Physiological mechanisms of lung volume reduction coils in emphysema

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Declaration of originality

The data presented in this thesis is as a result of my own work carried out in fulfillment for the degree of Doctor of Philosophy at Imperial College, London. The data was collected at the Royal Brompton Hospital and Chelsea and Westminster Hospital between December 2012 and March 2016. All sources of information are appropriately referenced and the work of others is specifically acknowledged. The text was written wholly by me unless otherwise referenced, and permissions were obtained for reproducing my own work which has been previously published.

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Copyright Declaration

Abstract

Introduction

Emphysema is characterised by airflow limitation that is a result of both loss of elastic recoil and small airways disease. It is poorly responsive to medical therapy. Lung volume reduction coils improve symptoms and lung function in the short term. However their mechanism of action and medium term effectiveness is not fully understood.

Methods

A randomised controlled study consisting of thirty patients with severe chronic obstructive pulmonary disease was performed. Control patients crossed over to the treatment arm at 12 months. The primary outcome was 6 minute walk distance at 12 months. Changes in spirometry, lung volumes, computed tomography measured lung volumes and gas trapping were also assessed. In a small subgroup of patients detailed physiological characterization was performed to assess changes in airways resistance, ventilation heterogeneity and lung elastic recoil.

Results

In the randomised study at 12 months, there was no significant difference in 6 minute walk distance between treatment and controls (between group difference 25m, 95% CI -40 to 59, p = 0.7028). There was a trend to improvement in symptoms measured by SGRQ score (-6.53 points, 96% CI -17 to 0.2, p = 0.0589) and significant improvements in FRC (-0.41L, 95% CI -0.86 to -0.1, p = 0.0077). Including the crossovers there were 4 patient deaths (13.3%). Target lobe volume at both inspiration and expiration was reduced with no overall change in gas trapping. Airways resistance by plethysmography did not change significantly. There was no significant change in elastic recoil.

Conclusions

Treatment with lung volume reduction coils is effective at reducing lung volume

and may achieve its effect through volume loss. There could also be an effect through elastic recoil as there was a non-significant trend towards an increase after the intervention. There appears to be no effect on airways resistance. Careful patient selection is required as there is a risk of death following treatment.

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Abbreviations

AAT	Alpha-1 antitrypsin
ATS	American Thoracic Society
A_X	Reactance area
BMI	Body mass index
BTVA	Bronchoscopic thermal vapor ablation
CDI	Convection dependent inhomogeneity
CEV	Cumulative expired volume
C_{Ldyn}	Dynamic lung compliance
C_{Lstat}	Statitc lung compliance
COPD	Chronic obstructive pulmonary disease
CR	Coefficient of retraction
DCDI	Diffusion-convection dependent inhomogeneity
DSMB	Data safety monitoring board
ECSC	European Coal and Steel Workers Cohort
EELV	End expiratory lung volume
EFL	Expiratory flow limitation
ERS	Europrean Respiratory Society
ERV	Expiratory reserve volume
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
F_{res}	Resonant frequency
FVC	Forced vital capacity
GOLD	Global initiative for obstructive lung diseases
HRQL	Health related quality of life
HU	Hounsfield Units
Hz	Hertz
IC	Inspiratory capacity
ICS	Inhaled corticosteroid
IOS	Impulse oscillometry
IRV	Inspiratory reserve volume
IVC	Inspiratory vital capacity
LAA	Low attenuation area
LABA	Long acting beta agonist
LAMA	Long acting muscarinic antagonist
LCI	Lung clearance index
LLL	Left lower lobe
LUL	Left upper lobe
LV	Lung volume
LVRC	Lung volume reduction coil
LVRS	Lung volume reduction surgery
MBNW	Multiple breath nitrogen washout
MCID	Minimum clinically important difference
MLD	Mean lung density
mMRC	Modified Medical Research Council dyspnoea score
NETT	National Emphysema Treatment Trial
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence

NRT	Nicotine replacement therapy
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PASP	Pulmonary artery systolic pressure
PDE4	Phosphodiesterase 4
P_{el100}	Elastic recoil pressure at total lung capacity
PR	Pulmonary rehabilitation
QALY	Quality adjusted life year
$R_{20(In/Ex)}$	Resistance at 20Hz (inspiratory or expiratory)
R_{5-20}	Resistance at 5HZ minus 20Hz
$R_{5(In/Ex)}$	Resistance at 5Hz (inspiratory or expiratory)
$R_{aw\ (in/ex)}$	Airways resistance (inspiratory/expiratory)
R_{eff}	Effective airways resistance
RLL	Right lower lobe
R_{rs}	Resistance (by IOS)
RUL	Right upper lobe
RV	Residual volume
SABA	Short acting beta agonist
S_{acin}	Acinar airways ventilation heterogeneity
SAE	Serious adverse event
SAMA	Short acting muscarinic antagonist
S_{cond}	Conducting airways ventilation heterogeneity
$sG_{aw(in/ex)}$	Specific airways conductance (inspiratory or expiratory)
SGRQ	St George's Respiratory Questionnaire
S_n	Normalised phase III slope
sR_{aw}	Specific airways resistance
TLC	Total lung capacity
TL_{CO}	Transfer factor of the lung for carbon monoxide
TO	Lung turnover
UK	United Kingdom
US	United States
VATS	Video assisted thorascopic surgery
VC	Vital capacity
V_L	Volume of whole lung
$V_{NTL\ (insp/exp)}$	Non-target lobe volume (inspiration or expiration)
$V_{TL\ (insp/exp)}$	Target lobe volume (inspiration or expiration)
$X_{5\ (In/Ex)}$	Reactance at 5Hz (inspiratory or expiratory)
X_{5In-Ex}	Difference in reactance between inspiration and expiration
X_{rs}	Reactance (by IOS)
Z_{rs}	Impedance (by IOS)

Chapter 1

Introduction

Introduction

Chronic obstructive pulmonary disease (COPD) is a health problem contributing to significant morbidity and mortality around the world.(1) It causes debilitating symptoms including breathlessness and impaired exercise capacity that are often poorly responsive to current medical treatments. An understanding of the pathophysiology is crucial to explaining the mechanisms of breathlessness and developing treatments for COPD. Lung volume reduction surgery has achieved success in improving symptoms by altering lung mechanics. More recent treatments including lung volume reduction coils have been shown to be clinically effective in the short term in patients with emphysema. However the mechanisms underlying these clinical improvements has not been explored in detail. Further understanding may lead to better selection of patients and refinements in the technique to maximise patient benefits.

1.1 Chronic obstructive pulmonary disease

1.1.1 Definition

The current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define 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 characterised 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.*"(2)

COPD is a heterogeneous disease encompassing chronic bronchitis and emphysema. Whilst clinically and pathologically distinct, they share common aetiologies; frequently co-exist and are both characterised by the presence of poorly reversible airflow obstruction. Early descriptions of emphysema were reported in 1679 by Bonet where he described 'voluminous lungs' and by Morgagni's 1769 series of 19 cases of lungs 'turgid with air'.(3) It was Laënnec who made the first detailed description of the pathology of emphysema. He studied patients with a variety of respiratory diseases during their life and

performed post mortem examinations to correlate pathological findings. In some patients he found that the lungs were hyperinflated, frequently obstructed by mucus and did not empty well.

"In opening the chest, it is not unusual to find that the lungs do not collapse, but they fill up the cavity completely on each side of the heart. When experienced, this will appear full of air . . . The bronchus of the trachea are often at the same time a good deal filled with mucous fluid..."(4)

The chronic bronchitis component was described in the early 19th Century by Badham who used the word catarrh to refer to mucus hypersecretion and chronic cough.(5) Efforts to standardise the definitions were made in the 20th century in order to better characterise the phenotypic presentations of the disease and promote research. Chronic bronchitis has a clinical definition of chronic productive cough on most days for at least 3 consecutive months over at least 2 years where other causes of chronic cough have been excluded.(6) Emphysema is described in pathological terms as a condition characterised by an increase in size of the air spaces distal to the terminal bronchioles either from dilation or destruction of the alveolar walls and without obvious fibrosis.(7)

Over the decades it has become increasingly evident that there is a much wider array of phenotypes with differing clinical, genetic, molecular and pathophysiological characteristics. Understanding the differences in these phenotypes has become increasingly important as medicine evolves and is able to offer more selective, personalised treatments.

1.1.2 Diagnosis and staging

The diagnosis of COPD relies on eliciting a consistent clinical history, exposure to risk factors and spirometric evidence of airflow obstruction. COPD should be considered in any adult patient presenting with breathlessness, wheeze, chronic cough or sputum production and exercise intolerance and exposure to relevant risk factors.(2)

1.1.2.1 Clinical Features and natural history

The onset of symptoms is insidious and on reflection, patients may have been symptomatic for many years before diagnosis. There is usually a steady decline in symptoms over time as lung function worsens. Breathlessness is usually the predominant symptom and may be associated with wheeze or chest tightness. Cough may initially be intermittent or just associated with exacerbations and may variably be associated with sputum production. Whilst COPD symptoms are typically persistent, they frequently vary from day to day(8) and may be punctuated by acute exacerbations where symptoms temporarily worsen and then recover, although not always back to baseline levels.(2) There may be few signs on physical examination in early disease. However prolonged expiratory time, reduce breath sound, wheeze and evidence of hyperinflation in later disease may be present.

1.2.2.2 Systemic manifestations of COPD

COPD is associated with several systemic manifestations that contribute to functional impairment, poor health related quality of life and excess mortality. Therefore recognition and treatment is important to attenuate the risks and improve quality of life. Smoking induces a systemic inflammatory response, and there may be a 'spill over' of inflammatory mediators from the lung into the systemic circulation, inducing organ dysfunction at others sites. A variety of cytokines, acute phase proteins and inflammatory cells are raised in COPD that may drive some of the underlying systemic manifestations. (9)

Whilst cardiovascular disease and COPD share common risk factors, the prevalence of diabetes, hypertension and coronary artery disease are significantly increased in COPD, even when adjusting for factors including smoking.(10) There is consistent evidence that patients with COPD have a higher mortality from cardiovascular disease than the general population, independent of age, gender and smoking.(11,12)

Pulmonary arterial hypertension may develop as a result of hypoxic vasoconstriction and vascular remodeling in response to pulmonary vessel inflammation.(13) In a study of emphysema patients undergoing right heart catheter measurements, 38% had evidence of pulmonary hypertension, typically with mild to moderate elevations of mean pulmonary artery pressure. Severe pulmonary hypertension was seen in 2% of patients.(14) Pulmonary hypertension may lead to right ventricular remodeling, dilation and eventually failure, which is manifest as cor pulmonale. Pulmonary hypertension occurs more commonly in severe disease and when arterial hypoxaemia is present, conferring worse health status and increased risk of mortality.(15)

Weight loss is common, even in moderate COPD with a reduction in fat free mass.(16) This is in part due to a reduction in skeletal muscle mass associated with fibre shift from type I to the less fatigue resistant type II muscle fibres.(17) Muscle weakness is more strongly associated with worsening airflow obstruction and contributes to poor functional performance and health status.(16,18) Furthermore bone density is also reduced(19) with an increased risk of vertebral fractures.(20)

The risk of depression and anxiety are increased in COPD. When present it is associated with an increased risk of exacerbations and excess mortality.(21)

1.2.2.3 Diagnosis

Spirometry

Spirometry should be the first investigation in suspected COPD to confirm the presence of airflow limitation. It is assessed from post-bronchodilator spirometry and is present when the ratio of the forced expiratory volume in 1 second (FEV_1) to the forced vital capacity (FVC) is less than 0.7. The severity of the airflow limitation is graded by the FEV_1 expressed as a percentage of the predicted value for an individual's age, height and sex. Lower values of FEV_1 represent more severe disease and a grading system has been introduced by GOLD.(2)

Post-bronchodilator FEV_1/FVC	FEV_1 % predicted	GOLD Stage
< 0.7	≥ 80%	Stage 1 – Mild (with symptoms)
< 0.7	50–79%	Stage 2 – Moderate
< 0.7	30–49%	Stage 3 – Severe
< 0.7	< 30%	Stage 4 – Very severe

Table 1.1 GOLD Staging of COPD

Spirometric screening may overestimate the burden of COPD as older patients may have a ratio of FEV_1/FVC less than 0.7 as a normal physiological change in ageing.(22) Additionally, using a fixed ratio may underestimate the degree of airflow obstruction in younger patients.(23) An alternative approach is to use the lower limit of normal that classifies the bottom 5% of population values as abnormal.

The presence of bronchodilator reversibility, defined as a ≥ 12% and 200ml change in FEV_1 15 minutes following the administration of a bronchodilator, is not a useful test in the diagnosis or assessment of COPD. A proportion of patients with COPD will demonstrate significant reversibility but this is dependent on baseline FEV_1 and there is wide intra-test variability. It does not predict any clinically meaningful response to COPD treatments nor does it predict patients with a different clinical course.(24)

The rate at which FEV_1 declines annually is variable in COPD. The UPLIFT study reported a mean loss of 42ml/year in the control group.(25) In the TORCH study found GOLD stage II patients lost a mean of 60ml/year compared to 34ml/year in GOLD stage IV.(26) More recently the rate in annual decline in FEV_1 has been shown to be highly variable. The ECLIPSE study showed that over half of the cohort had a rate of decline no greater than would be considered physiological. There was an inverse relationship between rate of loss and FEV_1. Current smoking and presence of emphysema the biggest risk factors for rapid decline.(27)

Lung volumes and transfer factor for carbon monoxide

Assessment of lung volumes is not required for a diagnosis of COPD. However it may be useful where there is concern over mixed restrictive-obstructive pattern and in the identification of patients with hyperinflation who may benefit from targeted therapies.

The two most common methods employed are body plethysmography and gas dilution techniques. In patients with airflow obstruction, single breath gas dilution techniques may underestimate lung volumes as the tracer gas may fail to equilibrate in obstructed lung segments.(28) This can be overcome by the use of multiple breath techniques that allow for a longer period for equilibration to reduce inaccuracies. However rebreathing techniques are not widely in use.(29) The plethysmographic method of lung volume measurement had been considered the gold standard for measurement of lung volumes in patients with airway obstruction. However the technique may overestimate lung volumes when panting frequencies exceed 1 Hz or in severe obstruction as mouth pressure and alveolar pressure may not be equal.(30)

Markers of hyperinflation such as the residual volume to total lung capacity ratio (RV/TLC) and inspiratory capacity (IC) are more strongly associated with severity of dyspnoea and effort intolerance in COPD compared to FEV_1.(31–33)

Measurement of the transfer factor of the lung for carbon monoxide (TL_{CO}) provides a quantitative measure of gas transfer within the lungs. It is influenced primarily by the surface area and thickness of the alveolar-capillary membrane, the blood volume of the capillary bed and the haematocrit. In emphysema, destruction of the alveolar walls reduces surface area available for gas exchange and thus reduces transfer factor. However in the presence of severe airflow obstruction, gas mixing may not be complete and therefore a reduction in the alveolar volume can also contribute to a low TL_{CO}.(34) TL_{CO} is useful in the assessment of emphysema, particularly where the degree of breathlessness may seem out of proportion to the spirometric severity.

Oximetry and arterial blood gas analysis

GOLD guidelines recommend assessing oxygen saturations with pulse oximetry in all patients with an FEV_1 < 35% predicted. In patients with oxygen saturations less than 92% or in those with signs of respiratory failure and/or cor pulmonale and arterial blood gas should be performed to assess the need for oxygen therapy.(2)

Imaging

Imaging is not routinely required in the work up of COPD. The current GOLD guidelines recommend imaging with chest x-ray or computed tomography (CT) when there is diagnostic uncertainty, presence of red flag symptoms such as haemoptysis or concern over additional features such as bronchiectasis.(2) It is also useful in assessing patients with severe disease who may benefit from lung volume reduction treatments.(35)

Functional assessment

Patients with COPD frequently report impaired exercise tolerance and demonstrate physical inactivity.(36) Assessment of exercise intolerance in COPD is important, as it has one of the strongest associations with early mortality and impaired quality of life.(37) It also represents an objective measure of disability that is more closely linked to a patients activities of daily living.
Cardiopulmonary exercise testing is considered the gold standard for measurement of exercise capacity but its use is limited by the resources available. A variety of other measurements including the 6 minute walk distance(38), incremental(39) and endurance shuttle(40) walk tests have been developed and validated in COPD. These tests are easy to perform in a clinical setting with minimal equipment. The 6 minute walk distance has been shown to be an independent predictor of mortality in COPD.(41)

Prognostic scores

A multi-faceted approach to assessment of COPD with physiological and symptom based parameters is important, as individually these parameters may

predict morbidity and mortality from COPD poorly. Composite scores have been developed which aim to better characterise disease severity, disability and predict prognosis. The most well established of these is the BODE index developed by Celli et al.(42) It comprises four domains: nutrition (**B**MI), airflow **o**bstruction (FEV_1), **d**yspnoea (MRC breathlessness score) and **e**xercise capacity (6 minute walk distance). The BODE index is a 10 point scale with higher scores reflecting increased disease severity. It has been shown to outperform individual parameters such as FEV_1 in predicting 1 year mortality as well as predicting hospital admission.(43) Changes in BODE score following treatment with lung volume reduction surgery(44,45) and pulmonary rehabilitation(46) have been shown to correlate with survival. There is concern that BODE score may underestimate survival in mild disease and overestimate survival in more severe disease.(47) Nevertheless, it remains a useful clinical score that can be calculated in everyday clinical practice.

1.1.2 Causes of COPD

1.1.2.1 Tobacco and smoking

It is estimated that tobacco exposure accounts for up to 80% of COPD in developed countries and up to 50% in developing countries.(48) Epidemiological evidence of the link between tobacco smoking and mortality from chronic bronchitis was recognised by Doll and Peto in 1976. A 20 year cohort study of British doctors revealed an increased mortality related to COPD with a dose-response relationship between the amount of cigarettes smoked and risk of death.(49) In a prospective cohort of 792 London men followed for 8 years, an age related decline in FEV_1 was demonstrated. There appeared to be a group of smokers susceptible to developing COPD who had an accelerated decline in FEV_1. It was estimated that 12% of moderate smokers and 26% of heavy smokers developed airflow obstruction during the course of the study. Furthermore, smoking cessation attenuated the rate of decline in FEV_1.(50) Larger, more recent epidemiological studies have confirmed that the proportion of 'susceptible smokers' is estimated between 18% and 33%.(51,52) What determines susceptibility and how to identify those individuals at risk is not yet clear.

1.1.2.2 Occupational and environmental exposure

Just as cigarette smoke causes an inflammatory response in the lung, other noxious gasses and small particles may incite an inflammatory response within the lung. Atmospheric pollution has been shown to increase the rate of lung function decline in children and adults.(53–55) It has also been shown that exposure to pollution leads to higher levels of diagnosed COPD but causality is harder to demonstrate.(48) Furthermore exposure to pollution accelerates lung function decline in COPD.(56) In developing countries there is strong evidence that burning biomass fuels indoors is a risk factor for COPD.(57)

In the occupational setting exposure to dusts including coal, hard rock mining, tunnel work and concrete manufacturing are associated with the development of COPD.(58,59)

1.1.2.3 Early life exposures

Epidemiological studies suggest a role for pre-natal and early life exposures as risk factors for subsequent development of COPD. The impact of these exposures on the developing lung may alter lung structure, function, metabolism and immunological responses over a lifetime.(60) Impaired lung function in the early years attenuates the peak in spirometry in adulthood(61), meaning the decline in function over time may unmask obstructive lung diseases at an earlier stage in adult life. Pre-term birth is associated with obstructive lung disease in childhood(62) although the impact on the future development of COPD is not fully understood. Maternal asthma, paternal asthma, maternal smoking and childhood respiratory infections have all been identified as risk factors for impaired spirometry in adult life.(63) Indeed, the effect of maternal smoking has not only been shown to impair lung function in infants(64), but may also increase future susceptibility to cigarette smoke in causing COPD.(65) Severe childhood asthma is also a risk factor for adult chronic obstructive pulmonary disease.(66)

1.1.2.4 Genetics

It is likely that the determinants of lung function and susceptibility to risk factors for COPD are polygenetic and interact with the environment. Weak correlations between familial lung function have been described(67) and twin studies suggest that monozygotic twins have a much higher intrapair correlations than dizygotic twins in relation to lung function.(68) However only the alpha-1 antitrypsin deficiency has been well characterised as a cause of COPD. Between 1 and 5% of patients diagnosed with COPD have a deficiency of the serum glycoprotein alpha-1 antitrypsin that results in an increased risk of developing COPD at an early age.(69) Alpha-1 antitrypsin (AAT) is a serine proteinase inhibitor encoded by the SERPINA1 gene. It is the major inhibitor of protease enzymes such as neutrophil elastase. The normal genotype is homozygosity for the M allele. Homozygosity for the Z allele results in low serum levels of AAT as the protein accumulates in the liver where it is produced. Patients with a severe deficiency who are exposed to tobacco smoke or other exposures develop panacinar emphysema predominantly affecting the lower lobes from an early age.(70)

Other candidate genes that may infer susceptibility include interleukin-6 which is associated with cigarette induced inflammation; glutathione-S-transferase, a protein postulated to metabolise carcinogens and CHRNA 3/5 on chromosome 15 which encodes a nicotinic acetylcholine receptor.(71)

1.1.3 Epidemiology of COPD

1.1.3.1 Prevalence

The prevalence of COPD varies widely by geographic regions, gender and socioeconomic groups as a result of differences in exposures and possibly susceptibility to the disease. Overall, COPD is thought to affect between 5 and 10% of the population worldwide.(72) A meta-analysis of 32 studies reporting from 17 countries found variations in prevalence between 0.23% and 18.3%, with most surveys reporting a prevalence of 4-10%.(73) One of the largest population sampling studies, The Burden of Obstructive Lung Disease (BOLD) study, sampled 9425 patients from 12 countries across 6 continents. Subjects each underwent post bronchodilator spirometry and health related questionnaires to determine the presence of COPD based on GOLD criteria. The prevalence of GOLD stage II COPD or higher was 10.1% overall, affecting 11.8% of men and 8.5% of women over 40 years of age, largely reflecting higher smoking rates amongst men previously. Increasing prevalence with age was noted with less than 5% of adults aged 40-49 years affected and between 19 and 47% of men and 6 and 33% of women over the age of 70 affected. There was also an increasing prevalence in those with a higher smoking exposure.(74) The number of affected individuals is projected to rise in coming years reflecting an ageing population and changes in smoking patterns, occupational and environmental exposures worldwide.(75) The increase has been particularly marked in developing countries and in women due to changes in smoking patterns and potentially increased susceptibility.(76)

Prevalence estimates vary widely between epidemiological studies for a number of reasons. Methodological differences including population sampling,

diagnostic criteria and reporting methods often differ substantially between studies. Additionally there are variations in exposure to COPD risk factors between regions.(73)

In the United Kingdom (UK) prevalence data from general practice databases estimate a prevalence of 1.68% for diagnosed COPD. This translates to approximately 900,000 people in the UK with a diagnosis of COPD.(77) However, case finding studies based on national health surveys and spirometric screening suggest that 4.7% of people in the UK had symptoms and spirometry suggestive of COPD.(78) This suggests there are an estimated 3 million people living with COPD in the UK, of which the majority are undiagnosed.(79) Significantly, a substantial proportion of the undiagnosed cases are not confined to mild disease. Of those undiagnosed patients in screening studies, 25% had an FEV_1 < 50% predicted indicating severe or very severe disease.(78)

1.1.3.2 Phenotypes of COPD

Whilst COPD is defined by airflow limitation that is not fully reversible, it is a complex disease with heterogeneity in disease characteristics between patients. More detailed observational studies of COPD have described clinical, biological, radiological and physiological differences between patients. It is difficult to ascertain the true proportion of COPD patients with emphysema as large population studies without significant recruitment bias are lacking. The Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study is a longitudinal observational study of 2164 COPD patients. It found that the percentage of emphysema measured by the number of voxels <950 Hounsfield Units (HU) increased by GOLD stage. The mean percentage emphysema score varied from 11.2% in GOLD stage II patients to 28.6% in GOLD stage IV, compared to 4.2% in healthy controls.(80) There was no description of distribution or lobar heterogeneity in this study. In a primary care study of 110 patients recruited following an acute exacerbation, 51% of patients had radiological evidence of emphysema. It was confined to the upper lobes in 73% of cases. However presence of emphysema was determined by visual

assessment and there was no objective quantification of disease. Presence of emphysema was associated with worse lung function and higher smoking exposure.(81)

1.1.3.3 Morbidity and mortality

Mortality data suggests deaths from COPD are increasing and now represent the 3rd leading cause of death worldwide(1) with an estimated 3 million deaths annually.(82) Despite this, deaths from COPD remain under reported with many cases undiagnosed and deaths attributed to complications from the underlying condition or other comorbidities.(83,84) In England and Wales 26,267 deaths were caused by COPD in 2014, representing 5.1% of all deaths. It ranks as the 5th leading cause of death behind ischaemic heart disease, stroke, dementia and lung cancer.(85) Whilst in tends to occur in older age, it frequently affects people of working age and causes thousands of premature deaths making it the 4th biggest cause of years of life lost in the UK.(86) In recent years, COPD mortality has been declining in men but remained relatively static in women in the UK. This is in part due to the declining numbers of smokers since the 1970's in industrialised countries.(75)

The natural history of COPD is one of progressive decline in symptoms and function interspersed by acute exacerbations. Exacerbations account for a large proportion of the morbidity associated with COPD. The frequency of exacerbations is related to the severity of disease. In the ECLIPSE study exacerbation rates were 0.85 per year for GOLD stage 2, 1.34 per year in GOLD stage 3 and 2.00 per year in GOLD stage 4. Hospitalisations for COPD exacerbation were also related to COPD severity with 7%, 18% and 33% of GOLD stage II, III and IV respectively suffering an exacerbation requiring hospital care in the first year of follow up.(87)

1.1.3.4 Socioeconomic costs

The socioeconomic costs of COPD are substantial. Approximately 40% of people with COPD are of working age. 24 million sick days per year are attributable to

COPD in the UK, costing over £3.8 billion in direct costs to the economy.(79) The costs to the National Health Service (NHS) in 2000-2001 were estimated to be over £900 million.(88) 54% of these costs arose from inpatient care, with 130,000 admissions per year, making it the second most common reason for emergency admission to hospital, using over 1,000,000 bed occupancy days.(89) The National COPD audit found a 13% increase in the number of admissions for COPD between 2008 and 2014.(90) In primary care there are over 1.4 millions consultations for COPD annually.(89)

1.2 Pathophysiology of COPD

The physiological basis of airflow limitation in COPD is the result both airway disease and emphysematous destruction of lung parenchyma. This results in hyperinflation which is a major cause of breathlessness and exercise intolerance.

1.2.1 Airway structure and function

The airways consist of approximately 23 generations of dichotomously branching tubes from the trachea to the alveoli.(91) The main function of the airways is to ventilate the gas exchanging units of the lung. They also play a role in the conditioning of inhaled air, removal of particulate matter and immune defence within the lung.

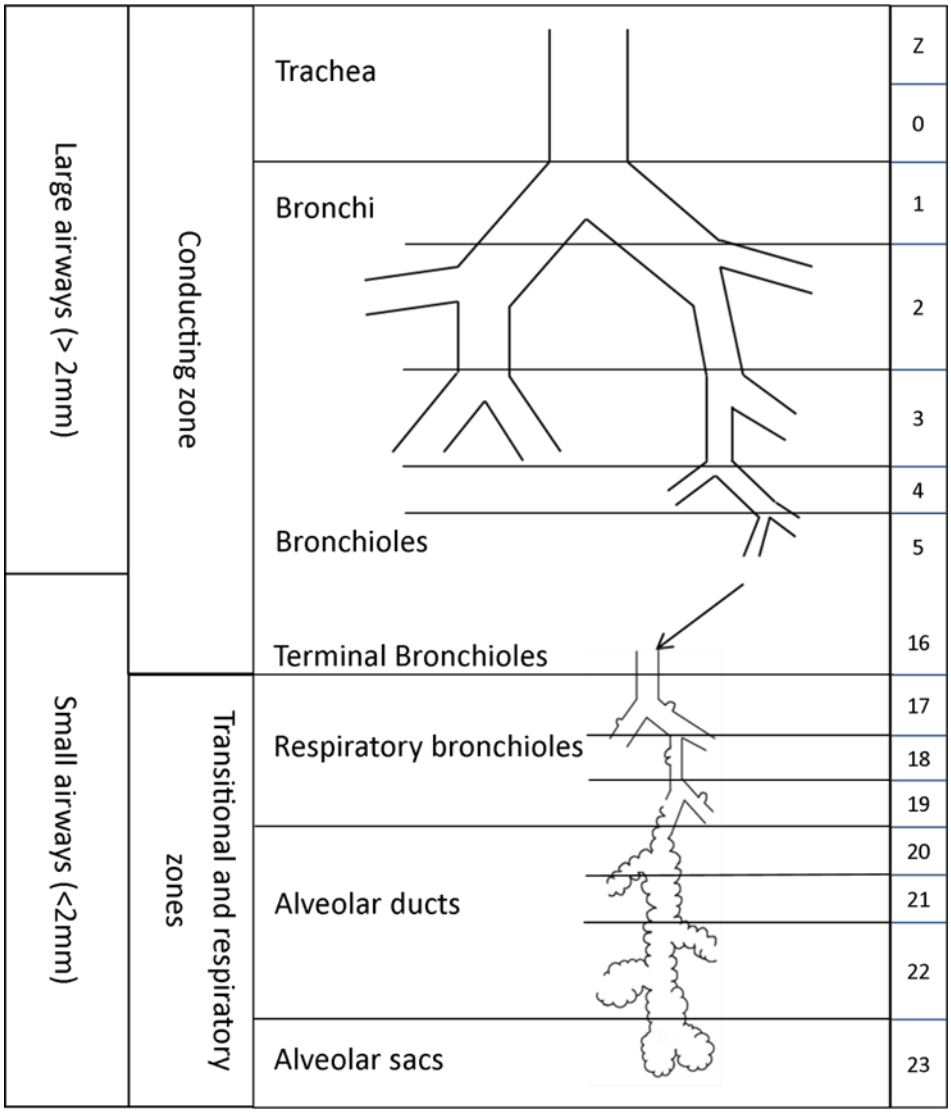

Figure 1.1 Structure of the airways

The first 15th generations of airways are called the conducting airways and take no part in gas exchange. They constitute the anatomical dead space, which is approximately 100-150mls in a human adult.(92) Beyond this region lie the respiratory bronchioles which have occasional alveoli budding from them. These continue to divide until they reach the alveolar sacs with a total surface area of 70-80m^2.(93) These airways take part in gas exchange and comprise the acinar airways.

The small airways refer to those airways less than 2mm in diameter.(94) These occur from approximately generation 8 and include a portion of the conducting airways as well as all the acinar airways. They have important structural and physiological differences from large airways. Firstly they lack the cartilaginous support seen in large airways and lack mucous glands. They are lined by surfactant which reduces surface tension and helps prevent them closing on expiration and at low lung volumes.(95)

Throughout successive airway generations there is a reduction in the length and diameter of the airway. Because of the exponential increase in airway number, there is a rapid increase in cross sectional area with each subsequent generation. This has two major effects on airway physiology. Firstly, for any given flow the velocity of gas transit within the lung decreases with increasing airway generation. The result of this is high velocity flow in the proximal airways which is turbulent and hence density dependent. In the small airways of the lung, flow is laminar and therefore independent of gas density.(96) At the interface of the conducting and acinar airways, there is a change from bulk convective flow to diffusion down a concentration gradient. However the distance for diffusion is small, approximately 0.2mm.(97) Secondly, the resistance to airflow in the small airways is low in health, comprising between 10 and 25% of total airways resistance.(98,99) Small airways resistance is largely independent of lung volume whilst large airways resistance is altered significantly with change in lung volumes.(98) These arrangements in the human lung help to achieve as equitable ventilation to lung units as possible, whilst maintaining low airflow resistance and work of breathing.

1.2.2 Airways disease in COPD

The small airways are the primary site of airflow obstruction in COPD. The seminal work by Hogg et al. examining post mortem lungs of patients with COPD, demonstrated that the resistance of the peripheral airways accounted for 76% of total airways resistance compared to an average of 25% in health.(99) Histological examination of the specimens confirmed the small airways were narrowed and contained mucus plugs. Further work has shown that there is an inverse relationship between airway diameter and peripheral airway resistance.(100) Yanai et al. demonstrated raised peripheral airway resistance in vivo in patients with COPD. Using an anterograde catheter technique performed during bronchoscopy they found a similar proportion of total airways resistance was accounted for by the small airways as described by Hogg et al.(101) Airways resistance is dependent on the number, length and most importantly, diameter of the airways. Pathological studies reveal that there are a number of causes for luminal narrowing in COPD, including inflammatory infiltrates, smooth muscle hypertrophy, mucus hypersecretion and peribronchial fibrosis.(102,103)

Inflammatory changes can be detected in smokers without any evidence of airflow obstruction as measured by spirometry.(104) A respiratory bronchiolitis consisting of luminal infiltrates of monocytes and macrophages within the lumen have been demonstrated in young smokers but without in the absence of airway fibrosis or emphysema. This suggests airway inflammation in response to cigarette smoke is an early stage of the disease that may be reversible.(105) Cosio et al. found an inflammatory reaction associated with airway fibrosis and connective tissue deposition in lung biopsy samples from smokers with normal spirometry. They were able to demonstrate abnormal measurements of small airway function including increased closing capacity and abnormal phase III slopes in a single breath nitrogen washout curve.(106) This has lead the small airways to be termed the “silent zone” where disease may accumulate before it is recognised by traditional lung function measures.(107)

Epithelial inflammation is associated with squamous cell and goblet cell hyperplasia in COPD.(106) The degree of goblet cell hyperplasia correlates with

measures of airflow obstruction.(108) The resultant excessive mucus secretion may occlude small airways, as demonstrated by the presence of mucus plugs.(106) Interestingly, there appears to be a difference in the type and degree of inflammation in small airways between smokers who develop COPD and those smokers that do not. There is an excess of CD8+ T lymphocytes in smokers who develop airflow obstruction(108) which could suggest that differences in the immunological response to smoking between individuals could determine the development of COPD. Hogg et al. found that the extent of inflammation increased with GOLD stage. Increased numbers of neutrophils, macrophages, B lymphocytes, CD4+ and CD8+ T lymphocytes all increased with worsening airflow obstruction.

Whilst inflammatory changes reduces airway diameter, the effect of inflammatory mediators they secrete is likely to play an important role in further structural changes that contribute to airway narrowing. Airway smooth muscle hypertrophy and hyperplasia is associated with increased levels of neutrophilic inflammation, suggesting that inflammatory mediators may drive this process.(109) Contraction of airway smooth muscle has been postulated as the most important determinant of airway diameter in COPD(110) and patients with COPD have significantly increased smooth muscle area compared to non-COPD smoking controls.(108) Peribronchiolar fibrosis is present in the small airways and may also be driven by inflammation and attempts to repair structural airway damage, resulting in further airway narrowing.(96)

The small airways are tethered to the parenchyma by alveolar attachments to the airway walls. This serves to transmit the forces of the lung movement on inspiration, providing maximal diameter and hence minimal resistance to airflow. They also support the airways on expiration by the effect of elastic recoil and prevent dynamic collapse. In smokers, the alveolar attachments are fewer in number, spaced further apart and more likely to be abnormal than non-smoking controls. The degree of abnormalities correlates with both the degree of airway inflammation and the elastic recoil pressure of the lung.(111) It seems likely that they are disrupted by the products of inflammatory cells and contribute to

dynamic airway collapse on expiration, further compounding airflow obstruction.(96)

It has been hypothesised that the inflammatory changes in small airways precede the onset of emphysema, and indeed, may be a factor in the development of it. This was recognised 60 years ago by Leopold and Gough who found that in the centrilobular form of emphysema, airway inflammation was found within the terminal airways supplying the secondary pulmonary lobule.(112) This is further supported by the identification of airway inflammation in young smokers without evidence of emphysema or clinical evidence of COPD.(105) More recent data examining the number and cross sectional area of small airways between 2 and 2.5mm on CT and microCT of explanted lungs shows the number and cross sectional area of small airways is reduced and worsens with the severity of airflow obstruction. The presence of reduced number of small airways is present before the onset of emphysema and further reduces with the severity of emphysema.(113)

The inflammatory changes in the small airways of patients with COPD persist after smoking cessation. However there is a reduction in the number of CD8+ lymphocytes and an increase in B cell lymphocytes in long term ex-smokers.(114) In severe disease, lymphoid follicles are present in small airways which raises the possibility of a role of the adaptive immune system.(115) There is a clonal proliferation of B cells suggesting they may be targeted to antigens present in cigarette smoke, or possibly extracellular matrix proteins, raising the possibility of autoimmunity driving ongoing inflammation in COPD.(116) Additionally infection may contribute to ongoing inflammation within the airways. Latent adenoviral infection is more common in COPD with higher levels of expression of adenoviral proteins within airway epithelial cells associated with increased airways inflammation.(117) The persistence of inflammatory changes suggests that it may become a self perpetuating process leading to further decline in lung function.

1.2.3 Lung parenchymal changes in COPD

Emphysema is defined as dilation and destruction of the lung parenchyma beyond the terminal bronchiole.(7) Whilst emphysema is described in pathological terms, there are clear radiological correlates which allow in vivo identification of the disease. There are three main subtypes of emphysema described: centrilobular, panlobular and paraseptal. Centrilobular emphysema refers to abnormal enlargement of the airspaces centred on the respiratory bronchiole. It is the most common form of emphysema in smokers and has a preponderance for the upper lobes.(118) On CT it appears as foci of low attenuation at the centre of the secondary pulmonary lobule.(119) The centrilobular low attenuation areas may coalesce in severe disease to form bullae. Panlobular emphysema involves the whole secondary pulmonary lobule and is classically associated with alpha-1 antitrypsin deficiency where it typically occurs in the lower lobes. There is diffuse destruction of the alveolar and respiratory bronchiolar walls, giving rise to wide spread low attenuation of the affected areas on CT.(120) Paraseptal emphysema arises at the distal portion of the secondary pulmonary lobule and typically affects areas of the lung adjacent to the pleura. This type of emphysema may give rise to 'vanishing lung syndrome' or giant bullous emphysema. It has an upper lobe predominance and is associated with an increased risk of pneumothorax.(121)

The radiological distribution of emphysema into heterogeneous and homogeneous disease has important clinical implications. Homogeneous disease refers to evenly distributed emphysema throughout ipsilateral lobes, whilst heterogeneous emphysema refers to emphysema predominantly affecting one lobe of the lung and can be either upper or lower lobe. This does not in itself reflect a pathological subtype of emphysema. In the National Emphysema Treatment Trial (NETT), CT scans were scored using a visual scoring system grading emphysematous destruction into quintiles. Heterogeneous disease was defined by a score ≥2 between upper and lower lobes. Overall 55% of patients were classified as heterogeneous with an upper lobe predominance in 65%.(122)

However it would appear that there may important physiological implications of this in response to treatment effects of lung volume reduction which are discussed below. There is no consensus as to what degree of heterogeneity is clinically significant, nor any agreed method of quantifying this as yet.

One of the central theories of how emphysema develops relates to the protease/antiprotease imbalance model. Early evidence of this arose from patients with alpha-1 antitrypsin deficiency, the serine proteinase inhibitor that inhibits neutrophil elastase.(123) Animal models have shown that emphysema can be induced by instillation of elastases into the lung.(124) Furthermore, mice with null alleles encoding the matrix metalloproteinase-12 gene do not develop emphysema when exposed to cigarette smoke.(125) Proteinases are released from inflammatory cells that are induced by smoking and other inhalational injuries. They damage key structural elements of the extracellular matrix such as elastin, resulting in an increase in the alveolar diameter.(126) The development of emphysema is also in part due to the lungs ability to maintain lung structure following injury. The variability amongst individuals to maintain lung structure has been linked to variable expression of trophic and maintenance factors such as vascular endothelial growth factor. This variability may explain why only 20-25% of smokers will develop airflow obstruction in response to smoking and why different phenotypes of the disease occur in response to the same noxious stimulus.(127) In addition to destruction of the extracellular matrix by proteinases there is loss of alveolar cells by apoptosis. This may be induced directly by oxidative stress from cigarette smoke and the mediators released from inflammatory cells.(126)

1.2.4 Expiratory flow limitation

Expiratory flow limitation (EFL) is a key pathophysiological concept in COPD. EFL is said to occur when expiratory flows generated during tidal breathing represent the maximum flow that can be achieved at that operating lung volume.(128) When EFL is present, expiratory flows cannot be increased by recruiting expiratory muscles, creating fixed time constants for emptying of lung units. Therefore flow is entirely dependent on the driving pressure (elastic recoil

of the lung) and airways resistance. Emphysema leads to a reduction in elastic recoil and hence driving pressure for flow. Airways resistance is increased by inflammatory changes and remodeling in addition to the loss of airway supports tethering the airways to lung parenchyma as described previously. (Figure 1.2)

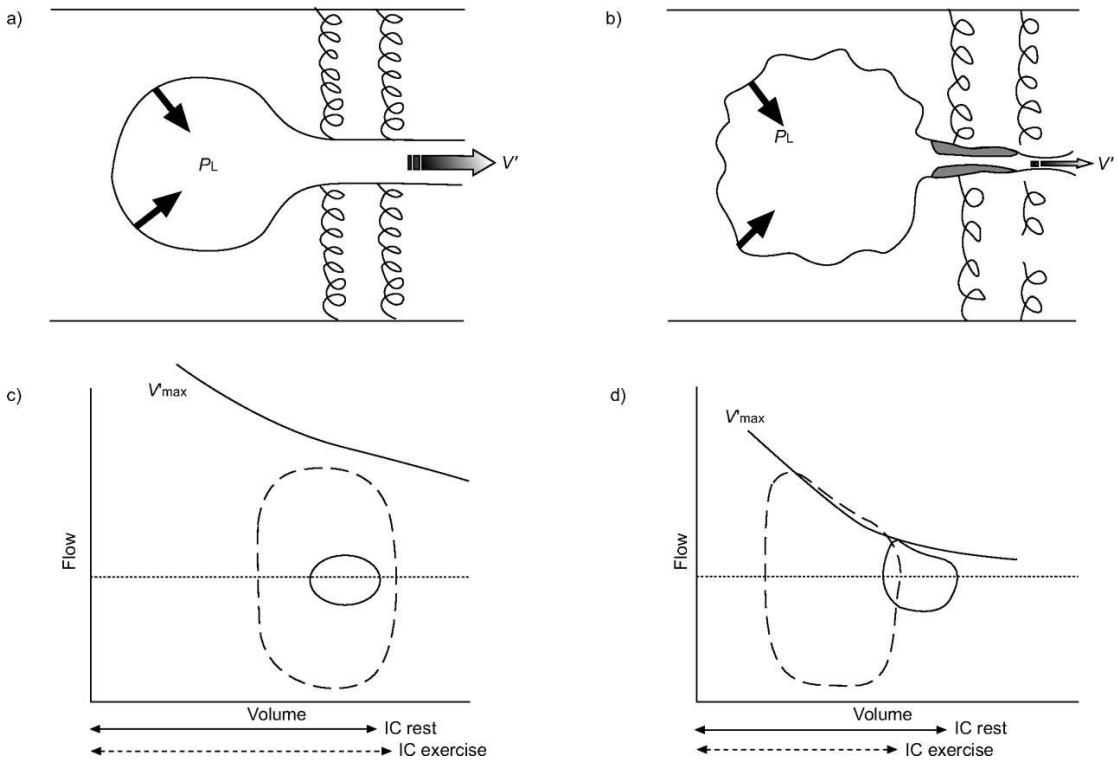

Figure 1.2 Expiratory flow limitation

Schematic representations of alveolar units a) in health and b) in chronic obstructive pulmonary disease (COPD), and their corresponding flow versus volume profiles in c) health and d) COPD. In COPD, expiratory flow limitation (EFL) occurs because of the combined effects of increased airway resistance and reduced lung recoil: alveolar emptying is therefore critically dependent on expiratory time, which, if insufficiently long, results in lung over-inflation (reduction in inspiratory capacity (IC)). The presence of EFL is suggested in COPD by the encroachment of tidal expiratory flows on the forced maximal expiratory flow envelope over the tidal operating lung volume range. In contrast to health, hyperinflation occurs in COPD during exercise, as indicated by the shift in end-expiratory lung volume to the left, i.e.reduced IC.PL: lung recoil pressure; V': gas flow; V'max: maximal expiratory flow. Solid, circular lines: tidal volume at rest; dashed, circular lines: tidal volume during exercise

Reproduced from O'Donnell & Laveneziana (129). Permission not required.

Mead et al. explained why expiratory flow cannot be increased using expiratory muscles, using the concept of the equal pressure point. Ohm's law states that flow is dependent on the driving pressure (alveolar pressure if mouth pressure is assumed to be zero) and airways resistance. Alveolar pressure is a product of the elastic recoil of the lung and the pleural pressure, which is positive during expiration and can be increased by expiratory muscle contraction in health. Pleural pressure is also transmitted to the airways and therefore will result in an increase in airways resistance as it rises. As air is expired there is a pressure drop along the airway and at some point this will match the pleural pressure, creating a transmural pressure across the airway of zero. This results in dynamic compression of airways up stream of the equal pressure point. Any attempt to further increase the driving pressure by increased muscular effort is also transmitted equally to the airways, and thus flow becomes independent of effort.(130)

1.2.4 Lung hyperinflation

Lung hyperinflation refers to an increase in lung volumes. In health, the resting lung volume, or functional residual capacity (FRC), is determined by the balance of forces from outward recoil of the chest wall and inward recoil of the lung.(129) This balance changes with age due to a reduction in the elastic recoil of the lung, such that FRC increases.(131) In emphysema the destruction of elastic fibres results in a more compliant lung and reduced elastic recoil. Thus the balance of outward chest recoil and lung recoil is altered resulting in static hyperinflation.(132) This is measured in the laboratory by static lung volumes using body plethysmography.

Due to expiratory flow limitation, lung units have fixed time constants for emptying. During exercise or acute exacerbations, the increased ventilatory demand results in an increased respiratory rate and therefore a shortened expiratory time. These flow limited lung units do not have sufficient time to empty back to their relaxation volume, leading to incomplete expiration and gas trapping. The end expiratory lung volume (EELV) gradually rises in a process known as dynamic hyperinflation.(129) This actually serves a physiological

purpose in early exercise, since the operating lung volume is shifted upwards and therefore airways resistance falls and expiratory flows can be increased. The result is the ability to increase ventilation to meet demands. However as dynamic hyperinflation worsens, it comes at the cost of an impaired inspiratory reserve volume (IRV), limiting any further increase in ventilation. Furthermore, the lung operating volume is shifted to the top of the pressure-volume curve of the lung, where the lung is less compliant. (Figure 1.3) This results in an increase in the work of breathing since greater pressures have to be generated to maintain tidal volume.(133) The respiratory muscles are placed at a disadvantage since they are maximally loaded.(134) There is an increase in neural drive that is not met by an increase in ventilation (neuromechanical uncoupling) and is sensed as unpleasant dyspnoea.(135)

Dynamic hyperinflation also leads to a number of other deleterious consequences aside from those changes in lung mechanics. Patients with significant V/Q mismatching and increased dead space may become hypercapnic and hypoxic during exercise, partly as a consequence of hyperinflation and impaired tidal volumes.(136) The increase in lung volume results in the generation of intrinsic positive end expiratory pressure (PEEP), compressing pulmonary vessels giving rise to pulmonary hypertension during exercise(137), impairing venous return to the heart and therefore reducing cardiac output.(138) Dynamic hyperinflation important cause of breathlessness and exercise intolerance in COPD.(133)

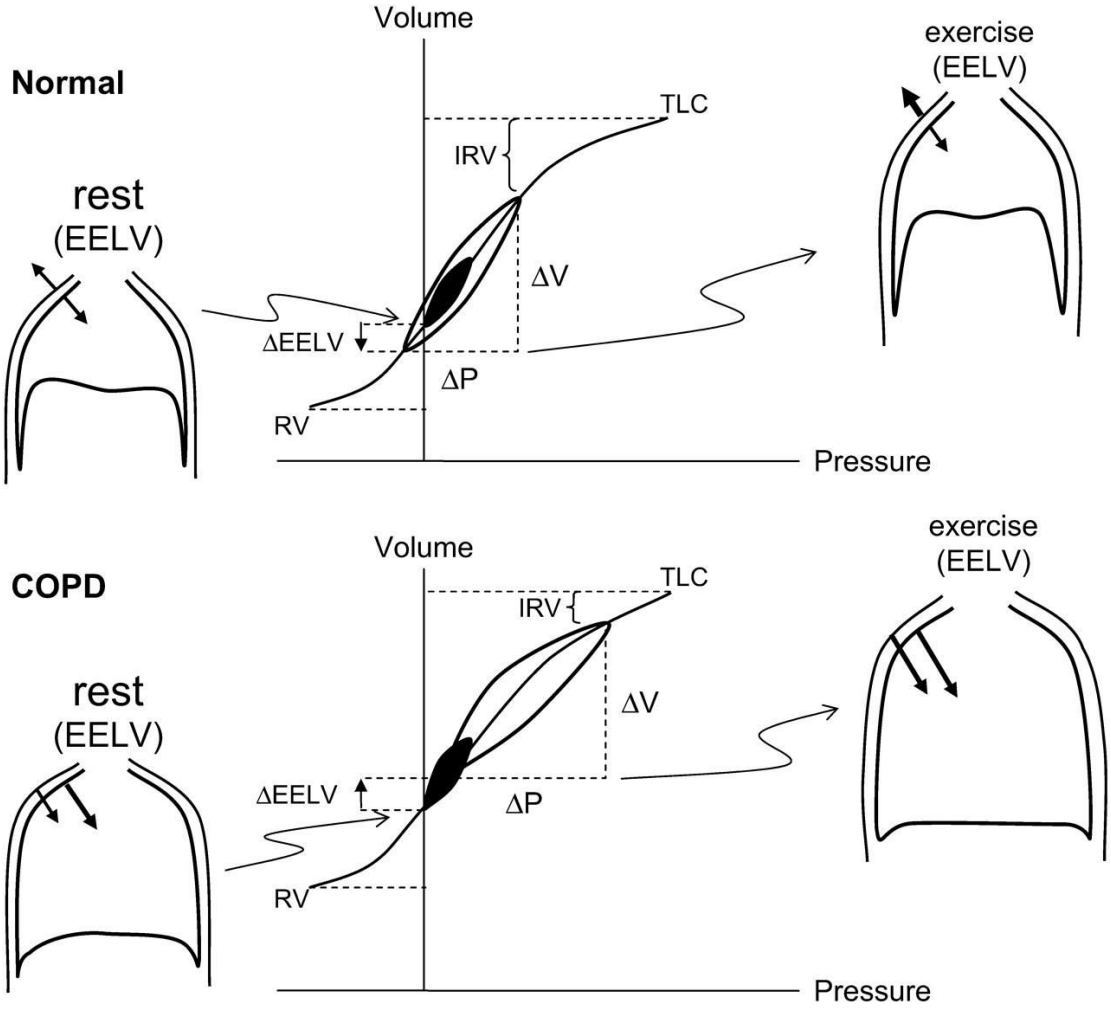

Figure 1.3 Dynamic hyperinflation

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O'Donnell et al. 2007. Proc Am Thorac Soc;4(2):145-68

1.2.5 Respiratory muscles in COPD

Airflow limitation and hyperinflation have profound effects on the respiratory muscles that contribute to breathlessness and exercise intolerance in COPD. Firstly there is increased load as a result of increased inspiratory airways resistance that may be increased fourfold in COPD.(139) The increase in intrinsic PEEP during dynamic hyperinflation represents an additional load that most be overcome before a negative pressure can be generated to initiate inspiration.(140) Additionally, at high lung volumes, the outward elastic recoil of the chest is reduced and further increasing the work of the respiratory

muscles.(141) These factors all increase the work of breathing and oxygen cost of ventilation which contribute to dyspnoea and effort intolerance in COPD.

The second factor is the reduced capacity of the respiratory muscles to generate force in COPD. Hyperinflation results in a shortening of the diaphragm which places them at a mechanical disadvantage since the length-tension relationship is impaired. In this state the diaphragm produces less tension for any given neural activation and ceases to act as an inspiratory muscle at lung volumes close to TLC.(142) Cassart et al. demonstrated this was largely due to a shortening and flattening in the zone of apposition of the diaphragm. This is the caudo-cranially arranged part of the diaphragm that is in contact with the chest wall and elevates the ribs on inspiration.(143) Respiratory muscle weakness is not purely a result of the effects of hyperinflation. Diaphragmatic muscle mass is reduced in COPD to a greater extent than body mass.(144) The expiratory muscles are not mechanically disadvantaged by hyperinflation and yet in some patients with COPD they have been shown to be weak, suggesting a generalised myopathy may also contribute to respiratory muscle weakness.(141) Other factors that contribute to this include malnutrition and muscle wasting. Patients with a reduced fat free mass have functional respiratory muscle weakness compared to those with preserved fat free mass despite similar levels of airflow obstruction.(145) Steroid myopathy also plays a role in reduced muscle mass and weakness.(146)

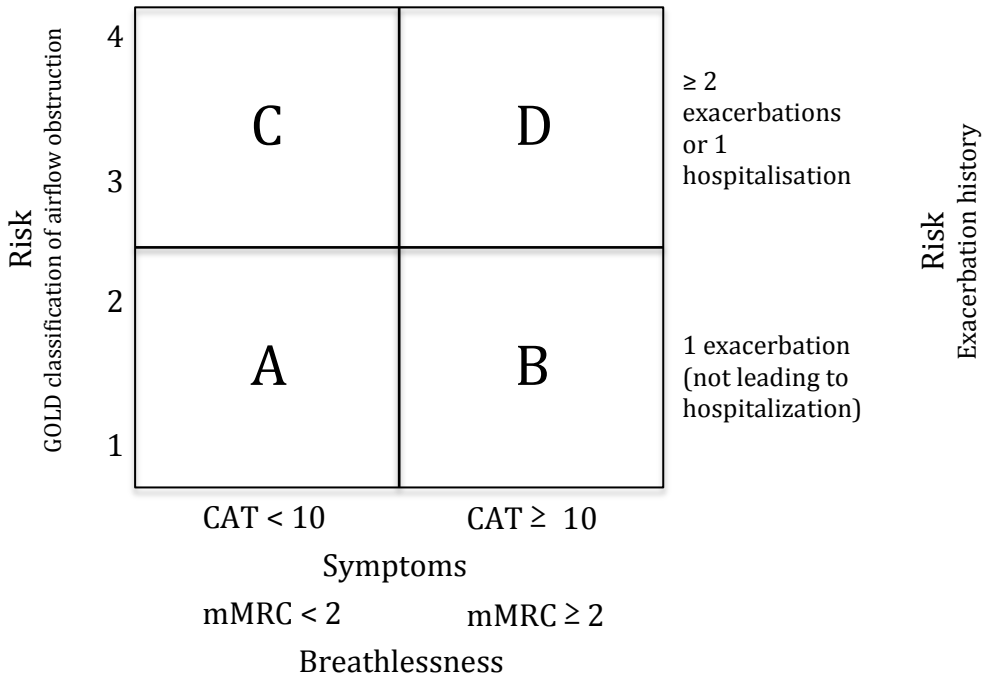
The changes in respiratory muscle mechanics result in a number of adaptations in COPD. In health, when the ratio of pressure generated by the diaphragm to the maximal diaphragmatic pressure is high, fatigue ensues. Since the work of breathing is high and the maximal diaphragmatic pressure is reduced in COPD it might be expected that patients with COPD would fatigue even during tidal breathing at rest.(147) Patients with COPD may adopt a rapid shallow breathing to compensate for this at the cost of alveolar hypoventilation resulting in hypercapnoea.(148) Changes in the respiratory muscle also occur with a fibre shift to increase the proportion of fatigue resistant type I muscle fibres and an increase in mitochondrial density.(149)

1.2.5 Collateral ventilation

Collateral ventilation (CV) is defined as the ventilation of alveolar structures through passages or channels that bypass normal airways. It is thought to occur through a variety of routes including pores of Kohn(150), alveolar-bronchiole connections(151) and interbronchiolar channels.(152) These connections exist in health in both humans and animals but there significance is uncertain. Resistance to flow through collateral channels is extremely high(153) and hence contribute very little to ventilation or gas exchange.(154) However in emphysema, collateral resistance is markedly reduced and is lower than airways resistance.(155) It seems likely that this occurs due to an increase in the size and number of alveolar fenestrations seen in emphysema.(156) Thus it would seem that CV channels offer alternative pathways for ventilation. This may serve to prevent deleterious effects atelectasis and contribute to gas exchange in obstructed lung segments.(157) Interlobar collateral channels have been demonstrated in two thirds of explanted emphysematous lungs and occur more commonly in patients with homogeneous disease.(158)

1.3 Treatment of COPD

The goal of COPD treatment is to reduce exposure to risk factors in order to prevent further decline and to relieve symptoms. The current GOLD guidelines recommend and individualised approach to treatment based on an assessment of severity of airflow exacerbation, symptoms and exacerbation risk. (Figure 1.4)



Patient category	Characteristics	Spirometric classification	Exacerbations per year	CAT	mMRC
A	Low risk, less symptoms	GOLD 1-2	≤ 1	< 10	0-1
B	Low risk, more symptoms	GOLD 1-2	≤ 1	≥ 10	≥ 2
C	High risk, less symptoms	GOLD 3-4	≥ 2	< 10	0-1
D	High risk, more symptoms	GOLD 3-4	≥ 2	≥ 10	≥ 2

Figure 1.4 GOLD model of symptom & risk evaluation for COPD

Reproduced with permission.(2)

1.3.1 Medical management of COPD

1.3.1.1 Smoking cessation

The first goal of treatment should be stop smoking. This is the single most effective intervention in modifying the course of the disease (159) and is the most cost-effective treatment for COPD.(2) A variety of pharmacological and behavioural therapies exist which increase cessation rates. Without any support, long term abstinence may be as low as 5%.(160) Behavioural support in the form of individual counselling, support groups and mobile telephone applications can increase the quite rate by as much as double.(161) In a Cochrane review of nicotine replacement therapies (NRT), the quit rate was increased by 60%.(162) The non-tricyclic antidepressant, bupropion, has both dopaminergic and adrenergic actions, and appears to be an antagonist at the nicotinic acetylcholinergic receptor. It has a similar efficacy to NRT, but there are concerns over neuropsychiatric side effects in vulnerable patients. Varenicline is a partial nicotine agonist and was superior to both NRT and bupropion in a meta-analysis of studies.(163) NICE guidance recommends the choice of agent should take into account patient preference, previous quit attempts and presence of co-morbidities including cardiovascular disease and depression.(164) Combinations of NRT or pharmacotherapy with behavioural support appear to be the most effective method.(165) More recently electronic cigarettes containing nicotine vapour have become increasingly popular but remain controversial due to the lack of rigorous efficacy and long term safety data. Nevertheless there is evidence that they improve smoking cessation rates.(166)

1.3.1.2 Influenza and pneumococcal vaccination

Pneumococcal and annual influenza vaccinations are recommended in patients with COPD. Influenza A vaccination reduces exacerbation rates by over one third (167) and reduces all cause mortality in patients with COPD.(168) The evidence for pneumococcal vaccination in COPD is less robust, with a trend to a reduction in exacerbations but no reduction in pneumonia, hospitalisations or all cause mortality.(169)

1.3.1.3 Inhaled therapies

Bronchodilators

Bronchodilators include a number of drugs that exert their effect by altering airway smooth muscle tone and hence increasing airway calibre. The result is an increase in airflow that can be measured by their effect on spirometric indices such as FEV_1. Beta agonists stimulate the beta-2 adrenoreceptor which are expressed on airway smooth muscle cells. Stimulation results in an increase in intracellular cyclic AMP which causes smooth muscle relaxation through a variety of mechanisms. Muscarinic antagonists inhibit the effects of the parasympathetic nervous system through blockade of pre and post ganglionic muscarinic receptors, resulting in airway smooth muscle relaxation. Additionally both beta adrenoreceptors and muscarinic receptors are expressed in inflammatory cells within the airways.(170)

GOLD guidelines recommend short acting beta-agonists (SABA) or short acting muscarinic antagonists (SAMA) as first line treatments for patients in group A with milder symptoms. SABA's such as salbutamol have a rapid onset of action and a duration of approximately 4 hours, whilst the SAMA ipratropium bromide has duration of 6 hours. Both classes produce small improvements in lung function and quality of life but have no effect on exacerbation frequency.(171)

Where patients suffer with more persistent symptoms, characterised by GOLD group B, there is an option of long acting beta-agonists (LABA) or long acting muscarinic antagonists (LAMA). LABA's include formoterol, salmeterol and the newer ultra-long acting agents such as indacterol and olodaterol. With the exception of the quick acting formoterol, the onset of action is longer than that of SABA's but the duration of action may be 12-24 hours depending on the drug used. Pooled data of studies examining LABA's in COPD found modest improvements in FEV_1 (+47mls), symptoms (SGRQ -2.0 points) and a 20% reduction in exacerbation risk salmeterol but not formoterol.(172)

LAMA's include tiotropium, aclidinium and glycopyronium. A meta-analysis of studies of tiotropium reported an improvement of 118ml in FEV_1, a -2.89 improvement in SGRQ scores and a 22% reduction in exacerbation risk, but no change in mortality.(173) There are small additional improvements in health related quality of life when a LABA is added to tiotropium.(174)

A number of bronchodilators have been shown to reduce dynamic hyperinflation and improve exercise tolerance in COPD.(32,33)

Inhaled corticosteroids

Inhaled corticosteroids (ICS) are primarily used to reduce the risk of exacerbations in patients who are at high risk in GOLD groups C and D. Meta-analysis of a number of different ICS at varying doses estimated a 17% reduction in the risk of exacerbation, equating to -0.26 exacerbations per patient year. A reduction in the rate of decline in health related quality of life was also reported.(175) The TORCH study published in 2007, examined the effect of inhaled fluticasone, salmeterol or a combination of the two versus a placebo over a three year follow up period. In the fluticasone group, the reduction in the decline in health related quality of life was 2.0 points in the SGRQ score. They also reported a significant reduction in the rate of decline in FEV_1 compared to placebo (176), but this has not been born out in the meta-analysis of ICS in COPD. Nor has there been any convincing evidence of mortality improvement with ICS. Recent re-examination of the ISOLDE data with stratification of patients by peripheral blood eosinophils has identified a group of patients who may benefit more from ICS. Those patients with a blood eosinophil count >2% of total leucocyte count had a significant reduction in the rate of decline in FEV_1.(177)

Combination therapies of ICS and LABA appear to have additive effects in improving symptoms and reducing exacerbation risk. When compared to ICS alone, the combination therapies provided a 9% reduction in exacerbation risk as well as a small improvement in FEV1 (40mls) and health related quality of life.(178)

Triple inhaled therapy (LAMA + ICS/LABA combination) is recommended in patients with a high risk of exacerbations or decline and significant symptoms (GOLD Group D). There is less evidence available to recommend this approach, however a recent meta-analysis demonstrated a small improvement in lung function and a significant improvement in health related quality of life.(179) The recent TRIOLOGY study of beclomethasone, formoterol and glycopyrronium in a single inhaler for patients with severe COPD was found to improve lung function, symptoms and exacerbation rates compared to beclomethasone and formoterol alone.(180)

ICS have a number of significant side effects that need to be taken into account when assessing the risk-benefit balance for treating patients. Oral candidiasis and sore throat are the most common risks. Perhaps the most concerning is the increased rate of pneumonia seen with long term ICS use. A meta-analysis of studies examining fluticasone and budesonide use found a 78% increase in the risk of non-fatal pneumonia with fluticasone use, equating to an extra 18 cases of pneumonia per 1000 patients treated. Budesonide appeared to have a lower risk of non-fatal pneumonia with an extra 6 cases per 1000 treated. There was no increased risk of serious pneumonias or pneumonia related mortality. Therefore this increased in pneumonia risk needs to be balanced with the potential benefit from the reduction in COPD exacerbations.(181)

1.3.1.4 Oral therapies

Corticosteroids

Short courses of oral corticosteroids are used in acute exacerbations of COPD. They have been shown to improve FEV_1, shorten hospital stay and reduce the risk of treatment failure (defined as death, mechanical ventilation, readmission and intensification of treatment). Two week courses are no less effective than longer courses.(182)

Long term treatment with oral steroids is not recommended. High doses of oral steroids may improve lung function over a short period but do not deliver

meaningful improvements in symptoms. Lower doses (<15mg prednisolone) do not appear to be effective.(183) There are significant long term side effects of steroids, including myopathy which contributes to both skeletal and respiratory muscle weakness.(184) Diabetes, osteoporosis and adrenal suppression may also be induced by long term steroid use. There are some patients who are unable to wean off a maintenance dose and these patients should have their bone mineral density monitored and be offered prophylaxis against insufficiency fractures.

Methylxanthines and phosphodiesterase inhibitors

Methylxanthines, such as theophylline exert a bronchodilator effect mediated through non-specific phosphodiesterase inhibition. In a Cochrane meta-analysis there was a mean improvement in FEV_1 of 100mls and a 210ml improvement in FVC. Maximal oxygen uptake was improved by 195mls/min but there was there is limited evidence that they produce any meaningful improvements in symptoms or walking distance.(185) They have a narrow therapeutic range which requires monitoring of serum levels. Side effects, notably nausea and arrhythmias are common and may limit tolerability for patients. There are also significant drug interactions which need to be taken into account.

Phosphodiesterase 4 (PDE4) inhibitors such as roflumilast are thought to promote bronchodilation and have anti-inflammatory effects by increasing levels of cyclic adenosine monophosphate in inflammatory cells. A meta-anaylsis of PDE4 inhibitors demonstrated small improvements in FEV_1 (45.6mls) and a modest effect in reducing exacerbations(OR 0.78). There is a small but clinically insignificant improvement in symptoms measured by the SGRQ (-1.04).(186) Side effects include gastrointestinal upset, weight loss and headache. They are not currently recommended for general use in NICE guidance.

Mucolytics

Mucolytics such as carbocysteine and N-acetylcysteine reduce the viscosity of sputum and make it easier to expectorate. In patients with a chronic productive

cough they reduce the number of exacerbations by 0.48 per patient year and number of days of disability by 0.48 per month. Whilst individual studies have reported improvements in FEV_1 and SGRQ scores, the meta-analysis failed to find any statistically significant difference.(187) Mucloytics should be continued if the patient experiences a benefit in symptoms or exacerbation frequency, but otherwise discontinued after a trial.

Long term antibitoics

Chronic mucus hypersecretion in COPD is a risk factor for airway bacterial colonisation which may drive the cycle of inflammation and infection. Whilst it might be presumed that antibiotics reduce bacterial load, a study of three antibiotics from different classes in stable COPD, failed to show any significant reduction.(188) However macrolide and fluoroquinolone antibiotics have direct immunomodulatory effects by reducing the production of pro-inflammatory cytokines.(189)

A meta-analysis of long term antibiotics (azithromycin, clarithromycin, erythromycin and moxifloxacin) demonstrated a significant reduction in the number of patients suffering an exacerbation. Quality of life was also improved with a reduction of 1.7 points in SGRQ score but there was no difference in hospitalisation or lung function.(190) There is a risk of hearing loss with azithromycin and monitoring is recommended. Additionally caution is needed in patients with a long QT interval on an electrocardiogram due to the risk of arrhythmias.

1.3.1.5 Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) combines a tailored programme of exercise with education and support. It is a multidisciplinary programme that may be delivered at home or more usually in a group setting supervised by physiotherapists. Its aim is to restore the patient to the best possible physical and social functioning. It addresses deconditioning, peripheral muscle dysfunction and approaches to self-management and coping. A typical

programme will last for 6-8 weeks and include strength and endurance training, respiratory muscle training, disease education and self management.(191)

Trials of pulmonary rehabilitation have demonstrated consistent improvements in symptoms, exercise capacity and an enhanced sense of control over the patients condition.(192) There have been conflicting results with regards hospitalisation following PR. Some trials have reported a reduction in the risk of hospitalisation(193) whilst others have shown no benefit, but a reduced length of stay during admission.(194)

The beneficial effects of PR decline over time, such that at one year post rehabilitation, participants return to their baseline activity and wellbeing levels.(195) Repeated courses of PR, typically provided after one year, provide similar short-term improvements but an additive effect.(193) Current NICE guidance in the UK recommends all patients who feel disabled by COPD should be assessed for rehabilitation and be prescribed a maintenance programme following treatment.(196)

1.3.1.6 Oxygen

Supplementary oxygen in hypoxaemic patients is one of the few interventions in COPD that has been shown to improve survival. Current guidelines recommend long term oxygen therapy (>15 hours per day) in patients with severe, resting hypoxaemia ($pO2 \leq 7.3kPa$) or in those with more moderate hypoxaemia ($pO2 \leq 8kPa$) and evidence of pulmonary hypertension, cor pulmonale or polycythaemia.(197)

The evidence for ambulatory oxygen is less robust and largely derived from laboratory experiments where improvements in endurance time, maximal exercise ability and breathlessness scores have been demonstrated.(198) There is no evidence to suggest that ambulatory oxygen improves quality of life, breathlessness scores or functional ability outside of the laboratory and therefore the current GOLD guidance does not recommend its use.(197)

1.3.2 Surgical management of COPD

It is clear that many of the medical treatments for COPD have only a small effect in improving symptoms, often below what is considered the minimum clinically important difference. Only two treatments have been shown conclusively to attenuate the decline in disease and improve survival. Part of the apparent lack of response to treatment lies in the heterogeneity of the disease. Whilst the current GOLD guidelines promote and 'individualised' treatment regime, this is based on crude physiological (FEV_1) and symptom/risk based characterisation and does not truly reflect the broad range of phenotypes of the disease. Secondly, in the emphysematous patient, a substantial proportion of the disease is related to pathological changes in lung mechanics that may not be amenable to pharmacological intervention. This undoubtedly leads to over-treatment of patients with COPD who will gain limited benefit from pharmacological treatments but are nevertheless exposed to potentially serious side effects.

The surgical and bronchoscopic treatments for COPD have largely focused on the emphysematous phenotype of COPD. This has required detailed physiological characterisation to identify patients with abnormal lung mechanics but meant the treatment has focused on a much smaller group of patients.

1.3.2.1 Lung volume reduction surgery

LVRS was pioneered in the 1950's by Brantigan and Mueller. They performed multiple wedge resections of the most emphysematous portions of lung through a thoracotomy. They hypothesized that removal of the most compliant parts of the lung would increase elastic recoil in the remaining lung and thus help relieve airways obstruction. They published a series of 33 patients and suggested symptomatic improvements in 75% of survivors.(199) However, they presented no objective measurements of improvement and concerns regarding operative morbidity and mortality lead to the procedure being abandoned.(200)

The procedure underwent a resurgence in the 1990's after improvements in surgical techniques made the operation safer. Cooper and colleagues resected

20-30% of the most emphysematous lung using a stapling technique performed through a median steronotomy. At a mean follow up of 6 months, they reported significant improvements in lung function with an 82% improvement in FEV_1 and 27% improvement in FVC. Symptom scores also improved substantially but there was no change in walking distance. Whilst prolonged air leaks occurred in over half of the patients, there were no deaths during the follow up period.(201) The striking results led to a resurgence in interest in LVRS. Despite the renewed interest, Medicare funding for the procedure in the United States was withdrawn due to lack of evidence of efficacy and concern over mortality rates.(200) This led to the development of the National Emphysema Treatment Trial (NETT) designed to examine the efficacy and safety of the treatment.(202)

The NETT study randomised 1218 patients to LVRS or best medical care. Both arms of the trial required all patients to undertake a 6-10 week course of pulmonary rehabilitation. Patients undergoing surgery had bilateral resections either through a median sternotomy or video-assisted thoracoscopic surgery. Prior to the results being published, the study group identified a group of patients who had a high surgical mortality, exceeding a pre-determined threshold. Those patients with and FEV_1 <20% predicted and with either a low TL_{CO} or homogeneous disease had a 30 day mortality of 16% compared to 0% in the medical care group. By 6 months, 35% of the high risk group had died. In the survivors there were small but significant improvements in FEV_1, exercise capacity and walking distance, but no improvement in quality of life. Following this publication, no further high risk patients were enrolled into the trial.(203)

The primary outcome for the study was mortality, in which there was no significant difference at the mean follow up of 29 months. There was an excess of early mortality (90 day) in the surgery group of 7.1% compared to 1.3% in the medical group. Surgical patients were however more likely to gain significant improvements in exercise capacity, lung function and quality of life. When the high risk patients were excluded, the 90 day mortality for surgical patients was 5.2%.

A sub-group analysis identified four groups based on pre-treatment exercise capacity and distribution of emphysema. Those patients with non-upper lobe emphysema and a high exercise capacity also had an increased mortality compared to medical treatment (OR 2.06, p = 0.02) and no significant benefits in exercise capacity or quality of life. Patients with non-upper lobe emphysema but a low exercise capacity had no mortality benefit or change in exercise capacity, but did have significant improvements in quality of life. It was the upper lobe emphysema patients who fared best with significant improvements in quality of life, lung function and exercise capacity, irrespective of pre-treatment exercise capacity. But those with a low exercise capacity also had a 53% reduction in mortality at follow up, making LVRS one of the few treatments in COPD to affect mortality, at least in a small subgroup of patients.(122) The long term outcomes of the NETT cohort demonstrated the durability of LVRS over a median follow up of 4.3 years. The survival benefit in the upper lobe predominant, low exercise capacity persisted with a relative risk of death of 0.57 ($p<0.01$). Despite a decline in exercise capacity, symptoms and lung function over time, significant benefits persisted in all upper lobe emphysema patients.(204)

Operative complications included a major respiratory complication in 29.8% of patients (tracheostomy, failure to wean, pneumonia, at least 1 postoperative intubation, or ventilator use for 3 or more days) and a major cardiac co-morbidity in 20% (arrhythmia requiring treatment, myocardial infarction or pulmonary embolus).(205) Post-operative air leaks developed in 90% of patients with a median duration of 7 days.(206) At one month 28.1% of patients undergoing surgery were still hospitalised or in a rehabilitation or care facility.

Despite strong evidence for the use of LVRS in selected patients, the uptake in both the US and Europe has been poor. The number of operations performed in the UK has remained relatively static at 100-140 per year between 2009 and 2014.(207) A survey of UK physicians' attitudes towards LVRS identified that there is often an overestimation of operative risk and lack of local multidisciplinary teams for assessment of patients may hamper referrals.(208) More recent audit data suggests the morbidity and mortality from surgery is

significantly lower, particularly with increased use of VATS surgery and staged bilateral procedures.(209) It does however remain an expensive operation with a cost per quality adjusted life year (QALY) of $77,000 dollars at 5 years in the NETT trial in the group of patients who derive the most benefit. The projected cost per QALY is projected to decrease significantly with time.(210)

1.3.2.2 Bullectomy

Giant bullae largely result mainly from emphysematous destruction of the lung although may occur congenitally.(211) They are considered giant when they occupy greater than a third of the hemithorax. They are thought to cause airflow obstruction through compression of surrounding tissue. Bullectomy is indicated when there is symptomatic and physiological impairment associated with a giant bulla.(200) Data regarding the safety and efficacy of bullectomy comes from a number of small cases series from a variety of authors reported over a long period. A systematic review of the literature identified that patients with an FEV_1 < 50% predicted and with normal underlying lung parenchyma are the most likely to benefit from treatment. Those with severe lung function impairment, particularly low TL_{CO} and extensive underlying emphysema are at increased operative risk and have less favourable improvements in symptoms and lung function. Long term follow up data is sparse, but it was estimated that sustained improvement was seen in a third to one half of patients. Operative mortality was estimated at 8%.(212)

1.3.2.3 Lung transplantation

Lung transplantation is a well established treatment for many end stage lung diseases. COPD is now the commonest reason for transplant referral, accounting for 38% of all transplants performed in the last 20 years.(213) However for most patients it is not a realistic prospect since most patients with COPD will not reach the end stage of their disease until after the age of 65, after which mortality for transplant rises significantly. This is compounded by the excess of co-morbidities that many patients with COPD have, that would preclude them as transplant candidates.(214)

It is debated whether there is any mortality benefit for patients with COPD. The median survival of a COPD undergoing lung transplant is 7 years.(213) Given the natural course of the COPD, it is possible that lung transplant may shorten the duration of life. Nevertheless it offers the prospect of improved quality of life and should be considered in appropriate patients in a timely manner.(214)

1.3.3 Bronchoscopic lung volume reduction in COPD

Bronchoscopic methods of lung volume reduction were developed following the rise in interest in LVRS. With concerns over operative mortality and morbidity, they were designed with the aim of achieving the success of LVRS with a less invasive technique, shorter recovery time and fewer complications. A number of techniques have been evaluated and this thesis will review those that are currently still in use.

1.3.3.1 PneumRx Lung Volume Reduction Coils®

The PneumRx Lung Volume Reduction Coil®, (LVRC) are medical implants designed to treat hyperinflation in patients with emphysema. They are formed from a nickel-titanium alloy known as nitinol that was developed in 1959 by the Naval Ordinance Laboratories in the United States. Nitinol is a shape memory alloy that exhibits superelasticity. The implants can be cast to a predetermined shape that allows deformation under stress and recovery of the predetermined shape upon release of the stress.(215) This facilitates insertion into the emphysematous lung in a minimally invasive manner through a therapeutic bronchoscope.

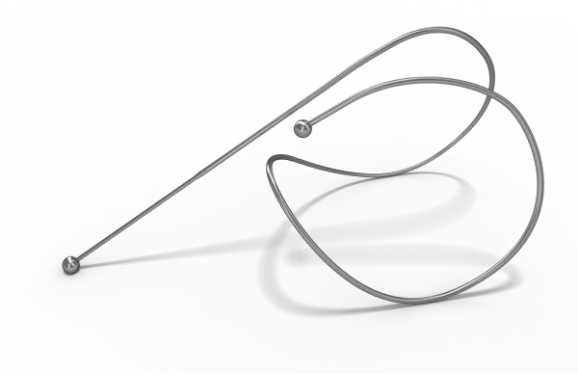


Figure 1.5 The PneumRx Lung volume reduction coil

Nitinol is biocompatible and has been used extensively in medical implants and devices including intravascular stents and bone implants. Whilst nickel is both allergenic and toxic, the amount of nickel ion release from the nickel containing implants is within safe levels.(216)

The LVRC system is a two part system consisting of the nitinol coil and a delivery system. The coils are manufactured in three sizes: 100mm, 125mm and 150mm. They are provided as sterile single use devices in individual cases. The most proximal end of the coil tapers and is less rigid, terminating in a smooth atraumatic ball. This is designed to reduce stress on the proximal airway walls and facilitate recapture.

The delivery system consists of:

- Guidewire (figure 1.6a)
  This is a specialised flexible wire with an atraumatic tip which can be passed into the distal airways under fluoroscopic guidance. It allows identification of suitable airways for treatment and includes three radiopaque markers that determine the size of coil to be deployed.

- Delivery catheter (figure 1.6b)
  The delivery catheter serves as a conduit to pass the coil into the target airway. It has a soft, radiopaque tip and a braided construction to resist kinking.

- Biopsy forceps (figure 1.6c)
  The non-serrated forceps allow the proximal tip of the coil to be grasped and pulled back into the loading cartridge. They are released when the coil is deployed and withdrawn through the delivery catheter.

- Loading cartridge (figure 1.6d)

The loading cartridge is a rigid plastic tube that is passed over the biopsy forceps. As the coil is drawn into the cartridge it is straightened which allows it to pass through the delivery catheter.

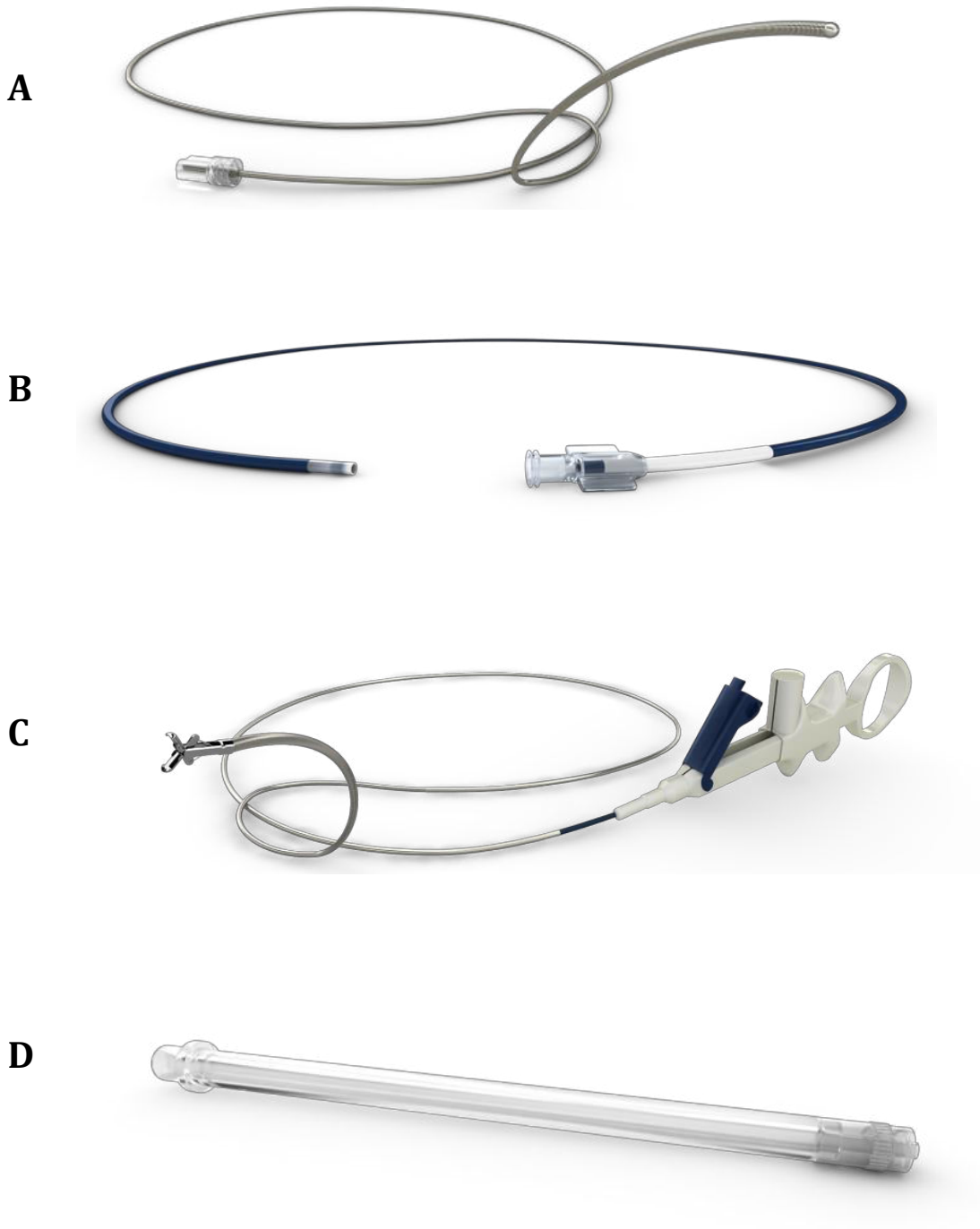


Figure 1.6 Lung volume reduction coil delivery system

a) guidewire b) delivery catheter c) forceps d) loading cartridge.

3.1.3 Clinical effectiveness

The clinical efficacy of lung coils has been tested in a number of European studies, the majority of which have been performed as staged procedures conducted under general anaesthetic. The inclusion criteria have been derived from the NETT study, including patients with GOLD stage 3 and 4 COPD who have severe hyperinflation and impaired exercise tolerance. Clinically significant improvements in lung function, quality of life and walking distance have been demonstrated with response rates exceeding the MCID in greater than 50% of patients. The results of the early studies, including the first randomised controlled trial of coils have been summarised in a meta-analysis. The results of this are presented in table 1.2.

	6 month follow up (n = 125)		12 month follow up (n = 95)	
Outcome	**Mean ±SD**	**p value**	**Mean ±SD**	**p value**
ΔRV (L)	-0.51 ±0.85	<0.001	-0.43 ±0.72	<0.001
ΔTLC (L)	-0.26 ±0.69	<0.001	-0.22 ±0.55	<0.001
ΔRV/TLC ratio	-0.04 ±0.07	<0.001	-0.04 ±0.06	<0.001
ΔFEV_1 (L)	0.05 ±0.19	<0.001	0.05 ±0.21	0.001
ΔFVC (L)	0.22 ±0.48	<0.001	0.22 ±0.43	<0.001
ΔTLCO (% predicted)	-0.61 ±7.8	0.440	0.01 ±5.1	0.993
ΔSGRQ score	-9.5 ±14.3	<0.001	-7.7 ±14.2	<0.001
ΔmMRC score	-0.56 ±1.05	<0.001	-0.53 ±0.86	<0.001
Δ6MWD	44.1 ±69.8	<0.001	38.1 ±71.9	<0.001

Table 1.2 Absolute change in clinical parameters at 6 and 12 months post treatment.(217)

To date three randomised controlled trials of lung coils have been published. The most recent of which, the RENEW trial(218), included data presented in this thesis. The first randomised controlled trial to be published in 2013 was the RESET trial in the UK. This included 47 patients with both heterogeneous and homogeneous disease and reported outcomes at 90 days following the completion of treatment.(219) Whilst the trial was not blinded and had no sham treatment, clinically meaningful improvements in quality of life, lung function

and exercise capacity were once again reported. 65% of patients treated achieved the MCID of a ≥ 4 point improvement in SGRQ scores and 74% met the threshold of a 26m improvement in 6 minute walk distance. The REVOLENS trial conducted in France was published in 2016 and examined both the efficacy, safety and cost-effectiveness of the lung coil at 6 and 12 months.(220) Whilst the primary outcome of a ≥ 54m improvement in 6 minute walk distance was met, the overall between group difference in walking distance was smaller than previously reported trials. Nevertheless, consistent with the other published data, significant improvements in lung function and quality of life were achieved with lung coil treatment. The clinical outcome data is summarised in table 1.3.

	RESET trial(219) (n = 47)		**REVOLENS trial(220) (n = 100)**			
	90 days post treatment		**6 months post treatment**		**12 months post treatment**	
Outcome	**Mean (CI)**	**p value**	**Mean (CI)**	**p value**	**Mean (CI)**	**p value**
RV (L)	-0.3 (-0.59 to -0.04)	0.03	-0.37 (-0.09 to -∞)	0.01	-0.36 (-0.10 to -∞)	0.004
TLC (L)	-0.11 (-0.29 to 0.07)	0.22	-0.20 (0.03 to -∞)	0.09	-0.20 (-0.04 to ∞)	0.06
FEV1 (% change)	10.62 (1.12 to 20.12)	0.03	11 (6 to ∞)	-.001	11 (5.2 to ∞)	0.002
SGRQ score	-8.36 (-16.24 to -0.47)	0.04	-13.4 (-8 to -∞)	<0.001	-10.6 (-5.8 to -∞)	<0.001
mMRC score	-0.15 (-0.60 to 0.3)	0.5	-0.45 (-0.17 to -∞)	0.01	-0.4 (-0.05 to -∞)	0.02
6MWD	63.55 (32.57 to 94.53)	<0.001	21 (-4 to ∞)	0.06	21 (-5 to ∞)	0.12

Table 1.3 Between group differences in clinical outcomes in the RESET and REVOLENS trials

3.14 Clinical Safety Data

The safety profile of the coils has appeared acceptable in the published literature to date. The meta-analysis of coil trials to 2014 included 259 bronchoscopies in 140 patients, demonstrating that patients with severe COPD could tolerate a procedure under general anaesthesia or sedation without serious complications. No procedural serious adverse events were reported and there were no deaths within the first 30 days of follow up. Severe exacerbations of COPD requiring hospitalisation, pneumonia and pneumothorax are the most common serious

adverse events reported in the first 30 days following treatment. All resolved with medical management. These adverse events occur less commonly in the longer term follow up of patients.(217) The adverse event data from the meta-analysis is presented in table 1.4.

Event	< 30 days		30-180 days		180-360 days	
	Mild	Severe	Mild	Severe	Mild	Severe
Chest pain	30.1%	2.1%	7%	4%	3.1%	0%
Haemoptysis	68.5%	0%	4.8%	0%	2.1%	0%
Pneumothorax	8.5%	4.2%	0.8%	2.4%	1.0%	0%
LRTI	2.9%	1.4%	10.4%	0%	3.1%	0%
COPD exacerbation	37.1%	5.7%	77.6%	14.4%	52.0%	13.5%
Pneumonia	7.1%	6.4%	5.6%	4.8%	3.1%	12.5%
Dyspnoea	12.1%	0.7%	14.4%	4.8%	0%	0%
Death	-	0%	-	1.6%	-	3.1%

Table 1.4 Adverse events following coil treatments (217)

LRTI: lower respiratory tract infection

In the RESET trial the total number of serious adverse events was higher in the treatment group, affecting 15% of patients compared to 4% in the control group ($p = 0.02$) in the first thirty days of follow up. There was no significant difference in SAE's from 30 to 90 days, occurring in 7% of treated patients and 13% of control patients ($p > 0.99$).(219) The REVOLENS trial found an excess of pneumonia occurring in 18% of patients in the first 30 days compared to 4% in the control group ($p = 0.03$).(220) There is some debate regarding the pneumonia diagnosis as coil associated opacities have been seen on chest X-ray following procedures but without a systemic inflammatory response. It is not known whether these opacities represent a local inflammatory response rather than a pneumonia with a microbiological cause.(217) No deaths were reported in the early follow period in either trial and there was no significant difference in deaths up to 12 months follow up, occurring in 8% of treated patients and 6% of control patients ($p = 0.99$).(219,220)

Little is known about the long term safety and side effect profile of lung coils since most of the published data is limited to 1 year follow up. Hartman et al. have published their long term clinical follow up data in 35 patients, with 22 patients followed up to 3 years. There were no late pneumothoraces, coil migration or major haemoptysis. Hospitalisation for COPD exacerbations occurred in just over one third of patients in years 2 and 3 of follow up and pneumonia occurred in 5% and 7% of patients respectively.(221) The RENEW trial will continue to follow up patients for 5 years to assess longer term safety.(218)

1.3.3.2 Endobronchial valves

Endobronchial valves aim to cause volume reduction through occlusion of an entire lobe. They are made from a silicone coated nitinol frame with a one way valve. This allows air and mucus to escape from the occluded lobe but prevent air entering the lobe on inspiration. Trapped air is absorbed and lobar collapse ensues. Endobronchial valves can be inserted under conscious sedation using a bronchoscope. A variety of sizes are available and this requires measurement of the airways using either a catheter or calibrated balloon to ensure adequate occlusion.

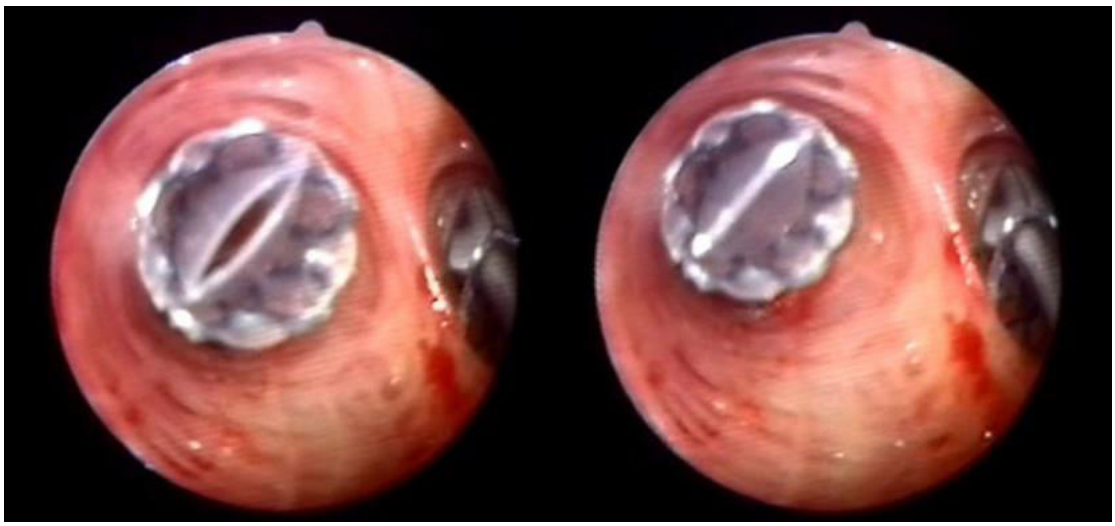


Figure 1.7 Endobronchial valves

Endobronchial valves placed in segmental airways. On expiration (left) and inspiration (right).

Early investigation of endobronchial valves was by a series of small, single center uncontrolled studies.(222–227) In a meta-analysis of these trials, a significant improvement in FEV_1 of 10.7% or 60mls, increase in FVC of 9.0% or 120mls and a reduction in RV of -4.9% or 0.35L were achieved. Exercise capacity improved 23% equating to 36.9m in the 6 minute walk distance. Patients with more severe disease or an RV >225% had more significant improvements in FEV_1. A unilateral, lobar occlusion also produced more impressive results and helped identify the optimal strategy for placement of valves.(228)

This lead to the VENT trial as the first randomised controlled trial of 321 patients in a 2:1 ratio of valve placement versus standard medical care.(229) Although statistically significant improvements in the co-primary endpoints of FEV_1 and 6MWD were noted, these were modest with a 6.8% (60mls) improvement in FEV_1 and 5.8% (19.1m) improvement in walk distance between the two groups at 6 months. When subgroups were analysed there were more marked improvements in FEV_1 (10.7%) and 6MWD (12.4%) in patients with higher degrees of heterogeneity between lobes. Where computed tomography (CT) showed there was evidence of complete interlobar fissures FEV_1 improvements of 16.2% at 6 months and 17.9% at 1 year were recorded. The EURO-VENT study also reported similar, modest differences in lung function, exercise capacity and quality of life overall at 6 months.(230) Just over a third of patients had intact fissures and when combined with complete lobar occlusion (assessed by CT) the outcomes were impressive. FEV_1 improved by 26% with 67% of patients achieving at least the minimum clinically important difference of 15%. 6MWD improved 22% with 56% of patients achieving more than a 35 metre improvement and SGRQ score fell 10 points. In these patients there was an 80% reduction in volume of the target lobe.

Since these studies work has concentrated on selecting appropriate patients with intact fissures and heterogeneous disease. The key to success appears to be the

absence of collateral ventilation. Collateral ventilation allows regions of the lung to be ventilated through channels or parenchymal defects in adjacent lung, thus preventing atelectasis. A bronchoscopic catheter has been developed which occludes lobar bronchi to assesses flow, resistance and pressure during normal spontaneous breathing. In the absence of collateral ventilation, airways resistance rises as airflow ceases, but fails to do so when collateral ventilation is present (Figure 1.8).(231) This technique, known commercially as Chartis assessment has been validated in a number of clinical trials.(232,233)

A surrogate marker of collateral ventilation is the presence of an incomplete interlobar fissure. When comparing the accuracy of Chartis against fissure assessment, the two methods appear to be similar in their efficacy. Schumann et al. retrospectively studied patients under going valve treatment and defined clinical response as a >350ml reduction in lobar volume. Intact fissures measured by quantitative CT predicted 78.8% of responders compared to 75.8% with Chartis.(234) Gomplemann et al. demonstrated similar findings and found the two methods were concordant in 68.1% of cases, with false positives occurring by both methods.(235)

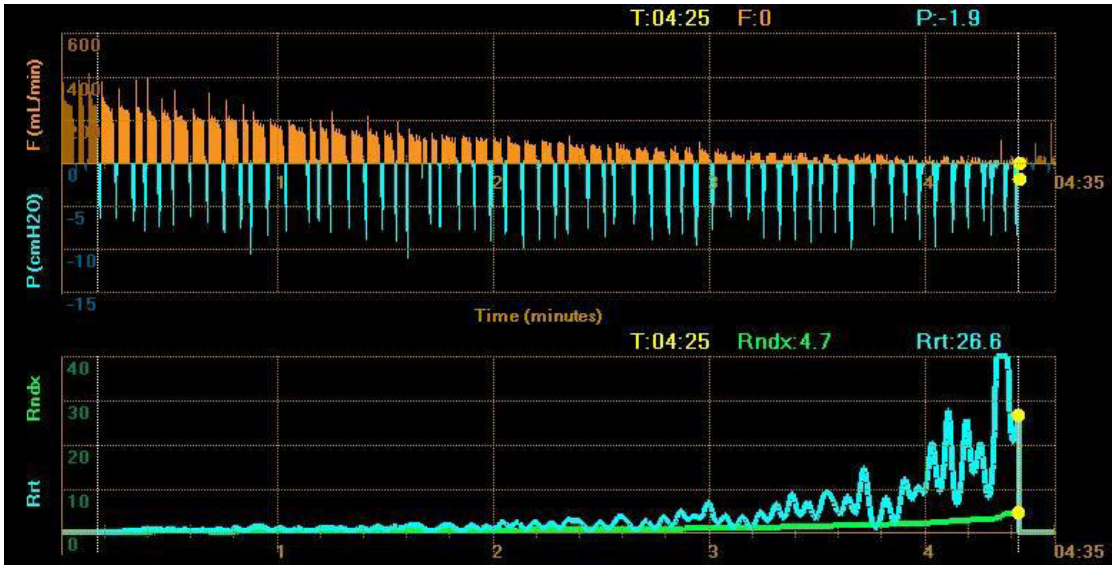


Figure 1.8 Assessment of collateral ventilation

Chartis assessment of a patient without collateral ventilation showing diminishing flow (yellow trace) with ongoing pressure swings and rising airway resistance (blue line).

The BeLieVR HIFi study examined whether patients could be prospectively selected on the presence of intact interlobar fissures by visual assessment in a randomised controlled trial. They reported a median improvement of 8.7% in FEV_1 and a significant reduction in FRC but not RV. Walking distance improved significantly, albeit below the minimum clinically important difference. There was no improvement in symptoms. However this study followed up patients 90 days post implant to determine changes in lung function rather than symptoms. In their cohort, 4/25 patients with intact fissures had evidence of collateral ventilation. When these were excluded from the analysis there was a significantly higher proportion of responders in those meeting the minimum clinically important difference in FEV_1, 6 minute walk distance, endurance time and CAT score.(236)

The recent STELVIO trial combined fissure integrity and collateral ventilation assessment in the inclusion criteria of the trial. They also allowed patients with homogeneous emphysema to take part in the trial as long as they had no evidence of collateral ventilation. They reported impressive improvements in lung function, exercise capacity and quality of life. At 6 months follow up compared to controls, FEV_1 improved by 140mls or 17.8%, with 59% of patients responding. 6 minute walk distance improved by 106m and SGRQ scores fell 14.7 points on average. Residual volume fell by more than the minimum clinically important difference in 71% of patients with significant reductions in RV/TLC ratio in 63%.(237) This trial demonstrated that careful selection of patients for endobronchial valve treatment can produce clinically important outcomes for patients with emphysema.

The most significant complications arising from endobronchial valves include pneumothorax, pneumonia, valve migration and COPD exacerbation. Death has occurred in 1-8% of patients in the aforementioned randomised clinical trials of

valves.(229,236,237) Pneumothorax occurred in 18% of patients in the STELVIO trial and 35% of patients required a repeat bronchoscopy for repositioning or replacement of migrated valves. Generally, pneumothorax occurs within the first few days following valve insertion. Interestingly, anecdotal evidence from authors suggest that patients with pneumothorax may achieve better outcomes because it is associated with volume loss.(237)

Despite clinical trials for endobronchial valves having been conducted for over 10 years, there is little long term follow up data. In the first in human trial of endobronchial valves, at a median duration of 64 months follow up, most patients had significant decline in lung function. In a number of patients who underwent transplant, histological analysis demonstrated excessive granulation tissue around the valves with mucus impaction behind them. 25% of patients had died by 36 months follow up which is similar to the control group in the NETT study.(238) In a small group of patients, Garner et al. have shown that there is a survival benefit in patients who achieved atelectasis following valve placement up to 12 years post treatment.(239) This important finding may mirror the response to LVRS in selected patients and requires prospective long term follow up of subsequent trials to confirm this finding.

1.3.3.3 Bronchial thermal vapor ablation

Bronchoscopic thermal vapor ablation (BTVA) is a non-occlusive method of achieving volume reduction by inducing inflammation and fibrosis within emphysematous areas of the lung. Heated water vapor is delivered bronchoscopically and induces a thermal reaction in the airways and lung parenchyma. Animal studies demonstrated an initial inflammatory response within 24 hours that results in fibrosis by 3 months.(240) This was associated with volume loss through contraction of lung tissue. In addition, fibrosis was predominantly seen around small airways and resulted in occlusion with distal atelectasis. The technique is designed to target segmental areas of the lobe, therefore being a more selective technique than valves and preserving healthier areas of the lung. Importantly, it is not dependent on the presence of collateral

ventilation.

An early feasibility trial reported a 716ml (48%) reduction in target lobe volume assessed by CT. Significant improvements were also reported in FEV_1 (+17%), SGRQ (-14 points), mMRC (-0.9) and 6 minute walk distance (+46.5m). Complications included cough, hemoptysis, dyspnea, fever and fatigue which were attributable to an inflammatory reaction within the lung. Serious adverse events included COPD exacerbations, pneumonia or lower respiratory tract infections. 1 death occurred 67 days post procedure and was due to end stage COPD. (241)

A subsequent randomised controlled trial of bilateral, segmental treatment showed compared to controls there was a 131ml (14..7%) improvement in FEV_1, a 30m improvement in walking distance and a 9.7 point improvement in SGRQ scores. Treated segments underwent a 33 to 44% volume loss, associated with an increase in the volume of the untreated segments and lower lobes. Data up to 12 months shows these results are sustained.(242) By 6 months follow up 24% of patients had a COPD exacerbation requiring hospitalisation, 18% had pneumonia requiring hospitalisation and 2% had a pneumothorax. There was 1 death (2%) which was related to the treatment.(243)

1.4 Mechanisms of physiological improvement following lung volume reduction

Hyperinflation is a key target for treatment in emphysema to address the deleterious effects on lung mechanics, respiratory muscles and gas exchange. Most clinical trials have focused on the effects on lung volumes, symptoms and exercise capacity. However a number of detailed mechanistic studies have explored the effect on lung volume reduction treatments underlying these improvements. Much of the work has focused on lung volume reduction surgery with comparatively less work examining the effects of bronchoscopic lung volume reduction.

1.4.1 Physiological changes following lung volume reduction surgery

Nearly 60 years ago, Brantigan and Muller postulated the improvement in lung function and symptoms was due to an increase in elastic recoil of the lung, increase airway conductance and reconfiguration of the respiratory muscles.(199) Later work has shown that all of these mechanisms play a role in the improvements related to LVRS.

1.4.1.1 Effect on lung elastic recoil

There has been consistent evidence that LVRS improves lung elastic recoil. Early studies of small cohorts of patients undergoing bullectomy for isolated bullae with relatively normal lung parenchyma, showed significant improvements in elastic recoil.(244,245) However in patients with underlying emphysema in the remaining lung, there is a less marked improvement in lung function and elastic recoil.(246,247) The explanation for this was that normal lung parenchyma is compressed and following bullectomy, it expands with a resultant increase in recoil pressure. However if the remaining lung is emphysematous, it has less elastic recoil than normal lung, albeit more than the excised bulla and therefore improvements are smaller. In the setting of LVRS, Gelb et al. have demonstrated that short term improvements in recoil pressure(248) are maintained 2 years following LVRS and correlate with improvement in expiratory flows.(249) Furthermore increased recoil pressure correlates with improvements in

symptoms, exercise capacity and a number of lung function measurements including FEV_1, RV, TLC and FRC.(250) Ingenito et al. examined a number of physiological factors including lung compliance, recoil pressure, small airways conductance and airway closing pressure in patients undergoing LVRS. Using a mathematical model to determine the relative contribution of these factors to changes in expiratory flow, they found that change in recoil pressure was the major determinant of improvement following LVRS. Lung compliance at FRC did not change significantly.(251) This suggests that the mechanism for improvement following increased recoil pressure is by increasing maximum expiratory flow, thereby relieving gas trapping. However, despite consistent improvements in lung recoil pressure following LVRS, baseline recoil pressure has not been shown to predict response to LVRS in either symptoms, exercise capacity or lung function.(252)

1.4.1.2 Changes in airways resistance

It follows that increased elastic recoil should improve airway resistance since this helps maintain airway patency. However results of studies examining airway resistance (or conductance, the reciprocal of resistance) have been mixed. Gelb et al. demonstrated improved airway conductance measured at FRC which they concluded was the result of increased elastic recoil providing greater stability of airways against collapse.(248) However Scharf et al. failed to show any improvement in airway resistance despite improvements in elastic recoil and expiratory flow. Indeed some patients had significant increases in airways resistance that was attributed to distortion of airways following re-expansion of the lung.(253) Ingenito et al. argued that airways resistance does not change significantly following LVRS and the increase in expiratory flows are almost entirely due to increased driving pressure related to elastic recoil. They did find that patients with high pre-operative airways resistance are less likely to benefit from LVRS.(251)

1.4.1.3 Changes in vital capacity

An alternative explanation for improvement in lung function has been put forward by Fessler and colleagues (Figure 1.9) . In the setting of heterogeneous emphysema (Figure 1.9 A), they argue that resection of the most diseased areas of the lungs results in a proportionately greater reduction in RV compared to TLC. Since the vital capacity (VC) is the difference between these two volumes, it increases following resection of emphysematous lung. Elastic recoil at TLC improves as a consequence of the remaining lung expanding to fill the thoracic cavity, but it does not cause the increase in VC. Compliance is unchanged. It follows that since FEV_1 is largely dependent on the VC, it too increases. This is supported by the observation that patients with the greatest improvements in FEV_1 have larger improvements in FVC.(254) In the context of homogeneous disease (Figure 1.9 B), there is a similar reduction in both TLC and RV along with a decrease in lung compliance and increase in elastic recoil. Thus whilst expiratory flow may still improve, it is to a lesser extent.(255) Evidence to support this theory comes from data demonstrating that a high RV/TLC ratio is associated with an improvement in FVC. However, whilst patients with a lower RV/TLC ratio did not have significant improvements in FVC, they still had similar improvements in $FEV_{1,}$. This would suggest other mechanisms still contribute.(256) This theory helps to explain why heterogeneous patients respond more favourably to LVRS.

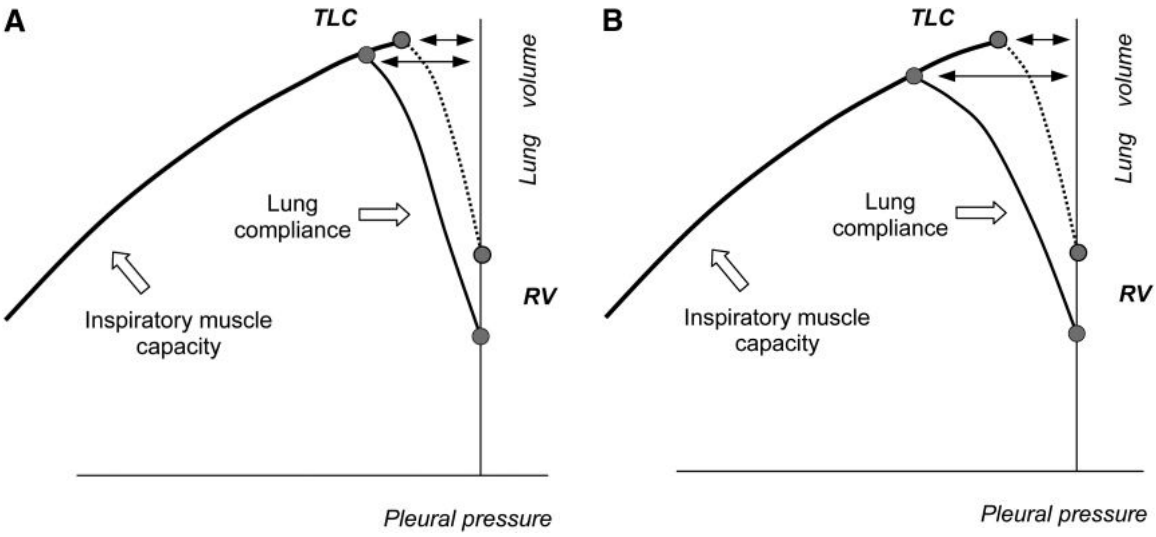


Figure 1.9 Effect of lung volume reduction in heterogeneous and homogeneous emphysema

(*A*) Effects of lung volume reduction surgery (LVRS) in heterogeneous disease. The *dashed line* represents the static relationship between pleural pressure and lung volume. Vital capacity (VC) is represented by the difference on the ordinate between total lung capacity (TLC) and residual volume (RV). Maximal elastic recoil pressure is shown by the *double-headed arrows* at TLC. The slope of the relationship is lung compliance.. Effects of LVRS are shown by the *thin vertical line*. Because this LVRS removed only destroyed lung, which does not contribute to lung elastic properties, compliance is unchanged. RV is reduced, and TLC is reduced by a lesser amount because the muscles can stretch the remaining lung further. The difference between them, the VC, increases. Recoil pressure also increases, but this does not *cause* the increase in VC. (*B*) Effects of LVRS in a patient with homogeneous emphysema. In this example, the resected lung includes parenchyma, which has some elastic recoil. Its removal decreases the compliance of the lung left behind. Note that now the recoil pressure rises by more than in (*A*), but the VC improves by less.

Fessler et al. 2008. Proc Am Thorac Soc; 5(4):416-20

1.4.1.4 Changes in respiratory muscle function

LVRS is associated with increased respiratory muscle strength.(257–260) Those patients with weaker pre-treatment respiratory muscle function and high RV/TLC ratio are more likely to gain improvements in walking capacity.(260) The changes in respiratory muscle function have been found to be most closely associated to improvements in RV and FRC, suggesting volume reduction may allow the respiratory muscles to return to a more efficient configuration.(259) This has been confirmed by evidence of increased diaphragm length(261) and an increase in the zone of apposition following LVRS.(262)

1.4.1.5 Changes in exercise capacity and dynamic hyperinflation

The NETT study included measurement of exercise capacity as part of a co-primary endpoint. Excluding high risk patients, 16% of patients undergoing LVRS achieved the 10W increase in exercise capacity compared to 3% in the medical treatment group ($p < 0.001$). The effect was most marked in those with upper lobe emphysema and a low pre-treatment exercise capacity where 30% achieved a 10W increase.(122) In a more detailed analysis of a subgroup of the NETT study, patients undergoing LVRS had a higher maximal minute ventilation, increased tidal volume and carbon dioxide output, and reduced dead space in addition to improved maximal work rate. They also reported less breathlessness during exercise.(263) O'Donnell et al. has demonstrated a reduction in dynamic hyperinflation during exercise following LVRS.(264) The oxygen cost of exercise is also reduced, primarily through a reduction in the energy expenditure of respiratory muscles.(265)

1.4.1.6 Changes in pulmonary haemodynamics

There is mixed evidence on the effect of LVRS on pulmonary haemodynamics. Two small studies indicated that there was a rise in post operative mean pulmonary artery pressure, caused largely by an increase in peripheral vascular resistance.(266,267) Removal of significant proportions of the vascular bed or distortion of remaining vessels was suggested as a potential cause. Yet pre-operative perfusion scans suggested the excised lung was relatively avascular

and angiography was not performed to directly assess the pulmonary vessels.(266) One study reported an improvement in right ventricular systolic function but no change in pulmonary artery pressures either at rest or during exercise. Changes in right ventricular indices correlated with the reduction in RV/TLC ratio suggesting that reduced intrathoracic pressure led to improved right ventricular filling and ejection fraction.(268) The largest study to date came from a group of 110 patients from the NETT study. There was a small reduction in pulmonary capillary wedge pressure, reflecting the decrease in hyperinflation and its effect on the left ventricle. There was an inverse correlation with both change in FEV_1 and 6 minute walk distance and the change in mean pulmonary artery pressure.(269)

1.4.2 Physiological changes following bronchoscopic lung volume reduction

1.4.2.1 Endobronchial valves

Since endobronchial valves aim to achieve volume loss, it could be assumed that the mechanisms are therefore similar to LVRS, yet there has been comparatively little work examining the physiological effect of endobronchial valves.

Hopkinson et al. have demonstrated improvements in cycle endurance time associated with improvements in dynamic hyperinflation. In a cohort of 19 patients undergoing unilateral valve placement, they found a 39% increase in endurance time, equating to 88 seconds. The effect was more marked in those patients who had radiological evidence of atelectasis, which occurred in only 5 of the 19 patients. Dynamic hyperinflation assessed by end expiratory lung volume was also reduced at peak exercise and isotime. Amongst those with a significant response to treatment, minute ventilation was unchanged but tidal volume increased and respiratory rate decreased suggesting more efficient ventilation. In a multivariate analysis of factors predicting change in cycle endurance time, only change in resting inspiratory capacity and change in TL_{CO} were significant. There was no change in static lung compliance and only maximal expiratory pressure increased following treatment. It is interesting that those patients

without atelectasis still derived benefit from treatment. The authors suggested this may be due to increased inspiratory resistance to airflow in the most emphysematous parts of the lungs, redirecting airflow to healthier lung with more favourable ventilation-perfusion matching. Improvements in exercise capacity and dynamic hyperinflation were confirmed in the same study. (225)

A single study has assessed the effect of endobronchial valves on ventilation and perfusion using 2D gamma scintigraphy. Following valve placement there was a 43% reduction in ventilation to the target area and a 42% reduction in perfusion. At the same time there were significant increases in perfusion to the contralateral lung, although there were small and non-significant changes in ventilation throughout the rest of the lung.(270) This would support the hypothesis that valves may also improve ventilation-perfusion matching in the lung.

1.4.2.2 Lung volume reduction coils

The putative mechanism of action is a combination of volume reduction by folding the lung around the coil and an increase in the elastic recoil of the lung. Restoration of elastic recoil in the lung may help tether the small airways open in the surrounding lung, thus further reducing static hyperinflation and attenuating dynamic hyperinflation. Importantly, these treatment effects should work independently of collateral ventilation and therefore offer a unique mechanism of action compared to other lung volume reduction techniques.

To date there has been little mechanistic work elucidating the mechanism of the lung volume reduction coil. Volume reduction has been consistently achieved with significant improvements in RV following treatment. In a meta-analysis of four clinical trials, the mean RV reduction was 0.51 L at 6 months and -0.43L at 12 months. TLC is also reduced, but to a lesser extent which results in an improved RV/TLC ratio and consequently, an improvement in FVC. This would support Fessler's theory that volume reduction with a decrease in RV/TLC ratio and resizing of the lungs to the chest is a key mechanism.(217) In a small group

of patients with homogeneous emphysema, airways resistance measured by plethysmography was shown to fall, despite the reduction in lung volumes given the inverse relationship of airways resistance and lung volumes.(271)

A recent study used dual energy CT to assess pulmonary perfusion following unilateral and bilateral coil treatment. They found an increase in perfusion of 65% around the coils and 61% in the remaining ipsilateral lung, but no change in the contralateral lung. The increase in perfusion also correlated which changes in 6 minute walk distance. It might be expected that the areas adjacent to the coils would have reduced perfusion since vessels may become distorted and hence increase resistance with reduced perfusion. However the authors only examined relatively small regions of interest within each lobe, avoiding the precise areas with coils.(272)

1.5 Aims of the study

The aims of this thesis are to examine the safety and efficacy of lung volume reduction coil treatment in patients with emphysema up to 1 year follow up. We will assess the changes in exercise capacity, lung function and quality of life. We will describe the radiological changes in lobar volumes, lung density and gas trapping in order to evaluate the effect of coils at a lobar level. Finally, we aim to describe the physiological changes in lung mechanics, airways resistance and ventilation heterogeneity following treatment. Understanding the mechanism of lung volume reduction coil treatment may help to identify clinical, radiological or physiological characteristics that help determine which patients are most likely to benefit from treatment and potentially refine the technique.

The primary alternative hypotheses for each chapter are as follows:

- There will be a significant improvement in walking capacity between the treatment and control group as measured by the six minute walk distance 12 months following treatment with lung volume reduction coils.

- There will be a significant reduction in the target lobe volume at full inspiration and expiration compared to the control group as measured by CT volumes 12 months following lung volume reduction coil treatment.

- There will be a significant improvement in elastic recoil of the lung and reduction in airways resistance following lung volume reduction coil treatment.

Chapter 2

Methods

2.1 Study design

The studies contained within this thesis relate to the Lung Volume Reduction Coil Treatment in Patients With Emphysema (RENEW) Study, registered on Clinicaltrials.gov (NCT01608490). The clinical study comprising Chapter 3 was designed and funded by the study sponsor (PneumRx, Mountain View, CA, USA) in association with out institution based on a previous randomised controlled trial conducted at our institution.(219) It is a prospective, multicentre randomised controlled trial of lung volume reduction coils compared to usual medical care. 29 centres across the United States and Europe recruited 315 patients to the trial. After completing baseline assessments and fulfilling the inclusion and exclusion criteria, patients were randomised in a 1:1 ratio of treatment to control. The primary outcome is between group difference in 6 minute walk distance at 12 months. The study will continue to collect safety and efficacy data in treated patients up to 5 years following randomisation. Patients in the control arm were eligible to enter a crossover study after 12 months with an identical protocol.

Our site recruited 30 patients to the trial and the results up to 12 months of those patients are presented in this thesis. All data collection, analysis, statistical analysis and interpretation including writing of this thesis were independent of the study sponsor. The analysis within Chapter 4 & 5 were designed and performed at our institution, independent of the sponsor's clinical trial. Patients undergoing the detailed physiological assessments presented in Chapter 5 signed a separate consent form.

Our institution was reimbursed for clinical trial expenses incurred for the RENEW trial, but all funds for the other studies were paid for by research funds held by Dr Pallav Shah (primary PhD supervisor).

2.2 Ethical approval

Ethical approval was provided for the RENEW study in the UK by the National Research Ethics Service – London Brent Committee on the 29th October 2012 (12/LO/1434). It was registered with Clinicaltrials.gov (NCT01608490). For the

crossover study, ethical approval was granted by the National Research Ethics Service – London Stanmore Committee on 14th March 2014 (14/LO/0376). NHS Research and Development Permission was granted by The Royal Brompton and Harefield NHS Foundation Trust and Chelsea and Westminster Hospital NHS Foundation Trust for both studies. The ethical approval covered the acquisition and analysis of CT scans.

Patients participating in the small airways physiology in lung volume reduction (Chapter 5) study signed a separate consent form. The study was approved by the National Research Ethics Committee of the South Central Berkshire board (14/SC/0193). Research and Development approval was granted by Imperial College, London.

2.3 Patient selection

Patients were recruited from referrals to the advanced COPD multidisciplinary meeting at the Royal Brompton Hospital. Those patients with GOLD stage 3 or 4 COPD with significant hyperinflation and impaired exercise tolerance were counselled regarding treatment options including lung volume reduction surgery where appropriate. Those wishing to consider taking part in the RENEW trial were offered detailed written information approved by the Research Ethics Committee. Following written informed consent, patients underwent screening to determine if they met the following inclusion and exclusion criteria.

Inclusion criteria:

- Aged ≥35 years of age.
- CT scan indicates bilateral emphysema, as determined by the Core Radiology Laboratory
- Post-bronchodilator FEV_1 ≤45% predicted.
- Total Lung Capacity >100% predicted.
- Residual volume ≥225% predicted.
- Marked dyspnea scoring ≥2 on mMRC scale.
- Patient has stopped smoking for at least 8 weeks prior to entering the study, as confirmed by a Cotinine level of < 10 ng/mL (or

carboxyhaemoglobin less than 2% if the patient was taking nicotine replacement).

- Patient has read, understood and signed the Informed Consent form.
- Patient has completed a pulmonary rehabilitation program within 6 months prior to treatment and/or regularly performing maintenance respiratory rehabilitation if initial supervised therapy occurred more than 6 months prior to baseline testing.
- Received pneumococcal and influenza vaccinations consistent with local recommendations and/or policy.

Exclusion criteria

- Severe homogeneous emphysema as determined by the Core Radiology Laboratory
- Co-morbidities that may significantly reduce patient's ability to improve exercise capacity (e.g. severe arthritis, planned knee surgery) or baseline limitation on 6MWT is not due to dyspnoea.
- Change in FEV_1 >20% (or, for patients with pre-bronchodilator FEV_1 below 1 L, a change of > 200 mL) post-bronchodilator.
- TL_{CO} <20% of predicted.
- Severe gas exchange abnormalities as defined by:
    - $PaCO_2$ >7.3kPa
    - PaO_2 < 6kPa on room air
- History of recurrent clinically significant respiratory infections, defined as 3 hospitalisations for respiratory infection during the year prior to enrolment.
- Severe pulmonary hypertension defined by right ventricular systolic pressure >50 mmHg via right heart catheterisation and/or echocardiogram.
- Inability to walk >140 metres in 6 minutes.
- Evidence of other severe disease (such as, but not limited to, lung cancer or renal failure), which in the judgment of the investigator may compromise survival of the patient for the duration of the study.

- Patient is pregnant or lactating, or plans to become pregnant within the study timeframe.
- Inability to tolerate bronchoscopy under moderate sedation or general anaesthesia.
- Clinically significant bronchiectasis.
- Giant bullae >1/3 lung volume.
- Previous LVR surgery, lung transplantation, lobectomy, LVR devices or other device to treat COPD in either lung.
- Patient has been involved in pulmonary drug or device studies within 30 days prior to this study.
- Patient is taking >20 mg prednisone (or equivalent dose of a similar steroid) daily.
- Patient requires high level chronic immunomodulatory therapy to treat a moderate to severe chronic inflammatory autoimmune disorder.
- Antiplatelet or anticoagulant therapy which cannot be stopped for seven days prior to procedure.
- Nickel allergy or sensitivity determined by clinical history.
- Allergy or sensitivity to drugs required to perform bronchoscopy
- Alpha-1 antitrypsin deficiency (PiZ).
- Patient has any other disease, condition(s) or habit(s) that would interfere with completion of study and follow up assessments, would increase risks of bronchoscopy or assessments, or in the judgment of the investigator would potentially interfere with compliance to this study or would adversely affect study outcomes.

Prior to recruitment into the study, all patients had a review in clinic to ensure they were on optimal medical therapy. Whilst there was no definition of optimal medical therapy, we felt that all patients should be on triple inhaled therapy to include a long acting antimuscarinic, a long acting beta agonist and inhaled corticosteroid unless there were contraindications to this. Other therapies for COPD such as long term macrolides, mucolytics, theophyllines, non-invasive ventilation and oxygen were allowed as needed. Any patient who required a

change to their therapy prior to entering the trial was given three months to reach a stable clinical state before baseline assessments.

In August 2014 a substantial amendment was approved by the National Research Ethics Service which proposed a change to the inclusion criteria. A residual volume ≥175% predicted was required to be included in the study. This was changed as a meta-analysis of data from previous studies demonstrating that patients with a lower RV could achieve significant clinical benefits. At this point, 22 out of the 30 patients had been recruited to the study. This RV criterion was carried forward into the crossover protocol.

2.4 Study Schedule

The study schedule is summarised in tables 2.1 for the treatment group and table 2.2 for the control group. At each visit, patients underwent a clinical examination and a review of symptoms, adverse events and medication use. Visit windows were -2 to +4 weeks for clinic visits and treatments to allow for recovery from any exacerbation of symptoms in order to assess the patient during a stable period.

Treatment procedures were performed 4 months apart in order to allow the patient to recover from any adverse events and allow an assessment of response to the first treatment. There was no sham procedure for control patients who received a telephone call in lieu of the first treatment and a clinic review in lieu of the second treatment. Telephone assessments were conducted 7 days following the treatment procedures (or control visit) and at 10.5 months following the first treatment.

The crossover schedule was identical to the treatment group schedule. Following the 12 month assessment, control patients exited the study and were invited to take part in the crossover study. Patients provided a separate written informed consent for the study. Lung function, 6 minute walk distance, SGRQ and mMRC scores from visit 10 in the RENEW study were permitted to be used as baseline

assessments for the crossover study if performed within 6 weeks of other baseline assessments. A separate visit was required to perform spirometry and those assessments not included in visit 10 of the RENEW study.

Procedure / Assessment	Visit 1 Pre-treatment screening	Visit 2 LVRC Placement #1	Visit 3 1 Week post Visit 2* (Phone Call)	Visit 4 1 Month post Visit 2** (Clinic Visit)	Visit 5* LVRC Placement#2 (4 Month post Visit 2**)	Visit 6 1 Week post Visit 5* (Phone Call)	Visit 7 1 Month post Visit 5** (Clinic Visit)	Visit 8 9 Months post Visit 2** (Clinic Visit)	Visit 9 10.5 Mo post Visit 2** (Phone Call)	Visit 10 12 Months post Visit 2** (Clinic Visit)
Informed Consent	X									
Inclusion/Exclusion	X									
Medical History	X									
Focused physical exam, vital Signs and SpO_2	X	X		X	X		X	X		X
SGRQ	X			X			X	X		X
Spirometry	X			X			X	X		X
Lung Volumes & Diffusing capacity	X			X			X	X		X
Blood panel and ABG	X									
Cotinine or other appropriate	X									
ECG	X									
Echocardiogram	X									
Dyspnoea Scale mMRC	X			X			X	X		X
6 Minute Walk Test	X			X			X	X		X
Concomitant Medication / O_2 Use	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing	X	X			X					X
CT Scan	X									X
Chest X-Ray	X	X			X					
Coil Placement		X			X					
Take subject status***			X	X	X	X	X	X	X	X

Table 2.1 Study schedule for treatment group patients up to 12 months

* Telephone visits window ± 3 days from scheduled date
** Clinic visit window -2 to +4 weeks from scheduled date
*** Subject status included medical history, adverse event assessment, medication use

Procedure / Assessment	Visit 1 Pre-Treatment (Screening)	Visit 2 (Phone Call)	Visit 3 1 Week post Visit 2* (Phone Call)	Visit 4 1 Month post Visit 2** (Clinic Visit)	Visit 5* 4 Months post Visit 2 (Clinic Visit)**)	Visit 6 1 Week post Visit 5* (Phone Call)	Visit 7 1 Month post Visit 5** (Clinic Visit)	Visit 8 9 Months post Visit 2* (Clinic Visit)	Visit 9 10.5 Mo post Visit 2** (Phone Call)	Visit 10 12 Months post Visit 2** (Clinic Visit)
Informed Consent	X									
Inclusion/Exclusion	X									
Medical History	X									
Focused physical exam, vital Signs and SpO_2	X			X	X		X	X		X
SGRQ	X			X			X	X		X
Spirometry	X			X			X	X		X
Lung Volumes & Diffusing capacity	X			X			X	X		X
Blood panel and ABG	X									
Cotinine or other appropriate test										
ECG	X									
Echocardiogram	X									
Dyspnoea Scale mMRC	X			X			X	X		X
6 Minute Walk Test	X			X			X	X		X
Concomitant Medication/O_2 Use	X	X	X	X	X	X	X	X	X	X
Pregnancy Testing	X									
CT Scan	X									
Chest X-Ray	X									
Take subject status***			X	X	X	X	X	X	X	X
Exit Study										X

Table 2.2 Study schedule for control group

* Telephone visits window ± 3 days from scheduled date
** Clinic visit window -2 to +4 weeks from scheduled date
*** Subject status included medical history, adverse event assessment, medication use

The small airways study was conducted alongside the RENEW study, with physiological assessments being conducted at baseline and the 9 month visit. Table 2.3 lists the additional study assessments. The 9 month visit was chosen to reduce the burden of tests performed at the final 12 month follow up on patients.

	Baseline	9 months
Impulse oscillometry	X	X
Multiple breath nitrogen washout	X	X
Static lung compliance	X	X
Dynamic lung compliance	X	X

Table 2.3 Small airways assessments

2.5 Study assessments

2.5.1 St George's Respiratory Questionnaire

Prior to any clinical assessment or testing taking place at each visit, patients were instructed to complete the St George's Respiratory Questionnaire (SGRQ). The questionnaire was completed by the patient, without intervention from the investigator. However, questionnaires were checked for completeness prior to being submitted.

The SGRQ is a validated health related quality of life (HRQL) questionnaire in chronic airflow limitation. It measures the effect of the disease in three domains: symptoms, activity and impact on daily life in the preceding 4 weeks. A score of 0 indicates the best possible health and a score of 100 indicates worst possible health.(273) In COPD, SGRQ scores correlate inversely with FEV_1 and 6 minute walk distance. A higher baseline score is independently associated with an increased risk of exacerbations and mortality.(274,275) Additionally a decline over a 1 year period is also associated with an increased risk of exacerbations, hospitalisation and mortality.(276) The minimum clinically important difference for SGRQ in response to treatment has been estimated at 4 points.(277)

2.5.2 Modified Medical Research Council Dyspnoea Score

The mMRC score was also performed prior to any clinical assessments or testing. Instructions were given by the investigator to choose a single statement that best described the limitation related to their breathlessness. The patients were left to rate their own limitation rather than the investigator.

The mMRC score grades the effect of breathlessness on daily activities.(278) It has been shown to decline over time and is correlated to changes SGRQ scores and lung function.(279) A higher score is an independent risk factor for mortality.(280) However, because of the limited number of categories it performs better as a discriminative tool between patients rather than being a longitudinal evaluative tool.

Score	Description
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

Table 2.4 Modified Medical Research Council Dyspnoea Score

2.5.3 6 minute walk distance

The 6 minute walk test is a standardised, self paced assessment of walking capacity. Patients are asked to walk at a sustainable pace in order to achieve the maximum distance in 6 minutes. The test was conducted according to ATS guideline.(281) All tests were performed by a research nurse blinded to the treatment allocation of the patient. Patients performed a practice walk test if they had not completed a 6 minute walk test within the previous 12 months.

Tests were performed on a dedicated 30m corridor at the Royal Brompton Hospital.

Six minute walk tests were conducted following lung function so that all patients had received bronchodilators prior to assessment. Patients were instructed to sit and rest in a chair prior to baseline assessment. Supplemental oxygen was administered to all patients with resting saturations below 90% to achieve a target saturation of >90%. Patients who were prescribed ambulatory oxygen had the flow rate increased by 1L/min if saturations were >94% and by 2L/min if resting saturations were 90-94%. All subsequent tests were carried out with the same oxygen prescription as the first walk test. A maximum of 6L/min of supplemental oxygen was allowed. Patients had to carry (or push) their own oxygen cylinder to avoid pacing by the research nurse. Walking aids were allowed if normally used by the patient. Following the rest period, baseline blood pressure, pulse and oxygen saturations were recorded. Patients were asked to rate their dyspnoea and fatigue on the Borg scale.

Standardised instructions were given to all participants as follows:
"The object of this test is to walk as far as you can in six minutes. You will walk back and forth along this corridor. You are permitted to slow down, stop and rest as necessary. You may lean against the wall to rest as necessary, but resume walking as soon as you are able. You will be walking back and forth between the cones. You should pivot around the cones as briskly as possible and continue walking back the other way without hesitation. Now I am going to show you. Please watch the way I turn without hesitation."

"Are you ready to do that? I am going to use this counter to keep a track of the number of laps you complete. Remember the object of this test is to walk as far as possible in 6 minutes, but do not run or jog. Start now or whenever you are ready"

Patients were given standardised encouragements at each minute and given warning of 1 minute and 15 seconds remaining. Patients were asked to stop walking and remain where they are at the end of the test and the distance was

measured to the nearest metre. Patients were then allowed to sit and measurements of blood pressure, pulse, oxygen saturations and dyspnoea and fatigue were made.

The six minute walk test is a reliable and validated measure in COPD. Although it is not a maximal test, it has moderate to strong correlations to peak $V'O_2$ measured by incremental cardiopulmonary exercise testing. It also has moderate to strong correlations with physical activity, reflecting its utility as an objective measure of functional exercise capacity. The relationship with severity of disease and symptom scores is less strong, indicating that it is not solely a surrogate marker of severity of disease, but reflects a multidimensional measure of the systemic effects of COPD on exercise capacity.(282) The six minute walk test has been shown to be responsive to treatment in the context of pulmonary rehabilitation.(283) There is a wide variety of estimates of the minimum clinically important difference (MCID) in COPD, ranging from 25-54m.(282) We chose to use the 26m MCID proposed by Puhan et al.(284) This was based on 1218 patients enrolled in the NETT study in which both the population and treatment was similar to our study.

2.5.4 Cotinine, blood tests and arterial blood gasses

Cotinine testing was performed on urine samples using NicAlert strips (Nymox, USA). A level indicated as <10,000ng/ml was considered negative. For those patients using nicotine replacement therapy, a carboxyhaemoglobin <2.5% was considered negative.

Venous bloods were taken by the investigator to assess haemoglobin, coagulation parameters and renal function to ensure there was no contra-indication to proceeding with sedation or general anaesthesia. Arterial blood gasses were taken from the radial artery following a modified Allen's test to assess arterial patency to the hand. All arterial blood gases were performed with patients breathing room air for at least 15 minutes. Arterial blood gases were analysed using a RapidLab 348 (Bayer, Germany).

2.5.5 Echocardiogram and electrocardiography

An echocardiogram and electrocardiography was performed at baseline to assess for pulmonary hypertension, left ventricular dysfunction and significant arrhythmia. If a patient had an echocardiogram within 6 months which did not show any contraindications to participation, they did not require a further study prior to enrolment. Tests were carried out by cardiac physiologists at the Royal Brompton Hospital.

2.5.6 Computed Tomography

CT scans were performed by radiographers at the Royal Brompton Hospital on a Siemens Somatom Sensation 64 and after June 2014, using a Siemens Definition Edge (Siemens, Erlangen, Germany). The details of CT protocols and reconstruction parameters are discussed in Chapter 4.

Investigators were responsible for clinical review of CT scans to ensure there were no findings requiring further investigation and follow up such as severe bronchiectasis, pulmonary nodules or suspicious lesions. CT scans were then electronically transmitted to a central laboratory (MedQIA, California, USA) for scoring and assessment of heterogeneity.

Assessment of heterogeneity was performed by visual scoring of each of the major lobes using the following categorisation:

Lobar score	Description
0	Lobes with normal tissue or limited to scattered small centrilobular emphysema. The majority of the parenchyma appears normal. In the context of hyperinflation, this pattern represents small airways disease.
1	Lobes with centrilobular emphysema with small defects 1-3mm in diameter making up the majority of the damage.
2	Lobes with centrilobular emphysema with numerous defects 3-20mm

	in diameter making up the majority of the damage.
3	Lobes with non-coalescent bullous emphysema with defects 20-30mm in diameter but without complete destruction of the secondary pulmonary lobule structure.
4	Lobes with panlobular emphysema or confluent emphysema with defects 30-50mm in size and complete loss of the secondary pulmonary lobule structure or lobes with paraseptal defects 50-75mm.
5	Lobes with a single confluent defect of >50mm or a paraseptal defect of >75mm and complete loss of the secondary pulmonary lobule structure.

Table 2.5 Visual scoring system for the assessment of lobar heterogeneity in CT scans

Any patient with a major lobe (upper or lower lobes) scoring a 5 in any lung was excluded as having severe emphysema. Patients who scored a 4/4 or a 3/4 in adjacent lobes were excluded as having severe, homogeneous emphysema. Where there was a 2 point or more difference in the scores of adjacent lobes, patients were categorised has having heterogeneous disease. Where the difference in scores between adjacent lobes was 0 or 1 the patient was categorised as having homogeneous disease.

A single lobe in each lung was designated as the treatment lobe. This was determined by the lobe with the highest emphysema score. In homogeneous disease, where upper and lower lobes were scored identically, the upper lobe was chosen for treatment. If a patient was determined as having homogeneous disease in one lung and heterogeneous disease in the other, they were classified as having heterogeneous emphysema.

Analysis of CT lobar volumes, density and emphysema scores were performed independently from the RENEW study by our group. The details of the analysis are discussed in Chapter 4.

2.6 Lung Function Measurements

Spirometry, lung volumes and gas transfer measurements were obtained by Respiratory Physiologists in the lung function laboratory of the Royal Brompton Hospital. Physiologists were blinded as to the treatment allocation of patients. All measurements were performed on the MasterScreen PFT System and MasterScreen Body Plethysmograph (Carefusion, Germany). The European Coal and Steel Cohort (ECSC) reference equations were used to obtain standardised reference values.(285) All measurements were obtained following the ATS/ERS guidelines for standardisation of spirometry(286) and lung volumes(28).

2.6.1 Calibration check

Ambient air pressure, temperature and humidity were recorded prior to calibration and patient testing. A calibration check was performed on all pneumotachographs prior to each patient being tested. A 3.0L syringe was used to determine the accuracy of the pneumotachographs over a range of flows varying from 0.5 to 12 $L{\cdot}s^{-1}$. The volume at which each flow rate should meet the accuracy requirement is ± 3.5%. The mouth pressure and box pressure transducers were calibrated daily. Gas analysers were zeroed on prior to each test and an automated two point calibration for known concentrations of gasses was performed daily. Linearity of gas concentration measurements was performed monthly. Additionally biological control tests of spirometry, lung volumes and gas transfer were performed on a weekly basis.

2.6.2 Spirometry

Patients underwent spirometry testing in the seated position whilst wearing a nose clip. A low resistance bacterial and viral filter was placed between the mouthpiece and pneumotachograph. Patients were coached by the respiratory physiologist prior to performing the test. They were instructed to form a tight seal around the mouthpiece and inhale rapidly to full inspiration from FRC. This was followed immediately by a forced exhalation to RV. The volume-time curve was inspected during the test to ensure no flow (<0.025L) for ≥ 1 second. Tests were considered unacceptable if there was evidence of artefact, for example

coughing or glottic closure. At least three acceptable attempts were recorded if the values of FEV_1 and FVC were within 0.15L of each other. The highest value of FEV_1 and FVC from any of the acceptable curves were recorded as the final values.

Bronchodilator reversibility testing was performed at baseline testing only. Patients were instructed not to use any inhaled long acting antimuscarinic drugs for at least 24 hours, long acting bronchodilators for ≥ 12 hours and any short acting inhalers for ≥ 4 hours. 400mcg of salbutamol was delivered via a spacer device in 100mcg actuations. Spirometry was repeated after 15 minutes as above. An improvement of ≥ 200ml or 12% in FEV_1 from baseline was considered significant reversibility.

2.6.3 Lung volumes

The patient was seated inside the plethysmograph in a comfortable position and the mouth piece adjusted to prevent excessive neck flexion or extension. A bacterial filter was placed between the mouth piece and pneumotachograph. A nose clip was worn for all measurements and the patient was instructed to place their palms on their cheeks to prevent any changes in pressure being absorbed by the compliance of their cheeks. The door was closed to allow the pressure and temperature to equilibrate. After a number of tidal breaths to allow FRC to stabilise, the shutter at the mouth piece was closed. The patient was instructed to take a number of gentle pants (~±1kPa) against the closed mouth piece at a frequency of 0.5-1Hz. Following this the shutter was opened and the patient asked to exhale fully, thus measuring the expiratory reserve volume (ERV). Then the patient was asked to inhale rapidly, performing an inspiratory vital capacity (IVC) manoeuvre. The manoeuvre was repeated until three acceptable values within 5% were returned.

It is recognised that some patients with severe obstructive lung disease find performing an ERV manoeuvre following panting difficult. Therefore patients were permitted to perform an unlinked manoeuvre if they were unable to

perform the linked manoeuvre satisfactorily. This involved a rapid inspiratory capacity (IC) manoeuvre on opening the shutter, followed by a vital capacity (VC) manoeuvre.

FRC is determined by application of Boyle's law which states that the under isothermal conditions, when a constant mass of gas is compressed or decompressed, the gas volume decreases or increases and gas pressure changes such that the product of volume and pressure at any given moment is constant.

Thus:

$P_{alv1}.V_{TG1} = P_{alv2}.V_{TG2}$

Where P_{alv1} and V_{TG1} are the pressure and volume at FRC prior to the panting manoeuvre and P_{alv2} and V_{TG2} are the pressure and volume after the panting manoeuvre. During the panting manoeuvre, the thoracic gas volume (TGV) is expanded and compressed with corresponding pressure changes measured at the mouth, since under conditions of no flow, mouth pressure is assumed to be equal to alveolar pressure. Because the plethysmograph is sealed, a rise in TGV causes a rise in box pressure. The shift volume is determined from the pressure change within the box which is of constant (and known) volume (Figure 2.1)

Thus FRC can be calculated from:

$$FRC_{pleth} = \left(\frac{\Delta V}{\Delta P}\right).(P_{alv1} - \Delta P)$$

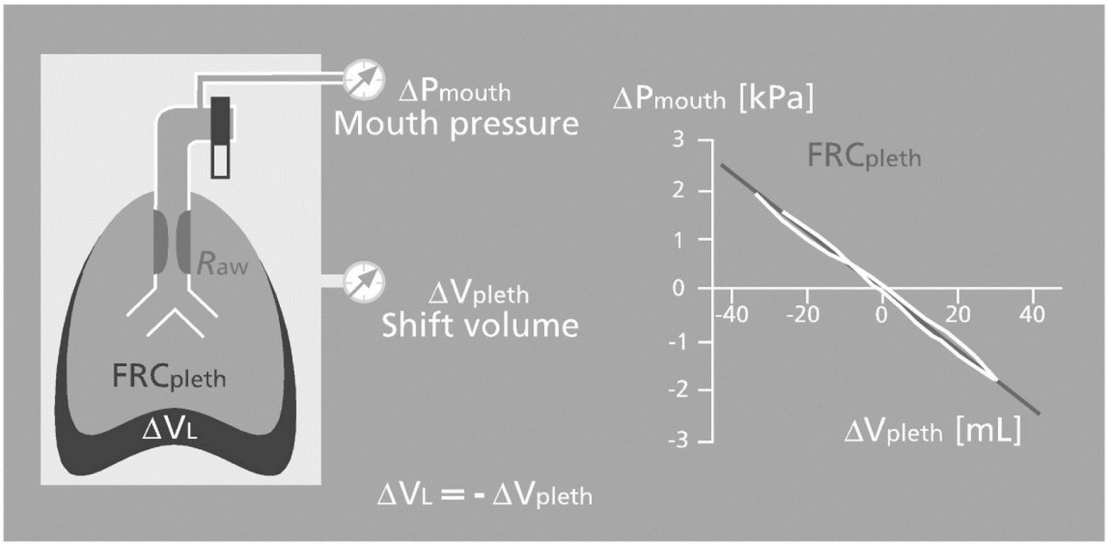


Figure 2.1 Diagrammatic representation of shift volume calculation

Reproduced with permission from reference (287)

The mean FRC is used as the reported value. The remainder of the lung volumes are calculated as follows (Figure 2.2):

$$RV = FRC - ERV$$

$$TLC = RV + IVC$$

In patients who performed unlinked manoeuvres they are calculated as follows:

$$RV = TLC - VC$$

$$TLC = FRC + IC$$

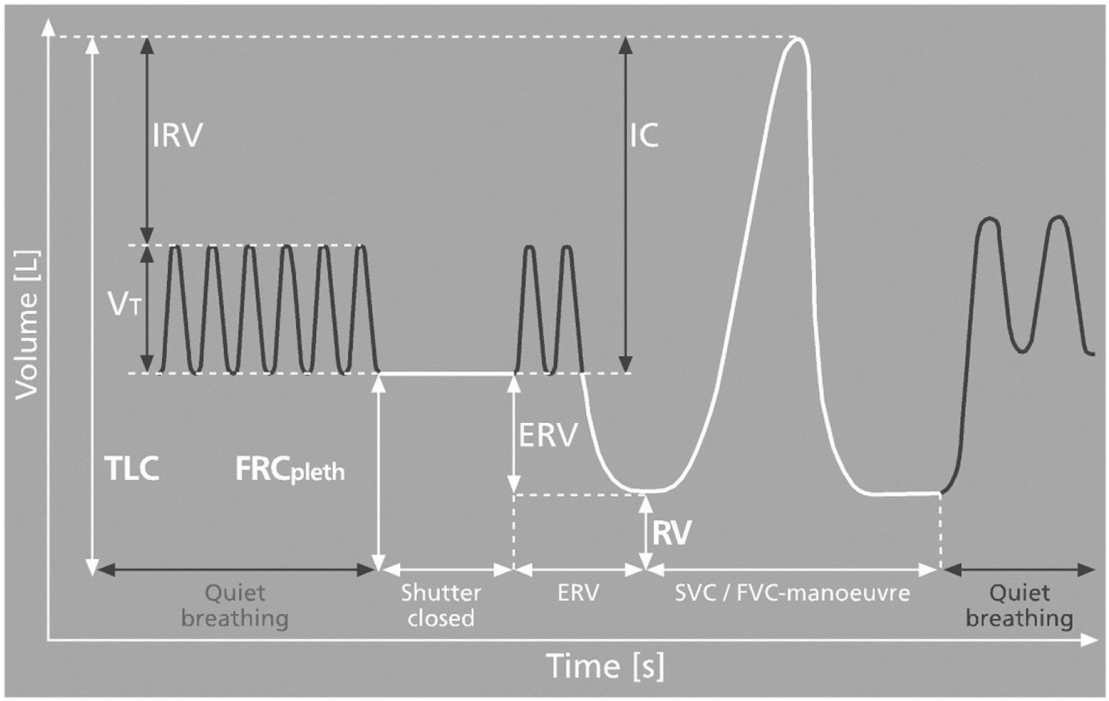


Figure 2.2 Derivation of subdivision of lung volumes

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2.6.4 Specific airways resistance

Specific airways resistance (sR_{aw}) was measured during normal tidal breathing in the body plethysmograph. Flow is recorded at the mouth from the pneumotachograph and plotted against the shift volume produced by thoracic compression and decompression. Airways resistance (R_{aw}) cannot be directly measured since the driving pressure ($P_{atm} - P_{alv}$) requires knowledge of the alveolar pressure which cannot be measured under conditions of gas flow without the use of an oesophageal catheter. Thus the shift volume is plotted on the *x* axis as this represents the change in volume (and hence change in pressure) required to generate flow. The shift volume excludes the lung volume change due to gas flow in and out of the lung. sR_{aw} is dependent on both airways resistance and lung volume. Therefore a patient with an FRC twice as large as another will have an sR_{aw} value twice as large when the R_{aw} is the same in both. Tangents were drawn on the specific resistance loop to calculate effective airways resistance (R_{eff}), inspiratory airways resistance (R_{awIn}) and expiratory airways resistance (R_{awEx}).

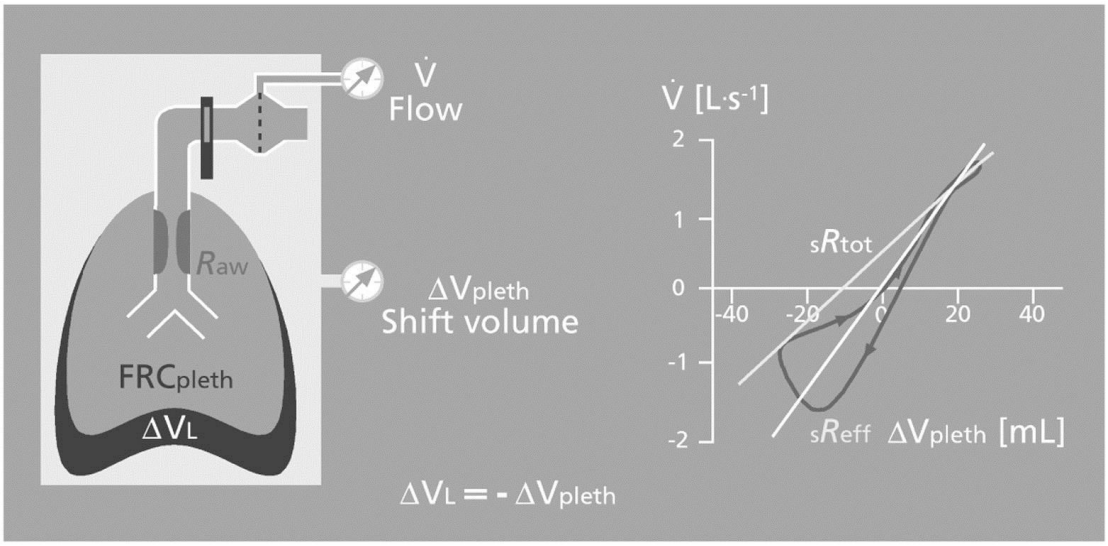

Figure 2.3 Specific airways resistance calculation

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2.6.5 Gas transfer

The single breath technique for gas transfer was performed as described in the ATS/ERS guidelines.(288) A 0.3% carbon monoxide, 10% helium, 21 % oxygen and balance nitrogen gas mix was used. Briefly, patients were sat without supplemental oxygen for at least 10 minutes. Whilst wearing a nose clip they were instructed to breath normally through the mouth piece until their respiratory pattern had stabilised. At this point they are asked to exhale completely and the test gas is switched on. They then inhale rapidly to full inspiration (confirming it is at least 85% of TLC) within a maximum of 4 seconds. The breath is held for 10±2 seconds and the patient exhales steadily. The first 750mls of exhaled gas is discarded as this contains dead space. A graphical display of the tracer gas confirms the concentration has plateaued and that any dead space gas is not included in the sample. A sample volume of 1L is analysed. Tests are acceptable if they met the above criteria. Three tests were performed with at least 4 minutes between tests to ensure the tests gasses have washed out. Results are included if they are within 1mmol·min^{-1}·kPa^{-1} or 10% of each other, whichever is the greater value. The mean of the results was quoted.

2.6.6 Lung compliance

Static and dynamic lung compliance was measured using the MasterScreen Body Plethysmograph and an oesophageal balloon catheter (Cooper Surgical, UK). The

catheter is 5Fr and 86cm long with a 9.5cm long balloon at its distal end. The differential pressure transducer was calibrated using application of 5cmH_2O pressure with a water manometer. A signal of 0.5kPa should be recorded on the computer. The balloon catheter was passed nasally after instillation of the nasal passage with lignocaine gel for patient comfort. The distance of the lower oesophageal sphincter was calculated using Zalpetal's formula (height in centimetres divided by 5.5 plus 9cm). The balloon was passed and then withdrawn no more than a few centimetres to reduce artifact from cardiac oscillations. The distance was noted and used for all subsequent measurements. The balloon was insufflated with 1ml of air and connected to the differential pressure transducer via a three-way tap. No bacterial filter was used for measurement of lung compliance due to the slight resistance created and subsequent change in mouth pressure. A nose clip was worn throughout the procedure. A trace of flow and transpulmonary pressure was reviewed during tidal breathing to ensure the balloon was in the correct position and was not over or under-inflated.

Once the patient is sat comfortably within the plethysmograph, they are asked to breath normally with the palms of their hands supporting their cheeks. During normal tidal breathing, measurements of dynamic lung compliance are made over a series of 5 breaths. Pressure-volume curves are inspected and should appear similar without artefact or drift. Three measurements are made and should agree within 10% of each other. The average dynamic compliance is quoted.

Following this the patient is instructed to inhale to TLC and performed a relaxed exhalation to FRC then encouraged to exhale fully to RV. During exhalation the shutter within the pneumotachograph closes automatically for 80ms after every 200ml of expired air to calculate transpulmonary pressure. Where vital capacity was below 2L, this was reduced to 100mls to ensure sufficient readings were made to construct a pressure-volume curve. The curve is inspected and a tangent of the curve is drawn on the straight part between FRC and FRC + 500mls (Figure 2.4). The procedure was repeated until three repeatable curves were

obtained with static lung compliance within 10% of each other. A minimum of 6 shutter points were required and traces should be free of artefact from glottic closure or oesophageal spasms. The reference equations for men published by Galetke et al were used.(289) No reference equations for women exist to our knowledge.

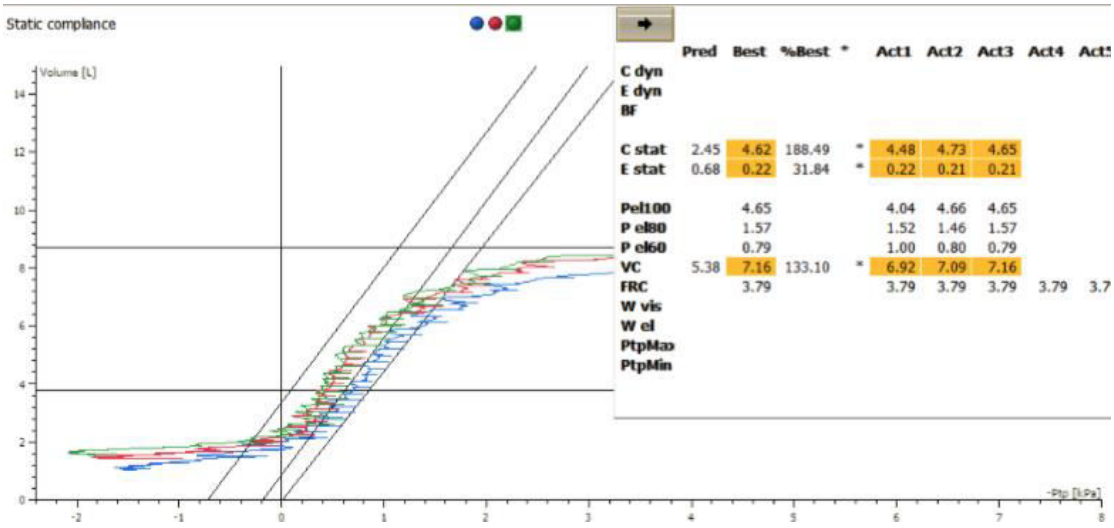


Figure 2.4 Static lung compliance curves

Measures of elastic recoil of the lung were taken from the transpulmonary pressure at TLC. The co-efficient of retraction was calculated by dividing the transpulmonary pressure by the total lung capacity.(290)

$$CR(kPa.L^{-1}) = \frac{P_{tp}TLC}{TLC}$$

The co-efficient of retraction allows the elastic recoil pressure to be standardised for variations in lung volume.

2.7 Multiple breath nitrogen washout

2.7.1 Equipment

Multiple breath nitrogen washout (MBNW) was performed using a custom built 'bag in box' system at the Royal Brompton Hospital Asthma Laboratory. (Figure 2.5 and 2.6)

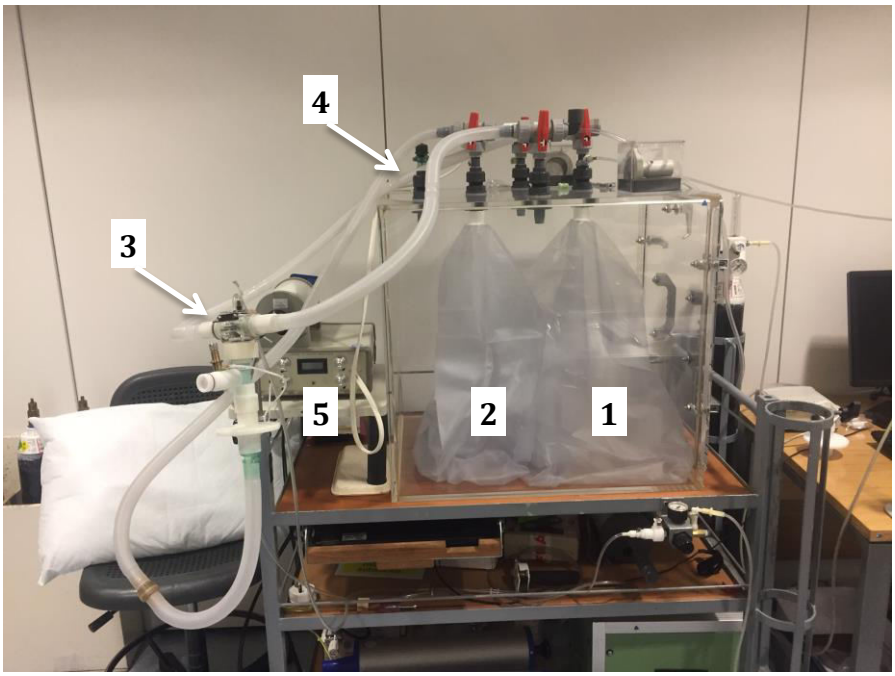


Figure 2.5 MBNW equipment setup

1) Inspiratory bag 2) Expiratory bag 3) 3 way valve
4) Pneumotachograph 5) Nitrogen analyser

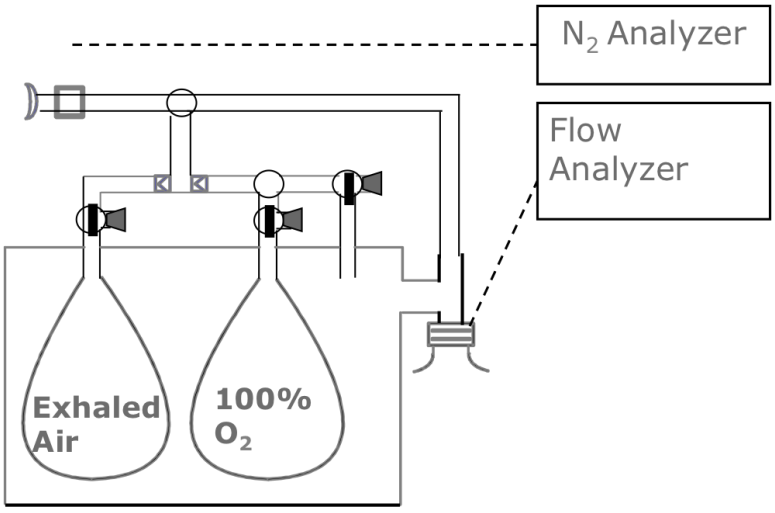


Figure 2.6 MBNW schematic diagram

The system consists of a Douglas bag filled with 100% oxygen from which the patient inhales, and another empty bag into which the patient expires. The inspiratory and expiratory bags are connected to the patient via non-rebreathing valves to separate inhaled and exhaled air. There is a further connection to the box to allow the patient to breathe air. A three-way directional balloon valve (Hans-Rudolph, USA) was used to control the switch between breathing room air and oxygen. A pneumotachograph is fitted to the box to measure flow and volume during subject breathing. Nitrogen concentration is analysed continuously adjacent to the mouth using a needle valve with continuous sampling of inhaled and exhaled air. Volume and nitrogen concentrations were acquired by a dedicated software system. The system was calibrated using a 1L syringe prior to use to ensure accuracy of flow and volume with no significant drift. The nitrogen analyser was adjusted to read 78% when testing the system with air.

2.7.2 Testing procedure

Patients were sat upright wearing a nose clip. A bacterial filter was used for all tests. Patients were instructed to breathe in a regular, relaxed pattern with a tidal volume of 1L. A visual display on the computer gave feedback regarding the achieved tidal volume with encouragement from the operator. Patients were coached to ensure they exhaled back to FRC to prevent progressive hyperinflation. Once a stable breathing pattern had been achieved with no drift in FRC, the valve was switched during expiration, such that the next breath was 100% O_2. The test continued with repeated encouragement for a stable breathing pattern until the end tidal concentration of N2 was 2%. Patients then came off the mouthpiece and rested 10 minutes between tests to allow washout of the residual oxygen within the lungs. At least two acceptable tests were performed for each patient.

2.7.3 Analysis

The data was analysed with a dedicated programme written in Turbo Pascal. A plot of the continuous nitrogen concentration plotted against time in order to generate the washout curve (Figure 2.7a) This plots the progressive decline in mean alveolar nitrogen concentration with each subsequent breath.

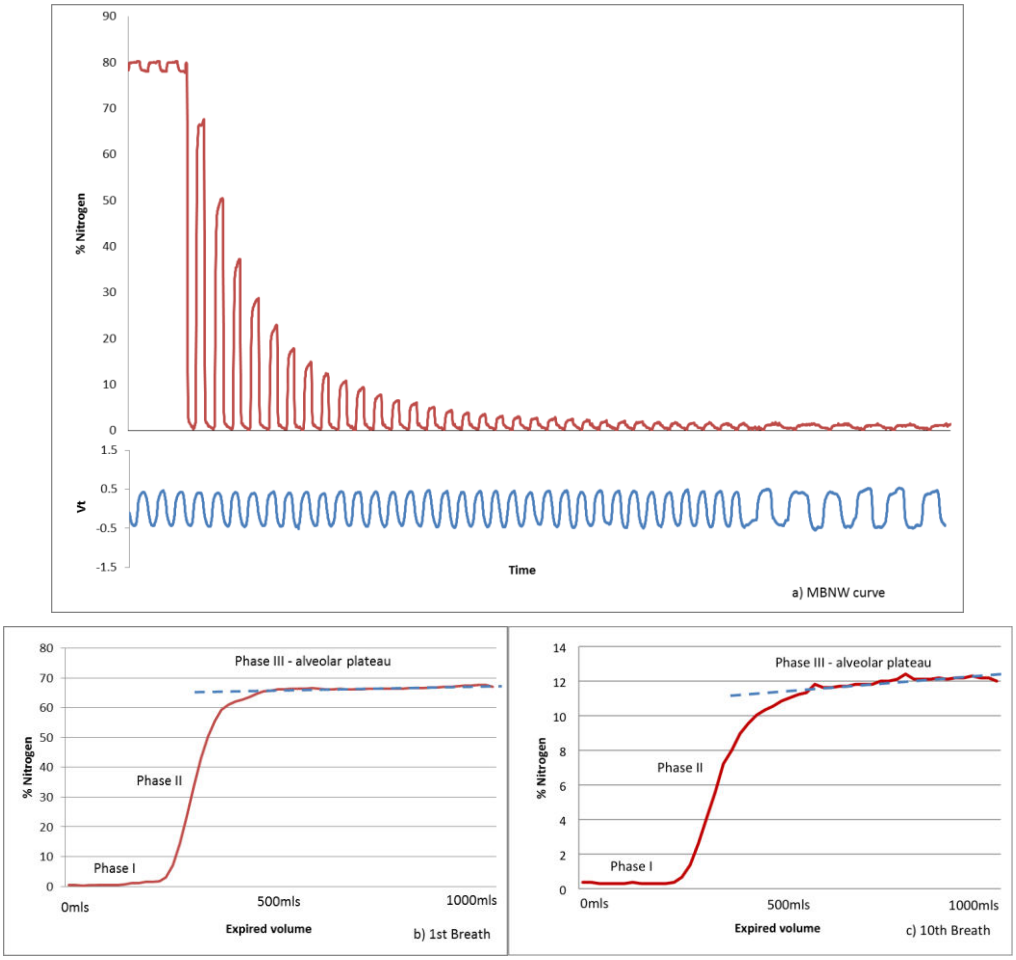


Figure 2.7 Nitrogen washout curves

a) MBNW curve. b) 1st breath with regression slope (S). c) 10th breath with regression slope

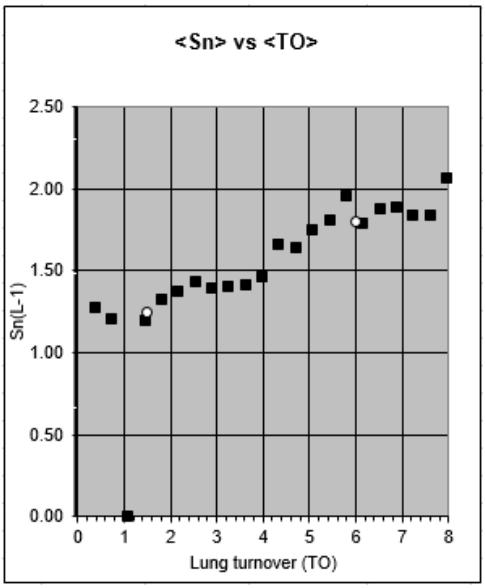


Figure 2.8 Plot of normalised phase III slope for each breath versus lung turnover

Each breath is analysed as a single nitrogen washout curve by determining the regression slope of phase III representing the alveolar plateau phase (Figure 2.7b & c). The slope is then divided by the mean concentration of exhaled nitrogen for each breath to give a normalised slope (S_n). For each breath, the value of the normalised regression slope is plotted against lung turnover (TO) (Figure 2.8). A lung turnover is calculated by the cumulative expired volume divided by the FRC. For example, with a patient with a 3L FRC and 1L tidal volume, 3 breaths would represent 1 lung turnover. This allows standardisation of results to allow comparison between patients with differing lung volumes and concentrations.

The lung clearance index (LCI), a measure of the efficiency of gas mixing in the whole lung may be calculated. It is defined as the number of lung turnovers (FRC equivalents) required to washout the tracer gas to $1/40^{th}$ of the original concentration. This is calculated by measuring the cumulative expired volume (CEV) required to washout the resident nitrogen and dividing it by FRC:

$$LCI = \frac{CEV}{FRC}$$

FRC may be calculated during the MBNW from the following formula, whereby the volume of tracer gas (i.e. N_2) is divided by the end-tidal concentration of the

tracer gas in the first breath minus the end-tidal concentration of the tracer gas in the last breath:

$$FRC = \frac{V_{[tracer]}}{C_{int} - C_{end}}$$

Two indices, S_{cond} and S_{acin} are determined from the plot of S_n against TO. S_{cond} represents the contribution of the conducting airways to the slope of S_n. It is calculated from the regression slope in the part of the washout where only conductive airways are known to contribute to the rise in S_n. This represents the portion between $TO_{1.5}$ and TO_6. S_{acin} is calculated by subtracting that portion attributable to the conductive airways from the slope of the 1st breath.

2.7.4 Theory of multiple breath washout

In health, ventilation of lung units is unequal and therefore alveolar gas mixing is incomplete during breathing. This is referred to as ventilation inhomogeneity and may arise from two distinct zones within the lung. Ventilation inhomogeneity may occur in the conducting airways where gas flows by convection (convection dependent ventilation inhomogeneity, CDI) and results from narrowing of conducting airways or increased stiffness in the subtended lung units. When the least well ventilated lung units empty relatively late in expiration, it results in a more positive slope, since those units have a higher nitrogen concentration.(291) In the periphery of the lung, where there is an interface of bulk convective gas flow and diffusion of gases, another mechanism operates. Ventilation inhomogeneity in the very distal acinar airways arises as a result of structural asymmetry between lung units, reflecting differences in the calibre of parallel acinar airways or the volume of subtended lung units.(291) Here it is referred to as diffusion-convection dependent inhomogeneity (DCDI). In health a degree of ventilation inhomogeneity exists due to natural asymmetries in the structure of the airways, resulting in incomplete alveolar gas mixing.(292) In COPD, the distribution of airways pathology is not uniform and therefore contributes to increased ventilation inhomogeneity.(293)

The phase III of the nitrogen washout provides information on ventilation inhomogeneity within the lung. It is a measure of the nitrogen concentration differences that are generated within the lung relative to the mean nitrogen concentration. The larger the ventilation inhomogeneity between lung units, the more positive the slope.(294) Traditional analysis of the alveolar plateau phase cannot distinguish between the site of small airways pathology. However, more detailed analysis of the changes in the alveolar plateau over the course of the washout test yields more information.

The diffusion-convection dependent inhomogeneity contribution to the rise in S_n reaches a plateau quickly during the MBNW test. This occurs because ventilation inhomogeneities resulting from the acinar airways reaches an equilibrium between the relative concentration differences and remain stable throughout the test. However, changes in the CDI contribution result in a steady increase in S_n as the test progresses, reflecting increasing concentration differences relative to the mean alveolar concentration. This occurs since there is an increasing disparity in nitrogen concentrations between the best ventilated lung units and those with the poorest ventilation.(292)

Therefore, S_{acin} represents ventilation inhomogeneities resulting from asymmetry within the peripheral lung and S_{cond} represents differences in the ventilation of any two lung units supplied by conducting airways. With these measures it is possible to estimate the site of pathology within the lung, although a precise anatomical location of this cannot be defined.

2.8 Impulse Oscillometry

2.8.1 Equipment

Impulse oscillometry (IOS) was performed using the Jaeger IOS system (Wurzberg, Germany). The system consists of a Lily type heated screen pneumotachograph to measure pressure and flow, with pressure transducers located close to the mouth. A loud speaker which generates impulses is mounted on top and connected via a Y adapter. A high impedance and low resistance

terminal resistor allows expiratory flow to exit with minimal resistance but prevents excessive leakage of impulses. The system delivers multifrequency impulses of a 45ms duration between 4 and 30Hz. The pneumotachograph was calibrated prior to each patient using a 3L syringe as previously described. The resistance was calibrated using a reference device of 0.2kPa/L.

2.7.2 Testing procedure

Testing was performed as per the ERS taskforce guidance for forced oscillation technique.(295) Patients were sat in a chair with their neck in a neutral position and wearing a nose clip. They were asked to breathe normally through the mouth piece with their hands supporting their cheeks. This reduces the oscillatory compliance of the upper airway and prevents the effect of upper airway shunt. Normal tidal breathing is observed for at least 30 seconds to ensure there is no drift in volume suggesting a leak and that a stable respiratory pattern has been achieved. The measurements are made over 30-60 seconds and inspected for any artefact such as glottic closure or an irregular breathing pattern. At least 3 technically acceptable results are obtained with the subject coming off the mouthpiece between measurements. The three values should agree within 10% of each other. The mean value of the three measurements is reported.

2.7.3 Theory of impulse oscillometry

Impulse oscillometry (IOS) applies oscillating pressure variations in the form of random noise to the respiratory system in order to determine the mechanical properties of the lung. The multiple frequencies between 4 and 30Hz are applied simultaneously as an impulse over normal tidal breathing. The resulting pressure and flow changes are measured at the mouth and analysed in a Fourier transformation to determine the impedance (Z) of the respiratory system. This is composed of the in-phase or 'real' part of the impedance, known as resistance (R_{rs}) and the out of phase, or 'imaginary' part called reactance (X_{rs}). In health R_{rs} is independent of oscillation frequency but becomes frequency dependent in the presence of airways obstruction. Reactance is determined by the elastic an

inertial properties of the lung and is frequency dependent. At low frequencies X_{rs} is negative and largely represents the elastic forces within the lung. At higher frequencies X_{rs} is positive and is determined by inertiance within the lung resulting from acceleration of airflow. At a point where the elastance and inertiance are equal and opposite, X_{rs} is 0; this is known as the resonant frequency (F_{res}) and occurs between 8 and 12Hz in healthy patients.(295)

Higher frequency signals (>15Hz) are absorbed by the respiratory system before reaching the small airways and hence reflect the contribution of large airways. Low frequencies (5Hz) penetrate deep into the lung and therefore represent the whole lung. The contribution of the distal airways may be determined by the difference between the two (R_5-R_{20}) and therefore can give insight into small airways pathology. The high temporal resolution of IOS allows separate analysis of the inspiratory and expiratory resistance and reactance measures.

Chapter 3

Lung volume reduction coils in the treatment of emphysema: a randomised controlled study

3.1 Introduction

COPD is an increasingly common condition worldwide with significant associated morbidity and mortality. It is characterised by airflow limitation that is as a result of both small airways disease and emphysema. Small airways disease is as a result of chronic inflammation, mucus plugging and fibrosis. Emphysema is the result of parenchymal destruction of the lung and results in a loss of elastic recoil, resulting in increased lung volumes. It also disrupts alveolar attachments which contributes to airflow limitation by dynamic closure of small airways during expiration.(111) The resulting hyperinflation has deleterious effects on lung physiology with an increased load on respiratory muscles and the generation of intrinsic positive end expiratory pressure adding an additional load to increase work of breathing.(134)

Emphysema is poorly responsive to medical therapy and there are few treatment options for patients with advanced disease. Lung volume reduction surgery has proven beneficial in improving symptoms, exercise capacity and lung function. In appropriately selected patients it also improves mortality; one of the few treatments for COPD to do so. However, there is a significant surgical morbidity associated with the procedure including prolonged air leaks, a long recovery time and a risk of mortality.(122) Many patients will not meet the criteria for surgery since they have a homogeneous distribution of emphysema throughout their lungs. In recent years, bronchoscopic techniques have been developed in order to achieve the same effects with the aim of increased recovery time and fewer complications. The most advanced of these is endobronchial valves which aim to cause volume reduction by occlusion of an entire lobe with consequent atelectasis or collapse. They have proven effective in improving symptoms, lung function and exercise capacity(236,237), and there are early signs that mortality may also be improved.(239) They are not without significant risk of complications including pneumothorax in over 20% of responders. Endobronchial valves are limited to patients with absence of collateral ventilation, of which intact interlobar fissures are a surrogate marker. They are

more effective in patients with heterogeneous disease than homogeneous disease.(229) This too limits the potential number of patients who will benefit from such treatment.

The lung volume reduction coil is a nitinol implant with an elastic memory, thereby recovering a predetermined shape whenever it is deformed. They are designed to compress the lung parenchyma causing volume reduction. They are postulated to increase elastic recoil and therefore prevent dynamic airway collapse on expiration. However there is no direct experimental evidence to support this. A number of small, uncontrolled trials have shown that they are effective in both heterogeneous and homogeneous disease at improving symptoms, lung function and walking distance in the short term.(296–300) More recently, data from a randomised controlled trial has confirmed this up to 90 days post treatment.(219) Only one randomised controlled trial has reported follow up to 1 year. No significant improvements in walking distance were achieved and only small improvements in FEV_1 were found. However there were clinically meaningful and statistically significant improvements in lung volumes and symptoms.(220) Whilst treatment with lung volume reduction coils appears safe and effective in the short term, there is a need for further studies to assess their medium and long term safety and effectiveness.

3.2 Aims and hypothesis

The aim of this study was to assess the safety and efficacy of lung volume reduction coil treatment in patients with severe emphysema and gas trapping.

Our primary hypothesis was:

- There will be a significant improvement in walking capacity between the treatment and control group as measured by the six minute walk distance 12 months following treatment with lung volume reduction coils.

The primary outcome of 6 minute walk distance was chosen by the study sponsor based upon the RESET trial performed at our institution.(219) 6 minute walk distance was found to be the most responsive outcome measure of lung

volume reduction coil treatment in a randomised controlled trial up to 3 months. Importantly it reflects a patient orientated outcome that is both repeatable and well validated in the population of patients undergoing lung volume reduction procedures. In addition to improvements in walking distance, we hypothesised that there would be significant improvements in health related quality of life and lung function.

3.3 Methods

The full methods for this trial are discussed in Chapter 2.

3.3.1 Randomisation

Following completion of baseline investigations, those patients meeting all inclusion and exclusion criteria were eligible for randomisation. Patients were block randomised in a 1:1 ratio of treatment to control, stratified by emphysema heterogeneity. Randomisation was performed using online software provided by the study sponsor. The block size was not known to the investigators.

3.3.2 Bronchoscopic Procedure

All procedures were carried out in the endoscopy department of the Chelsea and Westminster Hospital. Patients were supplied with instructions regarding preparation for bronchoscopy and signed a separate consent form on the day of the procedure. Patients were administered oral prednisolone and an antibiotic on the day of the procedure. 5mg of nebulized salbutamol was given immediately prior to the procedure to reduce the risk of bronchospasm. The majority of procedures were carried out under conscious sedation with midazolam and alfentanil. Topical lignocaine was applied to the oropharynx, vocal cords and tracheobronchial tree. As of April 2015, general anaesthesia facilities became available and subsequent procedures were carried out under general anaesthetic with propofol and fentanyl but without neuromuscular blockade. For procedures carried out under conscious sedation, patients were intubated with a cuffless oral endobronchial tube over the bronchoscope. For procedures carried out under general anaesthesia, a cuffed oral endobronchial tube was used with a port to allow bronchoscopic access. Examination of the tracheobronchial tree was performed prior to proceeding with the procedure.

The order in which target lobes were treated was chosen by the investigator, with the aim of treating the most diseased lobe first. Under fluoroscopic guidance the guidewire is passed into a subsegmental branch of an airway

(Figure 3.1a). The guidewire was passed to within no more than 2cm from the edge of the pleura and the number of marker visible on the guidewire determined the size of the coil to be placed. Airways which were too short for 1 marker to be visible or those which were tortuous were avoided.

The delivery catheter is advanced over the guidewire until their tips are aligned. The guidewire is then removed (Figure 3.1b and c). The coil is grasped by the forceps within its packaging and withdrawn back into the loading cartridge, with the forceps left attached. This is attached to the delivery catheter and the forceps are advanced forward down the delivery catheter under fluoroscopic guidance (Figure 3.1d). Once the tip of the coil is at the end of the delivery catheter, it is held in place whilst the delivery catheter is withdrawn. The coil begins to recover its shape (Figure 3.1d). Once the end of the delivery catheter is drawn past the jaws of the forceps, slight tension is put on the coil and the assistant is instructed to open the forceps. The coil is released and the forceps are withdrawn (Figure 3.1e and f)

The procedure is repeated with the aim of treating all segments of a lobe with as even as possible spread of coils throughout the lobe. The number of coils is determined by the operator based on the number of accessible airways but with the aim of approximately 10 coils per lobe.

It is possible to remove a malpositioned coil by reversing the procedure. The proximal tip of the coil is visualised and grasped by the forceps. The delivery catheter is extended over the coil which induces straightening of the coil and it can be recovered.

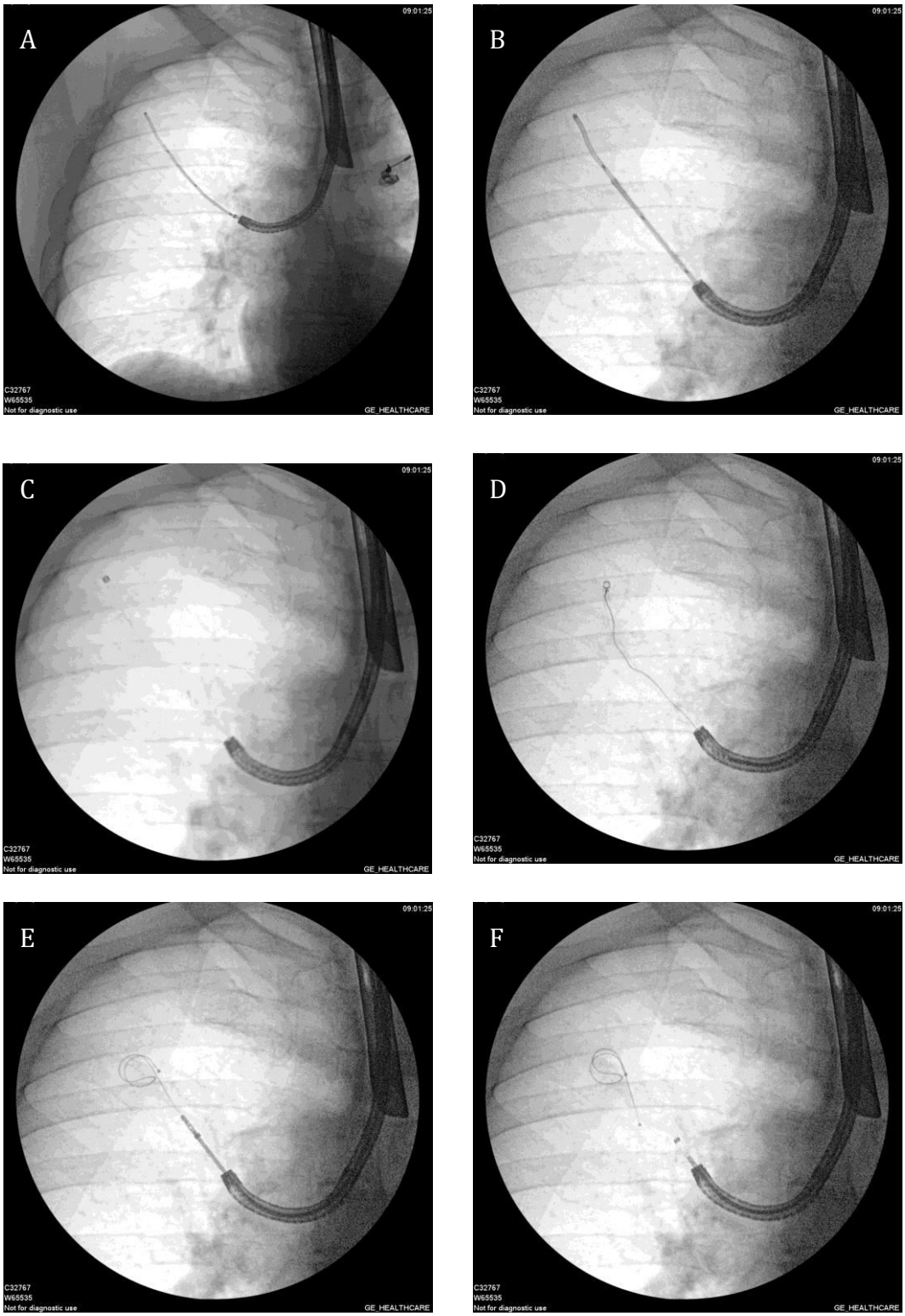


Figure 3.1 Fluoroscopic images of the coil deployment process

See text for description of each image

3.3.3 Post bronchoscopy care

Following the procedure the patient undergoes a chest x-ray at 1 hour and spends 2 hours in the recovery room. All patients were scheduled to stay overnight in hospital with a repeat chest x-ray the following day to exclude any early post-procedural complications. They are discharged a weeks course of prednisolone 30mg once daily and azithromycin 500mg once daily for three days. Chest x-rays following the procedure are shown in figure 3.4.

3.3.4 Adverse events

An adverse event was classified as serious if:

- It resulted in death
- It was life-threatening
- It resulted in a new or prolonged hospitalization
- It resulted in significant disability or incapacity

Serious Adverse Events (SAE's) and their relationship to the treatment or device were determined by the investigator. The sponsor hosted a clinical events committee which adjudicated on all adverse events. An independent data safety monitoring board (DSMB) was established which received quarterly information on adverse events for all participating hospitals. The DSMB was able to make recommendations on the conduct of the study. Stopping rules were established which included two or more deaths related to the treatment.

3.3.5 Statistical analysis

This analysis of our institutions data was not individually powered to detect a statistically significant difference since it was contributing to a larger data set. Based on previous data from the RESET study at our institution, assuming an alpha of 0.05 and a beta of 0.80, a sample size of 45 would be required in each group. Therefore analysis of our dataset had a power of 0.52 to detect a significant difference in the primary outcome.

An intention-to-treat analysis was conducted for all endpoints to reduce the risk of bias from patients withdrawing from the study or those lost to follow up. Where data was not available at follow up time points, the last known value was carried forward. If no data was available for follow-up, the baseline data was carried forward to assume no change.

For the primary and secondary outcomes, normally distributed data was analysed using a two-tailed unpaired t-test for the mean change between groups. Non-normally distributed data was analysed with the Mann-Whitney test. For paired data a paired t test was used for normally distributed data and a Wilcoxon matched pairs signed rank test for non-normally distributed data.

Responder analyses were conducted using Fisher's exact test to determine if there is a significant difference in the proportion of patients reaching the minimum clinically important difference between treatment groups.

For changes over time within groups, a repeated measures one-way ANOVA with Dunnet's multiple comparison test was performed on normally distributed data and a Friedman's test with Dunn's correction was performed on non-normally distributed data.

Analysis of the primary outcome and change in symptom scores will be undertaken with correlation to assess the association with changes in lung function. To determine the relationship of the primary outcome and symptom scores to the baseline variables, we will conduct univariate linear regression. Where more than one baseline variable has a significant relationship, we will undertake multivariate linear regression to determine an equation that may predict the change in primary outcome.

3.4 Results

3.4.1 Baseline data

30 patients were recruited at our institution; 17 were randomised to the treatment group and 13 to the control arm. 9 of the 13 patients in the control arm were eligible to enter the crossover study. Therefore baseline data is available for 17 treatment group patients and 13 control patients in the randomised study. The baseline characteristics are presented in table 3.1 along with the baseline data for all treated patients, including crossovers (n = 26).

	Treatment n= 17	**Control n = 13**	**p value**	**All treatment patients n = 26**
Male (%)	9 (60%)	6 (46%)	>0.9999¶	15 (63%)
Age	63.0 (±1.96)	61.7 (±2.3)	0.6351	63.9 (±1.49)
Homogenous (%)	16 (94%)	10 (76.9%)	0.2903¶	23 (88.5%)
FEV_1 (L)	0.74 (±0.05)	0.71 (±0.05)	0.6250	0.71 (±0.04)
FEV_1 % predicted	26.2 (±1.78)	28.2 (±2.27)	0.4953	26.5 (±1.34)
FEV_1/FVC ratio	23.7 (±1.36)	27.4 (±1.74)	0.0988	24.7 (±1.00)
TLC % predicted	142 (±2.29)	138 (±3.15)	0.3409	140 (±1.92)
RV % predicted	244 (194 – 315)	248 (210 – 355)	0.6801§	238 (189 – 315)
RV/TLC ratio	64.7 (±1.6)	67.2 (±1.08)	0.2462	65.2 (±1.34)
$TLCO_c$ % predicted	32.4 (20.6 – 71.8)	33.2 (23.3 – 75.6)	>0.9999§	32.5 (20.6 – 71.8)
6MWD (m)	330 (159 – 498)	282 (149 – 404)	0.0701§	295 (159 – 498)
SGRQ score	55.8 (±2.91)	61.6 (±2.67)	0.1614	59.6 (±2.48)
mMRC score	3 (2-4)	3 (2- 4)	0.6266§	3 (2 – 4)

Table 3.1 Baseline characteristics of the treatment and control groups

Data presented as mean (SE) or median (range). Unpaired t test.

¶ Fisher's exact test

§ Mann-Whitney test

3.4.2 Enrolment and outcomes

Participants were recruited between November 2012 and October 2014. The control group patients were eligible for crossover after completion of the 12 month follow up. The last control patient crossed over to the treatment group in September 2015. The CONSORT diagram presented in figure 3.2 details the participation of subjects within the study.

76 patients were screened for entry into the trial of which 30 met the entry criteria. The most common reason for failing screening was an RV of <225% predicted. In April 2015 a substantial amendment was approved to reduce the qualifying RV to 175% predicted. At this point, 23 out of the 30 patients had been recruited to the study. Of the next 7 patients, 4 had an RV between 175% and 225% predicted. Pulmonary nodules requiring further investigation or follow-up were detected in 14 patients.

At 12 months, 15 patients in the treatment group were available for follow up. 2 patients had died during the course of the study. The first death occurred in a patient during the first treatment procedure. A further death secondary to pneumonia occurred one week following the second treatment. There were two further deaths in the crossover treatment group. A third patient had not been well enough to attend the 5 month follow up and died from pneumonia at 6 months. There was one death attributable to pulmonary oedema and heart failure at 7 months. The deaths are discussed along with other serious adverse events in section 3.4.10.

All patients in the control group were followed up to 12 months. At 9 months, 2 patients were not able to attend assessment visits due to COPD exacerbations which did not recover fully within the window period. One patient had two admissions to hospital with mechanical ventilation due to an exacerbation by metapneumovirus. Despite recovering back to baseline he was ineligible for crossover due to the number of hospital admissions within 12 months. Two further patients were ineligible for crossover due to a significant improvement in FEV_1 above the minimum threshold, and a further for developing a pulmonary

nodule that required further investigation. One patient declined to participate because she felt the risks of treatment outweighed any potential benefits.

Patients with missing data had their last known value carried forwards to the 12 month follow up for the intention to treat analysis.

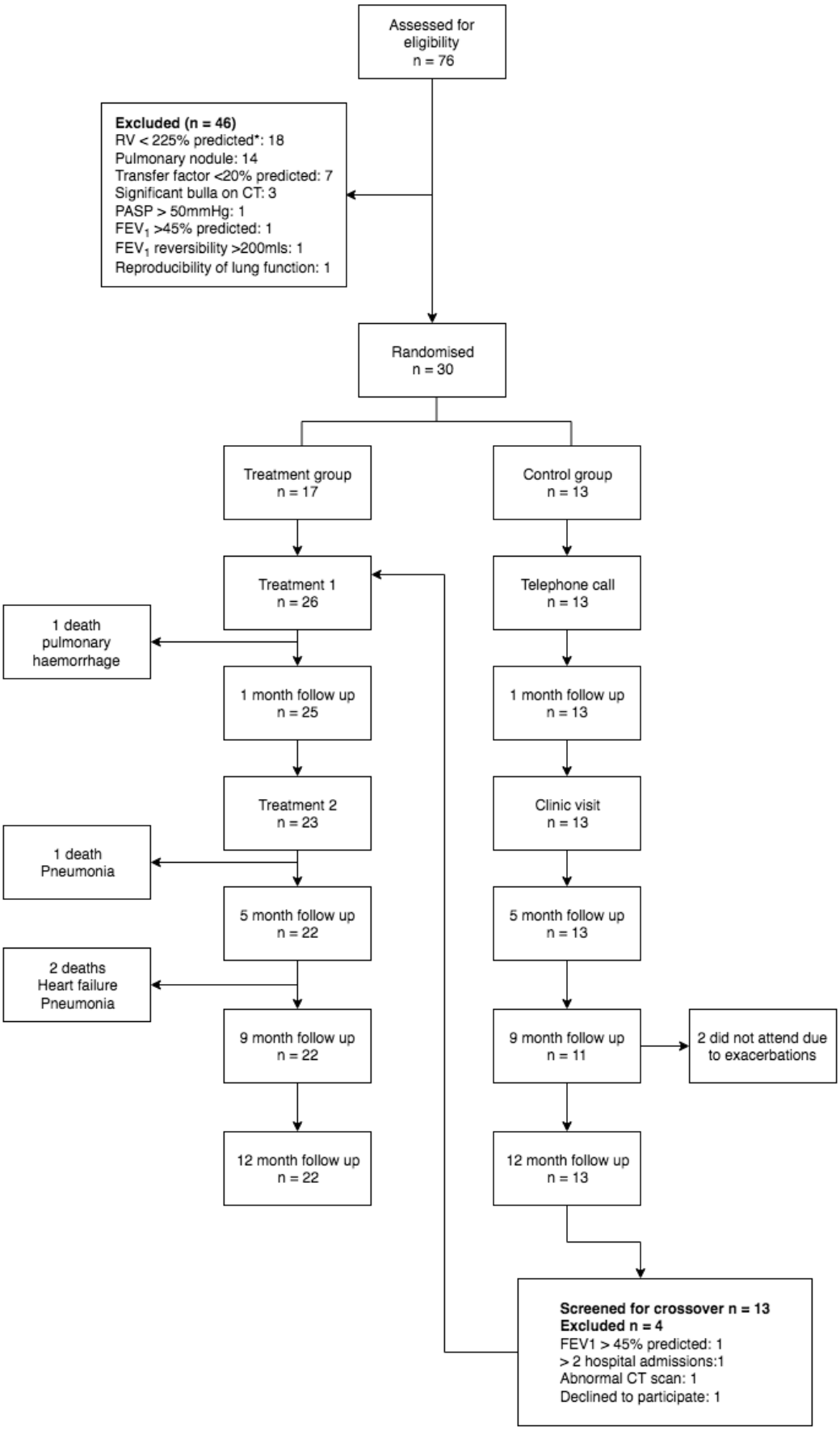


Figure 3.2 CONSORT diagram for the study

3.4.3 Procedural details

50 procedures were carried out in 26 patients. Two patients did not undergo a second procedure due to a death and a myocardial infarction which required a percutaneous coronary intervention with a drug eluting stent. The patient was started on clopidogrel which could not be stopped and the investigators felt that the risks of a second procedure would outweigh the benefits.

80% of the procedures were carried out under conscious sedation using midazolam and fentanyl as sedation. The remainder were conducted under general anaesthesia using propofol and fentanyl.

Table 3.2 presents the procedural details and figure 3.6 presents the proportion of treatments in each lobe.

Treatment 1			**Treatment 2**		
Procedure time (mins)		33.2 (± 10.9)	Procedure time (mins)		29.0 (± 6.0)
Fluoroscopy time (mins)		10.0 (± 2.2)	Fluoroscopy time (mins)		9.6 (± 1.9)
Target lobe	**Count**	**Coils/lobe**	**Target lobe**	**Count**	**Coils/lobe**
RUL	17	10	RUL	3	11.3
LUL	4	10.5	LUL	17	13.3
RLL	4	11.5	RLL	1	10.1
LLL	1	13	LLL	3	12.0
Coils used	100mm	64	Coils used	100mm	60
	125mm	181		125mm	193
	150mm	6		150mm	4

Table 3.2 Procedural details for treatments 1 & 2

Data presented as mean (±SD) for times.

RUL: right upper lobe; RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe

Of the 5 patients who had lower lobe treatments, 4 had both lower lobes treated and one had one upper lobe treatment and one lower lobe treated.

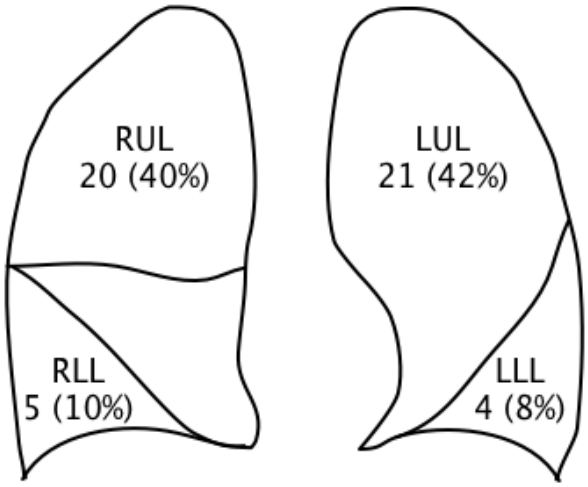


Figure 3.3 Distribution of target lobes for all treatments

3.4.5 Primary endpoint

At 12 months the between group median difference in change in 6 minute walk distance was not statistically significant. The median difference was 25m (95% CI -40 to 59), p = 0.7028. In the paired data analysis for all patients undergoing treatment (n = 26), there was no significant change in 6 minute walk distance when comparing paired data from baseline to 12 months in either group. In the treatment group the median difference from baseline to treatment was 0.5m (range -177 to 133), p = 0.7526. In the control group the median difference from treatment to baseline was -25m (range -253 to 79), p = 0.3757.

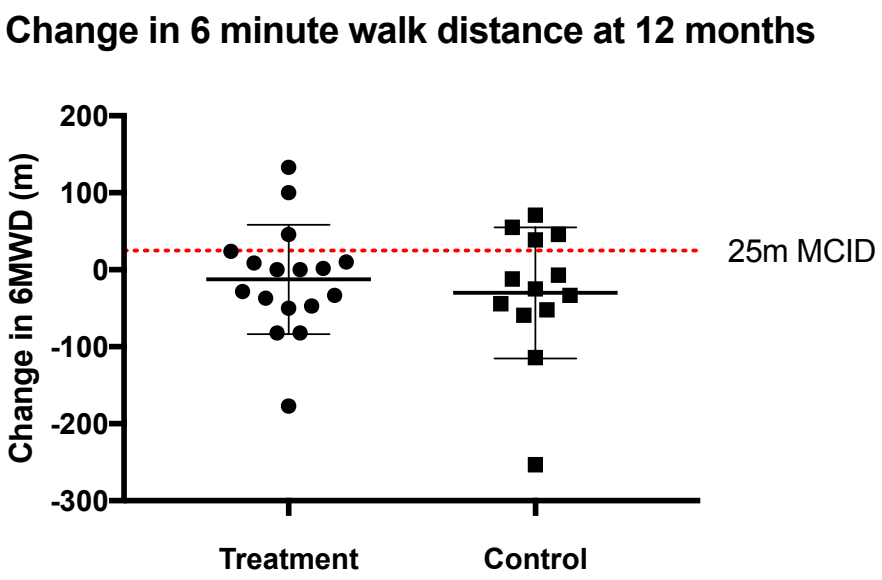


Figure 3.4 Box plot of change in 6 minute walk distance from baseline to 12 months

Bars represent median and interquartile ranges.

3.4.6 Secondary endpoints

The data for 12 month between group changes in primary and secondary outcomes is presented in table 3.3, figures 3.5 and 3.6. Table 3.4 describes the between group changes at all follow up points in the study. Tables 3.5 and 3.6 present the paired data for each follow up visit data for all 26 patients undergoing treatment and the control group respectively.

Percentage change in FEV_1

The between group difference in mean percentage change in FEV_1 was 9.5% (95% CI -1.9 to 25.7) which was not statistically significant (p = 0.1253). The absolute difference in FEV_1 between groups was 0.055L (95% CI -0.004 to 0.140), p = 0.1302.

Change in FVC

There was no significant difference in the change in FVC between the treatment group and control. The between group difference in median change in percentage FVC was 0.5% (95% CI -5.6 – 13.8) p = 03465. This equated to an absolute difference of 0.05L (95% CI -0.140 to 0.440) p = 0.3052.

Change in RV

There was a clinically but not statistically significant difference in the between group difference in change in RV. The between group difference was -0.382L (95% CI -0.818 to 0.054), p = 0.0835. In the paired analysis of all treated patients, the mean change from baseline was -0.344L (±0.554), p = 0.0041. There was a non-significant difference in RV from baseline to 12 months in the control group with an increase in RV of 0.08L (±0.554) p = 0.6154.

Change in TLC

There was no significant between group difference in median change in TLC, with a -0.04L difference, p = 0.1865.

Change in RV/TLC ratio

There was no significant difference in the between group mean change in RV/TLC ratio. The between group difference was -2.25 (95% CI -6.31 to 1.34), p = 0.2410.

Change in FRC

The between group difference in change in median FRC was – 0.412L (95% CI -0.86 to -0.10), p = 0.0077. This equated to a reduction in FRC of -.0330L in the treatment group (p = 0.0054) and a non-significant increase of 0.08L in the control group (p = 0.2439).

Change in IC

The between group difference in median change in IC was 0.280L (95.3% CI 0.04 to 0.513), p = 0.0256.

Change in TL_{COc} % predicted

There was no significant difference in the between group differences of percentage change in TL_{COc}.

Change in SGRQ score

The treatment group SGRQ score fell by 2.34 points and the control group SGRQ score increased by 4.19 points, resulting in a between group difference of 6.53 (95.3% CI -16.95 to 0.17), p = 0.0589.

Change in mMRC score

In the treatment group the median change in mMRC score was 0.0 (range -2 to 1) p = 0.1145. In the control group the median change was 0 (range -1 to 2), p = 0.8262. Thus the between group difference was 0 (95.3% CI -1 to 0), p = 0.1249.

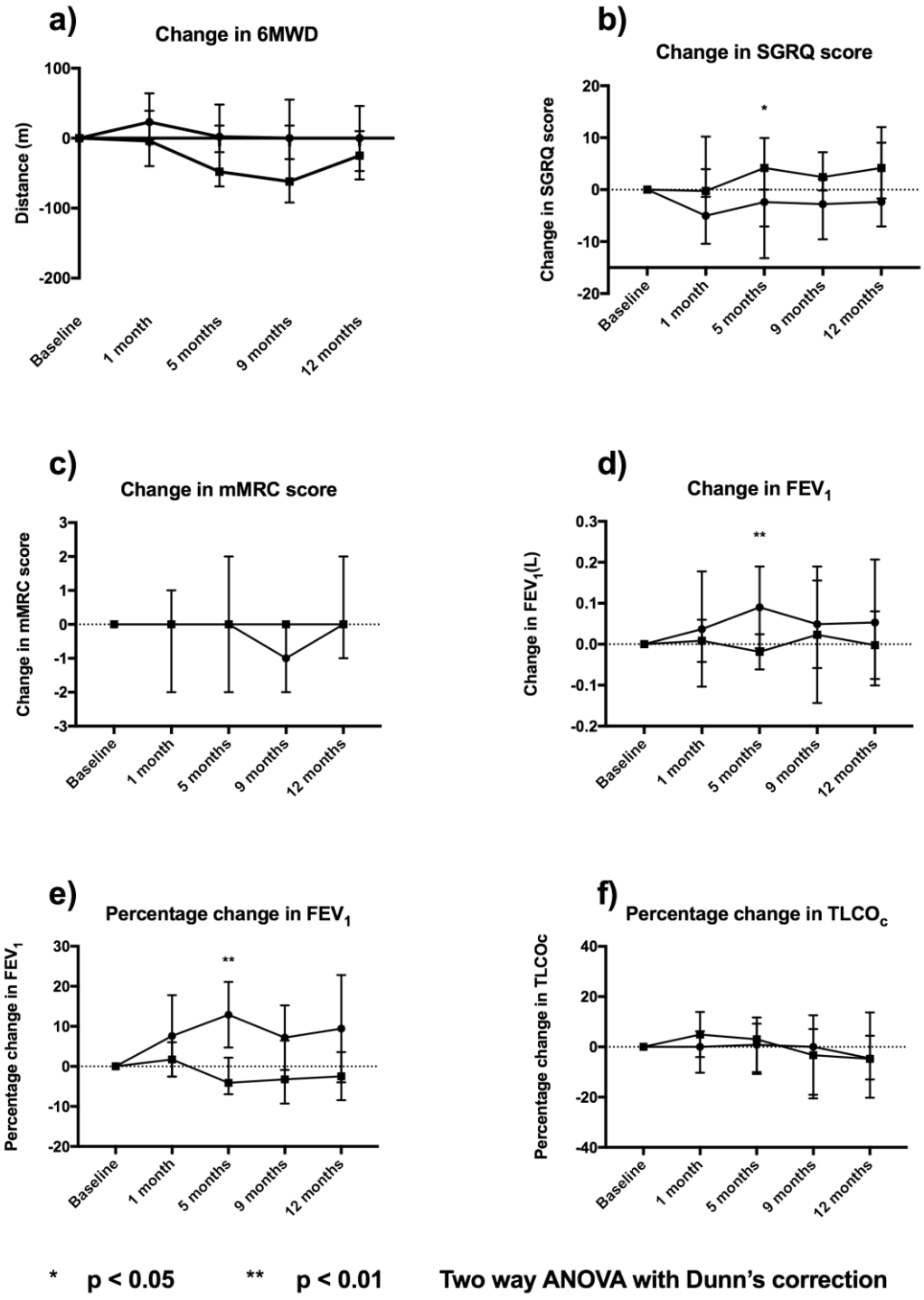


Figure 3.5 Between group differences in primary outcome measure, symptoms and spirometry

Graphs a, b, c and f are median with interquartile ranges. Graphs d and e are mean and 95% CI.

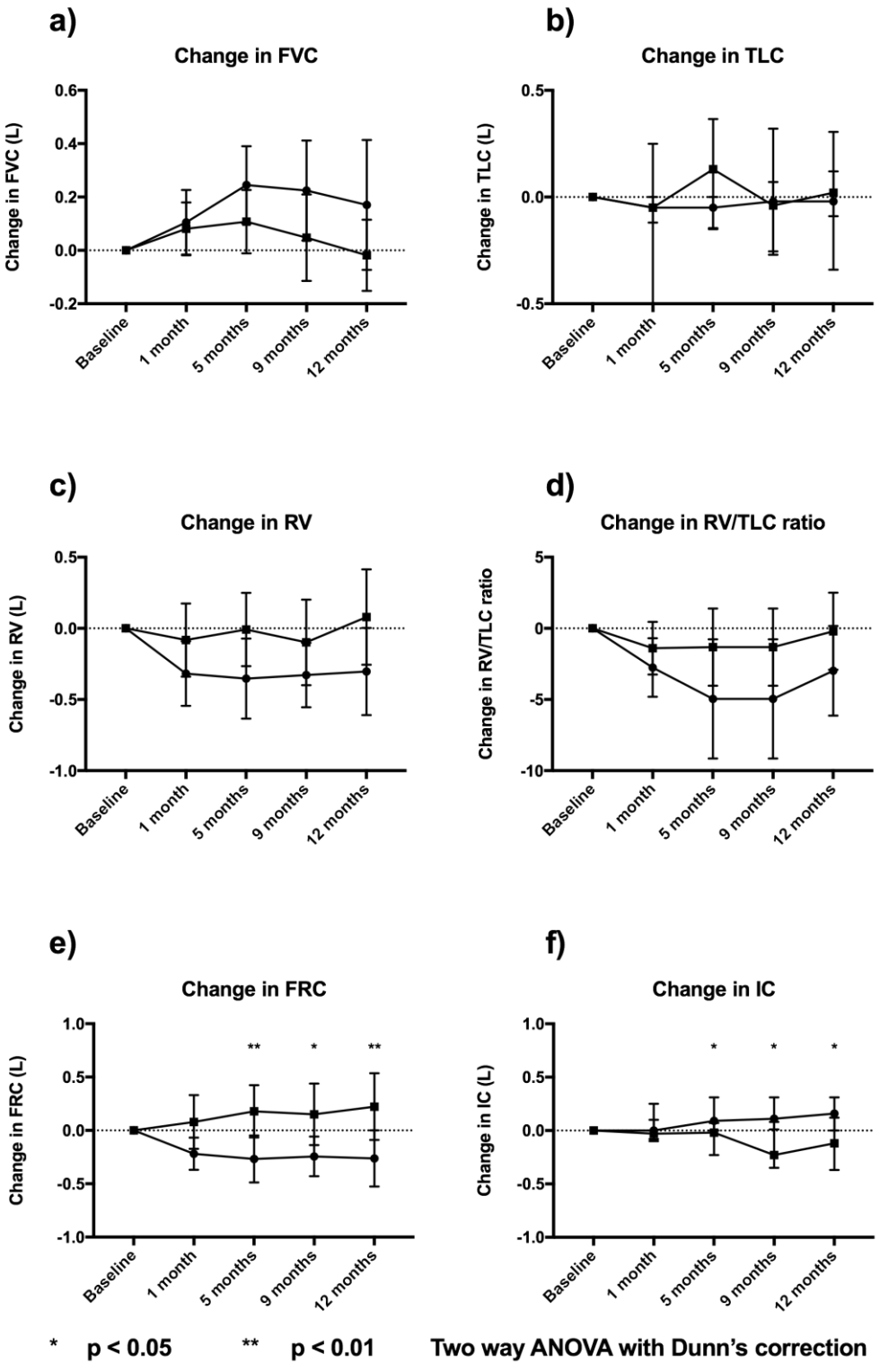


Figure 3.6 Between group differences in lung volumes

Treatment

Control

Graphs a, c and d are presented as mean with 95% CI and graphs b, e and f are median with interquartile ranges.

	Treatment group change n = 17		Control group change n = 13		Between group difference	95% CI	p value
	Change	SD or range	Change	SD or range			
6MWD (m)	0	-173 to 133	-25	-253 to 71	25	-40 to 59	0.7028§
SGRQ	-2.34	-31.77 to 17.11	4.19	-3.74 to 14.79	-6.53	-16.95 to 0.17	0.0589§
mMRC	0	-2 to 1	0	-1 to 2	0	-1 to 0	0.1249§
FEV_1 (L)	0.053	-0.21 to 0.36	-0.02	-0.12 to 0.21	0.055	-0.004 to 0.140	0.1302§
% change FEV_1	7.0	-28.9 to 66.0	-2.5	-17.9 to 22.8	9.5	-1.9 to 25.7	0.1253§
FVC (L)	0.100	-0.630 to 1.270	0.05	0.470 to 0.210	0.05	-0.140 to 0.440	0.3052§
% change FVC	2.8	-19.3 to 59.4	2.3	-17.5 to 9.2	0.5	-5.61 to 13.8	0.3465§
TLC (L)	-0.020	-1.050 to 0.600	0.020	-0.341 to 0.932	-0.04	-0.420 to 0.070	0.1865§
RV (L)	-0.303	±0.595	0.079	±0.554	-0.382	-0.818 to 0.054	0.0835
% change RV	-5.9	±11.1	0.8	±9.6	-6.7	-14.6 to 1.2	0.0917
RV/TLC ratio	-3.72	-19.51 to 9.97	-1.47	-5.9 to 7.2	-2.25	-6.31 to 1.34	0.2410§
FRC (L)	-0.330	-1.110 to 1.053	0.082	-0.312 to 1.343	-0.412	-0.863 to -0.101	**0.0077**§
IC (L)	0.162	-0.910 to 1.121	-0.122	-0.851 to 0.613	0.280	0.042 to 0.513	**0.0256**§
% change TLCOc	-4.6	-45.7 to 54.2	-4.8	-16.8 to 57.8	0.16	-22.9 to 9.5	0.5008§

Table 3.3 Between group differences in primary and secondary endpoints at 12 months

Data presented as mean (±SD) or median (range). § Mann-Whitney U test. Otherwise unpaired t test. 95%CI is calculated for median difference where distributions are similar.

	1 month		5 months		9 months		12 months	
	Group difference (95% CI)	**p value**	**Group difference (95% CI)**	**p value**	**Group difference (95% CI)**	**p value**	**Group difference (95% CI)**	**p value**
6MWD (m)	27 (-36 to 43)	0.8047	50 (-23 to 70)	0.3554	62 (-9 to 93)	0.0752	25 (-40 to 59)	0.7028
SGRQ	-4.75 (-10.44 to 4.16)	0.3411	-6.57 (-14.8 to -0.56)	**0.0379**	-5.18 (-14.3 to 1.16)	0.0715	-6.53 (-16.95 to 0.17)	0.0589
mMRC	0 (-1 to 0)	0.4409	0 (-1 to 0)	0.2373	-1 (-1 to 0)	0.3420	0 (-1 to 0)	0.1249
FEV_1 (L)	0.029 (-0.556 to 0.113)	0.4922	0.12 (0.050 to 0.170)	**0.0006**	0.070 (-0.02 to 0.131)	0.0729	0.055 (-0.004 to 0.140)	0.1302
% change FEV_1	6.1 (-5.6 to 17.9)	0.2958	13.8 (6.3 to 24.6)	**0.0006**	10.5 (-2.6 to 17.4)	0.0943	9.5 (-1.9 to 25.7)	0.1253
FVC (L)	0.025 (-0.132 to 0.181)	0.7510	0.080 (-0.090 to 1.270)	0.3406	0.200 (-0.080 to 0.370)	0.2087	0.050 (-0.140 to 0.440)	0.3052
% change FVC	0.1 (-6.7 to 7.0)	0.9736	2.8 (-3.5 to 8.8)	0.3909	7.5 (-3.8 to 12.9)	0.2454	0.5 (-5.6 to 13.8)	0.3465
TLC (L)	0.000 (-0.490 to 0.082)	0.3409	-0.182 (-0.51 to 0..674)	0.1867	0.02 (-0.342 to 0.183)	0.5021	-0.130 (-0.491 to 0.044)	0.1865
RV (L)	-0.235 (-0.563 to 0.092)	0.1527§	-0.345 (-0.728 to 0.031)	0.0708§	-0.299 (-0.581 to 0.122)	0.191§	-0.382 (0.818 to 0.054)	0.0835§

% change RV	-4.3 (-10.1 to 1.6)	0.1449§	-6.2 (-12.9 to 0.6)	0.0742§	-4.0 (-10.2 to 2.1)	0.1895§	-6.7 (-14.6 to 1.2)	0.0917§
RV/TLC ratio	-1.36 (-4.09 to 1.38)	0.3176	-2.41 (-6.39 to 1.35)	0.1698	-2.41 (-6.39 to 1.35)	0.1698	-2.24 (-6.31 to 1.34)	0.2410
FRC (L)	-0.101 (-0.562 to 0.033)	0.0923	-0.332 (-0.781 to -0.122)	**0.0062**	-0.392 (-0.731 to -0.073)	**0.0190**	-0.412 (-0.863 to -0.101)	**0.0077**
IC (L)	0.089 (-0.124 to 0.302)	0.3390	0.226 (0.005 to 0.446)	**0.0449**	0.293 (0.068 to 0.519)	**0.0127**	0.280 (0.042 to 0.513)	**0.0256**
% change TLCOc	-1.6 (-9.3 to 0.7)	0.1227	-2.2 (-15.6 to 12.8)	0.9918	3.3 (-20.3 to 12.4)	0.7106	0.16 (-22.9 to 9.5)	0.5008

Table 3.4 Between group differences in primary and secondary outcomes at each follow up interval

§ Mann-Whitney U test, data presented as median (95.3% CI)

Otherwise unpaired t test, data presented as mean (95%CI)

n = 26	Baseline	1 month		5 months		9 months		12 months	
	Mean (SD) or Median (range)	Mean (SD) or Median (range)	p value	Mean (SD) or Median (range)	p value	Mean (SD) or Median (range)	p value	Mean (SD) or Median (range)	p value
6MWD (m)	330 (159 – 498)	334 (146 – 542)	>0.9999	335 (120- 576)	>0.9999	335 (150 – 441)	>0.999	339 (130 – 436)	>0.9999
SGRQ	55 (35.7 – 77.6)	55.8 (32.8 – 84.8)	0.8490	55.3 (26.0 – 74.3)	0.1377	55.2 (14.9 – 75.3)	0.2940	55.2 (24.7 – 74.8)	>0.9999
mMRC	3 (2-4)	2 (1 – 4)	**0.0480**	2 (0 – 4)	**0.0429**	2 (0 – 4)	0.0718	2 (0 – 4)	0.1372
FEV_1 (L)	0.69 (0.47 – 1.15)	0.76 (0.52 – 1.21)	0.6587	0.80 (0.51 – 1.38)	**0.0065**	0.69 (0.48 – 1.38)	0.2232	0.78 (0.37 – 1.24)	0.4445
FVC (L)	3.15 (1.90 – 4.49)	3.3 (1.68 – 4.54)	0.2364	3.23 (2.05 – 4.81)	**0.0085**	3.12 (1.98 – 4.43)	0.0696	3.41 (1.89 – 4.44)	0.4060
TLC (L)	7.49 (5.73 – 11.15)	7.18 (5.62 – 11.35)	>0.9999	6.97 (5.55 – 11.42)	>0.9999	7.28 (5.48 – 11.42)	>0.9999	7.15 (5.52 – 11.26)	>0.9999
RV (L)	5.71 (±1.05)	5.39 (±1.23)	**0.0302**	5.35 (±1.24)	0.0549	5.38 (±1.67)	**0.0240**	5.4 (±1.33)	0.1547
RV/TLC ratio	64.7 (±6.5)	61.9 (± 6.8)	**0.0384**	61.3 (± 8.3)	**0.0283**	59.8 (±12.5)	0.0729	61.7 (±8.74)	0.1812
FRC (L)	6.81 (4.44 – 9.07)	6.60 (4.25 – 9.07)	0.1047	6.74 (4.51 – 9.07)	**0.0315**	6.88 (4.28 – 9.07)	0.1202	7.00 (3.77 – 9.07)	**0.0268**
IC (L)	2.08 (1.32 - 2.8)	1.99 (1.48 – 2.95)	>0.9999	2.04 (1.21 – 3.29)	0.1792	2.19 (1.39 – 3.22)	0.1202	2.08 (1.38 – 2.94)	0.0916
TLCOc %	32.4 (20.6 – 71.8)	34.9 (21.1 – 64.4)	>0.9999	32.4 (18.0 – 72.0)	>0.9999	30.9 (19.8 – 74.1)	>0.9999	33.3 (13.4 – 68.8)	>0.9999

Table 3.5 Paired data for all treated patients: primary and secondary endpoints at each follow up interval

Data presented as mean (±SD) or median (range). One way repeated measures ANOVA with Dunnet's correction for multiple comparisons

§ Friedman's test with Dunn's correction for multiple comparisons.

n = 13	Baseline	1 month		5 months		9 months		12 months	
	Mean (SD) or Median (range)	Mean (SD) or Median (range)	p value	Mean (SD) or Median (range)	p value	Mean (SD) or Median (range)	p value	Mean (SD) or Median (range)	p value
6MWD (m)	282 (149- 404)	299 (140 – 360)	>0.9999§	231 (154 – 339)	>0.9999§	222 (134 – 342)	0.1399§	263 (80-379)	0.4275§
SGRQ	62.9 (40.4 – 76.7)	62.6 (50.5 – 76.1)	>0.9999§	61.2 (49.2 – 85.7)	>0.9999§	63.1 (40.9 – 82.6)	0.6898§	69.1 (44.2 – 80.6)	0.8594§
mMRC	3 (2 – 4)	3 (1 – 4)	0.4202§	3 (2 – 4)	0.9970§	2 (1 – 4)	**0.0245§**	3 (2 – 4)	0.8262§
FEV_1 (L)	0.709 (±0.169)	0.718 (±0.172)	0.9334	0.691 (±0.173)	0.3819	0.732 (±0.269)	0.9622	0.707 (±0.229)	0.9999
FVC (L)	2.485 (±0.671)	2.566 (±0.653)	0.2765	2.593 (±0.709)	0.2032	2.533 (±0.798)	0.9150	2.467 (±0.610)	0.9940
TLC (L)	7.49 (5.73 – 11.15)	7.18 (5.62 – 11.35)	>0.9999§	6.97 (5.55 – 11.42)	>0.9999§	7.28 (5.48 – 11.42)	>0.9999§	7.15 (5.52 – 11.26)	>0.9999§
RV (L)	5.219 (±1.126)	5.137 (±1.219)	0.8896	5.212 (±1.238)	0.9999	5.121 (±1.211)	0.8829	5.298 (±1.423)	0.9578
RV/TLC ratio	67.2 (±3.89)	65.8 (±5.39)	0.3362	66.1 (±4.69)	0.6290	65.9 (±6.12)	0.6801	67.0 (±6.95)	0.9993
FRC (L)	6.06 (4.11 – 8.35)	5.78 (3.93 – 9.27)	>0.9999§	5.68 (3.95 – 9.36)	>0.9999§	5.90 (4.21 – 9.36)	>0.9999§	5.89 (3.81 – 9.31)	>0.9999§
IC (L)	1.7 (1.39 – 2.8)	1.69 (1.29 – 2.30)	>0.9999§	1.60 (1.29 – 2.59)	0.9847§	1.61 (1.29 – 2.59)	0.2512§	1.65 (1.13 – 2.81)	0.2572§
TLCOc %	33.2 (23.3 – 75.6)	38.6 (26.5 – 83.1)	>0.9999§	36.7 (15.5 - 77.9)	>0.9999§	37.9 (15.5 – 71.2)	>0.9999§	32.6 (20.7 – 79.0)	>0.9999§

Table 3.6 Paired data for control group: primary and secondary endpoints at each follow up intervals

Data presented as mean (±SD) or median (range). One way repeated measures ANOVA with Dunnet's correction for multiple comparisons

§ Friedman's test with Dunn's correction for multiple comparisons.

3.4.7 Responder analysis

At 12 months the proportions of patients meeting the MCID in change in 6 minute walk difference was not significantly between the treatment and control group. A significantly higher proportion of patients in the treatment group met the MCID of a 10% improvement in FEV_1 and a ≥ 4 point improvement in SGRQ scores.

	Treatment Group	Control Group	p value
6MWD ≥ 26m	26.9% (7/26)	30.8% (4/13)	>0.9999
FEV_1 ≥ 10%	42.3% (11/26)	7.7% (1/13)	0.0336
RV ≥ 0.35L	42.3% (11/26)	23.1% (3/13)	0.3039
SGRQ ≥ 4 points	53.9 (14/26)	0.0% (0/13)	0.0009

Table 3.7 Responder analysis at 12 months

p values represent Fisher's exact test

3.4.8 Predictors of response

Univariate logistic regression was performed to assess the relationship between change in 6 minute walk distance and baseline variables. These included 6 minute walk distance, SGRQ score, FEV_1, RV, RV/TLC and FRC. There was a weak association with baseline 6 minute walk distance and the change in 6 minute walk distance ($r^2 = 0.20$, $p = 0.0219$) (Figure 3.7). No other variables were associated with change in 6 minute walk distance, nor change in SGRQ score.

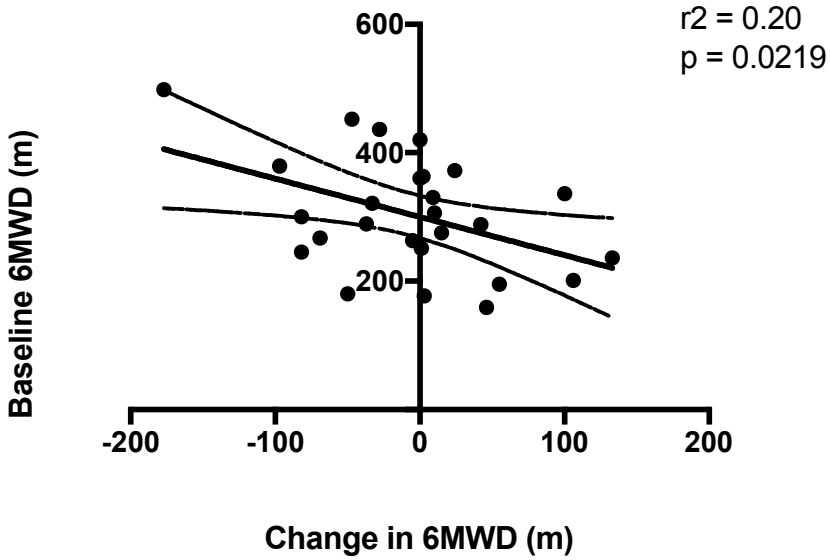


Figure 3.7 Linear regression of baseline 6 minute walk and change in 6 minute walk distance

3.4.9 Correlation of outcome variables

The change in 6 minute walk distance was strongly correlated with the change in symptom scores measured by SGRQ (Spearman's r = 0.7815, p < 0.0001). The primary outcome variable was also associated with the change in a number of physiological parameters following treatment. The strongest association of change in 6 minute walk distance was with percentage change in TL_{COc} (Spearman's r = 0.7103, p <0.0001). Change in residual volume, RV/TLC ratio, FEV_1, and FVC were also significantly associated with change in walking distance. Figure 3.8

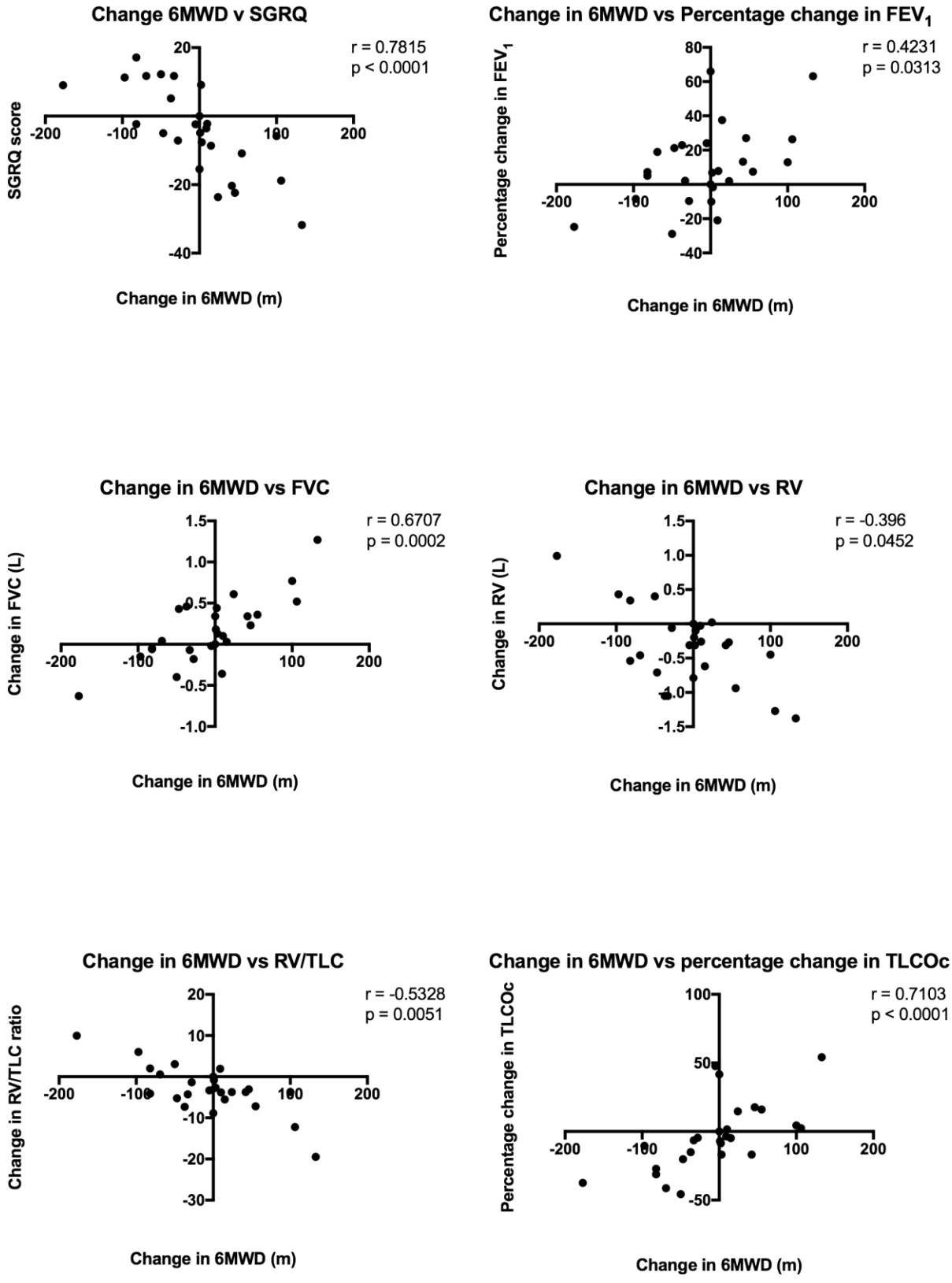


Figure 3.8 Correlation of primary outcome variable with symptoms and physiological parameters

r values reflect Spearman's Rho.

3.4.10 Adverse events

Adverse events occurring within 24 hours of the procedure are listed in table 3.8. Adverse events occurring within the 28 days following the procedures are listed in table 3.9. In both tables, the incidence of events is calculated by the number of events/number of procedures.

For the period of 1-12 months following the procedure (table 3.10), adverse event rates per patient year are calculated. This adjusts for the patients who died during follow-up and did not complete the study. Fisher's exact test is used to compare the proportions.

Procedural and recovery period adverse events

Minor haemoptysis with 24 hours of the procedure (defined as < 10mls) occurred following 34% of procedures (p = 0.0003). Transient chest pains were associated with 16% of procedures (p = 0.0453) but all resolved with simple analgesia. There was no incidence of pneumothorax in the immediate post procedure period or during follow-up.

COPD exacerbations were common in the month following the procedure associated with 34% of procedures including the one hospitalization, compared to 15.4% in the control group (p = 0.1709). The difference with the control group was not statistically significant although the small numbers mean that there is not sufficient power to detect a statistically significant difference.

COPD exacerbations

In the longer term follow-up, the incidence of non-serious COPD exacerbations was significantly higher in the control group (2.63 versus 0.67, p = 0.0056), although this in part reflects three patients who had frequent exacerbations throughout the year and the higher incidence of hospitalisations for COPD exacerbations in the treatment group. The incidence of hospitalization for COPD in the treatment group compared to the control group was 0.52 versus 0.27 respectively (p = 0.4967). When hospitalisations for all causes throughout the

study were examined, the incidence per patient year was 0.76 in the treatment group and 0.36 in the control group, although again this was not statistically significant (p = 0.3523).

Pneumonia

Pneumonia occurred in 3 patients in the treatment group and none in the control group (p = 0.5361). One case occurred within a month of treatment and resulted in death (discussed below) and the other two were successfully treated. There were three further cases where consolidation was seen on follow up scans but without evidence of systemic upset or infection.

Procedural or <24 hour adverse events							
	Treatment Group (50 procedures)			**Control group (26 procedure equivalents)**			
	Events	**Patients**	**Incidence**	**Events**	**Patients**	**Incidence**	p value[Ŧ]
Serious adverse events							
Death	1	1	2%	0	0	0%	>0.9999
Pulmonary haemorrhage	1	1	2%	0	0	0%	>0.9999
Non-serious adverse events							
Minor haemoptysis	17	15	34%	0	0	0%	0.0003
Chest pain	8	6	16%	0	0	0%	0.0453
Bronchospasm	4	4	8%	0	0	0%	0.2925
Unable to tolerate procedure	1	1	2%	0	0	0%	>0.9999
Dyspnoea	1	1	2%	0	0	0%	>0.9999
Urinary retention	1	1	2%	0	0	0%	>0.9999

Table 3.8 Adverse events occuring within 24 hours of the procedure

[Ŧ] Fisher's exact test.

Adverse events 1 – 28 days							
	Treatment group (50 procedures)			Control group (26 procedure equivalents)			
	Events	Patients	Rate	Events	Patients	Rate	p value[Ŧ]
Serious adverse events							
Death secondary to pneumonia	1	1	2.0%	0	0	0.0%	>0.9999
Pneumonia	1	1	2.0%	0	0	0.0%	>0.9999
Hospitalisation for COPD exacerbation	1	1	2.0%	0	0	0.0%	>0.9999
Non-serious adverse events							
COPD exacerbation	16	14	32.0%	4	4	15.4%	0.1709
Pneumonia	1	1	2.0%	0	0	0.0%	>0.9999
Chest pain	1	1	2.0%	0	0	0.0%	>0.9999
Cough	2	2	4.0%	0	0	0.0%	0.5439
Pharyngitis	2	2	4.0%	0	0	0.0%	0.5439
Dyspnoea	3	2	6.0%	0	0	0.0%	0.5469

Table 3.9 Adverse events occuring in the first 28 days following both procedures

[Ŧ] Fisher's exact test.

Adverse events 1 – 12 months							
	Treatment group (26 patients)			Control group (13 patients)			
	Events	Patients	Incidence	Events	Patients	Incidence	p value[T]
Serious adverse events							
Death	2	2	0.10	0	0	0.00	>0.9999
Hospitalisation for COPD exacerbation	11	8	0.52	3	3	0.27	0.4967
Pneumonia	2	2	0.10	0	0	0.00	>0.9999
NSTEMI	1	1	0.05	0	0	0.00	>0.9999
Pneumothorax	0	0	0.00	1	1	0.09	0.3636
Non-serious adverse events							
COPD exacerbation	14	12	0.67	29	12	2.63	0.0056
Minor haemoptysis	3	3	0.14	0	0	0.00	0.5361
Chest pain	4	3	0.19	0	0	0.00	0.2904
Consolidation	3	3	0.14	0	0	0.00	0.5361
Cough	2	2	0.10	0	0	0.00	>0.9999
Dyspnoea	3	2	0.14	0	0	0.0%	0.5361

Table 3.10 Adverse events occuring in the 1-12 month follow up period

Excludes the month following the procedures. Incidence rates are expressed as number of events per patient year.

[T] Fisher's exact test.

NSTEMI: Non-ST elevation myocardial infarction

Patient deaths

During the study, four patients died in the treatment group and none in the control group . Three of the deaths were definitely or probably linked to the procedure or device and one was felt to be unrelated. The baseline characteristics of each patient are presented in table 3.11.

	Patient 6	Patient 10	Patient 20	Patient 28
Sex	M	F	F	F
Age	66	70	59	70
Emphysema pattern	Homogeneous	Homogeneous	Homogeneous	Homogeneous
FEV1 (L)	0.69	0.57	0.40	0.48
FEV1 %	19.9	25.6	17.8	23.3
RV%	291	252	289	290
RV/TLC ratio	67.4	71.2	75.0	73.5
TLCOc %	32.4	22	30.9	20.6
6MWD	420	201	275	159
mMRC	4	2	3	4
SGRQ	55	67	75	74

Table 3.11 Baseline characteristics of patients who died during follow up

- Patient 6:

  The death occurred during the first treatment following placement of the second coil (150mm) into the right upper lobe. Haemorrhage from the treated subsegment was noted immediately after the placement of the coil. Despite treatment with bronchoscopic suction, ice cold saline and intrabronchial adrenaline the bleeding could not be stopped. An intrabronchial balloon blocker was placed and the other airways were cleared as best possible of clotted blood. The patient suffered a cardiac arrest on table and resuscitation attempts were unsuccessful. A post mortem examination identified pulmonary haemorrhage as the cause of death along with chronic obstructive pulmonary disease. There was no further information on the relationship of the coil to any local pulmonary or bronchial vessels.

  Following the death, recruitment and further treatments were suspended at our site. The sponsor undertook an investigation with the independent data safety monitoring board. Additionally Chelsea and Westminster Hospital and The Royal Brompton Hospital undertook a joint investigation led by an independent anaesthetist. Both teams came to the conclusion that it was an unforeseen event in a particularly physiologically frail patient. However they met all the inclusion criteria

and there was no evidence of deviation from the treatment plan. This was the first reported coil procedure death. The DSMB, hospital and local ethics committee were satisfied with the reports and allowed the trial to continue with an update of safety information to all patients.

- Patient 28:
  This death occurred 6 days following the 2nd procedure to their right upper lobe. The patient had been doing well at home when they suddenly became unwell complaining of breathlessness and became drowsy. They were admitted to their local hospital where they were found to be in decompensated type II respiratory failure and a chest x-ray showed a dense right upper lobe consolidation. The local team felt that due to the severity of the patient's illness and co-morbid COPD, invasive ventilation would not be appropriate. They died a few hours later after a trial of non-invasive ventilation.

- Patient 10:
  This death occurred approximately 7 months after the first treatment. The patient had initially done well, but a month after the second treatment suffered an exacerbation and was too unwell to attend the 5 month follow up. They continued to suffer repeated exacerbations including one hospital admission. A CT of the chest showed marked volume loss in the right upper lobe associated with cavitatory consolidation. A Stenotrophomonas species was cultured from the sputum shortly before death. Cause of death was recorded as exacerbation of COPD.

- Patient 20:
  This death occurred 6 months following the first treatment. The patient had attended the 5 month follow up and had symptomatic and physiological improvements. They collapsed at home after the sudden onset of breathlessness and died before they reached hospital. A post mortem examination confirmed the cause of death as pulmonary oedema

secondary to heart failure. There was no evidence of infection or haemorrhage around the coils. This death was felt to be unrelated to the procedure or device.

3.5 Discussion

Treatment with lung volume reduction coils resulted in no significant improvement in 6 minute walk distance 12 months following treatment in our cohort. There was a trend to improved symptom scores with a clinically significant difference between groups. Functional residual capacity and inspiratory capacity improved significantly with a trend to a reduction in residual volume. The data presented in this thesis represents 30 patients recruited at our centre who were randomised 1:1 ratio of treatment to control. This data formed part of the 315 patients recruited across 29 centres worldwide which has been published as the RENEW trial in 2016.(218) Control patients were eligible to crossover into a study with identical interventions and follow up and their data is presented as paired data in table 3.5 and used in the correlations and regression analysis. Table 3.12 describes the major outcomes for the whole RENEW study.

	Change in treatment group	Change in control group	Between group difference	p value
6MWD (m)	10.3 (-33.0 to 45.0)	-7.6 (-40.0 to 26.0)	14.6 (0.4 to ∞)	0.02
SGRQ	-8.1 (-10.2 to -6.0)	0.8 (-1.2 to 2.9)	-8.9 (-1.2 to ∞)	<0.001
% change in FEV_1	3.8 (-6.3 to 16.1)	-2.5 (-8.9 to 4.4)	7.0 (3.4 to ∞)	<0.001
RV (L)	-0.41 (-0.57 to -0.25)	-0.10 (-0.26 to 0.06)	-0.31 (-∞ to -0.11)	0.001
RV/TLC	-4.0 (-5.1 to -2.9)	-0.5 (-1.6 to 0.6)	-3.5 (-∞ to -2.1)	<0.001

Table 3.12 RENEW Study major outcomes

Table adapated from Table 2 within reference (218)

The results from the RENEW study are broadly in line with the results for our cohort. The magnitude of between group difference in walk distance are similar

although in our cohort the non-significant between group median difference of 25.5m is largely as a result of a decline in 6 minute walk distance in the control group. There was only a 0.5m median improvement between baseline and 12 month 6 minute walk distance in the treatment group. This difference is much lower than previously reported changes following treatment in studies with a shorter duration of follow up. The only randomised controlled studies to have reported data to 12 months have included the REVOLENS trial and the RENEW trial. In the REVOLENS trial the mean 12 month change in the treatment group was -2m, with a between group difference of 21m (-5 to ∞), $p = 0.12$.(220) This discrepancy between long term follow up and studies of shorter duration may suggest that the effects of the lung volume reduction coil on walking distance are not durable. However combined data from a number of single arm studies to 12 months found a 38.1m (± 71.9) improvement with treatment, $p < 0.0001$.(217) There was no significant between group difference at any of the follow up intervals in 6 minute walk distance, largely because there was inadequate power to detect a difference due to sample size. The magnitude of difference was largest at 5 and 9 months (51.5m and 62m respectively) in our cohort, but again this was largely driven by a fall in the control groups walking distance and was not significant. The overall response rate of ≥ 26m in 6 minute walk distance not significantly different to the control group and much lower than previously reported response rates.(217)

There are a number of possible reasons why the walk distance did not improve. Firstly, the size of our cohort meant this study was underpowered to detect a significant difference in the primary outcome based upon the data from the RESET trial. The baseline characteristics of our patients are broadly similar to those reported in the RESET, REVOLENS and RENEW trials. However the proportion of patients with homogeneous emphysema in our cohort was 88.5% compared to 77.2% and 64% in the RENEW and REVOLENS trials respectively. The NETT study found that patients with homogeneous emphysema were less likely to meet endpoints in symptom scores, exercise capacity and lung function, and were at higher risk of adverse outcomes.(122) The evidence of lung volume reduction coil efficacy in homogeneous patients is mixed. The meta-analysis of

125 patients from a number of observational trials did not detect a difference in outcomes between patients with heterogeneous and homogeneous emphysema.(217) Analysis of subgroups within the RENEW study has shown that response rates in 6 minute walk distance and lung function variables are lower amongst homogeneous patients, particularly those with an RV < 225% predicted.(218) In our treatment group 5 patients (19.2%) had homogeneous emphysema with an RV < 225% predicted. Thus the excess of homogeneous patients amongst our cohort may have reduced the response rates to treatment. Physiological deconditioning associated with skeletal muscle atrophy is an important contributor to poor exercise performance in COPD.(18) Whilst all of our patients in the study were required to have completed a pulmonary rehabilitation course within 12 months of enrollment, there was no standardised maintenance or exercise instructions prescribed following treatment. In the NETT study, all patients underwent rehabilitation immediately before randomisation and were required to participate in maintenance classes following treatment.(202) In order for the improvements in lung function to be translated into exercise improvements, it would seem intuitive that rehabilitation to address deconditioning would be appropriate. Thirdly, the rate of hospitalisation for any cause was 0.76 per patient year in the treatment group compared to 0.31 in the control group ($p = 0.3523$). Although the rates are not statistically significantly different, it is known that a patient's physical activity and quality of life is reduced following hospitalisation(301) which may impact on future exercise capacity and symptoms. Finally it may be possible that the significant physiological improvements in lung volumes were not sufficient to be translated in to an improvement in exercise capacity. However, these results were also associated with a significant improvement in symptom scores and the magnitude of change in RV was above the minimum clinically important difference that is associated with a subjective benefit.

The use of 6 minute walk distance as the primary outcome has a number of strengths. The test is standardised, objective and easy to perform. It has been validated as an outcome measure in COPD and has shown to be responsive to treatment.(282) Importantly it reflects a patient orientated outcome that is

associated with quality of life and activities of daily living.(302) Thus it can integrate the complex physiological changes that occur following lung volume reduction that may not be reflected in the lung function laboratory tests. However there are a number of limitations, not least that it reflects not just pulmonary reserve but cardiovascular and neuromuscular performance. It is also effort dependent and thus a range of factors including motivation and intercurrent illness may affect the result. The 6 minute walk distance has been shown to be subject to practice effects of approximately 7% in a similar cohort of patients undergoing two test, one day apart.(38) There was no requirement for a practice test at any of our patient visits, although a baseline practice test was undertaken if the patient had not previously performed one. In our study the assessors were blinded to the treatment allocation and used the standardised encouragements to minimise any assessor bias. The wide variability of the 6 minute walk distance means that relatively large sample sizes are required and estimating the size of treatment effect can be difficult. Whilst the lack of improvement in 6 minute walk distance in the treatment group is disappointing, it should be borne in mind that the annual rate of decline is 15m in GOLD stage 4 patients.(303) There are a number of estimates of the MCID for 6 minute walk distance ranging from 26 – 54m.(282) We chose the value of 26m suggested by Puhan and colleagues as it was derived from the NETT trial data in a very similar group of patients undergoing a lung volume reduction procedure.(284) Larger estimates of the MCID derived from different populations including milder disease may not be as appropriate in our cohort.

There was a trend to improvements in SGRQ scores 12 months following lung volume reduction coil treatment, although not quite reaching statistical significance. The magnitude of change in SGRQ score was similar to other previously reported values, although lower than the entire RENEW cohort. With a lack of sham procedure in the control group it could be argued some of the effect was due to the placebo effect. However, the EASE trial of airway bypass for emphysema showed no evidence of placebo effect in SGRQ score in their sham treatment arm.(304) Furthermore the change in SGRQ score was strongly correlated with the change in 6 minute walk distance in our study and clinically

significant improvements in lung volumes were achieved. This could suggest that a reduction in hyperinflation underlies some of the improvement in symptoms.

There was a 0.382L between group difference in the change in RV which was not statistically significant. However, the actual reduction in RV of 0.303L in the treatment group was below the threshold of 0.350L that is considered the minimum clinically important difference.(305) Overall, 42.3% of patients undergoing coil treatment achieved this compared to 0% in the treatment group. In our study, there was no significant change in the TLC. It has been argued that the reduction in RV/TLC is an important mechanism underlying lung volume reduction given that the difference between these two values represents the vital capacity. Thus for there to be an increase in vital capacity, the RV must reduce by a greater proportion that the TLC. In LVRS this is achieved by resecting the most emphysematous portions of the lung that have a higher RV/TLC ratio than the entire lung.(306) In our study there was no significant reduction in RV/TLC, although there was a trend to improvement in the treatment group. Given the preponderance of homogeneous disease in our study, the treated lobes may have had similar RV/TLC ratios to untreated lobes and thus reducing their volume had no overall effect on RV/TLC ratio. Nevertheless, an overall reduction in lung volume may still underlie symptomatic improvement due to a beneficial effect on the structure and function of the diaphragm as has been reported in LVRS.(259,307) However no measures of diaphragm configuration or function were examined in this study.

It is postulated that lung volume reduction coils do not simply act by reducing volume alone, but by increasing elastic recoil of the lung and thus reducing airways resistance and gas trapping. The FRC represents that balance of the inward elastic recoil of the lung and outward recoil of the chest wall. We demonstrated a significant reduction in FRC following LVRC treatment that may suggest there is a role of improved elastic recoil. Chapter 5 explores the physiological changes in lung mechanics following coil treatment in a number of patients.

The between-group difference in FEV_1 was not significant, although this study was not powered to detect the relatively small changes seen in FEV_1 following coil treatment. Whilst FEV_1 is widely reported in drug trials in COPD, it has been argued it is less relevant in patients with very severe disease where small changes approach the natural variation and measurement error of FEV_1.(308) It also correlates poorly with symptoms and exercise tolerance in COPD.(309,310) Changes in lung volumes, particularly IC are more sensitive to bronchodilator administration(311) and correlate more closely with changes in symptoms and exercise capacity than FEV_1.(31) In our study, there was a significant improvement in IC although the correlation with change in 6 minute walk distance was not significant ($r = 0.3524$, $p = 0.0724$). Given the strong relationship of dynamic hyperinflation with exercise intolerance, measures of IC during exercise may shed light on the mechanisms of coils and their effect on exercise tolerance.

The number of deaths occurring in the treatment group is concerning and warrants further examination. In our cohort there were a total of four deaths in the 26 patients undergoing treatment (15.4%). One death was directly related to treatment (pulmonary haemorrhage), two were possibly related (pneumonia and COPD exacerbation) and another was unrelated (heart failure). Of the four deaths, two occurred in the treatment arm of the randomised study (11.3%), compared to no deaths in the control group. A further two deaths occurred in the crossover arm of the study. Our data contributed to the RENEW trial (not including treated crossover patients) which reported a death rate of 6.5% (10 patients) in the treatment group compared to 5.1% (8 patients) in the control group ($p = 0.64$).(218) Further mortality figures for comparison are provided by the REVOLENS trial that reported a death rate of 8% in the treatment group which was not significantly different to the control group (6%).(220) The NETT trial reported an annualised death rate of 11% amongst its non-high risk patients. Thus whilst it seems from larger datasets that coil treatment is safe, the excess of deaths amongst our cohort still requires explanation. All of our patients had homogeneous disease and two patients (10 and 28) had the lowest recorded TL_{COc} percent predicted in the group. Patient 20 had the second lowest FEV_1 at

17.8% predicted. The patient that died from pulmonary haemorrhage was in the lower quartile of FEV_1 but the third quartile for TL_{COc}. All of these patients had very severe disease and therefore they would have had less physiological reserve to withstand a severe COPD exacerbation or pneumonia. It is interesting to note that two of these patients would have been considered high risk by NETT criteria (homogeneous disease and FEV_1 < 20% predicted) and the other two were only just above the 20% TL_{COc} cut off as a high-risk criterion. However, the baseline characteristics of our cohort was very similar to the wider RENEW study. The only significant difference was the proportion of homogeneous patients in our treatment group (94%) compared to the RENEW study treatment group (77%).(218) The death rates amongst homogeneous and heterogeneous patients has not been analysed in larger cohorts, but it is notable that homogeneous disease is a risk factor for death in patients undergoing LVRS.(203) Whilst it is not possible to draw firm conclusions regarding the safety of coil treatment amongst this subgroup, it certainly warrants further examination of large datasets to see if there is an identifiable high-risk group for coil treatment.

Excluding the death there were no other procedural serious adverse events. Treatments were well tolerated under conscious sedation and general anaesthesia. Minor haemoptysis (<10mls) was common in the 24 hours following the procedure and settled quickly without the need for any intervention. Chest pains were also common and all settled with analgesia and did not require further investigation. Bronchospasm occurred in four procedures and responded to nebulized salbutamol without the need to terminate the procedure.

In the first month following each procedure, there was one death (as described above) and one further hospitalisation for an exacerbation of COPD. 32% of procedures were associated with exacerbations of COPD, despite prophylactic antibiotics and steroids. All settled with a further course of treatment. One non-severe pneumonia case was reported which was treated as an outpatient. In the long term follow up of patients, hospitalisation was more common in the treatment group, albeit it not significantly. The number of non-severe

exacerbations was significantly less in the treatment group, but this may have reflected that they were more likely to be admitted to hospital and that there were a small number of frequent exacerbators in the control group. We have reported all COPD exacerbations leading to hospitalisation, although most of the published studies report the rate of those requiring >7 days hospitalisation. In our cohort there were two cases requiring prolonged admission in the treatment group (7.7%).

One patient suffered recurrent exacerbations requiring hospitalisation and grew Stenotrophomonas maltophilia in their sputum on multiple occasions following coil treatment. They suffered a significant decline in symptoms, walk distance and lung function. Treatment with prolonged courses of intravenous antibiotics including co-trimoxazole and ceftazidime did not result in any significant improvement. One further patient grew a Stenotrophomonas species following their second treatment. This was associated with a cavitatory pneumonia in the right upper lobe and the patient ultimately died of a COPD exacerbation. No other cases of new bacterial colonisation or positive sputum cultures were seen in the treatment group, although they were performed on relatively few patients. Stenotrophomonas species colonisation and infections are not uncommon in chronic lung disease and may be seen in COPD. It is of particular significance because it is a microbe that is inherently resistant to a broad spectrum of antibiotics. It produces a biofilm that allows adherence of the bacterium to surfaces. It is recognised that Stenotrophomonas can be associated with prosthetic implants such as joint replacements and therefore it is possible that coils may act as a nidus for colonisation or infection. It is not known what proportion of patients have a change in their lung microbiome following coil treatment, nor whether it may be significant and associated with a more rapid decline in symptoms and lung function. Given the staged nature of the coil procedures, it would be possible to design a study assessing the lung microbiome at baseline and following each coil treatment to see what effect they had. We did not see any excess of COPD exacerbations within the first year although the long term follow up remains to be seen.

There are a number of limitations to this study. Most importantly, as a cohort of patients contributing to a larger study, we did not have sufficient power to detect the small physiological improvements that may be seen following LVRC treatment. Additionally, it is difficult to estimate the true size of treatment effect due to the wide variance in the results. Accounting for patients lost to follow up is problematic with a small group. By not including them in the analysis, the risk of introducing a bias in the data is significant; favoring those that have been well enough to continue in the trial. More complex imputation models would not be appropriate for a small data set. Carrying data forward also has its limitations as the true effect of LVRC treatment becomes less certain. Of the four patients that died, two would have been considered responders in the primary outcome and two non-responders. The decision to carry forward missing values in an intention to treat analysis was made at the start of the study as the most equitable and practical solution to this.

There was no sham control treatment in this study in part due to the ethical considerations of subjecting patients with severe COPD to a bronchoscopy. Additionally it would have been difficult to maintain blinding as many of the patients experienced exacerbations and hospitalisations which will have lead to chest radiography at their local hospital, potentially leading to inadvertent unblinding by healthcare staff. In order to reduce bias in objective measurements of lung function and walk distance, the assessors remained blinded to the treatment group allocation with no reported unblinding. Both the EASE trial (304)and the BeLieVer HI-Fi trial(236) of endobronchial valves have successfully included sham control treatments and demonstrated that bronchoscopy can be safely performed as a sham treatment in this group of patients.

The crossover design used in this thesis was designed to increase the power to detect changes following treatment. However this has the potential to introduce selection bias because crossover patients still had to meet the original inclusion criteria after 1 year. Therefore those patients that had shown significant decline or repeated hospitalisation throughout the first year of follow up may no longer

be eligible for crossover to the treatment arm. This could remove 'rapid decliners' who may fare worse than the average patient and therefore biases the treatment group towards more stable patients. Of the four patients that were ineligible for crossover, one had a significant improvement in FEV_1 above the entry criteria and was no longer eligible. Another patient had a 51m improvement in 6 minute walk distance and felt clinically stable and did not want to risk potential side effects. Neither patient had any other significant improvements in outcomes. The patient with repeated hospitalisation was clinically stable on all endpoints at 12 months and a further patient with CT abnormalities at crossover screening had a significant decline in lung function, walk distance and symptoms.

The study suffered with slow recruitment initially, largely due to the difficulty in finding patients with an RV of ≥ 225% predicted. Many of these patients had significant emphysematous destruction which was outside of the inclusion criteria of the trial. Both the meta-analysis of coil treatment and the RENEW trial have identified that high baseline RV is a predictor of response to treatment.(217,218) In clinical practice the lack of patients with significant hyperinflation and sufficient lung parenchyma may limit the number of patients in whom LVRC treatment is an option.

This study is unable to answer a number of important questions due to limitations described above. The optimal number of coils to be placed in which lobe is still not known, nor is whether upper lobe treatments fair better than lower lobe treatments. In our cohort, 4 patients underwent bilateral lower lobe treatments. One patient met the MCID for SGRQ and FEV_1, but not for RV and the remainder met none of the responder thresholds. We aimed for approximately 10 coils in each lung with an even as possible distribution throughout the lobe. This number was suggested in the protocol based upon evidence from an early trial that suggested 10 coils produced encouraging clinical responses.(297) However, the placement of coils is limited by the number of subsegmental airways it is possible to access. Lower lobe treatments had more coils placed on average. It would not be feasible to conduct a study with multiple staged

procedures to assess changes in lung mechanics between treatments. However it would be possible to make repeated assessments of lung compliance under general anaesthesia with a ventilator following each placement of a coil. This may help understand the response of the lung to coil placement, but there is no evidence to suggest what degree of change is associated with a clinical response. A prospective trial comparing groups with differing numbers of coils would have to be very large to detect any difference and would be impractical. In our study we only treated one lobe in each lung, in line with most of the published evidence. The RESET study included a number of patients with homogeneous disease who had whole lung treatment with coils.(219) In theory this could benefit patients with homogeneous disease where gas trapping is reduced throughout the lung.

Currently treatment is performed as staged bilateral procedures. Three months were scheduled between procedures in order to allow patients to recover and assess the response to treatment. In our study the treatment group experienced the peak in 6 minute walk distance after the 1st treatment, maximal FEV_1 and RV improvements were seen after the second treatment at 5 months and the symptom scores improved the most at 9 months. Most of the outcome variables then declined by 12 months but were still above baseline values. The only long term experience of coils to date suggests that by three years patients have returned to their baseline values(221), but given the known decline in COPD over time, this is likely to represent a persistent treatment effect.

Another treatment plan that has not yet been explored is the segmental treatment of lobes, targeting those areas with the most emphysema radiologically. Segmental heterogeneity exists within lobes in emphysema(312) and a targeted approach with thermal vapor ablation using steam in COPD has proven to be an effective treatment.(242) There is no practical reason why coils could not be placed into the most diseased segments and avoiding adjacent healthier areas. Again, trials comparing this to whole lobe treatment would have to be large and therefore impractical to detect differences. It would be more

practical for individual physicians to assess lobar heterogeneity and plan treatment pre-procedure based on the CT scan.

Evidence from the RENEW trial suggests there may be some difference in response to treatment between patients with homogeneous and heterogeneous emphysema. Whilst this could not be formally assessed in this study, there are sound physiological reasons why this may be the case and it has already been described with LVRS.(122) In our cohort there were only three patients with heterogeneous disease, all of which met the MCID for reduction in RV, two of which met the SGRQ and FEV_1 MCID and one patient who met the MCID for 6 minute walk distance. In the experience of this study, the homogeneous patients were not a single phenotype. There were two major patterns: those with significant parenchymal destruction evenly distributed throughout the lung, and those with much milder emphysema with relatively preserved transfer factors but nevertheless, significant gas trapping. It is likely this latter group have small airways predominant disease rather than pure emphysema and therefore the mechanical properties of the lung are likely to be different. Of the three patients with a TL_{COc} above 50% predicted, one achieved a significant symptomatic improvement alone and none met the MCID in the primary outcome or lung function variables. The figure of a TL_{COc} >50% predicted chosen to represent milder emphysema is arbitrary and with such a small number of patients, the relatively poorer outcomes in this group may be entirely due to chance. However identification of and airways disease predominant phenotype in a larger dataset using validated CT markers would be appropriate.

There have now been a number of small and larger trials examining the efficacy and safety of lung volume reduction coils in emphysema. All of these trials have had similar outcome measures in exercise capacity, lung function and symptoms. Only high baseline RV and heterogeneous emphysema have been identified as predictors of success. Moreover, little detailed physiological work has been performed to help understand how treatment with lung volume reduction coils works. To date, no studies have examined the effect of treatment on CT changes within the lung following treatment, nor the association of baseline CT

characteristics other than emphysema heterogeneity with outcomes. Further detailed physiological and phenotypic studies are warranted to better characterise the factors that may predict success and elucidate the mechanisms behind this.

3.6 Conclusions

Treatment with lung volume reduction coils results in no significant changes in walking capacity, but significant improvements in functional residual capacity and inspiratory capacity as well as a trend to improvements in residual volume symptom scores up to 12 months following treatment. No significant improvements in spirometric measures are seen. There is a risk of death following treatment with lung volume reduction coils and careful selection of patients is warranted. Future trials should be designed to identify factors that may better identify patients who will benefit from treatment.

Chapter 4

Changes in CT lung volumes following treatment with lung volume reduction coils

4.1 Introduction

Computed tomography is a valuable tool in the assessment of COPD. It has the advantage of being able to image some of the pathological changes in the lung that directly contribute to airflow obstruction. Airflow obstruction results from a combination of emphysematous damage, where there is loss of elastic recoil, and from small airways obstruction where inflammation and airway thickening occur.(313) Both emphysema and small airways disease may be heterogeneously distributed throughout the lungs in COPD and therefore CT has the additional benefit of regional assessment of disease.(314) This is in contrast to most lung function tests that give a single result for the lungs as a whole and fail to adequately reflect the distribution of the disease. Regional assessment of emphysema is important in the context of lung volume reduction. It has been widely used to assess emphysema heterogeneity that predicts response to LVRS(122), endobronchial valves(229) and lung volume reduction coils.(218) In the research setting, it has also been used to measure lobar changes in lung volumes following lung volume reduction treatments.(230,315,316)

On CT, emphysema is represented by abnormal areas of low attenuation. Visual scoring of emphysema is widely used in clinical practice but may fail to detect subtle disease and does not allow precise quantification of disease.(317) The most commonly used quantitative method of detecting emphysema is by applying a density mask to the lung parenchyma and setting a threshold at below which all voxels are assumed to be emphysema. This is expressed as the percentage of low attenuation areas (%LAA). In healthy non-smokers, the upper limit of normal of %LAA at <950 Hounsfield Units (HU) has been estimated at 0.35% at full inspiration.(318) A number of thresholds have been suggested and there is debate as to which best assesses emphysema. In studies of explanted lungs or post-mortem subjects, comparison of CT graded emphysema has been compared to the gold standard of histological severity. Muller et al. found that a threshold of -910 HU correlated best with pathological scores of emphysema.(319) Gevenois et al. suggested that -950 HU was the most accurate threshold when comparing pathological score of emphysema in explanted lungs.

Emphysema scores are closely correlated with measures of airflow obstruction both on inspiratory and expiratory scans.(320–322) A number of studies have found that measurement of emphysema correlates most strongly with FEV_1 on expiratory scans in severe disease.(323–325) However, it has been suggested that emphysema is best assessed on inspiratory scans as low attenuation areas on expiratory scans may be due to a combination of emphysema and gas trapping from small airways disease. This is supported by observations that expiratory scan emphysema scores correlate most closely with measures of airflow obstruction and hyperinflation reflecting the contribution of small airways disease.(325) Measurements of diffusing capacity correlate well with emphysema score(321,322), although in the presence of very severe airflow obstruction the correlation is weak due imhomogeneity of gas mixing providing spuriously low diffusion capacity measurements.(326)

The small airways are below the resolution of CT and therefore cannot be directly imaged. A surrogate marker for small is airways disease is gas trapping. Because normally aerated lung has a mean density of -856 HU, this threshold has been suggested as a density mask for expiratory scans and has been validated in asthma.(327) In a large cohort from the COPDGene study $\%LAA_{-856HU}$ on expiratory scans had the strongest correlations with spirometric parameters.(328) However in COPD, this method does not compensate for the presence of low attenuation voxels caused by emphysema. Therefore the strong correlation represents contribution of both emphysema and small airways disease to airflow obstruction. In the same COPDGene cohort, subjects with severe emphysema had stronger correlations with spirometry and importantly, plethysmographic measures of hyperinflation, when it was compared with the ratio of mean lung density between expiration and inspiration ($MLD_{E/I}$).(328) Furthermore the $MLD_{E/I}$ ratio has been shown to have the strongest correlation with single breath nitrogen washout, a specific measure of small airways disease.(329) Whilst it is not possible to accurately measure separate the effects of emphysema and small airways disease emphysema on either lung function or CT, the $MLD_{E/I}$ ratio looks a promising marker. The ratio of volume inspiration and expiration ($LV_{E/I}$) has also been validated as a marker of gas trapping and is

highly correlated with the $MLD_{E/I}$ ratio and moderately correlated with the RV/TLC ratio.(330) With the ability of software to semi-automatically segment lungs(331), it is now possible to assess these markers in individual lobes. This makes it an ideal tool to assess COPD where there are regional differences and in studies of targeted treatments.

In the context of lung volume reduction coil treatment, CT has been used to assess the extent of emphysema, score heterogeneity and exclude patients with severe tissue destruction prior to treatment. However the majority of studies have used visual assessment of emphysema score based on the NETT criteria as discussed in Chapter 3. Both the RESET trial and the European multicentre trial of coils performed automated analysis of emphysema to score tissue destruction within lobes, but then converted this to a Likert scale which was comparable to the NETT scoring criteria. Heterogeneity was defined by a >1 point difference in emphysema, reflecting at least a 25% difference in emphysematous destruction. Despite the importance of emphysema heterogeneity, there has been no standardised definition of what it is. More recent trials of endobronchial valves have defined heterogeneity as a >15% difference in the $\%LAA_{-950}$.(237) With quantitative scoring of emphysema in patients undergoing LVRC treatment it should prove feasible to determine if there is a true effect of heterogeneity on outcomes. To date there has been only one study reporting CT changes following lung volume reduction coils. Klooster et al. reported a mean 263ml reduction in target lobe volume on inspiratory scans ($p = 0.037$) with no significant difference in untreated lobes, in their study of 10 homogeneous patients. No studies have reported the effect of coil treatment on gas trapping or lobar volumes on expiratory scans.

4.2 Aims and hypotheses

In our study, the primary aim is to describe the changes in target lobe volume following treatment with lung volume reduction coils. Because lung volume reduction coils are postulated to improve elastic recoil and relieve gas trapping, we aim to describe the changes in gas trapping by comparing inspiratory and expiratory scans. We will also examine the relationship of baseline CT variables to changes in lobar volumes and symptoms to try and identify any factors that may predict clinical and radiographic response to treatment.

Our primary hypothesis is that there will be a significant reduction in target lobe volume measured at inspiration and expiration 12 months following treatment with lung volume reduction coils.

4.3 Methods

4.3.1 Study design

This was a prospective study as part of the RENEW trial discussed in Chapter 3. All patients taking part in the study underwent CT scans at baseline and 12 months follow up. For those in the control group, a CT was only performed if they were screened for the crossover trial. CT's were performed as part of the study to assess eligibility and on follow up to assess complications. Ethical approval for the RENEW and RENEW Crossover study covered the examination of CT scans. However no a priori objectives were set by the sponsor in the study protocol regarding this. We set out to perform our own analysis of CT scans based on our hypotheses described above.

4.3.2 Outcome measures

The primary outcome measure of this study is between group difference in change in target lobe volume at inspiration (V_{TLInsp})and expiration (V_{TLExp}).

Secondary outcome measures for between group differences include:

- Change in target lobe gas trapping measured by the $MLD_{E/I}$ ratio
- Change in target lobe gas trapping measured by the $LV_{E/I}$ ratio
- Change in non-target lobe volume on inspiration (V_{NTInsp}) and expiration (V_{NTExp})
- Change in non-target lobe gas trapping measured by the $MLD_{E/I}$ ratio
- Change in non-target lobe gas trapping measured by the $LV_{E/I}$ ratio

Additionally we will assess the agreement between the baseline lung volumes to those measured by body plethysmography. We will also analyse baseline CT variables to see which predict a clinical and radiological response to LVRC treatment.

4.3.3 Subjects

All patients taking part in the RENEW and RENEW crossover study who had adequate baseline and 12 month follow up CT scans were analysed. There were

no additional inclusion or exclusion criteria beyond those outlined for the RENEW study.

4.3.4 CT acquisition and reconstruction

CT scans were performed between November 2012 and June 2014 on a Siemens Somatom Sensation 64. From July 2014 until September 2016 all scans were performed on a Siemens Definition Edge (a 128 detector scanner). Both scanners used the same software and allowed identical reconstruction parameters for all CT scans in order for them to be comparable. Scanners were calibrated on a weekly basis as per the manufacturers instructions.

CT scans were undertaken by a senior radiographer at the Royal Brompton Hospital. Breathing instructions were provided by identical automated prompts and the radiographers coached all patients regarding breathing instructions prior to the scan being undertaken. All scans were performed in the supine position without intravenous contrast. The following instructions were given:

"Breathe all the way in, then hold your breath."

Following which the inspiratory scan was performed. Patients were allowed a short break to breathe normally and then instructed

"breathe all the way out and hold your breath."

The patient was asked to indicate they had reached full exhalation by moving their foot and then the expiratory scan was performed.

The parameters were used to perform the scan and reconstruct images are listed in table 4.1.

Parameter	Setting
kV	120
Gantry rotation time	0.5 seconds
mAs (dependent on body habitus)	80-100
Pitch	1.5
Table speed	54mm/second
Scan time (40cm thorax)	7.4 seconds
Slice thickness	1mm
Reconstruction interval	1mm
Reconstruction kernel	B40f

Table 4.1 CT settings and reconstruction parameters

Abbreviations: kV (kilovoltage), mAs (milliampere/second)

4.3.5 Lobar volume, density and emphysema score measurement

All scans were analysed using dedicated commercial software, Myrian XP-Lung (Intrasense, France). The lungs were automatically segmented into right lung, left lung and central airways. This process is performed by algorithms that assume that all lung tissue is below a certain density. A seed point is identified and the region grows until the density threshold is reached i.e. it meets an object of a density above the threshold. This allows the software to delineate the lung from surrounding chest wall and mediastinal structures. It also excludes high attenuation areas including pulmonary vessels and lung volume reduction coils from the analysis. It was not possible to have a blinded assessor perform CT analysis as coils are clearly visible on the scans.

The Myrian XP-Lung software is not able to identify interlobar fissures. This was performed manually by a single operator. In the sagittal plane, the oblique fissure of each lung was identified in turn. A line was drawn along the fissure with multiple points anchoring the line to the fissure. This is repeated on multiple slices of the lung. The software interpolates the fissure throughout the rest of the lung and each slice is inspected and manually adjusted as necessary. Where the fissure is not clearly visible an estimate of the likely path is made with reference to the pulmonary vasculature and airways. Each lung is then divided into the upper and lower lobes. For the right lung, the horizontal fissure is then added to delineate the right middle lobe. Lobar volumes, density and LAA_{-910HU} are automatically calculated.

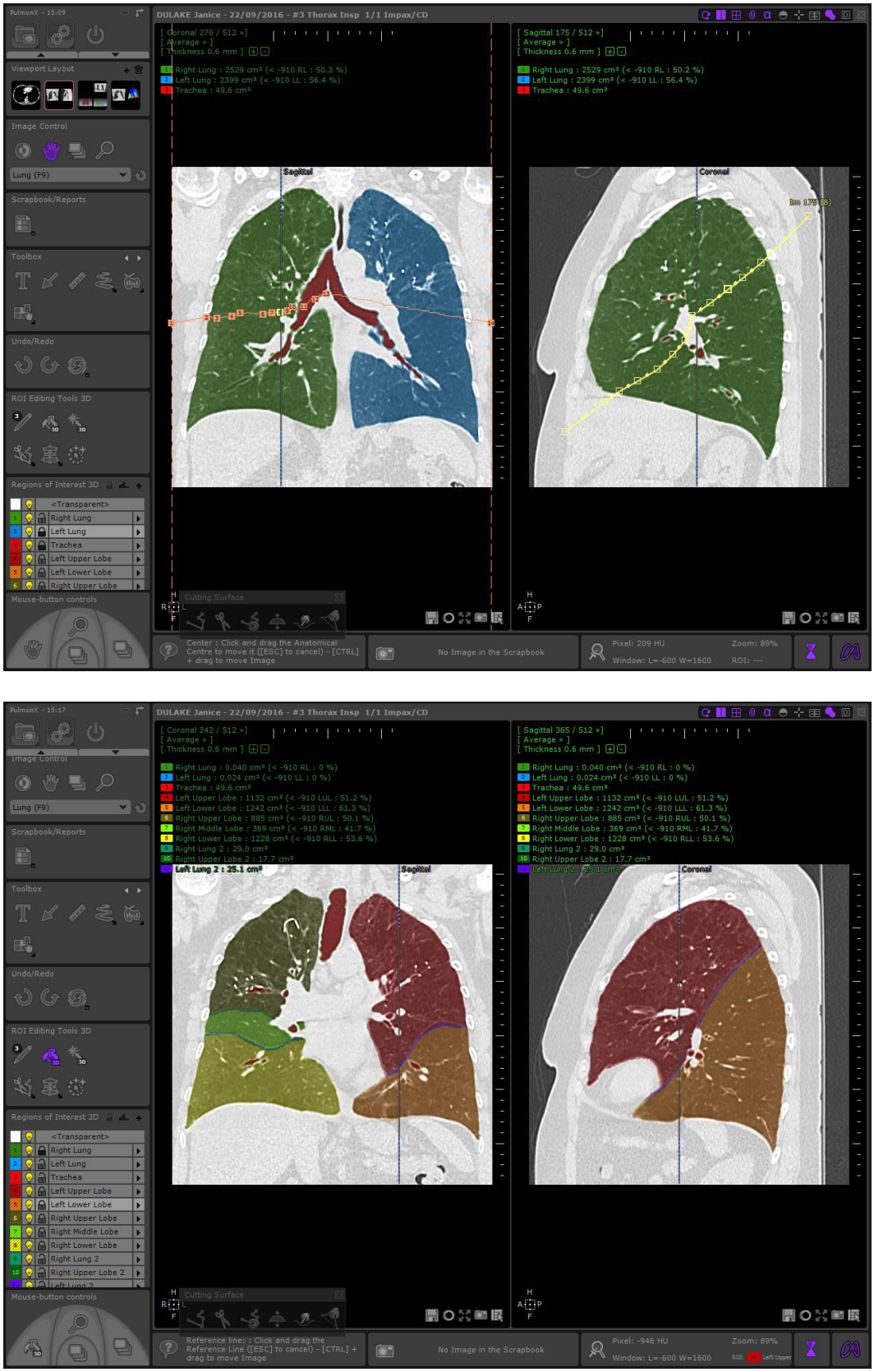


Figure 4.1 Lobar segmentation in Myrian XP

Automatic segmentation of trachea, left and right lungs with manually drawn fissure (above). Lobes following manual segmentation (below).

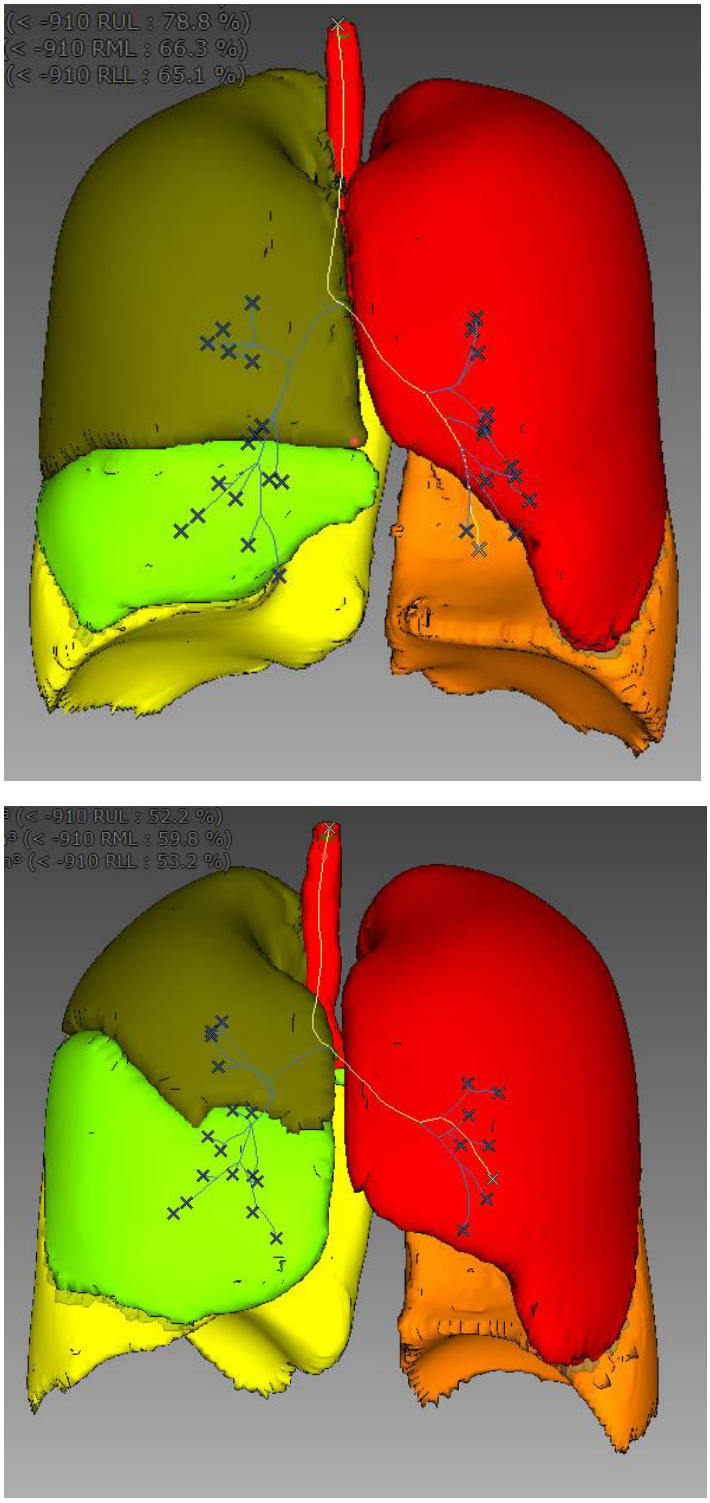


Figure 4.2 3D reconstruction of lungs

Reconstructions of inspiratory scans prior to treatment (above) and following bilateral upper lobe treatments (below).

4.3.6 Statistics

Descriptive statistics will be expressed as mean (standard deviation) for normally distributed data and median (range) for non-normally distributed data. Between group differences (treatment versus control) in the primary and secondary outcomes will be analysed using the unpaired t-test for normally distributed data and the Mann Whitney test for non-normally distributed data. Within group changes will be analysed with the paired t-test for normally distributed data and the Wilcoxon matched pairs signed rank test for non-normally distributed data. Comparison of lung volumes measured by body plethysmography and CT volumes will be performed using Bland-Altman plots. Univariate logistic regression will be used to identify any baseline CT variables that predict response to treatment. Multivariate linear regression will be used to predict the relationship between outcome and baseline variables. Correlation of CT changes with outcome measures will be performed using Pearsons r correlation for normally distributed data and Spearmans Rho for non-normally distributed data.

4.4 Results

4.4.1 Baseline characteristics

Thirty one patients had scans available for full analysis. Four patients had died before the 12 month CT scan, in two cases there were no expiratory images available and in a further case, motion artifact made the scan unusable.

There were no significant differences between the treatment and control group in the clinical and radiological baseline characteristics. Table 4.2 describes the baseline characteristics of the patients and CT scans.

Parameter	Treatment group n= 19		Control group n = 11		
	mean	SD	mean	SD	p value
Clinical parameters					
Sex (M/F)	13/6	-	6/6	-	-
Age	62.6	8.24	61.3	7.97	0.6671
FEV_1 (L)	0.78	0.219	0.73	0.166	0.4917
FEV_1 % predicted	28.1	6.98	28.1	8.55	0.9952
FVC (L)	3.00	0.816	2.60	0.643	0.0815
FEV_1/FVC	24.9	4.84	27.1	6.45	0.2860
$TL_{CO}c$ % predicted	39.1	13.1	37.7	14.26	0.7864
Whole lung CT parameters					
V_{LInsp} (mls)	7809	1654	7262	1742	0.3871
V_{LExp} (mls)	5840	1374	5492	1629	0.5823
$L_{VE/I}$ ratio	75.1	2.25	75.1	2.25	0.9842
MLD_{Insp}	-888	17.8	-887	17.4	0.9747
MLD_{Exp}	-852	30.9	-856	31.3	0.7088
$MLD_{E/I}$	95.6	2.71	96.7	2.67	0.3067
$\%LAA_{-910Insp}$	60.5	10.25	60.6	10.11	0.9793
$\%LAA_{-910Exp}$	44.8	14.74	47.3	13.48	0.6386
Target lobe parameters					
V_{TLinsp} (mls)	1814	457	1642	476	0.1632
V_{Lexp} (mls)	1436	441	1284	450	0.1970
$L_{VE/I}$ ratio	78.7	11.89	77.3	8.56	0.6070
MLD_{Insp}	-896	20.8	-897	20.8	0.8957
MLD_{Exp}	-864	37.7	-867	39.1	0.8054
$MLD_{E/I}$	96.5	2.47	96.6	2.34	0.7653
$\%LAA_{-910Insp}$	64.2	11.96	65.3	12.34	0.7314
$\%LAA_{-910Exp}$	50.1	18.90	51.5	18.52	0.7740

Table 4.2 Baseline parameters

Unpaired student's t-test

Table 4.2 abbreviations:

V_{LInsp}: inspiratory lung volume; V_{LExp}: expiratory lung volume; $L_{VE/I}$: lung volume inspiratory/expiratory ratio; MLD_{Insp}: mean lung density at inspiration; MLD_{Exp}: mean lung density at expiration; $MLD_{E/I}$: mean lung density expiratory/inspiratory ratio; $\%LAA_{-910Insp}$: percentage of low attenuation areas at -950 HU on inspiration; $\%LAA_{-910Exp}$: percentage of low attenuation areas at -910HU on expiration; V_{TLInsp}: inspiratory target lobe volume; V_{TLExp}: expiratory target lobe volume.

The target lobes were identified by a core radiology laboratory based on a visual scoring system as described in the methods. When compared to the ipsilateral lobe (excluding the right middle lobe), the target lobes had a significantly higher expiratory volume but not inspiratory volume. There was significantly more gas trapping when comparing the $LV_{E/I}$ ratio and $MLD_{E/I}$ ratio. They also had significantly higher emphysema scores than non-target lobes. Table 4.3 describes the differences between target and non-target lobe (excluding right middle lobes) in patients undergoing coil treatment.

Parameter	**Target lobe n = 37**		**Non-target lobe n = 39**		
	mean	**SD**	**mean**	**SD**	**p value**
V_{Insp} (mls)	1814	457	1774	478	0.7096
V_{Exp} (mls)	1436	441	1251	349	**0.0464**
$L_{VE/I}$ ratio	78.7	11.9	71.6	12.7	**0.0130**
MLD_{Insp}	-896	20.8	-878	25.4	**0.0008**
MLD_{Exp}	-865	37.7	-832	39.4	**0.0005**
$MLD_{E/I}$	96.5	2.47	94.8	3.22	**0.0173**
$\%LAA_{-910Insp}$	64.2	11.96	55.7	13.64	**0.0051**
$\%LAA_{-910Exp}$	50.1	18.99	36.7	17.09	**0.0018**

Table 4.3 Target lobe baseline radiological parameters

Unpaired student's t test

4.4.2 Agreement in lung volume measurements

To assess the agreement in lung volumes between CT and plethysmography, Bland-Altman plots were constructed for comparison of total lung capacity and V_{LInsp}, residual volume and V_{LExp}. For the RV/TLC ratio, the $LV_{E/I}$ ratio was used as the CT measure, being the ratio of expiratory to inspiratory volume.

CT volumes at TLC were smaller than measured by body plethysmography with a bias of 0.664L (Table 4.4). However, the expiratory volume was larger when measured by CT compared to RV by body plethysmography with a bias of -0.629L. There was a trend such that patients with a larger RV had a greater underestimation of expiratory volume measured by CT. Consequently the $LV_{E/I}$ ratio was also overestimated in patients with larger lung volumes measured by plethysmography.

	Bias	SD	95% limits of agreement
TLC	0.664 L	0.5041	-0.324 to 1.652
RV	-0.629 L	0.8879	-2.369 to 1.111
RV/TLC	-10.8	7.99	-26.5 to 4.9

Table 4.4 Bland Altman analysis of CT versus plethysmographic lung volumes

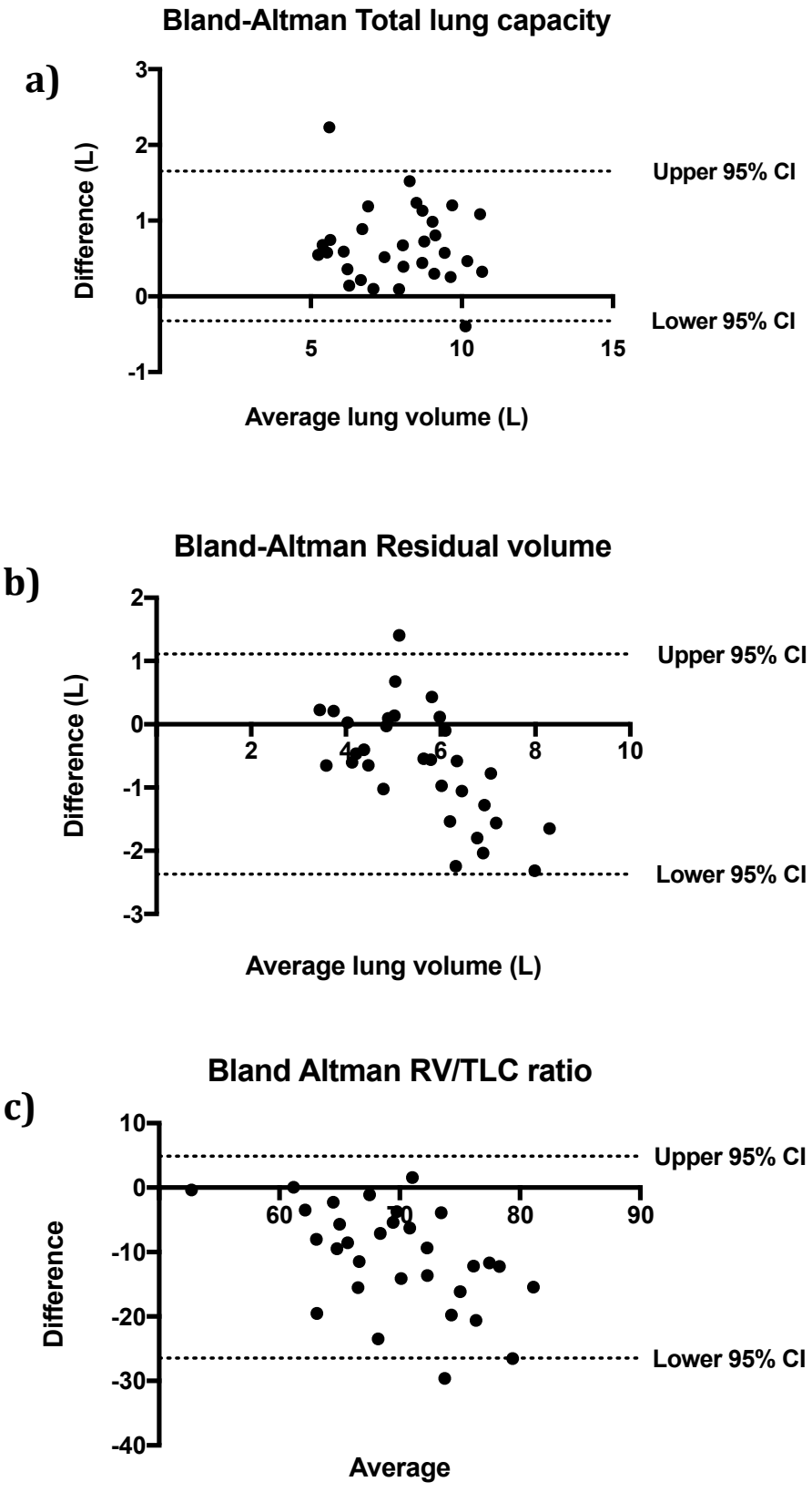


Figure 4.3 Bland Altman analysis of lung volumes

a) TLC b) RV and c) RV/TLC ratio

4.4.3 Repeatability of CT volume and density measurements

In order to assess the repeatability of CT derived lung volumes and density measurements, we measured the co-efficient of variability in the 11 control subjects over 12 months. Table 4.5 lists the co-efficient of variation of the whole lung volumes, mean lung density and low attenuation areas.

	Inspiratory scan	Expiratory scan
	Co-efficient variation	Co-efficient variation
Volume	3.1	6.4
MLD	0.62	0.8
LAA%	4.8	7.6

Table 4.5 Co-efficient of variation of CT volume and density measurements

Parameters on inspiratory scans varied less that 5% over a 12 month period suggesting that lung volumes and desnities are stable over this period. On the expiratory scans the variation over 12 months was slightly greater, perhaps reflecting the variability of the lung volume they were measured at.

4.4.4 Changes in lung volumes

In the target lobes there was a significant reduction in the median inspiratory volume of the treatment group from baseline to post treatment of 125ml, with a between group difference of 118ml (95% CI -208 to -60, $p < 0.0001$). On expiration, the target lobe volume fell significantly by a median of 89mls ($p = 0.0468$) and the between group difference was 205mls (95% CI -311 to -56, $p = 0.0027$). There were no significant differences in the volumes of the non-target lobes at either inspiration or expiration. When comparing the volume of the entire lungs, there was a significant reduction in inspiratory volume but not expiratory volume.

4.4.5 Changes in lung density and gas trapping

There was no significant change in the expired volume (inspiratory volume – expiratory volume) in the treated lobes, untreated lobe or whole lung in either group. Nor was there any significant difference in the $LV_{E/I}$ ratio or $MLD_{E/I}$ ratio to suggest a reduction in gas trapping. The mean lung density did however

decrease significantly at inspiration (-13HU, $p < 0.0001$) and at expiration (-10HU, $p = 0.0500$) in the treatment group. There was also a significant reduction in the emphysema score at inspiration (-5.63 percentage points, $p < 0.0001$) but not on expiration. There was no change in lung density or gas trapping in the untreated lobes in either group.

Table 4.6 lists the between group changes in the whole lungs, table 4.7 the target lobes and table 4.8 the non-target lobes.

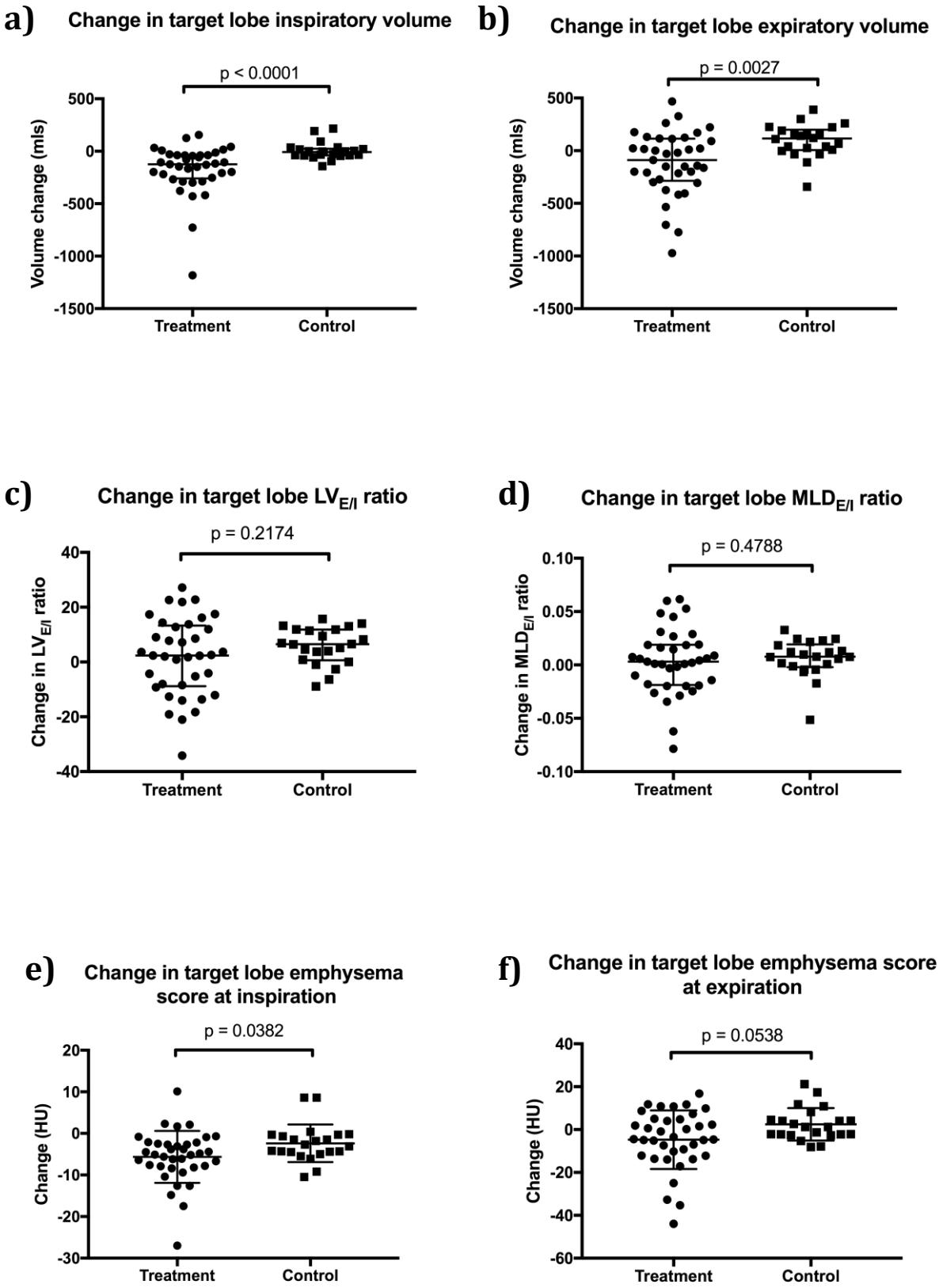


Figure 4.4 Changes in target lobe parameters

Graphs a, b, d and f: error bars represent median and interquartile range

Graphs c & e: error bars represent mean and 95% confidence interval

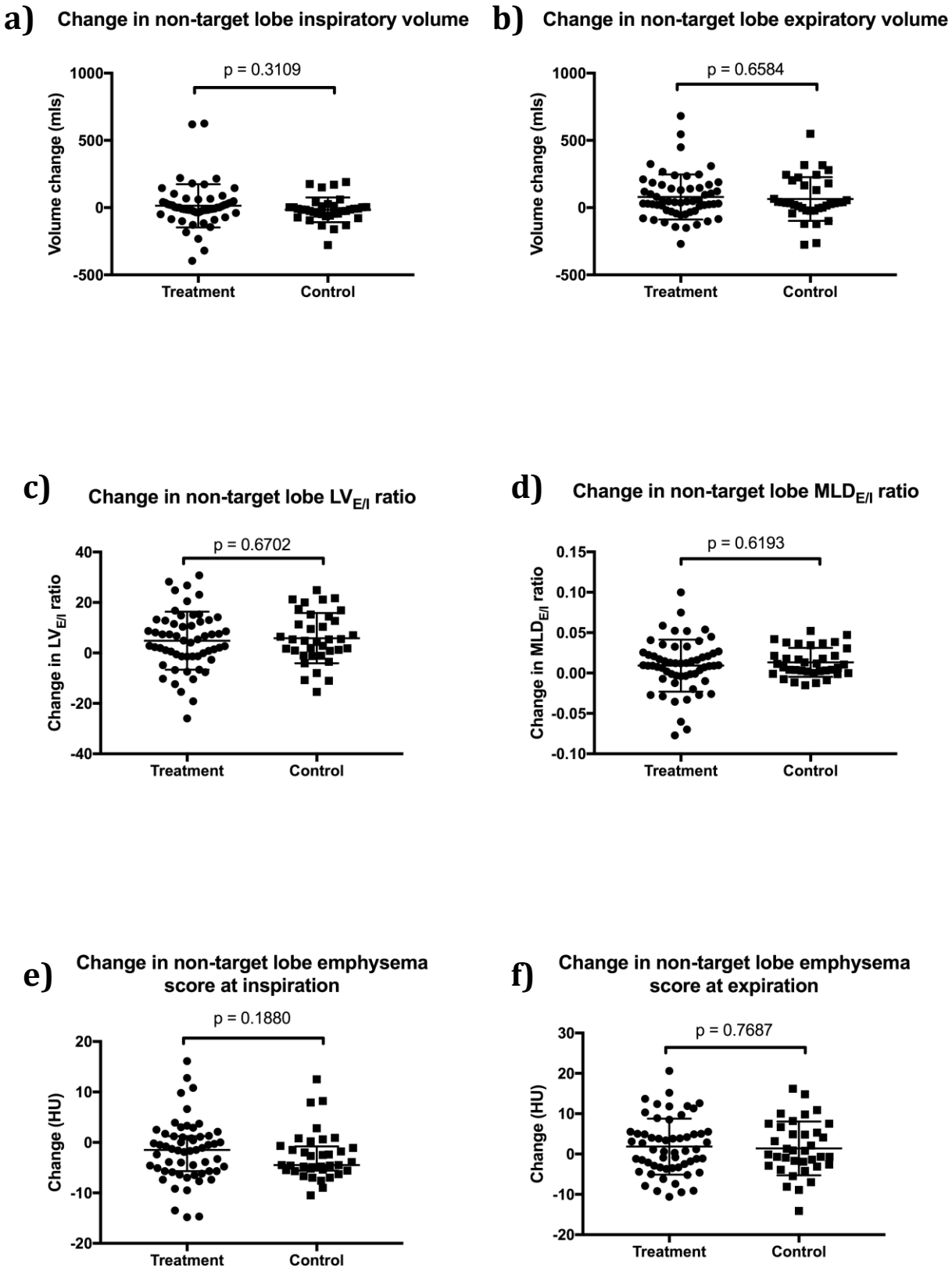


Figure 4.5 Changes in non-target lobe parameters

Graphs a, & b: error bars represent median and interquartile range

Graphs c, d, e & f: error bars represent mean and 95% confidence interval

	Treatment n = 19		Control n = 11		Between group difference		p value
	Change	SD or range	Change	SD or range		95% CI	
V_{LInsp} (mls)	-296	-993 to 197	-28	-520 to 691	-256	-559 to -36	**0.0160**§
V_{LExp} (mls)	183	-1061 to 1824	312	-734 to 1743	-129	-968 to 166	0.1905§
Expired volume (mls)	-336	-2160 to 951	-272.5	-1455 to 364	-63.5	-530 to 720	0.9205§
$LV_{E/I}$ ratio	3.95	-16.68 to 23.14	3.90	-4.28 to 16.62	0.05	-10.20 to 6.29	0.6458§
MLD_{Insp} (HU)	4.6	-25.6 to 39.2	0.85	-28.5 to 24.7	3.75	-15.4 to 18.6	0.5962§
MLD_{Exp} (HU)	9.3	-16.0 to 19.7	7.4	-14.8 to 14.8	1.9	-3.3 to 10.1	0.2826§
$MLD_{E/I}$ ratio	0.51	2.55	0.50	2.01	0.01	-1.80 to 1.81	0.9913

Table 4.6 Whole lung changes in volume, density and gas trapping

§ Mann-Whitney U test, otherwise unpaired t-test

	Treatment n = 37		**Control n = 22**		**Between group difference**		**p value**
	Change	SD or range	Change	SD or range		95% CI	
V_{TLInsp} (mls)	-125	-1182 to 155	-7	-142 to 215	-118	-208 to -60	**<0.0001**§
V_{TLExp} (mls)	-89	-972 to 467	115	-343 to 389	-205	-311 to -56	**0.0027**§
Expired volume (mls)	-53	-573 to 506	-104	-293 to 201	51	-74 to 146	0.5311§
$LV_{E/I}$ ratio	1.78	14.24	5.82	6.72	-4.04	-10.53 to 2.45	0.2174
MLD_{Insp} (HU)	13	-16 to 70	6	-13 to 18	7	2 to 11	**0.0022**§
MLD_{Exp} (HU)	10	-44 to 102	-0.5	-28 to 57	10.5	1 to 23	0.0500
$MLD_{E/I}$ ratio	0.31	-7.85 to 6.16	0.77	-5.15 to 3.27	-0.46	-1.58 to 0.74	0.4788§
$LAA_{-910Insp}$	-5.63	6.25	-2.39	4.52	-3.24	-6.31 to -0.18	**0.0382**
$LAA_{-910Exp}$	-4.51	-44.0 to 16.8	1.2	-8.1 to 21.2	-5.7	-11.21 to 0.20	0.0538§

Table 4.7 Target lobe changes in volume, density and gas trapping

§ Mann-Whitney U test, otherwise unpaired t-test

	Treatment n = 58		Control n = 36		Between group difference		p value
	Change	SD or range	Change	SD or range		95% CI	
V_{NTInsp} (mls)	14	161	-16	92	30	-29 to 88	0.3109§
V_{NTExp} (mls)	80	168	64	163	16	-54 to 86	0.6584§
Expired volume (mls)	-66	198	-80	172	14	-65 to 94	0.7723
$LV_{E/I}$ ratio	4.87	11.48	5.86	9.99	-0.99	-5.62 to 3.63	0.6702
MLD_{Insp} (HU)	4	-43 to 27	8.5	-23 to 19	-4.5	-7 to 1	0.1389§
MLD_{Exp} (HU)	-6	22	-5	16.9	0	-9 to 8	0.9691
$MLD_{E/I}$ ratio	1.08	2.75	1.32	1.79	0.25	-1.22 to 0.73	0.6193
$LAA_{-910Insp}$	-1.5	-14.8 to 16.1	-4.5	-10.5 to 12.5	3.0	-0.8 to 3.6	0.1880§
$LAA_{-910Exp}$	1.8	6.9	1.4	6.7	0.4	-2.5 to 3.3	0.7687

Table 4.8 Non-target lobe changes in volumes, density and gas trapping

§ Mann-Whitney U test, otherwise unpaired t-test

4.4.6 Correlation of radiological changes with clinical outcomes

Changes in target lobe volumes at inspiration and expiration were correlated against clinical outcomes including the primary outcome of change in 6 minute walk distance, change in SGRQ score and change in spirometric measures and RV/TLC ratio. For the purposes of comparison with clinical variables, both the left and right target lobes were combined to produce a single value. (Table 4.9 and figure 4.6) There were moderate strength correlations with all clinical outcomes and the degree of volume change in the target lobe at expiration. Additionally there were moderate strength correlations with change in target lobe volume loss at inspiration and lung function measures. There was no association between the change in gas trapping measured by the $MLD_{E/I}$ ratio and $LV_{E/I}$ ratio and clinical outcomes.

n = 19	ΔV_{TLinsp}	ΔV_{TLexp}	$\Delta MLD_{E/I}$ ratio	$\Delta LV_{E/I}$ ratio
Δ 6MWD	-0.371	**-0.590****	-0.375	-0.335
Δ SGRQ	0.392	**0.604****	0.398	0.356
Δ FEV_1	**-0.465***	**-0.605****	-0.388	-0.297
Δ FVC	**-0.5132***	**-0.627****	-0.407	0.251
Δ RV/TLC	**0.6042****	**0.611****	0.277	0.191

Table 4.9 Correlation of changes in radiological and clinical parameters

Pearson r value

* $p < 0.05$

** $p < 0.01$

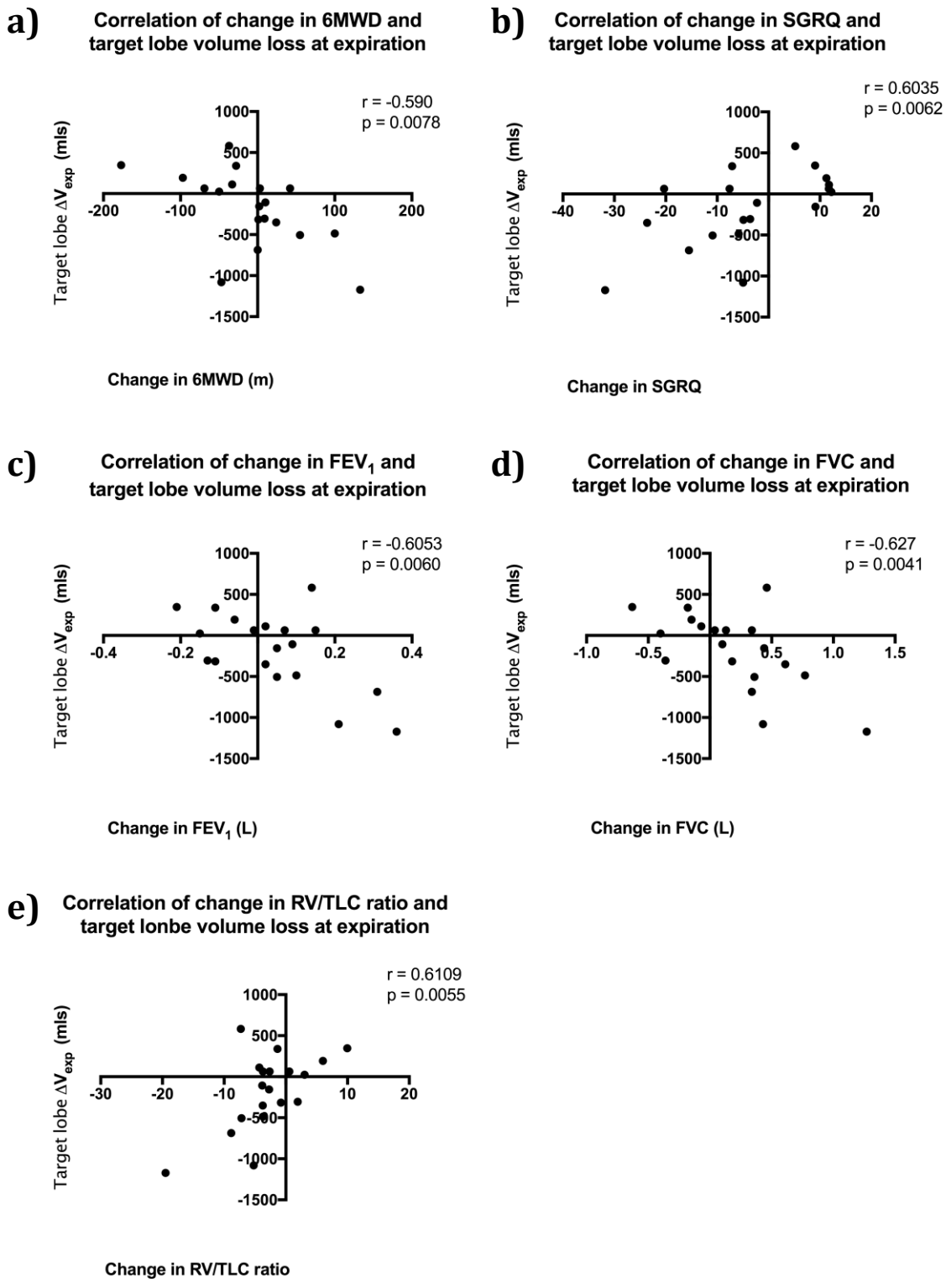


Figure 4.6 Correlation of changes in target lobe volume loss at expiration and clinical parameters

4.4.7 Radiological predictors of lobar volume loss

Univariate analysis of baseline radiological factors associated with target lobe volume loss at expiration was performed (Table 4.10). We chose target lobe volume at inspiration and expiration, emphysema score at inspiration, $MLD_{E/I}$ ratio and heterogeneity as potential variables. Since heterogeneity was determined by a core radiology laboratory as a dichotomised variable, we calculated a heterogeneity score for each lobe. This was determined by subtracting the non-target lobe emphysema score from the ipsiliateral target lobe emphysema score (ignoring the right middle lobe). The heterogeneity score was then used as a continuous variable. In the visual scoring, 2 treatment group patients and 3 controls were identified as having heterogeneous disease. In the quantitative scoring of heterogeneity, 11/37 (29.7%) target lobes in the treatment group and 7/26 (26.9%) control target lobes were classified as heterogeneous.

	R^2	p value
Heterogeneity score	0.2749	0.0009
V_{TLInsp}	0.0103	0.5498
V_{TLExp}	0.1500	0.0179
MLD_{Insp}	0.1915	0.0068
$MLD_{E/I}$ ratio	0.3514	0.0001
$LAA_{-910Insp}$	0.1856	0.0078

Table 4.10 Univariate linear regression of radiological parameters associated with target lobe volume loss

In a backwards multivariate linear regression analysis to predict target lobe volume loss at expiration, baseline MLD at inspiration was excluded from analysis because of significant colinearity with emphysema score.

In the final model heterogeneity and $MLD_{E/I}$ score were retained as predictors of target lobe volume loss. A significant regression equation was found ($F(2,34) = 11.204$, $p < .000$), with an R^2 of 0.397.

Table 4.11 lists the beta co-efficients for each parameter. Lobar volume loss was predicted by the equation:

$$\Delta V_{TLexp} = -5137 + -5.602(heterogeneity) + -5406(MLD_{E/I})$$

	β co-efficient	Standard error	p value
Heterogeneity	-5.602	3.483	0.117
$MLD_{E/i}$	-5406	2057	0.013

Table 4.11 Mutlivariate linear regression parameters

4.4.8 Radiological predictors of clinical outcomes

Univariate analysis was performed to predict change in the primary outcome of change in 6 minute walk distance and for change in SGRQ score. For each patient, a weighted mean score of the two target lobes was calculated using the target lobe volumes as the weighting measure. Baseline radiological parameters included in the analysis were: target lobe volume at inspiration and expiration, emphysema score at inspiration, MLD at inspiration and $MLD_{E/I}$ ratio. Heterogeneity was not be included since a mean heterogeneity score cannot be calculated for a combined lobar score as it is dependent on the ipsliateral lobe and cannot be weighted by target lobe volume. Table 4.12 lists the R^2 values for each parameter. The $MLD_{E/I}$ ratio was weakly associated with change in SGRQ score, such that those patients with a greater degree of gas trapping achieved a greater symptomatic benefit from treatment with lung volume reduction coils. No radiological parameters were associated with the change in 6 minute walk distance, although there was a trend to a weak association with $MLD_{E/I}$ score.

	Change in 6 minute walk distance		Change in SGRQ score	
	R^2	p value	R^2	p value
V_{TLInsp}	0.3776	0.4253	0.0171	0.5934
V_{TLExp}	0.0545	0.9798	0.0306	0.4738
MLD_{Insp}	0.0001	0.9616	0.0027	0.8325
$MLD_{E/I}$ ratio	0.2068	0.0504	0.2775	**0.0205**
$LAA_{-910Insp}$	0.0001	0.9616	0.0027	0.8325

Table 4.12 Univariate linear regression of change in 6 minute walk distance and change in SGRQ score with radiological parameters

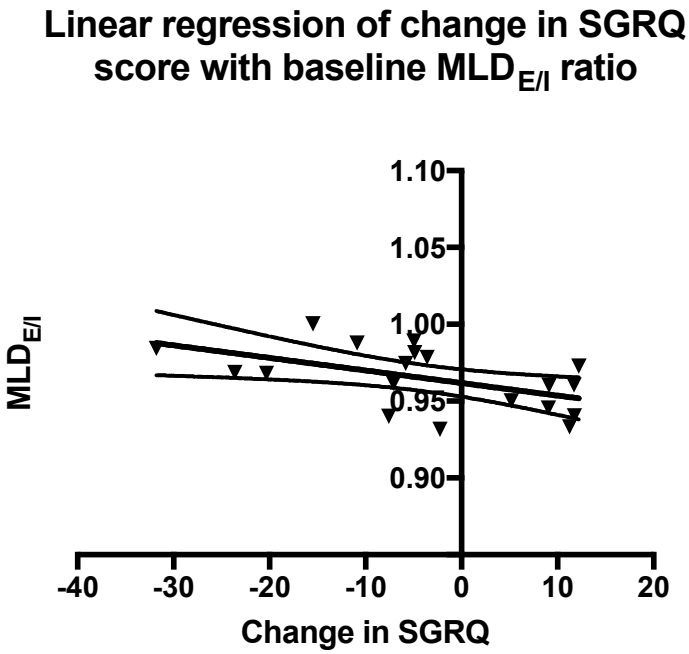


Figure 4.7 Linear regression of change in SGRQ score with baseline $MLD_{E/I}$ ratio

4.5 Discussion

Treatment with lung volume reduction coils results in a significant reduction in the target lobe volume at inspiration and expiration compared to controls. The median reduction of 129mls at inspiration and 89mls at expiration are of a similar magnitude and hence there is no significant change in the expired volume from treated lobes, nor any reduction in gas trapping measured by either the $MLD_{E/I}$ or $LV_{E/I}$ ratios. Lung density and emphysema score measured on inspiratory scans also improved significantly.

We did not detect any significant change in the non-target lobes volumes, gas trapping or density. However, when considering the total lung volumes, there was a significant reduction in volume at inspiration, but not in expiration. This may suggest that there is a degree of non-target lobe compensatory hyperinflation that offsets the small, but significant reduction in target lobe volume at expiration. There was a small and non-significant rise in non-target lobe expired volume of 80mls. It must be borne in mind that there are three untreated lobes, therefore the summative effect of this volume increase may become more significant. Indeed, the expiratory volume of the whole lung did rise following treatment, but to a lesser degree than the control group. When comparing whole lung volumes measured by CT to plethysmography, the reduction in TLC in this group of patients was 179mls, slightly less than the estimate by CT volumes. The mean reduction in RV was 329mls when measured by body plethysmography, significantly different to the overall increase of 183mls when measured by CT. This reflects the fact that the scans were not performed at residual volume.

To date, only one study of lung volume reduction coils has reported change in CT measured lobar volumes. Klooster et al. demonstrated a 263ml reduction in the combined treated lobes in patients undergoing bilateral upper lobe treatment. There was no assessment of volume change in the untreated lobes. This is broadly inline with our findings. In their study, only inspiratory scans were analysed and no measures of density or gas trapping were performed.(300) No lung volume reduction coil studies have attempted to identify radiological

predictors associated with clinical outcomes, beyond visual scoring of heterogeneity. Our results provide evidence that both heterogeneity and target lobe gas trapping are important factors in predicting radiological volume loss.

Target lobe volume changes have been widely reported following endobronchial valve treatment, with an accepted minimum clinically important difference of 350mls on inspiratory scans.(233–235,237) Target lobe volume reduction is correlated with improvement in FEV_1(233) and those patients who achieve >350mls volume loss have a greater degree of improvement in walking distance, spirometry and lung volumes.(234) Quantitative CT has been investigated to predict which radiological factors predict outcomes in endobronchial valve treatment. Fissure integrity, low attenuation clusters (an alternative measure of emphysema severity) and peripheral vessel volume are the major determinants of success.(234) Whilst the degree of volume loss is significantly less with coils than endobronchial valves, it is likely that their mechanisms differ. Endobronchial valves aim to cause complete lobar collapse but coils are thought to increase lung recoil pressures and hence improve expiratory flows. The relative contribution of increased elastic recoil versus volume loss to improvement following coil treatment is not known. No endobronchial valve studies have reported the influence of gas trapping measures from paired inspiratory/expiratory CT's on outcomes. One small study of 10 patients undergoing LVRS demonstrated reduction in MLD on inspiratory and expiratory scans following treatment. The authors found significant reductions in lung volume and anecdotally reported re-expansion of the remaining lung. However, they were unable to quantify individual lobar volumes.(332)

There were moderate strength correlations with clinical and lung function outcomes and target lobe volume loss in our cohort of patients. The correlations were strongest with the reduction in target lobe expiratory volume. There were no significant correlations with markers of gas trapping which is suggested as a radiographic marker of small airways disease. This may suggest that the main mechanism of action with coils is volume reduction, rather than relieving gas trapping by splinting open small airways through its effect on elastic recoil. Since

the small airways are beyond the resolution of CT, we could not make any further assessment of the influence of coils on their patency, other than surrogate markers of gas trapping. Relatively few patients had overt evidence of atelectasis around coils, however those that did often had marked volume loss in the target lobe. Although we cannot make any direct measurements of elastic recoil from CT images, it is quite possible that an increase in elastic recoil results in volume reduction in the absence of overt atelectasis. If coils do increase recoil pressure of the lung, then this would alter the balance of outward chest recoil and inward lung recoil. The result would be a reduction in TLC and FRC, both of which we demonstrated in Chapter 3. This could also explain why the degree of volume loss is greater at inspiration. At full inspiration, the coils may be deformed, thus increasing their tension and hence elastic recoil within the lung as they try to recover their natural shape. The tension generated in the lung at end expiration may be expected to be less as the coils are closer to their natural shape.

Fessler argues that volume reduction achieves its effect through a greater reduction in RV than TLC, with a consequent increase in FVC.(255) Therefore a comparatively greater reduction in TLC would not be expected to improve lung function. Target lobe expiratory volume change was positively correlated with change in RV/TLC ratio, suggesting that those who achieve greater target lobe expiratory volume loss have a greater reduction in gas trapping and better clinical outcomes.

High levels of emphysema heterogeneity and gas trapping predicted target lobe volume loss in the multivariate regression. Two patients classified as having heterogeneous disease by the visual reading had homogeneous disease by quantitative CT. This arose because there were isolated bullous areas in lower lobes, purposefully ignored by the visual estimates. In these patients the upper lobe destruction was more confluent and felt to be a better target for treatment. A more favourable response to treatment in heterogeneous patients has been observed in studies of LVRS(122), endobronchial valves(229) and lung volume reduction coils.(218) We have demonstrated that heterogeneity measured by

quantitative CT predicts volume loss at expiration, but we were unable to associate it with clinical outcomes, since it would not be valid to create single heterogeneity score for two lobes. Additionally, gas trapping measured by the $MLD_{E/I}$ score was associated with greater target lobe volume loss. This is consistent with the theory that heterogeneous patients gain the most benefit from LVRS by targeting areas of lung with the greatest level of emphysema and gas trapping, thus reducing overall RV/TLC ratio. However we did not find a reduction in either $MLD_{E/I}$ or $LV_{E/I}$ following treatment. This may have been underestimated because of the lung volume achieved on expiratory scans. In the univariate regression to predict clinical outcomes, only $MLD_{E/I}$ had a weak relationship with changes in symptom scores and narrowly missed a significant association with change in walking distance.

It was intended that inspiratory scans should reflect TLC and that expiratory scans should be undertaken at RV to allow direct comparison with lung function data. Patients were coached prior to their CT scan and played automated instructions for breathing during the scan. The Bland-Altman analysis of the agreement in lung volumes between CT and plethysmography is poor. At full inspiration the mean difference between the two volume measurements was 0.664L, with plethysmography overestimating TLC in all but one case. It is recognised that inspiratory scans report lower lung volumes than plethysmography, with estimates of up to 1.2L mean difference in the literature.(333) The degree of overestimation increases with the severity of airflow obstruction. This occurs when there is high airways resistance and changes in alveolar pressure are not truly reflected at the mouth during plethysmographic measurement. An underestimation of alveolar pressure during the panting manoeuvre results in an overestimation of lung volumes.(30) Measuring lung volumes using an oesophageal catheter to estimate alveolar pressure results in lower values being obtained in the presence of airway obstruction.(334) Furthermore there may be a small contribution to the overestimation from compressible gas within the gut.(335)

On expiratory scans, CT overestimated RV by a mean of 0.629L, however there was a much greater variation. There was also a trend, such that patients with larger lung volumes had a greater degree of underestimation. This is likely to have arisen from the prolonged expiratory times required in severe airflow obstruction. In the lung function laboratory, some of our patients had forced expiratory times in excess of 20 seconds, far greater than the time allowed to expire in the CT scanner. Therefore those patients with larger lung volumes, and hence a larger vital capacity would have had less time to reach RV. This is a major weakness of this study since it potentially introduces a source of bias. MLD measurements are dependent on the tissue to air ratio in the lung. Those patients with larger lungs volumes would have a greater degree of underestimation of expiratory MLD and hence reduction in gas trapping. This could explain why we did not find any significant change in gas trapping markers on CT. The only published data of comparison of expiratory scans and lung volumes found that expiratory volume was closer to FRC than RV, but with a strong correlation for both measures.(324) We compared our expiratory volumes to FRC in a Bland Atlman analysis and there was a mean difference of -0.408L, with CT values lower than plethysmographic values. Although there is closer agreement of FRC and expiratory volume, it is likely that the expiratory lung volume represents a measure somewhere between FRC and RV. CT assessment of lung volumes is not without error, since in the supine position, there may be a fall in VC up to 10% in healthy subjects.(336) This arises because of an increased load placed on the diaphragm from the abdominal organs. In the presence of functional respiratory muscle weakness, which is present in COPD, this could further reduce vital capacity.(337)

Spirometrically gated CT has been used as a technique to try and standardise the level of inspiration and expiration prior to performing the scan. In a study of patients with COPD, there was a significant difference in MLD at inspiration and expiration when comparing spirometrically gated CT and standardised breathing instructions.(338) In this study the authors noted that some patients found the technique difficult. In such severely obstructed patients as in our study, breath holding at RV for the entire scan time could prove difficult. Without confirmation

of the level of inspiration, it is quite possible that some of the variation in lung volume and density measurements may have reflected variation in the level of inspiration, rather than a true treatment effect. However there was a significant increase in target lobe MLD at inspiration compared to controls, which is consistent with a reduction in the inspiratory volume.

There are a number of other limitations of our study, beyond the accuracy of inspiratory and expiratory volumes. The small number of patients in this study limits the power to be able to accurately detect an effect of coil treatment when the changes in CT parameters are small. A single investigator undertook all CT analysis and therefore there can be no estimate of inter-observer reliability when performing lobar segmentation. The segmentation process relies on being able to see the fissures clearly which are not infrequently disrupted in severe emphysema. This was particularly the case for the horizontal fissure. Therefore an estimate of the likely path had to be made by reference to the airways and pulmonary vessels. This potentially increases the margin of error for accurately delineating each lobe. Since coils are high density objects and clearly visible, there was no way of blinding the investigator to the treatment allocation.

The Myrian XP Lung software had a fixed threshold of < -910 HU for the detection of emphysema. Whilst there is debate as to which threshold is best, the majority of studies published in relation to endobronchial valves have used <-950 HU as the threshold. A lower threshold results in a greater emphysema score and therefore it is possible our software overestimates the degree of tissue destruction. Similarly, some authors have found that measures of gas trapping are best assessed using -856 HU on expiratory scans, although this has not been as extensively validated in COPD.

During the course of the study a new scanner was used (64 vs 128 detector), however both were produced by the same manufacturer and used identical software. All acquisition and reconstruction parameters were kept the same, which should minimise any variation due to a change in hardware. It is recognised that different models of scanner produce significant variations in

lung density assessments, however much of this relates to variation in manufacturer, software and radiation dose.(339)

This study has important findings that may influence future selection of patients undergoing lung volume reduction coil treatment. Our target lobes were chosen on the basis of a visual estimation of emphysema. In several cases, the quantitative CT emphysema score disagreed with the visual assessment which could have potentially changed which lobe was treated. Furthermore there were non-target lobes that had a higher degree of gas trapping than the target lobes. Since these factors may predict radiological volume reduction, it would make sense to use them in selection of patients. A much larger study would be required to determine if there are thresholds of these parameters above which clinical and radiological improvements are more significant.

There are a number of other investigations that could be performed to try and elucidate the mechanism of lung volume reduction coils. Distinguishing the relative contribution of gas trapping as a result of small airways disease and emphysema on airflow obstruction is difficult using the methods described above. More recently a technique called parametric response mapping has been developed which may allow more accurate assessment. The technique involved digitally co-registering inspiratory and expiratory scans. A voxel by voxel comparison is performed to determine the relative amounts of emphysema and gas trapping as a result of functional small airways disease. This technique has been validated in the COPD gene cohort.(340) It has been used to track progression in COPD(340,341), but not yet applied in testing response to treatments. This could offer an non-invasive way of assessing the effect of coil treatment on small airways and potentially identifying phenotypes of disease which will benefit from treatment. Emphysema is associated with significant ventilation-perfusion mismatch within the lung.(342) It is not clear what effect coil treatment will have on the pulmonary vasculature. A single study using dual energy CT demonstrated an increase in pulmonary blood flow around coils,(272) but was not able to assess the relative change in ventilation perfusion matching. 3-dimernsional single photon-emission tomography allows lobar quantification

of ventilation and perfusion.(343) This offers an opportunity to examine the effect of coil treatment on ventilation-perfusion matching and assess whether changes are associated with improvements in outcomes.

4.6 Conclusions

Treatment with lung volume reduction coils results in a significant reduction in target lobe volume at inspiration and expiration, but no observable effect on gas trapping. Target lobe volume reduction is significantly correlated with improvement in walking capacity, symptoms and lung function. Heterogeneity and gas trapping may serve as useful markers to predict which patients will benefit the most from treatment.

Chapter 5

Changes in lung mechanics following treatment with lung volume reduction coils

5.1 Introduction

Lung volume reduction coils are postulated to improve elastic recoil by direct tensioning of the lung parenchyma. By doing so they may increase expiratory flow and reduce gas trapping by splinting small airways open.(297) This mechanism is potentially unique amongst other lung volume reduction therapies. Clinical trials have consistently reported volume loss and reduction in gas trapping, but evidence of improvement in expiratory flow has been mixed.(218–220,297–299) There is little direct experimental evidence of increased elastic recoil or reduced airways resistance. A single study of 10 homogeneous patients found a significant reduction in airway resistance measured by both plethysmography and impulse oscillometry.(300) To date, no studies have reported the effect of coils on elastic recoil and compliance.

LVRS is perhaps the most widely understood therapy in terms of the physiological changes following treatment. Whilst the mechanisms underlying treatment may differ from coils, studies examining the physiological changes following treatment have shed light on the potential mechanism underlying the clinical benefit that is seen following LVRS. These mechanisms may be pertinent to the changes following coil treatment. Increase in elastic recoil following LVRS is thought to be the major determinant of increased expiratory flow and relief of gas trapping.(251) Since the remaining lung is relatively less emphysematous, expansion of the lung results in a shift up the pressure-volume curve, hence increasing its recoil pressure. It might be predicted that at a higher lung volume, airway resistance will also decrease. However the evidence of improvement in airways resistance is mixed.(250,251,306) Coils may differ from LVRS by providing direct tensioning of the emphysematous parenchyma and therefore increasing recoil pressure of the lung. This should result in a reduction in volume, as we have demonstrated in Chapter 3, since the balance between the outward chest recoil and inward lung recoil is altered. In theory the increase in recoil pressure should result a reduction in airway resistance if the recoil forces are transmitted to the small airways. Therefore examining the changes in elastic

recoil and airways resistance directly may help to better understand the mechanism of lung volume reduction coils.

FEV_1 is the most commonly used physiological marker of airflow obstruction. It is relatively easy to perform, highly reproducible and well validated as biomarker in COPD.(344) The main physiological determinants of FEV_1 are airways resistance and lung recoil as the driving pressure for flow.(345) In health, the large airways are the major site of airflow limitation and hence have the largest impact on FEV_1. However, in COPD it is the small airways that account for the majority of airways resistance.(99) Therefore improvements in recoil pressure and airways resistance should increase FEV_1. Evidence from clinical trials of lung volume reduction coils has shown relatively modest and sometimes insignificant changes in FEV_1.(218–220,298,299) The use of FEV_1 as a marker of airflow obstruction has its limitations. It is recognised that FEV_1 is relatively insensitive to changes in bronchodilation compared to airways resistance by plethysmography or impulse oscillometry.(346–348) Furthermore it is a forced manoeuvre, dependent on effort and does not represent a physiological pattern of breathing.

Measurement of specific airways resistance by plethysmography (sR_{aw}) is considered the current gold standard.(349) It has been used in both the assessment of bronchodilators in COPD(350) and changes following lung volume reduction surgery.(306) In the context of bronchodilators, change in sRaw was found to be more closely associated with changes in lung volumes and dyspneoa scores than changes in FEV_1.(350) This technique has advantages over spirometry since it is measured during gentle breathing and thus avoids any potential bronchodilation associated with deep inhalation or dynamic airway compression on forced exhalation. Since sR_{aw} is dependent on lung volume, it can be standardised for any given FRC to give airways resistance (R_{aw}). The reciprocal of resistance is conductance and is independent of lung volume. This makes it particularly suitable for longitudinal assessment, particularly where lung volume may vary over time. Whilst it is sensitive to bronchodilation, there is a wider intra-test variability than spirometry and thus larger proportional

changes (greater than 40%) are required to be certain of significant changes.(287) R_{aw} is not specific to small airways pathology and can be heavily influenced by changes in proximal airways. Furthermore, inaccuracies in estimating FRC will have a significant effect on airways resistance measurements. This is particularly pertinent in patients with severe airflow obstruction where changes in mouth pressure may lag behind changes in alveolar pressure, thus overestimating FRC and consequently underestimation of R_{aw}.(349)

An alternative measure of airways resistance is by impulse oscillometry. The application of specific frequencies at the mouth, superimposed on tidal breathing allow measurement of subsequent pertubations in pressure and flow. It is easy to perform, requiring only tidal breathing by the patient and has a high temporal resolution allowing discrimination of inspiratory and expiratory impedance. The impedance of the respiratory system (Z_{rs}) is composed of the in phase resistance (R_{rs}) and out of phase reactance (X_{rs}). Reactance is determined by the elastic an inertial properties of the lung and is frequency dependent. At low frequencies X_{rs} is negative and largely represents the elastic forces within the lung. At higher frequencies X_{rs} is positive and is determined by inertiance within the lung resulting from acceleration of airflow. At a point where the elastance and inertiance are equal and opposite, X_{rs} is 0 which represents the resonant frequency of the respiratory system (F_{res}).(295) IOS allows discrimination of the relative contributions of large airways, representing higher frequencies, and the small airways which are assessed by low frequencies. The difference in resistance between 5Hz and 20Hz (R_{5-20}) has been proposed as a marker of distal airway function.(351) In COPD, there is an increase in R_{rs} and at high frequencies and a negative frequency dependence at low frequencies.(352) R_{rs} at low frequencies correlates well with R_{aw}(353), however in severe airflow obstruction this relationship becomes weaker and X_{rs} correlates more strongly with both R_{aw} and FEV_1.(354) Furthermore it correlates more closely with transpulmonary resistance measured by an oesophageal catheter than R_{rs}.(355) X_{rs} falls dramatically in the presence of expiratory flow limitation and the inspiratory – expiratory reactance at 5Hz has been demonstrated to accurately identify

this.(356) Therefore IOS may present a novel way of investigating changes in airways resistance and potentially expiratory flow limitation in a group of patients undergoing lung volume reduction coil treatment.

Multiple breath nitrogen washout allows assessment of ventilation heterogeneity. Measures such as the lung clearance index provide an overall assessment of ventilation inhomogeneity, whilst examination of the early part of the washout can localise the site of ventilation inhomogeneity to the acinar or conducting airways.(293) It also allows measurement of the FRC and comparison to FRC by plethysmography allows an estimation of trapped gas to be made, representing unventilated lung units.(357) In the context of COPD, MBNW has been shown to be very sensitive to early disease, becoming abnormal before spirometric indices do.(358) The measure of conducting airways ventilation inhomogeneity (S_{cond}) correlates well with FEV_1, FEV_1/FVC ratio and airways conductance. Acinar ventilation inhomogeneity (S_{acin}) correlates best with measures of diffusing capacity.(293) There is limited data concerning MBNW measures as outcomes for COPD, partly because of the lack of commercially available systems until now and the complexity of analysis. In a paper examining the response to tiotropium in COPD, no changes in S_{cond} or S_{acin} were demonstrated despite improvements in inspiratory capacity and FEV_1.(359) It is feasible that lung volume reduction coil treatment may improve ventilation heterogeneity, potentially by reducing airway resistance and therefore increasing ventilation of the most obstructed lung units.

5.2 Aims and hypotheses

The aims of this study are to explore the changes in lung mechanics following lung volume reduction coil treatment. A number of techniques will be used to describe changes in lung recoil pressure, airways resistance and ventilation heterogeneity. There has been relatively little experimental work examining the role of IOS and MBNW in the assessment of severe emphysema and therefore we plan to test the feasibility of performing these measurements in a cohort of severely obstructed and hyperinflated patients. Furthermore we plan to identify

whether baseline airways resistance or elastic recoil predicts clinical outcomes following coil treatment.

The primary alternative hypotheses for this study are:

- There will be a significant increase in lung recoil pressure at total lung capacity following lung volume reduction coil treatment.

- There will be a significant reduction in airway resistance measured by body plethysmography following lung volume reduction coil treatment.

5.3 Methods

5.3.1 Study design

This is a prospective, single arm interventional study examining the physiological changes in lung mechanics following treatment with lung volume reduction coils. Ethical approval was granted in May 2014 and Sponsor approval/NHS R&D permission in September 2014. Neither the investigators nor the patients were blind to the treatment. All tests were undertaken by a single investigator with the assistance of the Respiratory Physiologists and Simon Ward for lung compliance measurements and Dr Martyn Biddiscombe for MBNW and IOS measurements.

5.3.2 Patient selection

Patients who had passed screening assessments for the RENEW clinical trial and the Crossover study were approached following their baseline assessments. Those wishing to take part in the study signed a separate consent form to undergo additional tests.

There were no additional inclusion criteria for this study other than those listed in Chapter 2. However, there were a number of additional exclusion criteria:

1. Inability to provide written, informed consent
2. Contra-indications to performing lung function testing
    - Aortic aneurysm >6cm
    - Unstable cardiovascular disease (unstable angina, MI or pulmonary embolism < 4 weeks prior)
    - Severe aortic stenosis
    - Pneumothorax
    - Cerebral aneurysm
    - Thoracic or abdominal surgery < 4 weeks prior
3. Contra-indications to passing oesophageal balloons
    - Oesophageal ulceration or varices

- Sinusitis, recent nasal surgery or epistaxis

5.3.3 Study assessments

Study assessments are described in Chapter 2. Physiological assessments were performed at 9 months, using the lung function and symptom scores from the same visit. This was chosen rather than the 12 month visit to reduce the burden of testing on patients.

5.3.4 Statistics

This was an exploratory study testing the feasibility of measuring lung compliance, recoil and airways resistance. As there was not sufficient published data to generate a sample size calculation, we planned to estimate the treatment size effect and standard deviation to power a future study. We planned to recruit 20 patients into the study.

Descriptive statistics will be used to present data as mean (SD) or median (range) as appropriate. Paired data will be tested for significance using the Student's paired t test or the Wilcoxon signed rank sum tests as appropriate. Correlations will be performed using Pearson's r for normally distributed data and Spearman's rho for non-normally distributed data.

5.4 Results

5.4.1 Baseline data

10 patients were recruited for this study. Baseline characteristics are shown in table 5.1. Only 6 patients were available for follow up as 3 patients died (patients 10, 20 and 28 as detailed in Chapter 3) and a further patient did not attend their follow up. Airways resistance by plethysmography was included in the RENEW study following an amendment to the protocol and hence there is data for 17 patients who had both baseline and follow up data.

For elastic recoil, compliance and impulse oscillometry measurements we assessed the within-patient repeatability at baseline using the coefficient of variation. The mean coefficient of variation is presented along with baseline values in table 5.1. We did not assess repeatability of airways resistance by plethysmography since the measurements met the ERS/ATS standards of three repeatable tests within 10% of each other. We were unable to obtain usable data for the majority of patients undergoing multiple breath nitrogen washout which is discussed in section 5.5.

The coefficient of variation for all IOS and elastic recoil/compliance measurements was under 10% except for X_{5ln}. These estimates for coefficient of variation were inline with published data from healthy patients for both elastic recoil(360) and IOS measurments.(361)

Parameter	Median	Range	Mean coefficient of variation (%)
Sex (M/F)	3/7	-	
Age	68	55 - 78	
FEV_1 (L)	0.6	0.4 – 1.2	
FEV_1 % predicted	28.1	17.8 – 39.8	
FVC (L)	2.25	1.58 – 4.49	
FEV_1/FVC ratio	24.8	19.8 – 31.7	
RV (L)	5.02	3.26 – 5.99	
RV/TLC ratio	63.9	52.5 – 75.1	
TL_{COc} % predicted	31.7	20.6 – 51.1	
6MWD (m)	271	159 – 436	
SGRQ	66	44 – 78	
R_{awIn} (kPa.L.$^{-1}$.s)	0.68	0.33 – 1.13	
R_{awEx} (kPa.L.$^{-1}$.s)	1.34	0.54 – 3.61	
sG_{awIn} (kPa.L.$^{-1}$.s)	0.30	0.15 – 0.44	
sG_{awEx} (kPa.L.$^{-1}$.s)	0.17	0.05 – 0.34	
P_{el100} (kPa)	0.73	0.29 – 1.93	8.8
C_{Ldyn} (kPa.L^{-1})	1.85	1.16 – 5.01	3.5
C_{Lstat} (kPa.L^{-1})	1.65	0.52 – 3.19	2.5
R_5 (kPa.L.$^{-1}$.s)	0.67	0.41 – 0.97	4.2
R_{5In} (kPa.L.$^{-1}$.s)	0.46	0.34 – 0.72	3.5
R_{5Ex} (kPa.L.$^{-1}$.s)	0.69	0.36 – 0.99	6.9
R_{20} (kPa.L.$^{-1}$.s)	0.35	0.20 – 0.62	2.9
R_{20In} (kPa.L.$^{-1}$.s)	0.31	0.21 – 0.47	3.4
R_{20Ex} (kPa.L.$^{-1}$.s)	0.33	0.20 – 0.51	5.3
X_5 (kPa.L.$^{-1}$.s)	-0.59	-0.91 - -0.19	6.2
X_{5In} (kPa.L.$^{-1}$.s)	-0.26	-0.55 - -0.15	11.6
X_{5Ex} (kPa.L.$^{-1}$.s)	-0.94	-1.35 - -0.28	5.7
A_X(kPa.L.$^{-1}$)	5.76	1.85 -10.57	7.0
F_{res} (Hz)	30.2	22.0 – 44.1	3.9

Table 5.1 Baseline clinical and lung function parameters

Abbreviations for table 5.1:

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; TL_{COc}: corrected transfer factor of the lung for carbon monoxide; 6MWD: 6 minute walk distance; SGRQ: St George's Respiratory Questionnaire; R_{awIn}: inspiratory airways resistance, R_{awEx}: expiratory airways resistance; sG_{awIn}: inspiratory specific airways conductance; sG_{awEx}: expiratory specific airways conductance; P_{el100}: elastic recoil at total lung capacity; C_{Ldyn}: dynamic lung compliance; C_{Lstat}: static lung compliance; R_5:resistance at 5Hz, R_{20}: resistance at 20Hz; X_5: reactance at 5Hz; A_X: reactance area; F_{res}: resonant frequency

	FEV_1	FEV_1/FVC	RV/TLC	R_{20}	R_5	R_{5-20}	X_5	A_X	R_{awIn}	R_{awEx}	sG_{awIn}	sG_{awEx}	C_{Ldyn}	C_{Lstat}	P_{el100}
FEV_1															
FEV_1/FVC	0.31														
RV/TLC	**-0.90*****	-0.38													
R_{20}	-0.62	0.04	**0.66***												
R_5	-0.59	0.22	0.59	0.53											
R_{5-20}	**-0.70***	-0.01	**0.67***	0.46	**0.96*****										
X_5	0.49	-0.19	-0.35	-0.13	**-0.85****	**-0.89*****									
A_X	**-0.67***	-0.01	0.61	0.41	**0.94*****	**0.98*****	**-0.92*****								
R_{awIn}	**-0.80****	-0.34	**0.81****	**0.78****	0.54	**0.63***	-0.32	0.56							
R_{awEx}	**-0.75***	-0.39	**0.78**$_{**}$	**0.82****	0.37	0.46	-0.13	0.41	**0.96*****						
sG_{awIn}	**0.77****	0.57	**-0.89*****	-0.57	-0.47	-0.61	0.28	-0.54	**-0.90*****	**-0.85****					
sG_{awEx}	**0.86****	0.50	**-0.89*****	-0.59	-0.52	**-0.65***	0.41	**-0.63***	**-0.86****	**-0.84****	**0.93*****				
C_{Ldyn}	0.23	-0.59	-0.01	-0.36	0.11	0.24	-0.19	0.25	0.02	-0.10	-0.32	-0.18			
C_{Lstat}	0.57	-0.48	-0.52	-0.58	-0.37	-0.24	0.09	-0.19	-0.25	-0.27	0.13	0.23	**0.72***		
P_{el100}	0.40	-0.59	-0.24	-0.49	-0.10	0.04	-0.08	0.07	-0.10	-0.18	-0.14	-0.01	**0.95*****	**0.90***	

Table 5.2 Correlation matrix of baseline lung function parameters

Pearsons r values
* $p < 0.05$
** $p< 0.01$
*** $p< 0.001$

n = 10 for all variables except C_{Ldyn}, C_{Lstat} and P_{el100} where n = 9

5.4.2 Correlation of lung function parameters

We sought to assess the relationship between the lung function parameters. Airways resistance and conductance by plethysmography correlated strongly with FEV_1, but the only IOS parameter to do so was R_{5-20}. Airways resistance measures also correlated strongly with gas trapping measured by the RV/TLC and the only IOS parameters to do so were R_{20} and R_{5-20}. R_{20} had the strongest correlations with airways resistance measures, although R_{5-20} also correlated with inspiratory resistance and conductance. Lung elastic recoil and compliance measures did not have any significant correlation with either airways resistance or IOS parameters.

5.4.3 Changes in lung elastic recoil and compliance following treatment

9 patients underwent baseline measurements as an oesophageal balloon catheter was unavailable for 1 patient at baseline testing. Only 4 patients were available for follow up as one patient declined repeat compliance measurements in addition to the 4 other patients without follow up data. There were consistent increases in elastic recoil pressure at total lung capacity (P_{el100}) and the median coefficient of retraction (CR) more than doubled following coil treatment. There were only very small median increases in static and dynamic lung compliance with a heterogeneous response amongst patients (Table 5.3 and Figure 5.1). Individual static lung compliance plots are shown in Figure 5.2.

n = 4	**Pre treatment**	**Post treatment**	**Median change**
	Median (range)	**Median (range)**	
P_{el100} (kPa)	0.92 (0.29 -1.19)	1.71 (0.51 – 2.53)	0.73
CR ($kPa.L^{-1}$)	0.098 (0.041 – 0.186)	0.235 (0.073 – 0.257)	0.137
C_{Ldyn} ($kPa.L^{-1}$)	1.88 (1.16 – 3.70)	1.94 (1.16 – 3.6)	0.065
C_{Lstat} ($kPa.L^{-1}$)	1.65 (0.87 – 3.19)	1.94 (1.06 – 3.5)	0.25

Table 5.3 Changes in lung elastic recoil and compliance

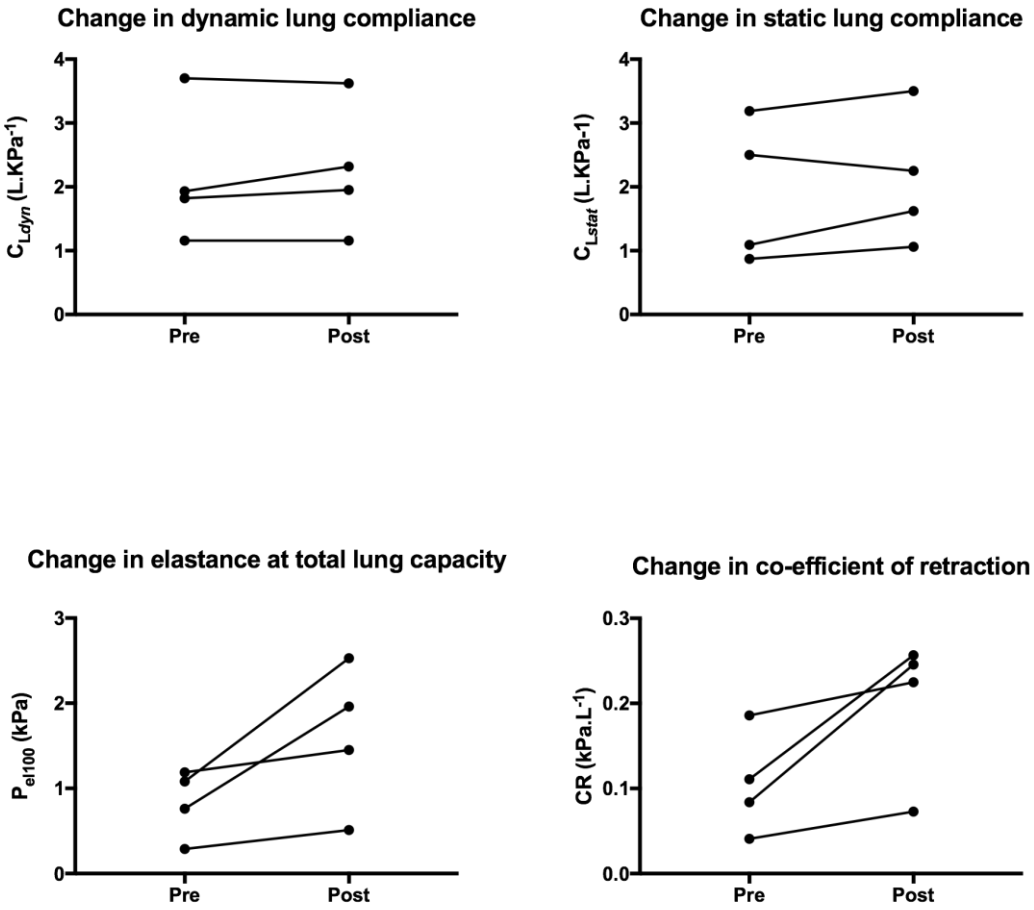


Figure 5.1 Changes in lung elastic recoil and compliance

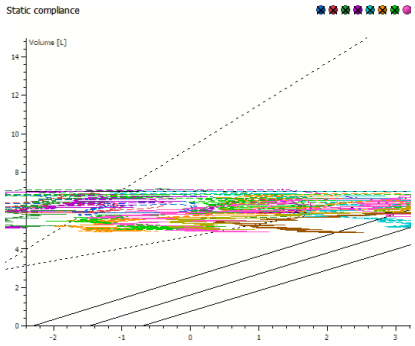
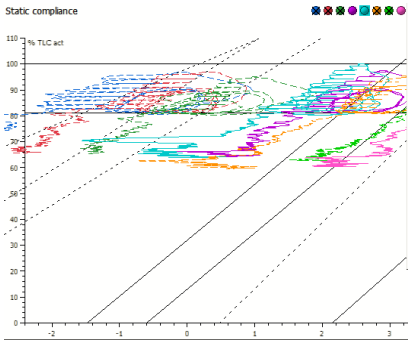
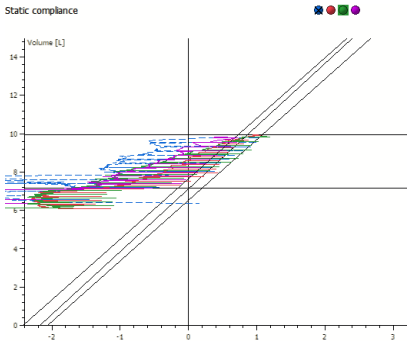
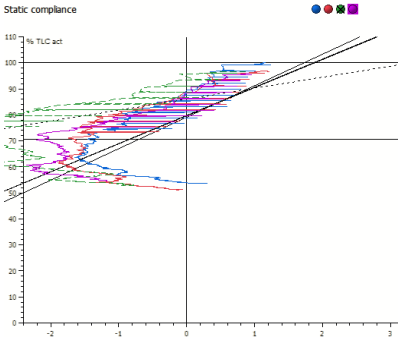
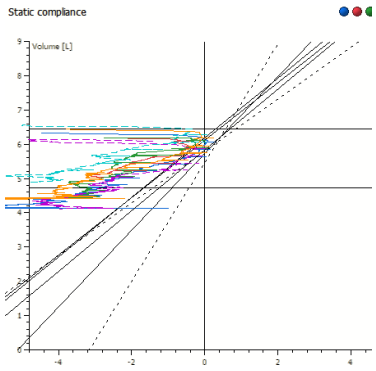
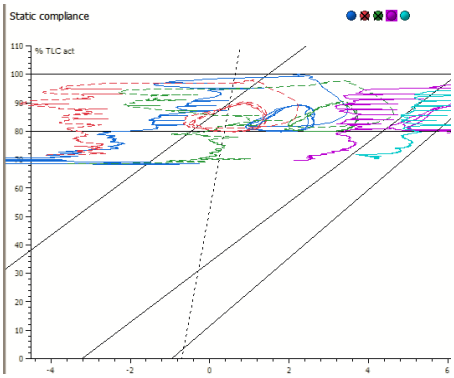
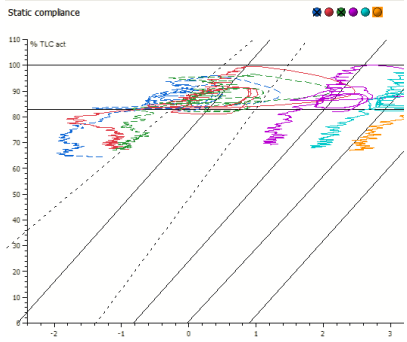
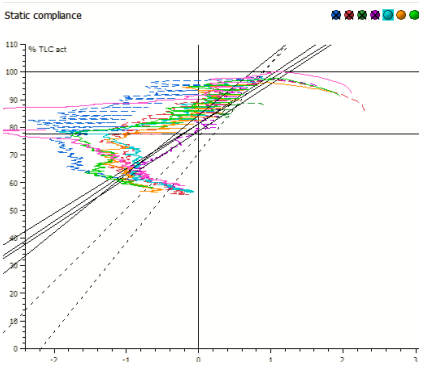
	Pre-treatment	Post-treatment
Patient 1		
Patient 2		
Patient 3		
Patient 4		

Figure 5.2 Individual static lung compliance plots before and after treatment

x axis indicates transpulmonary pressure (P_{tp}, kPa), y axis is volume (L) with the tangents measured at FRC +500ml indicating the static compliance ($kPa.L^{-1}$). All patient attempts are shown, but three consistent values from acceptable curves are used to calculate values. Elastic recoil is the Ptp at TLC.

5.4.4 Changes in airways resistance by plethysmography following treatment

We found no significant change in the inspiratory or expiratory airways resistance (R_{aw}) or specific conductance (sG_{aw}). Expiratory airways resistance was markedly higher than inspiratory resistance in all patients at baseline.

n = 17	Pre treatment	Post treatment	Change	p value
	Mean (SD)	Mean (SD)	Mean (SD)	
R_{awIn} (kPa.L.$^{-1}$.s)	0.588 (0.343)	0.569 (0.235)	0.019 (0.159)	0.6325
R_{awEx} (kPa.L.$^{-1}$.s)	1.241 (0.544)	1.220 (0.522)	0.021 (0.279)	0.7586
sG_{awIn} (kPa.L.$^{-1}$.s)	0.326 (0.109)	0.340 (0.115)	0.014 (0.056)	0.3170
sG_{awEx} (kPa.L.$^{-1}$.s)	0.160 (0.079)	0.163 (0.080)	0.003 (0.037)	0.7487

Table 5.4 Changes in airways resistance by plethysmography

Student's paired t-test.

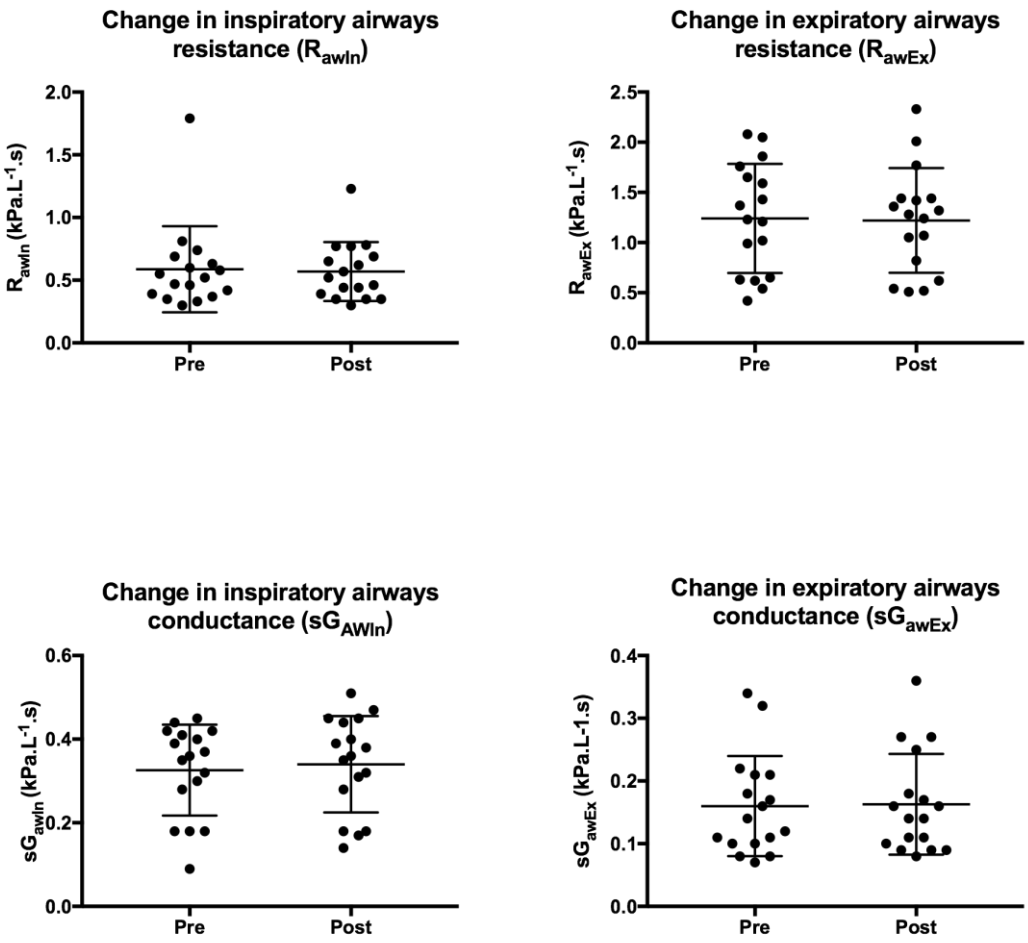


Figure 5.3 Changes in airways resistance and conductance by plethysmography

5.4.5 Changes in impulse oscillometry parameters following treatment

There was a trend to increasing resistance measurements measured 20Hz (R_{20}), reflecting the large airways. But there was a more heterogeneous response to changes in R_5, reflecting all airways and the small airway specific R_{5-20}. Changes in reactance measures were also mixed (Table 5.5 and Figure 5.4). With the small number of data it was not possible to determine if changes in IOS parameters were associated with changes in clinical outcomes and lung function.

n = 6	Pre treatment	Post treatment	Median change
	Median (range)	Median (range)	
R_5 (kPa.L.$^{-1}$.s)	0.55 (0.41 – 0.82)	0.63 (0.37 – 0.86)	0.08
R_{5In} (kPa.L.$^{-1}$.s)	0.44 (0.34 – 0.61)	0.49 (0.32 – 0.65)	0.05
R_{5Ex} (kPa.L.$^{-1}$.s)	0.6 (0.36 – 0.83)	0.69 (0.39 – 0.84)	0.09
R_{20} (kPa.L.$^{-1}$.s)	0.3 (0.2 – 0.44)	0.36 (0.2 – 0.66)	0.05
R_{20In} (kPa.L.$^{-1}$.s)	0.30 (0.21 – 0.35)	0.35 (0.20 – 0.49)	0.02
R_{20Ex} (kPa.L.$^{-1}$.s)	0.30 (0.20 – 0.44)	0.36 (0.19 – 0.44)	0.05
R_{5-20} (kPa.L.$^{-1}$.s)	0.25 (0.17 – 0.41)	0.24 (0.05 – 0.44)	0.01
X_5 (kPa.L.$^{-1}$.s)	-0.42 (-0.89 - -0.23)	-0.36 (-0.95 - -0.08)	0.06
X_{5In} (kPa.L.$^{-1}$.s)	-0.19 (-0.55 – 0.15)	-0.19 (-0.24 - -0.08)	0.00
X_{5Ex} (kPa.L.$^{-1}$.s)	-0.68 (-1.35 - -0.28)	-0.54 (-1.3 - -0.08)	0.08
X_{5In-Ex} (kPa.L.$^{-1}$.s)	0.49 (0.12 – 1.11	0.32 (0.01 – 1.18)	0.17
A_X(kPa.L.$^{-1}$)	3.52 (1.85 – 7.38)	2.99 (0.71 – 8.16)	0.28

Table 5.5 Change in resistance and reactance measures by impulse oscillometry

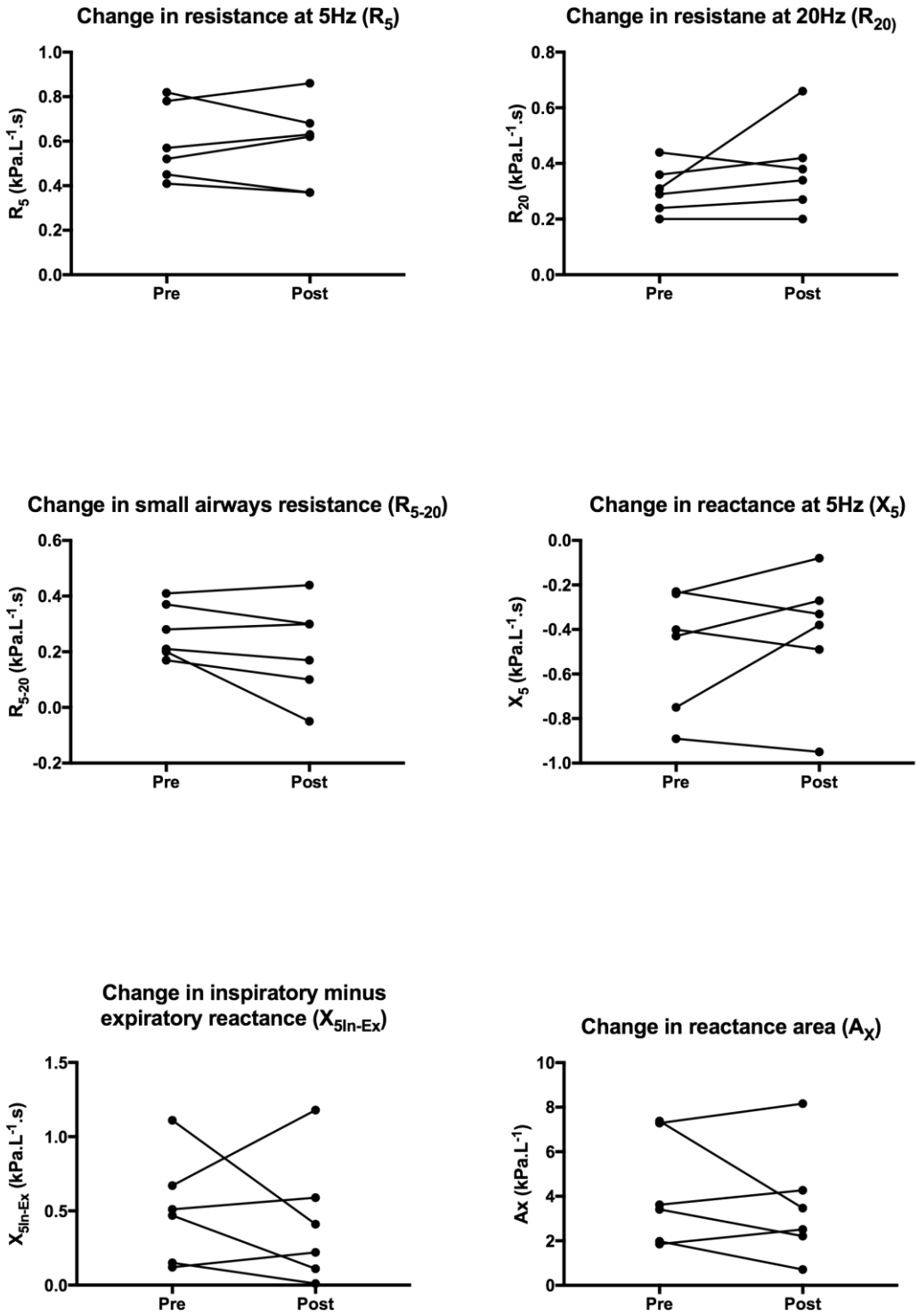


Figure 5.4 Changes in resistance and reactance measures by impulse oscillometry

5.4.6 Multiple breath nitrogen washout analysis

Analysis of MBNW data was performed after it had been collected on a separate computer. Therefore it was not possible to tell if satisfactory data had been collected at the time of testing. The process involved semi-automatically drawing a regression line through phase III of the washout curve for each individual breath. The software was unable to compute values for the normalised phase III slope for many breaths and therefore excluded them from analysis. This may have reflected the steepness of the regression line indicating the severity of ventilation inhomogeneity amongst our patients. As a result we could not obtain reliable data to compute S_{cond}, S_{acin}, LCI or FRC from the washout data. An example of a graph used to compute S_{cond} and S_{acin} from a patient in the study is shown (Figure 5.5). The wide variability in breath by breath normalised phase III slopes makes accurate estimation of parameters difficult. Furthermore, many patients did not fully washout (i.e. reach 2% exhaled nitrogen) before the 150L supply of oxygen was exhausted.

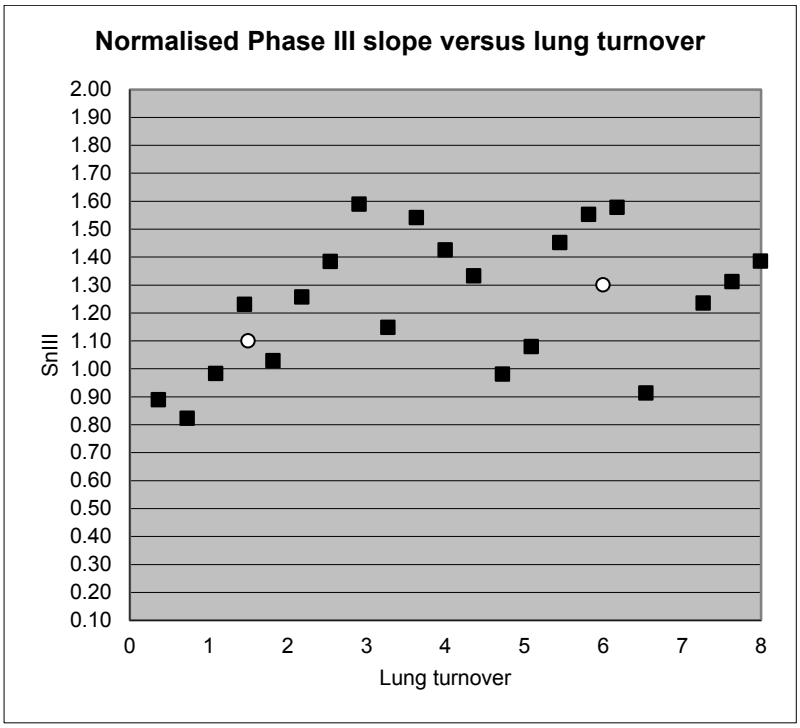


Figure 5.5 Normalised phase III slopes versus lung turnover for a severely obstructed patient

5.4.7 Baseline predictors of clinical and lung function improvement

In a univariate analysis of airways resistance variables to predict clinical and lung function outcomes, neither baseline inspiratory nor expiratory airways resistance predicted response in FEV_1, RV, SGRQ or 6 minute walk distance. We had insufficient data to determine if baseline lung elastic recoil was related to clinical or lung function response.

5.5 Discussion

Lung volume reduction coils resulted in no significant change in either inspiratory or expiratory airways resistance measured by plethysmography. There was insufficient data to make any conclusions regarding changes in elastic recoil or compliance. However, all four patients with follow up data experienced an increase in elastic recoil and the coefficient of retraction. There was insufficient data to conclude what, if any changes occur in oscillometric parameters, with a heterogeneous response amongst the six patients with follow up data. Nevertheless, we were able to demonstrate that it was feasible to measure elastic recoil, airways resistance and reactance with reproducible results in a group of severely obstructed and hyperinflated patients.

The major limitation of this study is the small numbers of patients at both baseline and follow up. Approval for the RENEW study in Chapter 3 was granted in November 2012, the same month it started recruiting. This protocol was written following the start of the study and not approved until September 2014, by which time 26 out of 30 patients had been recruited. It had been anticipated that the crossover patients would be studied leading to a total of 16 patients from an original target of 20. Eventually 10 patients were recruited for this study, however three of the deaths during the study occurred in the control group and a further patient was lost to follow up for detailed physiological testing. Whilst this limits the conclusions that may be drawn from this small

group, we have shown it is feasible to conduct detailed physiological testing amongst this group of patients.

The only coil study to examine airways resistance by plethysmography was in a group of 10 homogeneous patients. Klooster et al. reported a 25% reduction in airways resistance following coil treatment.(300) However, the degree of volume loss and improvement in expiratory flows in their patients was greater than that observed in ours. In the context of lung volume reduction surgery, most studies have shown that there is no significant change in airways resistance and that increased expiratory flows are the result of increased elastic recoil.(251,306) There are several reasons why airways resistance may not have changed following coil treatment. Firstly, the increase in elastic recoil may not have been sufficient to provide tension to airways undergoing dynamic collapse on expiration. Histological examination of emphysematous lung shows that elastic fibres tethering the parenchyma to airways are reduced in number and often abnormal.(111) This could have prevented increased recoil forces being transmitted to the airways. The small airways are obliterated early in the course of COPD, before the onset of significant emphysema.(113) Inflammatory changes within the small airways are prominent(115) and would not have been reduced by coils. Hogg et al. concluded that it is primarily inflammatory changes, mucus plugging and fibrosis of airways that contributes to narrowing and obliteration, rather than a reduction in elastic supports.(99) Therefore it is unlikely coils would have any effect on these changes.

Whilst we hypothesised that coils would reduce airway narrowing, histological examination of explanted lungs following coil treatment may suggest this is not the case. In a small number of specimens examined 1-4 years post treatment, there were chronic inflammatory and fibrotic changes in the segmental and subsegmental airways where coils were placed. Fibrosis extended into the alveolar septae.(221) Therefore it is quite possible that coils increased airways resistance in these areas through a combination of torsion and fibrotic changes. This may be the mechanism through which volume loss is achieved by coils and

therefore underlie the improvement following treatment rather than reduction in gas trapping through splinting airways open.

Nevertheless, we did not see an increase in airways resistance to support this. It is possible that there is a mixed response within the lung. Treated lobes may have had an increase in airways resistance but this could have been offset by a reduction in resistance in the surrounding untreated lung or ipsilateral lobe. This would be difficult to demonstrate with lung function tests since a single value is provided for the whole lung rather than individual lobes or segments. There may be two methods by which this could be solved. Firstly, examination of airways using CT scans to determine airway wall dimensions in treated and untreated segments could be performed. This technique has been shown to be associated with physiological measures of airways resistance, but CT is unable to resolve airways less than 2mm accurately. Despite this, CT measures of airway dimensions still correlate with physiological markers of small airways.(321) An alternative method would be to assess segmental airways resistance using the retrograde catheter technique during bronchoscopy. This has been shown to identify the contribution of both peripheral and central airways resistance.(101) Examination of treated segments or lobes against untreated segments and lobes may provide a more localised understanding of changes in airways resistance.

Finally, there are limitations to the use of airways resistance by plethysmography in the presence of severe obstruction. Since calculation of airways resistance is dependent on lung volume, any inaccuracies in lung volume will have an effect on calculated resistance. Plethysmography is known to overestimate FRC in the presence of severe obstruction, since pressure measured at the mouth does not always reflect alveolar pressure. This in turn underestimates airways resistance.(362) Examination of specific resistance loops in COPD is subjective. In health, specific resistance loops approximate a straight line yet in COPD they produce clubbed sigmoid shaped curves. Thus drawing a tangent to reflect the resistive flow is subjective. Because of a relatively high coefficient of variation in airways resistance, relatively large changes are required (30-40%) to be certain of a true effect. We chose to

measure effective specific airways resistance (sR_{eff}) rather than total specific airways resistance (sR_{tot}) since it has a lower coefficient of variation. However, it becomes less sensitive to changes in small airways disease as a result.(362) We also chose to separate inspiratory and expiratory specific resistance since this allows a more accurate tangent to be drawn on the resistance loops. Separating inspiratory and expiratory resistance is also of scientific interest since high inspiratory resistance has been shown to predict a poor response to LVRS.(251) In our cohort, we found no relationship between inspiratory or expiratory airways resistance and lung function or clinical outcomes. Ingentio et al. argued that high inspiratory airways resistance represents a greater degree of airway narrowing due to inflammation rather than emphysema. Therefore LVRS would have no effect in ameliorating airway inflammation and hence these patients would be less likely to benefit. Similarly it could be argued that those with high expiratory resistance relative to inspiratory resistance have a greater degree of dynamic airways collapse secondary to emphysema. However we found no change in R_{awEx} following coil treatment.

It is not possible to make any conclusions regarding changes in oscillometric parameters in such a small group of patients. We saw a mixed response amongst patients with regards most of the parameters we measured. Klooster et al. reported a small reduction in R_{5-20}, the proposed marker of small airways resistance following coil treatment in their cohort of 10 homogeneous patients.(300) Outside of this, there are no trials reporting the use of IOS in the setting of lung volume reduction. Our data showed that we were able to produce repeatable data at one visit, with similar reproducibility to published data. We did not test the coefficient of variability over time in a control group, however published data in healthy subjects and COPD shows that this is relatively stable over time.(363) The only parameters to correlate with FEV_1 was R_{5-20} and reactance area (A_X), a finding that has been reported in other cohorts in addition to R_5.(364) In the same cohort of patients, airways resistance and conductance measures by plethysmography correlated more strongly with FEV_1 than IOS measures, similar to our findings. The only IOS parameter to correlate with airways resistance was R_{20} in our study. This has been reported in a larger

cohort of patients with COPD, however stronger correlations were found with both R_5 and X_5.(365) Our baseline data represents a small homogeneous group of COPD patients and therefore it is likely that there was insufficient power to detect other significant relationships.

IOS may be a useful tool for assessing response to lung volume reduction techniques. It is a relatively easy technique for patients to perform, requiring just tidal breathing for periods of 30 – 60 seconds at a time. Because of its high temporal resolution, it is able to discriminate between inspiratory and expiratory impedance parameters. This has shown to be useful in differentiating asthma from COPD.(366) The R_{5-20} measure has been shown to be more reflective of small airways pathology and therefore IOS has advantages over FEV_1 and plethysmography, since both measures may be heavily affected by changes in large airway resistance.(351) This may help to identify where coils have their effect, if any, on airways resistance. Reactance measures have been shown to better distinguish between grades of severity in COPD than resistance measures.(367) There has been additional interest in reactance measures since the difference between inspiratory and expiratory reactance at 5Hz is sensitive in detecting expiratory flow limitation.(356) Since this is a key pathophysiological mechanism in COPD, and target for treatment, it would be interesting the study whether high levels of EFL predict the response in reactance to lung volume reduction. One limitation of using IOS in assessing response to lung volume reduction coils is that it is not clear what effect a metallic object would have on the pressure waves transmitted to the lungs. A future study of this could include a group of LVRS patients to see if there are any objective differences in response.

We demonstrated a consistent increase in recoil pressure and the coefficient of retraction in all four patients following coil treatment. Whilst no firm conclusions can be drawn regarding the effect of coils on elastic recoil, it seems likely that there is a signal worthy of further investigation. It was our original hypothesis that this would be the case and it is biologically plausible that coils increase elastic recoil. The tensile strength of coils may act to increase elastic

recoil and to a greater extent at higher lung volumes as they are distorted and try to recover their natural shape.

The degree of elastic recoil measured in our cohort of patients at baseline was similar to that reported by other authors investigating LVRS. Sciurba reported a baseline elastic recoil of 0.90 $kPa.L.^{-1}$, increasing to 1.18 $kPa.L.^{-1}$ following LVRS.(250) Gelb et al. reported similar changes from 1.01 $kPa.L.^{-1}$ to 1.4 $kPa.L.^{-1}$.(306) The degree of increase in elastic recoil from 0.92 to 1.71 $kPa.L.^{-1}$ was actually much greater in our cohort, yet the reduction in volume and improvement in expiratory flow was significantly less. It seems likely that the proportionately larger increase in recoil was as a result of the properties of the coils, but it is not clear why this did not translate into improved expiratory flow. Since the degree of volume loss in our patients reported in Chapter 3 was less, and there were only small reductions in the RV/TLC ratio, then according to Fessler's theory of LVRS we would expect less improvement in flow, as there has not been a proportionate increase in FVC.(256)

There were small increases in dynamic and static lung compliance, but the magnitude of these changes were small and the significance of this is not clear in a very small group of patients. In all of our patients, both the dynamic and static lung compliance measured was within the normal range. It must be born in mind that the normal values are taken from a single study of a small group of men and are broad.(289) But it may seem counterintuitive that in a disease characterised by hypercompliant lung, we detected normal compliance. In the setting of such severe hyperinflation as seen in our patients, the operating lung volumes around FRC are shifted up the pressure-volume curve to a point where they encroach upon the flatter part approaching TLC. Here the lung is less compliant which may explain the values we obtained. Any increase in compliance could be as a result from a reduction in FRC, which we observed in Chapter 3, resulting in the operating lung volume being shifted down to the steeper part of the curve. Analysis of the changes in the pressure-volume curve would be needed in a larger cohort of patients to detect if there is a real effect.

Multiple breath nitrogen washout was included in our protocol to allow assessment of ventilation heterogeneity. We hypothesised that with a reduction in airways resistance we might expect a decrease in ventilation heterogeneity in the conducting airways and overall lung clearance index. We were unable to extract any usable data from the multiple breath nitrogen washout analysis. A number of problems occurred both during testing and analysis. Testing required tidal breathing of 100% oxygen with a tidal volume of 1L. Patients found this difficult to keep to during the tests, often resulting in incomplete expiration and dynamic hyperinflation detected as drift of FRC during the test. Additionally the oxygen was dry and uncomfortable to breathe for prolonged periods. Because of the severity of obstruction, washout tests were prolonged, sometimes exceeding 15 minutes. In some cases, the Douglas bag containing oxygen was exhausted before washout was complete. The severity of obstruction also meant that long periods (up to 30 minutes) were required between tests to ensure nitrogen was "washed in". This limited the number of tests that could be performed for each patient.

During the analysis a large number of breaths had to be excluded from analysis because of inadequate or excessive volumes. Similarly the software used to measure the regression line through the phase III slope was unable to compute a number for some of the final breaths. This left us with inadequate data to present.

Most of the published data relating to MBNW has been performed in less severe COPD and has related to the detection of early disease.(293,358,359,368,369) It has proven a useful marker of small airway abnormalities, becoming abnormal before the onset of abnormal spirometry in smokers who develop COPD. The phase III slope in single breath nitrogen washout is also associated with histological abnormalities in early COPD.(106) Few studies have examined the role of MBNW in response to treatment. Two authors found that there were no change in MBNW parameters in response to tiotropium(359) or bronchodilators(370) despite improvements in other lung function measures. The latter study did include a small group of patients with severe COPD and

marked hyperinflation. This study used one of the first commercially available systems that allows fully automated and instantaneous analysis of results. Additionally it uses a piped oxygen supply such that it cannot be readily exhausted. Our custom built system used software that is over 20 years old and struggled to cope with the analysis of our patients. It may be that improved software in commercial versions will allow more accurate measurement of ventilation heterogeneity. However, in severely obstructed patients it will remain a difficult test to perform in terms of patient comfort and repeatability.

5.6 Conclusions

Airways resistance by plethysmography does not change significantly following treatment with lung volume reduction coils. Lung elastic recoil, compliance and impulse oscillometry are feasible to perform in a group of severely obstructed and hyperinflated patients and may provide additional information on the mechanisms of lung volume reduction coils. There may be a signal that treatment increases elastic recoil which warrants further investigation.

Chapter 6

General discussion and future directions

6.1 Summary of findings

This thesis describes the clinical, radiological and physiological changes following lung volume reduction coil treatment in a group of COPD patients with severe airflow obstruction and hyperinflation. The clinical study of lung volume reduction coils presented in Chapter 3 supports the evidence of medium term outcomes from a randomised controlled trial. Significant improvements in lung volumes and clinically meaningful improvements in quality of life were demonstrated 1 year following treatment. No significant change in the primary outcome of 6 minute walk distance was found, nor spirometric measures. Residual volume decreased by more than the minimum clinically important difference although failed to reach statistical significance. However there was only a small and non-significant reduction in the RV/TLC ratio as a measure of gas trapping. Improvement in the 6 minute walk distance was correlated significantly with improvements in FEV_1, FVC, RV and RV/TLC ratio. This suggests those patients who achieve the greatest degree of volume loss and reduction in gas trapping derive the most in terms of functional capacity. Baseline 6 minute walk distance was a weak predictor or clinical response.

The changes in both target lobe volume, untreated lobe volume and CT derived measures of gas trapping following coil treatment have been described for the first time in this thesis. Target lobe volume was reduced significantly at both inspiration and to a lesser degree at expiration. Measures of gas trapping did not change significantly following coil treatment and there were no significant changes in volume or gas trapping in untreated lobes. When considering the lungs as a whole, only volume at inspiration fell significantly. Changes in expiratory target lobe volume were strongly correlated with improvements in symptom scores and 6 minute walk distance in addition to FEV_1 and changes in gas trapping measured by RV/TLC ratio. Radiological markers of heterogeneity and gas trapping measured by the $MLD_{E/I}$ score were shown to predict target lobe volume loss. Additionally, $MLD_{E/I}$ score was weakly associated with symptomatic improvement.

Airways resistance by plethysmography did not change significantly following treatment. Baseline inspiratory resistance did not predict lung function or clinical outcomes following treatment. In a small group of patients, lung elastic recoil increased following treatment. Whilst we cannot draw a firm conclusion from this change, it may be one of the mechanisms by which coils work since this would be supported by the reduction in FRC. Using impulse oscillometry to assess airway function is a novel way to examine airway function and is feasible in this group of patients. It may add additional information regarding expiratory flow limitation that is not available from the other techniques we have examined.

6.2 Clinical findings arising from this work

Whilst lung volume reduction coil treatment is effective in improving symptoms and lung function, there is a risk of significant adverse events that need to be borne in mind when selecting patients for treatment. Whilst mortality in other published trials has been relatively low, four of our patients died during the 1 year follow up period, equating to 14.8%. This is well in excess of the 6-7% quoted in the larger trials of coils up to the same period, (218,220) and slightly higher than the 11% annual death rate in the NETT study.(122) Only one death was directly related to treatment with a further two being classed as 'probably' related and both being as a result of infective complications. Therefore there was no single factor amongst the deaths that might suggest they were as a result of systematic procedural issues at our institution. All of our deaths occurred in patients with relatively more severe lung function impairment. Two of these had both an FEV_1 <20% and homogeneous disease which were characteristics identified by the NETT trial as high risk criteria.(203) Furthermore, whilst the rate of COPD exacerbations was not significantly higher in the treatment group, there were numerically more than in the control group within the first month. The proportion of those requiring admission to hospital was also higher. Though this may in part have represented a bias of those patients known to have undergone a trial treatment and therefore extra clinical caution being taken. The excess mortality and increased rates of hospitalisation does however serve to exercise caution when selecting patients with severe lung function impairments

who may not be able to tolerate severe complications such as pneumonia or pulmonary haemorrhage. Analysis of meta-data from the previous clinical trials may help to accurately identify any high risk criteria for treatment with coils.

The work contained in this thesis has identified potential factors that may predict success following treatment that have not previously been identified. Meta-analysis from previous studies had identified only baseline RV as a predictor for improvement in lung function.(217) From the clinical data, baseline 6 minute walk distance was weakly associated with clinical response. This is interesting since it is analogous to the NETT trial where a low baseline exercise capacity was a predictor of both improvement in exercise capacity and mortality.(122) It may be that those patients with a low baseline 6 minute walk distance represent the most deconditioned patients due to the severity of their disease and therefore have the most to gain. Those patients with high baseline 6 minute walk distance may be unable to increase their exercise capacity significantly and may indeed decline if they experience significant exacerbations following treatment.

The current method of assessing the degree of emphysema suitable for treatment and identifying the target lobe has been visual assessment, both in clinical practice and previous trials. Analysis of baseline CT parameters has not previously been undertaken. In our study both heterogeneity based on quantitative emphysema score and the $MLD_{E/I}$ ratio were predictors of radiological volume loss. In the analysis of changes in clinical parameters, only $MLD_{E/I}$ score weakly predicted improvement in SGRQ score. Heterogeneity by visual scoring was found to be a predictor of better clinical outcomes in the published RENEW trial. It is too early to suggest that this be included as an inclusion criterion. There is still evidence that coils are effective in homogeneous patients(217,300), but perhaps to a lesser extent than heterogeneous patients.(218) These findings warrant validation in the larger RENEW cohort when the analysis of CT scans is published to see if the effect remains.

6.3 Physiological insights into lung volume reduction coil treatment

The original hypotheses of this thesis were that lung volume reduction coils would increase elastic recoil, reduce airway resistance and result in a reduction in gas trapping and improved expiratory flows. Due to small numbers of patients included in the detailed physiological study, we are unable to draw firm conclusions regarding this. It seems likely that elastic recoil improves following treated since we saw a large and uniform increase in elastic recoil in the four patients studied. There was no reduction in either expiratory or inspiratory resistance. This is similar to some authors' experience with LVRS. Ingenito et al. derived a mathematical model regarding physiological parameters in LVRS and determined that increased recoil was the major determinant of increased expiratory flow following LVRS, with little change in airways resistance.(251) These authors who have described improvement in airways resistance or conductance have often done so in the context of bullous lung disease.(245,247,371) This may represent a distinct situation from emphysema, particularly homogeneous emphysema, since the underlying lung is relatively normal and may be compressed by a space occupying bulla. Thus when it is removed, the remaining lung is able to expand and airway conductance is increased. In the setting of diffuse emphysema, the remaining lung is already hyperinflated with narrowed or obliterated airways due to inflammation, fibrosis and mucus plugging. Therefore, following treatment, the airways are fewer in number and less able to increase their dimensions, resulting in no overall change in airways resistance or conductance. It is speculative to suggest that the same process occurs following coil treatment since the two treatments differ considerably. We cannot be sure that there is not a mixed response within the lung, whereby treated areas have increased airways resistance due to torsion and folding of airways with a compensatory reduction in adjacent areas through the effect of elastic recoil. Direct intrabronchial measurement of airways resistance may be the only way to solve this.

If elastic recoil does improve significantly following coils and is the major determinant of improved expiratory flow in LVRS, then why did we not see significant improvements in FEV_1 following coil treatment? The Fessler-Permutt

model of LVRS may help explain this. In their model, increased expiratory flows are dependent on an increase in FVC, which is the main determinant of FEV_1. They argue that following LVRS, both FEV_1 and FVC improve but there is no change in FEV_1/FVC ratio. This suggests that it is not a change in the degree of obstruction (i.e. airways resistance), but it is simply the case of a relatively greater reduction in RV than TLC. Since FVC is the difference between the two, a greater reduction in RV than TLC results in a bigger FVC.(255) The lung function data presented in Chapter 3 shows a greater reduction in RV than TLC. However, the actual RV/TLC ratio only changes by a few percentage points and is not statistically significant. Consequently there are no significant improvements in expiratory flows. This may also explain why we found that heterogeneous patients or those with more gas trapping measured by CT derived greater benefit. Targeting the areas with the highest RV/TLC ratio will result in a proportionately large decrease in whole lung RV/TLC and consequently a more favourable response.

6.4 Future work

Whilst lung volume reduction coils appear effective in reducing lung volumes and improving symptoms there is still a heterogeneous response amongst patients. In our cohort of patient, responder rates in RV and FEV_1 were observed in 42.3% of the group, although 53.9% achieved a significant symptomatic response. This is lower than previously published response rates of 50-60% amongst these variables.(217) Therefore a significant proportion of patients undergoing treatment will be exposed to potential side effects without benefit. Therefore there is a need to more accurately identify the phenotype of patients that will best respond to treatment. Further physiological studies to assess the response to treatment and predict which variables are associated with a clinical response are required.

Together with a Dutch institution, the University Medical Centre of Groningen, we have developed a protocol for detailed physiological analysis of patients undergoing coil treatment. Identifying REsponders and exploring mechanisms of ACTION of the endobronchial coil treatment for emphysema (REACTION study)

has now received ethical approval and is currently recruiting at our site and in the Netherlands. Its primary outcome is change in physical activity at 3 months following treatment. This endpoint was chosen as it is important to patients and represents a 'real world' outcome that is often overlooked in studies of lung volume reduction. Detailed physiological characterisation of patients will give greater insight into potential mechanisms. Following work included in this thesis, we have included lung elastic recoil, compliance and impulse oscillometry within the protocol. Additionally we will ask patients to undertake cardiopulmonary exercise tests to assess the effect on oxygen uptake and exercise capacity. This will also allow assessment of changes in dynamic hyperinflation through measurement of inspiratory capacity during exercise. Dynamic hyperinflation is strongly linked to effort intolerance and symptoms.(133) If coils increase elastic recoil then they may reduce this by improving expiratory flows during exercise. The effect on respiratory muscle strength will also be examined. Finally we plan to perform 3 dimensional SPECT ventilation-perfusion scans to assess changes in lobar ventilation and perfusion.

A separate study is also underway to investigate the changes in the microbiome associated with coil implants. Following two cases of Stenotrophomonas infection identified in patients this thesis, we sought to identify whether coils are associated with a change in the lung microbiome. This is particularly relevant for a treatment involving implants where biofilm producing organisms may colonise the coils. In the two patients who developed the Stenotrophomonas infection, one patient died and another had a rapid decline in symptoms and lung function. Prior to coil treatment, bronchoalveolar lavage is being performed on the target lobe and a control lobe at baseline. Following the first treatment, a bronchoalveolar lavage will be repeated in the previously treated lobe and the new target lobe. Finally, these will be repeated in the treated lobes and control lobe. Analysis of samples will be undertaken with routine culture and polymerase chain reaction for16s RNA to detect bacterial colonisation. This may identify patients with pre-exisiting colonisation that increases their chance of subsequent infection. It could potentially be used to target antibiotic treatment

following coil treatment to prevent an accelerated decline in the event of a serious infection.

There are still further questions that require consideration for future studies:

- Is whole lung treatment with coils more effective than lobar treatment? This may be particularly relevant in patients with homogeneous disease who currently appear to have less favourable responses to treatment. However it is likely to require a large number of patients to determine a statistically significant difference which may make it less feasible.
- What is the optimal number of coils to place within the lung? The current aim for 10 coils per lung has been based on clinical experience. A dedicated trial with multiple groups would be unfeasibly large. In any case, the optimal number of coils may well be that it varies amongst individuals. Performing treatment under general anaesthesia allows assessment of lung compliance through a ventilator and therefore may be able to identify a point where a plateau in compliance is reached.
- What is the cost-effectiveness of treatment in the setting of the UK's National Health Service? The REVOLENS trial reported on cost-effectiveness which was exceptionally high ($782,598 per quality adjusted life year).(220) However, coil treatment is associated with front-loaded costs and may improve if long term follow up shows them to be effective. A study in the setting of the UK's health service would be more relevant to our practice.
- How effective are coils in comparison to LVRS or endobronchial valves? Whilst many patients may be limited in their choice of lung volume reduction for reasons of surgical risk or presence of collateral ventilation, there are many who will have several options. There are currently no trials examining the effectiveness of coils against other treatments. A randomised controlled trial of endobronchial valves versus LVRS is currently underway in London and Leicester.

6.5 Lung volume reduction coils as a therapy for emphysema

There is now evidence from three randomised controlled trials that treatment with lung volume reduction coils results in significant improvements in lung function and health related quality of life.(218–220) The evidence of improvement in 6 minute walk distance is mixed, with the 3 month data from the RESET trial showing a large and statistically significant improvement but both the REVOLENS and RENEW trials showing no clinically meaningful improvement at 6 and 12 months respectively.(218,220) Subgroup analysis of the RENEW cohort has shown that heterogeneous patients with an RV >225% predicted achieve response rates of greater than 50% in lung function, symptoms and walking distance. Those with homogeneous emphysema and an RV <225% predicted have the poorest outcomes with response rates of just over 20% for improvements in FEV_1 and 6 minute walk distance, although response rates for symptom improvement are still in excess of 50%.(218) Mortality related to coil treatment appears acceptable, with lower 1 year mortality rates than published rates for LVRS.(122)

Identification of subgroups of responders is similar in many ways to the progress made in both LVRS and endobronchial valve treatment. During the 1990's there was enthusiastic uptake of LVRS in the United States but with variable clinical results. The publication of the NETT trial in 2003 was perceived negatively amongst many physicians and surgeons since the overall findings showed very small response rates in terms of exercise capacity and symptoms. Furthermore, the identification of a high risk subgroup at increased risk of death was published prior to the main study findings, further damaging the perception of LVRS as a risky treatment with limited benefit.(203) This perception has remained over a decade later, with many physicians still underestimating potential benefit and overestimating potential risk.(208) Consequently the number of operations performed in the UK has remained relatively low, although may be increasing in recent years.(207) This is despite excellent evidence that in appropriately selected patients, LVRS improves quality of life, exercise capacity and lung function. It is one of the few therapies in COPD to have a proven mortality benefit, persisting at over 4 years post treatment.(204)

The place for lung volume reduction coils as a treatment for emphysema is not yet clear. There is certainly good evidence that they improve clinical outcomes in emphysema, but the group with the most successful outcomes (heterogeneous patients with a high RV) are likely to have other treatment options including endobronchial valves or LVRS. Furthermore, patients with homogeneous emphysema were not thought to derive benefits from either LVRS or endobronchial valves. This group of patients had been proposed as the main candidates for coil treatment with few other treatment options. This is now being challenged with increasing evidence that homogeneity per se does not preclude a successful outcome of endobronchial valves, but the presence of collateral ventilation or disrupted interlobar fissures is more important.(234,237) This is also the group with the least favourable response to coil treatment. Direct comparisons of coils against both endobronchial valves and LVRS will be required to determine their relative efficacy. More information is needed on long term safety and cost-effectiveness before they can be recommended for routine clinical use. It seems likely that there will be a group of patients for whom coils represent the best treatment option. This may well be those patients with collateral ventilation and contra-indications or personal preference against surgery.

Endobronchial valves for emphysema now have response rates in terms of clinical outcomes exceeding 70% in some studies(237), significantly better than lung volume reduction coils, although without direct comparison. It should be remembered that the initial findings of the pivotal VENT trial of valves reported only modest and clinically insignificant improvements in clinical outcomes.(229) Detailed work examining the clinical, physiological and radiological predictors of success has led to significant improvements in outcomes, albeit at the expense of the potential number of patients who will achieve benefit. Lung volume reduction coils are several years behind endobronchial valves in terms of development. It is highly likely that the treatment will continue to be refined as a more detailed understanding of their physiological effect achieved. This should help improve outcomes for patients. In the meantime further treatment with

coils should be in the context of clinical trials in experienced centres with access to a COPD multidisciplinary team in order to maximise patients benefit and safety.

Publications arising from this thesis

Sciurba FC, Criner GJ, Strange C, Shah PL, Michaud G, Connolly TA, Deslée G, Tillis WP, Delage A, Marquette C, Krishna G, Kalhan R, Ferguson JS, Jantz M, Maldonado F, McKenna R, Majid A, Rai N, Gay S, Dransfield MT, Angel L, Maxfield R, Herth FJF, Wahidi MM, Mehta A, Slebos D, for the RENEW Study Research Group. Effect of Endobronchial Coils vs Usual Care on Exercise Tolerance in Patients With Severe EmphysemaThe RENEW Randomized Clinical Trial. *JAMA.* 2016;315(20):2178-2189. doi:10.1001/jama.2016.6261

The work contained within this thesis was under embargo since it constituted part of a wider pivotal IDE trial. Further publications are expected regarding CT changes. Therefore individual analysis of findings in each chapter have not been independently published. The detailed physiological studies are ongoing and will be published as an Investigator led study.

Details of my contributions and of others

The study protocol for the RENEW trial was written by the study sponsor (PneumRx, USA) in conjunction with the primary supervisor and other key investigators, based upon the results of a previous trial at our institution.

The ethical approval for the RENEW study was obtained by Dr Pallav Shah and Dr Zaid Zoumot. I obtained ethical approval for the Crossover study and small airways study.

Dr Zaid Zoumot assisted me with the recruitment of the first 4 patients to the study. Cielito Caneja assisted with booking treatments at Chelsea and Westminster and administering the device accountability logs.

Due to blinding requirments, all lung function tests (spirometry, lung volumes and transfer factor) were performed by three respiratory physiologists: Jo Ming, Chris Nelson and Peter Robinson. All walk tests were performed by a number of Biomedical Research Unit nurses including Iris Nelson, Dolly John and Katharine Carter.

All procedures were performed by Dr Pallav Shah as the primary bronchoscopist placing the coils. I assisted with all the procedures, helping with bronchoscope positioning and coil deployment. During the course of the study I was trained to place coils independently.

I designed the protocols for the CT assessment (Chapter 4) and small airways assessment (Chapter 5), in conjunction with Dr Pallav Shah and Dr Omar Usmani. I recruited all the patients and performed all follow up visits. I assisted Dr Pallav Shah with all the treatments. I analysed all CT scans with the exception of two performed by Dr Justin Garner for training. I also performed all lung compliance tests with the assistance of Simon Ward, Jo Ming and Peter Robinson to teach me the techniques. Dr Martyn Biddiscombe taught me the nitrogen washout and IOS techniques which were performed on all patients by myself.

For all studies, I personally collated and analysed all data and performed the statistical analysis presented in this thesis.

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