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RADIOLOGICAL IMAGING OF PULMONARY EMPHYSEMA

**PREOPERATIVE EVALUATION OF CANDIDATES FOR
LUNG VOLUME REDUCTION SURGERY**

Kerstin Cederlund



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ABSTRACT

Lung volume reduction surgery (LVRS) for pulmonary emphysema, first described by Brantigan in 1957, was re-introduced by Cooper et al in 1995. From a surgical point of view, information on the extent and distribution of emphysema is mandatory and also partly determines the outcome. No consensus exists on the best method for describing emphysema severity and heterogeneity in candidates for LVRS.

The aims of this thesis were to define a suitable computed tomography (CT) technique for visual evaluation of severe emphysema, to design an objective model for classification of emphysema heterogeneity and to evaluate the additional information gained by lung perfusion scintigraphy (LPS) in classification of emphysema.

Study I investigated whether radiologists in evaluating severe emphysema subjectively preferred high resolution computed tomography (HRCT) or spiral CT. HRCT was preferred in 56%, spiral CT in 19% and in 25%, the techniques were considered equal.

Study II investigated which of three types of images yielded the best results in estimating the degree of emphysema. In the grading of emphysema, the radiologists performed similarly with both HRCT and spiral CT, while “density-masked” images (an image of a quantitative measurement) gave significantly better results.

Study III investigated whether spiral CT was superior to HRCT in evaluating the heterogeneity of emphysema and whether the combination of both CT-techniques improved the evaluation. Spiral CT was significantly better compared to HRCT, while the combination of the techniques did not improve the evaluation.

Study IV presented a method for classification of emphysema heterogeneity that was calculated objectively, surgically oriented and classifies each lung separately.

Study V investigated whether LPS contributes to the preoperative classification of emphysema heterogeneity compared to classification based only on CT. The answer was yes, and hence both CT and LPS should be included when assessing emphysema heterogeneity prior to LVRS.

To conclude, in contrast to subjective preferences, visual evaluation of emphysema should be based on spiral CT (10 mm slice thickness and reconstruction with a high spatial algorithm) instead of HRCT in potential candidates for LVRS. The presentation of images as “density-masked” images improves the visual evaluation of degree of emphysema. This type of imaging can easily be performed on all CT scanners and can thus be recommended as part of a complete CT examination. The addition of lung perfusion scintigraphy to spiral CT of the lungs improves the classification of emphysema heterogeneity in candidates for LVRS. A method for objective classification of emphysema heterogeneity has been developed.

LIST OF PUBLICATIONS

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

- I. Thin-section CT versus spiral CT in candidates for Lung Volume Reduction Surgery (LVRS). A comparison based on radiologists subjective preferences.**
Kerstin Cederlund, Lott Bergstrand, Staffan Högberg, Elsbeth Rasmussen, Bertil Svane
European Radiology 2001;11:402-408.
- II. Visual grading of emphysema severity in candidates for Lung Volume Reduction Surgery. A comparison between HRCT, spiral CT and "density masked" images.**
Kerstin Cederlund, Lott Bergstrand, Staffan Högberg, Elsbeth Rasmussen, Bertil Svane, Peter Aspelin
Acta Radiologica 2002;43:48-53.
- III. Visual classification of emphysema heterogeneity compared with objective measurements: HRCT versus spiral CT in candidates for Lung Volume Reduction Surgery (LVRS).**
Kerstin Cederlund, Lott Bergstrand, Staffan Högberg, Elsbeth Rasmussen, Bertil Svane, Ulf Tylén, Peter Aspelin
European Radiology 2002;12:1045-1051.
- IV. Classification of Emphysema in Candidates for Lung Volume Reduction Surgery: A New Objective and Surgically Oriented Model for Describing CT Severity and Heterogeneity.**
Kerstin Cederlund, Ulf Tylén, Lennart Jorfeldt, Peter Aspelin
Chest (accepted)
- V. Is lung perfusion scintigraphy prior to Lung Volume Reduction Surgery necessary?**
Kerstin Cederlund, Staffan Högberg, Lennart Jorfeldt, Flemming Larsen, Mats Norman, Elsbeth Rasmussen, Ulf Tylén
Submitted

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LIST OF ABBREVIATIONS

CLE	Centrilobular emphysema
CT	Computed tomography
CXR	Chest x-ray
EI	Emphysema index
EID	Difference in emphysema index between two images
EIM	Mean emphysema index
EIM-III	Mean emphysema index in study III
HRCT	High resolution computed tomography
HU	Hounsfield unit
LPS	Lung perfusion scintigraphy
LVRS	Lung volume reduction surgery
MR	Magnetic resonance
MRI	Magnetic resonance imaging
PLE	Panlobular emphysema
RCT	Randomised controlled trial
ROI	Region of interest
^{99m} Tc-MAA	Technetium labelled macro-aggregate of albumin

1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Emphysema

Emphysema is a pathological diagnosis and defined as a condition of the lung characterized by abnormal, permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of the alveolar walls and without obvious fibrosis (1,2). These two features, permanence of enlargement and destruction, are most important, because they indicate that the process is non-reversible. Although strictly speaking, emphysema can be diagnosed only pathologically, certain alterations in pulmonary function and radiological features allow its detection in vivo and an estimation of its severity can be obtained. Emphysema interferes with respiratory function because of parenchymal destruction and changes in the mechanics of respiration. The elastic properties of the lungs can be defined as the elastic recoil. This intrinsic tendency of the elastic tissue in the alveolar walls to recoil when stretched is the driving force behind the process of emptying the lungs. Emphysema is associated with a progressive loss of lung elastic recoil, which leads to decreased expiratory flow by loss of driving pressure and premature airway closure (3,4,5). The loss of pulmonary elastic recoil also leads to expansion of the lung, with an increase in residual volume and total lung capacity. The hyperinflated thorax in emphysema is mechanically inefficient and consequently the respiratory muscles cannot be used to their maximal potential (6). As the disease progresses, physical activities decline, and patients in advanced stages become dyspneic with minor exertion or even at rest. Drug therapy with bronchodilator and anti-inflammatory drugs directed at decreasing airway resistance has only a minor effect. Many patients require supplemental oxygen.

Despite all available therapies, end-stage emphysema is characterized by impaired lung function, exercise tolerance and reduced quality of life (7).

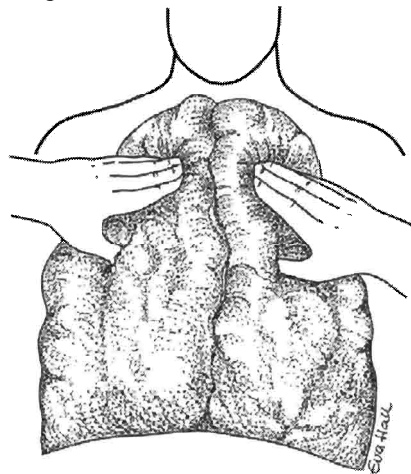


Figure 1. *An artist's illustration of severe emphysema - voluminous, slack lungs.*

1.1.2 Pathogenesis of emphysema

In 1963 Laurel and Eriksson in Malmö (8) reported the association between lack of a serum protein called alpha-1-antitrypsin and emphysema. This discovery led to the elastase-antielastase hypothesis that is still believed to explain the genesis of emphysema. The underlying cause of emphysema is widely accepted to be an imbalance in the activities of proteolytic and antiproteolytic enzymes in lung tissue, resulting in destruction of the alveolar walls (9,10). The imbalance can emanate either from a deficiency of antiprotease, as in alpha-1-antitrypsin deficiency, or from excess protease, as in emphysema related to cigarette smoking.

1.1.3 Histopathology of emphysema

The presence and severity of emphysema is usually assessed pathologically on gross specimens with the naked eye. The minimum requirements for diagnosis should be careful examination of a slice of inflated lung, knowledge of the normal appearance, and standards to compare with and grade emphysema as mild, moderate or severe (11). Two main methods were traditionally used to macroscopically quantify the severity of emphysema: the point counting developed by Dunhill (12) and the panel-grading proposed by Thurlbeck (13). The panel-grading system is based on the comparison of paper-mounted sagittal lung sections with a set of standards, scoring emphysema from 0 to 100 at intervals of 5 or 10. This method has often been used to correlate pathological findings with computed tomography (CT) findings. Gross examination can be supplemented by histological examination of blocks of tissue and by assessments that are more objective. A number of techniques have been proposed to quantify and characterize emphysema microscopically (11).

Different morphologic subtypes of emphysema have been described according to their location in the secondary pulmonary lobule. This anatomic unit is the smallest discrete portion of the lung surrounded by connective tissue septa, polyhedral in shape and 1 to 2.5 cm per side (figs 2 and 3).

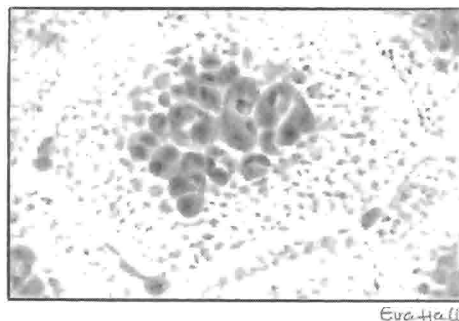


Figure 2. *Centrilobular emphysema. Cross-section of a polyhedral, secondary pulmonary lobule. Destruction of alveolar walls seen in the central part, surrounded by normal parenchyma.*

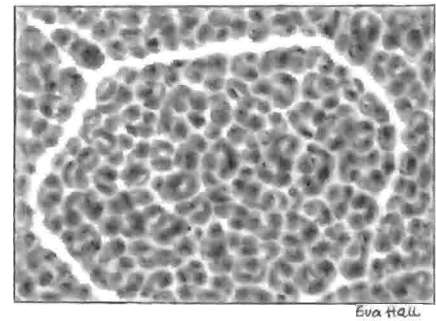


Figure 3. *Panlobular emphysema. Cross-section of a polyhedral, secondary pulmonary lobule. Destruction of alveolar walls is uniformly distributed.*

1.1.3.1 Centrilobular emphysema

Centrilobular emphysema (CLE) is the most common subtype of emphysema and is strongly associated with cigarette smoking. Anatomically, it involves the central portion of the secondary lobule surrounding the proximal respiratory bronchioles (fig 2). Early morphologic abnormalities can occur in the absence of the gross pathological changes of emphysema. The earliest microscopic change is dilatation of respiratory bronchioles accompanied by loss of adjacent alveolar septa. The reason for the localization of early disease to parenchyma around respiratory bronchioles is not clear, but may reflect the “spill-over” into this site of inflammatory cells centred on these airways (14). With progression of the disease, pathologic abnormalities become more evident. Several respiratory bronchioles become confluent, creating an enlarged space supplied by a terminal bronchiole. At this stage, the disease is clearly visible for the naked eye. The

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key observation for pathological diagnosis is multiple grossly visible sites on the cut surface of a lung where both normal alveolar architecture and enlarged spaces with tissue loss are situated immediately adjacent to one another (1). With further progression, the relatively discrete foci of mild disease become confluent, so that an entire lobule or segment of lung is eventually affected. Although completely empty spaces can be formed in this way, blood vessels or fine strands of residual lung parenchyma often traverse the emphysematous spaces.

CLE is typically more severe in the lung apices, particularly affecting the apical and posterior segments of the upper lobes and the superior segments of the lower lobes (fig 4) (1,15,16,17). A variety of factors might theoretically contribute to this zonal predilection. Among these factors is the relatively greater ventilation-perfusion ratio in the lung apices, leading to a greater concentration of inhaled material at the lung apices (18).

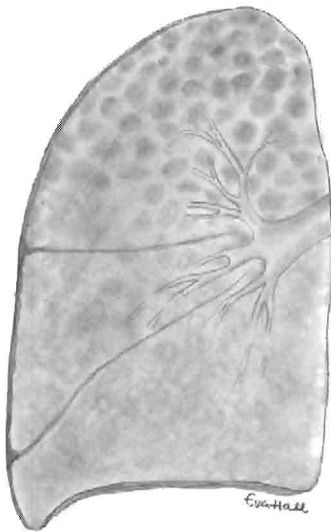


Figure 4. *Centrilobular emphysema is often more severe in the lung apices and is visualized as “holes” surrounded by more normal parenchyma.*

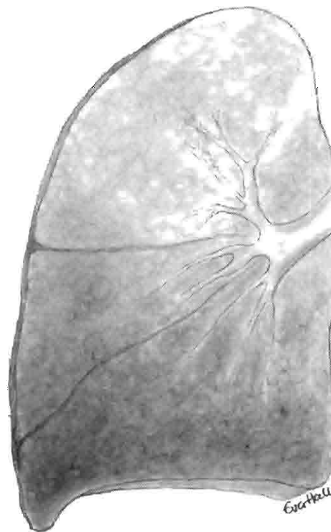


Figure 5. *Panlobular emphysema is often more severe in the lung bases and is visualized as evenly distributed “loss” of lung parenchyma.*

1.1.3.2 Panlobular emphysema

Panlobular emphysema (PLE), is characteristically observed in patients with alpha-1-antitrypsin deficiency. PLE is the most common form of emphysema in non-smokers. Anatomically, it involves all of the components of the secondary lobule uniformly (fig 3). PLE is also characterized by destruction of alveolar walls evenly distributed in the lung (1), but with a predilection for the lower lobes (fig 5), (1,15,16,17). Macroscopically, mild to moderate PLE is subtle. On lung slices, only prominent bronchovascular bundles, projected above the cut surface, may indicate the diffuse loss of parenchymal tissue. In severe disease, affected parenchyma may consist of no more than large air spaces through which strands of tissue and blood vessels pass like struts.

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Protease circulating in the blood stream is preferentially distributed to the lower parts of the lungs, where there is greater perfusion. In patients with alpha-1-antitrypsine deficiency, the imbalance between protease activity and the anti-proteas activity is greatest at the lung bases, possibly explaining the lower lobe predominant distribution in these patients (18).

Using microscopic criteria, CLE and PLE can be differentiated and correlated with changes in lung elastic recoil and airway function. CLE is associated with small airway inflammatory changes, while PLE is more closely related to loss of lung elasticity (19,20).

The pathogenetic significance of the different anatomic patterns of emphysema is not exactly known, but it has been suggested that different mechanisms are related to the genesis of CLE and PLE. It is possible that the diffuse, even destruction seen in PLE results from a blood-borne mechanism with little relation to airway abnormalities, while the uneven pattern of lung destruction seen in CLE is associated with more severe abnormalities in small airways, suggesting that centrilobular destruction is related to airway inflammatory processes (19,20).

1.1.3.3 Severe emphysema

Differently defined types of emphysema can usually be diagnosed histopathologically as long as the disease is mild or moderate. In more advanced emphysema the differentiation is more difficult (20,21). Some pathologists claim that CLE progresses into PLE (2). Even in the original classic description of emphysema from 1835, Laennec pointed out that emphysema rarely involved all lung portions equally. In nearly all cases, some areas were worse than the others and the disease might be limited to one lung, lobe or segment. *It is this heterogeneous distribution that makes the LVRS (lung volume reduction surgery) possible, while the histopathological type of the emphysema has no direct impact on selection of patients for LVRS.*

1.1.4 History of emphysema surgery

Throughout the 20th century, several operations have been advocated as methods of treatment for patients with emphysema. The methods were often promoted as offering potential cures. Unfortunately, most of these procedures attempted to treat the wrong physiological or anatomical deficit so the results were unpredictable or frankly disastrous (22, 23). Except for bullectomy for emphysematous bullous lung disease, none of these procedures has stood the test of time. Once it was realised that hyperinflation was a consequence, rather than the cause of emphysema, interventions aimed at reducing the volume of the lung parenchyma was tested. Among these, the concept of volume reduction proposed by Brantigan in the late 1950s (24) was perhaps the most attractive. He postulated that in patients with distended lungs due to severe emphysema, the normal “outward circumferential pull” on the bronchioles had been lost, causing their collapse during expiration. He proposed that reducing the overall lung volume, by means of multiple wedge resections would restore the outward elastic pull on the small airways and reduce expiratory airway obstruction. The operation was performed on 33 patients. Despite the apparent improvement seen in several patients, the high perioperative mortality and substantial postoperative complication rate (particularly persistent air leak) resulted in poor acceptance of the procedure. The operation was buried until 1995, when

Joel Cooper (25) successfully reintroduced the concept of reducing lung volume to improve pulmonary function in emphysema. Currently, there are three surgical options available in emphysema: bullectomy, lung transplantation and LVRS.

1.1.5 Lung volume reduction surgery

Cooper, a pioneer also in lung transplantation for terminal respiratory insufficiency, made certain observations in his transplantation patients leading to renewed interest in the work of Brantigan and suggested that the approach by Brantigan might be valuable as an alternative or “bridge” to lung transplantation. These observations included the ability of the thorax to return rapidly to a normal configuration after transplantation despite years of distension, the ability to oxygenate the patient on a single lung during the transplant procedure despite pulmonary function so reduced that replacement was needed, and the ability to perform the transplantation procedure without the use of cardiopulmonary bypass. In combination with anecdotal reports of improved function following resection of cancers in severely emphysematous patients and considerations of physiological principles, these observations, led to the development of a revised surgical procedure for reducing lung volume to improve pulmonary function (25). The promising result of this study renewed the interest for surgery in patients with severe emphysema (26,27,28,29). Since 1995, approximately 500 papers about LVRS have been included in the Medline database.

1.1.5.1 Rationale for LVRS

The idea of removing lung in a disease characterized by lung destruction to improve pulmonary function may seem counterintuitive. The premise is that reducing lung volume allows the thorax to return to a more normal configuration (fig 6), thus improving respiratory mechanics and reducing the work of breathing. The major underlying mechanism is restoration of the retracting force of the lung parenchyma with the secondary effect of increasing the airway diameter (30,31). The effect of the operation is thus similar to a spiral, which has become too lax: by shortening it, one can to some extent restore its former recoil. Furthermore, by removing parts of the lung where the recoil is non-existent or extremely low, space is provided for the excursion of the remaining parts of the lungs which was formerly not possible. Another consequence of the re-established recoil of the lungs is an improvement of the chest wall mechanics (32,33). It is generally considered that hyperinflation plays a crucial role in the sensation of dyspnea, and reduced hyperinflation has been proposed to be one main causes of relief of exertional breathlessness after LVRS (34).

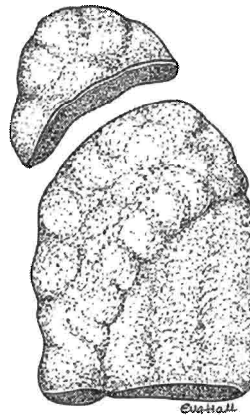


Figure 6. Lung volume reduction surgery imply removing the most diseased parts of the lung.

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1.1.5.2 Patient selection

LVRs has emerged as a palliative treatment option for select patients with advanced pulmonary emphysema. Potential candidates for LVRs are patients who have emphysema with incapacitating symptoms not palliated by medical therapy, severe air flow obstruction (forced expiratory volume during one second, $FEV_{1.0} < 25-30\%$) and lack of significant co-morbid medical conditions. Anatomic features appropriate for surgery includes hyperinflation and surgical “target areas” of severe emphysema. Chest X-ray (CXR), CT and pulmonary scintigraphy are usually included in the preoperative evaluation to assess these anatomic features. Except for determining the severity and distribution of emphysema, CT in candidates for LVRs also serves to detect unsuspected bronchogenic carcinomas, bronchiectasis, pleural scarring, indirect evidence of cardiovascular disease and pulmonary hypertension; these findings may warrant further evaluation and possibly exclude patients from LVRs (26,35). Many aspects of patient selection remain subjective and difficult, particularly the interpretation of imaging studies for evaluating the severity and distribution of emphysema. The selection criteria are constantly being refined and no general agreement for selection of patients for LVRs exists (28,36). The main exclusion criteria are continued smoking, diffusion capacity $< 20\%$, age $> 70-75$ years, high degree of “asthma”, bronchiectasis, pleural adhesions and fibrosis or scarring of the lung. In patients with symptoms of emphysema, a good correlation of CT and lung function tests has been shown (37). Among pulmonary function tests indicating emphysema, CT grading of emphysema correlates best with decreased diffusion capacity followed closely by airflow obstruction (38,39). In mild degree emphysema, it is possible by HRCT to detect morphological changes before symptoms develop (40,41).

1.1.5.3 Operative procedure

LVRs can be achieved successfully in a variety of approaches. The procedure proposed by Cooper and colleagues (25,42) involves bilateral wedge resections of the most emphysematous portion of the lung to reduce total lung volumes by 20-30%. The non-segmental resections are performed by means of median sternotomy with use of a linear stapling device. Bovine pericardium is used to buttress the staple lines and reduce the occurrence of prolonged air leaks (43). Staples, lasers or a combination of both have been used in open or closed (video assisted thoracoscopic surgery, VATS) procedures, either unilaterally or bilaterally. Stapling is more effective than laser resection (44). At the Karolinska Hospital in Stockholm, the original technique described by Cooper has most frequently been used.

1.1.5.4 Complications

The severity of complications range from prolonged hospitalisation to death (0-10%). Prolonged air leak is the most frequently observed postoperative complication leading to prolonged hospitalisation, this despite reinforcement of the resection lines (42).

1.1.5.5 Outcome and referral

The results of many studies (30,31,32,42,45,55,87,46,88) show symptomatic and functional improvement after LVRs. However, several problems exist when trying to draw conclusions regarding outcome from the numerous reports of LVRs. These include different surgical techniques and selection criteria, short postoperative follow-up period,

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incomplete retrospective data collection and the absence of a control group in most of the published reports. In the review regarding LVRS by Hensley et al published in the Cochrane Library in 2001 (36), it is concluded that the lack of randomised controlled trials makes it still unclear as to whether LVRS improves health outcome in diffuse emphysema more than a pulmonary rehabilitation program. However, results from the Swedish VOLREM-study (112) seem to be very promising. This is a prospective randomised controlled trial, comparing LVRS with an intensive exercise training program. The study shows that in severe emphysema, LVRS dramatically increases health-related quality of life with fairly stable effects for at least one year.

The referral of potential LVRS-patients to the Thoracic Clinics at the Karolinska Hospital started 1994, and during that year, three patients were operated. Most operations were performed during 1996 with 31 patients operated, but thereafter a rapid decrease in number of referred patients as well as operations has been noted. Since 1999 only a few LVRS procedures has been performed annually. In a survey of LVRS in Europe, an increase of cases until 1997 was registered (47). Thereafter, the number seems to have reached a plateau (personal communication, Weder, June 2001). Scientific publications, per year, concerning LVRS have declined, from 105 publications 1997 to 48 publications 2000 (based on a search in Medline with the combination of "emphysema and surgery and reduction"). The decline in referrals, as well as operations in our hospital, may be influenced by the ongoing and recently finished randomised, controlled trials regarding LVRS in Sweden and other countries.

1.1.6 Bullectomy and lung transplantation

Bullectomy refers to the resection of large bullae and does not involve removal of much lung parenchyma although the volume reduction may be substantial. The basic indications for bullectomy are the presence of giant bullae that compress adjacent lung tissue in patients who are dyspneic with airflow obstruction and exercise intolerance (48). Lung transplantation is a surgical treatment alternative for patients with end-stage obstructive lung disease. The operation is reserved for patients with markedly limited life expectancy despite optimal medical management. Pulmonary emphysema including α_1 -antitrypsin deficiency is the single most common primary disease in patients undergoing lung transplantation, accounting for about half of recipients (49). The shortage of lung donors remains the major limiting factor keeping the total number of transplantations at about 1000 per year worldwide.

1.2 IMAGING OF EMPHYSEMA

1.2.1 Chest X-ray

The clinical imaging of emphysema was often limited to CXR before the reintroduction of LVRS. Radiological abnormalities in patients with emphysema generally reflect increased lung volume and/or lung destruction (reduced vascularity and areas of low attenuation) (50,51,52). These signs alone, or in combination have variable sensitivity for emphysema detection, ranging from 40% to 80% compared to pathological diagnosis (53). The more severe emphysema, the more likely that a radiological diagnosis will be made, no matter what criteria are used (11). In general, moderate to severe emphysema is radiologically detectable, mild emphysema is not (54).

In the preoperative imaging of potential LVRS patients a CXR is always performed. The examination may include posterior-anterior and lateral chest radiographs obtained in inspiration and expiration. These provide information regarding the degree of thoracic distension, impairment in the chest wall and diaphragm movement, general severity and distribution of emphysema. Potential exclusion features, such as bronchiectasis, active

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infection, lung cancer, evidence of prior surgery, or pleural disease can also be identified. Thus, CXR provides a considerable amount of information, and CXR alone might be adequate for initial screening of potential LVRS candidates (26,55,56).

1.2.2 Computed tomography

1.2.2.1 An outline of techniques

CT can be performed in a wide variety of ways, partly reflecting the technical evolution of the CT scanners. *Conventional* or *standard CT* usually implies single slice imaging with 7-10 mm slice thickness and reconstruction with a standard algorithm. However, reconstruction with a high spatial resolution algorithm can also be performed with 7-10 mm images (fig 7). *High resolution CT (HRCT)* implies thinner collimation with 1-2 mm slice thickness in combination with a high spatial resolution reconstruction algorithm (fig 8). *Spiral CT* scanning enables imaging of the entire thorax during one single breath-hold. This method involves simultaneous transport of the patient at a constant speed through the CT gantry while data are continuously acquired over multiple gantry rotations. Thus, data for a volume rather than a single slice is collected. From this volume, continuous or overlapping images can be reconstructed. With this type of CT scanner, both standard CT and HRCT can be performed. *Quantitative CT* involves the post-processing of CT images and can be performed irrespective of scanning technique. In “*density masked*” images, pixels below a defined threshold are depicted in white (65). See also table 1.

The images in figure 7 to 10 are all at the same anatomic level in the same patient.

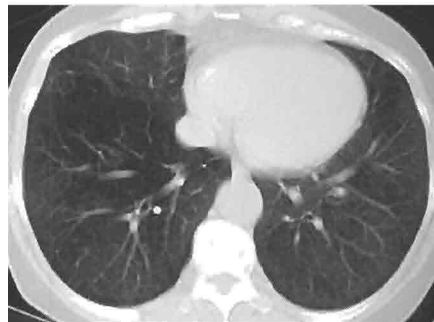


Figure 7. *Computed tomography, 10 mm slice thickness and reconstruction with a high resolution algorithm.*

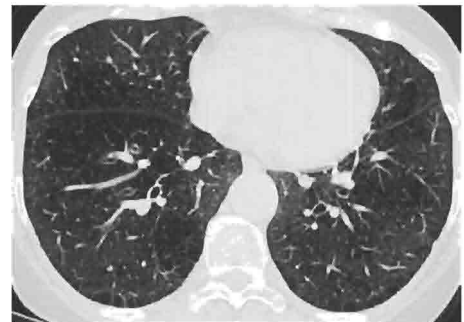


Figure 8. *High resolution CT, 2 mm slice thickness and reconstruction with a high resolution algorithm.*

Table 1. Summary of the most important settings for different CT examinations of thorax and typical fields of application. Std (standard), HR (high resolution).

Technique	Slice thickness, mm	Algorithm	Common field of application
(Spiral) CT	7-10	Std	Staging of lung cancer
(Spiral) CT	7-10	HR	Visualization of pulmonary vessels
HRCT	1-2	HR	Visualization of fine anatomic details
Quantitative CT	1-10	Std/HR	Computer-assisted measurements
"Density masked" CT	1-10	Std/HR	Images based on quantitative CT

1.2.2.2 CT

Emphysema diagnosed by CT was briefly described in 1978 (57). It was pointed out that CT gives a good demonstration of the pulmonary parenchyma and vasculature and is thus suitable for detecting emphysema. This was followed by a more comprehensive report by Goddard et al in 1982 (58). Since emphysema is a disease that is defined by alteration of normal lung structure, CT is well suited to the study of emphysema in vivo. CT can image fine anatomic details and thereby provide a non-invasive method of assessing lung morphology (11). Several studies have compared the morphological assessment of emphysema from resected lungs or lobes with results of CT images. Correlation of CT scores and pathological grading has ranged from good to excellent, partly depending on the imaging parameters used. (59,60,61,62,63,64,65,66,67,68,69).

1.2.2.3 HRCT

The first reports of HRCT regarding assessment of lung disease came in 1985 (70). A significant improvement in the resolution of lung architecture was noted (fig 8) (71,72). Since 1987, HRCT has been used in most studies regarding emphysema. Scientific support for this change from standard CT to HRCT in diagnosing emphysema can be found in only a few studies. A small increase in accuracy using 1.5 mm slice thickness compared with 10 mm has been shown (66,68). Due to high spatial resolution, providing anatomic detail similar to that available from gross pathological specimens or lung slices, HRCT has become the gold standard for the in vivo assessment of diffuse lung diseases including the diagnosis of emphysema (73,74). *In patients with emphysema considered for LVRS, the disease is advanced and CT is not necessary for diagnosis, but is important for determining the distribution of disease.* In this respect it has not been investigated whether HRCT is superior to conventional CT, except for the studies included in this thesis.

1.2.2.4 Quantitative CT

Hayhurst et al first described quantitative CT of emphysema in 1984 (60). They assessed the frequency distribution of the attenuation of pixels on a single CT image

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and observed that patients with emphysema had significantly more pixels in the attenuation range between -900 HU and -1000 HU (Hounsfield units) than in normal individuals. In the lung, the CT pixels density is determined by the relative amounts of blood, tissue, and air contained in the slice thickness. In emphysema, the proportion of pixels with the lowest attenuation values increases due to the relative reduction in blood and tissue, accompanied by a subsequent relative increase in air (75).

Müller et al in 1988 (65) described a method for quantifying emphysema using built-in software on the CT scanner called “density mask”, which highlights pixels within a selected range of HU (fig 9). They found good correlation between the extent of emphysema as assessed by the “density mask” and the pathological grade of emphysema. Thus, the percentage of lung with attenuation below a threshold value is directly related to the amount of macroscopic emphysema. Expanding on this study, Kinsella et al (76) in 1990, showed a significant correlation between the extent of emphysema seen on CT images (as determined by using a density mask outlining areas with attenuation values less than -910 HU) and pulmonary function indices of emphysema.

Commercially available software has been developed that automatically recognizes the lungs, traces lung contours, presents histogram of attenuation values and calculates the lung area occupied by pixels within a predetermined range of HU (77). The degree of emphysema can thereby be expressed as an emphysema index (EI), which expresses the percentage of the lung area in an image with pixels below a defined threshold (fig 10).

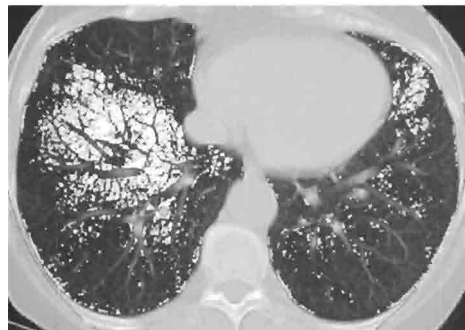


Figure 9. A “density masked” image with pixels below a defined threshold of HU (Hounsfield units) high-lighted.

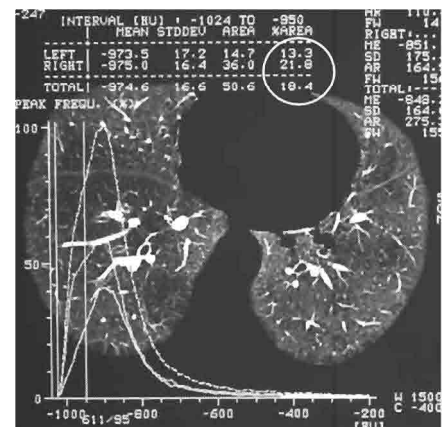


Figure 10. Quantitative measurements based on a CT image. The percentage of the lung area with pixels below -950 HU is calculated (marked with a circle).

Attempts to determine the best attenuation threshold for the identification of emphysema have been performed. Gevenois et al in 1995 (78) demonstrated that the relative area of lung occupied by attenuation values lower than -950 HU and calculated on HRCT obtained in full inspiration should be the best threshold for an objective quantification of macroscopic emphysema in vivo. Expiratory quantitative CT is not as accurate as inspiratory CT for quantifying pulmonary emphysema and probably reflects air trapping more than reduction in the alveolar wall surface (79).

INTRODUCTION

It is important to be aware that both CT scanner, the type of software, level of inspiration, use of contrast medium, slice thickness, algorithm and threshold value all influence calculations of emphysema index (80). When referring to the degree of emphysema as EI, details about these settings must be given.

One advantage of computer-assisted quantification is the reproducibility of the technique between readers of varying expertise and experience and between institutions, enabling more accurate comparison of results among different centres (29). Conversely, the advantage of a subjective scoring system is the ease of application and no requirement for dedicated software. Systematic overestimation and moderate interobserver agreement may compromise visual grading of emphysema and subjective visual grading should be supplemented with objective methods to achieve reader-independent quantification of emphysema (81). Panlobular emphysema may be underestimated, whereas centrilobular emphysema is often overestimated even by experienced radiologists (61).

1.2.2.5 Radiological signs of emphysema

Normal lung parenchyma has a homogeneous grey texture on CT interlaced by branching vessels and bronchi. The radiological signs of emphysema are low attenuating areas, altered vascular pattern (thin and sparse vessels with few branches), or a combination of these two findings (50,61). The low attenuating areas correspond to the enlarged spaces with alveolar wall destruction seen histopathologically. The altered vascular pattern in emphysema is caused by loss of the alveolar capillary bed associated with the parenchyma that has been destructed. This leads to decreased blood flow to a given region that is manifested as pulmonary oligemia or vascular deficiency. In centrilobular emphysema, the radiological findings consist of multiple small, localized areas of decreased attenuation, often with sharp borders to less emphysematous parenchyma (fig 11) and predominantly in the upper lobe (61). In panlobular emphysema, the radiological findings consist of large areas with a diffuse and uniform decrease in attenuation without sharp borders to adjacent normal parenchyma, accompanied by a reduction in the number and calibre of blood vessels (fig 12) (1).

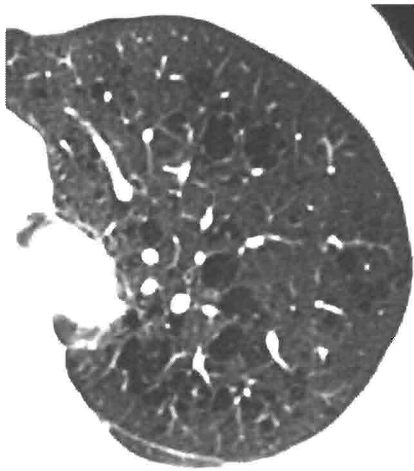


Figure 11. *Centrilobular emphysema with localized areas of low attenuation surrounded by less diseased parenchyma.*



Figure 12. *Panlobular emphysema in the anterior part of the lung, with diffuse decrease in attenuation.*

1.2.3 Fractal analysis and tissue characterization

Quantification of pulmonary emphysema by computer-assisted methods is based on mathematic approaches, namely metrics, which can be used to describe the heterogeneity of the spatial distribution of attenuation values within the reconstructed image. These metrics include very simple parameters, such as mean lung density or areas of low attenuation based on single or a range of densities. Fractal dimensions are more complex metrics. Fractal geometry has found widespread applications in the physical sciences because it is a suitable method for objective quantification of spatial heterogeneity (82). A common definition of a fractal is a shape composed of smaller parts that when enlarged, are similar to the whole shape. Thus, copies of itself can be found at any scale. The methodology of characterizing fractals has been successfully applied to pulmonary anatomy and physiology. For example, fractal properties in the relationship between the generation number and mean diameter of airways in the bronchial tree has been found (83). Pulmonary blood flow was also reported to have fractal properties (84). In order to differentiate normal from emphysematous areas in the lungs, Upplauri et al (85) developed a CT based, adaptive multiple features method based on fractal analysis. They concluded that this method could differentiate between normal and emphysematous tissue with 100 % accuracy. However, it is not clear whether this method would detect early emphysema. Mishima et al in 1999 (86), attempted to detect early emphysema based on fractal analysis. They concluded that D (the exponent of the power law distribution), appears to be a powerful (CT based) index for the detection of the terminal airspace enlargement that occurs in early emphysema. In these studies of emphysema, fractal analysis is still only used as a research tool, but indicates another interesting line of approach for further studies regarding the structure of the emphysematous lung.

1.2.4 Heterogeneity of emphysema

Heterogeneity of emphysema implies the unevenness of the distribution of the parenchymal destruction. This characteristic of emphysema in candidates for LVRS has gained a lot of attention and will be further described.

1.2.4.1 Impact of heterogeneity on patient selection

The original work of Cooper et al in 1995 (25) suggested that patients with emphysema predominantly in the upper parts in combination with mostly intact lower lung regions would be the obvious group to benefit from LVRS. Support for this concept came in 1997 from separate series, in which the selection of patients was based on CT and radiographic data. The best results after LVRS were in patients with heterogeneously distributed emphysema, which was predominantly in the upper part of the lung and associated with both areas of almost normal parenchyma and compressed lung (45,55,87). Although the more heterogeneous the distribution of emphysema, the better the results of LVRS, some patients with homogeneous disease also exhibited decreased dyspnoea and improved pulmonary function after LVRS (87,88,89).

1.2.4.2 Radiological types of emphysema heterogeneity

In clinical practice and supported by the above-mentioned studies, heterogeneity is considered an important feature to assess. However, heterogeneity has been defined

only loosely in terms of visual analysis. Uniformly severe emphysema represents low heterogeneity; areas of severe emphysema adjacent to mainly normal lung represent high heterogeneity. Most patients have a distribution somewhere between these two extremes. There is currently no consensus with respect to radiological classification of emphysema heterogeneity (90). Not only the definition of heterogeneity differs between studies, but also the imaging technique upon which identification is based. Both qualitative methods (visual assessments) and quantitative methods (objective measurements) have been used.

1.2.4.3 Qualitative (subjective) methods for defining heterogeneity

Visual assessment is the ground for subjective methods. In a study from Cooper's group (55), emphysema severity was scored on a subjective five-point scale based on CT for the separate lobes and heterogeneity was scored from uniform distribution to extreme differences in regional severity with clearly defined "target areas" of severe emphysema. Weder et al (87) determined emphysema morphology, also based on CT, according to a simplified, surgically orientated classification (homogeneous, intermediately heterogeneous and markedly heterogeneous) (fig 13). In another study (91), emphysema severity was scored based on chest radiograph on a subjective four-point scale. Each lung was divided into six zones, and mathematical models were used to explore the differences and ratios between the most diseased and least diseased lung zones assessed heterogeneity.

Systemic overestimation and moderate interobserver agreement may compromise subjective visual grading of emphysema (81). This suggests that visual grading of emphysema should be complemented with objective methods to achieve precise, reader-independent quantification of emphysema.

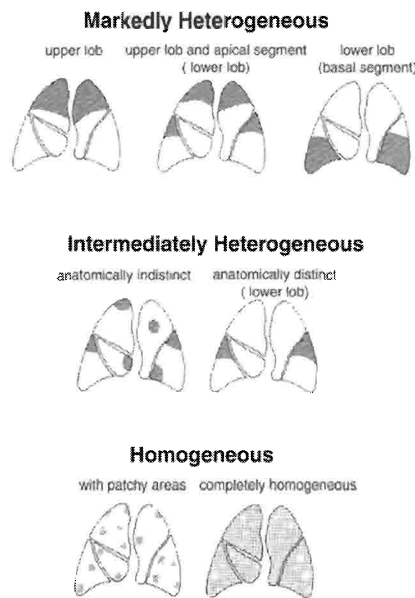


Figure 13. Three major types of emphysema used for visual classification (87). Reprinted with permission from the Society of Thoracic Surgeons (*Ann Thorac Surg* 1997;64:313-320).

1.2.4.4 Quantitative (objective) methods of defining heterogeneity

Computer-assisted quantification is the base for objective methods. Gierada et al in 1997 (92) defined quantitative CT parameters thought to be analogous to morphologic features of emphysema considered clinically important in the evaluation of patients for LVRS. Indexes defined as heterogeneity were full width at half maximum of the attenuation frequency curve (FWHM) and standard deviation of mean lung attenuation. They concluded that quantitative CT in emphysema correlates with outcome. Rogers et

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al (93) used quantitative CT measurements to determine the volume and severity of emphysema before and after LVRS and showed that the decrease in total lung volume following LVRS was entirely accounted for by a decrease in the volume of severe emphysema. Flaherty et al (94) recently presented their quantitative CT measurements as an index of the cranio-caudal distribution of emphysema.

In summary, no generally accepted method for describing emphysema heterogeneity exists, either visually or objectively.

1.2.5 Lung scintigraphy

Lung scintigraphy provides information regarding the relative distribution of emphysema. When emphysema is mild, perfusion defects occur in the absence of ventilation defects (95), when emphysema becomes advanced, the defects are usually matched. Therefore, lung perfusion scintigraphy (LPS) has received the most attention, and ventilation scintigraphy is used infrequently in the evaluation of potential LVRS patients. Several studies have shown that information from perfusion scintigraphy is at least equivalent if not superior to ventilation scintigraphy in predicting postoperative pulmonary function in patients who undergo lung resection (96,97). Unlike CXR and CT, scintigraphy reflects physiology rather than anatomy. Although regional differences in severity can be well shown, the absolute degree of disease cannot be estimated accurately.

Perfusion scintigraphy of the lungs has also been used for determining emphysema in patients undergoing LVRS (98). Heterogeneity was defined as the regional variation of emphysema and scored on a ten-point scale. The severity was defined as the visually estimated percentage of maximal perfusion in the lungs.

1.2.6 Magnetic resonance imaging

Magnetic resonance imaging (MRI) of candidates for LVRS is not commonly used, but has been reported with different approaches. Gierada et al (99) have shown that magnetic resonance (MR) measurements of lung volume are comparable with those of CT, and that changes in thoracic dimensions after LVRS are consistent with improved respiratory mechanics. MR perfusion imaging has been shown to be superior to LPS in the evaluation of pulmonary parenchymal perfusion in patients with pulmonary emphysema (100). Hyperpolarized ^3He MR imaging is a newly developed technique that is capable of producing high-spatial-resolution MR images of the lung air spaces after inhalation of laser-polarized helium gas (101). The contrast in these MR images reflects the gas distribution in ventilated portions of the lung. However, these images do not provide information about the integrity of the lung microstructure in the ventilated regions. Salerno et al (102), recently reported an MR imaging technique that is sensitive to changes in peripheral lung structure associated with emphysema. This new application of diffusion MR imaging methods in combination with hyperpolarized ^3He imaging appears to be capable of depicting structural changes in the distal airways, which would allow assessment of the extent and severity of emphysema (103). However, in this aspect, MR has not yet been reported in candidates for LVRS.

2 AIMS

The general purpose of this thesis was to study the radiological evaluation of emphysema in candidates for LVRS, and to suggest a suitable imaging regime for this patient group preoperatively.

In the different papers the specific aims were:

- I. To investigate whether radiologists in evaluating severe emphysema preferred HRCT or spiral CT with 10 mm slice thickness, and whether there was a difference between the upper or lower lobe in preference of technique.
- II. To investigate whether HRCT or spiral CT was superior for visual estimation of the degree of emphysema, and whether presentation of density masked images could improve the visual estimation.
- III. To investigate whether spiral CT is superior to HRCT in evaluating the radiological heterogeneity of emphysema.
- IV. To develop a model for classification of emphysema heterogeneity, which is based on objective calculations and applicable in a surgically orientated model, offers the possibility of evaluating right and left lung separately and finally, to test this model on a group of patients being candidates for LVRS.
- V. To evaluate whether lung perfusion scintigraphy contributes to the preoperative classification of emphysema heterogeneity compared with classification based solely on CT.

3 MATERIAL AND METHODS

3.1 PATIENTS (I-V)

Between November 1994 and December 1997, 105 patients underwent preoperative CT evaluation of emphysema at the Department of Thoracic Radiology at the Karolinska Hospital. All patients were referred to the hospital with clinical suspicion of severe emphysema to determine if they were suitable candidates for LVRS. The studies included in this thesis were all based on retrospective evaluations of the examinations. In 11 of these 105 examinations, data were incomplete and could not be evaluated retrospectively. The remaining 94 examinations were performed according to the same CT protocol.

Study I and III: All 94 patients were included. Their mean age was 65 yrs (38-75), 48 women and 46 men.

Study II: Sixty-six patients examined between January 1996 and December 1997 was included. At the time when this study was performed, data from the earliest examinations included in study I had been deleted and could not be reconstructed as “density masked” images, necessary for inclusion in this study. The mean age was 64 yrs (37-76), 34 women and 32 men.

Study IV: Sixty-six patients examined between May 1995 and May 1997 were included. Their mean age was 63 yrs (37-75) and there were 40 women and 26 men. The patients were divided into two groups consisting of 45 (design group) and 21 (test group), respectively. The patients from both groups were examined randomly distributed during the 24 months. The grouping was transferred from study V, where the 45 patients (design group) had performed pulmonary scintigraphy at the same department as the CT examination, and thus were included in study V.

Study V: Forty-five patients were examined between May 1995 and May 1997 (24 months), including both CT and lung scintigraphy performed at the same department. Their mean age was 62 yrs (37-72) and there were 27 women and 18 men.

3.2 METHODS (I-V)

Study I-III: These studies were performed by visual evaluation of emphysema by four thoracic radiologists with differing experience in interpreting CT examinations of emphysema. Depending on the purpose of the study, different CT images were selected and the evaluation was differently performed for each separate study.

Study IV: This study was an elaboration of an objective model for classification of emphysema heterogeneity, based on quantitative CT measurements.

Study V: This study was performed by classification of CT examinations and lung perfusion scintigraphy. The classification of heterogeneity was correlated to the classification obtained from study IV.

3.2.1 Computed tomography technique (I-V)

The examinations were performed with a Siemens Somatom Plus S scanner (Erlangen, Germany) and included both spiral CT and HRCT. All examinations were performed in maximal inspiration and without intravenous contrast enhancement. The spiral CT was performed with 10 mm slice thickness and pitch 1.0-1.2 depending on the length of the lungs. The scanning direction was cranio-caudal. For spiral CT, the tube current was 210 mA, the exposure time (rotation time) 1 second and the voltage 120 kV.

The HRCT was performed with 2 mm slice thickness and 20 mm interspace covering the entire lung, the tube current was 275 mA, the exposure time 1 second and the voltage 137 kV. Both the 2 and 10 mm images were reconstructed with a high-spatial frequency algorithm (defined for the actual CT unit as AB 7541).

3.2.2 Image selection (I-V)

Study I-III: From each patient, images at 4 levels of the cranial part of the lung and at 4 levels of the caudal part were selected. In the cranial part the uppermost level was chosen from a HRCT slice, which included a reasonable amount of lung tissue in both lungs. The 3 following levels were interspaced by 20 mm. In the caudal part the lowermost level was chosen from a HRCT slice which included no or only a small part of the diaphragm. Three higher levels were also selected and interspaced by 20 mm.

Study I and II: The selected images were printed on film sizes 35x43 cm; with 4 images on each film, window width 1500 HU, and window level -400 HU (figs 14a,b). Eight images from the spiral CT examination at corresponding levels were also printed.

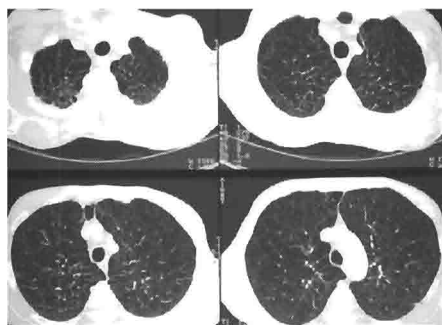


Figure 14a. Four images from the cranial lung (HRCT).



Figure 14b. Four images from the caudal lung (HRCT).

The term "cranial part of lung" was preferred to upper lobe since some of the cranial images selected for this study included both the upper lobe and the apical segment of the lower lobe. For the same reason "caudal part of lung" was the terminology used instead of lower lobe.

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Study III: In this study only the right lung was included. After the selection of 4 cranial and 4 caudal levels (see above), the uppermost image from the cranial lung and the uppermost image from the caudal lung were regarded as an image pair (figs 15a,b). The next selected image from the cranial lung and from the caudal lung was regarded as another image pair etc. This resulted in 4 image pairs with spiral CT and 4 image pairs with HRCT for each patient, resulting in a total of 376 image pairs (94 patients x 4 image pairs) for each CT technique.

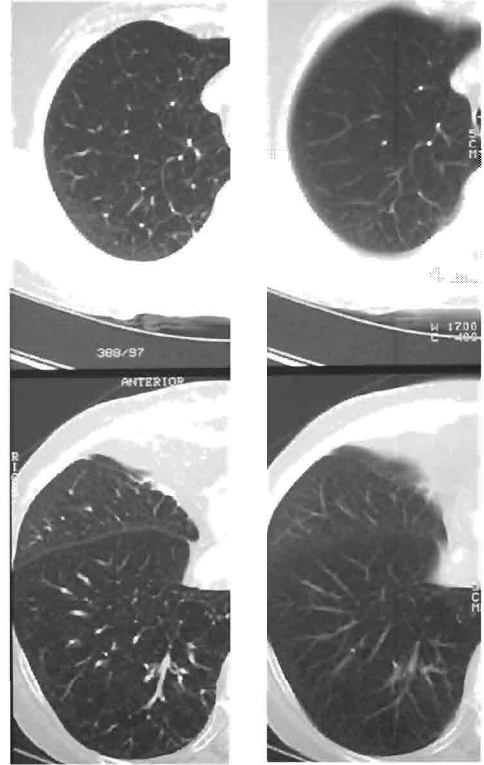


Figure 15a. HRCT image pair.

Cranial part of lung above, caudal part below.

Figure 15b. Spiral CT image pair (10 mm).

Cranial part of lung above, caudal part below.

Study IV: In this study, all the HRCT images, covering the entire lungs, were used for the calculations.

Study V: All images of the complete HRCT and spiral CT examinations were used as well as all the LPS images. In this study, the expression “CT examination” implies both HRCT and spiral CT examinations.

3.2.3 Image processing and emphysema index (I-V)

The severity of emphysema was defined by an emphysema index (EI). This is an objective quantification, assessing the extent of emphysema in a CT image and eliminating the observer variability. By comparing quantitative CT-data with histopathologic specimens, these types of indexes have been validated (65,63,69). The EI in study I-III, were defined as the relative area of the CT-image occupied by pixels between -1024 and -960 HU calculated on the 10 mm image, and in study IV and V the pixels between -1024 and -950 HU calculated on the 2 mm image. The images were analysed with the aid of Siemens Pulmo CT (Erlangen, Germany),(fig 10). This software automatically recognizes the lung, traces lung contours, presents histogram of attenuation values and calculates the lung area occupied by pixels within a predetermined range of HU (77).

Thus, the resulting EI is expressed as the percentage of the area of the actual image consisting of pixels in the defined interval of HU.

CT images with pixels corresponding to emphysema depicted in white ("density masked" images) (65) cannot be reconstructed in the Pulmo CT program. Instead, we had to use the ROI (Region Of Interest) -function of the Somatom Plus scanner with the same interval for density masking as for calculation of EI. The ROI is a manually marked area of variable size and form that can be used for measurements of for example, area and mean attenuation, but also for producing images with pixels within a certain interval high-lighted as white dots (fig 9). This ROI-function has no automatic contour detection of the lung and central bronchi; consequently only the image, but not the area or the attenuation numbers can be used.

Study I and II: The mean value of EI (EIM) was calculated separately for the four cranial images and the four caudal images for all patients. EI was only calculated for the spiral CT images. The degree of emphysema for each film was defined as the EIM value.

Study II: Four classes of different EIM were defined: A=0-10%, B=11-20%, C=21-30% and D>30%. Based on this definition, the 132 spiral CT film sheet had the following distribution: 63 film sheets had EIM according to A, 31 according to B, 22 according to C and 16 according to D. "Density masked" images was also used in this study.

MATERIAL AND METHODS

Study III: In this study, calculation of difference in EI (EID) between the two images in an image pair was performed. This difference in degree of emphysema between the cranial and caudal image (EID) was defined as heterogeneity. Five classification groups of heterogeneity were also defined (table 2). The limits were intentionally chosen so that the visual differences should not be too obvious (fig 16).

The mean value of EI for an image pair in this study (EIM-III) was calculated separately for all image pairs.

Table 2.

Computer calculated classification of heterogeneity ranging from predominantly upper lobe emphysema (class.group=1) to predominantly lower lobe emphysema (class.group =5). EID= difference in emphysema index between right cranial and right caudal image.

Class.group	EID (%)	Cranial vs. caudal
1	>16	" > "
2	6-15	" > "
3	0-5	" = "
4	6-15	" < "
5	>16	" < "

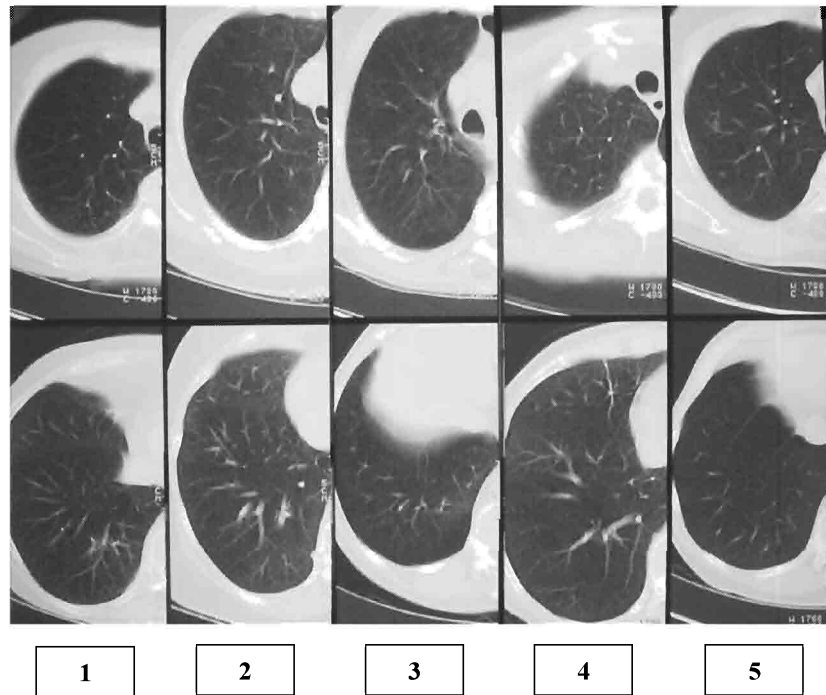


Figure 16. Image pairs with different degree of heterogeneity (EID). Upper lobe emphysema (1) to the left, lower lobe emphysema (5) to the right.

Study IV: The variation of EI between different parts of the lung was graphically illustrated in a diagram (fig 17). The EI:s for each lung were considered to distribute along a straight line which was determined by a least square fit. The slopes, k , of these lines, $y = kx + l$, were calculated. As a simple measure of the variation of EI within each lung, we calculated the EI-difference as the highest EI minus the lowest EI for each lung. In order to separate different types of emphysema we assumed that: **a)** a low value of EI-difference represents homogeneous emphysema, **b)** a high value of EI-difference in combination with a low slope of the fitted line represents intermediately heterogeneous emphysema and **c)** a high value of EI-difference with a steep slope of the fitted line represents markedly heterogeneous emphysema (either upper- or lower lobe dominance). In order to validate the model, calculations of k -values and EI-differences were also performed for 21 additional examinations (test group).

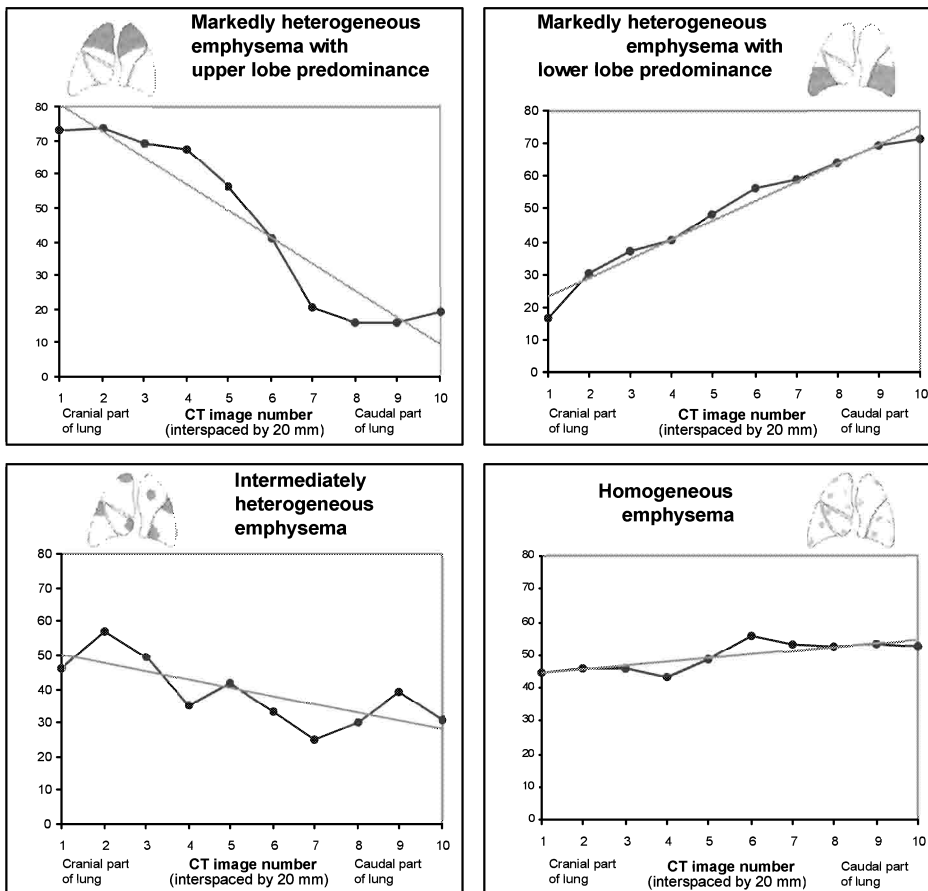


Figure 17. Graphic illustration of emphysema index (EI) in 4 separate lungs representing the major types of distribution of emphysema illustrated in figure 13. The CT-image position in the lung is represented on the X-axis, the cranial part to the left and the caudal part to the right and with 20 mm between each image. The Y-axis represent the corresponding values of EI. The slope line of each lung is depicted in grey.

3.2.4 Visual evaluation (I-III, V)

Study I: The images were presented to the four radiologists as film pairs consisting of one film with 4 HRCT images, and one film with 4 spiral CT images at corresponding levels in the same patient. Film pairs from the cranial and caudal part of the lung in various patients were evaluated independently and in random order. The radiologists performed the evaluation individually and they were asked to say for each film pair which technique they preferred in evaluation of emphysema, or if the techniques could be considered equal in this regard.

Study II: The images were presented to the radiologists on three different occasions: first 132 film sheets with HRCT images with cranial and caudal film sheet mixed, thereafter the 132 film sheets with spiral CT images and finally the 132 film sheets with density masked images. The radiologists were asked to classify each film sheet into one of the four classes (A-D) of degree of emphysema (see “Image processing and emphysema index” p.19). They were not aware of the calculated degree of emphysema, EIM, or the defined levels of EIM for A-D. The classification was made by comparison to standard films with each class of emphysema degree and thereafter selection of A, B, C or D for each film sheet (fig 18).

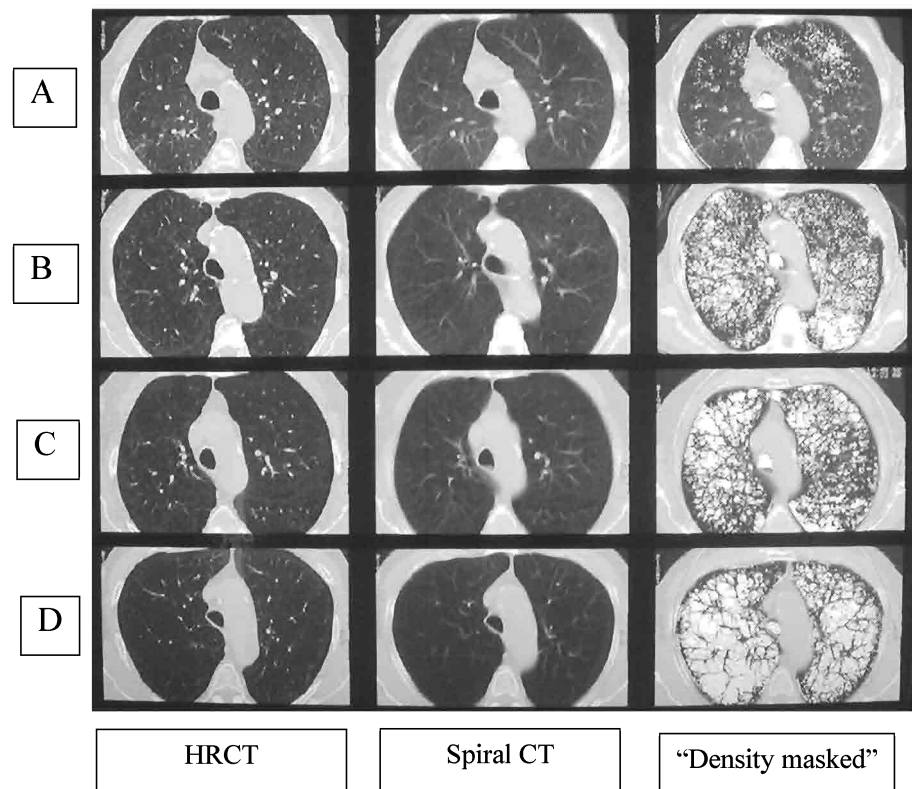


Figure 18. Three different types of CT-images at corresponding levels. Four different degrees of mean emphysema index (EIM), A-D. A=0-10%, B=11-20%, C=21-30% and D>30%.

MATERIAL AND METHODS

Study III: The selected image pairs were printed on 35x43 cm film; with two images on each film and window width 1500 HU and window level -400 HU. The visual evaluation and classification was performed at two different sessions with each radiologist working independently. In session 1 the radiologists had to review image pairs from either technique (HRCT or spiral CT) mixed in random order and classify each image pair into one of the five groups of heterogeneity. They were not aware of the calculated EID (table 2) or the defined levels for the different classes of EID. Instead, they had access to film sheet with examples of the different classes of EID (both techniques) to visually compare the image pairs with and thereafter select a class of heterogeneity for each film pair (table 3). The visual classification was regarded as correct when the visually chosen class of heterogeneity (table 3) for an image pair corresponded with the calculated class of EID (table 2).

Table 3.

Visual classification of heterogeneity (EID) ranging from predominantly upper lobe emphysema (class.group=1) to predominantly lower lobe emphysema (class.group=5).

Class. group	Visual classification
1	Obviously more emphysema in the cranial image
2	Somewhat more emphysema in the cranial image
3	Equal extent of emphysema in both images
4	Somewhat more emphysema in the caudal image
5	Obviously more emphysema in the caudal image

In session 2 the image pairs performed with HRCT and the corresponding spiral CT were displayed together and the radiologists were again asked to classify the image pairs regarding the heterogeneity, EID. The time between the two sessions was 1-5 days. The visual evaluation (both session 1 and 2) was repeated by three of the radiologists about 4 weeks later and the correlation coefficient was calculated.

Study V: The evaluation of the images was performed at three different sessions involving: a) CT only, b) LPS only, c) CT and LPS in combination.

Session a): two thoracic radiologists routinely involved in diagnosing emphysema classified all CT examinations and a consensus was obtained.

Session b): two clinical physiologists routinely involved in diagnosing emphysema classified all LPS and a consensus was obtained.

Session c): one thoracic radiologist and one clinical physiologist, both routinely involved in diagnosing emphysema (not the same persons as in the other sessions) classified both CT and LPS together and a consensus was obtained.

3.2.5 Lung perfusion scintigraphy (V)

The perfusion distribution between and within the lungs was evaluated using ^{99m}Tc -labelled macro-aggregate of albumin administered intravenously in the supine position. Anterior, posterior and lateral views were obtained with a dual-headed gamma camera and a dedicated computer (SMV DST – XL, Sopha Medical Vision, France; Vision workstation RS/6000, IBM, USA). Each projection was collected on a matrix of 128 x 128 pixels (pixel size 4.5mm), generating eight different images. From the anterior and posterior perfusion image data, the total counts in each lung were summed and expressed as percentage of the total counts in both lungs. Paper copies of the collected images were obtained in 19 x 19 cm format, using a laser printer (Phaser 560, Textronic Inc, USA).

3.2.6 Visual classification of heterogeneity (V)

The lungs of each patient were classified visually (the right and the left lung separately) in three categories of emphysema distribution according to the surgically oriented model proposed by Weder (87)(fig 13) with the following definitions :

Markedly heterogeneous: a distinct regional difference in the severity of emphysema present in at least two adjacent lung segments.

Intermediately heterogeneous: a distinct regional difference in severity of emphysema may be present maximally in the area of one or more than one but not in adjacent lung segments.

Homogeneous: no regional or only very minor differences in the severity of emphysema discernable.

Both CT and LPS were visually classified according to the same model.

3.2.7 Statistical methods and data analysis (I-V)

Repeated measurements analysis was used to analyse time dependent data and in order to evaluate hypotheses of variables in contingency tables, the chi-square test was used. In the study, there are also dependent effects and the method proposed by Fleiss (104) was used in order to compare the different dependent proportions. All calculations in the comparisons were based on the true frequencies. Regression analysis were used in order to evaluate the dependency between variables and the Spearman rank correlation coefficient was used in order to test independence between variables. In addition, descriptive statistics have been used to characterize the data. All analyses were carried out on the SAS system from SAS Institute and the 5, 1 and 0.1% levels of significance were considered.

4 MAIN RESULTS

The principal findings were:

In *study I* the radiologists preferred HRCT images in 56% of the readings, spiral CT in 19% and the techniques were considered as equal in 25%. Spiral CT images were preferred more often in the caudal part of the lung and in more advanced emphysema compared with the HRCT images.

In *study II* the conventionally presented images from HRCT and spiral CT yielded the same results in assessing the degree of emphysema irrespective of localisation. Significantly improved results were obtained when the spiral CT images were presented as density masked images.

In *study III* the spiral CT images was shown to be superior to HRCT for classification of emphysema heterogeneity. Combination of the techniques did not improve the evaluation.

In *study IV* the variation of EI in the cranio-caudal direction was determined by the absolute value of the slope, k , and another diagram was constructed with k on the X-axis and EI-difference on the Y-axis. This resulted in a diagram enabling the differentiation of markedly heterogeneous, intermediately heterogeneous and homogeneous emphysema.

In *study V* it was shown that the combination of CT and LPS improves the evaluation of emphysema heterogeneity compared to a classification based on CT only.

5 RESULTS AND METHODOLOGICAL DISCUSSION

5.1 STUDY I: SUBJECTIVE PREFERENCES OF CT TECHNIQUE

In order to evaluate whether the 10 or 2 mm technique (spiral CT or HRCT) was preferred, and if this differed between the cranial and caudal part of the lung, specially selected images were printed for visual evaluation (figs 14a,b). Due to practical reasons, we considered it impossible to evaluate, and compare, the complete examinations on printed films. We arbitrarily chose the number of 4 cranial images and 4 caudal images, however, not evenly distributed throughout the lung. The “middle” part of the lung (in the cranio-caudal direction) was usually not included in the selected images. Our intention was to separate the upper lobe from the lower lobe as much as possible in order to study the subjective preference of CT technique in cranial versus caudal parts of the lung. The selection of images in this study of 94 patients and two techniques resulted in 94 image pairs (one film sheet with 2mm images and one film sheet with 10mm images) of the cranial part and 94 image pairs of the caudal part of the lungs. Thus, 188 film pairs were evaluated by the four radiologists resulting in 752 readings.

The HRCT technique was preferred in 56% of all readings, in 19% the radiologists preferred the spiral CT technique and in 25% the two techniques were regarded as equally good in evaluation of emphysema (table 4).

Table 4.

Preferred CT-technique in evaluation of emphysema in 752 readings of film pairs.

EIM=Mean Emphysema Index.

	HRCT	Spiral CT	Equally good
Preferred technique (%)	56	19	25
Cranial/caudal distribution (%)	55/45	34/66	51/49
EIM	13,6	17,4	21,7

To evaluate whether the degree of emphysema had an impact on the radiologists' preference, the mean value of emphysema index (EIM) was calculated. Since emphysema seldom has an even distribution in cranio-caudal direction, the horizontal plane or between right and left lung, this mean value of EI calculated from 4 images is not a very good description of emphysema. However, we considered it sufficient as a measure of severity of emphysema for the purpose of this comparison of CT techniques.

When the HRCT technique was preferred, 55% were from the cranial and 45% from the caudal part of the lung. The EIM in this group of film pairs were 13,6. Thus, the degree of emphysema was lowest in this group.

In the group where the spiral CT-images were preferred, 34% were from the cranial and 66% from the caudal part. This distribution differed significantly from the distribution when HRCT was preferred ($p < 0.001$). The difference in EIM between these two groups, 13,6 and 17,4 respectively, was also significant ($p < 0,001$).

The two techniques were considered equally good in evaluation of emphysema in 25% of the readings of the film pairs and distributed as 51% in the cranial and 49% from the caudal part. EIM was 21,7 and significantly different from the two other groups ($p < 0.001$). Thus, the degree of emphysema was highest in this group.

5.2 STUDY II: ESTIMATION OF THE DEGREE OF EMPHYSEMA

The selection of images for this study resulted in three sets of images: HRCT, spiral CT and density masked images (fig18). The criteria for the image selection were the same as in study I. The images selected in this study of 66 patients and 3 techniques resulted in 66 films of the cranial part and 66 films of the caudal part of the lungs for each technique. Thus, the degree of emphysema was estimated in 132 films of 3 different techniques by 4 radiologists resulting in 1484 estimations.

There was no significant difference between HRCT and spiral CT in visual evaluation of the degree of emphysema. For all radiologists, the HRCT resulted in 60% correct classifications and 62% for spiral CT. The density masked images resulted in 74% correct classifications, which was a significantly better result compared to the conventionally presented images from both HRCT and spiral CT ($p < 0.001$) (table 5).

Table 5

Correct classification (%) for four radiologists separately and combined for the three different types of images

Observer	Cranial lung			Caudal lung			Cranial+caudal		
	HRCT	Spiral CT	Density-masked CT	HRCT	Spiral CT	Density-masked CT	HRCT	Spiral CT	Density-masked CT
Radiologist 1	61	64	77	59	59	84	60	61	81
Radiologist 2	62	71	70	59	61	72	61	66	71
Radiologist 3	61	68	73	62	54	80	61	61	76
Radiologist 4	53	62	65	67	56	70	60	59	67
All radiologists	59	66	71	61	58	77	60	62	74

When the results for the cranial and caudal part of the lung were analysed separately, there was no significant difference between HRCT and spiral CT in visual evaluation of the degree of emphysema for all radiologists. In the cranial part of the lung, HRCT images resulted in 59% correct classifications and spiral CT in 66%. In the caudal part of the lung, HRCT images resulted in 61% correct classifications and 58% for spiral CT. In the cranial part of the lung, the results for “density-masked” images (71%) were significantly better ($p < 0.05$) compared to HRCT (59%), but not when compared to spiral CT (66%). In the caudal part of the lung, the results for “density-masked” images (77%) were significantly better ($p < 0.001$) compared to both HRCT (61%) and spiral CT (58%)

5.3 STUDY III: VISUAL CLASSIFICATION OF HETEROGENEITY

Another type of image pairs was constructed in this study (fig15a, b). Calculation of EID, the difference in degree of emphysema between the cranial and caudal image, was an attempt to create a simple and objective description of the difference in degree of emphysema between the cranial and the caudal part of the lung. The only intention with this simplified, computer calculated model of emphysema heterogeneity was to render it possible to compare 2mm and 10mm images visually, and to use this calculated EID as a reference for visual evaluation. It was not planned for selection of patients preoperatively. Due to the common finding of different degree of emphysema between the right and left lung, only the right lung was included in the study. This choice was due to the fact that

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problems with artefacts from the heart are common in images of the left lung. Of the total number of 376 image pairs, we initially decided to select 100 image pairs. Our goal was to have an equal distribution in both the degree of emphysema, EIM-III, and the degree of heterogeneity, EID, among the 100 selected image pairs. Since there was no image pairs with the combination of low EIM-III and low EID, 95 image pairs of each technique were finally included in the study (fig 19).

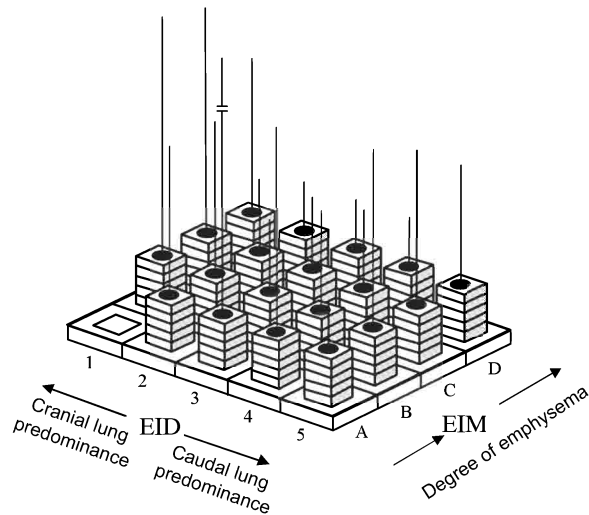


Figure 19. The two classifications (EID and EIM-III) resulted in 20 combinations from 1A to 5D. We decided to use 5 image pairs from each group (indicated by the blocks) resulting in 100. However no image pairs fulfilled the criteria of 1A, resulting in 95 image pairs for each technique. The lines on each column of blocks indicate the distribution of the total number of image pairs from all patients.

With 4 radiologists, this resulted in 380 classifications for each technique.

We found that visual evaluation of emphysema heterogeneity based on spiral CT images was superior to HRCT. The mean value for all radiologists was 47% correct classifications with spiral CT compared with 40% for HRCT ($p < 0.05$) (table 6).

Table 6.

Correct classifications (%) for the different techniques separately and when combined.

Observer	HRCT	Spiral CT	HRCT+ Spiral CT
Radiologist 1	30	40	34
Radiologist 2	37	43	37
Radiologist 3	49	49	50
Radiologist 4	42	54	46
All radiologists	40	47	42

RESULTS AND METHODOLOGICAL DISCUSSION

No improvement in classification could be shown when the radiologists had access to corresponding image pairs performed with different techniques displayed together, compared with evaluation based on the techniques separately. Forty-two percent of the combined image pairs were correctly classified.

When the results obtained by the individual radiologists were analysed separately, no significant difference between the techniques was found.

Five classification groups of heterogeneity were defined, EID 1-5 (table 2). The limits were intentionally chosen so that the visual difference was not too obvious (fig 16). If the difference between the five groups had been too large, and hence too obvious to the radiologists, there would probably not have been any significant difference between the groups. Concordant with this we did not find any significant difference between the two CT techniques when group 1 and 2 of EID were combined and 4 and 5 were considered as one group. We consider the "relatively poor" outcome of 47% correct classifications to express a correct level of difficulty and that our model for comparing the two different CT techniques was suitable.

5.4 STUDY IV: NEW MODEL FOR CLASSIFICATION OF HETEROGENEITY

Weder et al (87) have presented a qualitative (visual) classification with three types of surgically relevant morphologic types of emphysema distribution (fig 13). In our attempt to develop an objective model for describing emphysema, we chose Weder's classification as a basis for our work.

A diagram including 90 lungs (45 patients) was constructed with the absolute value of slope, k , on the X-axis and EI-difference on the Y-axis. Thus, whether the slope was positive (lower lobe emphysema) or negative (upper lobe emphysema) was not considered.

According to our assumptions a-c (fig 17), different types of emphysema could be represented in a four-field manner in a diagram. Two discrimination lines can define these fields (fig 20).

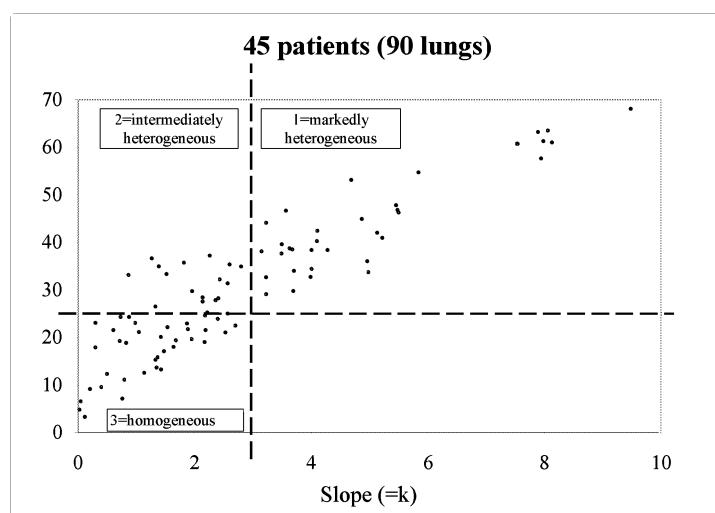


Figure 20. The slope ($=k$) was calculated as well as the difference between the highest and lowest EI (EI-difference) in each lung, graphically illustrated in this diagram for the 90 lungs in the design group. The different types of emphysema heterogeneity are separated by a discrimination level for the k -value of 3 and for the EI-difference of 25 (as indicated by the dotted lines).

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The value of the discrimination level for k was determined by a statistical analysis showing that above 3, the k -value of all the fitted lines were significantly different from zero. Thus, lungs with $k > 3$ were defined as markedly heterogeneous emphysema. The EI-differences for all lungs with $k > 3$ were greater or equal to 29, and the value of 25 was chosen to discriminate between homogeneous and heterogeneous emphysema.

Thus:

markedly heterogeneous emphysema;	$k > 3$
intermediately heterogeneous;	$k < 3$ and EI-difference > 25
homogeneous emphysema;	$k < 3$ and EI-difference ≤ 25

To test the model an additional group of 21 patients (42 lungs) was also evaluated according to the model. In this test group, all k -values above 3 were significant and these lungs also had an EI-difference above 25.

The total material consisted of 66 patients. All patients were classified according to the model presented. Nineteen patients fulfilled the criteria of bilateral markedly heterogeneous emphysema (12 with upper lobe emphysema and 7 with lower lobe emphysema), 3 of bilateral intermediately heterogeneous emphysema and 18 of bilateral homogeneous emphysema. Twenty-six patients had different types of emphysema in right and left lungs (table 7).

Table 7.

Calculated type of emphysema in right and left lung of the 66 patients.

Patients with equilateral findings are marked with thick numbers.

Left lung	Right lung		
	Markedly heterogeneous	Intermediately heterogeneous	Homogeneous
Markedly heterogeneous	19	3	3
Intermediately heterogeneous	3	3	3
Homogeneous	7	7	18

5.5 STUDY V: COMPARISON OF CT AND LPS

Visual evaluation of all 90 lungs (independent of type of heterogeneity) resulted in 50 correct (=in accordance with the objective classification presented in study IV) classifications based on CT, in 40 based on LPS and in 68 correct classifications based on the combination of CT and LPS. There was no difference between the evaluations based on CT compared with LPS, while the combination of the two examinations resulted in significantly more correct classifications ($p < 0.01$) compared with the techniques separately.

Table 8.

Correct visual classifications of different types of emphysema heterogeneity compared to the computer based emphysema index (EI) method in 90 lungs. Computed tomography (CT). Lung perfusion scintigraphy (LPS)

	n	CT	LPS	CT+LPS
Markedly heterogeneous	35	23	21	30
Intermediately heterogeneous	16	9	8	8
Homogeneous	39	18	11	30
All lungs	90	50	40	68

Analysis of the different emphysema types separately, resulted in no difference between the classifications based on CT compared with the classifications based on LPS. The combination of CT and LPS resulted in more correct classifications compared to CT alone in homogeneous emphysema ($p < 0.01$). The combination of CT and LPS also resulted in more correct classifications compared to LPS in markedly heterogeneous ($p < 0.05$) and homogeneous emphysema ($p < 0.01$) (table 8).

6 DISCUSSION

In order to achieve the best possible improvement after LVRS, it is crucial to identify factors that determine outcome and optimise the selection of candidates for the operation accordingly. The specific features of emphysema can be assessed on CT scans with high accuracy (62,64,66). Heterogeneity and anatomical distribution of emphysema are among the strongest predictors of successful outcome after LVRS (45,55,87). Several authors have used different definitions of severity and distribution of emphysema, both qualitatively and quantitatively (56,87,92,105), but there exists no single generally accepted grading system. Visually estimating the volume and severity of emphysema generally or regionally is difficult and these estimations are subject to interobserver and intraobserver variations (81). Visual interpretation may also be influenced by several factors, including scanner type, window and level for filming. Quantitative assessment of emphysema using CT virtually eliminates these problems and may allow a standardised assessment. Before quantitative CT selection guidelines can be determined, several technical issues must be more rigorously studied in order to define settings for quantitative assessments. The optimal scanning method must be defined, for visual assessment as well as for quantitative measurements to be based on.

At our hospital, LVRS started in 1994 and CT-examinations from many different hospitals are sent for evaluation. Most of these examinations are performed solely as HRCT. The use of HRCT increases the sensitivity of detecting mild emphysema (64,66,68). However, this technique has not been shown to be the method of choice in patients with advanced emphysema. At our department, both HRCT and spiral CT with 10 mm slice thickness are routinely used in patients with emphysema.

6.1 STUDY I-III

Study I-III was mainly based on two observations during clinical work: that HRCT only, was usually not sufficient to answer the surgeons question about the distribution of emphysema, and that radiologists at our department preferred images with 10 mm slice thickness in the lower part of the lung and 2 mm slice thickness in the upper part when evaluating emphysema. These clinical impressions led to the following questions:

- a) although HRCT seems to be preferred by many radiologists in evaluation of emphysema in candidates for LVRS, is spiral CT superior in this regard?
- b) or is the combination of HRCT and spiral CT the method of choice?
- c) is there a difference in evaluation of emphysema in the upper lobe versus the lower lobe?
- d) does the degree of emphysema influence the questions above?

In short, *study I* was intended to study the subjective preference of CT technique followed by *study II*, intended to investigate whether the subjective preference was in accordance with the ability to estimate the degree of emphysema. In the third step, *study III*, it was investigated whether there was any difference between the two techniques in the radiologists ability to evaluate the distribution of emphysema.

In *study I*, it was shown that the HRCT images were subjectively preferred most frequently. This was expected and in accordance with our observation that most CT examinations from other departments are performed solely as HRCT (1-2mm). This will be further discussed together with *study III* below.

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The results of *study I* also show that different preferences exist for different parts of the lung. Although HRCT is most often preferred in evaluation of emphysema, in almost a fifth (19%) of all the films the spiral CT images were preferred. In this group, where spiral CT images were preferred, the caudal images were more common and the degree of emphysema higher compared with the group where HRCT were preferred. Some anatomical features might explain this different preference of technique in different parts of the lung:

Firstly, different histopathologically defined types of emphysema are predominantly localized to different parts of the lung and have distinctly different CT appearance (1). *Centrilobular emphysema* is more common in the upper lobes where both normal alveolar architecture and enlarged spaces with alveolar wall destruction are situated immediately adjacent to each other. The radiological finding consists of multiple small, localized areas of decreased attenuation, often with sharp borders to less emphysematous parenchyma and predominantly in the upper lobe (10). In severe emphysema this can be observed with both techniques, but more easily and more distinctly with HRCT, due to the higher resolution (fig 21).

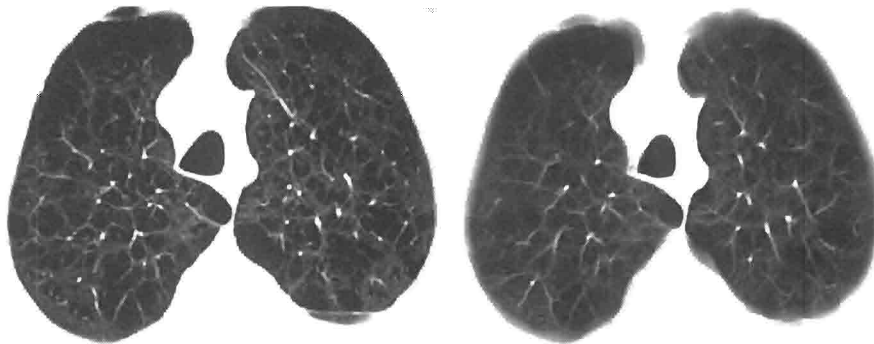


Figure 21. *High resolution CT image (left) and spiral CT image (right) at corresponding levels in the cranial part of the lung. Most vessels run perpendicular to the image plane and are seen mainly as dots irrespective of slice thickness, which means that the vascular alterations are less easy to see. The low attenuating areas consistent with centrilobular emphysema are clearly visualized on the left image.*

Panlobular emphysema is often somewhat more dominating in the lower lobes and is pathologically characterised by destruction of alveolar walls evenly distributed in the lobule as well as in the lung (1). The radiological findings consist of large areas with diffuse and uniform decrease in attenuation without sharp borders to adjacent normal parenchyma, accompanied by a reduction in the number and calibre of blood vessels (10). When HRCT is used, this gradual change in attenuation is difficult to appreciate, rendering the visual evaluation of severe emphysema more problematic. Both vessel anatomy and the gradual change in attenuation can be seen more readily on spiral CT images with 10 mm slice thickness (fig 22).

Secondly, the large- and medium sized vessels in the cranial part of the lung tend to have a more cranio-caudal course than in the lower lung. Therefore, most vessels of this size run perpendicular to the image-plane (scanning-plane) and are seen mainly as dots irrespective of slice thickness. This means that the vascular alterations are harder to see (fig 21). Preference of HRCT in the cranial lung can thus be explained by its superior ability to show the sharp border of the centrilobular emphysema and by the fact that

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thicker slices are not better than thin ones in showing the architecture of the vessels in the cranial lung. In the caudal part of the lung, the vessels tend to run more obliquely to the image plane, which means that longer vascular segments are visualized on 10 mm spiral CT images allowing better evaluation of the altered vascular pattern (fig 22).

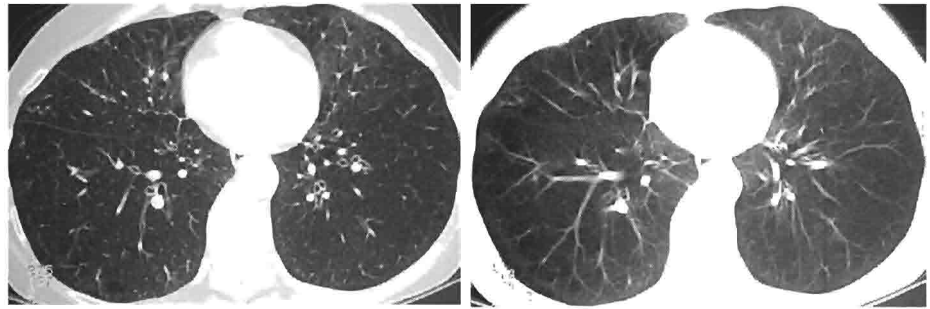


Figure 22. *High resolution CT image (left) and spiral CT image (right) at corresponding levels in the caudal part of the lung. Diffuse and uniform decrease in attenuation, without sharp borders to less diseased parenchyma consistent with panlobular emphysema. Vessel anatomy and thereby the vascular alterations are more readily seen on the spiral CT image.*

A third factor might be that artefacts due to cardiac motion and breathing are more pronounced in the caudal parts of the lung. On HRCT images these artefacts are more disturbing than on the 10 mm images, since these artefacts are partly seen as dark areas which can be difficult to distinguish from low attenuation caused by emphysema. On 10 mm images motion artefacts are seen mostly as double contours, which are easily distinguished from emphysema (106).

These three factors: the distribution of CLE versus PLE, the vessel anatomy and the appearance of motion artefacts probably contribute to the result that when spiral CT is preferred it is more often for evaluation of the lower lobes.

In 25% of the film-pairs, the different techniques were considered equal and in this group the degree of emphysema was higher than in the other groups. The probable explanation for this is that when emphysema is very severe the technique used is of less importance.

In *study II* was investigated whether spiral CT or HRCT was superior for visual estimation of the degree of emphysema. The intention was to use the same material (images) as in *study I*. The reason was to minimise the differences between the images to make it possible to draw conclusions about subjective preference versus visual estimation of degree of emphysema. Unfortunately, image data of only 66 of 94 patients could be retrospectively reconstructed. Despite this, we showed that HRCT and spiral CT with 10 mm slice thickness were equally accurate in estimating the degree of emphysema, although HRCT was subjectively preferred by radiologists more than twice as often as spiral CT as shown in *study I*.

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Presentation of CT images is generally made with pre-defined window settings. Another form of CT image presentation is “density masked” images (65). In *study II*, we also investigated whether presentation of “density masked” images could improve the visual estimation of the degree of emphysema. Wisser et al (105) have also used this type of “density masked” images as part of a morphologic grading system for patients undergoing LVRS. In their study, including 47 patients, “density masked” images at 3 levels were generated. The severity of emphysema was estimated on a 5-graded scale by three readers. Good interobserver agreement was shown. As expected, we found that “density masked” images significantly improved the visual estimation compared to conventionally presented images. Visual estimation of emphysema can be divided in two parts: first identification of the emphysematous alterations and secondly the estimation of its degree. Using “density masked” images implies that the computer has already performed the first part and only the estimation of the degree remains. It must, however, be remembered, that in a clinical situation several other aspects of the CT examination of candidates for LVRS have to be considered, for example concomitant diseases such as bronchogenic carcinoma etc. Consequently, there is also a need for conventional images covering the entire thorax. Unlike calculations of emphysema index, the “density masked” images can easily be made on almost all commonly used CT-units and thus, their use should be recommended for this type of patients as a part of a complete CT examination.

In *study III*, it was investigated whether spiral CT was superior to HRCT in evaluating the radiological morphology of emphysema (heterogeneity) and whether the combination of both CT-techniques improved the evaluation. In *study I and II* was shown that there was a difference between subjective preference (*I*) and accuracy in the visual estimation of degree of emphysema (*II*). To further penetrate this field we wanted to test the different CT techniques, not only regarding estimation of degree of emphysema, but also in evaluation of emphysema heterogeneity. We simplified the definition of heterogeneity to enable a comparison between HRCT and spiral CT and defined EID, which expresses the difference of emphysema between one image of the cranial lung and one image of the caudal lung. The calculated EID was used to construct image pairs with different degree of heterogeneity representing a range from predominantly upper lobe emphysema to predominantly lower lobe emphysema. Our results showed that spiral CT was superior to HRCT in determining heterogeneity (as EID) of emphysema visually. This was quite contrary to the results of *study I*.

Thus, when the subjective preference (*study I*) were replaced by a classification of heterogeneity (*study III*), we were able to verify our clinical impression that spiral CT with 10mm slice thickness was superior to HRCT in evaluation of clinically relevant aspects of severe emphysema.

We have searched for an explanation to this diversity. A quick backward glance at radiographic diagnosis of emphysema in the 1960's, exposes a conflict concerning the best criterion to diagnose emphysema. In the British literature, vessel scarcity on chest films was considered the best criterion for recognising emphysema (50). Studies in North America (107) indicated that this pattern was less reliable and instead stressed the value of the radiological signs of hyperinflation in diagnosing emphysema. With the introduction of CT in diagnosing emphysema, it was pointed out that CT gives a good demonstration of the pulmonary parenchyma and vasculature and is thus suitable for detecting emphysema. The radiological signs of hyperinflation in diagnosing emphysema were abandoned. As long as CT was performed with thick slices (10-13 mm), both low attenuating areas and vascular alterations were commonly used as CT

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criterion of emphysema. With the transition towards CT with thinner slices as HRCT (66), and particularly quantitative CT, the vascular alteration as a classical, British radiological sign of emphysema seems to have been forgotten. Should this have an impact on subjective preference of many radiologists for HRCT in evaluation of emphysema? Yes, it might be so. If radiologists today are taught to recognise emphysema by low attenuation areas that can be seen perfectly well on HRCT images, why bother about “old-fashioned” 10 mm images? In our opinion, radiologists *should* “bother” about 10mm images because they are helpful in evaluating vascular alterations which in turn are a reliable sign in diagnosing PLE, usually accompanying severe CLE. Vascular alterations cannot be evaluated as well on HRCT images due to the thin collimation, resulting in a cut off of all vessels that then appear as “dots” instead of branching tubular structures as on 10 mm images.

A remarkable increase in image quality has evolved during the last 20 years. Both images in fig 23 are 10 mm thick, and are in that sense conventional or standard CT. At the time when HRCT was introduced, the existing image quality is illustrated by the example in fig 23.

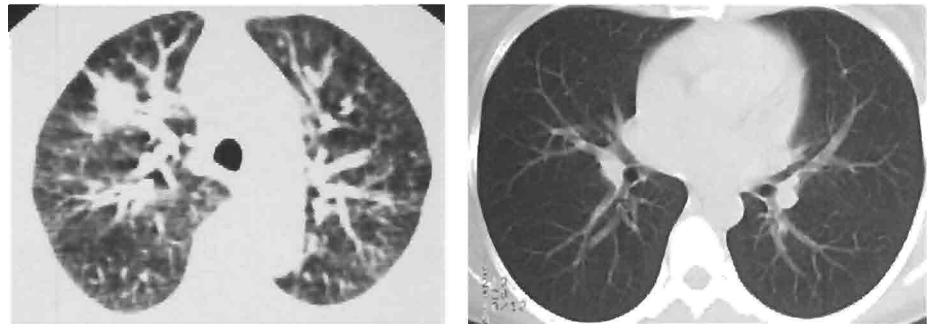


Figure 23. *The left image is performed in 1982 and the right image is performed in 2002. Slice thickness of both images are 10 mm.*

The increased image quality offered by HRCT was obviously a big step forward at that time. However, today it is possible to reconstruct all images of the lung parenchyma, regardless of slice thickness, with a high resolution algorithm. Thereby the spatial resolution, “sharpness”, of all structures is increased. This feature is readily available on all CT scanners, but at almost all other departments, the algorithm is only used with the HRCT images. Thereby, the maximum image quality for assessing vascular alterations is not achieved and the images can thereby, correctly, be looked upon as old-fashioned.

In short, a possible explanation might be that the value of the “sharpness” that HRCT images provides in areas low attenuation is overestimated while the usefulness of altered vascular pattern as a sign of severe emphysema, which is best evaluated on thicker images is underestimated.

Theoretically, it can also be discuss whether the “trendy” technique HRCT should actually be performed with high resolution. The use of a standard algorithm instead, leads to differences in attenuations being better appreciated (used for example in metastases in

the liver with only slight attenuation difference from the ordinary parenchyma). Since the sign of emphysema on HRCT commonly used is low attenuating areas, this attenuation difference from normal parenchyma should theoretically be better visualized with a standard algorithm. Thus, a new and unconventional way of performing CT of emphysema might be the following combination:

- 1) thick images reconstructed with a high resolution algorithm
- 2) thin images reconstructed with a standard algorithm!

Only type 1 has been evaluated in this thesis, and has as far as we know, only been reported in one study from 1989 (108). The usefulness of images of type 2 has yet to be proved in the diagnosis of emphysema.

6.2 THRESHOLDS FOR DEFINING EMPHYSEMA

In *study I-III* we calculated EI based on the combination of 10 mm thick images and the threshold -960 HU. Several studies have advocated different optimal attenuation thresholds for defining emphysema when pathological correlation has been performed. In 1995, a study by Gevenois (78) was published, aimed at determining the most appropriate CT threshold for emphysema. They recommend the combination of 1 mm thick images and a threshold of -950 HU to be used. However, their material consists mostly of patients surgically treated for lung cancer and only a few had macroscopically severe emphysema, which is pointed out as a limitation in the conclusion of the study. Our combination of 10 mm images and a threshold of -960 HU were arbitrarily chosen for severe emphysema at the time when evaluation of LVRS candidates started at our department in 1994. In 1997 another group reported the same combination as "severe emphysema index" (92). With this threshold a stronger correlation with outcome measures was shown compared to the -900 HU threshold.

In *study IV and V*, we calculated EI based on the combination of 2 mm thick images and the threshold -950 HU. The settings were chosen to enable a comparative study with CT-pathology correlation (78). Since pulmonary emphysema is defined through pathological criteria, new methods of diagnosis and quantification should be validated by comparisons against histopathological references. Which threshold should be used in advanced emphysema has yet to be evaluated, as well as other factors known to influence the EI (80), for example the type of CT-unit, algorithm, slice-thickness, and software for EI measurements.

6.3 STUDY IV-V

"What is heterogeneous distribution of pulmonary emphysema" was discussed in an editorial by Austin in 1999 (109). Salzman also stressed the problem in a recent editorial: "A consensus on the best method for describing CT severity and heterogeneity has yet to emerge" (90). Due to this lack of a generally accepted method, or "gold standard", for defining emphysema heterogeneity we developed, in *study IV*, a quantitatively calculated, CT based model for the classification of emphysema heterogeneity. The purpose of this model was initially to enable the comparison between CT and LPS in *study V*. However, the model should also be considered as an alternative to other published quantitative CT based methods for emphysema measurements. Procedures for quantitative measurements of emphysema can be divided in 1) methods for detecting and estimating degree of emphysema, and 2) methods for describing distribution of emphysema. Only methods trying to describe heterogeneity are discussed here. Sakai et al in 1994 (110), described an

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automated method to estimate the extent of low attenuation areas on chest CT scans. The method has seldom been reported in the literature, but had the advantage of trying to describe the spatial distribution of emphysema. Gierada et al in 1997 (92) compared quantitative CT and outcome after LVRS. Some moderately strong correlations were found between the values of the quantitative CT indices and improved postoperative outcome measures. Two indices for heterogeneity were used: the standard deviation of the mean lung attenuation and the full width at half maximum (referring to the pixel frequency distribution). However, none of these indices reflect the spatial distribution of emphysema and therefore, they cannot be considered directly analogous to the degree of emphysema heterogeneity, i.e. unevenness of the spatial distribution of emphysema or presence of surgical target areas. Upplauri et al in 1997 (85), examined the use of an automated texture-based adaptive multiple feature method in normal and emphysematous patients. In short, this methodology is based upon the underlying pattern of disease and is not based on a single attenuation index threshold. This might be a way of improving quantitative CT in the future. Rogers et al in 2000 (93), showed that CT morphometry, an objective, computerised algorithm for partitioning the volume of the lung into three compartments based on density (severe emphysema, mild/moderate, and normal), predicts response to LVRS and suggested mechanisms leading to improvement. This quantitative CT technique is, however, not used for defining heterogeneity. Flaherty et al in 2001 (94), evaluated selection criteria and duration of benefit after LVRS. They introduced the CT emphysema ratio, an index of the craniocaudal distribution of emphysema. The percentage of emphysema (threshold -900 HU) was calculated for the upper and lower halves of the lung and the index was calculated.

From this summary regarding some of the published studies of quantitative CT and emphysema, it is obvious that few, if any, are suitable for classifying the heterogeneity of emphysema in a clinical routine.

In *study IV*, a new method is proposed, based on objective measurements, for describing emphysema by CT in patients who are candidates for LVRS. The method allows for a surgically orientated classification into the categories markedly heterogeneous, intermediately heterogeneous and homogeneous emphysema adopted from Weder et al (87), establishing upper or lower lobe predominance and comparisons between left and right lung. The intention with our method was to create a model applicable in clinical practice in the selection of candidates for LVRS. The only equipment necessary is computer software for quantitative CT measurements and linear regression analysis. The type of CT-unit, algorithm, slice thickness, software for EI measurements and threshold value for EI that were used, however, are important factors that influence both the slope (k) and EI, and thereby the classification (80). The proposed method describes the basic relationship between the k -value and EI-difference. Each investigator must, according to their conditions, establish their own level for k and EI-difference. The definition of k and EI-difference for the three types of emphysema heterogeneity in this study may be valid only for the combination of these factors in our study.

Two-years' outcome after LVRS of patients with the different morphologic emphysema types has been published by the same group that originally presented the classification of heterogeneity shown in fig 13 (89). Visual classification into these three types of emphysema was correlated to pulmonary function, walking distance and dyspnea. Their data show a functional and subjective benefit that was statistically and clinically significant in patients with homogeneous and intermediately emphysema as well as patients with marked heterogeneity. This diversity in postoperative outcome, between studies, in relation to radiologically assessed emphysema morphology, might in part be

DISCUSSION

explained by the lack of consensus in defining emphysema heterogeneity. Our proposed method could be the solution to this lack of consensus.

In *study V*, it was investigated whether lung LPS contributes to the preoperative classification of emphysema heterogeneity compared to classification based only on CT (in this study both HRCT and spiral CT were included in the expression “CT”). Among the qualitative and quantitative imaging techniques that have been proposed in the literature, the relative value of each individual investigation in the selection of patients suitable for LVRS, has yet to be established. At our hospital, imaging of LVRS candidates includes CXR, CT and LPS. Patients are selected during multi-disciplinary “LVRS sessions” with a thoracic radiologist, a thoracic surgeon, a pulmonologist, a clinical physiologist and a physiotherapist participating. All images and all clinical information are evaluated at these meetings. Our clinical impression has been that CT and LPS often were equal in defining surgically appropriate target areas, despite the fact that CT shows emphysema morphology and LPS reflects pulmonary perfusion. Therefore, the question arose whether both CT and LPS should be performed. The use of CT in the preoperative assessment of candidates for LVRS is mandatory, not only for the evaluation of emphysema but also to detect concomitant diseases that influence the selection of patients. We therefore compared CT and LPS to evaluate if LPS could be omitted. We designed this retrospective study so that it was comparable to our clinical work and therefore, choose a visual evaluation of CT and scintigraphy. The simple, and surgically oriented grading system for emphysema heterogeneity proposed by Weder (87) seemed suitable for visual evaluation of both techniques, well aware of the difference in the morphologic distribution of emphysema shown by CT and the functional information reflected by LPS. With the objective classification method presented in *study IV* as reference, the present study showed that the information obtained from CT and LPS together was superior in classifying emphysema heterogeneity compared to classification based only on CT. Thus, LPS should be included in the preoperative assessment of candidates for LVRS. However, this was contrary to the findings of the study by Cleverly et al (111), who concluded that lung perfusion scintigraphy might be superfluous in the pre-operative evaluation of patients scheduled for LVRS. This conclusion was based on a correlation between HRCT and LPS in evaluating the extent of normal pulmonary vasculature in patients with emphysema. Thurnheer (88) concluded that LPS had a limited role in the prediction of outcome, but that it may help to identify target areas for resection in LVRS candidates with homogeneous emphysema.





Several studies have suggested that CXR alone may be sufficient for at least initial screening of potential candidates for LVRS (26,55,56). In our initial work regarding *study V*, visual classification of CXR was included as a separate method and was compared to CT, LPS and the combination of CT and LPS. We found that CXR was superior to CT and LPS separately, but not to the combination of CT and LPS in diagnosing homogeneous and markedly heterogeneous emphysema. This preliminary, and not published data is hence in accordance with the earlier studies indicating that CXR alone might be adequate for initial screening of LVRS candidates.

We consider our study performance comparable to the clinical situation and we suggest that LPS is added to CT in the preoperative investigation. Whether only CXR is sufficient for the final classification of heterogeneity preoperatively has yet to be studied.

7 CONCLUSIONS AND FINAL REMARKS

The general purpose of this thesis was to study the radiological evaluation of emphysema in candidates for LVRS, and to suggest suitable imaging for this patient group preoperatively.

This thesis support the following conclusions regarding preoperative radiological evaluation of candidates for LVRS:

-  The radiologists subjectively preferred HRCT in evaluating severe emphysema.
-  In grading of the degree of emphysema, the radiologists performed similar with HRCT and spiral CT, while “density masked” images resulted in significantly better results.
-  The radiologists classified emphysema heterogeneity based on spiral CT significantly better compared to HRCT.
-  Lung perfusion scintigraphy contributed to the preoperative classification of emphysema heterogeneity compared to classification based only on CT.

In addition to these conclusions, a new method for classification of emphysema heterogeneity that is objectively calculated, surgically oriented and classifies both lungs separately was developed.

Thus, in contrast to subjective preferences, visual evaluation of emphysema should be based on spiral CT (10 mm slice thickness and reconstruction with a high spatial algorithm) instead of HRCT in potential candidates for LVRS. The presentation of images as “density masked” images improves the visual evaluation of degree of emphysema. This type of images can easily be performed on all CT scanners and can thus be recommended as part of a complete CT examination. The addition of lung perfusion scintigraphy to spiral CT of the lungs improves the classification of emphysema heterogeneity in candidates for LVRS. A new method for objective classification of emphysema heterogeneity has been developed and might be considered as “golden standard” in the future.

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