different perfusion patterns [Fig 3]. Perfusion gradients were then extracted in the body-oriented orthogonal directions using the described procedure and these gradients were then compared to the known values.

Qualitative assessment of V/P SPECT images

In study I, V/P SPECT images were visually interpreted by two experienced physicians in consensus that were blinded to clinical information. Findings were regarded as normal when an even regional distribution of ventilation and perfusion with dorsal predominance was seen. PE was diagnosed when a segmental or subsegmental V/P mismatch (perfusion defect with preserved ventilation) of at least two subsegments or one segment was found.[145,209] In agreement with previous observations, congestive LHF was regarded as present when a general redistribution of perfusion to upper and ventral lung zones was seen.[131-133,210,217] The redistribution should not cause perfusion defects of segmental character. However, as the redistribution of ventilation is less prominent, mismatch of non-segmental character is often observed. Possible presence of V/P patterns indicative of COPD, pneumonia or ancillary were not further analyzed in this study. These diagnoses were grouped as "others".

In study II and III, all V/P SPECT images were independently reviewed by two physicians that were unaware of clinical information, and in study II also of what type of ^{99m}Tc-aerosol that had been used. All V/P SPECT images were available to the physicians. Images were reviewed according to a predefined standardized scoring system. A training session was held with the physicians before the study began to achieve consistency of scoring. Ventilation images were assessed and graded using 3 qualitative parameters: unevenness of aerosol distribution, central hot-spots (i.e., deposition of aerosol in major and intermediate conductive airways), and peripheral hot-spots (i.e., focal deposition of aerosol in distal airways). Each of these parameters was scored from 0 (none or normal) to 10 (very high). Thereafter, ventilation and perfusion images were assessed together. The extent of matched (V = P), mismatched (P < V) and reverse mismatched (V < P) defects were expressed as a percentage of the total lung volume. The sum of these was used to estimate the extent of total reduction in lung function. Scintigraphic signs of obstructive disease were graded, in accordance with other terminology, as absent (=0), mild (=1: affecting < 20% of the total lung function), moderate (=2: affecting 20%-50% of the total lung function), or severe (=3: affecting > 50% of the total lung function). V/P SPECT images were finally reviewed according to the criteria described for study I, assessing the presence of PE and LHF. If PE was present, the extent of lung perfusion reduction was scored as a percentage of the total lung volume.

In study IV, V/P SPECT images were reviewed by two physicians who were blinded as to whether they reviewed the acute examination, the 2-week, the 3-month or the 6-month follow-up. Segmental ventilation and perfusion defects were quantified in terms of "RoVent" (Reduction of Ventilation) and

"RoPer" (Reduction of Perfusion) points, which has been described in previous studies.[196,218] Reduced function in a segment or a complete loss of ventilation or perfusion in a subsegment was attributed one RoVent or RoPer point. When function was completely lost within a segment this was attributed two points. The lungs were considered to have 18 segments in total. The theoretical maximum score is hence 36 points. Segmental or subsegmental regions with loss of perfusion but preserved ventilation were scored as mismatch points. PE was diagnosed when more than one subsegmental or segmental region of mismatch were found, i.e. at least two mismatch points were required. Mismatch points were used to quantify the extent of PE perfusion defects.

Statistical analysis

All continuous data are expressed as mean ± standard deviation unless otherwise is specified. The null hypothesis was rejected when *P* was less than 0.05 throughout the studies. In study I, Mann-Whitney U test was used to compare differences in perfusion gradients. In study II, paired Wilcoxon signed-rank test was used to compare the differences between ^{99m}Tc-DTPA and ^{99m}Tc-Techengas variables. Differences between the two aerosols were also illustrated in Bland-Altman plots.[219] In study III, Spearman rank correlation test was used to evaluate relationship between MRC, CCQ, spirometry, V/P SPECT and HRCT parameters. For comparison between groups, two tailed Mann-Whitney U was employed. In study IV, comparisons between the follow-up occasions were performed with the paired Student t test.

Result and Comments

V/P SPECT in the diagnosis of LHF (Study I)

LHF is common, especially among the elderly. When the left ventricle fails to meet the functional demands of the body, symptoms such as dyspnea, fatigue and pulmonary edema will occur. Modern treatment has resulted in better long term survival in patients with LHF and it is therefore important to identify these patients early.

In study I we investigated if LHF could be diagnosed using V/P SPECT. An algorithm to objectively calculate perfusion gradients was also developed. The algorithm was validated in a mathematical phantom. Errors in gradient determination were essentially independent of gradient direction or magnitude. When edge effects were added to the predefined gradient phantom, the measurement error was still modest (SD of the fitted Gaussian distribution=0.45%/cm) [Fig 4A]. When random structures were added to simulate conditions such as obstructive lung disease, gradient precision suffered, as expected, but could still to a reasonable degree discriminate between positive and negative gradients (SD=1.48%/cm) [Fig 4B].

The study retrospectively included 247 patients (61% in-house patients) who had been referred to V/P SPECT due to clinical suspicion of PE. Among the 247 consecutive patients, as many as 36 patients (15%) were qualitatively identified as congestive LHF with V/P SPECT [Fig 5]. In three of these patients LHF was combined with PE. PE was in total identified in 25% of the patients. Among PE and LHF patients it was common with ventilation and perfusion abnormalities indicative of other coexisting disease. This illustrates the importance of taking ancillary diagnoses into consideration. Only 67 patients (27%) had a normal V/P SPECT pattern. Clinical follow-up of the patients with LHF pattern was performed through hospital records. Heart failure diagnosis was confirmed in 32 out of the 36 patients (PPV = 88%). The four remaining patients all had heart disease but the diagnosis of LHF could not be established with assertion.

As perfusion gradients had shown promising results in the phantom studies

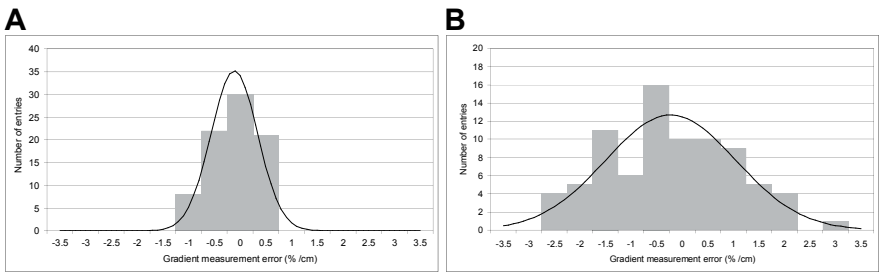

Figure 4. Fidelity in perfusion gradient extraction: (A) Summary of results of automatic 3-D gradient extraction from the phantom seen in figure 3A. The trial consisted of 27 slice sets, each having known gradients in three body-oriented orthogonal directions. The histogram shows the distribution of measurement error in these 81 measurements. SD of fitted Gaussian is 0.45%/cm. Summary of results as in (A), but with random gross structures added (phantom seen in fig 3B). SD of fitted Gaussian is 1.48%/cm.

they were applied to the patients scintigraphic data. Perfusion gradients could confidently be calculated in 244 out of the 247 patients. The median cranio-caudal gradient of the patients was -1.22%/cm and the median dorso-ventral gradient was -1.05%/cm. In V/P SPECT examinations which were regarded as normal, the median cranio-caudal gradient was -0.81%/cm and the median dorso-ventral gradient was -3.58%/cm [Fig 6]. In the 36 patients with LHF pattern, the perfusion gradients differed significantly from those found in normal patients in both cranio-caudal (-2.33%/cm, P=0.0001) and dorso-ventral directions (4.08%/cm, P<0.0001) [Fig 6]. The overlap of the dorso-ventral perfusion gradient values between LHF patients and those who were considered as normal was modest, indicating that this could be a potential tool in the diagnosis of LHF. It is notable that five of the patients who were initially reported as normal, had positive dorso-ventral perfusion gradients. In these five patients, heart failure was never considered as a differential diagnosis in medical records but all patients had accelerating breathlessness and one of the patients had earlier suffered from myocardial infarction. One may speculate if some of these patients suffered from pulmonary congestion at the time of V/P SPECT examination. Another observation made with V/P SPECT, was a fast normalization of perfusion distribution in patients after anticongestive treatment.

Thus, this study showed that LHF is common among patients with suspected PE. This study also indicates that V/P SPECT can be used in the diagnosis of LHF. If V/P SPECT is useful in the follow-up of LHF needs to be further studied.

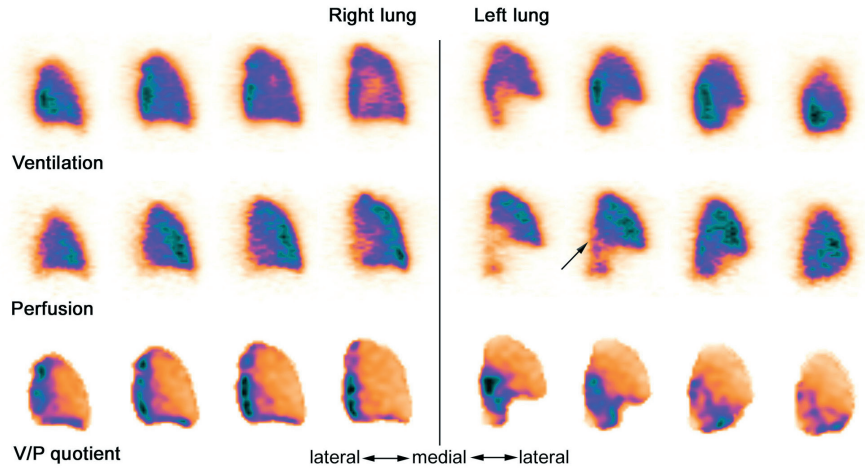

Figure 5. Patient with known left heart failure. Images obtained with the patient in supine position. Redistribution of perfusion to ventral parts of the lungs (arrow). Because ventilation is not affected to the same degree, non-segmental mismatch is seen.

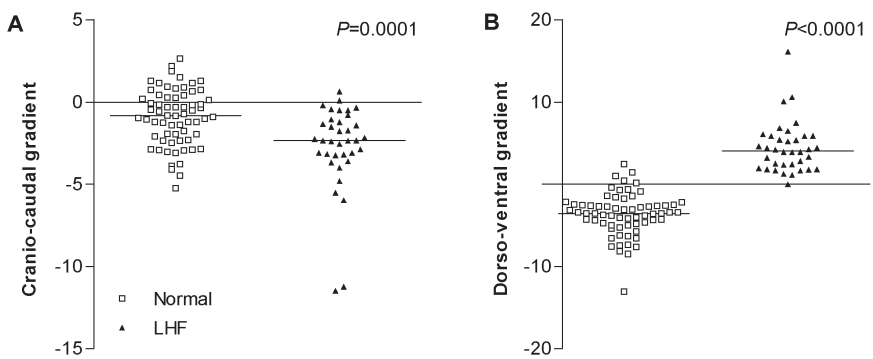

Figure 6. Comparision of perfusion gradients (%/cm) in patients with normal and left heart failure (LHF) pattern in ventilation-perfusion single photon emission computed tomography (V/P SPECT). (A) Perfusion gradients in the cranio-caudal direction. (B) Perfusion gradients in the dorso-ventral direction. The Mann-Whitney test was used for statistics.

Comparison of ^{99m}Tc-DTPA and ^{99m}Tc-Technegas (Study II)

Radioaerosols are widely used in lung scintigraphy to assess regional ventilation. ^{99m}Tc-DTPA and ^{99m}Tc-Technegas are the most commonly used radioaerosols. Although they have different particle size and ability to form bonds with water they have not been compared in a head-to-head study. This was important to evaluate before the role of V/P SPECT in COPD could be further studied. The aim of study II was therefore to investigate the differences between ventilation studies performed ^{99m}Tc-DTPA and ^{99m}Tc-Technegas. 63 out of the 65 included

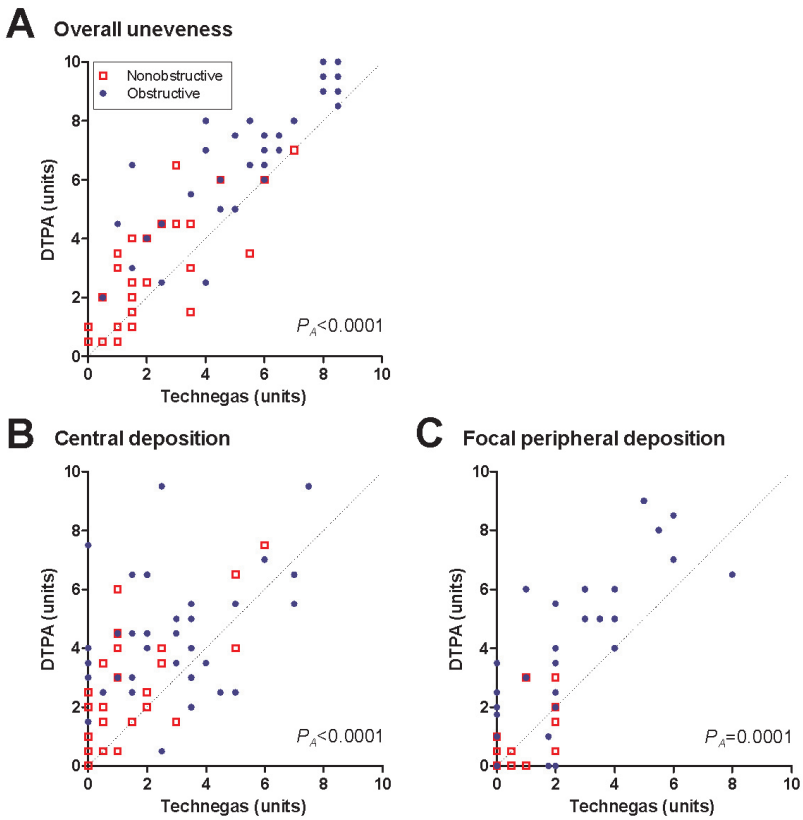

Figure 7. Relationship between ^{99m}Tc-DTPA and ^{99m}Tc-Technegas ventilation SPECT images regarding the degree of overall unevenness (A), central deposition (B) and peripheral deposition (C). Dotted lines are identity lines. *P*-value for paired comparision is shown for all patients (P_A). Statistics was performed with Wilcoxon signed-rank test.

patients were available for blinded analysis. Both patients with and without known obstructive lung disease were included.

In patients with normal or near normal ventilation there was a good resemblance between ^{99m}Tc-DTPA and ^{99m}Tc-Technegas ventilation images. This is consistent with previous studies in which the diagnostic properties of ^{99m}Tc-DTPA have been comparable to those of krypton, in the diagnosis of PE.[146,162] However, in patients who did not have a normal ventilation, there were differences between the two ventilation agents. ^{99m}Tc-Technegas, with its smaller particle size and hydrophobic properties, was more homogenously distributed in the lungs with less deposition in central and peripheral airways [Fig 7]. ^{99m}Tc-Technegas showed a better peripheral penetration which lead to fewer areas with reverse mismatch. Adequate distribution of radioaerosol to peripheral airways and alveoli is important as ventilation otherwise could be underestimated. In study II, this was illustrated by the finding of V/P mismatch consistent with PE in three COPD patients when ^{99m}Tc-Technegas was used as ventilation agent. This mismatch was not recognized with ^{99m}Tc-DTPA. PE is common among patients with COPD as well as other cardiopulmonary conditions and is therefore important to identify. Among patients without known obstructive disease, six patients with findings consistent with PE were identified with ^{99m}Tc-DTPA and seven patients when ^{99m}Tc-Technegas was used. In Figure 8, the distribution of ^{99m}Tc-DTPA and ^{99m}Tc-Technegas in selected patients is illustrated.

We concluded that ^{99m}Tc-Technegas should be regarded as the aerosol of choice to increase the diagnostic accuracy in patients with suspected PE or other cardiopulmonary disease.

	MRC		CCQ		$Emphysema_{HRCT}$		$TotRed_{V/P\ SPECT}$		$Obstr_{V/P\ SPECT}$	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
%VC (% pred)	-0.19	0.32	-0.06	0.74	0.11	0.58	-0.15	0.43	-0.18	0.33
$\%FEV_1$ (% pred)	0.08	0.66	-0.04	0.85	-0.27	0.17	-0.62	0.0003	-0.64	0.0001
FEV_1/VC	0.33	0.08	0.07	0.70	-0.56	0.002	-0.74	<0.0001	-0.71	<0.0001
$\%FEV_1/VC$ (% pred)	0.36	0.05	0.06	0.75	-0.47	0.012	-0.70	<0.0001	-0.67	<0.0001
%TLC (% pred)	-0.30	0.11	0.01	0.97	0.50	0.007	0.39	0.035	0.29	0.11
%RV (% pred)	-0.28	0.14	0.02	0.90	0.35	0.064	0.42	0.020	0.37	0.047
%FRC (% pred)	-0.16	0.41	0.10	0.60	0.20	0.31	0.18	0.33	0.18	0.35
%DLCO (% pred)	-0.15	0.45	-0.21	0.29	-0.42	0.037	-0.37	0.05	-0.35	0.06
$Emphysema_{HRCT}$ (%)	0.12	0.53	0.04	0.85			0.69	<0.0001	0.66	0.0001
$TotRed_{V/P\ SPECT}$ (%)	-0.09	0.64	0.00	0.99	0.69	<0.0001			0.96	<0.0001
$Obstr_{V/P\ SPECT}$ (u)	-0.10	0.59	-0.02	0.92	0.66	0.0001	0.96	<0.0001		

Table 1. Spearman correlation matrix between spirometry, symptom questionnaires, emphysema extent, V/P SPECT assessed reduction in lung function and obstructive disease grade.

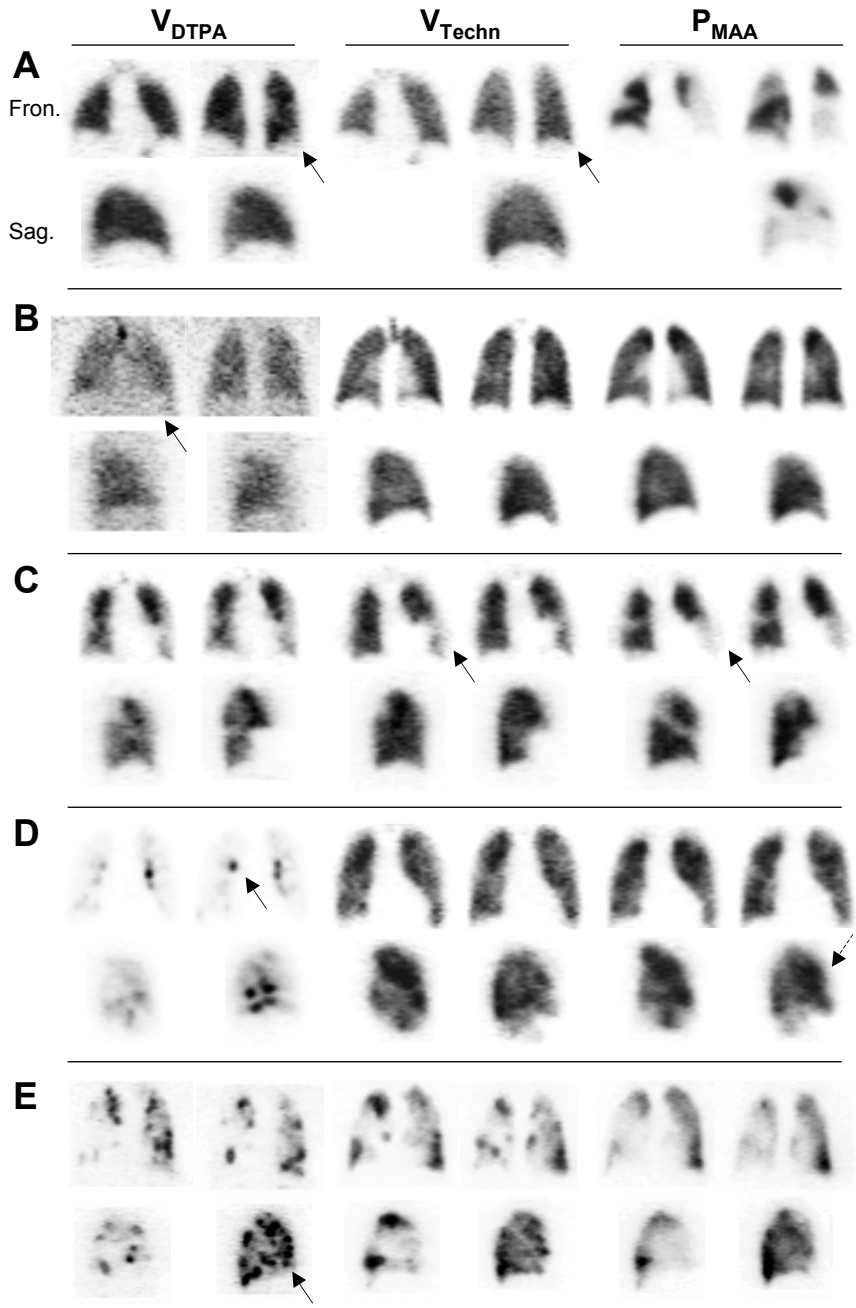
V_{DTPA}
V_{Techn}
P_{MAA}
A
Fron.
Sag.
B
C
D
E

Figure 8 (opposite page). V/P SPECT with ^{99m}Tc-DTPA and ^{99m}Tc-Technegas. (A) Images from a patient with suspected PE show extensive, mismatched perfusion defects of segmental character. Technegas tends to better delineate the parenchyma in the costodiaphragmatic recesses (arrow). (B) Patient with alveolitis observed as an elevated background activity only in DTPA images (arrow). (C) Mild obstructive lung disease. Signs of pneumonia in lingular segments on CT with corresponding nearly matched reduction in V/P scans (arrows). PE was clinically suspected as was also the case when Technegas ventilation images were used. (D) Moderate COPD and congestive heart failure. Severe central deposition (solid arrow) lead to interpretation difficulties when DTPA was used. Dashed arrow shows redistribution of perfusion to ventral parts of the lung as a sign of heart failure. (E) Reduced ventilation and perfusion due to severe COPD and emphysema. Considerable peripheral deposition of ventilation pharmaceutical is seen (arrow).

V/P SPECT in the diagnosis and classification of COPD (Study III)

The diagnosis and classification of COPD, is according to GOLD and ATS/ERS criteria presently based on FEV_1. FEV_1 do not explain the pathophysiology behind the airflow limitation and has a low sensitivity to early changes in COPD. Early detection of COPD is essential so that efforts to modify its course can be made. In study III, our aim was to evaluate the potential of V/P SPECT in the diagnosis and characterization of COPD. 30 patients with moderate to very severe COPD were studied. The patients were examined with Technegas V/P SPECT, HRCT and spirometry. They were also examined regarding static lung volumes and D_LCO. Symptoms, dyspnea and functional state were assessed with the MRC dyspnea and the CCQ scale. Spearman correlation matrix is shown in [Table 1].

We found no correlation between the two symptom scales and the objective measures of lung function or alveolar destruction. Both CCQ and MRC have been used to predict morbidity and mortality in COPD populations but, in agreement with our results, the correlation with FEV_1 has been weak or absent.[117,119] This may be one of the reasons why COPD diagnosis often is delayed. V/P SPECT was used to assess the degree of lung function reduction (ventilation and/or perfusion) as a percent of the total lung volume. V/P SPECT was also used to classify the degree of obstructive lung disease, if present, as mild, moderate or severe. Classification was based on the effect that the obstructive changes had on regional ventilation and perfusion. In patients with COPD, we

found that the parameters indicating obstructive lung disease, according to VP SPECT, inversely correlated to FEV_1 and FEV_1/VC [Fig 9]. Emphysema extent was assessed with HRCT. The extent of emphysema increased with increasing reduction of lung function and scintigraphic degree of obstructive disease. The extent of emphysema did not correlate with changes in FEV_1, but a moderate correlation was seen with FEV_1/VC [Fig 9]. In four of the COPD patients, redistribution of regional perfusion indicating LHF was found. Three out of these patients had known heart disease. LHF diagnosis was previously only known in one of the four patients. In three patients segmentally mismatched perfusion defects consistent with PE were observed. LHF and PE are important to detect among COPD patients. Although no spirometry was performed in the 33 patients from study II, which were used in this study to avoid interpretation bias, 28 of them had no known obstructive disease. Only three out of these 28 patients were classified as having mild obstructive lung disease on V/P SPECT.

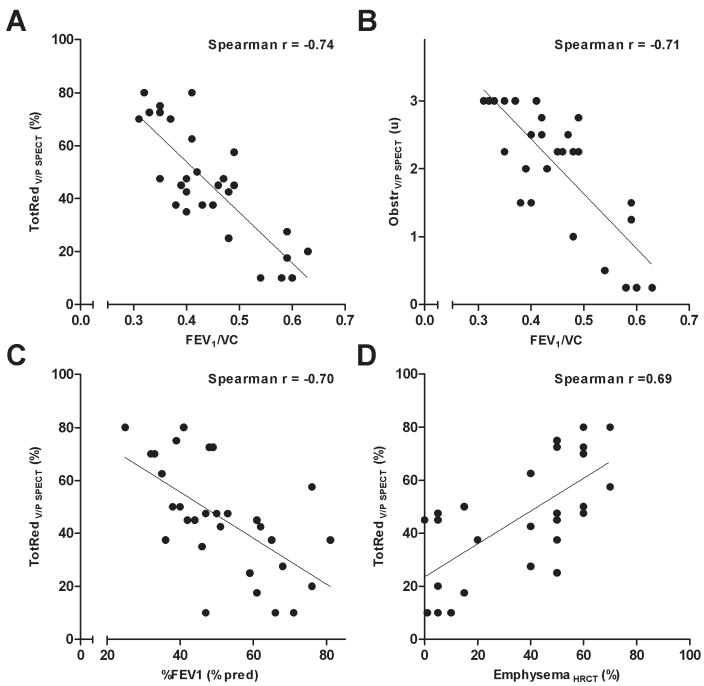

Figure 9. Relations between: (A) FEV_1/VC and total reduction in lung function as assessed with V/P SPECT ($TotRed_{V/P\ SPECT}$); (B) FEV_1/VC and the degree of obstructive lung disease as assessed with V/P SPECT ($Obstr_{V/P\ SPECT}$); (C) FEV_1 as percent of predicted (%FEV_1) and $TotRed_{V/P\ SPECT}$; and (D) emphysema as assessed with HRCT ($Emphysema_{HRCT}$) and $TotRed_{V/P\ SPECT}$.

Ventilation scintigraphy has previously been shown to be more sensitive to obstructive lung changes than spirometric flow rates and lung volumes.[220] ^{99m}Tc-Technegas ventilation SPECT and HRCT has been compared in the detection of early histological changes of small airway disease including emphysema.[213] V/P SPECT has in this and other studies been shown to be more sensitive than HRCT in the detection of early changes of alveolar destruction as well as other small airway disease.[212,213,221]

Although larger studies are needed, our study shows that V/P SPECT has a clinical role in the diagnosis of COPD. V/P SPECT can also be used to characterize the severity of COPD.

V/P SPECT in the follow up of treated PE (Study IV)

In PE symptoms are nonspecific. Therefore the diagnosis of PE relies on medical imaging. Treatment of PE with heparin followed by an oral anticoagulant is well established. However, the most favourable duration of anticoagulant treatment has been the subject of debate. Follow-up and decisions on treatment duration is today based on continuing symptoms and presence of risk factors. An objective follow-up on whether the acute episode of PE has been effectively treated is rarely performed. CTPA is not suitable for follow-up. In study IV, we used V/P SPECT to monitor the course of treated PE. While on anticoagulant treatment,

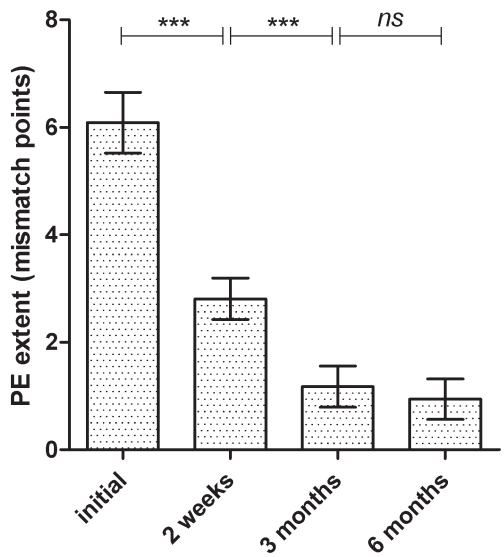

Figure 10. Mean extent of PE perfusion defects at the time of diagnosis, 2-week, 3-month and 6-month controls. Whiskers represent standard error of the mean (SEM).

serial V/P SPECT examinations were performed on the patients in the study. Patients were examined at 2 weeks, 3 months and 6 months after the time of diagnosis. Clinical follow-up by was performed at the same occasions.

All patients were symptomatic at the time of diagnosis. The most common symptoms were dyspnea and chest pain when breathing. After a few days of anticoagulant treatment, symptoms became less frequent, and after tree months of treatment all patients were asymptomatic.

During the first 2 weeks of treatment we observed a significant decline in PE extent (P<0.001) [Fig 10]. PE extent decreased in all patients except one. At 2 weeks, 43% of the patients were regarded as free from PE. This is consistent with previous observations.[222] After 3 months, >70% of the patients were free from signs of PE. However, five patients showed residual PE perfusion defects at 3-month follow-up. In all these patients, persistent perfusion defects were still found after six months treatment with anticoagulants. Four out of the five patients were regarded as chronic PE. Patients with chronic PE are important to identify as this is a risk factor for the development of chronic thromboembolic pulmonary hypertension.[52] The findings in study IV indicate that V/P SPECT can contribute to the definition of PE therapies, better aimed at individual patients.

Hence, follow-up of PE with V/P SPECT is feasible and will help to evaluate treatment effectiveness and to identify patients who develop chronic PE. Resolution of perfusion defects after PE occurs within the first three months of treatment.

Major conclusions

The major conclusions of each paper were:

I. LHF is common among patients with suspected PE. V/P SPECT can be used to diagnose LHF with a high positive predictive value. An inverted perfusion gradient in the gravitational direction should lead to the consideration of LHF diagnosis.

II. ^{99m}Tc-Technegas is the aerosol of choice in V/P SPECT studies.

III. V/P SPECT can give additional information in the diagnosis of COPD. Scintigraphic signs of COPD should therefore, whenever found, be reported. V/P SPECT can also be used to characterize the severity of COPD.

IV. Follow-up with V/P SPECT after acute PE is feasible to evaluate treatment effectiveness. Restoration of regional perfusion after PE occurred during the first 3 months of treatment, but not thereafter. V/P SPECT follow-up after an episode of PE seems important since about 20% of the patients had remaining perfusion defects at three months after diagnosis, although all were free from symptoms.

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Papers I-IV