LONGITUDINAL STUDY OF LUNG STRUCTURE AND AIRFLOW LIMITATION IN SMOKERS USING COMPUTED TOMOGRAPHY AND SPIROMETRY

by

REN YUAN

B. Med., Tongji Medical University, 1997
M.Sc., Tongji Medical University, 2001

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ABSTRACT

Early detection of chronic obstructive pulmonary disease (COPD) is crucial since the protective effect from smoking cessation diminishes when the disease becomes severe. Little is known about early changes before the onset of airflow limitation. In addition, the natural history of COPD has not been extensively investigated in longitudinal studies.

In this work, I firstly compared quantitative CT densitometry between low- and regular-dose CT images, and between different CT scanners. I found a significant overestimation of “emphysema” using densitometry measurements from low-dose CT images, while measurements were comparable between the two scanners. Secondly, I validated a CT measurement of %overinflation using both a dynamic cutoff (maximal lung inflation) and CT cluster analysis, by comparing them to the histological gold standard for emphysema, the lung surface area to volume ratio. In addition, CT cluster analysis supplemented CT lung density in quantifying pulmonary emphysema. Thirdly, I tested the contributions of parenchymal overinflation and airways’ remodeling to airflow limitation in a cross-sectional study design. In COPD subjects, the “airway-dominant” phenotype had less severe airflow limitation but smaller airway lumen area compared to the “emphysema-dominant” phenotype. Smokers who had normal spirometry showed less parenchymal overinflation but there was considerable overlap with those who had established COPD. The fourth original investigation is a longitudinal study of spirometry and CT analyses in heavy smokers without COPD. I found that baseline parenchymal overinflation was significantly associated with the subsequent rate of decline in lung function. This novel finding suggests that CT analysis could serve as a useful biomarker to identify those “susceptible” smokers who will develop COPD. Lastly, I showed that progressive airflow limitation was associated with worsening airway abnormalities only in smokers without COPD at baseline, whereas it was only associated with progression in parenchymal destruction in smokers with pre-existing COPD. In addition, smokers who had, or did not have, established COPD at baseline showed a comparable rate of progression of airflow limitation and parenchymal overinflation.
In summary, these cross sectional and longitudinal studies of a unique cohort of smokers, using validated CT measurement tools, provide important insights regarding the onset and natural history of COPD.
# TABLE OF CONTENTS

ABSTRACT........................................................................................................................................... 1
TABLE OF CONTENTS .......................................................................................................................... iv
LIST OF TABLES ........................................................................................................................................ ix
LIST OF FIGURES ..................................................................................................................................... xi
ACKNOWLEDGEMENTS ...................................................................................................................... x ii
DEDICATION ........................................................................................................................................... x iv
CO-AUTHORSHIP STATEMENT ........................................................................................................ x v

CHAPTER ONE. LITERATURE REVIEW AND INTRODUCTION TO THESIS ........................................... 1

1.1 INTRODUCTION ............................................................................................................................... 1
1.2 GENERAL BACKGROUND OF COPD .............................................................................................. 1
1.3 CT QUANTIFICATION OF PULMONARY EMPHYSEMA - GENERAL METHODS ........................................ 2
   1.3.1 Subjective Assessment of Emphysema .............................................................................. 2
   1.3.2 Objective Assessment of Emphysema ........................................................................... 3
1.4 CT ASSESSMENT OF AIRWAYS – GENERAL METHODS ............................................................... 6
   1.4.1 Subjective Assessment of Airways .............................................................................. 6
   1.4.2 Objective Assessment of Airway ................................................................................. 7
1.5 UTILITY OF CT IN COPD ............................................................................................................. 11
   1.5.1 CT Scan in Diagnosis of COPD .................................................................................. 11
       1.5.1.1 CT Scan in Differential Diagnosis of COPD ...................................................... 11
       1.5.1.2 CT Scan in Diagnosing Onset of COPD .............................................................. 11
   1.5.2 CT Scan in Therapeutic Decision Making in COPD .................................................... 14
       1.5.2.1 CT Scan and Lung Volume Reduction Surgery in COPD .................................... 14
       1.5.2.2 CT Scan in Phenotyping Subjects with COPD .................................................... 15
   1.5.3 CT Scan as One Outcome in COPD ............................................................................. 17
   1.5.4 CT Scan and the Prognosis of COPD ............................................................................ 20
1.6 CT TECHNIQUES IN LONGITUDINAL STUDIES ........................................................................ 21
   1.6.1 CT Densitometry in Longitudinal Study .......................................................................... 21
   1.6.2 CT Airway Measurements in Longitudinal Study ......................................................... 23
1.7 RATIONALE FOR STUDY ........................................................................................................... 23
1.8 OBJECTIVES AND HYPOTHESES OF THE THESIS ............................................................... 24
1.9 REFERENCES ............................................................................................................................... 30

CHAPTER TWO. THE EFFECTS OF RADIATION DOSE AND COMPUTED TOMOGRAPHY MANUFACTURER ON MEASUREMENTS OF LUNG DENSITOMETRY ......................................................... 45

2.1 INTRODUCTION ............................................................................................................................... 45
2.2 METHODS ....................................................................................................................................... 46
   2.2.1 Subject Selection .............................................................................................................. 46
   2.2.2 CT Scan Technique ......................................................................................................... 46
   2.2.3 Quantitative CT Analysis .............................................................................................. 47
4.2.4.1 Assessment of Emphysema ............................................. 87
4.2.4.2 Assessment of Airway Dimensions .............................. 88
4.2.5 Statistical Analysis .............................................................. 89
4.3 RESULTS .............................................................................................................. 90
  4.3.1 Subject Characteristics ....................................................... 90
  4.3.2 Comparison of Quantitative CT Assessments of Lung Structures between non-COPD Group and COPD Group .. 90
  4.3.3 Univariate and Multivariate Models Predicting FEV1 and FEV1/FVC in COPD Subjects ............................................. 90
  4.3.4 Two Phenotypes in Subjects with COPD ....................... 91
4.4 DISCUSSION ..................................................................................... 92
  4.4.1 Association between the CT Measurements of Lung Structure and FEV1, FEV1/FVC in Subjects with COPD ................. 93
  4.4.2 “Two Phenotypes of COPD” ............................................... 94
  4.4.3 CT Measurements of Lung Parenchyma in Smokers without COPD ................................................................. 96
  4.4.4 Limitations ........................................................................... 97
  4.4.5 Conclusions ........................................................................ 97
4.5 REFERENCES ................................................................................. 104

CHAPTER FIVE. PREDICTION OF RATE OF DECLINE IN FEV1 IN SMOKERS USING QUANTITATIVE COMPUTED TOMOGRAPHY ...... 109

5.1 INTRODUCTION .................................................................................. 109
5.2 METHODS .......................................................................................... 110
  5.2.1 Subject Selection ......................................................................... 110
  5.2.2 Lung Function ............................................................................ 110
  5.2.3 CT Technique ............................................................................ 111
  5.2.4 Quantitative CT Analysis .......................................................... 111
    5.2.4.1 Assessment of Emphysema ............................................. 111
    5.2.4.2 Assessment of Airway Dimensions ................................ 112
  5.2.5 Statistical Analysis .................................................................... 113
5.3 RESULTS ........................................................................................ 113
  5.3.1 Baseline Characteristics ......................................................... 113
  5.3.2 Follow-up Measurements of FEV1 ......................................... 114
  5.3.3 Risk Factors Associated with Annual Change in FEV1%predicted ................................................................. 114
5.4 DISCUSSION ................................................................................... 114
  5.4.1 %Overinflation Predicts the Decline in FEV1 ......................... 115
  5.4.2 Airway Dimensions and the Decline in FEV1 ....................... 116
  5.4.3 Initial FEV1 and the Rate of Decline in FEV1 ......................... 117
  5.4.4 Limitations ............................................................................ 118
  5.4.5 Limitations ............................................................................ 118
5.5 REFERENCES ................................................................................. 124
CHAPTER SIX. LONGITUDINAL STUDY OF LUNG STRUCTURE AND FUNCTION IN HEAVY SMOKERS USING COMPUTED TOMOGRAPHY AND SPIROMETRY .............................................. 128

6.1 INTRODUCTION ............................................................................ .128
6.2 METHODS ................................................................................... 129
   6.2.1 Subject Population ............................................................ 129
   6.2.2 Lung Function ................................................................. 130
   6.2.3 CT Technique .................................................................. 130
   6.2.4 Quantitative CT Analysis .................................................. 131
      6.2.4.1 Assessment of Emphysema ..................................... 131
      6.2.4.2 Assessment of Airway Dimensions....................... 132
   6.2.5 Statistical Analysis ......................................................... 132
6.3 RESULTS .................................................................................... 133
   6.3.1 Subject Characteristics .................................................... 133
   6.3.2 Rate of Annual Change in CT and Spirometry Measurements in GOLD 0 and COPD Groups ................................................................. 133
   6.3.3 Association between Annual Change in %overinflation and Annual Change in Cluster Analysis ......................................................... 134
   6.3.4 Association between Changes in Spirometry Measurements and Changes in CT Measurements in GOLD 0 and COPD Groups ................................................................. 134
6.4 DISCUSSION ............................................................................. 135
   6.4.1 Annual Change in Lung Function in GOLD 0 and COPD Groups ........................................................................................................ 135
   6.4.2 Annual Changes in CT Measurements of Emphysema in GOLD 0 and COPD Groups ................................................................. 136
   6.4.3 Annual Changes in CT Measurements of Airway Dimensions in GOLD 0 and COPD Groups ................................................................. 137
   6.4.4 Natural History of Smokers in Stage GOLD 0 ................. 138
   6.4.5 Associations between Annual Change in Lung Function and Annual Change in CT Measurements of Emphysema and Airway Dimensions in GOLD 0 and COPD Groups ................................................................. 138
   6.4.6 Limitations ...................................................................... 140
   6.4.7 Conclusions ................................................................. 140
6.5 REFERENCES ............................................................................. 147

CHAPTER SEVEN. GENERAL DISCUSSION AND FUTURE DIRECTIONS .. 152

7.1 GENERAL DISCUSSION ................................................................. 152
   7.1.1 The Effects of Radiation Dose and CT Manufacturer on Measurements of Lung Densitometry ................................................................. 152
   7.1.2 Quantification of Lung Surface Area Using Computed Tomography .................................................................................................. 153
   7.1.3 Computed Tomographic Assessments of Emphysema and Airway Dimensions in Smokers - Correlation with Airflow Limitation ................................................................. 153
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1.4 Prediction of the Rate of Decline in FEV1 in Smokers Using Quantitative Computed Tomography</td>
<td>154</td>
</tr>
<tr>
<td>7.1.5 Longitudinal Study of Lung Structure and Airflow in Heavy Smokers Using Computed Tomography</td>
<td>155</td>
</tr>
<tr>
<td>7.2 STRENGTHS AND LIMITATIONS OF THE RESEARCH</td>
<td>156</td>
</tr>
<tr>
<td>7.2.1 Strengths of the Thesis Research</td>
<td>156</td>
</tr>
<tr>
<td>7.2.2 Limitations of the Thesis Research</td>
<td>157</td>
</tr>
<tr>
<td>7.3 FUTURE RESEARCH DIRECTIONS</td>
<td>158</td>
</tr>
<tr>
<td>7.3.1 General Future Directions</td>
<td>158</td>
</tr>
<tr>
<td>7.3.2 Future Research in Standardization of CT Protocols</td>
<td>160</td>
</tr>
<tr>
<td>7.3.3 Future Research in the Use of CT in Smokers with COPD</td>
<td>160</td>
</tr>
<tr>
<td>7.3.4 Future Research in the Predictive Value of the Early Emphysema</td>
<td>162</td>
</tr>
<tr>
<td>7.3.5 Future Research Regarding the Association between Changes In CT and Changes in Airflow</td>
<td>163</td>
</tr>
<tr>
<td>7.4 POTENTIAL APPLICATIONS OF RESEARCH FINDINGS</td>
<td>163</td>
</tr>
<tr>
<td>7.5 REFERENCES</td>
<td>165</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 2-1  Anthropomorphic and Spirometric Characteristics of Subjects in the X-ray -Dose and CT Manufacturer Studies........................................54

Table 2-2  Comparison of quantitative CT measurements between Low-Dose and High-Dose CT Scan images (n=50) ..........................................55

Table 2-3  Comparison of Quantitative CT Measurements between CT Scan images acquired using a GE Lightspeed Ultra (8 slice) and a Siemens Sensation 16 (16 slice) scanner (n=30) ...............................56

Table 3-1  Subjects Demographics ........................................................................................................74

Table 3-2  Quantitative Histological and CT Measurements for 140 Tissue Samples and Averaged Values for 14 Cases ..................................75

Table 4-1  Characteristics of Study Population (160 non-COPD and 153 COPD) ..........................................................98

Table 4-2  Comparison of CT Assessments between Non-COPD and COPD Groups .................................................................99

Table 4-3  Univariate Models Predicting FEV1 and FEV1/FVC (each model including 1 spirometry measurement and 1 CT measurement) ....100

Table 4-4  Multivariate Models Predicting FEV1 and FEV1/FVC (each model including 1 spirometry measurement and 3 quantitative CT measurements) .................................................................101

Table 4-5  Akaike's Information Criterion (AIC) Results .................................................................................102

Table 4-6  Comparison between Two Phenotypes in Subjects with COPD ..................................................103

Table 5-1  Baseline Characteristics of Study Population ...............................................................................119

Table 5-2  Characteristics of Baseline Quantitative CT Assessments .........................................................120

Table 5-3  Comparison of ΔFEV1%predicted/y Cross Four Quartiles ..........................................................121

Table 6-1  Baseline Characteristics of Subjects in GOLD 0 and COPD Groups .........................................................142

Table 6-2  Annual Change in Lung Function and CT Measurements in GOLD 0 and COPD Groups .........143
### Table 6-3
Associations between the Annual Change of FEV1 (L) and the Annual Changes in Quantitative CT Measurements in GOLD 0 and COPD Groups

### Table 6-4
Associations between the Annual Change of FEV1%pred and the Annual Changes in Quantitative CT Measurements in GOLD 0 and COPD Groups

### Table 6-5
Associations between the Annual Change of FEV1/FVC and the Annual Changes in Quantitative CT Measurements in GOLD 0 and COPD Groups
LIST OF FIGURES

Figure 1-1  Two Common Approaches to Detect Emphysema on CT .............27

Figure 1-2  “Full Width at Half Maximum” Method to Estimate Airway Wall Area on CT ............................................................................ 28

Figure 1-3  Regional Distribution of Emphysema ............................................ 29

Figure 2-1  Hounsfield Unit Frequency Distribution Histograms from Low-Dose and High-Dose CT Images ............................................................ 57

Figure 2-2  Hounsfield Unit Frequency Distribution Histograms from GE and Siemens CT scanners ................................................................... 58

Figure 3-1  Matching CT Images and Lung Specimens .................................. 76

Figure 3-2  Association between the Histological SA/V and CT-Median Lung Density .......................................................................................... 77

Figure 3-3  Association between the Histological SA/V and CT Cluster Analysis Value D .......................................................................................... 78

Figure 3-4  Heterogeneity of Lung Tissue Destruction ..................................... 79

Figure 3-5  A Schematic Showing the Relationship between Lung SA/V and Density under Two Scenarios .......................................................... 80

Figure 3-6  Examples of Hematoxylin and Eosin-stained Images of Tissue Samples Corresponding to Areas A and B ........................................ 81

Figure 5-1  Comparison of The Annual Decline in FEV1%predicted Cross Four Quartiles of Baseline %overinflation ............................................ 122

Figure 5-2  The Annual Decline in FEV1 (L) of Subjects with Greater Baseline %overinflation (i.e. quartile 3 and 4) and with less %overinflation (i.e. quartile 1 and 2) ............................................................................ 123
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DEDICATION

To my daughter: Vickie Wang
my husband: Gang Wang

&

my mother: Yanfen Ren
my father: Xiaoning Yuan
CO-AUTHORSHIP STATEMENT

Sections of this thesis have been published or are in preparation for publication in referred journals. Details of each author’s contributions are provided here.

Presented in Chapter Two.

The thesis author had primary responsibility for developing the research question, analyzing CT images and data, conducting the literature review and preparing the manuscript. Dr. Mayo assisted in interpreting the summary data, editing the manuscript and provided editorial comments on the manuscript. Drs. Hogg, Paré, McWilliams and Lam provided editorial comments on the manuscript. Dr. Coxson provided guidance with the development of the research questions and the interpretation of the summary data, assisted in writing and editing the manuscript and provided editorial comments on the manuscript.

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The thesis author had primary responsibility for developing the research question, analyzing CT images, conducting the literature review and preparing the manuscript. Dr. Paré provided guidance with the development of the research question and the interpretation of the summary data, assisted with writing and editing the manuscript and provided editorial comments on the manuscript. Drs. Hogg, English and Mayo provided editorial comments on the manuscript. Dr. Nagao, Elliott WM, Loy L, and Kalloger SE provided technical support. Xing L assisted with statistical analysis. Dr. Coxson assisted in writing and editing the manuscript, and provided editorial comments on the manuscript.
Presented in Chapter Five.
The thesis author had primary responsibility for developing the research question, performing the experiment, analyzing data, conducting the literature review and preparing the manuscript. Dr. Hogg provided guidance with the development of the research question and the interpretation of the summary data, assisted with writing and editing the manuscript and provided editorial comments on the manuscript. Drs. Paré, Sin, and Coxson assisted with editing the manuscript and provided editorial comments on the manuscript. Dr. McWilliams and Lam provided editorial comments on the manuscript.

Presented in Chapter Four.
The thesis author had primary responsibility for developing the research question, performing the experiment, analyzing data, conducting the literature review and preparing the manuscript. Dr. Paré and Dr. Hogg provided guidance with the development of the research question and the interpretation of the summary data, assisted with writing and editing the manuscript and provided editorial comments on the manuscript. Dr. Sin and Dr. Coxson assisted with writing and editing the manuscript and provided editorial comments on the manuscript.

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CHAPTER ONE. LITERATURE REVIEW AND INTRODUCTION TO THESIS

1.1 INTRODUCTION

This is a manuscript-based dissertation, which is an approved thesis style of the Faculty of Graduate Studies, University of British Columbia. It is comprised of an introductory chapter, followed by five research papers, each with its own introduction, methods, results, discussion and reference sections. The final chapter is a summary and discussion of the results of the research studies and recommendations for future research.

In this introductory chapter, I provide a brief introduction to COPD, an introduction to the general methods of quantitative Computed Tomography (CT) in assessing lung parenchyma and airway dimensions, followed by discussion of the use of CT in clinical, and mainly research fields related to chronic obstructive pulmonary disease (COPD). At the end, I briefly summarize the current problem with CT in longitudinal studies. This chapter concludes with a description of the structure of the thesis with an overview of the chapters which make up this body of work.

1.2 GENERAL BACKGROUND OF COPD

The Global Initiative for Obstructive Lung Disease (GOLD) defines COPD as:

... a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases... (1)

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1Sections of this chapter has been published or used in the following papers:
GOLD further categorizes disease severity according to forced expiratory volume in the first second (FEV1) and the ratio between FEV1 and forced vital capacity (FVC) - the total amount of air exhaled (FEV/FVC). COPD imposes a large economic and social burden worldwide. It is currently the 12th leading cause of disability in the world and is predicted to be 5th by the year 2020 (2, 3). In the United States alone, COPD causes more than 500,000 hospitalizations and more than 100,000 deaths each year (4, 5). COPD is a costly disease and the exacerbations of COPD account for the greatest burden on the health care system in developed countries (1). COPD is a complex condition in which environmental factors interact with genetic susceptibility to cause disease (6). Tobacco smoking is considered as the most important environmental risk factor (7). Unfortunately, the treatment options available to patients with COPD are limited, and no pharmacologic therapy slows the progressive loss of lung function that occurs (8). Smoking cessation slows the decline in FEV1 (8), but its protective effect diminishes as the disease becomes severe (9). Therefore, patients should be identified as early in the course of the disease as possible, and certainly before the end stage of the illness when there is substantial disability.

1.3 CT QUANTIFICATION OF PULMONARY EMPHYSEA – GENERAL METHODS

1.3.1. Subjective Assessment of Emphysema

The extent of emphysema can be estimated subjectively by visual inspection of the CT images. In each region, the proportion of the lung that appears emphysematous is roughly estimated using scores between zero and 4. 1: less than 25% of the area; 2: 26% to 50% of the area; 3: 51% to 75% of the area; score 4: 76% to 100% of the area. This four point scale can be expanded to five levels by defining score 0 as normal (10-12). The region may be one or both lungs; upper, middle, or lower zone of each or both lungs, and dorsal or ventral portions of each or both lungs. Emphysema distribution can be visually determined as one of the following: upper
lobe-predominant, lower lobe-predominant, diffuse, or superior segments of lower lobes predominant (13).

The severity of emphysema has been less often quantified using subjective scoring. A scheme used two decades ago was 0: none, 1: low attenuation areas less than 5 mm, 2: circumscribed low attenuation areas greater than 5 mm in addition to smaller ones, or 3: diffuse low-attenuation without normal lung or large confluent areas of very low attenuation (11). This was applied to the whole lung scan but also was applied regionally.

The majority of studies have shown good correlation between the CT emphysema score and the extent and severity of emphysema on pathological specimens (12, 14-19). However, there is an inherent limitation of this subjective visual scoring: it is very vulnerable to the users’ experience and image viewing settings. This method often requires "mental adjustments" because the scans are presented as "cross-sectional" (i.e. horizontal) images but the viewer needs to apply the scoring system in a top to bottom grading panel (20). This may reduce the reproducibility of the grading system and introduce unwanted variability between observers. Consistent with this notion, one study showed poor inter-observer agreement in the determination of upper lobe predominant emphysema using this method (13).

1.3.2 Objective Assessment of Emphysema

The characteristic presentation of emphysema as areas of low CT attenuation values, and the digital nature of the CT data inspired the development of objective quantification of emphysema on CT scans.

Approaches to Detect Emphysema on CT. Currently, two approaches have mainly been used for objective quantification of emphysema on CT (Figure 1-1). (1) “density mask or pixel index”, can be traced back to Müller (17). A particular threshold value is selected in Hounsfield units (HU) that is thought to be representative of abnormally decreased lung density secondary to emphysema, and the amount of lung with a HU value less than this threshold value (i.e. low attenuation area, LAA) is then calculated and usually expressed as a percent of total lung volume.
(i.e. %LAA), or highlighted in color (17, 21-23). The “percentile point method”, first introduced by Gould (24), derived from lung CT attenuation HU histograms, is defined as “the cut-off value in HU below which a predetermined percentage of voxels are distributed” (25). It remains popular in Europe. The measurement of the mean lung attenuation is an alternative estimate of the overall lung parenchymal destruction and can be used in conjunction with either the density mask or the percentile point technique (26-29).

The main controversy in emphysema detection using quantitative CT methods has long been which HU cutoff (for density mask technique), and which percentile (for percentile point method) is more accurate to represent emphysema. Since McLean et al recommended that pulmonary emphysema should be measured microscopically rather than macroscopically (30), comparisons between CT and morphometry have also included microscopic measurements, such as alveolar wall per unit of lung volume (24), alveolar surface area to volume ratio (23), mean inter-alveolar wall distance and mean perimeter per field (31, 32). To date, many cutoffs of have been validated by comparing them to the macro- and/or microscopic emphysema ranging from -980HU to -856 HU for density mask method (17, 21, 23, 31-35) or ranging from 1st to 15th for percentile point method (24, 31, 32).

Although data from these validation studies supported different cutoff values, we should be aware firstly that significant correlations only indicate that CT and pathological scores are statistically linked, but do not imply that the percentage area obtained by CT quantifications are equal to the percentage area occupied by emphysema on the pathological specimen. Second, when choosing a specific CT cutoff that has been validated the CT scanning protocols should also be kept comparable as it is well known that CT quantitative densitometry of the lung can be affected by the imaging acquisition protocols (20, 36, 37).

Size Distribution of Emphysematous Lesions. Quantitative measures combine information about severity and extent of emphysema in one number, which offers simplicity, but sacrifices some descriptive information such as the distribution and size of individual emphysematous lesions. The concept of fractals, first introduced by Mandelbrot is used for a structure with a non-integer number of dimensions (38).
Fractal geometry has found widespread application in the physical sciences because it is a suitable model for objective quantification of spatial heterogeneity (39). The properties of fractals are scale-invariance, self-similarity, and fractional dimension (20).

Mishima et al first attempted to detect early emphysema using fractal analysis (40). They quantified the size distribution of LAA clusters on 2-mm thick HRCT slices obtained at full inspiration in 30 healthy subjects and 73 COPD patients. These authors found that (1) there was a linear log-log relationship of the size of the LAA clusters versus the number of clusters of that size (the inverse slope of this relationship was the power-law exponent, D); a smaller D indicates a greater proportion of large-sized LAAs. (2). There was a correlation between D and %LAA, and between D and carbon monoxide diffusing capacity of the lung; (3) in healthy subjects and COPD patients who had comparable %LAA (both < 30%), D value was smaller in COPD subjects suggesting amalgamation of low attenuation voxels and greater loss in gas exchange surface in these subjects. They concluded that the cluster analysis represents the size distribution of LAA or emphysematous lesions. Because this variable can detect the enlargement of distal airspaces resulting from the coalescence of neighboring LAA even when there is not an abnormal increase in the LAA value, therefore, it might be more sensitive in detection of terminal airspace enlargement that occurs in early emphysema (40). Currently, the cluster analysis is less widely used than the density mask approach except in patients with very severe disease (e.g. candidates for lung volume reduction surgery) (41, 42). In addition, the validation of cluster analysis method is lacking (31).

Regional Distribution and Types of Emphysema. The next step in the image processing of emphysema is to look at the distribution and types of emphysema present. Regional assessment requires division of the lungs into regions from top to bottom, from ventral to dorsal, core to rind or into lobes.

There are reports of successfully quantifying the cranio-caudal distribution of emphysema in the lungs (43, 44). Stavngaard et al plotted the %LAA against table position with a small number referring to the cranial part of the lung and they assumed a linear relationship. The slope is positive if emphysema is most pronounced in the
caudal part of the lung, and negative if it is most pronounced in the cranial part of the lung (43). They showed this approach separated those with a1-antitrypsin deficiency from those with emphysema without a1-antitrypsin deficiency although they both had a similar amount of LAA. Parr et al did a similar analysis and they defined an “apical” or “basal” group based on whether the location of the peak number of voxel index was within the upper- or lower- third of the lung, respectively (44). Plotting the amount of emphysema on CT images from top to bottom has been shown to help characterize individuals’ degrees of emphysema heterogeneity (45).

Lobar segmentation by computer has also been accomplished (46, 47). Zhang and Hoffman et al have developed a semiautomatic method for identifying the fissures on CT images. This automated method will facilitate the evaluation of regional abnormalities and speed up the process.

Another approach to assessment of regional involvement is to measure density in the core versus the periphery, or “rind” of the lung (46, 48). Subjects with greater extent of severe emphysema in the rind of the upper lung derived greater benefit from LVRS because it identifies the lesions most accessible to removal by LVRS (48).

It is not presently possible to quantify the types of emphysema (i.e. centriacinar, panacinar, or subpleural emphysema) on the CT chest images with current image processing techniques. It is hoped that the ability to classify emphysema along accepted pathological appearances will be forthcoming in the future (37).

1.4 CT ASSESSMENT OF AIRWAYS – GENERAL METHODS

1.4.1 Subjective Assessment of Airways

A number of CT scoring systems have been developed that allow an assessment of the extent and distribution of airway abnormalities. These scoring systems have been applied at several stages of a variety of diseases, such as cystic fibrosis (49, 50), sarcoidosis (51), bronchiectasis (52), bronchiolitis obliterans syndrome (53) and pulmonary fibrosis (54). Few studies have assessed the diagnostic role of HRCT in chronic bronchitis and COPD and the information available
is limited (55, 56). However, scoring systems rely on the subjective detection and grading of direct and indirect abnormal signs of airway abnormalities, such as airway wall thickening, luminal dilation, mosaic perfusion and/or gas trapping by comparing inspiration- and expiration scans, therefore, there is considerable inter- and intra-observer variation when interpreting airway anomalies. In addition, CT image window settings can markedly influence airway features, and the analysis is very time consuming; all of these factors have limited the application of the subjective assessment of airways (57-59).

1.4.2 Objective Assessment of Airways

**Manual Approach.** The first attempts at objectively measuring airways involved manually tracing the airway on the printed image (60-64). Because airways were still visualized and evaluated by human eyes, the inherent drawbacks to these techniques are similar as those of subjective approaches; therefore, computer-aided automated techniques have been developed.

**Automated Detection of Lumen Area.** McNitt-Gray et al reported that the airway lumen area could be accurately measured by summing all pixels within the airway with an attenuation below –500 HU (65), and King et al subsequently reported that a cutoff of -577 HU produced the least error in measuring lumen area (66).

**“Full Width at Half Maximum”.** The most popular method for measuring airway wall thickness is the “full width at half maximum” method (Figure 1-2) (67). In this approach, rays are cast from the centroid through the airway wall and into the lung parenchyma, and a plot of the x-ray attenuation along the ray against the distance from the centroid is generated. The attenuation increases from a minimum as a ray starts from the centroid, reaches the maximum somewhere in airway wall, and then falls again as the ray passes into the lung parenchyma. The technique assumes the gray level at the airway wall is estimated to be halfway between the minimum and maximum gray levels along this ray crossing the edge, and the lumen area and wall area are measured by calculating the pixels falling into the corresponding area. However, this approach depends on the shape of the X-ray attenuation distribution along the rays, which is dependent on various parameters, including the
reconstruction algorithm, partial volume averaging due to field of view, orientation of the airway within the CT image, and the inevitable blurring of edges due to the point spread function of the CT scanner, therefore, this approach may not be applicable across all airway sizes and/or all airways with different orientation (68). Validation studies showed an underestimation of airway lumen and concurrent overestimation of wall thickness using this technique (69, 70). Furthermore, the errors tend to be more prominent in smaller airways (69).

**“Maximum Likelihood Method”**. Reinhardt et al proposed a new measurement method based on a model of the scanning process. In this approach they examine the gray-level profile of a ray crossing the airway wall and use a maximum-likelihood method to estimate the airway inner and outer radius. Using CT scans of a physical phantom, the authors suggested that this approach is more accurate than the Full Width at Half Maximum” method for estimating wall thickness (70).

**“Score Guided Erosion Algorithm”**. This method was developed by King and co-workers for the measurement of airway dimensions (66). It consists of an edge finding algorithm that assumes that airways are circular and has a relatively high density compared with the surrounding parenchyma. Using this approach, a density map of the image is shifted and subtracted from the previous image. A pixel that has a large change after this shift can therefore be assumed to be an edge. Using this technique, these authors were able to calculate the wall area with much greater precision than had previously been possible. In addition, since the errors due to volume averaging are particularly important when airways are oblique to the scan panel, which is actually the case with the majority of airways, King et al attempted to compensate this obliquity of the section by defining the angle of deviation of each airway. Using a combination of the “score guided erosion algorithm” and an angle correction factor, the authors demonstrated that accurate measurements of airway lumen and wall thickness could be made in those airways in a phantom or a pig lung that were not cut perpendicularly to the cross sectional plane.

**“Ellipses Fitting”**. Saba et al have developed an alternate technique for measuring airways that are not cut in cross-section. This method involves fitting an
ellipse to the airway lumen and wall, and shows great promise in correcting the errors in measurement of obliquely cut airways (71).

**Air Trapping.** This approach allows indirect study of airways that are too small to visualize on CT. The method involves the assessment of air trapping by comparing inspiratory and expiratory CT scans. Small airways obstruction causes air to be trapped in peripheral lung units that are distal to the obstruction site and leads to a decreased CT attenuation, which can be best demonstrated on expiratory CT images (72). On the other hand, blood flow redistribution to normal lung area results in an increased vasculature and therefore increased CT attenuation in those areas. The combination of decreased attenuation in diseased areas and increased attenuation in normal areas is known as mosaic perfusion on an inspiratory CT. Theoretically, regional CT lung density measurements can be of help in the diagnosis of certain diseases that cause such changes.

**Three Dimension Airway Algorithms.** The angle of airway relative to the plane of section has been a major factor that limits the accurate measurement of airway dimensions. Multi-detector row CT scanning, which enables the acquisition of contiguous images through the whole lung and allows segmentation of the airway tree in three dimensions, is expected to overcome the error caused by airway “angling”. Hasegawa and colleagues reported an approach based on a 3D reconstruction technique (73). The automated program firstly reconstructs the 3D bronchial skeleton as distal as possible using isotropic voxel data. Then, users can identify any specific bronchus in the source images of axial, sagittal, and coronal slices. The selected bronchial pathway is automatically converted to a curved multiplaner reconstruction image and its long axis appears as a straight pathway, which allows measurement on the short-axis images exactly perpendicular to the long axis at any site. The measurements of airway dimensions are obtained based on the “full width at half-maximum principle”. The validation study using a phantom showed that measurements were accurate and reproducible for airways with an inner diameter $\geq 2$ mm. Using this approach, these authors compared measurements of the right apical and basal segmental bronchus at different branch points between the third and sixth generation. They found that airflow limitation in patients with COPD is more closely
associated with the dimensions of the more distal airways than to those of the more proximal airways, which has been subsequently confirmed by other investigators (74, 75).

More recently, Tschirren and colleagues developed an automated segmentation, skeletonization, and branchpoint matching method (76). The airway tree is identified using a seeded region and a growing algorithm, starting from an automatically identified seed point within the trachea and projecting out to the peripheral smaller airways. The binary airway tree is then skeletonized to identify the 3D centerlines of individual branches and to determine the branchpoint locations. Branchpoints are used to define airway tree segments, which are then automatically labeled by comparing to a modified standard. This new feature allows investigators to compare exactly the same airways across individuals or follow-up the same airway(s) over time. This method has been reported to reliably segment the first five to six airway generations, and the measurements have been shown to be associated with airflow obstruction in COPD subjects (74). This new approach still needs to be validated against histology.

Since the analysis of airways using three-dimensional algorithms is still in its infancy we still lack data for application in this area. An obvious practical problem with the 3D approach is that many airways can be “named” and measured, but investigators need to know how many airways or how many airway paths to measure when conducting studies (77).

It also must be noted that with any of the current approaches, we are not measuring the real “small airways”. The right apical segmental bronchus which has been selected for measurement in many studies is a large central airway. Even with a three-dimensional algorithm, Hasegawa reported that the internal diameter of the 6th generation airways was greater than 2 mm on average therefore they are not “small airways” (73) which have consistently been shown to be the site of airflow limitation (78, 79). Nakano et al has demonstrated that measuring airway dimensions in large airways allowed a rough estimation of small airway dimensions, therefore, thickening and narrowing of the large airways measured by CT may serve as surrogate for the changes in the small airways (80). This has been backed up previously by
histological data, which shows that there is a thickening of the airway wall in the large airways as well as the small airways in subjects with COPD (81).

1.5 UTILITY OF CT IN COPD

1.5.1 CT Scan in the Diagnosis of COPD

The most widely used current definitions of COPD are provided by two current clinical practice guidelines: GOLD consensus guideline and the joint statement by the American Thoracic Society and European Respiratory Society (1, 82). In both, there is only one criterion required for the diagnosis of COPD: the presence of airflow limitation after an inhaled bronchodilator. However, the diagnosis of COPD should also exclude other disorders that are associated with airflow limitation.

1.5.1.1 CT Scan in Differential Diagnosis of COPD

It has been suggested that a chest CT scan be considered in two distinct clinical scenarios: (1) to rule out other causes of airflow obstruction such as cystic fibrosis, bronchiolitis, bronchiectasis, chronic respiratory infections or their sequellae, hypersensitivity pneumonitis, asthma, congestive heart failure, lung cancer, lymphangioleiomyomatosis, sarcoidosis, and tracheobronchomalacia. (2) In patients with nonreversible airflow limitation, who do not have a clear history of environmental or occupational respiratory exposures known to cause COPD (83). Because most patients with COPD are current or past smokers, an argument could be made that never smokers who demonstrate nonreversible airflow limitation should also have a chest CT scan to exclude other disorders.(7).

1.5.1.2 CT Scan in Diagnosing Onset of COPD

…Little is known about early changes, before the onset of significant airflow limitation, that occur in the lungs of smokers who will develop COPD…

…Improved understanding of COPD during the slow progression from preclinical to moderate disease would aid
the development of strategies for primary and secondary prevention… (84)

What Changes Occur in the Lung Early Before the Onset of COPD? The GOLD committee in their original document included “Stage 0, at risk”, which was used to pool subjects who had chronic symptoms (cough, sputum production) but demonstrated normal lung function (7). However, this stage was abolished in the 2007 GOLD report, because it was unclear whether this stage provided any predictive information regarding disease progression or morbidity (1). Vestbo and Lange found that after 5 and 15 years, 13.2 and 20.5% of smokers with GOLD Stage 0 had developed COPD GOLD Stage 1 or worse and this was the case for 11.6 and 18.5% of smokers without respiratory symptoms (85). These data indicate that “GOLD stage 0” is not predictive of subjects who develop COPD. However, this conclusion has been controversial. Lindberg et al reported that GOLD stage 0 disease appears to discern those at risk for COPD, and that chronic respiratory symptoms including cough and sputum production were related to the development of COPD (86). Antonelli-Incalzi et al. showed that the health status GOLD 0 and GOLD II overlapped remarkably suggesting that the former is an abnormal group (87). Ekberg-Aronsson et al reported that among smoking men, stage 0 was associated with a significantly increased risk of all-cause mortality, suggesting that individuals at this stage may have an unfavorable prognosis (88). Recently, Maleki-Yazdi compared St. George’s Respiratory Questionnaire (SGRQ) score in 91 normal subjects and 223 COPD subjects ranging from stage 0 to stage III. They found that stage 0 subjects exhibited a significant impairment in their quality of life compared to normal individuals; furthermore, such smokers had worse health status than those in stage I (89).

Smokers at “stage 0” also demonstrate structural changes in their lungs. Data from surgically resected specimens have shown that substantial amounts of emphysema can be present in patients with normal lung function (90). In this cross sectional study the authors measured the prevalence and the severity of macroscopic emphysema on resected lung specimens in relation to pre-operative lung function (n =407). They found that the prevalence of the macroscopic emphysema, rather than its extent and severity increased as FEV1 decreased. FEV1 ranged from >110% to
<50% of the predicted value, while the prevalence of macroscopic emphysema ranged from 9% to 50% and the emphysema score ranged from 24±19 to 32±15.). Since CT is a useful tool to assess the lung parenchyma in vivo, the presence of early emphysema in smokers with normal airflow has been found in several studies (40, 91).

To date, the natural history of GOLD stage 0 is unknown, and there are no clinical measures available that assist in identifying subjects susceptible to the detrimental effects of smoking - smokers “at particular risk.” (85). The concept of a “susceptible minority” was first mentioned by Fletcher in his classic study of “the natural history of chronic bronchitis and emphysema” based on 792 working men in West London (9). Fletcher and the colleagues showed that over 8 years of follow-up, only 13% of participants experienced a rapid decline in FEV1 and ended with a FEV1 low enough to satisfy the current diagnostic criteria for COPD. Although more recent data suggests that this small fraction may have been an underestimate, the concept that only a minority of heavy smokers develop COPD has not been challenged (92).

After the revelation that small airway disease played an important role in the early stages of COPD in the 1970s (79, 93, 94), an intense period of investigation followed based on the hypothesis that early detection of peripheral airway disease would identify the susceptible smokers and therefore prevent progression. However the results failed to predict which smokers with normal lung function would go on to develop COPD because most smokers demonstrated small airway dysfunction and airway inflammation (95-97). The Lung Healthy Study, a multicenter clinical trial of smoking intervention and inhaled bronchodilator in almost 6,000 middle-aged smokers with mild-to-moderate COPD, provided the best understanding of the relationship of lung function decline with various clinical factors including tobacco use (98). This study showed that the airway hyperresponsiveness (using Methacholine reactivity) (99), repeated respiratory infections or bacterial colonization of the respiratory tract (100), and many relevant genes (101, 102) were powerful predictors of rate of loss of FEV1 in continuous smokers. However, for the factors which predicted disease onset in smokers that haven’t yet developed airflow obstruction have not yet been identified.
In light of the evidence of abnormal lung structure and lower quality of life in smokers at “stage 0”, further investigations should be performed to study the heterogeneity in these subjects with regard to the inflammatory status, biomarkers, radiographic changes of lung structure, genomics, proteomics, genetics, health status, etc, all of which could help to identify those smokers “at particular risk” of developing COPD. The significance of early emphysema in their lungs definitely needs to be clarified, which might be revealed by conducting a longitudinal study to follow up those smokers.

1.5.2 CT Scanning for Therapeutic Decision Making in COPD

1.5.2.1 CT Scanning and Lung Volume Reduction Surgery in COPD

Currently, there are two surgical therapies for COPD (bullectomy and lung volume reduction surgery, LVRS) that mandate the use of a chest CT scans to select appropriate candidates since they are superior to the chest X-rays in terms of accurately assessing the presence, extent, and distribution of bullae and emphysema (103). Pre-operative CT scanning has been shown to predict the post-operative outcomes in these subjects. Early reports of LVRS suggested those patients with severe, upper lobe emphysema (104-106), and with emphysema distributed in the rind of the upper lung benefited most from such surgery (48). The National Emphysema Treatment Trial (NETT) extended these observations and the results of the NETT form the basis for current selection criteria for LVRS such that the greatest improvement in quality of life post-surgery was in subjects with upper lobe–predominant emphysema and low exercise capacity (107, 108). In addition, some investigators also tested the cluster analysis of lower attenuation area on pre-operative CT in predicting post-operation outcomes and found that patients with large upper lobe lesions, namely small cluster analysis values, responded better to LVRS than did patients with small uniformly distributed disease, namely larger cluster analysis value (41, 42).
1.5.2.2 CT Scan in Phenotyping Subjects with COPD

COPD represents as a spectrum of overlapping diseases with important extrapulmonary consequences. The phenotypes of COPD can be broadly classified into one of three groups: clinical (e.g. “blue bloater” versus “pink puffer”), physiologic (bronchodilator responsiveness, rapid decliner, airways hyper-responsiveness, hyperinflation, etc.), and radiographic (presence, pattern and severity of emphysema, and airway abnormalities) (109). A “phenotype” describes the outward physical manifestations of a particular disease, and combines anything that is part of the observable structure, function or behavior of an individual (109). There is increasing evidence that COPD phenotypes have different clinical characteristics and therefore different outcomes and response to treatments.

Nakano and colleagues were the first to report the observation that airway wall dimensions and burden of emphysema were independently associated with FEV1, which raised the concept of “emphysema-dominant vs. airway-dominant phenotypes” (67). A summary of studies of two phenotypes of COPD are provided in the next section.

In one study, Orlandi et al (110) separated 42 COPD subjects into two groups based on whether subjects fulfilled the clinical criteria of chronic bronchitis, and they showed that the group with chronic bronchitis had thicker airway walls and the group without chronic bronchitis had higher emphysema scores. In general, the results show that compared to an emphysema-dominant group, subjects with airway-dominance have higher values of body mass index (BMI), less pack years of smoking (111), higher prevalence of dyspnea, less impaired lung function including FEV1 and DLco (67, 110-115), and more features similar to those of asthma such as wheezing, and higher serum IgE (111, 113-115), and more airway wall thickening detected on CT or chest X-ray (67, 110, 112). In addition, airway-dominant subjects showed greater reversibility of airflow limitation in response to inhaled β2-agonists and corticosteroids. In particular, the airway wall thickening in this group was associated with a higher dyspnea score, sputum eosinophilia and more reversibility of airflow limitation in response to inhaled corticosteroids (ICS) (111, 115). Airflow obstruction (i.e. FEV1/FVC) was only associated with CT emphysema measurements in the
emphysema-dominant group, while it was associated with CT assessments of both emphysema and airway wall in airway-dominant group (110).

In recently published data from the International COPD Genetics Network (ICGN), Patel et al found that emphysema was more prevalent in the siblings of probands with significant emphysema than in the siblings of probands without emphysema (OR, 2.3; 95% CI, 1.3–4.0; P <0.004). Similarly, sibling airway wall thickness was significantly associated with proband airway wall thickness (P < 0.0001) (116). These data indicate there is a significant familial concordance of airway disease or emphysema.

All of these findings give insight into the different pathogenic processes in two subgroups of COPD, which may result in differential symptoms, and responses to therapy. Despite the distinction, it is clear that the different pathological abnormalities can coexist in many patients with COPD, though one clinical phenotype, such as emphysema or airway disease may predominate (68). Although current guidelines for the treatment of COPD are based primarily on the severity of airflow obstruction rather than according to structural abnormalities on CT, the separation of these two subtypes of COPD may be useful in applying specific therapies designed to prevent or ameliorate either the airway remodeling or the parenchymal destruction. In addition, it is conceivable that specific therapy directed at one of these processes could be contraindicated in individuals in whom the other process was predominant (68, 117). In light of the familial concordance phenotypes, specific primary and secondary prevention might be more efficient if it is applied to the family members of patients who have a specific phenotype.

In most of the studies separating COPD patients into these phenotypes the, investigators defined the two subgroups according to CT emphysema score (111-113, 115, 116), and direct CT airway assessments were largely lacking since they were not crucial for the purposes of studies (i.e. airway predominant was defined as airflow obstruction without CT emphysema rather than by using measurements or airways). Airways were quantitatively assessed on selected airway(s) (67, 110), or more generally (116) in only a few studies. In addition, an important estimate of emphysema, cluster analysis hasn’t been included in the description of “two
phenotypes”. It is also noted that those studies discussing “two phenotypes” also contained a very small proportion of females (6%~12%) (110, 112-114). Although Patel’s study included an equal proportion of both genders, they didn’t provide detailed quantitative CT data (116).

Other than grouping subjects with COPD into “emphysema-dominant vs. airway-dominant” phenotypes, CT can also be used to describe distinct pathological types of emphysema. Kim et al showed that the pathologic phenotypes of emphysema also have functional associations: small airway wall thickening is more closely associated with the degree of emphysema and airflow limitation in smokers with centrilobular emphysema, whereas these associations were not found in subjects with panlobular emphysema (118). Based on these findings, the authors postulate that close association between small airway wall thickening and the centrilobular form of emphysema might justify their combination as a single target in the development of new therapies for COPD, whereas the small airways represent a secondary target when the panlobular emphysema is the major disease phenotype.

In addition, another common approach in using CT to phenotype subjects is to assess the regional distribution of emphysema (i.e. upper- vs. lower-lobe predominant distribution) (Figure 1-3), which has been largely applied in LVRS and will be discussed later in section 1.5.4 of this chapter.

1.5.3 CT Scan as One Outcome in COPD

Diminished FEV1 has a long-established association with increased mortality in COPD and the decline in FEV1 over time has been used as the “gold standard” measure of disease progression in premorbid COPD (6). The comparison of other variables to FEV1 has always been used as a tool to test the significance of the variables being tested. Although the importance of FEV1 has not been challenged, emerging evidence indicates that a variety of measures can be assessed to monitor disease progression and to evaluate response to therapies in COPD, including physiologic derangements such as exercise capacity, anemia, cachexia, reductions in lean body mass; subjective assessments such as dyspnea and health related quality of life, exacerbation frequency and severity, the course of the disease, systemic
consequences, and other lung function parameters including lung volumes, diffusing capacity and arterial blood gas tensions (119).

Longitudinal CT monitoring of emphysema and airway disease can directly detect changes in lung structure and thus has the potential to serve as a primary outcome in either observational studies or clinical trials in COPD. The ability to document progression of emphysema by CT in COPD has been confirmed by many studies using kinds of CT estimates of emphysema: such as mean lung density (120), %low attenuation area (cutoffs: -910~960HU) (25, 120-125); the 15th percentile point (25, 123-127); and CT emphysema score (128).

Furthermore, longitudinal CT data has been shown to be associated with changes in lung function, exercise ability and health status after interventions. Rogers et al revealed that after LVRS, improvement in lung function such as FEV1, residual volume, and total lung capacity had significant linear relationships with the deduction in severe emphysema estimated using CT (106). Coxson et al found that the improvement of cardiopulmonary exercise correlated with the decrease in percentage emphysema and an increase in the cluster analysis value D, both derived from CT image data (greater D value indicates less proportion of large-sized lesions) (41). In a recent study evaluating the bronchial valve placement procedure, the authors followed 57 subjects with severe emphysema who received this procedure in left or right upper lobes (129). They found that at 6 month post procedure, the lung volume in the treated upper lobes decreased significantly, while the volume of the untreated lobes increased compared to baseline, so that the total lung volume did not change with treatment. CT changes in regional lung volume and interlobar shifts in volume were associated with clinically meaningful health status improvements, but not with clinically meaningful changes in pulmonary function tests. These studies provided good examples of the application CT scanning to longitudinal and interventional studies.

Controversially, some studies have reported that longitudinal CT data of emphysema were not relevant to the longitudinal change in FEV1 (121, 122, 124, 126, 127). However, a lack of association to FEV1 doesn't necessarily mean that the measure is less meaningful than FEV1 as one parameter might not be enough to
evaluate the various aspects of disease. An alternate approach is to the magnitude of
the change in CT and lung function parameters over time. If the change per unit time
in one of the measurements is greater, then it may be more sensitive in detecting
changes in the disease than the other one. This has been best defined in α1
antitrypsin deficient subjects.

Dirksen et al conducted a small, 3-year placebo-controlled double-blind trial of
α1-antitrypsin replacement therapy in 56 ex-smokers with severe α1-antitrypsin
deficiency and moderate emphysema. Subjects were randomized to either treatment
or placebo for no less than 3 years (127). The primary parameter of this study —
annual decline in FEV1 was not significantly different between the placebo and
treatment group (mean±SEM: -25.2±22.0 vs. -26.5±15.1 ml respectively, p=0.96). However, the loss of lung density, measured using the CT percentile point method
(15th percentile point), was almost twice as great for the placebo group as compared
with the treatment group (mean±SEM: 2.6±0.41 vs. 1.5±0.41 g/L per year,
respectively, p=0.07). Power analysis showed that the protective effect of treatment
would be significant in a similar trial with 130 patients, while calculations based on
annual decline of FEV1 showed that 550 patients would be needed to show a 50%
reduction in annual decline. The sensitivity of CT to disease progression was further
demonstrated using the ratio of the mean value of change per year to the standard
error in Dowson’s study (121). They also showed that CT analysis of emphysema was
most sensitive in detecting disease progression compared to FEV1, vital capacity,
SGRQ, or physical function. In this sense, using CT assessment in clinical trials
might save money since fewer subjects would need to be recruited and/or followed for
a shorter period, which could compensate for the cost of the CT technique itself.

In fact, a large Phase II study of a gamma-selective retinoid agonist (Treatment
of Emphysema with a Gamma-Selective Retinoid Agonist (TESRA)) includes
longitudinal assessment of lung density as a pre-specified secondary endpoint.
(http://www.clinicaltrials.gov/ct2/show/NCT00413205?term5retinoic1acid1AND1
emphysemaandrank=2).

An extension of these concepts to the CT assessment of airways has been
applied in another investigation (122). Ohara and colleagues examined the annual
changes in the dimensions of the anterior, lateral, or posterior basal segmental bronchi in 38 COPD subjects over 4 years and found that the annual change in FEV1%predicted was significantly inversely associated the annual change in wall thickness/yr \((r = -0.417, p=0.009)\) and WA%/year \((r = -0.363, p=0.025)\).

All of these results support the concept that the CT scan has potential to serve as a sensitive tool for monitoring of disease progression and the evaluating therapeutic effects of new interventions in COPD. The main advantage of using FEV1 in monitoring disease is that it is a comprehensive measure of lung pathology. On the other hand, the principal advantage of CT is that it can measure emphysema and airway dimensions separately, which enables separation of their contributions to the disease, to disease progression and/or to therapeutic response. In observational studies, the use of CT scanning may allow us to better understand the natural history of COPD progression, and in interventional studies this may enable us to assess effects of new intervention on specific phenotypes. Lastly, since most of studies in this area are limited to selected subgroups of COPD subjects (i.e. a1-antitrypsin deficiency and LVRS candidates); more data are needed in unselected COPD subjects.

1.5.4 CT Scanning and the Prognosis of COPD

It has long been recognized that the baseline FEV1 is the single best indicator of survival in patients with COPD (130). However, a more recent study indicated that a composite index, the so called BODE score, incorporating FEV1, body mass index, exercise capacity measured by the distance walked in six minutes, and shortness of breath measured by the Modified Medical Research Council Dyspnea Index was a better predictor of survival than FEV1 alone (131). The BODE score is now included as an outcome measure in clinical trials of COPD (132).

It also seems intuitive that structural abnormalities such as the presence and/or severity of emphysema, and/or airway disease, should be associated with a poor prognosis in COPD. In fact, this has been proved in selected subgroups with COPD. Dawkins et al investigated the predictive potential of several baseline parameters, including CT scanning, for mortality in 170 patients with severe a1-antitrypsin deficiency.
deficiency using a Cox proportional hazards model (133). They found that those who
died had worse baseline health status (i.e. higher SGRQ scores), lung function (i.e.
lower FEV1), and quantitative emphysema on CT scans. More interestingly, upper
zone emphysema on expiratory CT scans had the best association with all cause (p =
0.001) and respiratory mortality (p<0.001), whereas baseline FEV1 (p = 0.158 all
cause, 0.015 respiratory) and KCO (p = 0.002 all cause, 0.012 respiratory) had poorer
associations with mortality. Although the detection of emphysema was only based on
two representative CT images, the result that CT scanning appeared to be superior to
lung function parameters, especially FEV1, in predicting mortality in this specific
cohort is still very encouraging.

Similarly, in NETT, investigators tested whether emphysema quantified on per-
operative CT predicted post-operative survival (42). The data showed that the
distribution of emphysema estimated on baseline CT scans was the most important
prognostic marker out of all the variables tested. Those patients with lower lobe
predominant emphysema had a 1.80 (95% CI: 1.22–2.66, p=0.003) relative risk of
post-operative mortality in a multivariate model compared with those with upper lobe
predominant emphysema.

In both scenarios, the regional distribution of emphysema on baseline CT
predicted future survival in subjects with severe stages of disease. This can be also
regarded as an extension of the use of CT in phenotyping COPD subjects according
to the predominance of regional emphysema distribution as referred at the end of
section 1.5.2.2.

1.6 CT TECHNIQUES IN LONGITUDINAL STUDIES

Moving from cross-sectional to longitudinal studies involves increased cost and
complexity but has a greater potential for discovering causal or the predictive
relationships. Longitudinal studies are advantageous when intra-individual variation is
small compared to inter-individual variation, and this is usually the case when using
CT lung density as an outcome in clinical trials (127). Furthermore, in longitudinal
studies, it is essential to minimize intra-individual variation (of repeated measures) to
maximize statistical power (134). Noise in CT mainly results from the CT image acquisition and reconstruction protocols.

1.6.1 CT Densitometry in Longitudinal Study

In longitudinal studies the CT protocols for image acquisition and reconstruction are of critical importance, especially for CT densitometry measurements. These CT image acquisition and reconstruction factors include the scanner manufacturer as well as the type of scanner used (135), the radiation exposure (kVp, mA) (136), slice thickness (136) and image reconstruction kernel (137-139). Furthermore, the impact of CT scanning protocols on quantitative CT assessments of emphysema measured using the threshold cutoff value varies when using different thresholds (136). In addition, since in reality, many studies are conducted based on a convenience sample of pre-collected CT scans, prospective control of CT scanning technique is not always possible. Every effort should also be made to test whether the combination of certain scan settings between different scanners provide similar image noise to be used in research.

Another group of factors that have an impact on CT image noise is so called “biological noise”, mainly due to variation in inspiratory lung volume during the CT scan (77). Lung volume at the time of the scan is an important characteristic to take into account, and there have been methods proposed to compensate for this, such as using spirometric gating of the CT scan (140-142), or using volume adjustment. Volume adjustments include either the simple inclusion of total lung volume at the time of the CT scan as a covariate in the statistical model (124, 125, 127, 143), or based on a physiologic model (144). Although some believe that spirometric gating of CT is necessary (142), others have shown that spirometric gating does not improve the accuracy of the results of CT densitometry measurements (140, 141). In contrast, a correction for lung volume using statistical tools has been shown to be useful especially using with modern statistical packages (125).

Lastly, the precise boundary that separates fully expanded normal lung from early emphysema on CT has not yet been agreed on as discussed earlier in this chapter. The CT cluster analysis, an estimate of the organization of low attenuation...
areas has not yet been proved as a valid measurement of microscopic emphysema (31).

1.6.2 CT Airway Measurements in Longitudinal Study

Longitudinal analysis of airways is very problematic because the effect of CT image acquisition parameters such as X-ray dose, subject position, and the lung volume during scanning are largely unknown (77). It is also unknown how to sample airways to capture disease heterogeneity and how many airways should be measured to achieve sufficient sampling and also to avoid overwhelming work.

Previously, Nakano compared the CT measurements of percent airway wall area (WA%) for the right apical segmental bronchus (RASB) with the average WA% value derived from all visible airways (other than the RASB) in the whole lung images in 20 smokers. They found that the two measures were highly correlated with the measurements of the WA% in the RASB being slightly smaller (67). Recently, Ohara et al compared the airway dimensions in the upper lobe (i.e. RASB) to the lower lobe (anterior, lateral or posterior basal segment bronchus) in 30 COPD patients and they aimed to test whether there is heterogeneity in the airway dimensions at different anatomic locations. They found no significant differences between the airway wall assessments, including wall thickness, wall area% and the wall thickness/outer diameter ratio of RASB and those of the basal segmental bronchi. They found the correlation coefficient between %WA area measurement from RASB and basal segment bronchus was nearly identical to 1 (145). They concluded that patients with COPD had no significant heterogeneity in airway dimensions at different anatomic locations. However, whether one can use one airway to represent all the airways in whole lungs is still unresolved.

1.7 RATIONALE FOR STUDY

This review of the literature revealed five important unanswered questions that needed to be addressed to make quantitative CT scanning a useful research tool in COPD. These questions formed the themes for this program of research.
CT holds promise in quantifying lung structure in COPD. Use of CT in “grouping” subjects with COPD is of potential in terms of understanding the pathogenesis of COPD and therefore may guide individual therapeutic strategy. Although there have been many clinical studies of the two subgroups of COPD (i.e. emphysema- or airway-dominant phenotype), detailed quantitative CT data such as cluster analysis of emphysema and airway dimensions are still lacking in making a comprehensive profile of the CT features of the two phenotypes.

Early detection of the onset of COPD is very crucial since the only efficient preventative treatment for COPD is smoking cessation and the effectiveness of this preventative measure diminishes as the disease progresses. Early emphysema in smokers without airflow limitation has long been observed, however, the significance of it to the subsequent development of airflow obstruction has never been investigated in a longitudinal fashion.

The lung structure-function association in COPD has been established based on cross-sectional studies. The next step moving forward would be to test this in a longitudinal fashion. CT estimates of emphysema have been shown to be able to detect disease progression and have been related to change in FEV1, mainly in selected COPD subgroups. Longitudinal data on unselected COPD subjects will provide more important information on the nature history of COPD.

In order to answer the questions above, we will be using CT to quantify emphysema; therefore we need to choose a valid cutoff to define emphysema on CT. We also need to validate CT cluster analysis as it has been shown to be sensitive to detect early loss of alveolar surface but has been shown not related to histopathological measurement of emphysema. Also, when we collect CT data for comparison across individuals or for analyzing serial CT scans in the same individual(s) overtime, we should only use those CT scans that provide similar image noise so that the quantitative CT measurements are comparable.

1.8 OBJECTIVES AND HYPOTHESES OF THE THESIS

In this thesis, I will investigate the longitudinal association between lung structure and function in COPD using CT and spirometry in heavy smokers. The
project is made possible because of access to the lung function and CT scans of a large population of smokers who were screened for possible malignancy in a prospective lung cancer screening study. Since those with suspicious lesions were followed up with repeat CT scans there is a possibility of longitudinal assessment. Nevertheless, the first methodological issue that I had to address was the comparability of scans performed with different parameters.

**Study 1.**

**Objective.** To examine the differences in CT densitometry measurements between low-dose and regular-dose CT scans, and between different manufacturers of CT scanners.

**Hypothesis.** Low-dose CT scans yield increased image noise and therefore lead to an overestimation of emphysema by CT. However, a combination of certain CT scanning and reconstruction protocols from different scanner manufacturers might provide comparable image noise.

**Study 2.**

**Objective 1.** To validate a CT estimate of pulmonary emphysema - %overinflation, by comparing it to the histopathological measurement of emphysema. %overinflation is calculated based on a dynamic inflation cutoff that is obtained for each individual by dividing the predicted total lung mass by the predicted total lung capacity.

**Objective 2.** To validate a CT estimate of pulmonary emphysema - CT cluster analysis, by comparing it to the histopathological measurement of emphysema.

**Objective 3.** To test whether the combination of CT lung density and cluster analysis can improve the association with the histopathological measurement of emphysema.

**Hypothesis.** Both CT %overinflation and CT cluster analysis are associated with the microscopic measurement of emphysema. The combination of CT lung density and cluster analysis can provide more accurate and comprehensive diagnosis of microscopic emphysema.
Study 3.

Objective 1. To test the contributions of two pathologies: emphysema and airway dimensions, to airflow obstruction in subjects with COPD.

Objective 2. To describe and compare the differences between the two phenotypes of COPD: the “emphysema-dominant” phenotype and the “airway-dominant” phenotype.

Objective 3. To describe the heterogeneity of lung structure using CT in heavy smokers who have normal spirometry but are at risk of developing COPD.

Hypothesis. In subjects with COPD, emphysema and airway remodeling both contribute to the airflow obstruction, and their contributions are independent of each other. There are distinct abnormalities in the lung structure and lung function between COPD subjects with an “emphysema-dominant” phenotype and those with an “airway-dominant” phenotype. Heavy smokers at risk to develop COPD present a wide variation in terms of lung emphysema and/or airway abnormalities.

Study 4.

Objective. To test the correlation between the early emphysema detected on baseline CT scan and the subsequent rate of decline in FEV1 in heavy smokers at risk to develop COPD.

Hypothesis. The early emphysema detected on baseline CT scan can predict rapid rate of decline in FEV1 in heavy smokers with normal airflow but at risk to develop COPD.

Study 5.

Objective. To describe the interval changes in lung structure and function (i.e. airflow) in two groups of heavy smokers initially with- or without airflow obstruction; and to test the association between the two measurements within each group.

Hypothesis. Longitudinal analysis of CT and spirometry can both detect disease progression. Deterioration in lung structure assessed using CT is associated with the worsening in airflow obstruction assessed using spirometry.
Figure 1-1. Two Common Approaches to Detect Emphysema on CT.
a) Density mask method: the area under the curve left to the cutoff value (e.g.- 950HU); b) Percentile point method: arrow head indicates the cut-off value in HU below which a predetermined 15 percentage of voxels are distributed.
Figure 1-2. “Full Width at Half Maximum” Method to Estimate Airway Wall Area on CT.
Figure 1-3. Regional Distribution of Emphysema. a) upper-lobes predominant distribution; b) lower-lobes predominant distribution.
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CHAPTER 2. THE EFFECTS OF RADIATION DOSE AND COMPUTED TOMOGRAPHY MANUFACTURER ON MEASUREMENTS OF LUNG DENSITOMETRY\(^1\)

2.1 INTRODUCTION

Quantitative Computed Tomography (CT) has become a very popular method to quantify the extent and severity of pulmonary emphysema (1-3). Previous studies have shown that CT estimates of total lung volume, mass, mean lung density and percentage of emphysema are reproducible (4-7) and are significantly correlated with both lung function test (8-11) and pathology (12-18). Furthermore, two advantages of CT image analysis are that it allows the assessment of lung structure in vivo and it is relatively easy to obtain in most centers. These are important features because it is now possible to investigate the pathogenesis of lung destruction and/or the effect of interventions on the disease process in large multi-center cohorts of subjects. Examples of these multi-center applications are the National Emphysema Treatment Trial (19) and the lung tissue repository consortium (Presented at the 2005 annual meeting of the Radiological Society of North America) in the United States and the alpha-one antitrypsin deficiency network in Europe. Additionally, many centers are actively involved in the longitudinal follow-up of suspicious lung nodules in subjects that are susceptible to lung cancer. As these subjects are also at risk for the development of emphysema there is great interest in using these cohorts for more comprehensive studies of smoking related lung disease.

However, before large-scale longitudinal studies are undertaken it is important to assess the possible effect that parameters such as scanner manufacturer, slice thickness, reconstruction algorithm, and lung volume control have on both image quality and comparability of quantitative CT data. The purpose of this study was to

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1 A version of this paper has been published:
evaluate the effect of CT radiation dose (radiograph tube current) and scanner manufacture on quantitative CT measurements of lung morphology in smokers with emphysema.

2.2 METHODS

2.2.1 Subject Selection

Subjects for this study were selected from the British Columbia Cancer Agency “Lung Health Study” (20). The study was approved by the clinical ethics review boards of the British Columbia Cancer Agency and the University of British Columbia. All subjects signed informed consent to allow their spirometry and CT images to be used for research. This is a cohort of heavy smokers who have been screened for the presence of lung nodules using “low-dose” CT scans (i.e. a CT scan with a tube current time product less than 100mAs (21). If suspicious nodules are noted the subjects receive follow-up “high-dose” CT scans for up to two years. At entry into the study, smoking status was documented and baseline spirometry was collected using American Thoracic Society criteria. Subjects also underwent periodic spirometry testing over the next 2 years. Fifty consecutive subjects who had received a baseline low dose and high dose follow-up CT and spirometry tests within 6 months of the CT scan dates were selected from this cohort to investigate the effect of radiation dose (i.e. radiograph tube current) on CT measurements of lung structure. In addition, thirty consecutive subjects who underwent baseline CT scans using a General Electric scanner and follow-up CT scans using a Siemens scanner were selected to study the effect of CT scanner manufacturer on lung densitometry measurements. Subjects were not selected for the study on the basis of lung function or the presence and extent of emphysema. There were seven subjects who were involved in both studies.

2.2.2 CT Scan Technique

All CT scans were acquired in the volume scan mode at suspended full inspiration without the use of intravenous contrast media while the subject was in the supine position resulting in more than 200 images per CT scan (range: 212-323). The
low-dose CT scans were acquired using a GE Lightspeed Ultra multi-slice CT scanner (General Electric Healthcare, Milwaukee, WI). Image acquisition parameters were an x-ray tube potential of 120 kVp, a tube current of 80 to 100 mA (48 of 50 cases with 100 mA, and 2 of 50 with 80 mA), 0.5-second gantry rotation time, pitch 1.35 (average effective mAs = 30 mAs), and 1.25-mm slice thickness; images were reconstructed using an intermediate spatial frequency reconstruction algorithm (i.e. “Standard”). The high-dose CT scans were acquired approximately six months after the low dose scans (mean [±SD] time, 0.5±0.2 years) using the same GE scanner and image parameters with the exception of the tube current, which was set at 320 mA (average effective mAs = 320×0.5/1.35=118 mAs). In the second set of subjects images were acquired first using the GE Lightspeed Ultra scanner and the high-dose (average effective mAs = 320×0.5/1.35=118 mAs) protocol followed 1.2±0.4 years later with images acquired using a Siemens Sensation 16 multi-slice scanner (Siemens Medical Solutions, Erlangen, Germany). The Siemens protocol consisted of an x-ray tube potential of 120 kVp, a tube current of 250 mA, a rotation time of 0.5 seconds and pitch 1.25 (average effective mAs = 250×0.5/1.25=100 mAs). Images were reconstructed using a slice thickness of 1 mm and an intermediate spatial frequency reconstruction algorithm (i.e. “b35f”).

2.2.3 Quantitative CT Analysis

CT scan images were analyzed using custom software (Emphy|xJ; University of British Columbia; Vancouver, BC, Canada), as previously described (13, 22, 23). Briefly, the lung parenchyma was segmented from the chest wall and large central blood vessels in all CT images using a modified border-tracing algorithm with a prior position-knowledge algorithm. Lung volume was calculated by summing the segmented pixel area in each slice and multiplying by the slice thickness to acquire the total lung volume. The mean CT attenuation of the lung (in Hounsfield units [HU]) was calculated and converted to a measure of density (in gram per milliliter) by adding 1,000 to the HU number and dividing by 1,000 (13, 22-24). The mean density of the lung was then multiplied by the lung volume to estimate lung mass. The extent of low-attenuating voxels was estimated using both the threshold (%low-attenuation
area, %LAA) and percentile techniques as previously described (5, 12-18, 25-27). The cut-off values chosen for the threshold technique were -950, -910 and -856 HU and the lowest 5th and 15th percentile points were used for the percentile technique. The mean, median, mode, standard deviation and variance of CT attenuation (HU) values in total lungs was also calculated to test the effect of dose and CT manufacturer on the pattern of HU distribution.

2.2.4 Statistical Analysis

Total lung mass, mean lung density, %Emphysema, and percentile points derived from images with different dose or CT manufacturers were tested using repeated measures analyses of variance (ANOVAs) (SPSS, version 10.0.5; SPSS, Inc; Chicago, IL) where radiograph dose and CT manufacturer were considered independent variables and total lung volume was used as a covariate to test for interactions. A probability level of 0.05 was considered to be significant.

2.3 RESULTS

2.3.1 Subject Characteristics

The subjects’ demographic data are summarized in Table 2-1. There were more males in the CT dose study than CT manufacture study and more current than former smokers in each study group. There were no significant differences (p>0.05) in the spirometry measurements between study groups.

2.3.2 Radiation Dose Study

A summary of the measurements of total lung volume, total lung mass, mean lung density, %emphysema and percentile points obtained using the low and high dose CT images are shown in Table 2-2. There were significant differences in all of the quantitative measurements (p<0.05) except the total lung volume (p=0.68). There was a significant main effect for dose on measurements of mean lung density and total lung mass (p=0.037 and p=0.024). There was also a significant interaction between radiation dose and total lung volume for mean lung density and total lung
mass (for both, p=0.035). This interaction indicates that, at the low radiation dose, a low total lung volume results in an increased mean lung density. Conversely, at the high radiation dose, an increased total lung volume results in an increased mean lung density. The same pattern was observed for total lung mass.

There was a similar main effect of dose on measurements of emphysema at the -910 HU and -856 HU threshold (p < 0.001 and p = 0.030) and an interaction between radiation dose and total lung volume (p < 0.001 and p = 0.017) as there was for mean lung density. For both cut-off values, at low lung volumes, the low dose indicated more emphysema than the high dose; at high volumes, the high dosage was suggestive of more disease. The –950 HU cut-off did not interact with lung volume, indicating that the %emphysema identified at low dose radiation was significantly higher than at high dose. The 15\textsuperscript{th} Percentile point also showed a significant main effect due to dose and an interaction between total lung volume and radiograph dose (p < 0.001 for both) indicating that at low lung volumes, a low dose identified a greater degree of emphysema than a high dose. At high volumes, the high dose was indicative of greater pathology than the low dose. The 5\textsuperscript{th} percentile point was free of this interaction and occurred at a significantly lower HU value on the low-dose images, compared with those on high-dose images.

The HU frequency distribution histogram from a representative subject shows that in a subject a CT scan performed at the same lung volume, the histogram from low-dose CT was broader than that from high-dose CT (Figure 2-1).

2.3.3 CT Manufacturer Study

The quantitative CT measurements derived from different CT manufacturers are shown in Table 2-3. Most of the measures of emphysema (-910 HU, -950 HU threshold and the 5\textsuperscript{th} and 15\textsuperscript{th} percentile points) did not differ significantly between the two scanner types. However, there was a significant main effect for scanner and an interaction between scanner type and total lung volume for mean lung density (p=0.010 and 0.023) and %Emphysema at -856 HU (p=0.005 and 0.016), such that at low lung volumes, the GE scanner yielded higher estimates of mean lung density and smaller proportion of emphysema. At high lung volumes, the Siemens scanner tended
to estimate higher mean lung densities and smaller proportion of emphysema.

The HU frequency distribution histograms (Figure 2-2) from a representative subject at a comparable lung volume were very similar between the two CT scanner manufacturers.

2.4 DISCUSSION

Quantitative CT imaging has become a very important tool to quantify the extent of emphysema in subjects with chronic obstructive pulmonary disease (COPD). However, most published studies arise from a single institution scanning a small numbers of subjects using a single CT scanner and a site specific scanning protocol. It is now apparent that to advance the knowledge of how the lung changes with time, either in a diseased state or with an intervention, quantitative CT must be applied to larger cohorts acquired from multiple centers or/and over longer time frames. Furthermore, because of increased concern over the effect of radiation exposure on subjects who are receiving numerous radiologic investigations researchers have started to decrease the radiation dose that a subject receives as part of longitudinal studies. The results from a number of studies have shown that it is important to standardize all the components of the CT scan protocol to achieve comparable CT lung densitometry measurement (4, 6, 7, 28-30).

The results from our study show that different CT protocols can make a difference in the measurements of lung density and the extent of emphysema. While the radiograph dose and manufacturer of a CT scanner does not affect the measurements of total lung volume, which are obtained using a simple segmentation of low attenuating regions (lung) from high attenuating regions (chest wall and soft tissue), the volume of the lung during the scan can have significant effects on the densitometry measurements themselves through interactions with either the radiograph dose or the type of CT scanner. We think that these interactions are due, at least in part, to the noise profile of CT images. Other investigators (6, 31, 32) have shown that image noise is directly proportional to the slice thickness and radiograph dose according to the following equation:
\[ \sigma^2 \propto \sqrt{\frac{f}{zD}} \]

Where \( \sigma \) is image noise, \( f \) is the spatial resolution of the reconstruction algorithm, \( z \) is slice thickness and \( D \) is radiograph dose. This equation indicates that as radiograph dose decreases (i.e. lower radiograph tube current, mAs), there is an increase in the quantum noise within the image. This increased noise causes broadening of the frequency distribution of the x-ray attenuation values for an object of uniform attenuation. In the central regions of CT attenuation (e.g. water, 0 HU) the broadening of the frequency distribution of radiograph attenuation values is symmetric and there is no change in the mean attenuation value. However in the extreme low or high attenuation ends of the HU value scale (e.g. emphysematous or well-inflated lung tissue) the effect of increased noise and broadening of the frequency distribution of radiograph attenuation values is no longer symmetric as the HU scale is truncated at -1000 HU. This truncation causes an interaction between factors that affect the shape of the distribution curve (i.e. radiograph dose, scanner manufacturer) and factors that affect the mean lung density (i.e. total lung volume). Therefore, since measurements are inherently imperfect, and since radiograph dose is a central part of the measurement of density a change in this mechanistic part of the measurement process will result in a different estimate of lung density. Furthermore, since measurements of emphysema rely on choosing a threshold or percentile value at the extreme end of this frequency distribution, any change in noise will result in a change of the emphysema estimate. In this study we show that when the effective radiograph dose was increased from 30 mAs to 118 mAs, the %Emphysema dropped from 10% to 5% using a cut-off value of -950 HU and the lowest 5\(^{th}\) percentile point increased from -959 HU to -938 HU. These data suggest that if lung volume and radiation dose values are not controlled in longitudinal studies they may interact through changes in image noise and impact on emphysema measurements, possibly falsely suggesting disease progression or improvement.

These data complement the recent work of Boedeker et al (33) who measured the mean transfer factor in different CT scanners and using different reconstruction kernels and showed that as the spatial frequency of the kernel increases so does the
image noise through the same mechanism as in equation 1. These data once again illustrate the need for careful CT scan parameter setting in multi-center and longitudinal studies.

Finally, it has been shown that the fundamental differences between CT scanners produced by different manufacturers can still have complicated effects on measurements of lung morphology even if standardized acquisition protocol are used (34). Our data provides important information that two modern multi-detector CT scanners using comparable scan protocols produce images with a similar noise spectrum and, therefore, have fewer interactions with lung volume. These data suggest that CT scans obtained using these scanners can be compared to assess changes in lung structure.

There are several limitations to our study. Firstly, while we were able to obtain serial CT scans on subjects, both lung volume and the CT scan parameters were changed thereby eliminating the opportunity to calculate a correction for lung volume such as that Shaker (35) has proposed. This correction factor may make it possible to account for the interaction of lung volume on the measurements of emphysema in serial CT studies and compare results between CT manufactures. However, we contend the evidence that the emphysema at the -950 HU threshold or the lowest 5th percentile decreases with decreased image noise indicates that the noise spectrum within the CT image is of primary importance in longitudinal studies. Therefore, radiation dose is the most important parameter to control in longitudinal CT emphysema studies. Secondly, as our subjects have a significant smoking history it is possible that over the duration of this study actual changes in lung density occurred due to disease improvement or progression and may have obscured or exaggerated the differences we have ascribed to CT scan parameters. However, we think that a change in the extent of emphysema is unlikely considering the short time interval between CT imaging studies (0.5±0.2 years for the dose study and 1.2±0.4 years for the manufacturer study). Furthermore, there was no significant change in the subjects pulmonary function during this timeframe so we think that the difference that we observed in the measurements of lung density are due to the CT scan parameters and not to changes in lung structure.
In summary, this study confirms previous data showing that parameters affecting signal to noise ratio have to be carefully controlled in order not to introduce a bias in the quantitative CT measurements. Furthermore, this study extends the previous studies by describing the effect that decreased radiation dose has on quantitative emphysema measurements. The current data also shows that when all the image acquisition parameters are standardized between different CT scanner manufacturers comparable measurements of lung structure are obtained. This data will assist in the interpretation of longitudinal trials performed in multi-center settings. Finally the choice of thresholds to identify emphysema is critical because although the proper validation of these thresholds now have been performed using modern CT scanners and CT protocols (36), these values are only appropriate when using the same scanner acquisition and reconstruction settings (i.e. dose and reconstruction kernel) as those in the validation study. However, if these variables are carefully controlled, valuable quantitative data can be obtained from CT scans that will yield important information on pathogenesis and intervention without exposing the subject to potentially high levels of ionizing radiation.
Table 2-1. Anthropomorphic and Spirometric Characteristics of Subjects in the Radiation-Dose and CT Manufacturer Studies

<table>
<thead>
<tr>
<th></th>
<th>Dose Study (n=50)</th>
<th>CT Manufacturer Study (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female : Male</td>
<td>18 : 32</td>
<td>17 : 13</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170.0±9.6</td>
<td>169.2±10.3</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>84.6±18.8</td>
<td>76.8±12.9</td>
</tr>
<tr>
<td>Current : Ex-smokers</td>
<td>33 :17</td>
<td>21:9</td>
</tr>
<tr>
<td>Age at 1st CT scan</td>
<td>56.6±13.1</td>
<td>60.1±5.4</td>
</tr>
<tr>
<td>Age at 2nd CT scan</td>
<td>57.2±13.2</td>
<td>61.4±5.5</td>
</tr>
<tr>
<td>Time between CT scans (yr)</td>
<td>0.5±0.2 (range: 0.3-1.5)</td>
<td>1.2±0.4 (range: 0.2-2.4)</td>
</tr>
<tr>
<td>Spirometry at 1st CT scan time</td>
<td>FEV1 (L)</td>
<td>2.9±0.9</td>
</tr>
<tr>
<td></td>
<td>FEV1%predicted</td>
<td>87.3±20.2</td>
</tr>
<tr>
<td></td>
<td>FEV1/FVC (%)</td>
<td>73.3±9.4</td>
</tr>
<tr>
<td>Spirometry at 2nd CT scan time</td>
<td>FEV1 (L)</td>
<td>3.0±0.9</td>
</tr>
<tr>
<td></td>
<td>FEV1%predicted</td>
<td>89.1±16.2</td>
</tr>
<tr>
<td></td>
<td>FEV1/FVC (%)</td>
<td>74.9±7.1</td>
</tr>
</tbody>
</table>

Values are given as the mean± SD
Table 2-2. Comparison of Quantitative CT Measurements between Low-Dose and High-Dose CT Scan Images (n=50)

<table>
<thead>
<tr>
<th>Estimates</th>
<th>Low dose</th>
<th>High dose</th>
<th>Paired Difference</th>
<th>p</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>scanner</td>
<td>GE</td>
<td>GE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>kVp</td>
<td>120</td>
<td>120</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mAs</td>
<td>40±2</td>
<td>160</td>
<td></td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Pitch</td>
<td>1.35</td>
<td>1.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective mAs</td>
<td>30±2</td>
<td>118</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Lung Volume(ml)</td>
<td>5550±1513</td>
<td>5504±1578</td>
<td>46±785</td>
<td>0.68‡</td>
<td>/</td>
</tr>
<tr>
<td>Total Lung Mass(g)</td>
<td>864±153</td>
<td>858±155</td>
<td>5±44</td>
<td>0.024</td>
<td>0.035</td>
</tr>
<tr>
<td>Mean Lung Density(g/ml)</td>
<td>0.162±0.04</td>
<td>0.163±0.03</td>
<td>-0.001±0.02</td>
<td>0.037</td>
<td>0.035</td>
</tr>
<tr>
<td>%LAA (-950HU)</td>
<td>10.0±7.4</td>
<td>5.1±5.6</td>
<td>4.9±3.9</td>
<td>0.045</td>
<td>0.739</td>
</tr>
<tr>
<td>%LAA (-910HU)</td>
<td>28.8±16.5</td>
<td>24.7±17.5</td>
<td>4.0±8.9</td>
<td>0.000</td>
<td>0.001</td>
</tr>
<tr>
<td>%LAA (-856HU)</td>
<td>58.3±17.6</td>
<td>59.3±18.5</td>
<td>-0.9±12.5</td>
<td>0.030</td>
<td>0.017</td>
</tr>
<tr>
<td>5th Percentile point</td>
<td>-958.6±20.5</td>
<td>-938.2±21.8</td>
<td>-19.4±12.2</td>
<td>0.000</td>
<td>0.085</td>
</tr>
<tr>
<td>15th Percentile point</td>
<td>-933.9±21.4</td>
<td>-912.4±26.2</td>
<td>-19.2±12.9</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Values are given as the mean±SD
%LAA: low-attenuation area with attenuation lower than certain cutoffs, expressed as percentage of total lung volume
Paired Difference: (low-dose value) – (high-dose value)
‡: Total lung volumes derived from images with low- and high-dose CT compared using paired two-tailed t-tests.
p: p value for ANOVA analysis
p*: p value testing the interaction between radiograph dose and total lung volume
Table 2-3. Comparison of Quantitative CT Measurements between CT Scan Images Acquired Using a GE Lightspeed Ultra (8 slice) and a Siemens Sensation 16 (16 slice) Scanner (n=30).

<table>
<thead>
<tr>
<th>Estimates</th>
<th>GE</th>
<th>Siemens</th>
<th>Paired difference</th>
<th>p</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>kVp</td>
<td>120</td>
<td>120</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mAs</td>
<td>160</td>
<td>125</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitch</td>
<td>1.35</td>
<td>1.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective mAs</td>
<td>118</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Lung Volume (ml)</td>
<td>5227±1627</td>
<td>5311±1459</td>
<td>84±599</td>
<td>0.45‡</td>
<td></td>
</tr>
<tr>
<td>Total Lung Mass(g)</td>
<td>828±146</td>
<td>820±143</td>
<td>-7±41</td>
<td>0.305</td>
<td>0.171</td>
</tr>
<tr>
<td>Mean Lung Density(g/ml)</td>
<td>0.17±0.04</td>
<td>0.16±0.03</td>
<td>-0.006±0.025</td>
<td>0.010</td>
<td>0.023</td>
</tr>
<tr>
<td>%LAA (-950HU)</td>
<td>3.5±3.4</td>
<td>4.0±3.6</td>
<td>0.5±2.2</td>
<td>0.954</td>
<td>0.662</td>
</tr>
<tr>
<td>%LAA (-910HU)</td>
<td>22.0±16.3</td>
<td>24.1±15.0</td>
<td>2.1±8.6</td>
<td>0.073</td>
<td>0.137</td>
</tr>
<tr>
<td>%LAA (-856HU)</td>
<td>58.2±20.1</td>
<td>62.0±17.2</td>
<td>4.9±14.4</td>
<td>0.005</td>
<td>0.016</td>
</tr>
<tr>
<td>5th Percentile point</td>
<td>-942.0±19.4</td>
<td>-941.8±19.6</td>
<td>0.2±6.5</td>
<td>0.139</td>
<td>0.135</td>
</tr>
<tr>
<td>15th Percentile point</td>
<td>-921.4±20.9</td>
<td>-922.4±20.3</td>
<td>-0.9±7.2</td>
<td>0.640</td>
<td>0.782</td>
</tr>
</tbody>
</table>

Values are given as the mean±SD.
Paired difference: (Siemens value) – (GE value)
‡: Total lung volumes derived from images with low- and high-dose CT compared using paired two-tailed t-tests.
p: p value for ANOVA analysis
p*: p testing the interaction between CT scanner manufacturer and total lung volume
Figure 2-1. Hounsfield Unit Frequency Distribution Histograms from Low-Dose and High-Dose CT Images. The HU distribution histograms derived from a representative subject who underwent both a low-dose CT scan (solid line) and a follow-up high-dose CT scan (dashed line) whose total lung volume was very similar at two CT scan time points (low-dose CT scan, 5,285 mL; high-dose CT scan, 5,381 mL). Note that the distribution of the HU is broader in the low-dose CT scan than it is in the high-dose CT scan.
Figure 2-2. Hounsfield Unit Frequency Distribution Histograms from GE and Siemens CT scanners. The HU distribution histograms derived from using a GE scanner (solid line) and a Siemens scanner (dashed line) in a representative subject whose total lung volume was very similar at the two CT scan time points (GE scanner, 4,965 mL; Siemens scanner, 4,928 mL). Note that the distribution of HU obtained from both scanners is almost identical.
2.5 REFERENCES


11. Watanuki Y, Suzuki S, Nishikawa M, Miyashita A, Okubo T. Correlation of


CHAPTER THREE. QUANTIFICATION OF LUNG SURFACE AREA USING COMPUTED TOMOGRAPHY

3.1 INTRODUCTION

The major pathological components responsible for the decrease in maximal expiratory flow that is characteristic of Chronic Obstructive Pulmonary Disease (COPD) include increase in airway resistance, through small airway remodeling, and decrease in elastic recoil secondary to parenchymal tissue destruction (1-3). Separating the contribution of each of these two components can provide better understanding of the nature history of disease, monitor the disease progression, guide the most appropriate therapeutic target in individual patients and evaluate the therapeutic intervention. The fact that pulmonary function tests cannot measure these components in isolation (4), and pathological estimates can only do so in postmortem specimens, has led to attempts to use CT scans of the thorax to measure these changes in vivo.

Emphysema is defined with histopathological criteria - an abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of the alveolar walls, and without obvious fibrosis (5). On CT scans, emphysema is characterized by areas of lung with reduced attenuation coefficients. Currently, “density mask” (6-12) and “percentile point method” (9, 10, 13) are the main objective methods to detect emphysema on CT, and variety of threshold values with each method have been shown related to histological gold standard of emphysema.

By definition, “emphysema” doesn’t take into account any fibrosis of the lung that may accompany parenchymal inflammation; however, there is increasing evidence that emphysema is also accompanied by “remodeling” of the lung parenchyma which may be associated with fibrosis (14-16). Therefore, CT lung

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1 A version of this paper has been submitted for publication:
densitometry alone might not be enough to detect and quantify emphysema because it is premised on the assumption that the loss of lung tissue and alveolar surface area that occurs is directly related to decreased density. Mishima was the first to introduce cluster analysis of lower attenuation areas which represents an assessment of the size distribution of lower attenuation clusters (17). We reasoned that cluster analysis would supplement the lung densitometry measurement in detection and quantification of emphysema since it is less likely affected by tissue deposition.

In the present study, we attempted to: 1) develop a dynamic lung inflation cutoff – the maximal lung inflation, by dividing the predicted total lung volume by the predicted lung mass for each individual, and to test the validity of this threshold value by comparing it to the histopathological standard of reference - airspace surface area per unit lung volume (SA/V); 2) to test the validity of the CT cluster analysis value D by comparing it to SA/V, since it has not been shown correlated to histological measurement of emphysema (9); 3) to test whether CT cluster analysis could supplement the lung densitometry measurement (e.g. median lung density) in quantifying emphysema in relation to the histological gold standard. We hypothesized that the combination of those two variables would be superior to either of them alone in predicting the histological measurement of SA/V.

3.2 METHODS

3.2.1 Subject Selection

This study was performed on 14 subjects who underwent either pneumonectomy (n=4) or lobectomy (n=10) for lung cancer. The study was approved by the hospital and university ethical review boards and all subjects provided written informed consent for the use of all materials and data.

3.2.2 CT Technique

All subjects received a pre-operative, non-contrast helical CT scan in the supine position at the end of full inspiration. 11 subjects were scanned using a GE LightSpeed Ultra CT scanner (General Electric Medical Systems, Milwaukee, WI) with
the following settings: 120kVp, 190 mA, 5mm slices thickness, and GE-standard reconstruction kernel; and 3 subjects were scanned using a Siemens Sensation 16 CT scanner (Siemens Medical Solutions; Erlangen, Germany) with following parameters: 120 kVp, 232 mA, 5.0mm slice thickness, and B45f reconstruction kernel. Prior to surgery, all subjects had a spirometry measurements and the Diffusing capacity (DLco) was measured by the single-breath method of Miller and associates (18).

3.2.3 Quantitative Histology

Following surgery, the resected specimen was transferred directly from the operating room to the laboratory. The specimen was inflated with Bouin fixative at a constant distending pressure of 25 cm of water and immersed in formalin overnight. Post fixation, each specimen was cut into ten slices with 5-8mm thickness in the axial plane and photographed using a digital camera (Nikon Coolpix, Nikon Corp., Japan). A grid of $2 \times 2$ cm squares was superimposed over each lung slice, one square was randomly selected and the tissue beneath it was excised, embedded in paraffin, sectioned and stained with haematoxylin and eosin, which resulted in 140 tissue sample in total. Ten random images per histology section were captured using a light microscope (Nikon Microphot) equipped with a digital camera (JVC3-CCD KY F-70, Diagnostic Instruments) at a magnification factor of four. The digital images were analyzed using stereological techniques and a custom program written for Image Pro Plus® digital-image-analysis software (Media Cybernetics) as described elsewhere (19). Briefly, each image was binarized and a grid of lines was superimposed on the image. The program automatically counts the number of intersections between the superimposed lines and the alveolar wall, as well as the number of line endpoints that fall on tissue. Surface area per unit lung volume (SA/V) was calculated using the following equations:

Surface density of the tissue-air interface: $S_v(tissue) = \frac{4}{L} x \left( \frac{\sum I}{\sum P_{tissue}} \right)$ (Equation 1)

Volume Fraction of Tissue: $V_v(tissue) = \frac{\sum P_{tissue}}{\sum P_{total}}$ (Equation 2)

Where $L$ = the length of the line, $I$ = the number of intercepts counted, $P_{tissue}$ = the number of points falling on tissue; $P_{total}$ = the number of points counted, tissue and
non-tissue.

Surface area per unit lung volume: \( SA/V = S_v (\text{tissue}) \times V_v (\text{tissue}) \)  \hspace{1cm} (Equation 3)

The shrinkage factor is determined by measuring the length of one side of the blocks prior to fixation processing and then dividing by the length of one side of the cut sections after processing. \( SA/V \) for each of the samples was corrected for shrinkage by multiplying the shrinkage factor of each sample.

3.2.4 Matching CT Images and Lung Specimens

The regions of lung where the histology samples were taken were identified on the CT image by comparing the cut surface of the gross lung specimen to the CT image (Figure 3-1). The difference in lung inflation between the \textit{in vivo} (i.e. CT images) and fixed state (i.e. histology samples) was determined by comparing the area of the cut surface on the fixed specimen to that \textit{in vivo} CT slice area. The area of the cut surface on the fixed specimen was measured using ImageJ, (Rasband, W.S., ImageJ, U. S. National Institutes of Health, Bethesda, Maryland, USA, http://rsb.info.nih.gov/ij/, 1997-2007), and the area of the lung specimen on \textit{in vivo} CT slice was measured using custom software (EmpyhlxJ, James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, Vancouver, B.C, www.flintbox.com) (20). Using EmpyhlxJ, the lung parenchyma was segmented from the chest wall and large central blood vessels in all CT images using a modified border-tracing algorithm with a prior position-knowledge algorithm. The lung area on each CT image was calculated by summing the segmented pixel area in each slice.

3.2.5 Quantitative CT

A square, size corrected for inflation, was superimposed upon the CT image and quantitative CT measurements of parenchyma were obtained as described below.

\textbf{Median Lung Density.} For each pixel within that square, the mean X-ray attenuation values (Hounsfield Unit, HU) were obtained and converted to gravimetric density (g/ml) by adding 1000 to the HU value and dividing by 1000 (21). The median CT lung density value was chosen to use from the frequency distribution curve of lung density within each square because the frequency distribution curve is skewed to the
right therefore the median value is more meaningful.

%overinflation. The degree of lung inflation (i.e. volume of gas per gram of tissue) was also calculated by subtracting the inverse of tissue density from the inverse of CT lung density (12). The density of tissue was assumed to be 1.065g/ml (22). The predicted maximal lung inflation was calculated for each individual using Equations 1, 2 and 3 (23-25).

\[ \text{Predicted TLC (ml)} = 59 \times \text{Height (cm)} - 4527 \text{ (female)} \]
\[ = 79.5 \times \text{Height (cm)} + 3.2 \times \text{Age (yr)} - 7333 \text{ (male)} \]

\[ \text{Predicted Lung Weight (g)} = 15.7 \times \text{Height (cm)} - 1697.6 \text{ (female)} \]
\[ = 15.7 \times \text{Height (cm)} - 1619.3 \text{ (male)} \]

\[ \text{Predicted Maximal Lung Inflation (ml/g)} = \frac{\text{predicted TLC}}{\text{predicted Lung Weight}} \]

The extent of overinflation for the entire lung (%overinflation) was calculated as the percentage of the lung inflated beyond the subjects’ predicted maximal lung inflation and used as an estimate of the “extent of pulmonary emphysema”.

CT cluster analysis. A cluster analysis was used to estimate the distribution of sizes of the overinflated areas within each square (17, 26). The inverse slope of the log-log relationship of the size of the clusters (number of contiguous voxels that are inflated beyond the predicted value for maximum lung inflation for that individual) versus the number of clusters of that size is the power-law exponent (D).

### 3.2.6 Statistical Analysis

The primary outcome was the histological measurement of SA/V, and the independent variables included three CT measurements: median CT lung density, %overinflation and the CT cluster analysis value D. We used a linear mixed model to incorporate the within-subject variance of the measurements since each ten samples were taken from a same lung specimen, and to examine the association between variables (27). 1). To validate the dynamic lung inflation cutoff – maximal lung inflation, we examined the association between %overinflation and SA/V. 2). To validate of the CT cluster analysis value D, we examined the association between D and SA/V. 3). To test whether CT cluster analysis could supplement the lung densitometry measurement (i.e. median lung density) in detecting and quantifying the
histological emphysema, we compared the two models for association with SA/V using either median CT lung density or the CT cluster analysis value D to the third model, which incorporated both variables using Akaike’s Information Criterion (AIC) based on the Maximum Likelihood Estimation (28). The model with the smallest AIC value is considered to be the best model. The histologically measured SA/V and the predicted SA/V values using the best model were both correlated to DL\textsubscript{CO} using simple regression analysis. Analysis was performed using SAS version 9.1 (Carey, N.C.). Statistical significance was defined at the p-value less than 5% level. Continuous variables are expressed as mean ± SD.

3.3 RESULTS

3.3.1 Subject Characteristics

The subject demographics are shown in Table 3-1. The level of airway obstruction of the subjects was relatively mild with only one subject in stage 3 according to Global Initiative for Obstructive Lung Disease (GOLD) category (29), five in stage 2 and two in stage 1, and the remaining six subjects had normal lung function.

3.3.2 Quantitative CT and Quantitative Histology Measurements

The histological measurements of SA/V and quantitative CT measurements for all 140 tissue samples and the averaged values for the 14 cases were summarized in Table 3-2. These data show that the variances for both histological and quantitative CT measurements are greater among the 140 tissue samples than that among the 14 subjects.

3.3.3 Association between Histological SA/V and Quantitative CT Measurements

Linear mixed models showed that the median CT lung density, %overinflation using maximal lung inflation threshold value, and the CT cluster analysis value D were significantly associated with histological SA/V respectively (all p<0.0001). (Figures 3-2, and 3-3).
The prediction equations of SA/V using CT lung density alone, the CT cluster analysis value D alone, and the combination of these two measurements were as following:

\[
\text{SA/V} = 4.62 + 1631.99 \times \text{median CT lung density};
\]

\[
\text{SA/V} = 168.44 + 69.21 \times \text{the CT cluster analysis value D};
\]

\[
\text{SA/V} = 6.04 + 1597.05 \times \text{median CT lung density} + 11.19 \times \text{the CT cluster analysis value D}.
\]

A comparison of the three models using the Akaike's Information Criterion showed that the third model incorporating both CT lung density and cluster analysis is the best model for predicting SA/V (the AIC was 904 for CT lung density alone, 927 for CT cluster analysis alone and 897 for the model incorporating CT lung density and CT cluster analysis).

### 3.3.4 Association between Histological and predicted SA/V and DLco

There was a similar correlation between the DL\textsubscript{CO} and either the actual histological measurements of SA/V \((r=0.608, p=0.021)\) and the CT predicted SA/V using the model incorporating both CT lung density and cluster analysis \((r=0.606, p=0.021)\).

### 3.4 DISCUSSION

The most important findings in this study are that: 1) the quantitative CT measurement of %overinflation using a dynamic cutoff - maximal lung inflation, and the CT cluster analysis value D were both valid estimates of the histological measurement of emphysema (i.e. airspace surface area per unit lung volume, SA/V); 2) the combination of CT median lung density and the cluster analysis value D provided a more accurate prediction of SA/V then either variable alone.

#### 3.4.1 Matching Regions of Interest on CT Images and Lung Specimens

One challenge for validation of CT measurements is the marked heterogeneity of the emphysematous process. Even in lungs severely affected by emphysema,
some regions may have normal architecture making sampling for pathological examination critical as shown in Figure 3-4. In many of previous validation studies, the commonly applied approach is to randomly sample multiple tissues from lungs, calculate the averaged value from these random samples to obtain one histological measurement for each subject, and comparing this value to the CT measurement obtained from the whole lung of the same subject (7, 9, 10, 12, 13). However, by that approach, the CT measurement is global and incorporates all regions, diseased or relatively normal, whereas the histological measurements are averaged from multiple samples taken from different regions of the resected lungs. In the present study, we have refined this approach by using the modified program, which enabled us to obtain CT measurements from the exact regions of the lung where the histological measurements were taken and compare the regional CT measurement to the histological measurement of the same region. We think this precise matching can provide more accurate results. Nevertheless, we cannot consider 140 tissue samples as 140 independent samples since each ten of them were taken from one same individual. Therefore, in statistical analysis, we applied a linear mixed modeling approach (the REstricted Maximum Likelihood method, REML) to account for the random effects arising from inter-individual variance, and we could obtain prediction equations at the group level by using this approach.

3.4.2 Validation of CT %overinflation and CT Cluster Analysis

The current data suggest that CT %overinflation using a dynamic threshold, maximal lung inflation, is a valid estimate of pulmonary emphysema. The maximal lung inflation is calculated by dividing the individual's predicted total lung capacity by his/her predicted lung mass, since we believe that normal lung tissue should not distend beyond its maximal inflation.

Our data also suggest that the CT cluster analysis value D, per se, is a valid CT estimate of emphysema since it significantly correlates with the histological measurement of the extent of emphysema - SA/V (Figure 3-3). This contradicts the findings in the study of Madina et al (9). We think this discrepancy might be because we chose different HU cutoffs to define the “lower attenuation clusters”. Madini et al
chose -960HU and the 1st percentile point as cutoffs whereas we used a relatively higher HU value: maximal lung inflation ranging from 5.8 ml/g to 6.2 ml/g, the corresponding HU ranging from -851~ -859HU.

3.4.3 Combination of CT Lung Density and Cluster Analysis in Quantifying Histological Emphysema

Our current data show that combining both the CT median lung density and the cluster analysis value D provides better correlation to histological measurement of SA/V than either of them alone. Basing an estimate of emphysema solely on a measure of lung density assumes that the decrease in alveolar surface area which accompanies emphysema is mirrored by a proportional reduction in lung tissue mass. Although it is clear that tissue destruction is part of the process, there is increasing evidence that emphysema is also accompanied by “remodeling” of the lung parenchyma which may be associated with fibrosis (14-16). To the extent that “remodeling”, the relationship between lung density and SA/V can be confounded. This phenomenon is illustrated in Fig 3-5. In this schematic, normal lung architecture (Normal) and two examples of “emphysema” (A and B) are shown. In example A, there is a loss of alveolar walls with a corresponding loss of lung mass. In example B, there is a similar loss of the number of alveolar walls but a thickening of the retained alveolar walls such that the mass of the lung is comparable to Normal and greater than in A although both A and B have comparable loss in the lung SA/V.

Cluster analysis of lower attenuation area is the second method to quantify emphysema by describing whether low attenuation voxels are clustered into large lesions or presented as diffuse small lesions. It has been shown that there is an inverse power law relationship between the size of the clusters and number of clusters where the slope of this relationship becomes smaller with increasing lesion size (17). We think this variable would be less likely affected by the accumulation of connective tissue since it measures clustering of low attenuation CT voxels, therefore it would be expected to be complimentary to the measure of lung density to detect emphysema when there is a tissue deposition accompanying tissue destruction. Examples of these theoretical considerations was actually observed in our data. For
example, points A and B in Figure 3-2 and 3-3 represent two samples with comparable values for SA/V and CT clusters analysis values but very different CT lung density. The examination of the histology in these two samples shown in Figure 3-6 is consistent with the theory illustrated in Figure 3-5. For these two examples the cluster analysis provides a more accurate estimate of SA/V than does lung density for sample B but the two methods are comparable for sample A.

In the present study, we did not test the combination of CT %overinflation and CT cluster analysis for its relationship to SA/V. The reason we did not do this analysis is that these two variables are highly correlated with each other. The CT median lung density and the cluster analysis value D are less tightly correlated ($r=0.67$) than are %overinflation and D ($r=0.83$), thus it is more appropriate to incorporate them into one model to test the association with SA/V. We also think that because all lung densitometry measurements are derived from the X-ray attenuation distribution curve, all such measurements will be similarly affected by the deposition of tissue (e.g. fibrosis) that may accompany emphysema in some cases. Therefore, we assume that the complementary role of cluster analysis to measurements of CT lung density will hold true for other CT densitometry measurements.

In the current study, we chose SA/V as the histological reference as previously described because it has been shown able to separate normal lung from emphysema (12, 30). Furthermore, SA/V is a very important parameter to be quantified in emphysema since the alveolar wall is site of inflammatory destruction and therefore an important target site for therapeutic intervention.

### 3.4.4 Limitations

This study has some limitations. First, while we have taken great care to orient and register the gross lung slices with the corresponding CT images, there is a slight difference in slice thickness of the lung specimen and CT images (5-8 mm vs 5 mm for CT cuts). However, the volume averaging throughout the 5 mm CT collimation could potentially offer a minor compensation for “off-centre” cuts on the gross lung slices. Secondly, there are differences in the size of structures present in the ex vivo pathological specimens as compared to the in vivo CT imaging due to blood loss,
differences in transpleural pressure on removal from the thoracic cavity, as well as tissue shrinkage imparted by chemical fixation and processing. To overcome these difficulties, anatomic landmarks present on both the pathology and CT slices were matched as shown in Figure 3-1, and corrections were made for deflation and shrinkage of the specimen. Smaller sample size and thick-slice CT scan are also shortages of the present study. Further investigation with a larger sample size and thin-slice CT image will definitely increase the power of the study.

3.4.5 Conclusions

In conclusion, we validated %overinflation using a dynamic and individualized threshold, and the CT cluster analysis value D, by comparing them to a histological reference SA/V. This study also provides a more precise and comprehensive prediction equation for histological measurement of emphysema (i.e. SA/V) by mapping the location of the histology sample to the in vivo CT and obtaining regional CT measures. Additional precision was accomplished by incorporating the CT lung density and the CT cluster analysis value D into a single analysis since cluster analysis is not affected by the tissue deposition that may accompany emphysematous tissue destruction and confound the relationship between histological SA/V and CT lung densitometry.
Table 3-1. Subjects Demographics

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67.0 ±3.1</td>
<td>61.8 – 72.0</td>
</tr>
<tr>
<td>Gender</td>
<td>5 female:9 male</td>
<td></td>
</tr>
<tr>
<td>Smoking (pack yrs)</td>
<td>59.6 ± 44.4</td>
<td>24.8 – 173.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.1 ± 7.2</td>
<td>157.0 – 180.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.6 ± 12.5</td>
<td>44.0 – 90.0</td>
</tr>
<tr>
<td>Post-FEV1%pred (%)</td>
<td>78.7 ± 16.1</td>
<td>46.7 - 114.5</td>
</tr>
<tr>
<td>Post-FEV1/FVC</td>
<td>67.5 ± 8.8</td>
<td>45.9 – 79.0</td>
</tr>
<tr>
<td>DLco %pred</td>
<td>69.7 ± 12.0</td>
<td>38.9 - 90.6</td>
</tr>
</tbody>
</table>

Post-FEV1%pred: post-bronchodilator forced expiratory flow in one second / predicted value
Post-FEV1/FVC: post-bronchodilator forced expiratory flow in one second / post-bronchodilator forced vital capacity
DLco: diffusing capacity
Table 3-2. Quantitative Histological and CT Measurements for 140 Tissue Samples and Averaged Values for 14 Cases

<table>
<thead>
<tr>
<th></th>
<th>140 tissue samples</th>
<th>14 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology-SA/V (cm²/cm³)</td>
<td>222.78 ± 91.90</td>
<td>221.26 ± 71.73</td>
</tr>
<tr>
<td></td>
<td>(39.22 ~ 464.09)</td>
<td>(83.33 ~ 359.62)</td>
</tr>
<tr>
<td>%Overinflation</td>
<td>53.85 ± 30.37</td>
<td>53.96 ± 28.44</td>
</tr>
<tr>
<td></td>
<td>(0.00 ~ 99.36)</td>
<td>(0.90 ~ 94.04)</td>
</tr>
<tr>
<td>Median CT lung density (g/ml)</td>
<td>0.14 ± 0.05</td>
<td>0.14 ± 0.04</td>
</tr>
<tr>
<td></td>
<td>(0.02 ~ 0.26)</td>
<td>(0.04 ~ 0.23)</td>
</tr>
<tr>
<td>CT cluster analysis value D</td>
<td>0.77 ± 0.54</td>
<td>0.77 ± 0.47</td>
</tr>
<tr>
<td></td>
<td>(0.08 ~ 2.48)</td>
<td>(0.23 ~ 1.60)</td>
</tr>
</tbody>
</table>

Values are given as the mean ± SD (range)
Figure 3-1. Matching CT Images and Lung Specimens. A grid is superimposed over the fixed lung slice (A), and a 2 x 2 cm square section (sample E) is randomly selected for histological processing and measurement of surface area per unit lung volume (SA/V). The corresponding region on CT is then identified (B) and lung density is measured for the region of interest using program (EmphylxJ). Note that the size of the region of interest on CT has been corrected based on lung inflation to match the size of the histological specimen.
Figure 3-2. Association between the Histological SA/V and CT-Median Lung Density. There is a significant association between the SA/V (cm$^2$/cm$^3$) measured histologically and the median CT-lung density (g/ml) measured by CT ($r=0.82$, $p<0.0001$). Data point A and B refer to samples with comparable SA/V value but very different CT density measurement (sample A: SA/V=247 cm$^2$/cm$^3$, CT density = 0.14 g/ml; sample B: SA/V=258 cm$^2$/cm$^3$, CT density = 0.24g/ml). A and B refer to the same samples in Figure 3-3, 3-5, and 3-6. All subjects are shown using different symbols.
Figure 3-3. Association between the Histological SA/V and CT Cluster Analysis Value D. There is a significant association between the SA/V (cm\(^2\)/cm\(^3\)) measured histologically and the CT cluster analysis D value (r=0.74, p<0.0001). Data point A and B have comparable SA/V value and CT low attenuation cluster value D (sample A: SA/V = 247 cm\(^2\)/cm\(^3\), D = 0.91; sample B: SA/V=258 cm\(^2\)/cm\(^3\), D = 1.17). All subjects are shown using different symbols.
Figure 3-4. Heterogeneity of Lung Tissue Destruction. Examples of hematoxylin and eosin-stained images of tissue samples taken from the same individual but different lung regions. A: Normal tissue with SA/V = 439 cm$^2$/cm$^3$, tissue density = 0.19 g/ml, B: emphysematous tissue with SA/V = 183 cm$^2$/cm$^3$, tissue density = 0.14 g/ml.
**Figure 3-5.** A Schematic Showing the Relationship between Lung SA/V and Density under Two Scenarios. The top panel represents normal lung architecture with the dimensions of each “alveolus” being 100 x 100 µ yielding a total volume of the “lung” = 16,000 µ3 with a surface area of 6,400 µ2 and a SA/V of 0.4. If we assign a mass of 10 units to each 100 µ length of “alveolar wall” this “lung” has a mass of 400 units and a density of 0.025 units/µ3 (= 400 units/16,000 µ3). In A, the volume and thickness of the “alveolar walls” remains the same as those in “normal lung architecture” but the surface area is decreased due to destruction of “alveolar walls”. In this scenario, the reduction in SA/V and density is proportional. However in scenario B, the thickness of the “alveolar walls” is doubled increasing the mass. The resultant SA/V is the same as in A whereas the density is higher than in A and even in the Normal. Thus if there is addition of tissue, the relationship between SA/V and density is disrupted.
Figure 3-6. Examples of Hematoxylin and Eosin-stained Images of Tissue Samples Corresponding to Areas A and B in Figures 3-2, 3-3 and 3-5. The tissue shown in A has a SA/V of 247 mm²/mm³ and a CT density of 0.14 g/ml while the area in B has a SA/V of 258 mm²/mm³ and a CT density of 0.24 g/ml. Thus despite comparable SA/V, there is a substantial difference in CT density due to the deposition of extracellular matrix in B. On the other hand CT cluster analysis value D, which relies solely on the size of the low attenuation areas, was comparable in these two regions (0.91 in A and 1.17 in B)
3.5 REFERENCES


22. Hogg JC, Nepszy S. Regional lung volume and pleural pressure gradient


CHAPTER FOUR. COMPUTED TOMOGRAPHIC ASSESSMENTS OF EMPHYSEMA AND AIRWAY DIMENSIONS IN SMOKERS - RELATION WITH AIRFLOW LIMITATION

4.1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible due to a variable mixture of both small airway obstruction and parenchymal destruction (1). Although associations between lung function, parenchymal destruction (2-8) and airway abnormalities (2, 6-11) have been demonstrated by CT, relatively few studies of COPD have examined the combined contribution from both mechanisms to the airflow limitation (2, 6-8). A CT cluster analysis, first introduced into COPD research by Mishima et al, described the size distribution of the emphysematous lesions (5), and showed that it was related to the extent of parenchymal destruction and diffusing capacity but not airflow (5). However cluster analysis hasn’t been well applied widely in COPD subjects other than in those with end stage disease (i.e. candidates of lung volume reduction surgery) (12, 13).

Grouping subjects who have COPD into subtypes is of great interest to investigators since it has the potential to reveal different pathogenic processes responsible for airflow limitation in individual patients, and therefore could guide specific therapy (14). There have been descriptive data on the clinical features and structural features of the two subgroups (6-8, 15-19). Many of these studies included emphysema as the structural assessment using CT, while the quantitative CT assessments of airways were only available in a few of them (6-8), and two of them were only on a selected airway (6, 7).

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1 A version of this paper will be submitted for publication:
In the present study, we used contiguous thin-slice CT to quantify parenchymal destruction and airway dimensions for comparison with spirometry in 153 heavy smokers with COPD (1), and we hypothesized that measures of the extent of parenchymal destruction, cluster analysis, and airway dimensions would be respectively related to airflow obstruction in COPD. We also hypothesized that in subjects with COPD, “airway-dominant” and “emphysema-dominant” subtypes would have distinct structural and functional characteristics. In addition, we also attempted to describe the heterogeneity of lung structures in a group of 160 heavy smokers that haven’t developed COPD.

4.2 METHODS

4.2.1 Study Population

A total of 313 heavy smokers with a smoking history of ≥30 pack years were recruited from a subgroup of the “BC-Lung Health Cohort” at the British Columbia Cancer Agency between August 2005 and January 2008 (20). This subgroup is composed of heavy smokers who took part in a lung cancer screening study and had at least one suspicious pulmonary nodule on their initial low-dose CT scan. In most of these subjects serial follow-up CT scans have been subsequently obtained at different frequencies according to the appearance of the initial nodule(s). For the purpose of the present study, we included subjects that had an additional thin-slice CT scan with regular radiation dose after the initial low-dose CT scan, together with a concurrent spirometry measurement. The smoking status (i.e. quit smoking > 9 months prior to the study) or current smoker (i.e. smoking at the time of study or quit within 9 months of study initiation) was documented at the time of spirometry.

The study was approved by the hospital and university ethical review boards and all subjects provided written informed consent.

4.2.2 Lung Function

Pre-bronchodilator spirometry was performed using American Thoracic Society guidelines (21). Forced Expiratory Volume in one second (FEV1) were expressed as
a percentage of predicted value (i.e. FEV1%predicted) calculated using published equations (22). The ratio of FEV1 to Forced Vital capacity (FEV1/FVC) was calculated using actual values and expressed as a percentage. Normal spirometry is indicated by a FEV1%predicted ≥80% and a FEV1/FVC ≥70%, and COPD was diagnosed when FEV1/FVC was less than 70%, and by further dividing into the subjects into subgroups according to the Global Initiative for Obstructive Lung Disease (GOLD) categories (1).

4.2.3 CT Technique

All CT scans were acquired in the volume scan mode at suspended full inspiration without the use of intravenous contrast media with the subject in the supine position. In 87 subjects, CT scans were acquired using a General Electric Lightspeed Ultra scanner (GE Medical System, Milwaukee, WI, USA) with the following parameters: a beam potential of 120kVp, a beam current of 320 mA, a gantry rotation time of 0.5s, a 1.25mm slice thickness, standard- and bone- reconstruction kernels. In the remaining 226 subjects, CT scans were obtained using a Siemens Sensation 16 scanner (Siemens Medical Solutions; Erlangen, Germany) with the following parameters: 120 kVp, 250mA, 0.5s, 1.0mm slice thickness, B35f- and b60f-reconstruction kernels. These two image acquisition protocols have been shown to provide comparable CT densitometry measurements (23). Images reconstructed with high-spatial frequency algorithms (GE-bone and Simense-b60f) were used to measure airway dimension.

4.2.4 Quantitative CT Analysis

4.2.4.1 Assessment of Emphysema

A quantitative analysis of the pulmonary parenchyma was performed using custom software (EmphylxJ, James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, Vancouver, B.C, www.flintbox.com) as previously described (23). Briefly, the lung parenchyma was segmented from the chest wall and large central blood vessels in all CT images using a modified border-tracing algorithm with
a prior position-knowledge algorithm. Total lung volume was calculated by summing the segmented pixel area in each slice and multiplying by the slice thickness. For each pixel, the mean CT attenuation (HU) was calculated and converted to density (g/ml) by adding 1000 to the HU number and divided by 1000 (24). The degree of lung inflation (i.e. volume of gas per gram of tissue) was also calculated by subtracting the inverse of tissue density from the inverse of CT lung density (3). The predicted maximal lung inflation was calculated for each individual using Equations 1, 2 and 3 (25-27).

Predicted TLC (ml) = 59 × Height (cm) – 4527 (female)          Equation 1
= 79.5 × Height (cm) + 3.2 × Age (yr) – 7333 (male)

Predicted Lung Weight (g) = 15.7 × Height (cm) – 1697.6 (female)      Equation 2
= 15.7 × Height (cm) – 1619.3 (male)

Predicted Maximal Lung Inflation (ml/g) = \frac{\text{predicted TLC}}{\text{predicted Lung Weight}}         Equation 3

The extent of overinflation for the entire lung (%overinflation) was calculated as the percentage of the lung inflated beyond the subjects’ predicted maximal lung inflation and used as an estimate of the “extent of parenchymal destruction”. Another classic estimate of “emphysema”: %lower attenuation area with -950HU cutoff was also calculated to describe the quantitative CT assessments in the study population (28). A cluster analysis was used to estimate the size of the overinflated areas (5). The inverse slope of the log-log relationship of the size of the clusters (number of contiguous voxels that are inflated beyond the predicted value for maximum lung inflation for that individual) versus the number of clusters of that size is the power-law exponent (D). Individuals with diffuse small clusters of overinflated lung will have a steeper slope (i.e. greater D) than individuals with larger-sized clusters.

4.2.4.2 Assessment of Airway Dimensions

Images reconstructed with a high-spatial frequency algorithms (GE-bone and Simense-b60f) were used for quantify airway dimensions. Airway wall dimensions
were measured for all visible airways cut in cross section on each CT image using the “full-width at half-maximum” method (6, 29). Validation study showed that this method results in an underestimation of airway lumen area and overestimation of wall area, and this error tends to be more prominent in smaller airways (30). However, Nakano showed the airway dimensions of the large- and intermediate-sized airways (i.e. airway with an internal perimeter greater than 0.6cm), which can be accurately assessed using HRCT scanning, reflect airway dimensions in the smaller airways, which are the most important site of airway obstruction in COPD (31). Therefore, in the present study, we only used data generated from those airways with an internal perimeter greater than 0.6 cm. CT assessments of airway dimensions included: lumen area (Ai mm²), lumen perimeter (Pi, mm), and airway wall area (Awa mm²), expressed as a percent of total area: %Awa = Awa / (Awa + Ai) × 100. A normalized airway wall estimate for each subject was created by establishing the linear relationship between Pi and the square root of Awa (√Awa) (31). √Awa for an airway with a Pi of 10mm was calculated for each subject from the regression line (i.e. √Awa at Pi10).

4.2.5 Statistical Analysis

Differences between non-COPD and COPD groups were compared using the Wilcoxon test. In 153 subjects with COPD, we first used univariate models to investigate the relationships between each of the spirometry measurements (i.e. FEV1, in ml and in %predicted, and FEV1/FVC) and each of the quantitative CT measurements of the lung parenchyma and airway dimensions respectively (i.e. %overinflation, cluster analysis, %Awa, lumen area-Ai and √Awa at Pi10). Then, we used multivariate models to include three CT variables (i.e. %overinflation, cluster analysis, and √Awa at Pi10) and to test the combination of them in association with FEV1 and FEV1/FVC. These three CT measurements were chosen because they were associated with the spirometry measurements in the previous models. To test whether the combination of multiple CT measurements can improve the association to airflow limitataion, we compared the multivariate models to the univariate models using Akaike's Information Criterion (AIC) based on the Maximum Likelihood
Estimation (32). The model with the smallest AIC value is considered to be the best model. All models were adjusted for the following covariates: age, gender, smoking status (current smokers versus ex-smokers), body mass index (BMI), and lung volume at CT scan.

We divided the 153 subjects with COPD in half at the median value of %overinflation; subjects with greater %overinflation were considered as “emphysema-dominant” phenotype and subjects with smaller %overinflation were considered as “airway-dominant” phenotype. The comparison between the two phenotypes was performed using the Wilcoxon test. Data were expressed as Mean±SD, and statistical significance was defined at the 5% level. Statistical analyses were performed using JMP software (version 7.0.1 SAS institute, Cary, NC).

4.3 RESULTS

4.3.1 Subject Characteristics

There were 160 subjects without COPD and 153 with COPD in the current study. Subjects with COPD were further classified according to the GOLD category (GOLD1: n=47, GOLD2: n=51, and GOLD3&4: n=55). Subjects without COPD were on average younger than those in COPD group (Table 4-1).

4.3.2 Comparison of Quantitative CT Assessments of Lung Structures between non-COPD Group and COPD Group

On average, compared to those without COPD, smokers with COPD had larger lung volume; lower mean lung density; greater %overinflation and %lower attenuation area (-950HU) indicating more severe parenchymal abnormality, a smaller value for D on cluster analysis (i.e. more large-sized low density clusters), and thicker airway walls (Table 4-2). On average, there were 24.3 ± 3.8 airways measured per subject.

4.3.3 Univariate and Multivariate Models Predicting FEV1 and FEV1/FVC in COPD Subjects

Table 4-3 showed associations between each of the spirometry measurements...
(i.e. FEV1, in ml and in %predicted, and FEV1/FVC) and each of the quantitative CT measurements, respectively (i.e. %overinflation, cluster analysis, %Awa, lumen area-Ai and \( \sqrt{Awa} \) at Pi10) in 153 subjects with COPD. Models were adjusted for age, gender, smoking status, BMI, and lung volume at CT scan. The parameter estimate indicated the relationship between each spirometry measurement and each CT measurement. Data showed that in COPD subjects, %overinflation was inversely associated with FEV1 (ml), FEV1%predicted and FEV1/FVC; the CT cluster analysis value D was positively associated with FEV1 (ml) and FEV1/FVC; and \( \sqrt{Awa} \) at Pi10 was inversely associated with FEV1 (in ml and %predicted), after adjusting for gender, age, BMI, smoking status and lung volume at CT scan. Neither %Awa nor lumen area showed associations with airflow variables.

Table 4-4 showed the multivariate models that included three CT variables (i.e. %overinflation, cluster analysis value D, and \( \sqrt{Awa} \) at Pi10) to test the combination of them in association with FEV1 and FEV1/FVC as they were associated with spirometry measurements in univariate models shown in Table 4-3. Data in Table 4-4 showed that %overinflation and \( \sqrt{Awa} \) at Pi10 was associated with FEV1 (in L and in %predicted) in the multivariate model, and only %overinflation was associated with FEV1/FVC in the multivariate model. The association between the CT cluster analysis value D to FEV1 (L) and FEV/FVC seen in Table 4-3 was eliminated in multivariate models. Within group analysis revealed that cluster analysis value D was significantly related to %overinflation \( (r = -0.62, p<0.05) \), and to \( \sqrt{Awa} \) at Pi10 \( (r = 0.2, p<0.05) \).

Akaike's Information Criterion (AIC) results in Table 4-5 showed the comparison between univariate (i.e. models in Table 4-3) and multivariate models (i.e. models in Table 4-4). For FEV1 (in L and in %predicted), the combination of %overinflation and \( \sqrt{Awa} \) at Pi10 yielded the smallest AIC value therefore best association. For FEV1/FVC, the %overinflation alone yielded the smallest AIC value therefore best association.

### 4.3.4 Two Phenotypes in Subjects with COPD

We divided the 153 subjects with COPD in half at the median value
of %overinflation. Of 76 subjects falling in the “airway-dominant” phenotype, 25 subjects were GOLD1, 32 subjects were GOLD2 and 19 subjects were GOLD3&4; whereas in the 77 subjects grouped as the “emphysema-dominant” phenotype, 22 subjects were GOLD1, 19 subjects were GOLD2 and 36 subjects were GOLD3&4. We compared the demographic data, spirometry data and CT data between two phenotypes in Table 4-6.

Table 4-6 showed that the airway-dominant phenotype had less impaired airflow obstruction than the “emphysema-dominant” phenotype (FEV1%predicted: 66.24% vs. 58.41%, p=0.0236; FEV1/FVC: 61.61 vs. 54.93, p<0.0001). For the quantitative CT measurements, emphysema-dominant phenotype had significantly higher total lung volume (6985.97 ml vs. 5226.73 ml, p<0.0001), decreased mean lung density (0.12 g/ml vs. 0.16 g/ml, p<0.0001), and smaller D value on cluster analysis (1.28 vs. 1.44, p<0.0001) indicating greater proportion of larger-sized lesions; however, the mean airway lumen area was larger (9.61mm$^2$ vs. 9.11mm$^2$, p<0.05).

4.4 DISCUSSION

The main findings of the present study are that: 1) In subjects with COPD, the extent of parenchymal destruction, CT cluster analysis value D and airway wall dimension all contributed to airflow obstruction; the combination of emphysema and airway dimension improve the association to FEV1; 2) In subjects with COPD, emphysema-dominant phenotype had a more severe airflow obstruction and less airway narrowing compared to the airway-dominant phenotype; 3) Compared to smokers with COPD, smokers without COPD on average had less parenchymal destruction, less larger-sized lesions, less thickened airway wall and larger airway lumen; however, the extent of parenchymal destruction varied to a wide degree that was largely overlapped with that in subjects with COPD.

Of note is that for the main analysis, we did not use a fixed cut off value to define emphysematous parenchyma such as -950HU (19.1ml gas/gram lung) (we only presented descriptive data using -950HU in Table 4-2) or -910HU (10.2 ml/gram) as has been done in many other studies (2, 7, 8). Instead we used a dynamic cutoff;
pixels which were expanded beyond the predicted maximal lung expansion (unit: ml/g) were designated as “emphysema” on CT. Maximal lung expansion is calculated individually by dividing predicted total lung capacity by predicted lung weight. The calculated maximal lung expansion in the current study was 5.89±0.21 ml/g (range: 5.28 ~ 7.67 ml/g), and the corresponding HU cutoff would be -853.33±4.29 HU (range: -883.79 ~ -839.25HU). Using such a cut off value may cause some degree of overestimation of the extent of “emphysema” as shown in Table 4-2.

4.4.1 Association between the CT Measurements of Lung Structure and FEV1, FEV1/FVC in Subjects with COPD

The association between the pulmonary emphysema and airflow obstruction in COPD has been extensively investigated using measurements which estimate the extent of emphysema (2-4, 6-8). CT cluster analysis was first introduced by Mishima et al and they reported that the cluster analysis value D represents size distribution of lower attenuation area or emphysematous lesions, with a smaller value suggesting a greater proportion of large-sized lesions (5). They found D was relevant to the extent of emphysema as it was significant correlated to %lower attenuation area and diffusing capacity, but not with FEV/FVC. They also reported that the cluster analysis value D could separate normal subjects from those with COPD even when both had similar amounts of lower attenuation area on CT, therefore this variable might be more sensitive in detection of terminal airspace enlargement that occurs in early emphysema (5). This means that for a given extent of tissue destruction the coalescence of low attenuation airspaces into either a few bigger clusters or their separation into smaller clusters makes a big difference to gas exchange. Therefore, we hypothesized that CT cluster analysis might complement the CT estimate of emphysema (i.e. %overinflation) in relation to airflow obstruction in COPD. However, despite being related to FEV1 and FEV1/FVC in univariate analysis (Table 4-3), these relationships were eliminated after including %overinflation in the multivariate models (Table 4-4). Thereby, although CT cluster analysis and CT %overinflation are theoretically distinct, the two variables are too highly interrelated to be of independent predictive value. Mishima showed the correlation between the D on cluster analysis
and the extent of emphysema was as high as 0.904 (5) and it was 0.62 in the current data.

Small airway abnormalities are known to contribute to the development of airflow obstruction in COPD based on physiological (33), histological (34-36) quantitative (6-10) and non quantitative CT measurements (2, 15). Our data confirm that airway remodeling and the extent of parenchymal destruction are associated with airflow limitation and that the combined measurement of emphysema and airway dimensions is superior to either alone in establishing this association. To our knowledge, only two published studies have addressed this issue using similar methods (6, 8). The present results extend these reports by providing data on a larger number of COPD subjects more evenly distributed across severity stages. Moreover, the airway measurements presented here were generated by sampling airways cut in cross section on continuous CT scan images. Whereas the previous reports were based either on only one airway (6), or from CT images acquired at 2cm intervals (8). We think the procedures used in the present study provide more complete sampling and avoids the bias introduced by disease heterogeneity. Furthermore we also adjusted for potential covariates such as age, gender, BMI, smoking status and CT lung volume when testing for associations between lung function and airway measurements. This adjustment is based on the previous findings that the proportion of airway wall area to total airway area increases with aging (37) and that women with COPD have more extensive airway wall remodeling compared to men (reported both on histology (38) and on CT (19)). In addition we reasoned that airway dimensions would be influenced by the degree of inspiration taken during the CT scan. Since airways are imbedded in the parenchyma, a deeper inspiration will dilate them resulting in an increase in lumen area dimension, and decrease in wall dimension.

4.4.2 “Two Phenotypes of COPD”

The concept that there are “airway-dominant” and “emphysema-dominant” phenotypes of COPD is based the observation that COPD subjects with similar airflow obstruction can have very little evidence of emphysema while others have marked emphysema. Studies also showed that two phenotypes of COPD have different
clinical characteristics and response to treatments, for example, the “airway-dominant” phenotype had higher values of body mass index (BMI), less pack years (16), higher prevalence of dyspnea, less impaired lung function including FEV1 and DLco (6, 7, 15-19), and more features similar to those in asthma such as wheezing, and higher serum IgE (16-19). In these studies the separation of the two phenotypes of COPD have relied simply on the estimate of emphysema, for example, individuals who were obstructed but had little or no emphysema on CT were deemed “airway-dominant” (6-8, 15-19). However, quantitative CT measurements of airways were lacking in many of those previous studies; only two studies presented data on the right apical segmental bronchus (6, 7) and only in a very recent study, the authors measured more airways on CT images with 2-cm intervals (8).

In the present study, we used the median value of %overinflation to separate subjects with COPD into two phenotypes, and we performed objective and quantitative measurements of airways for all visible cross-sectioned airways on thin-sliced continuous CT images. Our data are in consistent with previous findings that subjects with an airway-dominant phenotype had less impaired lung function and more preserved lung density. In addition, we showed that they had smaller lumen area and less large-sized emphysematous lesions, but the airway wall dimension was not different between two phenotypes.

The observation that “airway-dominant” phenotype consistently shows impaired lung function compared to the emphysema-dominant phenotype is consistent with the concept that the “airway disease phenotype” is an early manifestation of COPD. The concept of small airway obstruction as an early lesion in COPD is reasonable especially in light of the fact that small airways are the initial site of airway obstruction in COPD (33, 39, 40). And, it is also clear that, uncommonly, individuals develop advanced COPD based predominantly on “bronchiolitis” without progression to emphysema.

We recommend that future investigations of these “two phenotypes” of COPD include equal numbers of female and males as the majority of the current studies which have defined “two phenotypes” contained a very small proportion of female (6%~15%) (6, 7, 15, 17-19) and only one study contained relatively comparable
number of females and males (8), and our COPD population included 40% females. Because we suspect gender differences in the presentation and natural history of COPD might be accounted for in these types of measurement (41, 42).

4.4.3 CT Measurements of Lung Parenchyma in Smokers without COPD

In this study the 160 heavy smokers with normal airflow can be considered to be in the former GOLD stage 0, which were considered to be at risk for developing COPD (43). However, whether this category is of any predictive value has been controversial (1, 44). In their early study, Fletcher et al reported that only a small proportion of heavy smokers who initially have normal lung function develop rapid decline in FEV1 and eventually develop COPD and that the presence of symptoms was of no value in predicting who would experience this decline (45). Recently, Maleki-Yazdi compared St. George’s Respiratory Questionnaire (SGRQ) score in 91 normal subjects and 223 COPD subjects ranging from stage 0 to stage III, they found that stage 0 subjects exhibited a significant impairment in their quality of life compared to normal individuals; furthermore, such smokers even had worse health status than those in stage I (46). Interestingly we found that, although on average smokers with normal spirometry (i.e. formerly GOLD stage 0) had on average less parenchymal destruction (i.e. %overinflation) compared to those with COPD; the range of this abnormality was greater in this group these smokers presented a wider range of this anomaly indicating that some had parenchymal destruction similar to that found in subjects with COPD (Table 4-2). The finding is consistent with previous reports showing a substantial amount of emphysema in smokers with normal lung function. Furthermore, Hogg et al concluded that it was the prevalence of the emphysema, rather than the extent and severity of these lesions, that increased as FEV1 decreased (FEV1 range from >110% to <50% of the predicted value, the prevalence of macroscopic emphysema ranged from 9% to 50% and emphysema score ranged from 24±19 to 32±15, correspondingly) (47). New studies based on longitudinal observations of the same individual are required to determine whether the increased prevalence of emphysema will serve as a biomarker that will identify the minority who will progress to end stage disease.
4.4.4 Limitations

There are several limitations in this study. First only demographic data, FEV1, FEV1/FVC were available from these subjects and other variables such as total lung capacity (TLC), functional residual capacity (FRC), and diffusing capacity (DLco) were not measured. Similarly no attempt was made to evaluate their clinical information with respect to symptoms and signs, or to measure either the local lung or systemic inflammatory response due to the limited access to those data. Secondly, we could only limit the error involved in using the “full width at half maximum” method (48), by analyzing data on large- and intermediate-sized airways, of which, the error is small.

4.4.5 Conclusions

In conclusion, quantitative CT data presented here reveals that parenchymal destruction and airway wall thickening are associated with airflow limitation in COPD. There are distinct demographic, functional and structural characteristics of "airway-dominant" and "emphysema-dominant" subtypes of COPD; "airway-dominant" might represent the early phase in COPD. Last but not least importantly, smokers without COPD display a wide variation of parenchymal destruction; the significance of it needs further investigation.
<table>
<thead>
<tr>
<th></th>
<th>non-COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (F:M)</td>
<td>74 : 86</td>
<td>61:92</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>60.0±6.5(45.3~72.9)</td>
<td>63.3±7.3(45.8~79.8)**</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.5±9.8(149.9~195.6)</td>
<td>172.4±10.1(137.2~198.1)</td>
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<tr>
<td>BMI (kg/cm²)</td>
<td>27.8±4.1(18.7~43.5)</td>
<td>27.3±4.6(18.1~48.2)</td>
</tr>
<tr>
<td>ex-smoker: current smoker</td>
<td>40:120</td>
<td>43:110</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
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<tr>
<td>FEV1actual (L)</td>
<td>3.1±0.8(1.8~5.7)</td>
<td>2.0±0.8(0.6~4.6)**</td>
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<tr>
<td>FEV1%predicted (%)</td>
<td>98.7±13.5(80.0~141.7)</td>
<td>62.3±22.0(14.8~108.1)**</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>78.0±4.2(70.1~88.0)</td>
<td>58.3±10.0(16.0~69.3)**</td>
</tr>
</tbody>
</table>

Values are given as the mean±SD (range).

**: p<0.001 vs. non-COPD group.
Table 4-2. Comparison of CT Assessments between Non-COPD and COPD Groups

<table>
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<tr>
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<th>non-COPD</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>total lung volume (ml)</td>
<td>5113±1351(2608~9861)</td>
<td>6112±1527(3060~10681)**</td>
</tr>
<tr>
<td>mean lung density</td>
<td>0.17±0.03(0.12~0.24)</td>
<td>0.14±0.03(0.07~0.23)**</td>
</tr>
<tr>
<td>%overinflation</td>
<td>58.98±16.45(15.91~83.84)</td>
<td>71.78±12.99(24.49~89.02)**</td>
</tr>
<tr>
<td>%LAA (-950HU)</td>
<td>2.99±2.66</td>
<td>12.20±11.00**</td>
</tr>
<tr>
<td>cluster analysis, D</td>
<td>1.47±0.20(1.16~2.15)</td>
<td>1.36±0.17(1.10~2.42)**</td>
</tr>
<tr>
<td>%Awa</td>
<td>72.92±3.21(66.07~83.84)</td>
<td>73.86±3.52(66.28~85.29)*</td>
</tr>
<tr>
<td>lumen area, Ai (mm²)</td>
<td>8.99±2.66(3.18~18.03)</td>
<td>9.37±3.31(2.75~20.85)</td>
</tr>
<tr>
<td>√Awa at Pi10 (mm)</td>
<td>4.37±0.26(3.90~5.14)</td>
<td>4.51±0.33(3.85~5.65)**</td>
</tr>
</tbody>
</table>

Values are given as the mean±SD (range),

%LAA (-950HU): percent lower attenuation area with a X-ray attenuation below -950HU;

%Awa = Awa/(Awa+Ai) × 100%; √Awa at Pi10: √Awa for an airway with a Pi of 10mm;

*: p<0.05 vs. non-COPD group;

**: p<0.001 vs. non-COPD group.
Table 4-3. Univariate Models Predicting FEV1 and FEV1/FVC (each model including 1 spirometry measurement and 1 CT measurement)

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>%overinflation</th>
<th>cluster analysis, D</th>
<th>%Awa</th>
<th>Lumen area, Ai (mm²)</th>
<th>√Awa at Pi10 (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1, L</td>
<td>-0.033**</td>
<td>1.228**</td>
<td>-0.017</td>
<td>-0.034</td>
<td>-0.492*</td>
</tr>
<tr>
<td>FEV1%predicted</td>
<td>-0.557**</td>
<td>19.940</td>
<td>-0.693</td>
<td>-0.844</td>
<td>-17.002**</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>-0.268**</td>
<td>12.410*</td>
<td>-0.159</td>
<td>-0.181</td>
<td>-3.072</td>
</tr>
</tbody>
</table>

%Awa = Awa/(Awa+Ai) × 100%; √Awa at Pi10: √Awa for an airway with a Pi of 10mm; Models were adjusted for gender, age, BMI, smoking status and lung volume at CT scan. *: p<0.05, **: p<0.01
Table 4-4. Multivariate Models Predicting FEV1 and FEV1/FVC (each model including 1 spirometry measurement and 3 quantitative CT measurements)

<table>
<thead>
<tr>
<th>Term</th>
<th>FEV1 (L) estimate</th>
<th>p value</th>
<th>FEV1%pred estimate</th>
<th>p value</th>
<th>FEV1/FVC estimate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>6.191</td>
<td>&lt;.0001</td>
<td>182.784</td>
<td>&lt;.0001</td>
<td>83.733</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.064</td>
<td>0.545</td>
<td>6.794</td>
<td>0.031</td>
<td>1.359</td>
<td>0.316</td>
</tr>
<tr>
<td>age (years)</td>
<td>-0.031</td>
<td>0.000</td>
<td>-0.489</td>
<td>0.048</td>
<td>-0.024</td>
<td>0.822</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>-0.015</td>
<td>0.271</td>
<td>-0.262</td>
<td>0.523</td>
<td>0.087</td>
<td>0.624</td>
</tr>
<tr>
<td>Current smoker=Yes</td>
<td>-0.016</td>
<td>0.822</td>
<td>0.643</td>
<td>0.761</td>
<td>0.482</td>
<td>0.599</td>
</tr>
<tr>
<td>Lung volume on CT</td>
<td>0.001</td>
<td>&lt;.0001</td>
<td>0.007</td>
<td>0.028</td>
<td>0.000</td>
<td>0.851</td>
</tr>
<tr>
<td>%overinflation</td>
<td>-0.036</td>
<td>&lt;.0001</td>
<td>-0.616</td>
<td>0.011</td>
<td>-0.247</td>
<td>0.018</td>
</tr>
<tr>
<td>cluster analysis, D</td>
<td>-0.214</td>
<td>0.685</td>
<td>-3.522</td>
<td>0.820</td>
<td>2.503</td>
<td>0.710</td>
</tr>
<tr>
<td>√Awa at Pi10 (mm)</td>
<td>-0.535</td>
<td>0.007</td>
<td>-17.732</td>
<td>0.003</td>
<td>-3.488</td>
<td>0.166</td>
</tr>
</tbody>
</table>

√Awa at Pi10: √Awa for an airway with a Pi of 10mm;
Models were adjusted for gender, age, BMI, smoking status and lung volume at CT scan.
Table 4-5. Akaike’s Information Criterion (AIC) Results

<table>
<thead>
<tr>
<th></th>
<th>Univariate Models</th>
<th>Multivariate Models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%overinflation</td>
<td>cluster analysis, D</td>
</tr>
<tr>
<td>FEV1, L</td>
<td>336*</td>
<td>354</td>
</tr>
<tr>
<td>FEV1%predicted</td>
<td>1366*</td>
<td>1372</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>1104*</td>
<td>1110*</td>
</tr>
</tbody>
</table>

√Awa at Pi10: √Awa for an airway with a Pi of 10mm;
*: significant in univariate models;
†: multivariate model included %overinflation and √Awa at Pi10 (mm) for testing the association with FEV1(in L and %predicted);
‡: multivariate model included %overinflation for testing the association with FEV1/FVC.
Table 4-6. Comparison between Two Phenotypes in Subjects with COPD

<table>
<thead>
<tr>
<th></th>
<th>airway-dominant (n=76)</th>
<th>emphysema-dominant (n=77)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, % of group</td>
<td>36, 47%</td>
<td>25, 32%</td>
<td>0.1161</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>62.75±7.14</td>
<td>63.93±7.40</td>
<td>0.3171</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.47±10.25</td>
<td>175.30±9.05</td>
<td>0.0002</td>
</tr>
<tr>
<td>BMI (kg/cm^2)</td>
<td>27.79±5.21</td>
<td>26.80±3.82</td>
<td>0.4801</td>
</tr>
<tr>
<td>Ex-: current smoker</td>
<td>25:51</td>
<td>18:59</td>
<td>0.1904</td>
</tr>
<tr>
<td>pack years</td>
<td>50.12±17.30</td>
<td>51.05±17.90</td>
<td>0.9008</td>
</tr>
<tr>
<td>FEV1actual (L)</td>
<td>1.98±0.73</td>
<td>1.93±0.94</td>
<td>0.3236</td>
</tr>
<tr>
<td>FEV1%predicted (%)</td>
<td>66.24±20.00</td>
<td>58.41±23.35</td>
<td>0.0236</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>61.61±7.23</td>
<td>54.93±11.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total lung volume (ml)</td>
<td>5226.73±1198.29</td>
<td>6985.97±1301.98</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean lung density</td>
<td>0.16±0.02</td>
<td>0.12±0.01</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>cluster analysis, D</td>
<td>1.44±0.19</td>
<td>1.28±0.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>%Awa</td>
<td>74.00±3.53</td>
<td>73.82±3.52</td>
<td>0.3052</td>
</tr>
<tr>
<td>Lumen area, Ai (mm^2)</td>
<td>9.11±3.73</td>
<td>9.61±2.83</td>
<td>0.0436</td>
</tr>
<tr>
<td>√Awa at Pi10 (mm)</td>
<td>4.50±0.34</td>
<td>4.51±0.32</td>
<td>0.3694</td>
</tr>
</tbody>
</table>

%Awa = Awa/(Awa+Ai) × 100%; √Awa at Pi10: √Awa for an airway with a Pi of 10mm; Values are given as the mean±SD.
4.5 REFERENCES


9. Coxson HO, Quiney B, Sin DD, Xing L, McWilliams AM, Mayo JR, Lam S. Airway wall thickness assessed using computed tomography and optical coherence...


43. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD)

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5.1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory lung disease caused by the inhalation of toxic particles and gases that results in the destruction of the lung parenchyma, and remodeling of the small airways (1). Tobacco smoking is the most important risk factor for COPD, but the fact that only a minority of smokers develop COPD strongly suggests that the host response is equally as important in the pathogenesis of this condition (2, 3).

That only a susceptible minority of smokers develop COPD was discovered in a classic study of “the natural history of chronic bronchitis and emphysema” based on 792 working men in West London (2). This study showed that over 8 years of follow up only 13% of participants experienced a rapid enough decline in Forced Expiratory Volume in one second (FEV1) to have a final FEV1 low enough to satisfy the current diagnostic criteria for COPD. (2) Although more recent data suggests that this small fraction may have been an underestimate, the concept that only a minority of heavy smokers develop COPD has not been challenged (3). By the late 1960s and early 1970s it was recognized that the airflow limitation that defines COPD is caused by a combination of increased resistance in the small conducting airways, and decreased parenchymal elasticity caused by emphysematous destruction (4, 5). Although many tests have been designed to detect small airway abnormalities at an early and hopefully reversible stage, they have been largely abandoned because they failed to identify the minority of smokers with normal expiratory flows that go on to develop COPD (6, 7).

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1 A version of this paper has been submitted for publication:

The introduction of non-invasive quantitative imaging of both emphysematous lung destruction and airways’ remodeling has provided a fresh approach to detect changes in the anatomy of the peripheral lung. Using these imaging approaches, investigators have shown that persons with normal lung function may have emphysematous destruction in their lungs (8, 9). These observations led to the hypothesis that early emphysematous destruction might be associated with a rapidly decline in FEV1 that results in clinically important levels of COPD severity. The present study used computed tomography (CT) scans from subjects participating in a lung-cancer screening study to quantify the inflation of the lung parenchyma and airway dimensions and correlated these results with serial spirometry to establish a subject’s individual decline in FEV1.

5.2 METHODS

5.2.1 Subjects Selection

Subjects in the current study were from the British Columbia Cancer Agency “BC-Lung Health Cohort” (10). The cohort is composed of smokers who had a normal spirometry at baseline (i.e. FEV1 no less than 80% of predicted value; the ratio of FEV1 to Forced Vital Capacity, FEV1/FVC, no less than 70%). These subjects had at least two spirometry measurements over at least 0.5 years apart; and a baseline CT scan obtained using either GE (GE Medical System, Milwaukee, WI, USA) or Siemens scanner (Siemens Medical Solutions; Erlangen, Germany). The study was approved by the University of British Columbia Clinical Ethics Review board and all subjects provided informed written consent for the use of all materials and data.

5.2.2 Lung Function

Spirometry was performed using American Thoracic Society guidelines (11). FEV1 were expressed as a percentage of predicted value (i.e. FEV1%predicted) calculated using Crapo’s equations (12). FEV1/FVC was calculated using actual value. The annual change in FEV1%predicted (i.e. \( \Delta \text{FEV1\%predicted/yr} \)) was
calculated for subjects with 2 visits as (FEV1%predicted at T1 - FEV1%predicted at T0) / follow-up yrs. For subjects with more than two visits, ∆FEV1%pred/yr was the slope of the regression line, in which all the available FEV1%predicted measurements were plotted against age. A negative value of ∆FEV1%predicted/yr indicates worsening of the lung function.

5.2.3 CT Technique

All CT scans were acquired in the volume scan mode, at suspended full inspiration, without the use of intravenous contrast media, and with subject in the supine position. These CT scans were acquired using a GE scanner (Lightspeed Ultra, 120kVp, 160mAs, 1.25mm slice thickness, and standard reconstruction kernel) in 36 cases (25%); using a Siemens scanner (Sensation 16, 120 kVp, 125mAs, 1.0mm slice thickness, and B35f reconstruction kernel) in 107 cases (75%). These two image acquisition protocols have been shown to provide comparable CT densitometry measurements (13).

5.2.4 Quantitative CT Analysis

5.2.4.1 Assessment of Emphysema

A quantitative analysis of the pulmonary parenchyma was performed using custom software (EmphylxJ, James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, Vancouver, B.C, www.flintbox.com) as previously described (13). Briefly, the lung parenchyma was segmented from the chest wall and large central blood vessels in all CT images using a modified border-tracing algorithm with a prior position-knowledge algorithm. Total lung volume was calculated by summing the segmented pixel area in each slice and multiplying by the slice thickness. For each pixel, the mean CT attenuation (HU) was calculated and converted to density (g/ml) by adding 1000 to the HU number and divided by 1000 (14). The degree of lung inflation (i.e. volume of gas per gram of tissue) was also calculated by subtracting the inverse of tissue density from the inverse of CT lung density (15). The predicted
maximal lung inflation was calculated for each individual using Equations 1, 2 and 3 (16-18).

**Equation 1**

\[
\text{Predicted TLC (ml)} = 59 \times \text{Height (cm)} - 4527 \text{ (female)}
\]

\[
= 79.5 \times \text{Height (cm)} + 3.2 \times \text{Age (yr)} - 7333 \text{ (male)}
\]

**Equation 2**

\[
\text{Predicted Lung Weight (g)} = 15.7 \times \text{Height (cm)} - 1697.6 \text{ (female)}
\]

\[
= 15.7 \times \text{Height (cm)} - 1619.3 \text{ (male)}
\]

**Equation 3**

\[
\text{Predicted Maximal Lung Inflation (ml/g)} = \frac{\text{predicted TLC}}{\text{predicted Lung Weight}}
\]

The extent of overinflation for the entire lung (% overinflation) was calculated as the percentage of the lung inflated beyond the subjects' predicted maximal lung inflation and used as an estimate of the "extent of parenchymal destruction". Zonal predominance was calculated using equation 4:

\[
\text{zonal predominance} = \frac{\text{upper overinflation (} \% \text{ of total upper lung)}}{\text{lower overinflation (} \% \text{ of total lower lung)}}
\]

The distribution was considered “upper zone predominant” if the result of Equation 4 was greater than “1”, and considered “diffuse” or “lower zone predominant” if it equaled to “1” or less than “1”, respectively. A “cluster analysis” was used to estimate the size of the overinflated areas (9). The inverse slope of the log-log relationship of the size of the clusters (number of contiguous voxels that are inflated beyond the predicted value for maximum lung inflation for that individual) versus the number of clusters of that size is the power-law exponent (D). Individuals with diffuse small clusters of overinflated lung will have a steeper slope (i.e. greater D) than individuals with larger-sized overinflated regions.

**5.2.4.2 Assessment of Airway Dimensions**

Airway wall dimensions were measured for all visible airways on each CT image using the “full-width at half-maximum method” (19). Airway dimensions included: lumen area (Ai), lumen perimeter (Pi), and airway wall area (Awa) expressed as a percent of total area: Awa% = Awa / (Awa + Ai). A normalized airway wall estimate for each subject was created by establishing the linear relationship
between Pi and the square root of Awa (√Awa) (20). √Awa for a standardized airway with a Pi of 10mm was calculated for each subject from the regression line (i.e. √Awa at Pi10).

5.2.5 Statistical Analysis

Statistical analyses were performed using JMP software (version 7.0.1 SAS institute, Cary, NC). The primary outcome was ∆FEV1%predicted/yr. Covariates included: 1) demographic factors including age, sex, body mass index (BMI), current smoking status (i.e. current- or ex-smoker), and pack years; 2) baseline spirometry measurements (i.e. FEV1%predicted and FEV1/FVC); and 3) baseline quantitative CT measurements of overinflated lung (i.e. %overinflation, zonal predominance and cluster analysis) and airway dimensions (i.e. Ai, %Awa and √Awa at Pi10). In multiple regression modeling, we used a stepwise approach for variable selection. To illustrate the relationship between ∆FEV1%predicted/yr and baseline %overinflation, we divided 143 subjects into quartiles according to baseline %overinflation (i.e. quartile 1 has the least %overinflation) and compared ∆FEV1%predicted/yr cross four quartiles using Wilcoxon test. A linear mixed effects modeling approach was used to calculate the annual decline in FEV1(ml/yr) for two groups (i.e. quartile 1,2 and quartile 3,4), respectively (21). A probability level of 0.05 was considered to be significant.

5.3 RESULTS

5.3.1 Baseline Characteristics

The study consisted of 143 heavy smokers. Subject demographic data are given in Table 5-1. There were similar female and male subjects, and more EX-smokers than current-smokers in this study. Descriptive characteristics of the quantitative CT assessments of lung parenchyma and airway dimensions at baseline are given in Table 5-2. There was 76.2% (102/142) of subjects presented an upper zone predominant distribution of parenchyma overinflation.
5.3.2 Follow-up Measurements of FEV1

Seventy-two subjects were seen twice over 2.3±0.8 years; 49 were seen 3 times over 2.3±1.1 years; and 22 were seen more than 3 times over 3.3±1.4 years. The average number of follow-up visits was 2.7±0.8 (range: 2~5 visits) over 2.5±1.1 years (range: 0.5~6.4yrs). ∆FEV1%predicted/yr observed over this time period averaged -2.3±4.7%/yr (range -23.0 ~ +8.3%/yr).

5.3.3 Risk Factors Associated with Annual Change in FEV1%predicted

Stepwise multiple regression analysis revealed that baseline CT %overinflation, FEV1%predicted, FEV1/FVC, and gender (male) independently predicted ∆FEV1%predicted/yr (coefficients were -0.04; -0.16; 0.19; and -0.73 respectively, all p<0.05). This indicates that there was a greater annual decline in FEV1%predicted if a subject is male, has a higher %overinflation, a low FEV1/FVC ratio, and a high FEV1%predicted at baseline. ∆FEV1%predicted/yr was associated with cluster analysis only in simple linear regression analysis (r=0.14 p<0.05). No relationship was found between ∆FEV1%predicted/yr and airway dimensions, zonal distribution of overinflation, age, BMI, smoking habit, and pack years. The comparison of ∆FEV1%predicted/yr across the four quartiles is given in Table 5-3 and Figure 5-1.

5.4 DISCUSSION

The present results show that a quantitative CT-based estimate of the extent of lung inflated beyond individual predicted maximal lung expansion (i.e. %overinflation) is an independent predictor of a rapid decline in lung function over time in smokers with normal baseline spirometry. Moreover, the group with a greater %overinflation at baseline established a rate of FEV1 decline beyond the normal values predicted by Fletcher et al (Figure 5-2) (2). These results suggest that when the FEV1 is normal, a quantitative structural assessment by CT can distinguish the smokers who will develop COPD from those who will not.
5.4.1 %Overinflation Predicts the Decline in FEV1

The possibility that emphysematous destruction is present in smokers with a normal FEV1 was controversial prior to the introduction of the CT scan (22-24) but recent studies have established that substantial amounts of “emphysema” can be present in persons with a normal FEV1 (8, 9, 25). In current study, we used standard prediction equations for total lung capacity and lung weight to estimate maximal normal lung inflation for each individual. The average value of predicted maximal normal inflation of the whole group was 5.9±0.2 ml/g (range: 5.3~6.5), which is equivalent to a corresponding HU cutoff of -830±5.3 (range: -846~ -811). This is substantially different from the fixed cutoffs of -950 HU or 19.1 ml gas/gram; or -910HU or 10.2 ml/gram currently used to define emphysema on CT. Importantly, we do not claim that the minimally overinflated tissue identified by this procedure has exclusively undergone emphysematous destruction because we have no direct evidence that alveolar dimensions are increased or that lung tissue has been destroyed in these regions. However, we postulate that the inflammatory and tissue-remodeling processes that initiate airway obstruction and emphysematous destruction in COPD are present in this tissue.

The primary lesion of the centrilobular form of emphysema most commonly found in smokers was first described in the respiratory bronchioles of the acinus near the center of the secondary lobule (26, 27). Interestingly, these early reports concluded that the dilatation and destruction of the respiratory bronchioles that defines this form of emphysema is preceded by disease in the terminal and pre-terminal bronchioles. Therefore, we strongly suspect that the minimal overinflation observed in the subjects who go on to develop a more rapid decline in FEV1 may be caused by either a minimal loss in the elastic recoil properties of the gas exchanging tissue and/or an increase in the resistance of the terminal conducting airways prior to the onset of true emphysematous destruction.

Only a small number of studies have examined the relationship between quantitative CT measurements of lung parenchyma and subsequent decline in lung function. In one of these, Remy-Jardin et al correlated thin section CT images with
pulmonary function in 111 smokers and non-smokers and reported that subjects with emphysema visualized by radiologists (i.e. emphysema score) at baseline had a more rapid decline in lung function than did those with normal CT scans (28). On the other hand, Parr et al found no relationship between baseline presence of emphysema on CT to the subsequent decline in FEV1 in 56 COPD patients (29). Stolk et al also reported that the annual change in FEV1 was independent of the severity of baseline emphysema in 87 smokers and non-smokers (30). Those studies recruited many subjects who already have an abnormal FEV1 at baseline, and this contrasts sharply from the present study that was specifically designed to determine whether quantitative CT might identify the smokers with a normal FEV1 and FEV1/FVC that subsequently develop COPD.

In contrast to the extent of overinflation, the size and location of the overinflated regions, as assessed by cluster analysis and zonal predominance was less helpful in identifying those “susceptible smokers”. Although cluster analysis was associated with $\Delta$FEV1%predicted/y in simple regression analysis, it was not significant using the multiple regression model suggesting that this parameter is related to the extent of overinflation and therefore, not independently associated with the outcome. Therefore, the extent of overexpansion is more important in predicting the future decline FEV1 and is consistent with the concept that widespread terminal and respiratory bronchiolitis precede the formation of clusters of emphysematous destruction in smokers developing COPD.

5.4.2 Airway Dimensions and the Decline in FEV1

Nakano et al demonstrated that CT measurements of thickening and narrowing of the relatively large airways serve as surrogate for the pathologic changes in the small airways that are not measurable on CT (20). However, in the present study, we failed to identify a relationship between the CT measurements of airway dimensions and the decline in FEV1%predicted. There are several possible reasons for this observation. Most importantly, the differences in airway dimensions that accompany a relatively small range of lung function are probably beyond the resolution of CT. Although many investigators have shown relationships between airway wall
dimensions and airflow obstruction in cross-sectional studies, the range of lung function in those studies was much larger than in the present study (19, 31). Secondly, quantitative histological studies have shown that statistically significant airway wall thickening does not become apparent until relatively severe stage of disease (GOLD stage 3 and 4) with an FEV1%predicted <50 (32). Finally, the method we used for measuring airway dimensions may not be optimal for assessing subtle changes. Hasegawa et al used volumetric scanning to show that airflow limitation in COPD is more closely related to the dimensions of the distal smaller airways (i.e. 5th and 6th generations) than those of proximal larger airways (i.e. 3rd and 4th generations) (33). Coxson et al recently confirmed Hasegawa’s results and extended them by showing that imaging devices, with higher spatial resolution such as optical coherence tomography, are more sensitive at detecting changes in airway wall dimensions compared to thin-slice CT (34).

5.4.3 Initial FEV1 and the Rate of Decline in FEV1

Fletcher et al were the first to show a relationship between level of the initial FEV1 and its subsequent decline and referred to it as “horse racing” effect: where the horses that are out in front get there because they are the fastest (2). However, Burrows et al observed a relationship between ΔFEV1 and initial FEV1 that is opposite to Fletcher’s, such that the higher the level of initial FEV1, the more negative the ΔFEV1 (35). Burrows et al pointed out that this association results from “regression toward the mean”, a phenomenon in which subjects performing especially well on their first test show a greater decline because a poorer performance on subsequent tests; while those with a poor initial effort appear to improve on subsequent tests. Burrows and Stanescu also observed an association between initial FEV1/FVC and ΔFEV1%predicted, and suggested that FEV1/FVC might provide a more reliable indicator of future loss in FEV1 (6, 35). The current data show the same relationships between ΔFEV1%predicted and initial FEV1/FVC as observed by Burrows and Stanescu. Furthermore, we also extend their observations by showing that CT evidence of lung parenchymal destruction is an independent predictor of FEV1 decline.
5.4.4 Limitations

A major limitation of this study is that it was added on to a lung cancer screening cohort, where the frequency of follow-up depended on the characteristics of the lung nodule(s) found on the initial scan. To overcome this difficulty, we used $\Delta FEV1\%\text{predicted/y}$ to normalize the difference in follow-up period and the number of sampling points among subjects. $\Delta FEV1\%\text{predicted/y}$ also adjusted for the normal annual loss due to aging, and corrected for differences between females and males.

5.4.5 Conclusions

In summary, these results show that the percentage of the lung occupied by tissue inflated beyond individually predicted maximal lung inflation, serves as an independent predictor in the heavy smokers with normal spirometry, who will develop a rapid decline in FEV1 that leads to COPD. Our working hypothesis is that the minimally overinflated lung contains the earliest forms of lesions that either increase peripheral airway resistance and/or increase lung compliance by initiating emphysematous destruction. We conclude that the quantitative assessment of initial CT scans proposed in this study may be able to identify the “susceptible minority of smokers” who eventually go on to develop COPD.
<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F/M)</td>
<td>66/77</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59.5±6.4</td>
<td>44.6~72.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.5±9.8</td>
<td>149.9~195.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81.6±14.7</td>
<td>52.2~122.6</td>
</tr>
<tr>
<td>BMI (kg/cm²)</td>
<td>27.7±3.8</td>
<td>18.7~37.5</td>
</tr>
<tr>
<td>Smoking status (packyrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers (n=38)</td>
<td>41.5±11.4</td>
<td>30~90</td>
</tr>
<tr>
<td>Ex-smokers (n=105)</td>
<td>49.3±21.0</td>
<td>30~172</td>
</tr>
<tr>
<td>Lung Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1actual (L)</td>
<td>3.2±0.8</td>
<td>1.8~5.7</td>
</tr>
<tr>
<td>FEV1%predicted (%)</td>
<td>99.4±12.8</td>
<td>80.2~140.7</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>77.9±4.4</td>
<td>70.0~88.0</td>
</tr>
</tbody>
</table>
Table 5-2. Characteristics of Baseline Quantitative CT Assessments

<table>
<thead>
<tr>
<th></th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung volume (ml)</td>
<td>5086.2±1350.3</td>
<td>2608.1~9861.1</td>
</tr>
<tr>
<td>Mean lung density (g/ml)</td>
<td>0.2±0.0</td>
<td>0.1~0.2</td>
</tr>
<tr>
<td>%overinflation</td>
<td>58.4±16.4</td>
<td>15.9~83.7</td>
</tr>
<tr>
<td>cluster analysis, D</td>
<td>1.5±0.2</td>
<td>1.2~2.1</td>
</tr>
<tr>
<td>upper zone predominant</td>
<td>n=102</td>
<td></td>
</tr>
<tr>
<td>diffuse distribution</td>
<td>n=7</td>
<td></td>
</tr>
<tr>
<td>lower zone predominant</td>
<td>n=34</td>
<td>/</td>
</tr>
<tr>
<td>Lumen area, Ai (mm²)</td>
<td>6.8±2.3</td>
<td>2.1~15.1</td>
</tr>
<tr>
<td>%Awa</td>
<td>76.8±3.5</td>
<td>67.5~84.9</td>
</tr>
<tr>
<td>√Awa at Pi10 (mm)</td>
<td>4.4 ±0.2</td>
<td>3.9~5.1</td>
</tr>
</tbody>
</table>

%Awa = Awa / (Awa + Ai); √Awa at Pi10; √Awa for an airway with a Pi of 10mm.
### Table 5-3. Comparison of ΔFEV1%predicted/yr Cross Four Quartiles

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Baseline %overinflation (mean±SE)</th>
<th>ΔFEV1%predicted/yr (mean±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>quartile1</td>
<td>37.1±1.5</td>
<td>-0.9±0.6 *</td>
</tr>
<tr>
<td>quartile2</td>
<td>52.6±0.8</td>
<td>-2.0±0.7 *</td>
</tr>
<tr>
<td>quartile3</td>
<td>67.0±1.1</td>
<td>-2.3±0.7</td>
</tr>
<tr>
<td>quartile4</td>
<td>77.2±0.6</td>
<td>-3.9±1.0</td>
</tr>
</tbody>
</table>

*: ΔFEV1%predicted/yr of quartile 1 and 2 was significantly different from that of quartile 4 (p<0.05).
Figure 5-1. Comparison of The Annual Decline in FEV1%predicted Cross Four Quartiles of Baseline %overinflation. The annual decline in FEV1%predicted was greater in quartile 3 and 4 compared to that in quartile 1 and 2 (p<0.05).
Figure 5-2. The Annual Decline in FEV1 (L) of Subjects with Greater Baseline %overinflation (i.e. quartile 3 and 4) and with less %overinflation (i.e. quartile 1 and 2). The line with surrounding grey band is the “normal range” (i.e. mean±2SD) of FEV1 observed in non-smokers by Fletcher et al (2). Open circles and triangles represent an extrapolation of the data from the current study. (Open circles are data from quartiles 1 and 2, and triangles are data from quartiles 3 and 4). The annual decline in FEV1 was 47ml/yr for quartile 1 and 2; and was 68ml/yr for quartile 3 and 4.
5.5 REFERENCES


CHAPTER SIX. LONGITUDINAL STUDY OF LUNG STRUCTURE AND FUNCTION IN HEAVY SMOKERS USING COMPUTED TOMOGRAPHY AND SPIROMETRY¹

6.1 INTRODUCTION

The chronic airflow limitation that characterizes chronic obstructive pulmonary disease (COPD) is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) (1). The introduction of computed tomography (CT) into medical imaging was a major step forward for the evaluation of lung structure (2), and this technology provides us great opportunity to evaluate these two major aspects of COPD. However, much of our knowledge of the natural history of the changes in lung structure in COPD comes from cross-sectional studies. Till recently, several longitudinal studies have addressed the chronological change in lung structure and related them to functional or changes and/or health status in subjects with emphysema (3-9); particularly on the form of emphysema associated with α1-antitrypsin deficiency (3, 4, 6, 8, 9). These studies have confirmed the ability of CT to document progression of emphysema in COPD. In these investigations, more attention was paid to the average trend of changes in structure and function based on the assumption that the contribution of different lung structural changes to the reduced lung function is same at different stages of disease.

Direct histological evidence has shown that there is a correlation between the extent of inflammation, fibrosis, and luminal exudates in small airways and reduced FEV1 and FEV1/FVC (10). Emphysema, is thought to be more closely associated with gas exchange abnormalities than with reduced FEV1, although it does contribute to the latter by causing loss of lung recoil and loss of alveolar attachments to small airways at severe stages of COPD (1).

¹ A version of this paper will be submitted for publication:

This led to our hypothesis that small airway disease and emphysema might be differentially associated with loss in lung function at different stages of COPD. According to the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, symptomatic smokers with normal lung function “GOLD 0” are no longer included in this classification (1). However, it is still controversial whether this stage may provide any predictive value for the development of more advanced stages of COPD (11-15). As there has been no longitudinal studies describing the joint evolution of structural and functional changes in smokers at this COPD stage the natural history remains unclear.

The purposes of the present study were to use quantitative CT to detect and compare the longitudinal changes in two important aspects of lung structure – parenchymal density and small airway remodeling, in two groups of heavy smokers; those without baseline airflow limitation (GOLD 0) and those with baseline airflow limitation (GOLD I~IV group) and to compare these changes with changes in lung function. We hypothesized that; 1) the abnormalities of lung structure would deteriorate over time in both groups; and 2) decline in lung function would be predominantly related to the progression of airway disease in the GOLD 0 group, and would be more closely related to lung destruction and hyperinflation (emphysema) in the group of smokers with existing COPD. These hypotheses are based on an underlying postulate that there is sequential development of airway disease followed by parenchymal disease as COPD develops in susceptible smokers.

6.2 METHODS

6.2.1 Study Population
Subjects in the current study were chosen from the British Columbia Cancer Agency “BC-Lung Health Cohort” (16). This subgroup is composed of heavy smokers with a smoking history of ≥30 pack years that have at least one suspicious pulmonary nodule on initial CT scan and thus require follow up. Serial follow-up CT scans were obtained at different frequencies according to the appearance of the initial nodule(s). The concurrent pre-bronchodilator spirometry was arranged at the time of follow-up CT scans. For the purpose of the present study, we only included subjects who have
at least two CT scans following certain scan protocols (17) in combination with two spirometry measurements. Smoking status (i.e. quit smoking > 9 months prior to the study) or current smoker (i.e. smoking at the time the study started or quit within 9 months of study initiation) was documented. We divided subjects into two subgroups according to their spirometry measurement of baseline as described in the lung function section.

The study was approved by the hospital and university ethical review boards and all subjects provided written informed consent.

6.2.2 Lung Function

Pre-bronchodilator spirometry was performed using American Thoracic Society guidelines(18). Forced Expiratory Volume in one second (FEV1) were expressed as a percentage of the predicted value (i.e. FEV1%predicted) calculated using Crapo’s equations (19). The ratio of FEV1 to Forced Vital capacity (FEV1/FVC) was calculated using the actual values. Normal spirometry is indicated by a FEV1%predicted ≥80% and a FEV1/FVC ≥70%, and COPD was diagnosed when FEV1/FVC was less than 70%, and by further dividing into the subjects into subgroups according to the Global Initiative for Obstructive Lung Disease (GOLD) categories (1). According to the baseline spirometry measurement, subjects were divided into two groups: smokers without airflow limitation or Stage GOLD 0, and smokers with COPD.

6.2.3 CT Technique

All CT scans were acquired in the volume scan mode at suspended full inspiration without the use of intravenous contrast media with the subject in the supine position. These CT scans were acquired either using a General Electric Lightspeed Ultra scanner (GE Medical System, Milwaukee, WI, USA) with the following parameters: a beam potential of 120kVp, a beam current of 320mA, a gantry rotation time of 0.5s, 1.25mm slice thickness, and standard- and bone- reconstruction kernels; or using a Siemens Sensation 16 scanner (Siemens Medical Solutions; Erlangen, Germany) with the following parameters: 120kVp, 250mA, 0.5s, 1.0mm slice
thickness, and B35f- and b60f- reconstruction kernels. These two image acquisition protocols have been shown to provide comparable CT densitometry measurements (17). Images reconstructed with a high-spatial frequency algorithm (GE-bone and Simense-b60f) were used to measure airway dimensions.

6.2.4 Quantitative CT Analysis

6.2.4.1 Assessment of Emphysema

A quantitative analysis of the pulmonary parenchyma was performed using custom software (EmphylxJ, James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research, Vancouver, B.C, www.flintbox.com) as previously described.(17) Briefly, the lung parenchyma was segmented from the chest wall and large central blood vessels in all CT images using a modified border-tracing algorithm with a prior position-knowledge algorithm. Total lung volume was calculated by summing the segmented pixel area in each slice and multiplying by the slice thickness. For each pixel, the mean CT attenuation (HU) was calculated and converted to density (g/ml) by adding 1000 to the HU number and divided by 1000 (20), and the lung inflation (i.e. volume of gas per gram of tissue) was calculated by subtracting the inverse of tissue density from the inverse of CT lung density (21). The predicted maximal lung inflation was calculated for each individual using Equation 1-3 (22-24).

\[
\text{Predicted TLC (ml)} = 59 \times \text{Height (cm)} - 4527 \text{ (female)} \quad \text{Equation 1}
\]

\[
= 79.5 \times \text{Height (cm)} + 3.2 \times \text{Age (yr)} - 7333 \text{ (male)}
\]

\[
\text{Predicted Lung Weight (g)} = 15.7 \times \text{Height (cm)} - 1697.6 \text{ (female)} \quad \text{Equation 2}
\]

\[
= 15.7 \times \text{Height (cm)} - 1619.3 \text{ (male)}
\]

\[
\text{Predicted Maximal Lung Inflation (ml/g)} = \frac{\text{predictedTLC}}{\text{predictedLungWeight}} \quad \text{Equation 3}
\]

The extent of overinflation for the entire lung (%overinflation) was calculated as the percentage of the lung inflated beyond the subjects' predicted maximal lung inflation and used as an estimate of the “extent of parenchymal destruction”. A cluster
analysis was used to estimate the size of the emphysema lesions (25). The inverse slope of the log-log relationship of the size of low attenuation clusters (number of contiguous voxels that are inflated beyond the predicted value for maximum lung inflation for that individual) versus the number of clusters of that size is the power-law exponent (D). Individuals with diffuse small clusters will have a steeper slope (i.e. greater D) than individuals with larger-sized clusters.

6.2.4.2 Assessment of Airway Dimensions

Images reconstructed with a high-spatial frequency algorithm (GE-bone and Simense-b60f) were used for quantify airway dimensions. Airway wall dimensions were measured for all visible airways cut in cross-sectioned on each CT image using the “full-width at half-maximum” method (26, 27). Validation study showed that this method results in an underestimation of airway lumen area and overestimation of wall area, and this error tends to be more prominent in smaller airways (28). However, Nakano showed the airway dimensions of the large- and intermediate-sized airways (i.e. airway with an internal perimeter greater than 0.6cm), which can be accurately assessed using HRCT scanning, reflect airway dimensions in the smaller airways, which are the most important site of airway obstruction in COPD (29). Therefore, in the present study, we only used data generated from those airways with an internal perimeter greater than 0.6 cm. CT assessments of airway dimensions included: lumen area (Ai, mm$^2$), lumen perimeter (Pi, mm), and airway wall area (Awa mm$^2$), expressed as a percent of total area: %Awa = Awa / (Awa + Ai) × 100. A normalized airway wall estimate for each subject was created by establishing the linear relationship between Pi and the square root of Awa ($\sqrt{Awa}$) (29). $\sqrt{Awa}$ for an airway with a Pi of 10mm was calculated for each subject from the regression line (i.e. $\sqrt{Awa}$ at Pi10).

6.2.5 Statistical Analysis

Descriptive statistics for GOLD 0 and GOLD I~IV groups were calculated at their entry into the study and the comparison between the two groups was performed using the Wilcoxon test. To investigate the annual change in lung function (i.e. FEV1,
FEV1/FVC) and quantitative CT measurements (i.e. %overinflation, the cluster analysis value D, %Awa, lumen area and √Awa at PI10) in each group, a mixed-effects regression model (30) was used, with each of lung functional variables or CT measurements as the dependent variable and time as the independent variable, “Patient” was consider as a random effect, and covariates were gender, body mass index (BMI), smoking status, and baseline age; the lung volume at the CT scan time was added as a covariate when the outcome variables were quantitative CT measurements (31). A negative annual change for spirometry measurements, the CT cluster analysis value D and lumen area; and a positive value for %overinflation, %Awa and √Awa at PI10 indicate worsening of disease. Within each group we used mixed-effects regression models tested for relationships between the change in %overinflation and the change in the CT cluster analysis value D, the relationships between the change in lung function and change in each of the quantitative CT measurements. Models also included “patient” as a random effect and were adjusted for the covariates (i.e. gender, BMI, smoking status, baseline age, follow-up time, and the CT lung volume at that scan time) Statistical analyses were performed using JMP software (version 7.0.1 SAS institute, Cary, NC). Data were expressed as mean±SD and statistical significance was defined at the 5% level.

6.3 RESULTS

6.3.1 Subject Characteristics

There were 190 subjects included in the present study with 142 in GOLD 0 group and 48 in GOLD I~IV group (n=10 in stage I, n=25 in stage II, and n=13 in stage III or IV). One hundred twenty of the subjects had two visits and 70 had more than two visits. The average follow-up period was 2.4±1.1 years (range: 0.5~6.1 years). Baseline characteristics are given in Table 6-1.

6.3.2 Rate of Annual Change in CT and Spirometry Measurements in GOLD 0 and COPD Groups

Table 6-2 shows the annual changes in lung function and CT measurements for
each group. Parameter estimates in Table 6-2 were derived from the mixed effects models and they indicated the annual rate of change in each of the spirometry or CT variables.

FEV1 declined in both group with a greater rate in the GOLD 0 group compared to GOLD I~IV group. FEV1/FVC improved in the GOLD I~IV group while remained unchanged in the GOLD 0 group.

Of CT parenchyma measurements, %overinflation significantly increased in both groups with a greater rate value in the GOLD 0 group; the cluster analysis value D decreased over time indicating an increased proportion of large-sized clusters, and this rate of airspace coalescence was faster in the GOLD I~IV group.

Of CT airway dimensions, the airway wall area, estimated using %Awa and √Awa at P10, was decreased in the GOLD I~IV group. The luminal area didn’t show significant change over time in either group.

6.3.3 Association between Annual Change in %overinflation and Annual Change in Cluster Analysis

Mixed effects models showed that there were inverse relationships between the change in %overinflation and cluster analysis in both groups (both estimates: -0.012, p<0.0001). These data indicated that the increase in the extent of emphysema was accompanied by a concurrent coalescence of smaller clusters to form fewer larger ones, therefore, an increase in cluster size.

6.3.4 Association between Changes in Spirometry Measurements and Changes in CT Measurements in GOLD 0 and COPD Groups

Parameter estimates in Table 6-3, 6-4 and 6-5 were derived from the mixed effects models. It indicates the relationship between the change in FEV1 (L) to the change in each of the CT measurements (Table 6-3), the relationship between the change in FEV1 (%predicted) to the change in each of the CT measurements (Table 6-4), and the relationship between the change in FEV1/FVC to the change in each of the CT measurements (Table 6-5).

In the GOLD 0 group, the change in FEV1 (in ml and as % of predicted value)
was inversely associated with the change in %overinflation, and positively associated with the change in the cluster analysis value D and the changes in lumen area. In addition, changes in FEV1/FVC were inversely associated with airway wall dimension (%Awa and √Awa at Pi10) and positively associated with changes in lumen area; however changes in FEV1/FVC were not associated with any changes in parenchymal measurements (Table 6-3, 6-4 and 6-5).

In the GOLD I~IV group, the changes in FEV1 (in ml and in % of predicted value) and FEV1/FVC both were inversely associated with the change in %overinflation and positively associated with the change in the cluster analysis value D. However, neither the change in FEV1 nor the change in FEV1/FVC was associated with the change in airway dimensions (Table 6-3, 6-4 and 6-5).

6.4 DISCUSSION

The main finding of this longitudinal study is that, 1) both lung function and lung structure showed progressive deterioration in heavy smokers regardless their level of airflow limitation; 2) progression in the extent of emphysema (i.e. %overinflation) was accompanied by a relative increase in the large-sized clusters (i.e. a decrease in the cluster value D); 3) we found a more rapid rate of decline in lung function in smokers in GOLD stage 0 than in those in GOLD stages I~IV; 4) worsening in airway abnormalities and progression in emphysema (%overinflation and the cluster analysis value D) both were associated with decline in lung function in the GOLD 0 group, whereas progression in emphysema was the sole variable related to deterioration in lung function in those in GOLD I~IV group.

6.4.1 Annual Change in Lung Function in GOLD 0 and COPD Groups

We observed a greater decline in FEV1 in smokers who started with normal airflow than in those who started with COPD; this is contrary to what was found by Fletcher et al. They described a “horse racing” effect to illustrate how those subjects with a higher initial FEV1 had a slower rate of decline and therefore, a higher I FEV1 at the endpoint (32). However, an important study by Burrows et al followed by
confirmatory studies from several other investigators observed an opposite result where the decline in FEV1 was negatively related to the initial FEV1 (4, 5, 7, 9, 33, 34). These data suggested “regression toward the mean”, where subjects performing especially well on their first test show a greater decline because of a poorer performance on subsequent tests (33). Another factor that could contribute is that subjects with established COPD would be more likely to receive medical therapy, which could attenuate further rapid loss in lung function.

6.4.2 Annual Changes in CT Measurements of Emphysema in GOLD 0 and COPD Groups

Progression in the extent of emphysema has been demonstrated in longitudinal studies, mainly in subjects with α1-antitrypsin deficiency. The CT measurements used to demonstrate these changes include mean lung density (7), %low attenuation area (cutoffs: -910~960HU) (4-8, 34); the 15th percentile point (3, 6, 8, 9, 34), and emphysema score (35). The present data confirm that CT can document progression of emphysema in unselected subjects with COPD. Data also show that the increased extent of emphysema was associated with a shift in the distribution of the number and size toward an increased proportion of larger-sized lesions (Table 6-2). Although the two processes could both contribute to disease progression, they are not necessarily related to each other (36). An increase in the extent of emphysema might be caused by the appearance of new lesions or an increase in the size of existing clusters of these lesions. An increase in lesion size, namely a decrease in the cluster analysis value D, can be caused by an increase in the size of each individual cluster, and/or the fusion of smaller clusters to form fewer larger clusters. The inverse relationship between the change in %overinflation and the change in the cluster analysis value D demonstrated in the present study suggests that progressive increase in %overinflation occurred by both enlargement of individual clusters and fusion of neighboring clusters. This finding is relevant to the centrilobular form of emphysema, which is the commonest type of emphysema observed in heavy smokers. These emphysematous areas tend to localize in the upper lung zone and are relatively closer to each other, therefore, they area likely to fuse. To our knowledge, this is the first
report documenting a longitudinal change in the cluster analysis value D and its relationship to changes in the extent of emphysema and lung function in a cohort of heavy smokers with wide range of lung function.

6.4.3 Annual Changes in CT Measurements of Airway Dimensions in GOLD 0 and COPD Groups

The current data showed there was a decrease in airway wall area over time in subjects with pre-existing COPD, while there was no change in airway dimensions in smokers with normal spirometry (GOLD-0) (Table 6-2). The longitudinal analysis of airway dimensions is currently limited to a single study by Ohara et al who investigated the anterior, lateral, or posterior basal segmental bronchus in 38 subjects with COPD over 4 years (5) and reported no significant annual change in %wall area (annual change: -0.3±1.1, p>0.05). The slight reduction in airway wall thickness observed in the present study might be explained in several ways. First it might have occurred due to an overall reduction in airway wall tissue as a result of a disease process that removes airway tissue in association with emphysematous destruction. Second, the shrinkage in airway wall content could possibly be a result of treatment. The third possibility includes a systematic error in the measuring process associated with the inability to match the exact airways over time. We analyzed intermediate- or large airways in an attempt to limit the systemic error caused by the “full-width at half-maximum method” employed in this study (29). Measuring the same “representative airway” over time might minimize some of these errors; however, this approach might be vulnerable to the heterogeneity of the disease. Although some studies have shown that measurements from a selected airway correlate well with measurements from more airways (27); and measurements from different airways at different locations within the lung (i.e. upper and lower lobes) are highly correlated with each other (37), the assumption that randomly chosen airways can represent the airway disease in the whole lung needs further testing. Measuring all of the available airways in a subject might compensate for heterogeneity; without volumetric CT images and three-dimension reconstruction it is not possible to match airways. We suspect that the serial use of volumetric CT scans with performance of the analysis on
the same airways might solve this problem (38-40). We fully recognize that the inherent errors associated with longitudinal estimation of airway dimension will continue to make this procedure very challenging.

6.4.4 Natural History of Smokers in Stage GOLD 0

The natural history of the progression of airflow limitation in subjects with a smoking history and symptoms that maintain normal lung function (formerly GOLD stage 0) is unknown (1). Vestbo and Lange found that after 5 and 15 years, the percentage of these persons that proceed to GOLD stage 1 or worse COPD was similar to that in smokers without respiratory symptoms (15). More recently, Maleki-Yazdi compared St. George’s Respiratory Questionnaire (SGRQ) score in 91 normal subjects and 223 COPD subjects ranging from stage 0 to stage III and reported that stage 0 subjects exhibited a significant impairment in their quality of life compared to normal individuals; indeed smokers in this category had even worse health status than those in stage I (14). In the present study, we noticed that the annual rate of decline in lung function was greater in the GOLD 0 group than in those with established COPD and this group also showed a similar rate of deterioration in lung parenchymal destruction/overinflation as the GOLD 1-4 subjects, even though they initially had significantly less disease in their lungs. These data provide evidence of disease burden and disease progression at this early stage of COPD, and highlight the importance of the need for clinical studies to further evaluate early intervention in such smokers.

6.4.5 Associations between Annual Change in Lung Function and Annual Change in CT Measurements of Emphysema and Airway Dimensions in GOLD 0 and COPD Groups

In longitudinal studies, concordance between change in lung structure and change in lung function is not always as expected on the basis of cross-sectional data. For example, although it has been shown that emphysema increases and lung function declines over time, the association between these two processes has been found to be significant (6, 7) or not (3-5, 8, 9). The present study revealed that in
general, the decline in lung function, except for FEV1/FVC in the GOLD 0 group, was associated with progression in measures of parenchymal destruction in all smokers. In fact “emphysema” was the only structural abnormality that contributed to change in lung function in the GOLD I~IV group (Table 6-3, 6-4 and 6-5). Interestingly, we found the worsening in airway dimensions (i.e. increase in %Awa and/or decrease in lumen area) was related to loss of lung function, only in the GOLD 0 group (Table 6-3, 6-4 and 6-5). To our knowledge, there have been no longitudinal data addressing the association between the changes in airway dimensions and lung function in smokers at an early COPD stages.

Ohara et al reported a study in 38 COPD subjects at stage II~ IV, and they found that the change in airway wall area but not the increase in emphysema was related to decline in FEV1 (5). The discrepancy between their data and ours might have several explanations. For example their estimate of emphysema was based on only three images at the upper, middle and lower lung levels while we used all contiguous images, they used -960HU as the cutoff while we used inflation beyond the “maximal lung expansion” value (corresponding to a range of HU cutoff between -840 ~ -865 HU), and finally we used different statistical methods to analyze the data.

We think our observation that worsening in airway abnormalities contributed to the lung function decline only in the early stage, namely GOLD 0, whereas progression in emphysema was the sole variable related to the deterioration in lung function in subjects who already had pre-existing COPD, fits with the pathophysiology and pathology of COPD. Initially decreased FEV1 primarily results from inflammation and narrowing of peripheral airways (10, 41), and these small airways serve as a “silent zone” due to their large cross sectional area (42), therefore, a large number of them need to be diseased before the physiological parameters becomes abnormal. Emphysema also contributes to airflow limitation by destroying some of the alveolar attachments to small airways and reducing the strength of the elastic recoil in those that remain. In addition, and perhaps more importantly, emphysematous destruction of the elastic recoil properties of the lung lengthens the time required to empty the lung by lowering the force available to drive out the air (42). In their initial description of the centrilobular form of emphysema which is now recognized as the most common
form of smoking-induced emphysema, Leopold and Gough recognized that this destruction was preceded by disease in the terminal and pre-terminal bronchioles (43, 44). Recently, Remy-Jardin observed a progressive replacement of micronodular pattern, indicative of small airway inflammation, by numerous small area of hypoattenuation, indicative of emphysematous changes on HRCT as COPD progresses (35). All of these findings support the hypothesis that an airway phenotype of COPD contributes to airflow limitation before emphysematous destruction becomes widespread throughout the lung.

6.4.6 Limitations

A major limitation of this study is that it was an add-on to a lung cancer-screening cohort, where the frequency of follow-up depended on the characteristics of the lung nodule(s) found on the initial scan. Therefore, the number and timing of re-examination was not standardized. This defect was addressed using a mixed effects model to generate group mean values for annual change in lung function and quantitative CT measurements. The selection of subjects by newspaper advertisement for heavy smokers rather than by random selection from the population may have biased the results. The fact that the selection criteria was heavy smoking but not airflow limitation resulted in a smaller sample size in the GOLD I–IV group compared to that in the GOLD 0 group. Unfortunately smoking cessation and treatment information was not available and we could not assess either current smoking or treatment on outcome.

6.4.7 Conclusions

The data presented here represent a comprehensive and detailed analysis of both emphysema and airway dimensions in a cohort of heavy smokers over time, and these are the first longitudinal data to address the natural history of GOLD 0 smokers in terms of both lung structure and function and the results highlight the needs of early intervention in such smokers. Our results provide evidence in support of the hypothesis that the smokers without airflow limitation (previously classified as GOLD Stage 0) experience a rapid reduction in FEV1 that is associated with an airway
obstructive CT phenotype of COPD, whereas those with established COPD experience a decline in FEV1 that is associated with CT evidence of progressive emphysematous destruction of the lung.
### Table 6-1. Baseline Characteristics of Subjects in GOLD 0 and COPD Groups

<table>
<thead>
<tr>
<th>Demographics</th>
<th>GOLD 0 (n=142)</th>
<th>GOLD I~IV (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F/M)</td>
<td>66 / 76</td>
<td>17 / 31</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59.6 ± 6.4</td>
<td>63.4 ± 7.3 *</td>
</tr>
<tr>
<td>BMI (kg/cm$^2$)</td>
<td>27.5 ± 3.9</td>
<td>26.6 ± 4.1</td>
</tr>
<tr>
<td>Ex-smoker: current smoker</td>
<td>105 / 37</td>
<td>31 /17</td>
</tr>
<tr>
<td>Pack years</td>
<td>46.6±19.1</td>
<td>50.5±18.3</td>
</tr>
<tr>
<td><strong>Baseline spirometry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1actual (L)</td>
<td>3.1 ± 0.8</td>
<td>1.9 ± 0.9*</td>
</tr>
<tr>
<td>FEV1%predicted (%)</td>
<td>98.9 ± 13.2</td>
<td>61.6 ± 21.6*</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>80.1 ± 4.3</td>
<td>57.4 ± 11.1*</td>
</tr>
<tr>
<td><strong>Baseline quantitative CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%overinflation</td>
<td>43.0 ± 18.8</td>
<td>61.3 ± 19.0*</td>
</tr>
<tr>
<td>cluster analysis, D</td>
<td>1.5 ± 0.2</td>
<td>1.4 ± 0.1*</td>
</tr>
<tr>
<td>%Awa</td>
<td>72.9± 3.2</td>
<td>73.9 ± 3.3*</td>
</tr>
<tr>
<td>Lumen area, Ai(mm$^2$)</td>
<td>9.0 ± 2.7</td>
<td>10.1 ± 4.0</td>
</tr>
<tr>
<td>√Awa at Pi10 (mm)</td>
<td>4.4 ± 0.3</td>
<td>4.5 ± 0.3*</td>
</tr>
</tbody>
</table>

%Awa = Awa / (Awa + Ai) × 100%; √Awa at Pi10: √Awa for an airway with a Pi of 10mm;
*: p<0.05 vs. GOLD 0 group.
Table 6-2. Annual Change in Lung Function and CT Measurements in GOLD 0 and COPD Groups

<table>
<thead>
<tr>
<th></th>
<th>GOLD 0 (n=142)</th>
<th></th>
<th>GOLD I~IV (n=48)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
<td>p</td>
<td>Estimate (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Spirometry measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1, ml</td>
<td>-89.71 (-109.08, -70.34)</td>
<td>0.000</td>
<td>-40.79 (-69.76, -11.82)</td>
<td>0.006</td>
</tr>
<tr>
<td>FEV1,%predicted</td>
<td>-1.99 (-2.60, -1.38)</td>
<td>0.000</td>
<td>-0.69 (-1.58, 0.19)</td>
<td>0.121</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>-0.06 (-0.24, 0.37)</td>
<td>0.673</td>
<td>0.67 (0.09, 1.26)</td>
<td>0.024</td>
</tr>
<tr>
<td>Quantitative CT measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%overinflation</td>
<td>0.85 (0.26, 1.43)</td>
<td>0.004</td>
<td>0.76 (0.12, 1.41)</td>
<td>0.020</td>
</tr>
<tr>
<td>cluster analysis, D</td>
<td>-0.009 (-0.02, -0.00)</td>
<td>0.043</td>
<td>-0.013 (-0.02, -0.00)</td>
<td>0.033</td>
</tr>
<tr>
<td>%Awa</td>
<td>-0.20 (-0.41, 0.01)</td>
<td>0.076</td>
<td>-0.48 (-0.77, -0.18)</td>
<td>0.002</td>
</tr>
<tr>
<td>lumen area(mm²)</td>
<td>0.11 (-0.07, 0.29)</td>
<td>0.233</td>
<td>0.17 (-0.27, 0.61)</td>
<td>0.444</td>
</tr>
<tr>
<td>√Awa at Pi10(mm)</td>
<td>-0.01 (-0.02, 0.00)</td>
<td>0.141</td>
<td>-0.03 (-0.05, -0.01)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

%Awa = Awa / (Awa + Ai) × 100%; √Awa at Pi10: √Awa for an airway with a Pi of 10mm.
Table 6-3. Associations between the Annual Change of FEV1 (L) and the Annual Changes in Quantitative CT Measurements in GOLD 0 and COPD Groups

<table>
<thead>
<tr>
<th></th>
<th>GOLD 0 (n=142)</th>
<th>GOLD I~IV (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>estimate</td>
<td>p</td>
</tr>
<tr>
<td>%overinflation</td>
<td>-0.008</td>
<td>0.001</td>
</tr>
<tr>
<td>cluster analysis, D</td>
<td>0.454</td>
<td>0.007</td>
</tr>
<tr>
<td>%Awa</td>
<td>-0.002</td>
<td>0.788</td>
</tr>
<tr>
<td>lumen area, Ai (mm²)</td>
<td>0.008</td>
<td>0.028</td>
</tr>
<tr>
<td>√Awa at Pi10(mm)</td>
<td>-0.021</td>
<td>0.827</td>
</tr>
</tbody>
</table>

%Awa = Awa / (Awa + Ai) × 100%; √Awa at Pi10: √Awa for an airway with a Pi of 10mm.
Table 6-4. Associations between the Annual Change of FEV1%pred and the Annual Changes in Quantitative CT Measurements in GOLD 0 and COPD Groups

<table>
<thead>
<tr>
<th></th>
<th>GOLD 0 (n=142)</th>
<th></th>
<th>GOLD I~IV (n=48)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>estimate</td>
<td>p</td>
<td>estimate</td>
<td>p</td>
</tr>
<tr>
<td>%overinflation</td>
<td>-0.208</td>
<td>0.004</td>
<td>-0.633</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cluster analysis, D</td>
<td>15.880</td>
<td>0.001</td>
<td>25.51</td>
<td>0.014</td>
</tr>
<tr>
<td>%Awa</td>
<td>-0.061</td>
<td>0.773</td>
<td>0.002</td>
<td>0.994</td>
</tr>
<tr>
<td>lumen area, Ai (mm²)</td>
<td>0.145</td>
<td>0.029</td>
<td>0.088</td>
<td>0.752</td>
</tr>
<tr>
<td>√Awa at Pi10(mm)</td>
<td>-1.944</td>
<td>0.497</td>
<td>2.100</td>
<td>0.603</td>
</tr>
</tbody>
</table>

%Awa = Awa / (Awa + Ai) × 100%; √Awa at Pi10: √Awa for an airway with a Pi of 10mm.
Table 6-5. Associations between the Annual Change of FEV1/FVC and the Annual Changes in Quantitative CT Measurements in GOLD 0 and COPD Groups

<table>
<thead>
<tr>
<th></th>
<th>GOLD 0 (n=142)</th>
<th></th>
<th>GOLD I~IV group (n=48)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>estimate</td>
<td>p</td>
<td>estimate</td>
<td>p</td>
</tr>
<tr>
<td>%overinflation</td>
<td>-0.007</td>
<td>0.845</td>
<td>-0.269</td>
<td>0.021</td>
</tr>
<tr>
<td>cluster analysis, D</td>
<td>2.83</td>
<td>0.237</td>
<td>17.13</td>
<td>0.010</td>
</tr>
<tr>
<td>%Awa</td>
<td>-0.245</td>
<td>0.016</td>
<td>0.017</td>
<td>0.938</td>
</tr>
<tr>
<td>lumen area, Ai (mm$^2$)</td>
<td>0.185</td>
<td>0.017</td>
<td>0.147</td>
<td>0.604</td>
</tr>
<tr>
<td>$\sqrt{Awa}$ at Pi10(mm)</td>
<td>-3.217</td>
<td>0.021</td>
<td>4.470</td>
<td>0.090</td>
</tr>
</tbody>
</table>

$\%Awa = Awa / (Awa + Ai) \times 100\%; \sqrt{Awa}$ at Pi10: $\sqrt{Awa}$ for an airway with a Pi of 10mm.
6.5 REFERENCES


31. Dirksen A, Friis M, Olesen KP, Skovgaard LT, Sorensen K. Progress of emphysema in severe alpha 1-antitrypsin deficiency as assessed by annual CT. *Acta
Radiol 1997;38:826-832.
43. Leopold JG, Gough J. The centrilobular form of hypertrophic emphysema and

CHAPTER SEVEN. GENERAL DISCUSSION AND FUTURE DIRECTIONS

7.1 GENERAL DISCUSSION

7.1.1 The Effects of Radiation Dose and CT Manufacturer on Measurements of Lung Densitometry

Summary of Findings. The work in Chapter 2 establishes the basis for the comparability of quantitative CT lung densitometry across different individuals and between follow-up scans in the same individuals. We compared quantitative CT assessments of lung volume, mass and lung density (i.e. mean lung density, percent low attenuation area using different cutoffs (i.e. -856HU, -910HU and 950HU), and percentile point (i.e. the 5th and 15th)) between CT images obtained using low- and regular-dose radiation; and using different CT scanners. This study demonstrated that there was a significant increase in image noise with low-dose CT images causing a broadening of the X-ray attenuation histogram. Therefore, CT estimates of emphysema, regardless of methods, were overestimated because they rely on choosing a threshold or percentile value at the extreme end of this frequency distribution. However, the CT images derived from different scanner manufacturers can be used if they were acquired using certain scanning protocols.

Contributions to the Field. Our data provided direct measure of differences in CT densitometry measurements between low- and regular-dose CT scans and we included the most commonly used densitometry measurements and most commonly used cutoffs for each method. By using an appropriate statistical approach, our results were also adjusted for lung volume, a very important biological factor that affects CT densitometry measurements; this approach enhanced the validity of this work. In reality, standardization of image acquisition and reconstruction protocol might be needed between different CT scan manufacturers. Our data also suggested a combination of certain CT settings from different CT scan manufacturers can achieve comparable lung densitometry measurements. In fact, the results from this work guided us to select suitable CT scans for comparison of quantitative CT measurements from a convenient database, and a protocol tested in the study has
also been used as a standard follow-up CT scan protocol in the British Columbia Lung Cancer Study during 2006 and 2007.

7.1.2 Quantification of Lung Surface Area Using Computed Tomography

**Summary of Findings:** The work in Chapter 3 is a validation study for the two CT estimates of parenchyma, %overinflation and the CT cluster analysis value D, both of which have been used throughout the thesis studies. In Chapter 3, we found significant correlation between these two CT variables and the histological measurement of emphysema - surface area per unit lung volume (SA/V) and therefore, they can be used as valid estimates of emphysema, and maximal lung inflation is a valid cutoff to define emphysema on CT. We also found that the combination of CT median lung density and the D value on CT cluster analysis was superior to either alone in predicting the histological measurement of emphysema.

**Contributions to the Field.** This work serves as a validation study for %overinflation using a dynamic cutoff - maximal lung inflation, and for D value on CT cluster analysis, as it has only been assessed by Madani et al and they didn’t find its correlation to a pathological gold standard (1). The results also indicates that one CT densitometry measurement of lung parenchyma is not enough to accurately diagnose tissue destruction if it is accompanied by some form of tissue deposition (e.g. fibrosis), because the later can confound the linear relationship between CT densitometry and SA/V: the D value on cluster analysis can help sort out this problem.

7.1.3 Computed Tomographic Assessments of Emphysema and Airway Dimensions in Smokers - Correlation with Airflow Limitation

**Summary of Findings.** Data in Chapter 4 are mainly provided to allow a description of the study population on which the longitudinal studies reported in Chapter 5 and 6 were conducted. In Chapter 4, we tested the independent and combined contribution of assessments of lung parenchymal destruction/hyperinflation and airway remodeling to airflow limitation in COPD subjects in a cross-sectional fashion. We confirmed that both pathologies are important factors and contribute independently to airflow limitation. Although we showed that the CT cluster analysis
value D added value to mean lung density in relation to prediction of the histological measurement of emphysema. In Chapter 3, we show that it does not provide any added-value to %overinflation as a contributor to airflow limitation. We attribute this to the high correlation between D and %overinflation. We compared the detailed quantitative CT analysis of lung parenchyma and airways in “emphysema-dominant” and “airway-dominant” phenotypes and our data showed that the “airway-dominant” phenotype indeed had a smaller lumen area indicating increased airway remodeling.

We also described and compared lung structure and function between a group of smokers without COPD and those with COPD. Our data showed a wide variation in the measure of parenchymal impairment in both groups and this finding suggested that the hypothesis tested in Chapter 5 (i.e. that baseline emphysema is a risk for progression) was reasonable.

**Contributions to the Field.** This study is the first report that included the CT cluster analysis value D, quantitative CT assessment of multiple airways (rather than a single airway) and percent parenchymal destruction (i.e. %overinflation in current data) in relation to airflow limitation in COPD. The statistical models were adjusted for potential confounders such as gender, age, and lung volume, which is strength of this work. In addition, the quantitative CT measurement in our data, especially those direct data for airways, complements the descriptions of the two phenotypes of COPD. In contrast many of the published studies have focused on clinical aspects for this separation.

### 7.1.4 Prediction of the Rate of Decline in FEV1 in Smokers Using Quantitative Computed Tomography

**Summary of Findings.** In Chapter 5, we retrospectively tested the association between quantitative CT measurements of parenchymal destruction on the baseline CT scan and the subsequent rate of decline in FEV1 in a group of heavy smokers who initially did not have airflow limitation. Our multiple regression analysis showed that a greater extent of parenchymal destruction on baseline CT was significantly associated with rapid annual decline in FEV1%predicted. We further superimposed our data onto Fletcher’s diagram showing that the “rapid decliner” and “normal
decliner” diverge and that the group with more extensive parenchymal destruction had a rapid decline of FEV1 that fell out of the range for those that were “normal decliners”.

**Contributions to the Field.** This work is the first study addressing the value of the early parenchymal abnormalities in predicting rapid decline in FEV1 in smokers initially with normal airflow flow. Although many investigators have attempted to find the “predictor” of the “susceptible minority of smokers”, which was first proposed by Fletcher (2), the presence of emphysema in non-obstructed smokers had not been investigated in longitudinal studies. In order to emphasize the “prediction of the onset of COPD”, we only included subjects with normal airflow at baseline when designing the study. We indeed detected an inverse relationship between baseline %overinflation and subsequent rate of decline in FEV1%predicted. This is a novel finding, and it is important for the development of strategies for secondary prevention. Knowing that the only effective treatment of COPD is smoking cessation and that its protective effect diminishes as disease gets more severe (3), this work actually highlights that early intervention and further investigation are needed in such smokers, especially those with obvious evidence of parenchymal impairment. In addition, this work also suggests that neither the other aspects of emphysema, such as size distribution (D) nor location of emphysema, nor airway dimensions at baseline are associated with rate of decline in FEV1.

### 7.1.5 Longitudinal Study of Lung Structure and Airflow in Heavy Smokers Using Computed Tomography and Spirometry

**Summary of Findings.** Much of our knowledge of the natural history of COPD, and the contribution of the two mechanisms (parenchymal destruction and airway disease) to airflow limitation have come from cross-sectional studies. Longitudinal data offer the potential to reveal causal relationships. Since we know that the primary pathology causing airflow obstruction is located in small airways, we hypothesized progression of airflow limitation would be related to worsening airway disease in smokers at an early COPD stages (without COPD or GOLD Stage 0), while progression would be related to parenchymal destruction in the later stages (those
with established COPD). In Chapter 6, we examined the relationships between longitudinal changes in lung function and lung structure in two groups of heavy smokers - those initially without- and with COPD. Our data showed that worsening in airway abnormalities contributed to the decline in lung function only in the GOLD 0 smokers, whereas progression in emphysema was the sole variable related to deterioration in lung function in those with pre-existing COPD. In addition, we found a more rapid decline in airflow and a similar rate of progression in emphysema in GOLD 0 stage smokers compared to smokers who had COPD.

**Contributions to the Field.** Our data represent the first comprehensive and detailed longitudinal analysis of both emphysema and airway dimensions in a cohort of heavy smokers. The findings that worsening in airway abnormalities contributed to the airflow decline only in GOLD 0 smokers, whereas progression in emphysema was related to deterioration in airflow in COPD subjects are novel and are concordant with what is known of the pathophysiology and pathology of COPD. In addition, these are the first longitudinal data to address the natural history of GOLD 0 smokers in terms of both lung structure and function and the results, together with our findings in Chapter 5, highlight the needs for early intervention in such smokers (4).

### 7.2 STRENGTHS AND LIMITATIONS OF THE RESEARCH

#### 7.2.1 Strengths of the Thesis Research

In this dissertation, I have conducted a detailed examination of a group of heavy smokers with and without COPD, and I have emphasized the longitudinal relationship between two pulmonary pathological processes – emphysema and airway disease, and airflow limitation. The five chapters containing original work are arranged in a logical order: 1) which CT image source can be used; 2) which tools are valid; 3) what are the characteristics of the study population; 4) does cross sectional data predict subsequent progression and 5) what is the longitudinal relationship between changes in structure and function. The most important strength of these studies is the availability of serial thin-slice CT scans on the same subjects over time from a lung cancer screening database. The lung cancer screening protocol contains
a baseline low-dose CT scan and subsequent serial follow-up CT scans with regular dose. This provided a unique opportunity to address the effect from CT scanning dose by comparing the screening and follow-up CT scans in Chapter 2. I was also able to compare the lung parenchyma and airways across subjects and within the same subject over time by using the follow-up CT scans with regular dose in Chapter 4-6. The longitudinal quantitative CT measurements based on serial CT scans with regular dose are superior to those from scans with low-dose, because there is less image noise and therefore more precision in measurements.

7.2.2 Limitations of the Thesis Research

The major limitation of this work is that it was conducted retrospectively. The retrospective design could lead to bias because I only included subjects who had multiple CT scans and spirometry data. Repeat CT scanning was based on the finding of a potentially malignant lesion(s) on the initial scan. Although this represents only a subset of the potential participants it should be noted that not all of the participants in the study required follow up. Nevertheless, this potential bias prevents the extrapolation of these results to a general population.

A second limitation of this body of research is that I was lacking some important clinical information, such as the changes in smoking status during the period of follow up. A detailed smoking history was only ascertained at entry into the study but was not consistently documented at follow-ups. Failure to account for the influence of changing smoking status could confound the relationships between the changes in lung structure and the changes in lung function addressed in Chapters 5 and 6.

A third limitation relates to the accuracy of the measurement tools and algorithms that were employed. For example, I used the “half width at full maximum” method to assess airway dimensions. Based on the resolution of HRCT I can only be confident with the measurements on medium to large sized airways. Whether this lack of resolution limited the detection of relationships between baseline airway dimensions and the rate of decline in FEV1 in Chapter 5 is not clear. The regional distribution of emphysema has only been determined and analyzed in the studies
described in Chapter 5 and this measure was lacking for Chapter 4 and 6. Automated calculation of the regional predominance of the distribution of emphysema by computer programs will significantly improve the precision of this measure and also make the process less tedious.

In addition, the spirometry protocol in the BC Lung Health Study was pre-bronchodilator spirometry and this might cause an overestimation of the degree of airflow limitation in some subjects.

The study design in Chapter 3 was based on the availability of pathological material from the resected lung. Since we retrospectively analyzed the subjects’ pre-operative CT scan we couldn’t make measurements on thin-slice CT scan images as the subjects didn’t have such CT scans before the surgery.

Finally, the mixture of two different CT scans (i.e. GE and Siemens) composite the primary data in this thesis work, which is still not optimal because subtle changes might be missed when switching from one scanner to another. In Chapter 2, we compared CT densitometry measurements between GE and Siemens scanners and we found no significant difference. Although we concluded that these two scanners provide us compatible CT measurements in longitudinal studies, we should also be aware that these data could also suggest that the mixture of CT scans may not be optimal for distinguishing the change in measurements. Consistency and sensitivity are both important aspects in longitudinal studies, we have paid great attention to achieve the consistency, and so should we do to the sensitivity.

7.3 FUTURE RESEARCH DIRECTIONS

7.3.1 General Future Directions

In terms of outcomes in COPD research, FEV1 and FEV1/FVC have long been used as primary outcomes to monitor disease progression or improvement, and to evaluate response to therapies in COPD. As has been increasingly recognized, COPD is a systematic disease and additional phenotypic measures can be assessed, including: 1) other measures of lung function (lung volumes and diffusing capacity), 2) arterial blood gas tension, 3) physiologic derangements such as exercise capacity, 4) anemia, 5) cachexia, 6) reductions in lean body, 7) exacerbation frequency and
severity, 8) subjective assessments such as dyspnea and health related quality of life, 9) the course of the disease, and 10) systemic consequences (5). Some of them might be more meaningful than airflow limitation and this is especially so when subjects present clear sub-phenotypes. In this study we have examined the usefulness of CT estimates of two of the specific components that contribute to COPD; emphysema and airway remodeling. Future investigations should include some, if not all, of these multidimensional measures, or a combination of certain measures as primary outcomes, and this will provide a more comprehensive profile of COPD.

From the technical point of view, three dimensional analyses of CT data has been a major step forward for the quantitative assessment of airway dimensions by overcoming airway angling and enabling the comparison of airways at the same anatomic site. Although this approach has not been validated against an anatomic gold standard it offers the promise of analysis of the airway tree at specific anatomic locations in smaller airways such as the 5th and 6th generations of airways with an internal diameter as low as 1.6mm (6) or a lumen area as small as 2 mm² (7). In fact in a recent study Hasegawa et al found that the measurements of airway dimensions in smaller airways correlated better with lung function than the same measurements in more central airways (6, 7). Three dimensional airway analyses should be used to reanalyze the difference in airway dimension between COPD phenotypes and test whether baseline airway disease can predict the subsequent decline in airflow; and how airway dimensions change over time, as well as how these changes related to changes in airflow.

As to the quantitative assessment of emphysema, the regional distribution of emphysema has not been thoroughly investigated except in Chapter 5. There are many questions that can be asked regarding this measure: 1) Are there differences in the regional distribution of emphysema in those with different severity of COPD disease, or between the “airway- dominant” or “emphysema-dominant” phenotypes? 2) As the disease progresses, is there an interlobular or inter-zonal shift of emphysema distribution? 3) If so, is this regional shift of emphysema associated with disease progression? Studies in α1-antitrypsin deficiency have given excellent
examples of the value of studying the regional distribution of emphysema. Parr, Holeme and Stockley et al found that although alpha1-antitrypsin deficiency often presents with “lower lobe predominant emphysema”, a smaller fraction actually have “apical-predominant emphysema”(8). They also found that “basal-predominant emphysema” is associated with a lower FEV1 and less impairment of gas exchange, while a lower DLco is associated with “apical-predominant emphysema” (8, 9). Furthermore, they found evidence of the inter-zonal shift of the predominant regional distribution of emphysema such that it starts from lower zones and progresses to greater deterioration in the upper zone suggesting that when the lower zones are largely destroyed, an active disease process eventually switches to the more normal areas of the lungs in apical regions.

7.3.2 Future Research in Standardization of CT Protocols

The pixel/voxel size hasn’t been recognized as an important factor that should also be standardized. CT measurements such as cluster analysis value D and airway dimensions can be affected by pixel/voxel size. The D value on cluster analysis is the slope of the log-log plot of the numbers of clusters (Y axis) against the size of clusters (X axis), in which, the size of clusters are estimated by counting the total number of adjacent low attenuation pixels. If the size of each pixel within that area is bigger, then the total number of pixels in that area is less, therefore, the “size” estimated by counting the number of pixels is smaller, while this “size” will be bigger if the dimension of each pixel in that area is smaller.

For airway measurements, larger pixels means that for a given airway size there will be fewer pixels falling into lumen/wall area. Therefore, including/excluding one pixel makes a big difference on the final measurements, and this is especially so when the measurement tool can not achieve a sub-voxel estimate. Three dimensional algorithms allow reconstruction of transverse images of individual airways by reorientation of airways, namely rearrangement the voxels that compose airways. If the original voxels are not isotropic due the different resolution in XY plane and in Z axis, this reorientation might introduce error into the airway measurements.
7.3.3 Future Research in the Use of CT in Smokers with COPD

The determination of the phenotypic characteristics of COPD is not only scientifically interesting but also clinically important because they may confer prognostic value and, more importantly, response to therapy. Our data have added detailed quantitative CT measurements to the current knowledge about the “airway-dominant” and “emphysema-dominant” phenotypes of COPD.

In currently published studies designed to separate two phenotypes the separation has been accomplished by analyzing only the emphysema on CT (except for one study where, investigators used both emphysema and airways scores on CT). Is this an efficient use of CT information? If airway dimensions are needed to make a separation, what is the criterion for diagnosis? We also don't understand the underlying pathogenesis that causes these differences. We don't know whether there is an overlap between these two phenotypes and other phenotypes of COPD (e.g. do individuals with the airway or emphysema phenotype have more or less systemic inflammation?)

To answer those questions further investigations need to include more clinical, laboratory and detailed lung function data. We also recommend that further investigations of the “two phenotypes” of COPD include a comparable fraction of females and males since in the majority of current studies females represent a very small proportion (6%~15%) (10-15) and only one study contained a relatively comparable number of females and males (16) as did our COPD population described in Chapter 4 (40% females). We are not clear about whether this would have any impact on any of the observations that have been mentioned in those studies, but there are some clear gender differences in the presentation and natural history of COPD (17, 18).

Another possible significance of CT in smokers with COPD is related to the comorbidities of COPD. The possible role of the chronic inflammation as a tumor promoter in the pathogenesis of cancer was first proposed by Virchow (19) and has been demonstrated in other organs (20-23). There is a growing recognition of the relevance chronic inflammation from cigarette smoking to the pathogenesis of lung cancer in COPD (24). Evidence of the link between chronic inflammation and lung
cancer has been reported at the molecular level (25-27), and from clinical studies (28-30). In addition, the incidence of lung cancer increases as COPD gets more severe (28, 31). More interestingly, Sin et al compared data from different cohort studies and suggested that lung cancer is one the main causes of death in mild or moderate COPD (24). In those studies COPD was defined by abnormalities of lung function, therefore, there were no data regarding the predominant phenotype of COPD, such as emphysema and airway disease. Thus an obvious question for further research is to test for an association between COPD sub-phenotypes and lung cancer. Are the prevalence and/or incidence of lung cancer greater in certain phenotypes of COPD? Another question is to define why the incidence of lung cancer is higher in subjects with more severe disease whereas death from lung cancer is higher in those who have mild or moderate COPD? These questions are important from the stand point of secondary prevention, and they can be examined in a lung cancer screening cohort.

7.3.4 Future Research in the Predictive Value of Early Emphysema

The current finding that the baseline extent of emphysema in smokers without airflow obstruction can predict the future decline in FEV1 was based on retrospective data and this should be further validated in a cohort study with longitudinal data from randomly-sampled, population-based populations. Currently, there are a few studies that can be candidates for such studies. On possibility would be the Burden of Lung Disease (BOLD) Study (32). This study involves randomly-sampled, population-based populations and it also contains subjects with normal airflow. CT scans would need to added to this cohort and longitudinal data obtained over many years. Another study that may answer some of these questions is the “Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints” study (ECLIPSE study) (33). This study contains a large number of COPD subjects and smokers without COPD at baseline. The ECLIPSE study is designed as a three-year longitudinal study with three annual low-dose CT data, detailed pulmonary function, and clinical and laboratory data, which makes it a great validation cohort for our findings.

Whether the early emphysema on CT, together with abnormal tests of small airway function can complement each other to improve the prediction of onset of
disease is another question worthy of further study. There was an intense period of investigations in small airway function tests after it was established that the important site of airflow limitation is the small airways in COPD. Despite initial enthusiasm the predictive usefulness of these studies was disappointing since most of smokers showed abnormalities of small airway function and these abnormalities did not predict subsequent progression(34). However, would abnormal small airway tests add value to the CT parenchymal abnormalities in the prediction of disease onset and progression? What are the recommendations to those smokers who have evidence of parenchymal impairment who don’t as yet have airflow limitation?

7.3.5 Future Research Regarding the Association between Changes in CT and Changes in Airflow

Longitudinal CT data hold promise in detecting disease progression/improvement, and the response to treatments. Our data in the current study provide a comparison of the concomitant change in lung structure and function in smokers grouped according to the initial lung function status. Many aspects of COPD can be examined using this tool.

One study that needs to be done is to compare the longitudinal changes in “airway-dominant” and “emphysema-dominant” phenotypes, respectively. In each phenotype, does the predominant pathology change during disease progression or improve more prominently in response to the treatment? Does the predominance of one pathology change as disease progresses? Early histology reports by Leopold and Gough described the primary lesion of centrilobular emphysema located in the respiratory bronchioles of the acinus near the center of the secondary lobule (35, 36). They concluded that dilatation and destruction of the respiratory bronchioles that defines centrilobular emphysema is preceded by disease in the terminal and pre-terminal bronchioles. This histological observations, together with the observation that “airway-dominant” phenotype consistently shows less impaired lung function compared to the “emphysema-dominant” phenotype, raise the question that the “airway-dominant” phenotype might transition to the “emphysema-dominant” phenotype during disease progression.
Smoking cessation is the only established efficient treatment in COPD and can slow the rapid decline in FEV1. How do the lung parenchyma and airways change in responding to smoking cessation, and what are these changes? Are there more changes in airway dimensions or in the parenchyma? Does smoking cessation particularly affect the predominant pathology in each phenotype?

7.4 POTENTIAL APPLICATIONS OF RESEARCH FINDINGS

Standardization of CT scanning protocols is necessary in multiple center studies and in longitudinal studies. Our findings regarding the reproducibility of CT densitometry measurements between a GE scanner and a Siemens scanner with a combination of certain protocols provide alternative options for different centers based on which scanner is available in that centre. Lung volume, due to inspiration level at the time of the scan is an important characteristic to take into account. We have observed an interaction between CT lung volume and CT scan protocol in affecting CT densitometry measurements in Chapter 2. Based on our analysis experience presented in Chapter 4-6, volume adjustments by the simple inclusion of total lung volume at the time of the CT scan as a covariate in the statistical mode is a practical tool, as has also been shown by other groups of investigators (37-40). Investigators should also consider including measurement of the fractal value in their objective assessment of emphysema as our findings show that adding the CT cluster analysis value D compliments CT densitometry in making an accurate prediction of histological measurements of emphysema. Assessment of the zonal distribution should also be included.

Our finding that early parenchymal impairment in smokers with normal airflow, is of predictive value with respect to significant deterioration in lung structure and lung function in these smokers, should alert researchers to consider CT as a useful tool in selecting those smokers who are at particular risk for rapid loss of lung function. This novel finding should also encourage researchers to develop strategies for the primary and secondary prevention of progression in this group of heavy smokers. Such interventions could include recommendation of an intensive smoking cessation program, or regular follow-up of small airway obstruction with more sensitive tests.
7.5 REFERENCES


