Novel Techniques for Lung Volume Reduction and its Assessment in Emphysema

Dr. Zaid Zoumot

The National Heart and Lung Institute at Imperial College School of Medicine, London

The NIHR Respiratory Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College, London

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For Faris,

(And his brother en route…)

'Live as if you were to die tomorrow. Learn as if you were to live forever.'

Mahatma Gandhi

Declaration of Originality

The data presented in this thesis is the result of my original work. The studies reported in this thesis were performed between 2010 and 2013, and data was collated and analysed by myself in all studies. 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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Abstract

Many patients with emphysema remain breathless despite optimal medical therapy. Non-pharmacological approaches to reduce the volume of hyperinflated lungs include lung volume reduction surgery (LVRS) which is effective in selected patients with upper lobe predominant emphysema and low exercise capacity. Bronchoscopic techniques to reduce lung volume are also being developed.

Studies of two bronchoscopic techniques to achieve lung volume reduction (LVR) are presented in this thesis; LVR coils (LVRCs) and endobronchial autologous blood instillation. In a trial of LVRCs we demonstrate for the first time in a randomised controlled setting, that treatment with LVRCs results in statistically and clinically meaningful improvements in quality of life, lung function and exercise capacity compared with controls, and that benefits are maintained up to 12 months following treatment compared to baseline. In two pilot studies, we used autologous blood instilled endobronchially aiming to achieve lung volume reduction by inducing parenchymal scarring and fibrosis. Instilling 180-240 mls of autologous blood withdrawn from patients during the bronchoscopic procedure directly into a giant bullae resulted in significant reduction in bulla size over subsequent months in three of five patients, with associated improvements in lung function, exercise capacity and quality of life. However a randomised controlled trial of instilling 60 mls of autologous blood into three segments of one lobe in patients with heterogeneous emphysema was ineffective.

In addition, I investigated the use of a novel 3-dimentional measurement system, optoelectronic plethysmography (OEP), to track abdominal and chest wall movements during respiration. This showed that successful lung volume reduction approaches were associated with significant improvements in lower rib cage paradoxical inspiratory movements after lung volume reduction. Improvements in chest wall asynchrony were larger the worse the asynchrony was at baseline, and those with larger improvements in asynchrony derived greater benefits in lung function and other clinical outcomes following LVR.

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Abbreviations

3D	3-dimentional
6MWD	6 minute walking distance
AB	Abdominal compartment
ABG	Arterial blood gas
AE	Adverse events
ATS	American Thoracic Society
BIABI	Bronchoscopic intrabullous autologous blood instillation
BMI	Body mass index
BODE index	BMI, Obstruction, Dyspnoea, Exercise capacity index
BTS	British Thoracic Society
BTVA	Bronchoscopic thermal vapour ablation
CAT	COPD Assessment Test
CE	*Conformité Européenne*
CO	Carbon monoxide
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
EASE	Exhale Airway Stents in Emphysema
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
EELV	End expiratory lung volume
ERS	European Respiratory Society
ERV	Expiratory reserve volume
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FRC	Functional residual capacity
FVC	Forced vital capacity
GOLD	Global initiative for chronic Obstructive Lung Disease
HRCT	High resolution computed tomography
IBV	Intrabronchial valve
IC	Inspiratory capacity
ITGV	Intrathoracic gas volume
kPa	Kilopascals
LABA	Long acting Beta2 agonist

LEPR	Leptin receptor genes
LTOT	Long term oxygen therapy
LV	Left Ventricle
LVR	Lung volume reduction
LVRC	Lung volume reduction coil
LVRS	Lung volume reduction surgery
MCID	Minimal clinically important difference
MMP1	Matrix metalloproteinase 1
MRC	Medical Research Council
mMRC	Modified MRC score
mls	Millilitres
NETT	National Emphysema Treatment Trial
NHBLI	National Heart, Lung, and Blood Institute
NICE	National Institute for Health and Clinical Excellence
NHANES	National Health and Nutrition Examination Survey
NOTT	Nocturnal Oxygen Treatment Trial
0_2	Oxygen
OEP	Optoelectronic plethysmography
PAH	Pulmonary arterial hypertension
PaO_2	Partial pressure of oxygen in arterial blood
PEEP	Positive end expiratory pressure
$PEEP_i$	Intrinsic PEEP
PFT	Pulmonary function testing
prn	Pro re nata – 'as needed'
QoL	Quality of life
RA	Relative area
RC,a	Abdominal rib cage
RC,p	Pulmonary rib cage
RV	Residual volume
SGRQ	St. George's Respiratory Questionnaire
TLC	Total lung capacity
TLCO	Total lung carbon monoxide uptake (transfer factor)
$TLCO_c$	Corrected TLCO
TNF	Tumour necrosis factor
TORCH	Towards a Revolution in COPD Health
TV	Tidal Volume

VEmax	Maximum minute ventilation
VENT	Valves for Emphysema Palliation Trial
V/Q	Ventilation-perfusion
Vab	Abdominal compartment volume
VC	Vital Capacity
Vcw	Total thoraco-abdominal chest wall volume
Vrc,a	Abdominal rib cage volume
Vrc,p	Pulmonary rib cage volume
VE	Minute ventilation
VEmax	Maximum minute ventilation
VO_2max	Maximum oxygen utilisation/uptake
V_T	Tidal volume
WHO	World Health Organisation
ϴRC	Phase shift angle between the pulmonary and abdominal rib cages
ϴDIA	Phase shift angle between the abdominal rib cage and abdominal compartment
ϴRC,p	Phase shift angle between treated and untreated sides of the pulmonary rib cage
ϴRC,a	Phase shift angle between treated and untreated sides of the abdominal rib cage
ϴAb	Phase shift angle between treated and untreated sides of the abdominal compartment

Chapter 1
Introduction

1.1 AIMS

The aim of this work is to assess the safety and efficacy of novel minimally invasive approaches to lung volume reduction in patients with severe emphysema, and to assess the role optoelectronic plethysmography can play in measuring responses to both surgical and bronchoscopic lung volume reduction with view to identifying those most likely to respond to a specific lung volume reduction technique thus improving patient selection and matching.

1.2 HYPOTHESES

- Patients with advanced emphysema could achieve sustained improvements in quality of life, lung function parameters and exercise tolerance 3 months following treatment with lung volume reduction coils when compared to best medical care, and benefits are maintained up to 12 months following treatment.
- Patients with advanced heterogeneous emphysema could derive benefits in lung function, exercise tolerance, and quality of life following treatment with endobronchial autologous blood lung volume reduction, as compared with sham treated controls.
- Bronchoscopic intrabullous autologous blood instillation into giant bullae could lead to significant reduction in bulla size with clinical benefit.
- Optoelectronic plethysmography (OEP) could demonstrate improvements in gas trapping during forced expiratory manoeuvres, demonstrate changes in compartmental lung volumes, and assess changes in thoracoabdominal chest wall asynchrony before and after lung volume reduction.

1.3 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is characterised by damage to small airways and alveolar walls, with an associated reduction of lung elastic recoil leading to airflow limitation. Premature airway closure during expiration leads to gas trapping with increased residual volume, and is accompanied by dynamic hyperinflation where increased operating volumes are necessary to maintain expiratory flow and minute ventilation. COPD is a common condition that

affects millions of adults worldwide with a prevalence and burden projected to increase in the coming decades due to ongoing exposure to tobacco smoke, particularly in the developing world, along with population demographic changes and increasing life expectancy.(1) It is now the third leading cause of death globally (2) with a prevalence above 5% in both Europe (3) and the United States.(4) Patients with COPD suffer from physical impairment, incapacity, reduced quality of life, and premature death. The high prevalence and chronicity of COPD begets high healthcare resource utilisation.

1.3.1 DEFINITION

COPD is an umbrella term incorporating features of chronic and minimally reversible airways obstruction associated with bronchitis, emphysema and chronic asthma. Chronic bronchitis and emphysema were initially described in the early 19th century by Charles Badham and René Laennec,(5) respectively. In 1961, clearer definitions of chronic bronchitis and emphysema were proposed at the CIBA Symposium,(6) and COPD definitions continued to distinguish these different phenotypes of COPD for several decades.

Chronic bronchitis is defined as a chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough have been excluded.(7) Airflow limitation in chronic bronchitis is secondary to narrowing of airway calibre and increase in airway resistance. Emphysema is defined as abnormal and permanent enlargement of the airspaces that are distal to the terminal bronchioles, accompanied by destruction of the airspace walls and without obvious fibrosis.(8) Airflow limitation in emphysema is due to small airway collapse resulting from the loss of elastic recoil and decrease in airway tethering. In practice, most patients with COPD suffer from a combination of emphysema and chronic bronchitis in varying degrees, and it is a rarity for a patient to suffer uniquely from one or the other of these two disease processes.

In 1998, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program was initiated by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO). The aim was to produce recommendations for the management of COPD based on the best scientific information available. The “Global Strategy for Diagnosis, Management and Prevention of COPD” report was first published in 2001 (9) and has been updated regularly since, with free global access via the GOLD website. These reports are a major worldwide reference for COPD care and have served to unify the varying definitions and

diagnostic criteria of COPD proposed by the American Thoracic Society (ATS), European Respiratory Society (ERS), and the British Thoracic Society (BTS) over the past 2 decades. GOLD defines COPD as *"a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is 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."* Of note is that this definition does not include any distinction between chronic bronchitis and emphysema, and it recognises the presence of non-pulmonary components of COPD. There is also a new emphasis on the "preventable and treatable" nature of this condition. This is an attempt at combating the prevalent nihilistic view taken by some healthcare professionals (and patients) that COPD is relentlessly progressive and irreversible, and that the available treatments are ineffective.

Although bronchodilators can, to a limited extent, improve airflow obstruction in patients with emphysema, most patients with emphysema–predominant COPD respond less well to medical therapy. Alternative treatments in the form of surgical and non-surgical lung volume reduction have therefore been developed and targeted at emphysematous lung disease.

1.3.2 DIAGNOSIS AND STAGING

Key symptoms which should raise suspicion of COPD include chronic cough, chronic sputum production, and dyspnoea, particularly if combined with a history of inhalational exposure to tobacco or biomass smoke or occupational dusts and chemicals. Patients with these features should undergo pulmonary function testing (PFTs) which are used to diagnose and determine the severity of COPD. A post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio (FEV1/FVC) of <0.7 indicates airway obstruction. If this is irreversible and there is no alternative explanation for the patient's symptoms and airflow obstruction (e.g., bronchiectasis, vocal cord paralysis, tracheal stenosis), then the diagnosis of COPD applies.

1.3.2.1 Assessment of severity

GOLD recommends assessment of four aspects of disease: Symptoms; degree of airflow obstruction; risk of exacerbations; and comorbidities.

The modified Medical Research Council (mMRC) dyspnoea scale or the COPD Assessment Test (CAT) (10) allow an assessment of the level of disability caused by dyspnoea, and the CAT also offers a broader range of information on the impact of COPD on the patient's life and well-being. Spirometry is used to assess the level if airflow obstruction, which generally correlates with symptoms, exercise tolerance, physical impairment, frequency of exacerbations and hospital admissions. However COPD is an extremely heterogeneous disease and there is huge variation in how patients are affected at different degrees of FEV_1 impairment. Nevertheless in the absence of a validated severity assessment tool that encompasses the multidimensional nature of COPD, GOLD, the ATS/ERS joint guidelines, and the National institute of Health and Clinical excellence (NICE) guidelines all recommend using FEV_1 as a percentage of predicted as a marker of the severity of airflow obstruction. There is acknowledgment in all guidelines that this may not reflect the impact of the disease in any individual particularly the risks posed by exacerbation rates, and thus the "Combined COPD assessment" was introduced by GOLD in 2011 (discussed below). In terms of the severity of airway obstruction, NICE changed the FEV_1 cut off points in 2004 to match those in the updated GOLD and the ATS/ERS guidelines, although the terminology was slightly different: an FEV_1 of 50–80% predicted constituted mild airflow obstruction, 30–49% moderate airflow obstruction, and 30% severe airflow obstruction. The GOLD and ATS/ERS guidelines describe symptomatic patients with FEV_1 >80% predicted (but FEV_1/FVC ratio <0.7) as suffering from mild (stage I) airflow obstruction, with moderate (stage II), severe (stage III) and very severe (stage IV) as one moves down the cut-off points. The 2004 NICE guidelines effectively ruled out COPD as a diagnosis in patients with an FEV_1/FVC ratio of <0.7 but FEV1 > 80% predicted. However, guidelines were adjusted in the 2010 update to mirror GOLD severity staging thereby diagnosing patients with FEV_1/FVC ratio of <0.7 and an FEV1 of >80% with mild COPD, provided they are symptomatic (Table 1.1).

Table 1.1: Grading of severity of airflow obstruction (11)

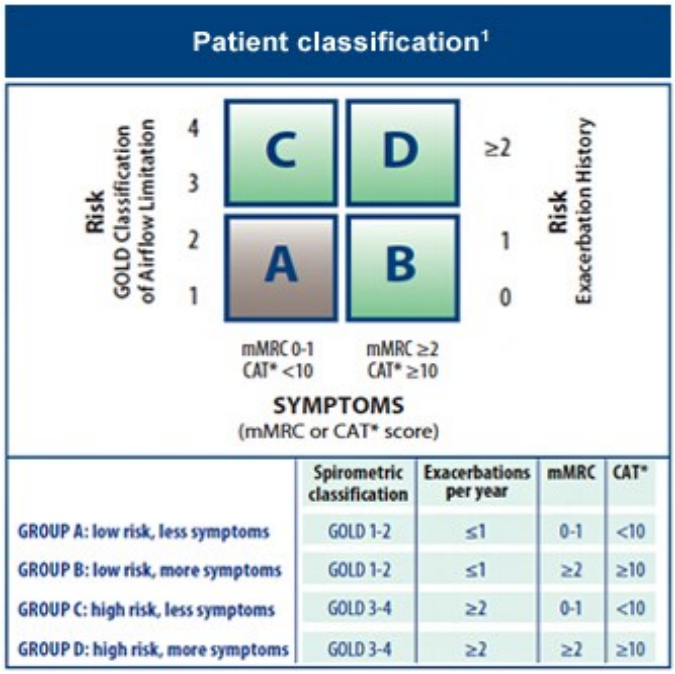
		NICE clinical guideline (2004)	ATS/ERS (2004) (7)	GOLD (2010)	NICE clinical guideline (2010) (12)
Post-bronchodilator FEV_1/FVC	**FEV_1 % predicted**	**Severity of airflow obstruction**			
< 0.7	≥ 80%		Mild	Stage 1 – Mild	Stage 1 – Mild*
< 0.7	50–79%	Mild	Moderate	Stage 2 – Moderate	Stage 2 – Moderate
< 0.7	30–49%	Moderate	Severe	Stage 3 – Severe	Stage 3 – Severe
< 0.7	< 30%	Severe	Very severe	Stage 4 – Very severe**	Stage 4 – Very severe**

*Symptoms should be present to diagnose COPD in people with mild airflow obstruction

**Or FEV_1 < 50% with respiratory failure.

Exacerbations in COPD accelerate the decline in lung function and have a significant negative impact on quality life and overall health status. High exacerbation rates thus correlate with poor outcomes generally and also with mortality. Therefore an assessment of exacerbation rates was felt to be an important component of assessing a patient's overall COPD disease severity. The combined COPD assessment (Figure 1.1) introduced by GOLD in 2011 aimed to address this with the first part of the assessment relating to symptoms status (mMRC ≥2 or CAT ≥10, vs. mMRC<2 or CAT<10). The degree of airflow obstruction (GOLD stage I-II vs. GOLD stage III-IV) then stratifies patients into high or low risk groups, with the annual exacerbation rate (≥2 or <2) further used to assess risk (the higher risk determines risk level in case of disagreement between airflow obstruction and exacerbation rate risk. Therefore patients can be classified into one of four groups (A,B,C or D) depending on symptom burden and risk of progression/mortality.

Figure 1.1: Combined COPD Assessment. GOLD 2011**.**



	Spirometric classification	Exacerbations per year	mMRC	CAT*
GROUP A: low risk, less symptoms	GOLD 1-2	≤1	0-1	<10
GROUP B: low risk, more symptoms	GOLD 1-2	≤1	≥2	≥10
GROUP C: high risk, less symptoms	GOLD 3-4	≥2	0-1	<10
GROUP D: high risk, more symptoms	GOLD 3-4	≥2	≥2	≥10

Other pulmonary function tests are also helpful in establishing a diagnosis of COPD and assessing severity. Reduction in inspiratory capacity (IC) and vital capacity (VC), accompanied by increased total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV) are indicative of hyperinflation and gas trapping. Impairment in the diffusion capacity of the lungs as measured by carbon monoxide diffusing capacity (TLCO) correlates with increasing severity of emphysema.

There is a growing recognition that COPD is a multisystem disorder with extrapulmonary manifestations which include nutritional abnormalities and skeletal muscle dysfunction. Frequently occurring comorbidities which should be considered when assessing a patient with COPD include cardiovascular disease, metabolic syndrome, osteoporosis, lung cancer and depression/anxiety.

1.3.3 EPIDEMIOLOGY

The Burden of Obstructive Lung Disease (BOLD) study showed that the pooled prevalence of COPD was 11.8% in men and 8.5% in women over 40 years old, with variations in geographical distribution and sex which correlate with differences in the prevalence of smoking.(13) Similar prevalence rates were found in a study of five Latin American countries (The Proyecto Latino Americano de Investigacion en Obstruccion Pulmonar (PLATINO) study).(14) The World Health Organisation (WHO) estimates that 80 million people have moderate to severe COPD, and that more than 3 million people died of COPD in 2005 - corresponding to 5% of all deaths globally(15). COPD is the only major cause of death whose incidence is on the increase and is now the third leading cause of death worldwide (exceeded only by ischaemic heart disease and cerebrovascular disease).(2, 16)

In the UK, the population prevalence of clinically significant COPD was estimated to be 1.7% for men and 1.4% for women – approximately 900,000 people.(17) However, it is estimated that a further 2 million people have undiagnosed COPD. (18) In 2005, 24160 people died as a result of COPD in the UK,(19) more than bowel cancer or prostate cancer. In fact, more women died of COPD than from breast cancer in 2005. Between 2007 and 2009, COPD accounted for 4.8% of all deaths in England.(2)

COPD imposes a heavy burden on the National Health Service (NHS). There are approximately 1.5 million GP consultations per year attributable to COPD and there are 24 million lost working days per year in the UK. COPD exacerbations account for 10% of emergency admissions to UK hospitals (>100,000 admissions), and over 1 million bed-days. Various studies have estimated the direct costs to be between 486 million to 982 million pounds per year with additional indirect costs totalling 1.5 billion pounds.(20, 21)

Both worldwide and in the UK, the gap between the prevalence of COPD in men and women is narrowing almost to equality, in par with the increase in smoking rates amongst women. In the UK, the rate of COPD has been increasing nearly three times faster amongst women than men.(22) There is evidence to suggest that women are more susceptible to smoking related COPD than men.(23)

1.3.4 RISK FACTORS

1.3.4.1 Cigarette smoking

The primary cause of COPD is exposure to tobacco smoke, overwhelmingly the most important risk factor accounting for as much as 90% of COPD risk.(24, 25) Tobacco smokers have a higher prevalence of respiratory symptoms and airflow obstruction, and an increased annual decline in FEV_1 compared to non-smokers (>60mls per year compared to the normal physiological decline of 20-30 mls per year). In fact, lung function testing abnormalities and lung structural changes probably predate the presence of clinical signs and symptoms of airway obstruction in cigarette smokers.(26) The risk of developing COPD and the severity of disease directly correlate with the length and degree of exposure to tobacco smoke, and the total pack-years smoked predicts mortality in COPD. Smoking cessation at any age reduces the risk of developing smoking related diseases, with smokers who give up by their early 30's avoiding most of these risks, and their life expectancy being not significantly different from those who have never smoked.(24)

It has been estimated that around 15% of smokers will develop COPD, with genetic and environmental risk factors influencing an individual's susceptibility to the damaging effects of tobacco smoke.(26) Cannabis smoke may have a synergistic effect in combination with tobacco smoke in terms of risk of COPD, in particular causing lung destruction and bullous emphysema.(27) However data is inconsistent on the association of cannabis smoke and worsening lung function. One study followed up a cohort of adult cannabis smokers for 8 years with no age related accelerated decline in FEV_1 seen.(28)

1.3.4.2 Environmental factors

COPD does occur in individuals who have never smoked. Traffic-related and industry-related air pollution may play a role in the aetiology of COPD, but this is likely a small role particularly compared to the effects of tobacco smoke.

An under-appreciated risk factor for COPD is exposure to occupational organic and inorganic dusts and chemical agents and fumes. The NHANESIII survey estimated that occupational agent exposure causes 19.2% of COPD overall, and 31.1% in never smokers.(29)

In developing countries, the use of wood, animal dung, crop residues and coal for indoor cooking and heating leads to high levels of indoor air pollution and is probably a major contributor to the worldwide prevalence of COPD, especially amongst young women. Almost 3 billion people use biomass fuels and coal as their main source of energy for cooking and heating worldwide, and this accounts for the high prevalence of COPD amongst non-smoking women in parts of the developing world.(30)

1.3.4.3 Airway Hyper-responsiveness

Numerous observational studies have suggested that heightened airway responsiveness to aero-allergens and other triggers is an independent risk factor for the development of COPD.(31, 32) It is stipulated that chronic bronchial hyper-reactivity and associated airway inflammation eventually result in airway remodelling leading to a more fixed obstruction similar to that seen in smoking-related chronic bronchitis. A particularly more accelerated decline in FEV_1 has been reported in patients who smoke tobacco and suffer from airways hyper-responsiveness, but the exact causative relationship between these two factors remains unclear.(33, 34)

Other observational studies have demonstrated an increased risk of COPD in atopic individuals. In a longitudinal study of over 1000 men without asthma, atopy predicted a 9.5 ml/year excess annual rate of decline of FEV_1.(35)

1.3.4.4 Molecular factors

Molecular mechanisms for COPD have been assessed using several different methods, including studies of gene polymorphisms, antioxidant enzyme function, metalloproteinase dysregulation, and abnormalities that cause excess elastase. These will be discussed in turn below and in the pathophysiology section of this chapter.

1.3.4.5 Genetic Factors

α-1 antitrypsin deficiency is the commonest known genetic risk factor for emphysema, causing approximately 1% of all cases of COPD. α -1 antitrypsin is a protease inhibitor synthesised in the liver, its main purpose being to neutralise elastases released by neutrophils in areas of inflammation and in response to tobacco smoke. Unopposed elastase activity, occurring in lungs when circulating α -1 antitrypsin levels are extremely low leads to destruction of structural elements in the lung interstitium and ultimately to panacinar emphysema. The average age at

which patients with α -1 antitrypsin deficiency develop emphysema is 40 years for smokers and 53 years for non-smokers. Over 70 alleles of the α -1 antitrypsin gene, which is found on chromosome 14, have been identified. Persons who are homozygous for the normal allele (PiMM) have normal serum levels of α -1 antitrypsin, whereas heterozygous individuals with one normal allele and one abnormal allele (commonest PiMS and PiMZ) will express a normal phenotype albeit with reduced serum levels of α -1 antitrypsin. The PiZ genotype accounts for over 95% of cases of severe α -1 antitrypsin deficiency emphysema.

Other gene polymorphisms which have been implicated in emphysema include polymorphisms of the tumour necrosis factor α (TNF-α), microsomal epoxide hydrolase, transforming growth factor β, and Leptin receptor (LEPR) genes. TNF-α gene polymorphisms may influence host defences by increasing long-term tissue inflammation leading to chronic bronchitis.(36) However, no benefit was seen with Infliximab therapy (anti-TNF-α antibody) in patients with moderate and severe COPD in a randomised trial.(37) A reduction of microsomal epoxide hydrolase, which reduces smoking related epoxide intermediaries, probably predisposes individuals to oxidative injury and subsequent COPD. (38) Gene polymorphisms of transforming growth factor β1, which are peptides involved in cellular growth, differentiation, and activation, have been associated with development of COPD in smokers.(39) Lung function decline in tobacco smokers has been associated with polymorphisms of the LEPR gene.(40)

A high prevalence of COPD is found in patients with inherited connective tissue disorders such as Marfan's syndrome, Ehler-Danlos syndrome, and cutis laxa.

1.3.4.6 Infections

History of severe as well as recurrent respiratory viral and bacterial chest infections in childhood have been associated with an increased risk of developing COPD in adulthood (41, 42) as has a history of airway bacterial colonisation.(43) It has also been suggested that latent respiratory viral infections may also play a role in the pathogenesis of COPD.(44) A history of pulmonary tuberculosis is associated with airflow obstruction due to a combination of scarring following airway infection, and lung parenchymal destruction with loss of airway tethering. A Chinese study of 8784 subjects demonstrated that prior pulmonary tuberculosis (based on radiographic evidence) was associated with an increased risk of airflow obstruction independent of other risk factors such as smoking.(45) Males were 4.1 times and females 1.7 times more likely to suffer from airways obstruction after adjusting for confounders in a sub-analysis of the PLATINO cohort (5751 subjects over 40 years of age).(46) Although an

association has been made between tuberculosis and COPD, the evidence is insufficient to infer a causative relationship.

1.3.4.7 Bronchopulmonary dysplasia

Bronchopulmonary dysplasia, also known as neonatal chronic lung disease, is a result of premature births, and is defined by dependence on supplemental oxygen for more than 28 days post-partum. Bronchopulmonary dysplasia leads to airflow obstruction and hyperinflation on pulmonary function testing, and radiographic emphysema on computed tomography (CT) in those who survive to adulthood.(47)

1.3.5 PATTERNS OF EMPHYSEMA

Emphysema is characterised by damage and destruction of the alveoli and airspaces distal to the terminal bronchioles thereby diminishing the alveolar surface area available for gas exchange. The loss of elasticity and hence elastic recoil due to the damage to the alveolar walls, as well as narrowing of the airways due to the loss of structural elements, both contribute to airflow limitation. The terminal bronchioles can also collapse on expiration due to the latter. These factors lead to gas trapping and hyperinflation. In severe cases, alveolar walls can become destroyed creating bullae and collateral ventilation.

Emphysema has three morphologic patterns: Centrilobular, panacinar, and paraseptal. In centrilobular emphysema, the destruction is limited to the respiratory bronchioles and the central portions of the acini, sparing the distal alveoli. Panacinar emphysema involves the alveolus distal to the terminal bronchiole in its entirety. Paraseptal emphysema involves distal airway structures, alveolar ducts, and sacs, and can lead to the formation of bullae.

Centrilobular emphysema is the morphology most commonly seen in cigarette smokers and is usually worst in the upper lobes. Panacinar emphysema is the morphology which is most often seen in patients with homozygous α-1 antitrypsin deficiency, and predominantly affects the lower lobes. Paraseptal emphysema is usually localised around the septae and pleurae, and can lead to pneumothoraces particularly in patients with apical disease. It may not be associated with airflow obstruction.

1.3.6 PATHOPHYSIOLOGY OF EMPHYSEMA

Most cases of COPD are the result of exposure to noxious stimuli, predominantly cigarette smoke. There is likely a significant genetic and/or epigenetic susceptibility as only 15-20% of smokers develop COPD. Chronic inflammation is thought to cause tissue destruction and impair tissue healing. It also disrupts immune defences increasing susceptibility to recurrent infections which themselves cause further damage to the airways, parenchyma and pulmonary vasculature. The noxious agents lead to an increase in the number of activated polymorphonuclear leukocytes and macrophages which release chemotactic factors and cytokines recruiting more cells and amplifying inflammation. Released proteases can directly cause lung damage, and growth factors lead to structural change. Proteases are usually cleared by antiproteases before destruction of elastin and structural elements ensues, but in patients with COPD this does not occur satisfactorily. The imbalance between proteases and antiproteases is worsened in predisposed individuals by a heightened inflammatory response, a deficiency of antiproteases, and direct impairment of antiproteases activity by tobacco smoke and free radicals.

Human leukocyte elastase is thought to be the main protagonist of lung destruction in emphysema. Others include proteinase-3, macrophage-derived matrix metalloproteinases (MMPs) and cysteine proteinases. The release of oxidants by phagocytes secondary to the free radicals in tobacco smoke can lead to increased oxidative stress and cell death. There is increasing evidence in the literature to suggest that dysregulation of apoptosis and ineffective removal of apoptotic cells by macrophages plays a major function in airway inflammation in emphysema.(48) Roles for CD8+ T lymphocytes, accelerated aging and autoimmune mechanisms have also been suggested in the pathogenesis of COPD.

The progressive damage to the alveolar walls accompanied by damage to the pulmonary capillary bed in emphysema results in a decrease of the surface area available for gas exchange and hence the ability to oxygenate blood. Hyperventilation and a lower cardiac output are the result leading to a significant mismatch in ventilation and perfusion. Excessive mucus production, mucus gland hypertrophy, and airway wall inflammation result in airflow obstruction. The loss of structural elements and pulmonary vasculature results in a reduction in the elastic recoil of the lung. To compensate, COPD patients breathe at higher lung volumes and this improves airway opening and lung recoil, at the expense of much higher work of breathing and inspiratory effort.

Airflow limitation in COPD is greatest during expiration as positive intrathoracic pressures tend to compress or collapse airways, which have lost some of their structural support mechanisms. Usually during exercise, increasing expiratory flow by breathing faster and more forcefully to increase pleural and alveolar pressures, allows complete exhalation of the increased tidal volume prior to the next breath. In COPD (particularly emphysematous lungs), however, increasing the force of breathing in expiration may not achieve this goal as this leads to increased small airway collapse and worsening airflow obstruction. As a result, exhalation may not be completed before the onset of the following breath. This is can also occur at rest but is commonest during exercise, when the respiratory rate is faster. The end expiratory lung volume (EELV) (already increased at rest due to reduced elastic recoil of the damaged lungs) gradually increases further as small volumes of air from the previous breath remain within the lungs before the following breath is initiated. This results in an increase in the volume of air in the lungs, or dynamic hyperinflation.(49)

In patients with emphysema, dynamic hyperinflation probably plays a more important role in the development of exertional dyspnoea than airways obstruction.(50) It is likely that the majority of dyspnoea relief following treatment of airway bronchospasm in an exercising COPD patient is a result of the correction of hyperinflation rather than the relief of bronchospasm *per se*.(51) In fact, the improvement in exercise capacity brought about by several treatment modalities, including bronchodilators, oxygen therapy, lung volume reduction surgery (LVRS), and manoeuvres learned in pulmonary rehabilitation, is more likely due to minimising dynamic hyperinflation rather than reducing airflow obstruction. Additionally, hyperinflation has been shown to predict survival better than FEV_1.(52)

1.3.7 RISK REDUCTION AND MEDICAL MANAGMENT OF COPD

A practical multi-dimensional approach to managing patients with COPD is advocated by NICE,(53) and this relies on addressing different factors in tandem to one another, rather than the previous “escalator” approach for the addition of therapy. These factors are smoking, breathlessness and exercise limitation, frequent exacerbations, respiratory failure, cor pulmonale, abnormal BMI, chronic productive cough and anxiety and depression. Similarly, updated GOLD guidance adopts the approach of targeting the most relevant components of symptom limitation and risk reduction depending on combined COPD assessment grouping.

1.3.7.1 Smoking cessation

Smoking cessation is the single most important intervention for all stages of COPD severity. Smokers who give up by their early 30's will avoid most of the risks of smoking-related diseases and their life expectancy will not be significantly different from those who have never smoked.(24) For all levels of COPD severity, giving up arrests the accelerated decline in FEV_1. The potential benefits are not in dispute. Encouragement of smoking cessation and referral to smoking cessation support programs as well as trials of therapy with bupropion, nicotine replacement therapy or Varenicline should be first line management for all COPD patients who continue to smoke.(12)

1.3.7.2 Breathlessness and exercise limitation

Bronchodilators are the cornerstone of managing the symptoms of breathlessness and exercise limitation, and the NICE guidelines (12) suggest initially a trial of pro re nata (prn) short-acting Beta2 agonists, followed by the additions of a short acting anticholinergic. If symptoms persist adding a long acting Beta2 agonist (LABA) or a long acting anticholinergic (LAMA) is suggested. Adding an inhaled corticosteroid in a combination inhaler for a trial period of 4 weeks is then suggested in patients with moderate to severe disease, with a plan to discontinue if there is no benefit, however this advice is controversial in the absence of exacerbations. New ultra-long acting bronchodilators are becoming available, combining a LABA and a LAMA in single daily dose inhalers with novel improved delivery mechanisms, and appear to offer a promising and superior alternative to currently available combinations. Regular theophylline is the final medical step in managing these symptoms.

Pulmonary rehabilitation is a process which encompasses physical training, disease education, psychological support, social support and nutritional advice. The UK guidelines recommend that all patients considered functionally disabled with an MRC score III or above should be offered pulmonary rehabilitation. However, evidence points to significant benefit irrespective of baseline lung function, age or exercise capacity.(54) Significant improvements in exercise tolerance, dyspnoea and fatigue are seen. Although these programmes do not significantly alter lung function they do have important effects on quality of life which far exceed benefits derived from the most effective bronchodilators. Furthermore, benefits to the cardiovascular system of regular exercise are well recognised. Pulmonary rehabilitation should be considered an essential component of COPD management, and therapy cannot be considered optimised

without regular participation in pulmonary rehabilitation courses crucially with maintenance of regular exercises and high activity levels following course completion.

1.3.7.3 Frequent Exacerbations

Annual influenza vaccination as well as pneumococcal vaccination for all patients with COPD is advised. Providing patients with "back-up" courses of antibiotics and prednisolone to be started early as symptoms of infective exacerbations begin to manifest is recommended. Adding long-acting inhaled corticosteroids (in a combination inhaler) for patients suffering two or more exacerbations in a one year period is recommended. A recent randomised controlled trial of 1577 patients with emphysema demonstrated a significant reduction in exacerbation frequency and an increase in the median time to the next exacerbation in those cohort treated with prophylactic azithromycin compared to placebo.(55) However this option needs to be considered with care in routine clinical practice as there is a significant risk of hearing impairment, arrhythmias (particularly those with long QT), and liver dysfunction.

1.3.7.4 Respiratory Failure

The beneficial effects of long term oxygen (O_2) therapy (LTOT) on survival in subjects with COPD and severe resting hypoxemia were demonstrated in two randomised controlled clinical trials: the Nocturnal Oxygen Treatment Trial (56) and the MRC study.(57) The NOTT demonstrated a survival benefit of continuous nocturnal oxygen therapy, and the MRC trial showed a survival benefit in those receiving O_2 for at least 15 hours per day over those receiving no O_2. This did not, however, appear until after 500 days. The benefit was seen in those with an arterial blood partial pressure of oxygen (PaO_2) on room air of <7.3kPa, or <8kPa in the presence of pulmonary arterial hypertension (PAH), right ventricular impairment, or polycythaemia. These trials demonstrated a relationship between survival and the average daily duration of O_2 use. Median survival in those using oxygen for 18 hours a day was approximately twice as long as those receiving no oxygen. Non-invasive ventilation is now standard of care in the treatment of both acute and symptomatic chronic type 2 respiratory failure in patients with COPD.

1.3.7.5 Abnormal Body Mass Index (BMI)

There is strong evidence that low BMI and reduced muscle mass directly correlates with deterioration of severity of COPD and quality of life parameters. Dietetic input, nutritional supplements and physiotherapy are useful. On the other end of the spectrum, high BMI can be detrimental and cause significant worsening of symptoms due to increasing workload of mobility and other day-to-day activities. A downward cycle of worsening symptoms and reduced activity levels can ensue. Weight reduction measures are advocated in those with high BMI.

1.3.7.6 Chronic productive cough

Mucolytics should be prescribed and continued in patients with chronic productive cough who show a positive response to these drugs.(12) The use of short 7 day courses of mucolytics for treatment of acute infective exacerbations is now licensed in the UK.

1.3.8 NON-MEDICAL MANAGEMENT OF COPD

COPD is progressive and irreversible and inevitably leads to an “end stage” which is minimally responsive to medical therapy. Surgical interventions have a risk of both morbidity and mortality, and are therefore directed only to patients who remain symptomatic despite optimal medical treatment. Attempts to surgically correct lung hyperexpansion and poor perfusion of emphysematous lung parenchyma included several procedures which have been unsuccessful in the past, such as costochondrectomy, phrenic crush, pneumoperitoneum, pleural abrasion, lung denervation, and thoracoplasty. Three surgical procedures have, however, demonstrated significant success and these are bullectomy, reduction pneumoplasty or lung volume reduction surgery (LVRS), and lung transplantation. Minimally invasive bronchoscopic techniques to achieve lung volume reduction (LVR) have also shown some recent success. The non-medical approaches to managing COPD will be discussed below.

1.3.8.1 Bullectomy

In severe cases of emphysema, areas of alveolar destruction coalesce creating bullae which can become so large that they occupy more than 30% of the hemithorax (termed "giant bullae"). These may compress adjacent lung tissue reducing perfusion and ventilation to healthier tissue. Surgical removal of giant bullae has been a standard treatment in selected patients for many years (58) and this has been achieved via standard lateral thoracotomy, bilateral resections via midline sternotomy, and video-assisted thoracoscopy (VATS).(59) Patients who are symptomatic and have an FEV_1 of less than 50% predicted have a better outcome after bullectomy.(58) Benefits result from expansion of compressed lung tissue and improved ventilatory mechanics, with short term benefits in hypoxemia, hypercapnia, gas trapping, and dyspnea reported in the published literature (predominantly uncontrolled retrospective studies).(59) A recent series of 43 patients treated with giant bullectomy reported significant improvements in spirometry, residual volume (RV) and exercise capacity as measured by the 6-minute walk distance (6MWD) with benefits persisting for at least 3 years.(60) Postoperative bronchopleural air leak is the main potential complication. Randomised controlled trials of giant bullectomy have not been performed. An alternative approach for frail patients with large single bullae is the Monaldi procedure and its modified form (the Brompton technique). (61)

1.3.8.2 Transplantation

Lung transplantation is a well-established therapeutic modality for patients with end-stage lung disease. It involves complex and meticulous care of the recipient and the donor pre-transplant, careful organ retrieval and preservation, a complicated transplant operation, and intensive postoperative care and follow-up. COPD has now become the most common diagnosis leading to lung transplantation, accounting for 37% of transplants worldwide.(62) There is much evidence showing that lung transplantation improves quality of life and functional indices in patients with COPD, however survival data is contradicting.(63) Nevertheless, transplantation is a palliative procedure and most clinicians feel that the improvements in quality of life justify the procedure in patients with end-stage COPD. This makes the decision to proceed to transplantation more difficult in COPD than in patient with other end-stage respiratory diseases where there is also a clear survival benefit. International guidelines have therefore been produced to aid clinicians and patients regarding the optimal timing of referral for this treatment option.(64) Previous LVRS or bullectomy are not contraindications for subsequent lung transplantation.

Referral to transplant centres should be considered in patients with diffuse disease when the BMI, Obstruction, Dyspnoea, Exercise capacity (BODE) index is ≥5, post-bronchodilator FEV_1 is <25 % of predicted, resting PaO2 <60 mmHg, there is evidence of chronic hypercapnoeic type II respiratory failure, there is an accelerated decline on FEV_1, or an increase in the frequency and severity of infective exacerbations. Lung transplantation should be offered to patients who have any of the following: FEV_1 <20% predicted; hypercapnoea; associated pulmonary hypertension; or a BODE score of ≥7. Potential lung transplant recipients must be ambulatory, have adequate nutritional status, and no co-morbidities that would hinder recovery in the peri- and post-operative periods or prohibit the necessary post-operative immunosuppressive and anti-infective therapies. An adequate social support network and high motivation and compliance levels are essential to ensure the intensive medical and rehabilitation treatments and follow-up appointments post-transplantation are strictly adhered to.

In recent years, more than 50% of COPD patients undergoing lung transplantation have had bilateral lung transplants, as recent data have shown divergence of the survival curves beyond one year following surgery.(62) Cumulative 5 year survival for COPD patients undergoing transplantation is 50%, with an 88% 1 year survival rate.

Despite offering the hope of improved survival and quality of life to many patients with COPD, 5 year survival remains disappointing with obliterative bronchiolitis, infection, renal insufficiency, and malignancy all contributing to late attrition. Nevertheless this survival rate remains higher than that of COPD patients managed with optimal medical therapy who have BODE scores of ≥7 or those with FEV_1 and transfer factor <20% of predicted, and therefore should always be considered and patient referred for transplant assessment if within the referral criteria detailed above. Unfortunately low lung donation rates, adverse donor demographics, preferential double lung use, and the relatively old age of most patients with COPD are likely to keep this option limited to a very small subgroup of the COPD population, but this should not deter from appropriately timed referrals to a transplant centre or deny patients the opportunity of an effective and proven therapy.

1.3.8.3 Lung Volume Reduction

Lung volume reduction improves lung function by improving the elastic recoil of the lung, which in turn increases the outward pull on the bronchioles. This reduces terminal bronchiole collapse and improves expiratory airflow thereby reducing gas trapping. The decrease in the functional residual capacity improves diaphragmatic and intercostal muscle function and reduces the work of breathing. In carefully selected patients, lung volume reduction surgery (LVRS) has

been clearly shown to be effective at improving outcomes.(65, 66) It is, however, associated with significant morbidity, a 5% mortality rate (66) and a modest cost-benefit return.(67) Unfortunately, only a small minority of patients with emphysema are fit enough to undergo LVRS, and therefore a variety of alternative techniques are being developed to achieve lung volume reduction. These techniques include the insertion of unidirectional endobronchial valves, insertion of lung volume reduction coils to internally compress hyperinflated emphysematous areas of lung, biologic endobronchial sclerosing agents, autologous intrabronchial blood instillation aimed at inducing lobar atelectasis and collapse, and percutaneous transpleural airway bypass ('spiracles'). The different lung volume reduction methods will be discussed in turn. Section 1.3.8.3.2 contains various modified excerpts from a review written by the author,(68) with the publisher's permission.

1.3.8.3.1 Lung Volume Reduction Surgery

Brantigan described unilateral thoracotomy and resection of the most diseased-appearing portion of emphysematous lungs coupled with lung denervation in 33 patients 1957.(69) However surgical mortality rates of over 18% meant the procedure never gained widespread acceptance. Cooper *et al*. revived LVRS in the early 1990s by refining the procedure with the use of staple sutures and pericardial strips to buttress the suture line, thereby reducing the incidence of post-operative air leaks and simplifying the procedure.(70) Volume reduction is achieved by making a series of wedge excisions in areas where the emphysematous changes are most marked. The aim is to resect 20-35 % of each lung, removing as much diseased lung as possible while preserving the greatest amount of functioning lung. The group demonstrated that LVRS improved symptoms, lung function and gas trapping with an acceptable operative risk (4.8% perioperative mortality) (70) and several small randomised controlled trials followed which showed superiority of LVRS over best medical care.(65, 66, 71)

Physiological effects of LVRS

Lung volume reduction surgery (LVRS) involves resection of the worst affected area of emphysematous lung. Lung volumes improve because bullous areas, which expand at the expense of healthier lung, have been resected. The precise mechanisms by which this translates to clinical improvement are not known with certainty, but is likely to be due to a combination of factors:

- The remaining relatively healthier lung has more preserved parenchymal structural integrity and therefore greater elastic recoil. This allows the lung to empty more

effectively.(72) Using the coefficient of retraction, an indicator of elastic recoil of the lung calculated as the ratio of maximal static recoil pressure (measured using oesophageal balloons) to total lung capacity, Sciurba *et al.* demonstrated a significantly greater increase in exercise capacity in 16 patients who demonstrated increases in elastic recoil following LVRS compared to 4 patients who did not have increased elastic recoil.(73)

- LVRS improves matching between the size of the lungs and the capacity of the thorax which contains them. This increases vital capacity (VC) and hence the FEV_1.(72)
- Removal of severely damaged and less ventilated portions of lung reduces dead space.
- Improvement in the outward circumferential pull on small airways and terminal bronchioles improves expiratory airflow by maintaining airway patency, or a "re-tensioning" effect.
- A return of the diaphragm to the usual curved shape and length due to reduction of the functional residual capacity (FRC) leads to improvement in the mechanical function of the diaphragm and intercostal muscles.(74, 75) There is contradicting evidence on whether diaphragm strength actually increases (76) or not.(77) Furthermore, increases in the abdominal contribution to tidal volume and improved synchrony of the diaphragm with other inspiratory muscles have been reported.(78)
- Reduction in dynamic hyperinflation is arguably the most significant factor contributing to improvements in exertional dyspnoea.(79)
- The benefits in lung ventilation mechanics with tidal breathing occurring at lower lung volumes might reduce respiratory muscle and diaphragm fatigue, and reduces the work of breathing.
- Decreased central respiratory drive might improve the patients' sensation of dyspnoea.
- The reduction of intrathoracic pressure improves left ventricular (LV) end-diastolic dimension and LV filling post LVRS, resulting in improved LV function.(80)

The best evidence around the indications for LVRS comes from the National Emphysema Treatment Trial (NETT), which randomised more than 1200 patients to LVRS or usual care.(66) An early result was the identification of a high risk group (FEV_1 <20% predicted with either a homogeneous pattern of disease or a TLCO of <20% predicted) which had a high mortality. Subsequent enrolment from this patient group was stopped. Analysis was based on *a priori* categories of exercise capacity and pattern of emphysema. At 24-months a survival benefit was apparent in surgical patients with a low exercise capacity and upper-lobe predominant emphysema. Excluding the high risk group, procedural (90 day) mortality was 5.5% in the NETT trial, with serious morbidity after LVRS observed in 59% of patients (persistent air leak (33%), respiratory failure (22%), pneumonia (18%), cardiac arrhythmias (24%)).(66)

A subsequent report from the NETT data demonstrated that the beneficial effects LVRS were sustained, with increased survival in the LVRS group at a median 4.3 years of follow-up (0.11 deaths per person/year in the LVRS group versus 0.13 in the medical group (RR=0.85; p<0.02). (67) Patients with upper lobe predominant emphysema and low baseline exercise capacity had the largest benefit with >70% still alive at 5 years compared with <50% of those treated medically (RR=0.57, p<0.01). This group also had improvements in exercise capacity (p<0.001) and quality of life (p<0.001). The cost of LVRS was $140,000 per quality adjusted life year (QALY) gained at 5 years, and projected to be $54,000 per QALY gained at 10 years.(67)

National and international guidelines now recommend that LVRS be considered in patients with upper lobe predominant disease and low exercise capacity.(8, 12) Yet LVRS remains vastly underutilised with only 90 LVRS operations performed in the United Kingdom in 2010 according to the Society of Cardiothoracic Surgery register, and 119 performed in 2008 under Medicare in the USA. This underutilization of LVRS is likely multifactorial and due to a combination of lack of expertise, a complicated and expensive certification system for Medicare in the USA, lack of knowledge by patients and physicians alike, and a misinterpretation of the NETT trial as showing no mortality benefit and high morbidity. Nevertheless, safer, faster and less invasive approaches to achieve lung volume reduction are needed. The approaches that have been studied are discussed in more detail below.

Table 1.2: Bronchoscopic Lung Volume Reduction Techniques. (Author's own work reproduced with permission from Clinics in Chest Medicine (68))

Approach	Technique	Mechanism of action	Pattern of disease most likely to benefit	Likely influence of collateral ventilation?	Possible limitations and complications	Available evidence	Active trials
Devices occluding airways	Endobronchial valves	One way valves allow air and secretions to escape the target segments of lung whilst preventing air from re-entering causing atelectasis.	Heterogeneous disease without collateral ventilation	Collateral ventilation prevents atelectasis and limits success	Effect limited in the presence of collateral ventilation. Risk of pneumothorax likely in the range of ~25% in the responder population.	Zephyr®: Single arm open label n=98 (81); RCTs n= 321 (82), 171 (83) Spiration®: Observational n=91 (84)	Pivotal trial recruiting Pivotal trial soon
Agents inducing an inflammatory response	Polymeric lung volume reduction	Air within the hydrogel foam sitting in the alveoli is absorbed leading to collapse of the alveoli with selective inflammation, shrinkage and scarring.	Heterogeneous disease	No effect	High risk of post procedural severe pneumonia and COPD exacerbation.	Phase 2 dose-ranging study n=25 (85), unblinded n=20 (86)	Pivotal trial recruiting
	Bronchoscopic thermal vapour ablation ('steam')	The steam causes acute tissue injury which is followed by scarring and fibrosis, and shrinkage of the targeted lung parenchyma.	Heterogeneous disease	No effect.	High risk of post-procedural pneumonia and COPD exacerbation.	Single arm unblinded n=44 (87)	Pivotal trial recruiting
	Bronchoscopic intrabullous blood instillation	Instilled blood induces an inflammatory response leading to scarring and contraction of giant bulla.	Giant bulla	No effect.	Blood in the airways post procedure may increase the risk of infection.	Single arm unblinded n=5 (88)	Safety and feasibility trial recruiting
Airway bypass techniques	Exhale® airway bypass drug eluting stents	Airway stents between emphysematous lung parenchyma and large airways offer a low resistance path for trapped air to escape.	Homogenous disease	Enhances effect – pathological connections between lobes allow trapped gas to escape form a wider area of emphysematous lung.	Maintaining stent patency is a major difficulty	Single arm unblinded n=36 (89) RCT n=315 (90)	Nil
	Percutaneous transpleural airway bypass ('spiracles')	The pneumonostomy tube provides an alternate route for gas trapped in the emphysematous lung to escape.	Homogenous disease	Enhances effect – pathological connections between lobes allow trapped gas to escape form a wider area of emphysematous lung.	A permanent pneumostoma and the need to change the pneumonostomy tube on a daily basis may deter patients. Spontaneous closure of pneumostoma.	Single arm unblinded n=6 (91)	Nil
Devices leading to mechanical compression	RePneu Coil® lung volume reduction	The coils internally compress treated segments of lung, and may increase lung recoil reducing gas trapping and preventing dynamic hyperinflation.	Heterogeneous and homogeneous, RV>200% predicted, no bullous destruction	No effect.	Many coils are no longer visible in the airways once released making the procedure irreversible. May preclude future LVRS.	Single arm unblinded n=11,16 (92, 93); RCT n=45 (94)	Pivotal trial recruiting

RCT = Randomised controlled trial; LVRS = lung volume reduction surgery

1.3.8.3.2 Bronchoscopic lung volume reduction

Table 1.2 summarises the bronchoscopic approaches, the most recent supporting evidence, and their ongoing study. It is worth noting that these approaches are generally in the early phases of development and the various trials have not adopted as strict a measure of optimisation of medical care (pharmacological non-pharmacological including pulmonary rehabilitation) prior to patient enrolment or in control arms as did the NETT trial and other randomised controlled trials of LVRS.

Endobronchial valves

This approach, the most widely studied non-surgical approach to lung volume reduction, involves placing unidirectional valves into segmental airways allowing gas to escape but not re-enter the worst affected lobe of the lung, with the aim of causing lobar collapse and atelectasis. The mechanisms of benefit resemble those of LVRS; improved ventilation and perfusion of previously crowded healthier lung parenchyma, re-tensioning of the small airways, and a return to the FRC reducing the work of breathing with improved respiratory mechanics. A valve is needed to allow air to leave the target segment as simple blockers have the risk of acting as valves in the wrong direction leading to acute localised hyperinflation.(95) Valves are deployed bronchoscopically and this can be done using moderate sedation or general anaesthesia. Early clinical experience showed that patients with significant lung volume reduction following valve placement had improvements in exercise capacity (96) and reduced dynamic hyperinflation.(97)

For this approach to be successful, complete occlusion and isolation of the target lobe is required. Damage to the interlobar fissures allows air to bypass the valves and enter via the adjacent lobe preventing atelectasis. Similarly, imprecise placement of the valves or unusual airway anatomy can prevent formation of a tight seal between the valve base and the airways. Improvement in lung function may occur in the absence of radiological volume reduction, perhaps by the diversion of airflow to healthier lung, but benefits are greatest where atelectasis occurs. Follow up of patients from an early Brompton case series of 19 patients treated using a first generation airway valve suggests that successful lung volume reduction with radiological atelectasis is associated with a survival advantage; 0/5 deaths at six years in patients who developed atelectasis compared to 8/14 deaths where atelectasis had not occurred ($p<0.02$).(98)

Lobar volume reduction is associated with a risk of pneumothorax which may be due to air leak (typically secondary to damage to the overstretched untreated lobe which expands fill the thoracic cavity), or occur *ex vacuo* as the target area of lung collapses. These may resolve spontaneously or require intercostal drainage.

There are two *Conformité Européenne* (CE) marked valves commercially available in Europe; the Zephyr® valve and the Spiration® (Intrabronchial Valve (IBV)). Neither is approved by the USA Food and Drug administration. The Zephyr valve, manufactured initially by Emphasys Medical (Redwood City, CA) and now by Pulmonx Inc. (Palo Alto, Calif., USA), is made of a nitinol frame structure with a silicone cover and a central duckbill-type valve (Figure 1.2). In the Endobronchial Valves for Emphysema PalliatioN Trial (VENT) trial (82) 321 patients with heterogeneous emphysema were randomly assigned to receive either endobronchial valves or standard medical care. At six months there was a statistically significant but not clinically meaningful benefit in FEV_1 and the 6MWD. This occurred at the expense of a small increase in COPD exacerbations (7.9%) and minor haemoptysis (5.2%). There were nine pneumothoraces (3 unresolved after 7 days), occurring in a significant proportion of the small number of patients who developed atelectasis (9 of 37, or 24%). However the officially quoted and misleading pneumothorax rate from this study is 4.5% for all treated patients. Higher emphysema heterogeneity was associated with a better response, and in patients where lobar exclusion was accomplished (intact interlobar fissures and correct valve placement confirmed on CT), there were much larger improvements in lung function (ΔFEV_1 +23%, ΔRV -57%). As mentioned above, this was the case in only 37 of the 214 patients in the endobronchial valve treatment arm. Prospective trials are needed to establish if this subgroup of responders (heterogeneous disease without collateral ventilation) can be accurately identified prospectively, and randomised controlled trials are being conducted at present.

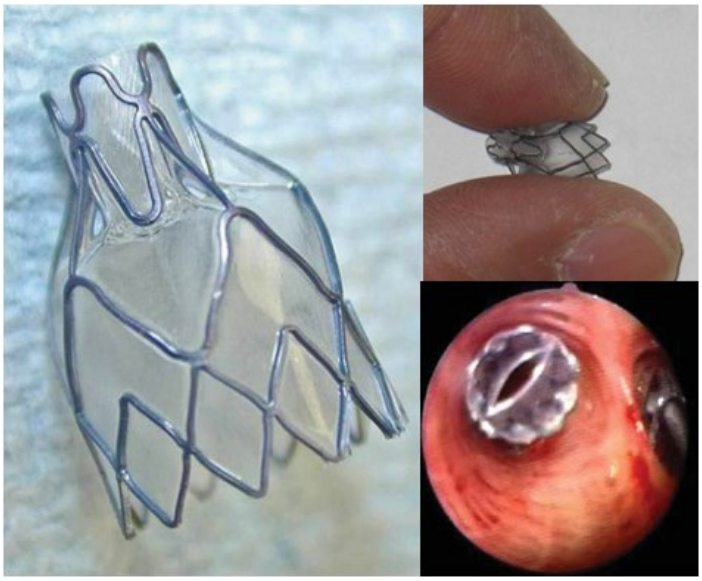


Figure 1.2: Zephyr® valve – duckbill valve open during expiration.

CT fissure integrity is currently, and somewhat arbitrarily, defined as fissures >90% complete in at least one axis. An endobronchial catheter-based device (Chartis® System, Pulmonx, Inc., Palo Alto, Calif., USA) has been developed for measuring collateral ventilation (Figure 1.3). Gomplemann *et al.* reported positive and negative predictive values of 71% and 83% respectively for treatment response. The overall accuracy of the test was 75%.(99) This may prove useful for target lobe selection however the additional benefit over accurate fissure analysis on cross sectional imaging, especially with the development of 3-dimensional software specifically designed to assess fissure integrity, is unclear and may not justify the high additional expense.

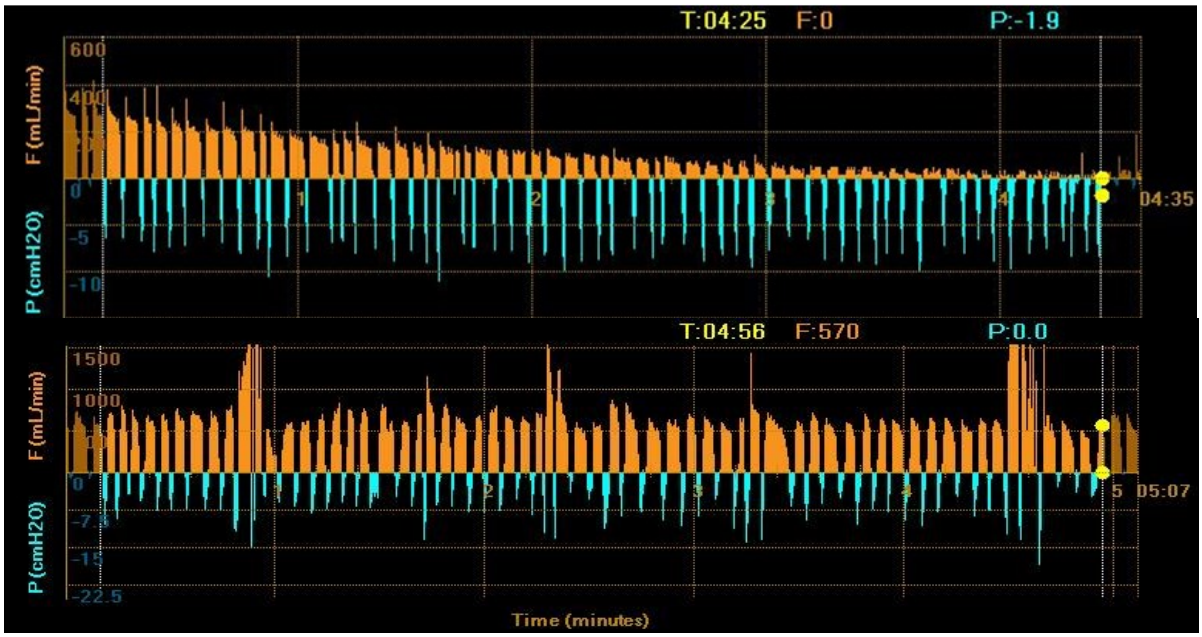


Figure 1.3: Chartis assessment. Outcomes from a lobe with (a) no collateral ventilation, and (b) one which is collateral ventilation positive. Expiratory flow (orange) gradually reduces in collateral ventilation negative lobes or is stable if collateral ventilation is present, whilst inspiratory pressure (blue) is maintained.

The IBV (Spiration Inc., Redmond, WA – now Olympus) is an umbrella shaped device which when expanded allows air and secretions to exit around the periphery of the valve (Figure 1.4). A central proximal rod can be grasped to collapse the umbrella and facilitate removal. In a multicentre pilot trial of 91 patients with severe heterogeneous emphysema, a mean of 6.7 valves were inserted per patient resulting in nine pneumothoraces and one fatality. Although quality of life and CT measured lobar volumes improved in this unblinded study, lung function did not.(84) This is probably because a non-lobar occlusion approach was adopted; the investigators elected to leave one segment of the right upper lobe and one segment of the lingua unoccluded in order to minimise the risk of pneumothorax. Eberhardt *et al.* later directly compared a unilateral occlusive strategy against a bilateral non-occlusive strategy,(100) and a greater improvement was seen in the unilateral complete occlusion group confirming our understanding regarding complete lobar isolation as a predictor of success for endobronchial valves.

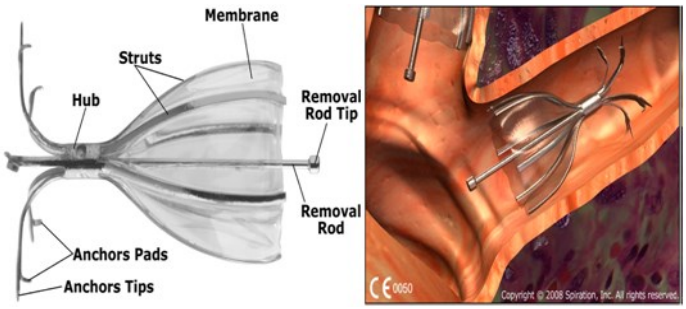


Figure 1.4: Spiration® Valve

Polymeric (biological) lung volume reduction

Biological lung volume reduction aims to reduce lung volume through tissue remodelling, by inducing an intense inflammatory reaction which leads to scarring and shrinkage of the treated lung segments. Benefits are not experienced for several weeks and the mechanism of action is independent of the presence of collateral ventilation.(101) Polymeric lung volume reduction (PLVR) (Aeriseal®, Aeris Therapeutics, Inc.; Woburn, MA) involves bronchoscopic deployment of a biodegradable gel into subsegmental bronchi. The solution, which contains aminated polyvinyl alcohol and buffered cross-linker creates a hydrogel foam when delivered to the distal airways. As gas within the foam (which fills damaged alveoli) is absorbed, the foam which is now adherent to the alveolar tissue collapses and as it does so reduces lung volume and hyperinflation. An open-label multi-centre exploratory phase II clinical study with PLVR hydrogel administered to eight subsegmental sites in 25 patients with upper lobe emphysema showed improvements in lung function and functional parameters, which persisted at 6 months (ΔFEV_1 +10%, ΔRV/TLC ratio -7.4%, ΔmMRC -1.0points, Δ6MWD +28.7m, ΔSGRQ 9.9 points).(102) The safety profile was acceptable in this study but almost all patients experienced an intense flu-like inflammatory reaction, leading to some severe COPD exacerbations. The Aeriseal® is now CE marked and a multicentre pivotal randomised controlled trial is currently underway.

Bronchoscopic thermal vapour ablation ("steam")

The bronchoscopic thermal vapour ablation (BTVA) system (Uptake Medical, Seattle, Wash., USA) delivers heated water vapour bronchoscopically via a dedicated catheter into the targeted emphysematous lung segments and like biological LVR aims to induce scarring and shrinkage by means of acute tissue injury which is followed by scarring and fibrosis, leading to lung volume reduction. The dose of thermal energy to achieve 10 calories/g lung tissues is calculated

from a pre-procedure CT assessment of lung density, with procedures to treat a single lobe lasting approximately 30 minutes. The pooled results of two single arm open label studies (87) comprising 44 patients showed a 716ml (48%) reduction in CT-measured volume of the target lobe, accompanies by improvements in FEV1 (Δ+17%), SGRQ (Δ-14 points), mMRC (Δ-0.9) and 6 minute walk distance (Δ+46.5m). Twenty nine serious adverse events were recorded of which the majority were COPD exacerbations or infections attributed to the inflammatory reaction, including one death.

Lung volume reduction coils

The *RePneu© co*il (PneumRx Inc., Mountain View, Calif., USA) is an implantable coil-like device composed of Nitinol, a super-elastic memory shape alloy. The self-actuating implant is delivered bronchoscopically under fluoroscopic guidance into the targeted airways and when its sheath is removed recoils to its original pre-determined shape (resembling a baseball seam) (Figure 1.5). The intended physiological benefit of the coil implant is to compress emphysematous lung thereby reducing lung volume with the resultant improvement in lung ventilation mechanics. The coils increases lung tension and elastic recoil which may prevent expiratory airway collapse. This reduces static gas trapping and probably dynamic hyperinflation as well. Two small pilot studies in predominantly heterogeneous disease demonstrated safety of coil insertion procedures with substantial improvements in physiological and clinical outcomes.(103, 104) Safety data after >1350 coils have been implanted in 164 patients has shown no deaths, no device migration or expectoration, six pneumothoraces (resolved quickly with intercostal chest drain insertion) and nine pneumonias in eight patients (which did not require prolonged hospital stay).(unpublished data from PneumRx)

This technique underwent further study at our institution as part of this thesis and is discussed in more detail in chapter 3.

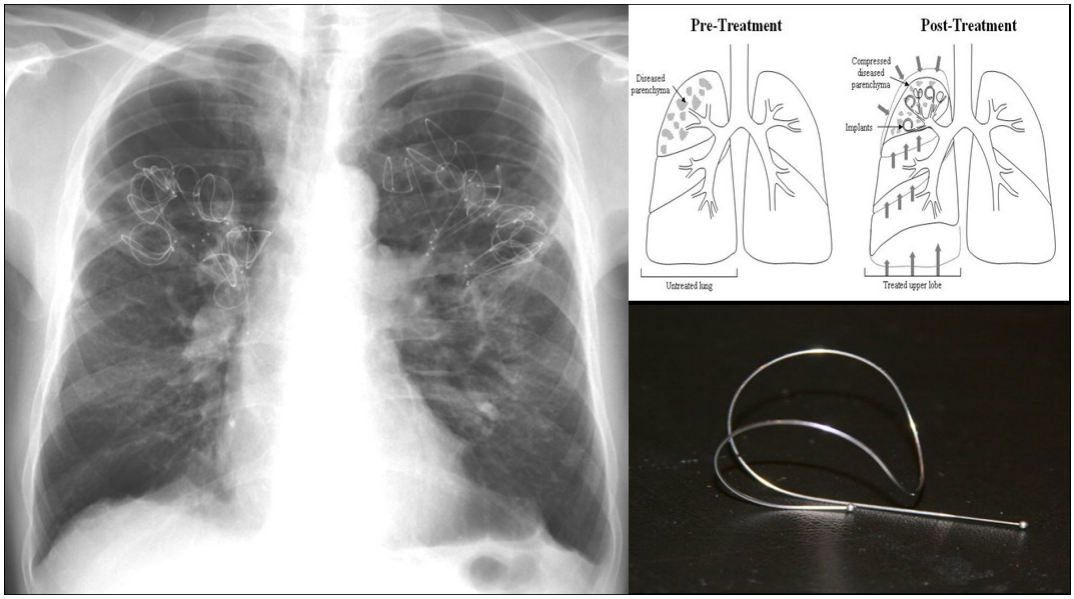


Figure 1.5: *RePneu*© lung volume reduction coil

Bronchoscopic instillation of autologous blood for lung volume reduction

The various bronchoscopic lung volume reduction techniques discussed here have in common major limitations in that they are very expensive and are likely to have limited availability, costing many thousands of pounds per procedure. They require the deposition of implants in the airways or the use of biological gels and sclerosants, which involve leaving foreign material risking infection, migration and device failure. Furthermore, the inclusion criteria are very specific limiting the suitability of these procedures to small subgroups of patients with emphysema. A Japanese group proposed the use of small volumes of autologous blood (2-5 mls) mixed with thrombin to achieve volume reduction, and in a case report they showed significant reductions in static lung volumes and dyspnoea in a 59 year old man with right upper lobe emphysema after infusion of blood and fibrinogen into a large bulla,(105) and a further open label series of 12 patients receiving this treatment had improvements in lung function, with no significant complications (unpublished data by Soichiro Kanoh, presented at the World Bronchology Conference, Tokyo 2008). This technique uses no foreign implants, and should represent dramatic cost savings. It has the potential of being performed at any bronchoscopy suite by any competent bronchoscopist. Unlike endobronchial valves, its success should be unaffected by the presence of collateral ventilation. If effective, it can theoretically be offered to patients with a wide variety of patterns of emphysema, including bullous disease, and not only restricted to heterogeneous upper lobe disease. This approach is examined in this thesis and will be discussed in more detail in chapter 4.

Artificial airway bypass tracts

A different approach to reduce gas trapping is creating artificial, extra-anatomical, low resistance airways which allow trapped gas to escape. In contrast to endobronchial valves, collateral ventilation is advantageous in this approach. To date, two techniques have been studied : Airway Bypass Stents and transpleural pneumonostomy.

Exhale® Airway Bypass drug eluting stents (Broncus Inc.; Mountain View, CA) are placed bronchoscopically through cartilaginous airways into emphysematous lung parenchyma, and serve as conduits which allow trapped gas to escape reducing both static and dynamic hyperinflation (Figure 1.6). CT mapping is used to target the areas with the most severe emphysema and a Doppler probe to avoid airway wall blood vessels. Initial pilot data in patients with homogenous emphysema showed encouraging benefits in physiological and functional parameters persisting up to 6 months post treatment.(89) However, results from a double-blind multicentre sham-controlled pivotal trial of 315 patients was disappointing.(90) Significant reductions in lung volumes were seen immediately post procedure but these did not persist. Two hundred and twelve patients with severe homogeneous emphysema and severe gas trapping were randomised to receive up to six Exhale stents implanted bronchoscopically, and 107 to sham bronchoscopy. On day 1 following the procedure, between group differences in the reduction in residual volume of 26% ($p = 0.017$) and an improvement in the FVC of 27% ($p<0.001$) were seen. Significant differences were also seen in CT-measured lobar volumes and FEV_1. Unfortunately, these benefits were not maintained, with lung function measures and CT-measured lobar volumes returning to baseline by 3 months following treatment. This was primarily a result of bypass airway occlusion by stent granulation tissue or mucus, or stent expectoration. Although this study served as a proof of concept of transbronchial airway bypass, the problem of stent occlusion will need to be addressed before further attempts to implement it are made. Sirolomus as an alternative to Paclitaxel and increasing stent diameter form possible options though these will probably be accompanied by an increase in adverse events.

A similar bypass physiologic approach but an alternative to the transbronchial one is creating a transpleural pneumonostomy (an airway bypass directly between the lung and the atmosphere through the chest wall). This is achieved through a minimally-invasive transthoracic surgical approach in a procedure that takes approximately 1 hour to complete. This is similar to an intrabullous drainage procedure (the Brompton/Monaldi technique (106)) but with a permanent tract being fashioned to allow a pathway for air to escape. The PortAero Pneumostoma System (PortAero Inc., CA) was developed and the patient is required to change

the PortAero tube daily to maintain tube patency. A pilot study was undertaken in six patients, and in the four patients who retained the bypass tube for 3 months or more, there was a 23% increase in FEV_1.(91) Refinement of the technique and tube system is underway to attempt prevention of tract closure and tube blockage.

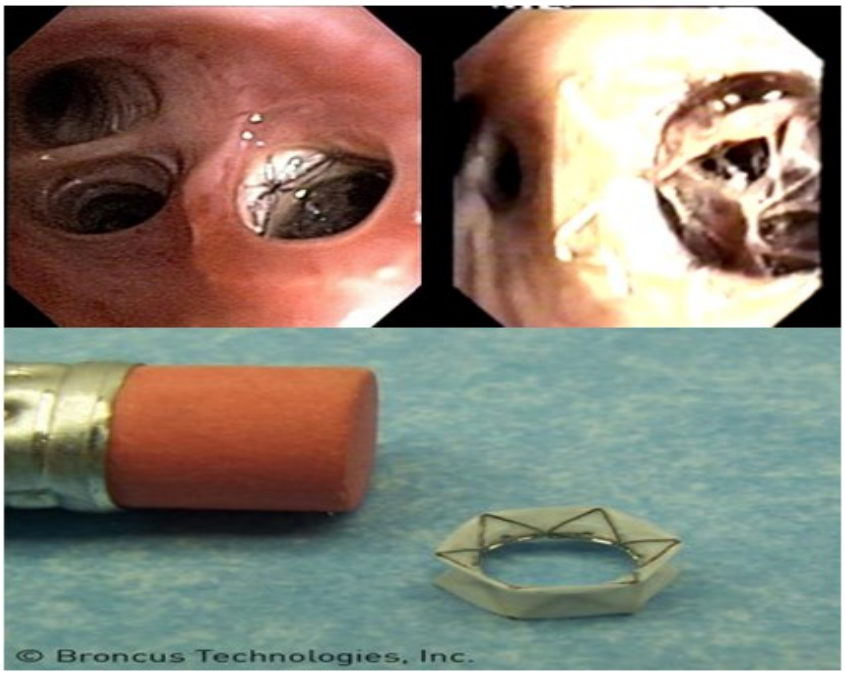


Figure 1.6: Exhale® stent with view through stent into emphysematous lung parenchyma.

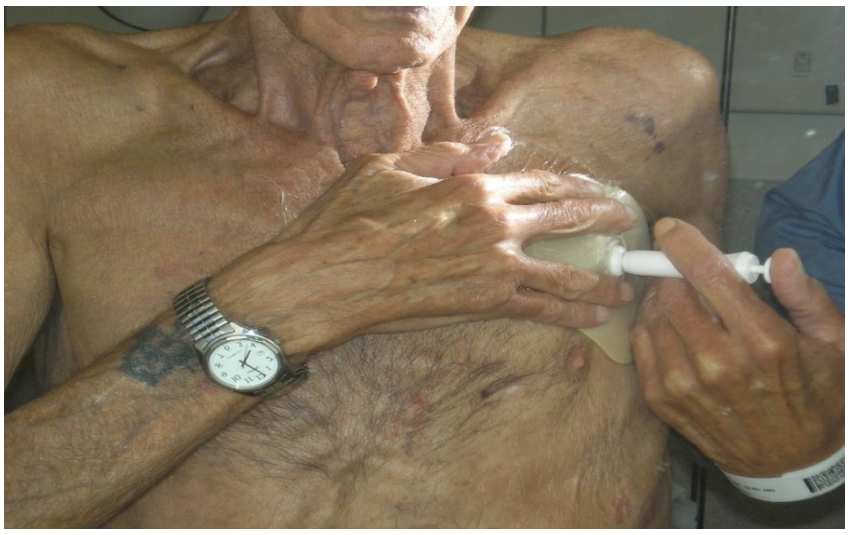


Figure 1.7: PortAero "spiracles". A patient self-replacing his pneumonostomy tube.

1.4 OPTOELECTRONIC PLETHYSMOGRAPHY

Optoelectronic plethysmography (OEP) is a system for indirectly measuring lung volumes based on an automatic motion analyser which detects the positions of 89 passive markers composed of a thin film of retro-reflective paper on plastic hemispheres (5-10mm diameter). The markers are placed on the skin using bioadhesive hypoallergenic tape. Six-eight infrared detection cameras surrounding the patient record non-invasively real-time breath-by-breath images of the markers and their movement (see Figure 1.8). Dedicated software uses the data received from the infrared cameras to compute 3-dimensional (3D) co-ordinates of the markers by stereo-photogrammetric techniques. The individual markers correlate to specific points on the chest wall, allowing for movements of the whole chest wall or any specific component of the chest wall to be accurately measured. It is a non-invasive and non-ionizing method that does not make assumptions regarding the number of degrees of freedom of the chest wall, does not require a mouthpiece, nose clip or any similar device, and its calibration does not require respiratory manoeuvres by a biological control. By combining chest wall volume changes with preliminary measurements of VC and FRC, it is possible to accurately determine absolute lung volumes at any point during the breathing cycle.(107, 108) These measurements also allow accurate measurement of not only total lung volumes, but also partial thoracic volumes. The standardised subdivisions of chest wall movements using OEP are upper rib cage, lower rib cage and abdomen. The lower ribcage movements have been shown to be a good estimate of diaphragmatic movement.(109)

1.4.1 HISTORY OF OEP

The technique of performing spirometry to measure dynamic lung volumes using a pneumotacograph, although a well known and generally reliable one, can in itself alter natural breathing frequency, TV, dead space ventilation and breath awareness. Hence breathing patterns during testing may not be representative of the subject's natural state.(110) Furthermore, results may be affected by humidity and temperature variations. Spirometry requires the subject to be fully cooperative, be able to follow commands, achieve a tight seal around a mouthpiece, and be in a seated upright position. The pneumotacograph needs to be calibrated before each test. In an attempt to address these problems, alternative methods of measuring lung function have been sought. Konno and Mead first attempted estimating changes in lung volumes using crude direct writing recorders to plot *x*–*y* axis coordinates of the thoracic

dimensions.(111) More accurate techniques of motion analysis to measure lung volumes were subsequently developed, such as a system which employed a linear magnetometer to estimate tidal volumes by using tuned coils placed on the anterior and posterior thorax to measure the cross-sectional area of the rib cage and abdomen. The next step was to develop a system which allowed differentiation between the lower and upper ribcage volumes, and Ferrigno and Pedotti's "*Elaboratore di immagini televisive*" motion analysis system (ELITE System; BTS, Milan, Italy) was developed in 1985 and used a digitised video system and automatic motion analyser to identify objects of predetermined shape (such as the person's chest) and monitor its trajectory in 3D and real time.(112) Using an algorithm originally developed to measure movements of the joints and limbs, calculations of the movements of the pulmonary ribcage, abdominal ribcage and abdomen were possible but the error was unacceptably high (±21·3%) compared with traditional spirometry. Rather than using circumferential geometry, Cala and colleagues (108) used traditional cubic geometry of 86 markers and this improved accuracy of measurement of the chest wall and decreased the error to <3·5%. This refinement of the ELITE technology was patented as the optoelectronic plethysmography system, or OEP (BTS Bioengineering, Milan, Italy). The latest technology uses 89 markers (seven horizontal lines, five vertical lines, two mid-axillary lines, and seven extra markers) arranged in anatomical structures between the sternal notch and the level of the superior iliac crest, being 37 anterior markers, 42 posterior and 10 lateral (figure 1.9), with up to eight infrared cameras improving accuracy even further. The boundary between the pulmonary rib cage and the abdominal rib cage is at the level of the xiphoid process, and between the abdominal rib cage and abdomen along the costal margins anteriorly and at the lowest point of the costal inferior margin posteriorly. The midline markers over the sternum and vertebral processes delineate left from right.

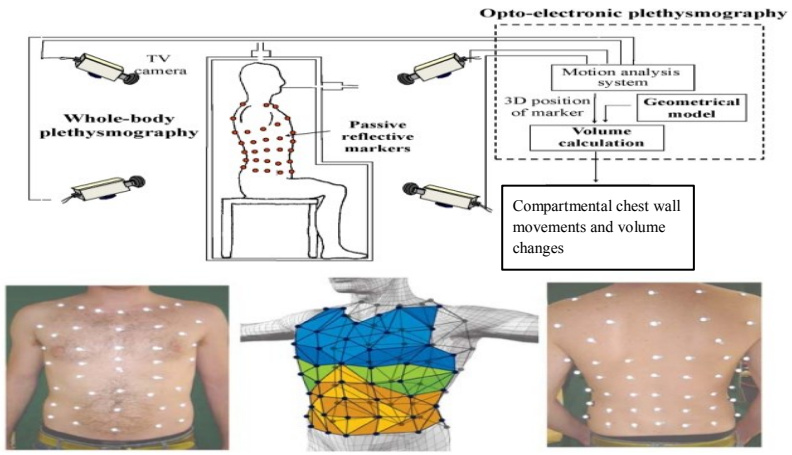


Figure 1.8: Optoelectronic plethysmography - principles of measurement. (BTS handbook 2011)

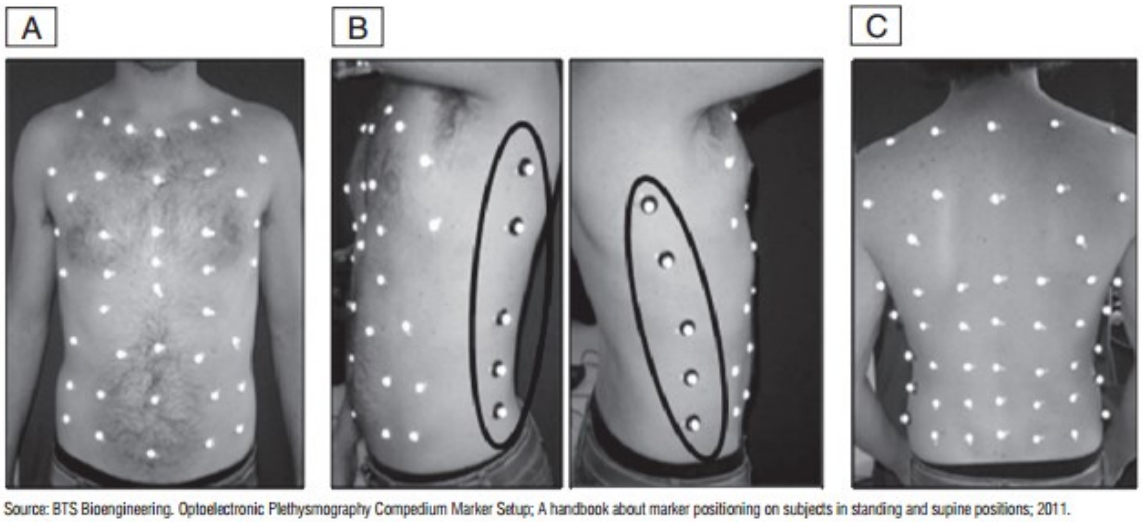


Figure 1.9: OEP Eighty nine marker configuration setup.

The OEP system at the Royal Brompton Hospital uses eight cameras which allow real time 3D determination of the coordinates of each marker, and visualisation of the geometric model being analysed. The cameras operate at 30-60 Hz and are synchronized with axial diodes that emit infrared light. Infrared beams are emitted by each camera and the reflection back from each marker is captured and transferred to a parallel processor, which calculates 2D coordinates of all markers "viewed" by at least two camera, before calculating the 3D coordinates of the different markers by sterophotogrammetry (3D geometric information is extracted from the combination of at least two 2D images obtained by two cameras at the same moment of time from two different positions). After the 3D coordinates of each marker are obtained, the volume of the chest wall is calculated through the connection of points to constitute a net of tetrahedral triangles. Gauss' theorem is then used to calculate the internal volume of each shape and the total chest wall volume being the sum of these volumes.

1.4.2 VALIDATION

Cala et al. demonstrated that OEP lung volume measurements correlate strongly with pneumotachographic values during both quiet breathing and slow vital capacity

manoeuvres.(108) There is no literature on correlation between OEP and forced expiratory manoeuvres as there is a discrepancy, with blood shift and gas compression the likely culprits. OEP lung volume measurements were validated in ventilated patients in intensive care,(113) in subjects in the supine and prone positions, (114) in newborns,(115) and in group of COPD patients.(116) In the latter study, OEP was also validated for use during cycle ergometry in COPD patients of both sexes. In terms of repeatability, there was <10% variability in lung volume measurements after repeated exercise of 9 healthy subjects.(117)

1.4.3 APPLICATIONS OF OEP

At present, OEP is used predominantly in the research setting. In the future it may have broad applicability to patient populations such as very young children, patients with neuromuscular disease and patients who cannot be tested with classical pneumotachographic testing, as it does not require breathing into a mouth piece and is less reliant on compliance and forced manoeuvres. It can obtain accurate measurements over the whole breathing cycle, and over extended periods of time. It may have applications in assessing response to medical and non-medical therapies, an area under investigation in this thesis.

Vogziatzis et al. have demonstrated that OEP can reliably detect exercise induced dynamic hyperinflation in patients with COPD.(116) The same group evaluated dynamic lung hyperinflation during incremental cycle ergometry in a later study,(118) with two phenotypic patterns found: 'early hyperinflators' demonstrated progressive increases in end-expiratory lung volume at the onset of exercise; and 'late hyperinflators' showed increases in end-expiratory lung volumes in the last third of exercise. Both groups achieved the same peak work rate despite a significantly greater end-expiratory lung volume in the "early hyperinflators". A subsequent study found that lower ribcage paradox (diaphragmatic paradoxical breathing) at rest is associated with early-onset hyperinflation, and in this group dyspnoea is the main factor limiting exercise, whereas leg fatigue becomes a more important symptom limiting exercise in COPD patients without diaphragmatic paradox.(119) OEP has also been used to study the effects of pulmonary rehabilitation in patients who had lung upper lobectomies. Tidal volumes improved by 32% in the non-operated lung following pulmonary rehabilitation, significantly compensating for the lost tidal volumes of the resected contralateral lobe.

In the context of emphysema and lung volume reduction, the ability to divide lung volumes into six different compartments offers the potential of detailed information on the effects of LVR in terms of changes in airways obstruction, ventilation volume shifts, changes in dynamic hyperinflation, diaphragm dysfunction and asynchronous respiration. Breath by breath data, which can be obtained at rest as well as during exercise, may allow a better understanding of the physiology and mechanics of lung ventilation in response to LVR, the focus of study in Chapter 5.

Chapter 2
Methods

2.1 ETHICAL APPROVAL OVERVIEW

The Ethics Committee of the Royal Brompton and Harefield NHS Trust approved the LVR coil study and autologous blood LVR study. The London-Westminster Research Ethics Committee approved the OEP LVR study. All subjects who participated in trials reported in this thesis provided written informed consent.

2.2 STATISTICAL ANALYSIS

Statistical analyses will be discussed in the appropriate chapters.

2.3 STATIC AND DYNAMIC LUNG VOLUMES AND GAS TRANSFER MEASUREMENTS

The clinical physiologists at the Royal Brompton Hospital lung function department performed all testing using the Compact Master Lab system (Jaeger, Germany). This ensured that the strict quality control measures adopted by this department of specialist physiologists applied to the results presented in this thesis. The European Coal and Steel Workers cohort was used to obtain standardised reference values.(120)

2.3.1 CALIBRATION

Calibration was performed on all pneumotachographs prior to every patient test using a 3.0 litre calibration syringe. The plethysmographs underwent automatic calibration twice daily, and a biological control was also used to test the equipment daily. The “body box” was also tested on a daily basis using a biological control. The gas analysers used to measure gas transfer were calibrated four times a day using a standard helium (He) calibration gas, and the pneumotachograph was calibrated using a 3.0 litre syringe prior to testing each patient.

2.3.2 TECHNIQUE

Spirometry was performed by placing a mouthpiece in the participant's mouth whilst in the sitting position, and applying a nose clip. The participant was then instructed to take a full breath in to TLC, and then exhale as hard and as fast as they possibly can until they reach the RV. At this point they were instructed to inhale as hard and as fast as possible until they are back to TLC. For bronchodilator reversibility testing, 400 mcg of salbutamol from a metered dose inhaler was administered using a spacer device after the first set of spirometry testing, which was repeated 15 minutes after the administration of salbutamol.

For static lung volumes, the patient was seated in the sealed body box with a nose clip applied and asked to breathe quietly for several breaths into a mouthpiece. The shutter was then closed at the tidal volume (TV) end-expiratory position (i.e., FRC), and the patient asked to pant. The gas volume trapped in the lungs was then calculated by applying Boyle's law; Intrathoracic gas volume (ITGV) at FRC being alveolar pressure multiplied by the change in the body box gas volume when panting, divided by the change in alveolar pressure (measured at the mouth) when panting against a closed shutter.

Gas transfer was measured using a single breath technique. The inspiratory and expiratory carbon monoxide (CO) concentrations were used to calculate the total lung CO uptake. Several measurements were performed to confirm that results were reproducible. TLCO was corrected ($TLCO_c$) to serum haemoglobin concentrations of 14.6 g/dl for adult males and 13.5 g/dl for adult females, using haemoglobin levels measured from capillary blood testing.

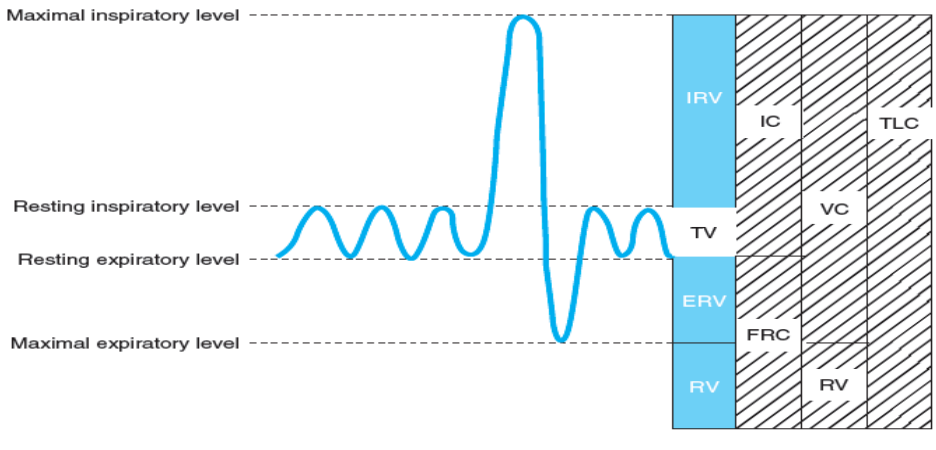


Figure 2.1: Lung volume compartments and subdivisions based on volume-time spirogram. Adapted from Forster RE et al. 1986.(121) (Publisher does not require permissions to re-use)

2.4 ARTERIAL BLOOD GASES

Arterial blood gas (ABG) analyses were performed by clinical physiologists at the at the Royal Brompton Hospital lung function department using end capillary blood samples from the participants' earlobe. Analysis for pH, and partial pressures of O_2 and CO_2 were performed using the Rapidlab 348 analyser (Bayer, Germany).

2.5 HIGH RESOLUTION COMPUTED TOMOGRAPHY OF THE CHEST

High resolution Computed Tomography (HRCT) scanning was performed using a Siemens Sensation 64 (a 32 detector scanner with a rotation time of 0.33 seconds). Non-contrast volumetric spiral acquisition with contiguous slices was taken with the participant in the supine position at full inspiration. Slices were reconstituted at 1mm slice thickness on 1mm for lung windows and 10mm on 10mm mediastinal windows for all patients studied as part of all studies in this trial. HRCTs of participants involved in the LVR coil trial also had images reconstituted as 6mm on 3mm for lung windows to allow optimal density assessments using dedicated software (discussed in more detail in chapter 3).

2.6 HEALTH RELATED QUALITY OF LIFE QUESTIONNAIRES

2.6.1 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

The St. George's Respiratory Questionnaire (122) is a 76-item health status survey specific for respiratory disease. It is designed to measure impact of the disease on overall health, daily life, and perceived well-being. It has been in existence for over 20 years, and there is a large body of evidence concerning its validity. A four point change in the score has been consistently found to correlate with a clinically significant change.(123) The participants self-completed the questionnaires taking the previous four weeks in consideration. A researcher was available to clarify any questions which the participants might have. Questionnaire answers were entered into a dedicated Excel calculator which provided total, impact, activity, and symptom SGRQ scores.

2.6.2 MRC DYSPNOEA SCALE

The Medical Research Council (MRC) breathlessness scale comprises five statements that describe almost the entire range of respiratory disability from none (Grade 1) to almost complete incapacity (Grade 5). It was devised by Fletcher and co-workers whilst studying the respiratory difficulties of Welsh coal miners at the Pneumoconiosis Unit in the 1940s and 1950s. It has been used extensively for over 50 years, and correlates with activity levels and prognosis. The "modified MRC scale" (mMRC) version of this breathlessness scale, with gradings from 0-4, was used in the studies reported in this thesis (Table 2.1).

Table 2.1: The modified Medical Research Council (mMRC) dyspnoea scale.

mMRC	Statement
0	I only get breathless with strenuous activity
1	I get breathless when hurrying on the level or up a slight hill
2	I walk slower than other people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level
3	I stop for breath after walking 100 metres or after a few minutes on the level
4	I am too breathless to leave the house

2.7 EXERCISE TESTING

2.7.1 6 MINUTE WALKING DISTANCE

The 6 minute walking distance (6MWD) is a well validated test of exercise capacity in patients with COPD, and is commonly used both in clinical practice and in research. In one study of 112 patients with stable severe COPD,(124) the mean smallest difference in 6MWD that was associated with a noticeable clinical difference in the patients' perception of exercise performance was 54m (95% confidence interval, 37–71m). Therefore an improvement of more than 70m in the 6MWD after an intervention is necessary to be 95% confident that the

improvement was significant. However many patients with COPD may only manage relatively short walking distances and in these circumstances a 10 % change in the 6MWD has been suggested to be of clinical significance.(125) More recent studies investigating the MCID for the 6MWD in larger COPD populations suggest lower distances than Redelmeier's et al.'s study; 26 metres in Puhan's study of the NETT trial cohort and response to lung volume reduction surgery (1218 patients) using quality of life measures as the anchor ,(126) and 30 metres in Polkey et al.'s study of 2112 patients from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study cohort where an MCID for change in 6MWD was assessed as a function of death.(127)

The ATS criteria (128) for measuring the 6MWD were strictly adhered to in all studies reported in this thesis. All tests were performed in the same 30 metre long corridor at the Royal Brompton Hospital. The participant was seated for 10 minutes at the start line before the start of the test. Blood pressure, heart rate, oxygen saturations and Borg scores (see below) for breathlessness and fatigue were taken. The following instructions were given to the participant:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation." Demonstrated.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now or whenever you are ready." (128)

The timer was started when the patient started walking. Standardised phrases of encouragement were given to the patient as per the ATS guidelines(128). The number of laps and partial laps was documented, as well as the number of stops. At the end of the 6 minutes, the participant was instructed to stop and a chair was wheeled to the patient. The walking distance was recorded, as well as the post-walk Borg dyspnoea and fatigue scores, blood pressure, and pulse rate and oxygen saturations.

2.7.2 CYCLE ERGOMETRY

Cycle ergometry was performed as part of the OEP study in chapter 5, simultaneously with OEP recordings. The reflective markers were positioned on the patient's torso before patients mounted the bicycle and the seat and arm rest heights adjusted. Standard positioning of the 12 lead ECG monitoring pads interfered with OEP marker tracking, and therefore if there was no evidence of inducible coronary ischaemia on maximal incremental cycle ergometry testing, the leads were positioned on the periphery of the OEP markers around the lower abdomen, maintaining accurate monitoring of pulse rate only, for the steady state submaximal cycle ergometry test. Cycle ergometry was otherwise unaffected by the OEP equipment and recordings. I performed all but two cycle ergometry tests with in conjunction with a respiratory physiologist.

Cycle ergometry was preferred to treadmill testing in my study as reduced walking capacity is associated with an excessively high ventilatory demand in COPD. Cycle ergometry is associated with a more efficient pattern of breathing in patients with COPD compared to treadmill walking.(129) Subjects wore a nose clip and breathed through a mouthpiece for the duration of their cycle ergometer test. A magnetically braked cycle ergometer was used (Jaeger Ergoline 800). Continuous monitoring of oxygen saturations and cardiac pulse via a 12-lead ECG trace were performed throughout testing. Breath-by-breath respiratory analysis was performed using a metabolic analysis system (Oxycon device, Jaeger Systems, Germany). Continual sampling of inspired and expired oxygen concentrations enabled calculation of oxygen uptake. Carbon Dioxide output was measured using an infrared CO_2 analyser. A turbine spirometer within the mouthpiece measured breath-by- breath TVs and minute ventilation (VE). The data from every eight breaths were averaged and data recorded. Minute-by-minute Borg scores of breathlessness and fatigue were recorded by asking the patient to point at the Borg scales during exercise.

During exercise, resistance was adjusted to maintain the required workload with the patient encouraged to maintain peddling at 60 revolutions per minute (RPM). Patients' maximum oxygen utilisation (VO_2max) and minute ventilation (VEmax) were determined by measured data from the last 30 seconds of every minute.

Prior to each exercise test automated gas and volume calibrations were performed and adjustments made for barometric pressures, humidity and room temperature. Weekly calibration of parameters was performed using biological controls.

2.7.2.1 Incremental cycle ergometry test

Five minutes of rest were recorded before subjects started to cycle. IC manoeuvres were performed with the patient sat on the cycle ergometer every minute throughout the test. Initial workload was set to 0 watts for 1 minute of cycling, and then increased by 5 Watts every minute. The participants cycled until they were no longer able to maintain peddling at 60rpm due to exhaustion. This was followed by 3 minutes of recovery. The reason for cessation of exercise was recorded. Borg scores for exertion and dyspnoea were recorded every minute. Standardised encouragement was given equally to all participants to ensure that subjects gave their best performance. The incremental cycle test was used to determine subjects' maximum workload. The incremental test was only performed on the first baseline visit.

2.7.2.2 Steady state submaximal cycle ergometry test

A minimum of two hours of rest after the incremental test was stipulated before the participant started the endurance test. Five minutes of rest were followed by 1 minute of unloaded cycling and then a constant workload set to 75% of the maximum workload achieved for at least 30 seconds during the incremental cycle test was applied. IC measurements were taken with the patient sat on the cycle ergometer every minute throughout the test. The subject cycled until exhaustion and this is followed by 3 minutes of rest. The cycling time and reason of cessation were recorded. Minute by minute Borg scores were obtained throughout the test.

2.7.3 BORG SCORE

The Borg scoring systems were developed to allow subjects to rate dyspnoea and perceived exertion, and have been validated as being reliable and reproducible.(130) When asked, subjects pointed to charts (Table 2.2) to indicate their level of symptoms. In studies performed as part of this thesis, scores were obtained before and immediately after the 6MWD and every minute during exercise testing.

Table 2.2: Borg's rating of perceived exertion

	Borg's scale of breathlessness
0	No breathlessness at all
0.5	Just noticeable
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very very severe
10	Maximal

	Borg's rating of perceived exertion
6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximum exertion

2.8 OPTOELECTRONIC PLETHYSMOGRAPHY

Before the start of the cycle ergometry tests, 89 reflective markers were carefully positioned on the subject's torso in a grid following a specific protocol (BTS biomedical engineering handbook) (Figure 1.9). This was done using two-sided hypoallergenic circular adhesive tape. Details of reflective marker and infrared camera positioning, OEP system calibration, patient testing and data analysis is discussed in depth in section 5.2 of this thesis.

Once the OEP setup was complete and a geometric model obtained, two sets of recordings were made: (1) Three forced expiratory manoeuvres (as described in section 2.3.2) with simultaneous recordings of pneumotachographic values with via a mouthpiece whilst in the sitting position and with nose clip applied; (2) Steady state submaximal cycle ergometry test as detailed above (section 2.7.2).

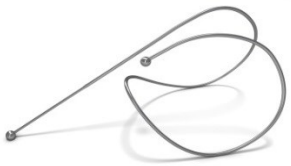
Chapter 3

Lung Volume Reduction Coils for the treatment of severe emphysema: A randomised controlled trial

3.1 BACKGROUND

The *RePneu*© lung volume reduction coil (LVRC) (PneumRx Inc., Mountain View, Calif., USA) is an implantable coil-like device composed of Nitinol, a biocompatible super-elastic memory shape alloy. The self-actuating implant is delivered bronchoscopically under fluoroscopic guidance into the targeted airways and when its sheath is removed recoils or "springs back" to its original pre-determined shape (figure 3.1). It was designed with the intended physiological benefit of replicating the effects of LVRS; to compress the most emphysematous areas of the lung parenchyma and hence reducing lung volume with resultant improvements in lung ventilation mechanics. Air flow to treated portions of lung should therefore reduce and more airflow diverted to healthier untreated portions (figure 3.2). Additionally, the coils increase elasticity and recoil to the whole lung thereby lessening expiratory small airway collapse thus improving expiratory flow rates and reducing compliance. Theoretically these factors should combine to reduce gas trapping and improve dynamic hyperinflation. Reducing the volume of the hyperinflated emphysematous lung improves diaphragmatic efficiency and reduces the work of breathing. Unlike unidirectional endobronchial valves, the coils' mechanism of action should be independent of the presence or absence of collateral ventilation, and should achieve immediate mechanical effect.

Figure 3.1: 150 mm lung volume reduction coil (LVRC)



The implant derives its strength from the Nitinol wire. Originally, implants were manufactured in seven lengths (70 mm, 85 mm, 100 mm, 125 mm, 150 mm, 175mm and 200 mm) however the manufacturers have limited these to the 100, 125 and 150 mm lengths in their 2nd generation of products. Smaller coils were very seldom used, and early data showed no additional benefit in patients treated with coils longer than 150mm, with a theoretical higher risk of pneumothorax due to puncture of the lung by the distal end of the coil. Ten millimetres of the proximal end of the implant has a smaller diameter than the rest of the coil to reduce rigidity, lessen the pressure of the coil in the proximal large airways, minimise airway wall trauma, and facilitate recapture if necessary. The distal and proximal ends of the coil terminate with a smooth atraumatic ball. The distal end is designed to reside in airways with a diameter of approximately 2 mm. The LVRC Delivery System is sterilised by Ethylene Oxide and the coils are sterilized by Electron Beam.

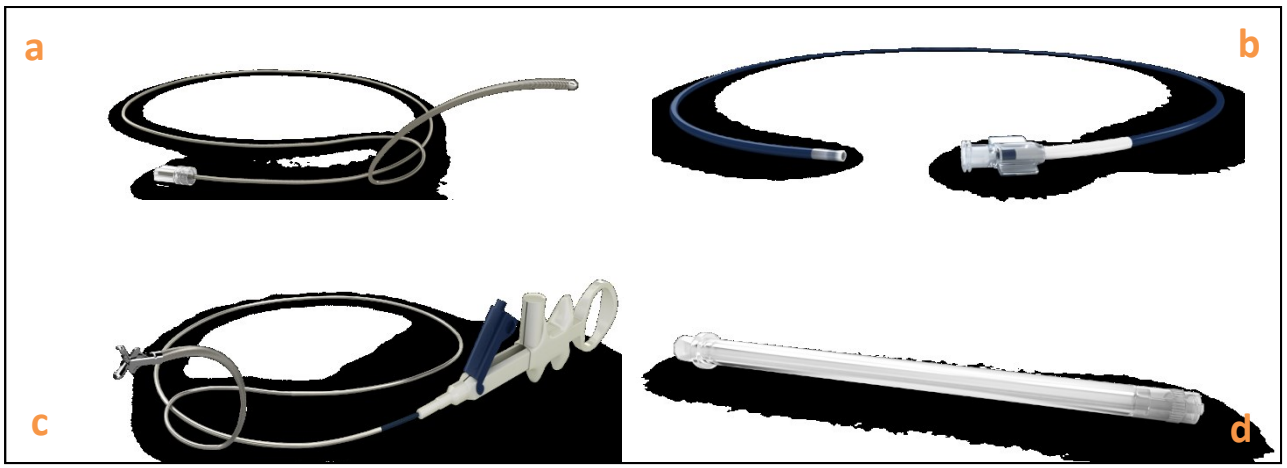


Figure 3.2: Lung Volume Reduction Coil Delivery system**.** (a) guide wire, (b) catheter, (c) modified forceps, (d) loading cartridge.

The delivery system includes a guide wire, delivery catheter, cartridge and forceps (figure 3.3). The guide wire serves as a flexible tool which enables the identification of suitable airways for treatment, and ensure the tip of the LVRC is a safe distance from the pleural edge (>35mm) after deployment. Once the guidewire is in the desired location, the delivery catheter is passed over the guide wire until the distal ends align. The Guide wire contains fluoroscopically visible markers which allow accurate determination of the appropriate coil length. The guide wire is then removed from within the delivery catheter and forceps are used to pull the desired coil into the rigid straight cartridge. The cartridge is then connected to the delivery catheter and the coil advanced inside the catheter until the distal end reaches the distal tip of the catheter. The catheter is pulled back whilst maintaining the position of the coil, which is monitored fluoroscopically as it recoils to its predetermined shape as it is released from the straightening effect of the catheter. The coil can be removed or repositioned by reversing the deployment procedure, provided the proximal end of the coil is visible and can be grasped using the forceps.

Pilot work informed the number of coils required per treated lung, with 10 coils achieving good safety and effectiveness.(103) At our institution, we perform these procedures using moderate sedation in the bronchoscopy suite unless there is a contraindication to do so, however most treatments worldwide are performed in the operating theatres under general anaesthesia.

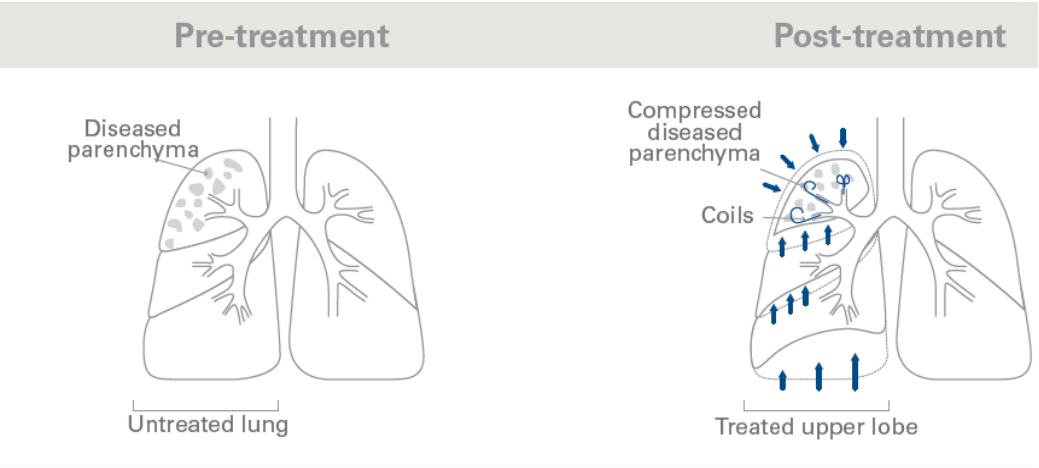


Figure 3.3: Diagram of the Lung Volume Reduction Procedure Using Coils. PneumRx ©

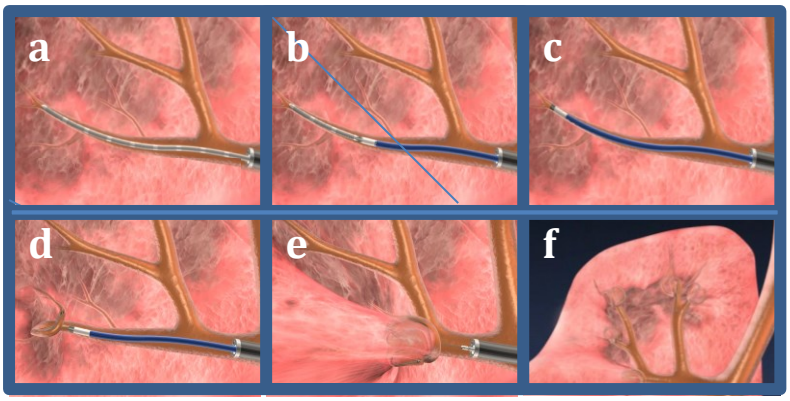


Figure 3.4: Pictorial representation of the coil deployment process**:** (a) guide wire inserted into target sub-segment, (b) catheter passed over guide wire, (c) guide wire removed and replaced with straightened coil, (d&e) catheter retracted releasing coil which retakes its predetermined shape, (f) multiple coils deployed in target lobe.

Two pilot studies of 11 (103) and 16 (104) patients with predominantly heterogeneous disease demonstrated the safety of coil insertion procedures and observed substantial improvements in physiological and clinical outcomes. These studies informed the design and power of a randomised controlled trial, which is the subject of this chapter. In addition to these early clinical trials, procedures have been performed commercially in three European centres and the manufacturer (PneumRx Inc.) has recently released efficacy (Table 3.1) and safety (Table 3.2) data combining data of the 2 clinical trials along with the procedures performed commercially (>1350 coils implanted in 142 subjects, including 28 patients treated at our institution). In terms of investigator reported serious adverse events (SAEs), there were no deaths, no episodes of device migration or expectoration, six pneumothoraces, and nine pneumonias in eight patients (which did not require prolonged hospital stay). The SAE profile of the coils was

comparable to the control patient population in the EASE trial (90), the largest sham procedure group in a similar population (all EASE trial procedures were performed under general anaesthesia). Twelve month outcome and safety data from 84 patients treated with LVRCs in non-randomised, unblinded multicentre studies was presented in a spoken abstract presentation at the Chest2012 conference in Atlanta, Georgia in October 2012.(131) The cohort included patients with varying degrees of heterogeneity as well as homogenous disease distribution (details were not provided). The authors reported mean ±SD improvements in the 6MWT of 63.04±13.79 metres, reduction in the RV of -0.61±0.13 litres, and reduction in the SGRQ of -12.06±2.43 points. These improvements were sustained at 12 months.

Table 3.1: Combined Efficacy data at 6 months from 250 LVRC procedures in 143 subjects

180 days post-baseline	Change from baseline	p-value	% Change from baseline	p-value
6MWD (m)	+49.07 ± 8.26	<.0001	+19.53% ± 3.46%	<.0001
RV (L)	-0.67 ± 0.09	<.0001	-12.08% ± 1.51	<.0001
FEV_1 (L)	+0.13 ± 0.02	<.0001	+17.30% ± 2.81%	<.0001
SGRQ (points)	-11.43 ± 1.41	<.0001		
TLC (L)	-0.29 ± 0.07	<.0001	-3.33% ± 0.82%	0.0001
RV/TLC	-11.43 ± 1.41	<.0001	-19.11% ± 2.56%	<.0001

Table 3.2: Combined safety data at 6 months from 250 LVRC procedures in 143 subjects (unpublished data, with permission from PneumRx Inc.).

Reported SAE	PneumRx studies (up to 6 Months)	EASE sham control (6 Months reported data)
Pneumothorax	4/246 procedures = 1.6%	1/107 procedures = 1%
Haemoptysis (>25mls)	2/246 procedures = 0.8%	0/107 procedures = 0%
COPD exacerbation/ pneumonia	45/246 procedures = 18.3%	18/107 procedures = 17%

The aim of our study was to investigate the safety and effectiveness of the LVRCs in patients with severe heterogeneous and homogeneous emphysema in a randomised controlled study. Patients with homogeneous disease were included in this study as the pilot data suggested similar benefits regardless of the degree of emphysema heterogeneity.

3.2 METHODS

3.2.1 STUDY DESIGN

This trial was a prospective randomised controlled open label trial. Research ethics committee and NHS Trust R&D approval was obtained and all patients provided written informed consent. Patients were recruited between February 2010 and October 2011.

After fulfilling all the inclusion and exclusion criteria, subjects were block randomised in a treatment to control ratio of 1:1 by opening pre-completed, opaque, sequentially numbered, sealed envelopes. The block size was 4 (the investigators were not aware of the block size until completion of study recruitment).

The primary outcome time point was 3 months following the final treatment, after which subjects in the control arm crossed-over to the treatment arm (treatment to control ratio of 2:1). Follow-up of all patients extended to 12 months following the final LVRC treatment.

3.2.2 STUDY OUTCOMES

Primary Endpoint

- The between group difference in the change in SGRQ from baseline to three month post final treatment.

Secondary Endpoints

1) The between group difference at three months post final treatment in:

- Percent change in FEV_1 from baseline.
- Percent change in FVC from baseline.
- Change in the RV from baseline.
- Change in the TLC from baseline.
- Change in the 6MWD from baseline.

- Change in the mMRC Dyspnoea Scale from baseline.
- Responder rates for primary and secondary outcome measures.

2) Change in SGRQ, FEV_1, FVC, RV, TLC, 6MWD and mMRC in the treatment arm 6 and 12 months after treatment as compared to baseline.
3) Adverse Event profile

3.2.3 SAMPLE SIZE CALCULATION

The number of patients needed to demonstrate statistical significance ($\alpha<0.05$, $\beta=0.84$) of the difference in the proportion of patients reporting an improvement in SGRQ of 4 points or more was estimated to be 42 (1:1 randomisation). This is based on a pilot study driven estimated treatment effect of 0.6 (60% treated patients report an SGRQ improvement > 4) and a placebo effect in the control group of 0.2 (20% Control patients report an SGRQ change >4). The aim was to recruit 45 subjects to account for possible drop-outs. This thesis reports on 36 subjects recruited at our institution.

3.2.4 PATIENT SELECTION

Subjects with GOLD stage III-IV emphysema were recruited from the respiratory clinics at the Royal Brompton Hospital and the Chelsea and Westminster Hospital, after discussion in an appropriate multidisciplinary meeting. Patients with severe airflow obstruction, significant hyperinflation and limiting breathlessness with no contraindications prohibiting bronchoscopy were considered. The inclusion and exclusion criteria are listed below.

Inclusion Criteria:

- Aged ≥35 years
- HRCT scan indicates unilateral or bilateral emphysema
- HRCT scan indicates homogeneous or heterogeneous emphysema
- Post-bronchodilator FEV_1 ≤45% predicted
- Total lung capacity >100% predicted

- Patient has marked dyspnoea score ≥2 on modified Medical Research Council scale
- Patient has stopped smoking for a minimum of 8 weeks before enrolment
- Patient (or legal guardian if applicable) read, understood, and signed the informed consent form

Exclusion Criteria:

- A change in FEV_1 greater than 20% post-bronchodilator
- A single-breath diffusing capacity for carbon monoxide <20% predicted
- A history of recurrent clinically significant respiratory infection, or clinically significant bronchiectasis
- Uncontrolled pulmonary hypertension defined by right ventricular pressure >50 mm Hg as evidenced by echocardiogram
- An inability to walk >140 metres in 6 minutes
- Other diseases that can compromise survival—e.g., lung cancer or renal failure
- An inability to tolerate bronchoscopy under heavy sedation or anaesthesia
- Giant bullae greater than a third of lung volume
- Previous lung volume reduction surgery, lung transplant, or lobectomy
- Participation in other pulmonary drug studies within 30 days of enrolment
- Taking greater than 20 mg prednisone (or similar steroid) daily
- On clopidogrel or unable to stop treatment for 1 week before the procedure
- Other disease that would interfere with completion of study or follow-up assessments, or that would adversely affect outcomes

The investigators ensured that patients had been on optimal medical therapy for at least 3 months prior to enrolment. This was performed at their initial clinic review before screening, which was delayed by 3 months if changes to treatment were made or felt needed. Definition of optimal medical therapy was not stipulated in the study protocol, but at our site we ensured that patients were on long acting inhaled beta-2 agonists and antimuscarinic agents, as well as inhaled corticosteroids if appropriate, and were complying with therapy. Additional medication such as theophylline, nebulised bronchodilators, prophylactic antibiotics, LTOT and NIV were prescribed as needed. Pulmonary rehabilitation was not an inclusion criteria for this trial, nevertheless we ensured all patients had taken part in a pulmonary rehabilitation course in the past and maintain regular exercises.

3.2.5 STUDY SCHEDULE

Tables 3.3 and 3.4 summarise the testing schedules for patients in the treatment and control arms, respectively. Subjects had a clinical examination and review of health status at every visit (except for the telephone assessments one week following each treatment visit, both in the control and treatment arms). The control treatment involved a clinical assessment with no other interventions or investigations. One week after each procedure, a researcher contacted the subject via telephone to check on overall status and ask about any possible adverse events.

All subjects at our institutions were recruited with a plan to proceed to bilateral sequential LVRC treatments. The more severely affected lung was treated first, followed by a follow-up assessment after 1 month. The contralateral lung was then treated at the earliest available opportunity provided there were no contraindications, with further follow-up assessments at 1 month, 3 months, 6 months and 12 months after the second treatment.

Subjects in the control group underwent an identical protocol of "control treatment" and follow-up visits to the treatment group up to the 3 month follow-up visit. Investigation results from this visit were considered the subjects' baseline results as they crossed over into the treatment arm and proceeded to follow the treatment arm schedule. A CT scan was performed at the 3 month visit in the treatment arm, but not in the control arm, in order to minimise radiation exposure on the basis that no parenchymal lung changes or volume changes should have occurred without any intervention.

Table 3.3: Testing schedule for patients in the LVRC treatment arm

Procedure /Assessment	Visit 1 Pre-Tx	Visit 2 Tx 1	Visit 3 Phone call (1 week post Tx 1)	Visit 4 F/u (1 month post Tx 1)	Visit 5 Tx 2	Visit 6 Phone call (1 week post Tx 2)	Visit 7 F/u (1 month post Tx 2)	Visit 8 F/u (3 months post Tx 2)	Visit 7 F/u (6 months post Tx 2)	Visit 7 F/u (12 months post Tx 2)
Informed Consent	X									
Medical History	X									
Physical Examination	X	X		X	X		X	X	X	X
SGRQ	X			X			X	X	X	X
Spirometry	X			X			X	X	X	X
Lung Volumes	X			X			X	X	X	X
Haematology, Coagulation, Blood Chemistry	X									
Blood Gases	X							X	X	X
ECG	X									
Echocardiogram	X									
mMRC	X			X			X	X	X	X
6 Minute Walk Test	X			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					
HRCT Scan	X							X	X	
Chest X-Ray	X									
Bronchoscopy / LVRC Placement		X			X					
Review Patient Status	X	X	X	X	X	X	X	X	X	X
Exit Study										X

Tx, treatment; F/u, follow-up; SGRQ, St George's Respiratory Questionnaire, ECG, electrocardiogram;, mMRC, modified Medical Research Council dyspnoea scale.

Table 3.4: Testing schedule for patients in the control arm

Procedure /Assessment	Visit 1 Pre-Tx	Visit 2 Control Tx 1	Visit 3 Phone call (1 week post control Tx 1)	Visit 4 F/u (1 month post control Tx 1)	Visit 5 Control Tx 2	Visit 6 Phone call (1 week post control Tx 2)	Visit 7 F/u (1 month post control Tx 2)	Visit 8 F/u (3 months post control Tx 2)
Informed Consent	X							
Medical History	X							
Physical Examination to include SpO_2	X	X		X	X		X	X
SGRQ	X			X			X	X
Spirometry	X			X			X	X
Lung Volumes	X			X			X	X
Haematology, Coagulation, Blood Chemistry	X							
Blood Gases	X							X
ECG	X							
Echocardiogram	X							
Dyspnoea Scale mMRC	X			X			X	X
6 Minute Walk Test	X			X			X	X
Concomitant Medication / O_2 Use	X	X	X	X	X	X	X	X
Pregnancy Testing	X							
High Resolution CT Scan	X							
Chest X-Ray	X							
Bronchoscopy / LVRC Placement								
Review Patient Status	X	X	X	X	X	X	X	X

Tx, treatment; F/u, follow-up; SGRQ, St George's Respiratory Questionnaire, ECG, electrocardiogram;, mMRC, modified Medical Research Council dyspnoea scale.

3.2.6 STATIC AND DYNAMIC LUNG VOLUMES AND GAS TRANSFER MEASUREMENTS:

Lung function testing was performed as per schedules summarised in tables 3.3 and 3.4. The lung function physiologists at the Royal Brompton Hospital lung function department performed all testing using the Compact Master lab system (Jaeger, Germany) as detailed in section 2.3. The European Coal and Steel Workers cohort is used to obtain standardised reference values(120).

3.2.7 ARTERIAL BLOOD GASES

Arterial blood gas (ABG) analysis was performed as per schedules summarised in tables 3.3 and 3.4 by the lung function department physiologists at the Royal Brompton Hospital. This is performed using end capillary blood sample from the participant's earlobe. Analysis for pH, and for partial pressures of O_2 and CO_2 were performed using the Rapidlab 348 analyser (Bayer, Germany).

3.2.8 HRCT ANALYSIS FOR EXCLUSION AND TREATMENT PLANNING

HRCT scanning was performed as per schedule summarised in tables 3.3 and 3.4 and detailed in section 2.5 Volumetric spiral acquisition with contiguous slices (1mm slice thickness on 1mm for lung windows, and 10mm on 10mm mediastinal windows) was taken with the subject in the supine position at full inspiration. Images were also reconstituted to form 6mm slices every 3mm for lung windows to optimise images for processing by the dedicated density analysis software Pulmo-CMS Version 2.1.5 (Medis Specials, Leiden, the Netherlands). This software was used to analyse all baseline CT scans and provide a density map of the lungs. The degree and distribution of emphysematous lung destruction allowed determination of suitability for LVRC treatment (severe bullous destruction excluded patients), as well as treatment planning. Patients with heterogeneous disease had treatment of the worst affected lobe. Patients with homogenous disease had coils inserted in the upper and lower lobes (avoiding the lingua/right middle lobe).

Pulmo-CMS automatically detected the lungs in CT volume scans after the investigator calibrated each scan for blood (using the aorta) and air (outside the patient). The investigator then selected a tracheal seed point and the lung fields were automatically detected by the software. The Relative Area (RA) of pixel values below -950 Hounsfield Units (HU) for each axial slice in each lung (ignoring the extreme apices and bases) was calculated, and heterogeneity of each lung determined by the lung's RA slope. This is defined as the slope in the plot of RAs (or percentage of lung with a density of less than -950 HU) against sequential slice numbers from superior to inferior (figure 3.5). Heterogeneous disease produced a slope-like profile (as in figure 3.5a), with a greater degree of destruction in the upper or lower portions of the lungs. Homogenous disease produced a flat RA curve (as in figure 3.5c).

In heterogeneous disease, the lung with the greater degree of heterogeneity was treated first, on the assumption that this would represent the better potential improvement in lung function. Similarly, in homogeneous disease, the lung with the higher degree of destruction was treated first. If a patient was shown to have one lung with a heterogeneous distribution of disease and one with a homogeneous distribution, the heterogeneous lung was treated first, owing to the greater body of evidence for lung volume reduction in this group.

In terms of inclusion and exclusion based on degree of lung destruction, patients with homogenous distribution were recruited if they had a plateau level of destruction below a threshold of 50% of parenchyma with density of -950HU. A higher level of destruction was accepted in heterogeneous disease provided the healthier portion of the lung had much lower levels of destruction (<25%). Large bullae or blebs excluded subjects from this trial as these will negatively impact on the LVRC's ability to tension the lung. The tension created by the coils will distort the blebs/bullae without significant retensioning of the surrounding parenchyma, as all the force is transmitted to the more compliant bullae. The axial slices of the CT were individually examined looking for blebs larger than 2cm in diameter (the size of a 50p coin). This was aided by Pulmo-CMS CT density reconstructions with a purple-scale (darker representing more destruction) as in figure 4.6. More than one dark purple bleb of this size excluded subjects from enrolment onto this trial. Data presented as a poster at the ERS conference in Barcelona 2010 (132) suggested that the 'ideal' heterogeneous lung has a percentage area destruction at the top 25th centile axial slice being more than twice as bad as at the 75th centile axial cut.

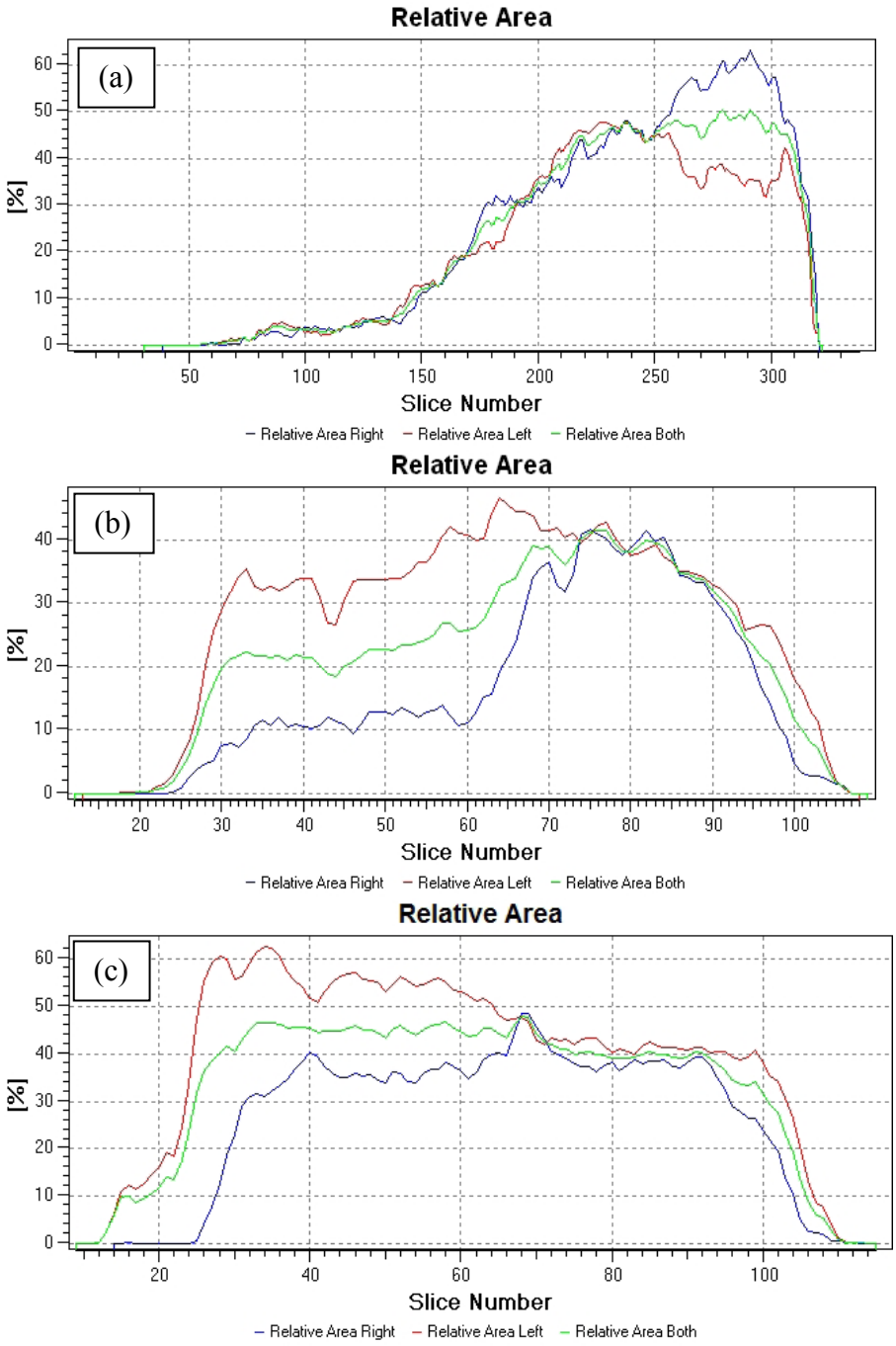


Figure 3.5: CT density graphical output of quantitative results using Pulmo-CMS. (a) Heterogeneous upper lobe predominant disease bilaterally. (b) Upper lobe predominant heterogeneous disease in right lung, homogenous disease in the left lung. (c) Homogenous disease bilaterally.

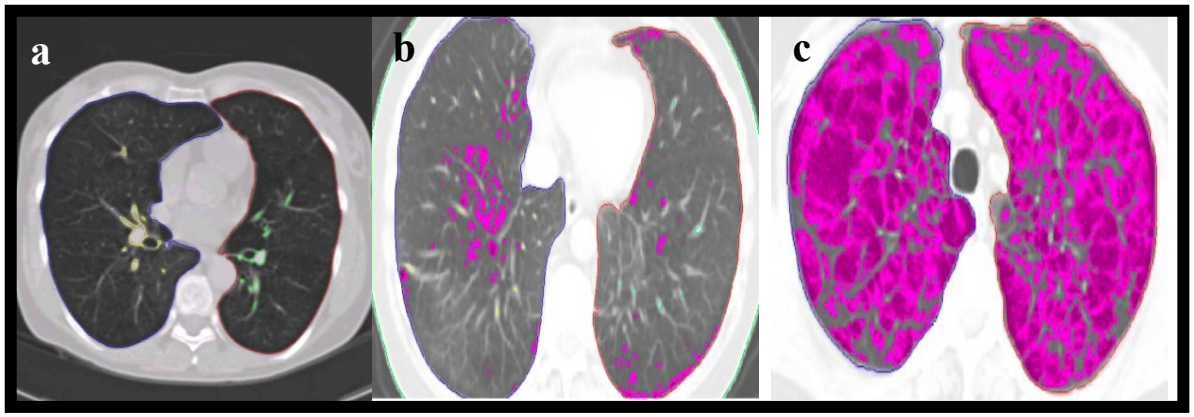


Figure 3.6: Pulmo-CMS images. (a) each lung is delineated and major blood vessels excluded from analysis. (b,c) axial images with density mapping; darker purple represents worse parenchymal damage.

3.2.9 6 MINUTE WALKING DISTANCE

The 6 minute walking distance (6MWD) is a well validated test of exercise capacity in patients with COPD, and is commonly used both in clinical practice and in research. In this study patients had their 6MWD measured as per schedule summarised in tables 3.3 and 3.4. The American Thoracic Society criteria(128) for the 6MWD were followed. All tests were performed in the same 30 metre long corridor at the Royal Brompton Hospital.

3.2.10 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE

The St. George's Respiratory Questionnaire (122) is a 76-item health status survey specific for COPD and other respiratory disease. It is designed to measure impact of the disease on overall health, daily life, and perceived well-being. The participants answered the questions considering the preceding 4 weeks on visits as per schedule summarised in tables 3.3 and 3.4.

3.2.11 MRC DYSPNOEA SCORE

Participants in this trial completed an mMRC score as per schedule summarised in tables 3.3 and 3.4.

3.2.12 BRONCHOSCOPIC PROCEDURE

The participant was given a bronchoscopy information leaflet to review with relevant instructions at least 24 hours in advance of the procedure. Departmental pre-procedure and post-procedure protocols for routine bronchoscopy were followed for patients in the treatment arm. Subjects were consented and 5mg salbutamol with 500mcg ipratropium bromide was administered via nebuliser before the procedure. Subjects were sedated using midazolam (2-5mg) and fentanyl (50-200mcg), or general anaesthesia as per anaesthetist preference. Lignocaine 2% topical spray (4-6 mls) was used to anaesthetise the pharynx, vocal cords and airways as per usual protocol for bronchoscopy. Once sedated, the subject was intubated using size 8-8.5 cuffless endotracheal tube. A diagnostic bronchoscopy was performed before the target lobe was approached.

The guide wire was carefully passed into the target subsegment and advanced under fluoroscopic guidance, avoiding sharp changes of direction, to a distance still safely away from the pleural edge (>35mm). The delivery catheter was then advanced over the guide wire. A measurement of the length of the guide wire was made by counting how many 25mm markers (visible on fluoroscopy) exist between the distal end of the bronchoscope and the tip of the guide wire (figure 3.7c). The LVR coil was sized by adding 50mm to the measured distance (over-sizing by 50mm). During our early experience of coil deployment we observed that the proximal end of the coil tended to recoil away from sight, prompting over-sizing to keep the proximal end of the coil within reach in case there is a need for removal in the future. The guide wire was then removed carefully ensuring that the delivery catheter remained in the same position. The appropriate sized coil was then prepared for deployment by extracting it from its casing directly into a straight deployment cartridge using forceps (figure 3.8a-c). The cartridge was coupled to the delivery catheter and the coil advanced through the bronchoscope and into the target subsegment. Under fluoroscopic guidance, coils were advanced until the distal tip reached the distal end of the delivery catheter (figure 3.7e). The sheath was then slowly pulled back (figure 3.7f). The nitinol coil regained its pre-determined shape as it was released from within the sheath, and gentle advancement of the coil and pulling back of the sheath was continued until the forceps was seen to exit from the distal end of the sheath. Under bronchoscopic vision, the forceps were then opened releasing the coil (figure 3.7g), with the proximal end of the sheath ideally visible in the target subsegment (figure 3.7h).

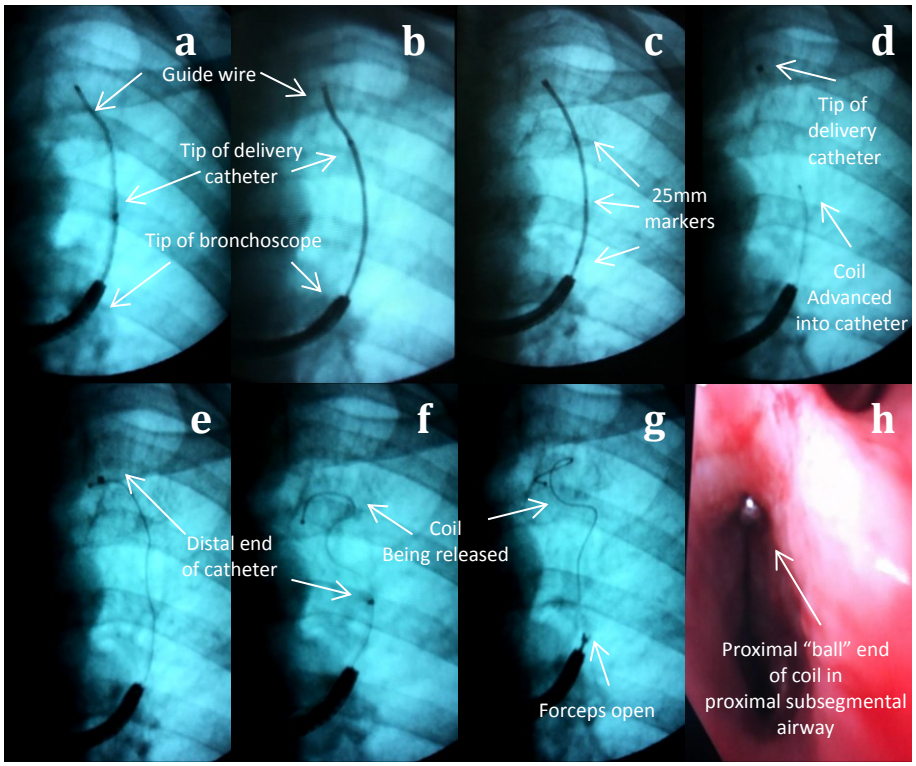


Figure 3.7(a-h): Coil deployment process. (a) the guide wire is inserted into the target subsegment, (b,c) the catheter is advanced until the distal tip aligns with the distal end guidewire, and measurement of required coil made by the number of visible 25mm markers, (d) the guidewire is removed and replaced by the coil, (e-h) the catheter is withdrawn and the coil released from the forceps in the proximal subsegmental airway.

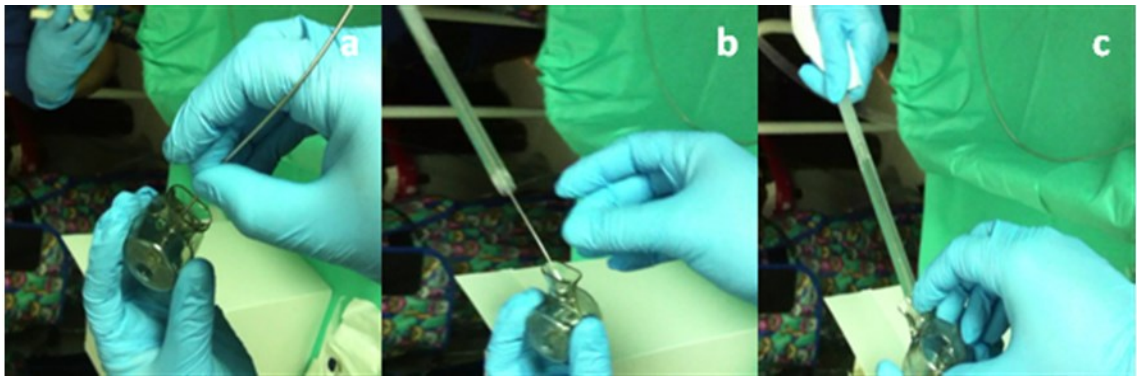


Figure 3.8: Coil preparation for deployment. (a) The proximal end of the coil is grasped with forceps whilst inside the packaging and (b-c) is then pulled into the straight loading cartridge ready for deployment through a delivery catheter.

The coil can be removed by reversing the deployment procedure: re-capturing the proximal end of the implant with the forceps and then advancing the catheter distally over the implant while maintaining the relative position of the implant to the bronchoscope.

In patients with heterogeneous disease, the worst affected lobes were treated by inserting a coil into every visible distinct subsegment whilst avoiding concentration of too many coils in one region and achieving a broad "spread" of coils on fluoroscopy (figure 3.9). Between 8 and 12 coils are generally required for lobar treatment. Patients with homogenous disease had coils inserted into all major accessible subsegmental airways in the upper and lower lobes (avoiding the lingua/right middle lobe), evenly distributed and up to a maximum of 14 coils per lung.

Post-procedure care is identical to routine post-bronchoscopy care, with added vigilance regarding the risk of hypoventilation secondary to sedation with opiates and benzodiazepines. None of our patients have required non-invasive ventilation (but it was used in recovery until sedation wore off in patients already on long-term domiciliary nocturnal non-invasive ventilation). A chest radiograph was performed one hour post procedure to rule out a pneumothorax. The subject was then transferred to the respiratory ward for overnight observation, and discharged the next morning if well. A 7 day course of prednisolone and suitable antibiotics was prescribed and started on the day of the procedure as procedure/coil induced bronchospasm has been reported in the early pilot studies.(103)

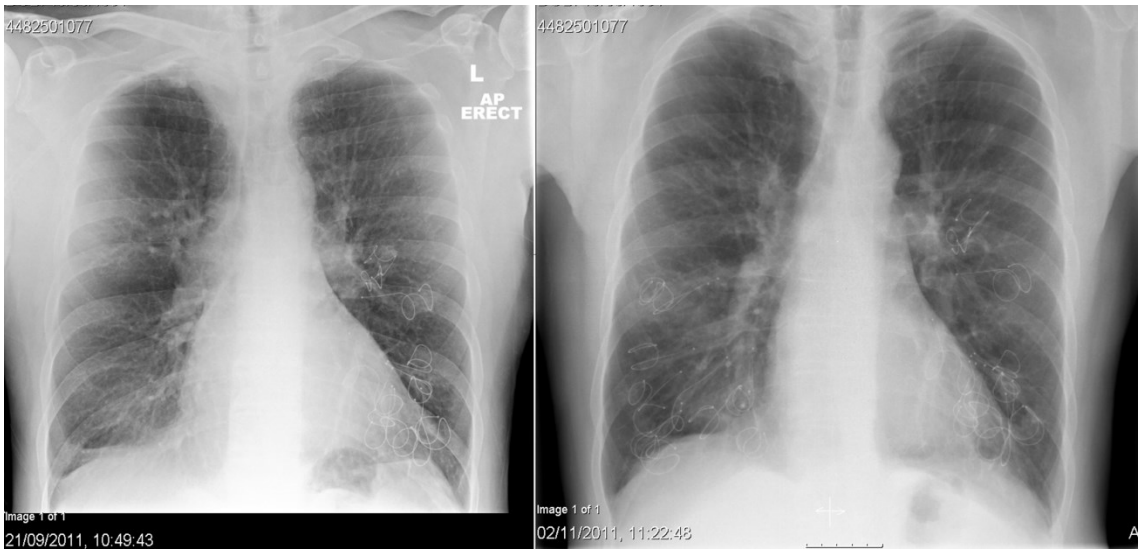


Figure 3.9: Chest radiographs of a patient with lower lobe predominant heterogeneous disease one hour after the first and second treatments. The coils are evenly spread throughout the treated lobes. The shape of the right hemidiaphragm is already altered one hour after the procedure.

3.2.13 STATISTICAL ANALYSIS

An intention to treat analysis was conducted for the primary endpoint, secondary endpoints and non-endpoint outcomes up to the 3 month time point. For subjects whose last recorded values were less than 3 months from the final treatment, their last recorded value was carried forward.

Secondary and non-endpoint analysis for 6 and 12 month follow-up data (uncontrolled) was performed using the available data.

Two-tailed unpaired t-tests were performed on the between group differences in mean change in outcomes, except for unpaired changes in mMRC score, where the Mann Whitney test was used. Two-tailed paired t-tests and repeated measures ANOVA with Bonferroni's multiple comparison test were performed on data at visits from 1 month post treatment visit 1 through 12 months post final treatment against baseline data within each group, except for paired changes in mMRC score where the Wilcoxon signed rank test and Friedman's test with Dunn's multiple comparison test were used.

3.2.14 ROLE OF THE SPONSOR AND CONFLICT OF INTEREST DECLARATION

The study sponsor and funder was PneumRx Inc., the manufacturer of the LVRCs. The sponsor assisted the chief investigator Dr. Pallav Shah with the trial design and financed the study, reimbursing my institutions for trial expenses. The sponsor facilitated independent safety and monitoring audit, as well as central data collation and appointed an independent statistician for data analysis. The data presented here was collated separately by the author who performed independent statistical analysis of data from patients recruited at this institution. The author received travel grants for the purposes of attending international conferences and presenting trial data.

3.3 RESULTS

3.3.1 BASELINE DATA

36 patients were recruited at our institutions, 18 randomised to the treatment arm and 18 to the control arm. Another 10 patients were recruited at a second site(Gartnavel Hospital, Glasgow, UK) as part of this trial. In this thesis, only data from patients recruited at our institutions are presented. All control subjects crossed over to the treatment arm after their 3 months post control treatment 2 follow-up visit. Therefore control baseline data are available on 18 subjects and treatment baseline data on 36 subjects. For control arm subjects who crossed over to the treatment arm, the 3 month post 2nd control treatment follow-up visit data was considered their treatment baseline data. Baseline demographics and lung function data are illustrated in table 3.3.

Table 3.5: Baseline characteristics and lung function for participants of the coil study.

	Treatment	Control	p value
Number	36	18	-
Age (y)	64.6 (8.52)	63.6 (8.05)	0.67 Δ
Male (%)	58%	67%	0.77 ∞
BMI	24.2 (4.38)	24.4 (4.64)	0.46 Δ
FEV1 % predicted	27.3 (7.31)	28.6 (7.44)	0.58 Δ
FVC % predicted	82.8 (17.6)	87.4 (17.5)	0.18 Δ
RV % predicted	231.9 (48.7)	241.7 (70.6)	0.70 Δ
RV/TLC	63.5 (6.4)	62.8 (7.6)	0.72 ₸
TLco % predicted	33.4 (10.2)	34.7 (11.1)	0.81 ₸
mMRC	2.53 (0.7)	2.33 (0.49)	0.32 ₸
SGRQ	59.1 (13.1)	53.2 (12.8)	0.09 Δ
6MWD (m)	305.4 (15.1)	338.6 (26.3)	0.24 Δ

Presented as mean (SD)

Δ Unpaired t-tests

∞ Fisher's exact test

₸ Mann-Whitney test

3.3.2 PROCEDURE DETAILS AND FOLLOW-UP DATA AVAILABILITY

The flow diagram in Figure 3.10 illustrates subject numbers in the trial at each data collection time point. Data on 18 control subjects and 32 treatment subjects were available at the 3 month primary endpoint visit. One subject improved sufficiently after his first LVR coil treatment to be able to return to full time work, and was unable to commit to further follow-up visits. He declined contralateral treatment and withdrew from the study. Two subjects died before their 3 month follow-up visits (details in adverse events section below). One further data set from the 3 month post 2nd treatment primary endpoint visit was not available owing to a prolonged hospital admission. For the intention to treat analysis, data from three subjects' latest 1 month post treatment visit and the baseline data of the patient who died before any follow-up visits were performed, were carried forward.

At the 6 month post final treatment time point, data was available for 33 subjects. At the 12 month time point, data was available for 29 subjects; Two subjects passed away, one subject moved home and was lost to follow-up, and one patient withdrew from the trial as she needed to focus her energy on caring for her husband who had been recently diagnosed with cancer.

A total of 68 treatment procedures were performed in 36 patients as part of this trial (one death and one drop out before the 2nd procedure, and two did not have a 2nd treatment for medical reasons). In one case the patient suffered from recurrent exacerbations and was not well enough for a sustained period to proceed with a second bronchoscopy, and the research team did not wish to perform a procedure which could trigger further exacerbations. Another patient had an extended hospital admission locally due to multiple unrelated medical conditions including urinary tract infections, severe urinary retention eventually requiring suprapubic catheter insertion, and later rectal bleeding requiring colonoscopy. The research team felt that it would not be in the patient's best interest to subject her to further bronchoscopy. The 3 month post 1st (and final) treatment visit data was used as the primary end point data for these two patients.

Sixty two of 68 bronchoscopic procedures were performed at the Chelsea and Westminster Hospital endoscopy unit using moderate sedation as day case procedures (mean (SD) dose of midazolam and fentanyl administered was 3.9 (1.6) mg and 86.3 (27.4) mcg, respectively). Three patients were known not to have tolerated bronchoscopy under moderate sedation in the past and had their procedures performed in the Royal Brompton Hospital operating theatres under general anaesthesia. The mean (SD) time from the final treatment to the 3 month

endpoint visit was 93.9 (15.2) days. Two subjects had died before attending any follow-up visits after final treatment.

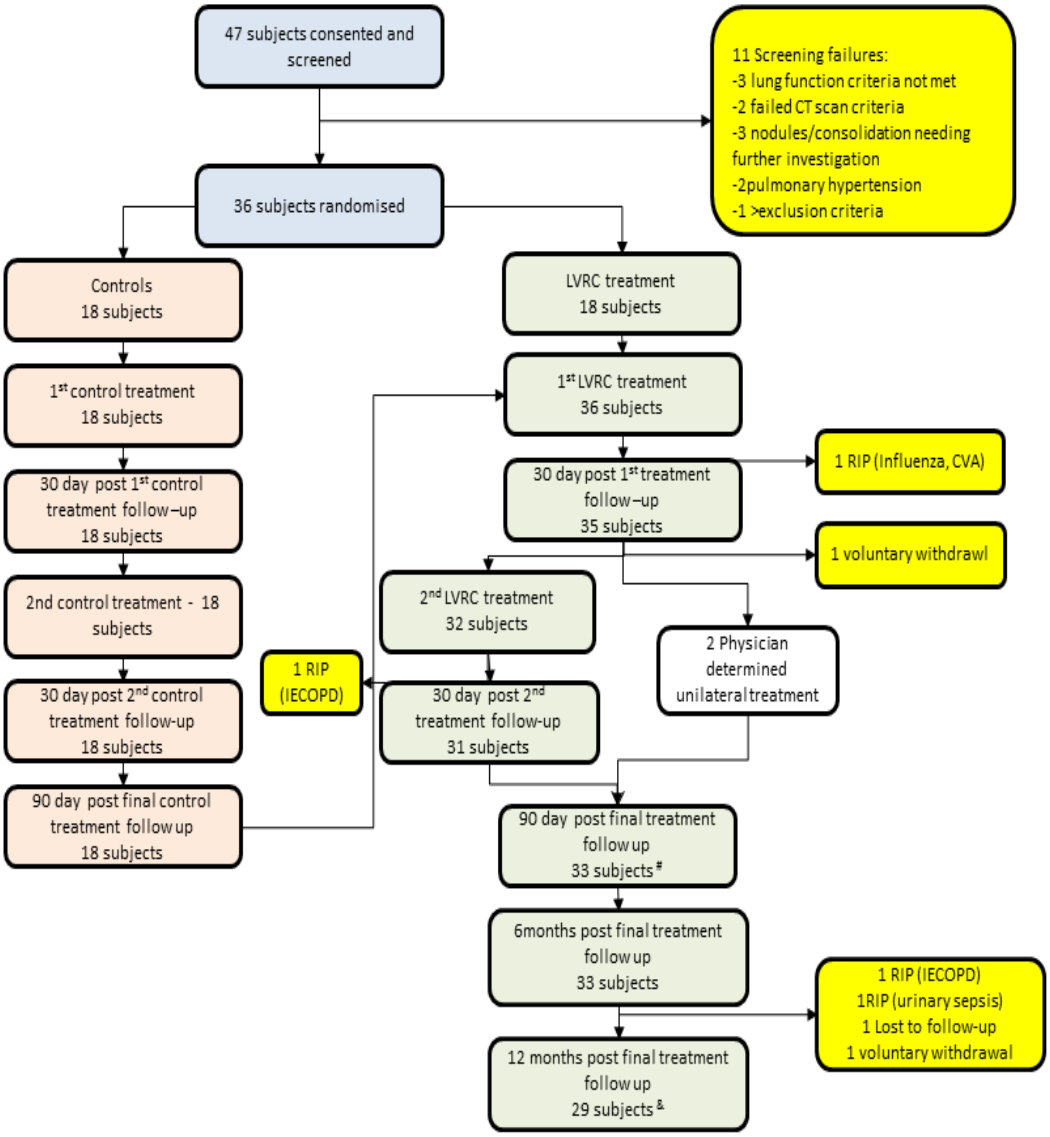


Figure 3.10: Flow diagram of subjects' journey through the coil study. LVRC, Lung Volume Reduction Coils); IECOPD, Infective exacerbation of COPD; CVA, Cerebrovascular accident.
#1 data set not available due to extended hospital admission covering follow-up visit timeframe.
&1 lung function set of results not available as subject refused to perform lung function during the visit.
A further 10 subjects were recruited at another site as part of this trial – not illustrated.

3.3.3 PRIMARY ENDPOINT

3 months following the final treatment there was a clinically and statistically significant mean (SD) reduction in the SGRQ of 6.32 points (11.4), p=0.0017 in the LVRC group compared to baseline. There was no significant change in the SGRQ in the control arm (Δ +2.59 (12.2),

p=0.38). The primary end point between group difference in the mean change in SGRQ was clinically and statistically significant at Δ-8.91 points, (95% CI -15.6 to -2.24), p=0.0097 (figures 3.11 and 3.12).

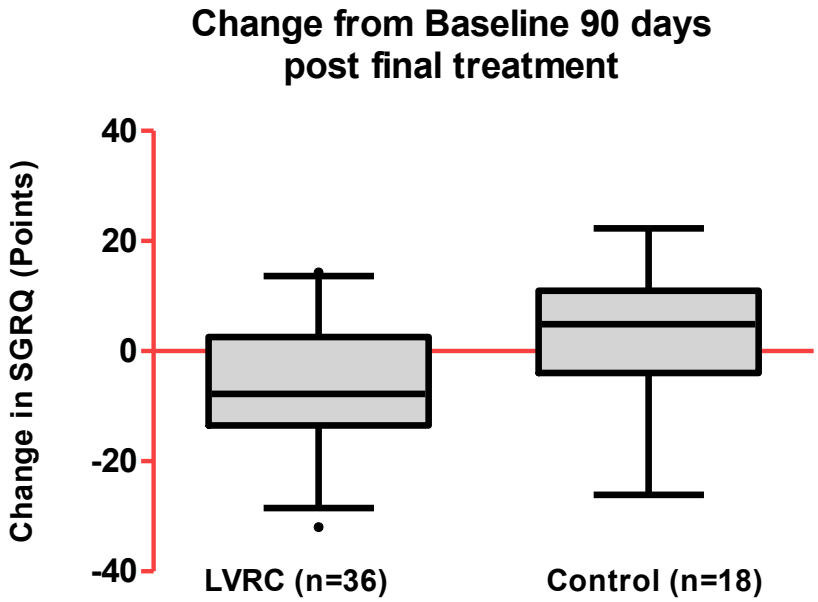


Figure 3.11: Boxplot analysis of the primary endpoint change in SGRQ in the intent-to-treat population.

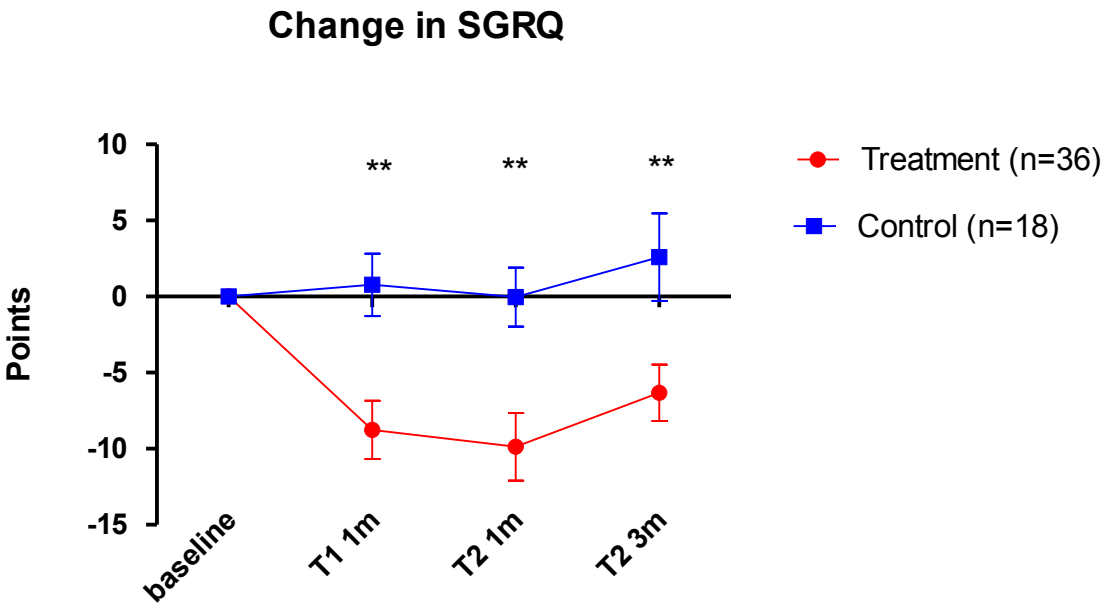


Figure 3.12: Change in SGRQ from baseline.

Unpaired t-tests between the LVRC and control groups at time points T1 1m (1 month post 1st treatment), T2 1m (1 month post 2nd treatment), and T2 3m (3 months post final treatment). ** <0.01

3.3.4 SECONDARY ENDPOINTS

1) Between group differences 3 months post final treatment in the change from baseline:

- ***Percentage change in FEV_1:*** 3 months following the final treatment there was a clinically and statistically significant mean (SD) percentage increase in the FEV_1 of 15.2 (16.8) %, p<0.001 in the LVRC group. There was no significant change in the FEV_1 in the control arm (Δ +0.097 (0.11) %, p=0.77). The between group difference in the mean change in FEV_1 was clinically and statistically significant at Δ15.2%, (95% CI 5.03 to 23.4), p=0.0031 (mean absolute volume 110mls) (figures 3.13 and 4.14).
- ***Percentage change in FVC:*** There was a significant between group difference in the % change in FVC 1 month after the second treatment (Δ13.1% (95%CI 5.42 to 20.1) p=0.0012) and 3 months after the final treatment (Δ9.35% (95%CI 2.8 to 15.9) p=0.006), but not 1 month after the 1st treatment (figures 3.13 and 4.14).
- ***Change in RV:*** The LVRC treatment group had a mean (SD) reduction in the residual volume of 0.386 (0.59) litres, p=0.0004 3 months post final treatment compared to baseline. There was no significant change in the RV in the control group 3 months post final control treatment as compared to baseline (Δ-0.027 (0.33) litres, p=0.74). The between group difference in the mean change in RV was statistically and clinically significant at Δ-0.359 litres (95% CI -0.66 to -0.059), p=0.019 (figures 3.13 and 4.14).
- ***Change in TLC:*** There was no significant change in the TLC in either group (LVRC group -0.130 (0.43) litres, control group 0.040 (0.20) litres), with a between group difference of Δ-0.172 litres (95% CI -0.131 to 0.107) p =0.17 (figures 4.12 and 4.13).
- ***Change in the 6MWD:*** The LVRC treatment group had a mean (SD) increase in the 6MWD of 69.2 (60.8) m, p<0.0001 3 months post final treatment as compared to baseline. There was no significant change in the 6MWD in the control group at 3 months post final treatment compared to baseline (Δ-10.8 (44.6) m, p=0.32). The between group difference in the mean change in the 6MWD was statistically and clinically significant at Δ+80.0 meters, (95% CI 47.5 to 112.5), p<0.0001 figures 3.13 and 4.14).
- ***Change in mMRC dyspnoea score:*** The LVRC treatment group had a mean (SD) reduction in the mMRC score of 0.44 (0.84) points p=0.003, 3 months post final treatment as compared to baseline. There was no significant change in the mMRC score in the control group 3 months post final treatment as compared to baseline (Δ-0.06

(0.73) points, p=0.75. There was no statistically significant difference between the medians of the change in mMRC score between the 2 groups (medians (range) 0 (-2 to 1) in the treatment arm, 0 (-1 to 2) in the control arm, p=0.17) (figures 3.13 and 4.14).

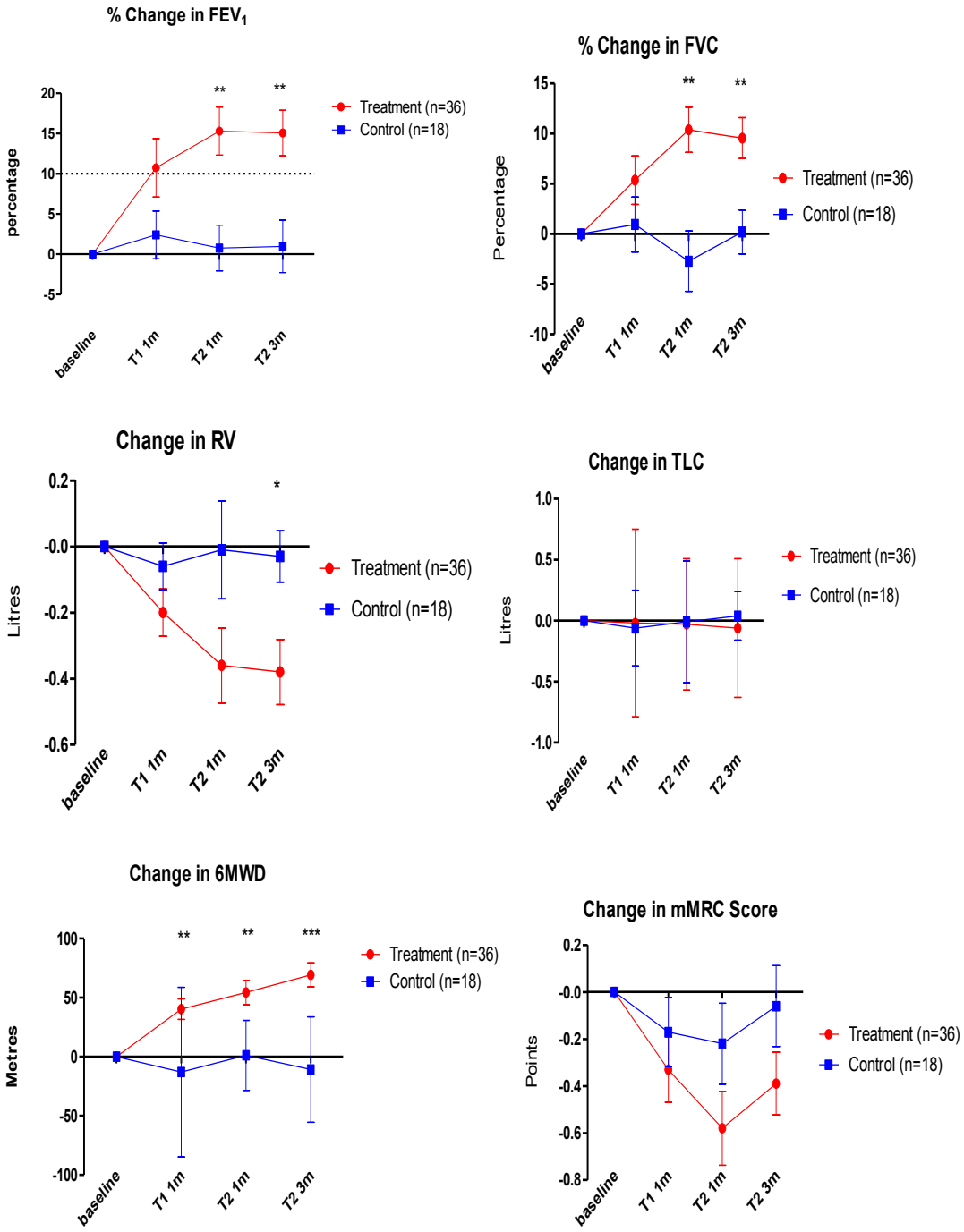


Figure 3.13: Between group differences in the secondary outcome measures.

Presented as mean with error bars. Unpaired t-tests except for mMRC (Mann Whitney test). Statistically significant differences identified where they occur with: * p<0.05, **p<0.01, *** p<0.001

- ***Responder analysis:*** Using an intention to treat analysis, a statistically significantly higher proportion of subjects met the responder criteria for reduction in SGRQ in the LVRC treatment arm compared to the control arm, both at the 4 point and 8 point minimally clinically important difference (MCID) thresholds (table 3.4). The responder analysis at the 8 point threshold was conducted alongside the accepted 4 point MCID threshold for this patient population (133) as this was an unblinded study and the primary outcome is a patient reported measure. There were significant differences in the responder rates between the 2 groups in reduction in RV below 0.35 litres (134) and improvements in the 6MWD above 26m,(126) but not in the FEV_1 increase of >12% MCID (135) (though if we adopt a 10% FEV_1 MCID threshold the difference between the groups is significant (58% in the LVRC arm vs 28% in the control arm, p=0.045) (Table 3.4).

Table 3.6: Responder Analysis of Efficacy Outcomes in the LVRC treatment and control arms -change from baseline at 90 days post final treatment.

	LVRC Treatment (n= 36)	**Control (n=18)**	**p-value ***
Primary outcome			
SGRQ- 4 Point improvement (133)	60.0% (22/36)	22.2% (4/18)	0.0096
SGRQ- 8 Point improvement	50.0% (18/36)	16.7% (3/18)	0.0209
Secondary outcomes			
RV - 0.35 L improvement (134)	55.6% (20/36)	11.1% (2/18)	0.0027
6-minute Walk Test- 26m improvement (126)	77.8% (28/36)	16.6% (3/18)	<0.0001
FEV_1- 12% improvement (135)	52.8% (19/36)	27.8% (5/18)	0.145

*p-value determined by Fisher's exact test.

Predictors of Response:

Univariate linear regression comparing baseline measures with outcomes has identified only one significant relationship: RV% predicted at baseline and change in RV (fig 3.14). Our data suggests that subjects with RV <190% predicted at baseline are less likely to respond to treatment in terms of reduction in RV. However there was no similar correlation with changes in exercise capacity or quality of life. There were no other significant correlations comparing FEV_1 % predicted, 6MWD, SGRQ and TLco with all other outcome measures suggesting our inclusion criteria were otherwise appropriate.

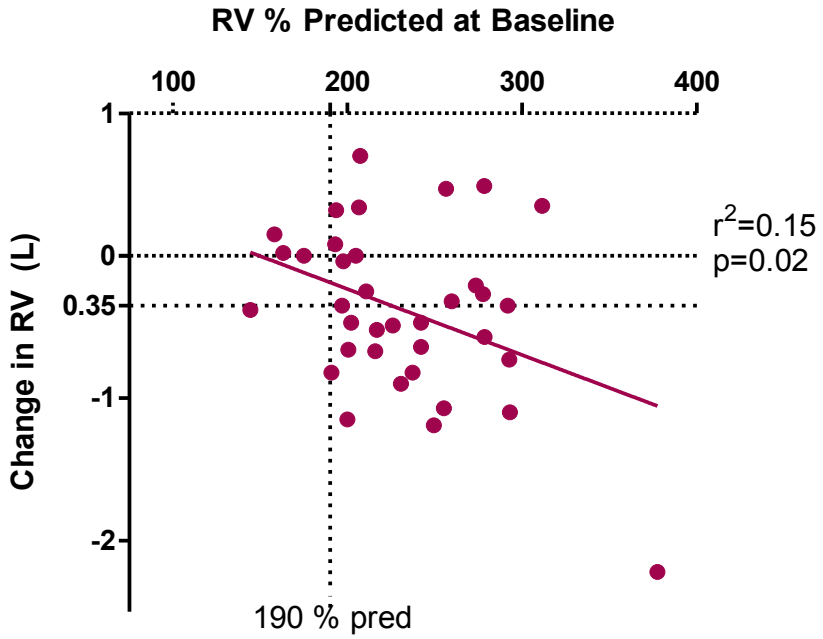


Figure 3.14: Correlation of baseline RV % predicted versus change in RV post LVRC treatment

2) Change in outcome measures 6 and 12 months post treatment:

The 6 and 12 month outcome data is detailed in Table 3.7 and illustrated in Figure 3.15. Repeated measures ANOVA and Bonferroni's multiple comparison tests were performed for statistical analysis for all outcomes except mMRC, where Friedman's test with Dunn's comparison of all pairs of columns was performed. For the subjects remaining in the study 6 and 12 months post final treatment, the SGRQ remained statistically and clinically significantly lower than baseline 6 months (Δ-11.7 (15.0) points) and 12 months (Δ-8.9 (13.2) points) following treatment. FEV_1 was statistically significantly higher than baseline at 6 months (Δ10.1 (20.7) %), and non-statistically significantly higher at 12 months (Δ10.7 (23.5) %); below the MCID of 12%. Similarly, the RV was statistically lower than baseline at 6 but not 12 months, at means under the MCID of -0.35 litres. The statistically and clinically significant benefits in the 6MWD seen at 3 months were maintained at 6 and 12 months though smaller in magnitude (Δ61.7 (52.6) and Δ47.9 (52.4) at 6 and 12 months, respectively). Reductions in the mMRC score of 0.64 (0.84) and 0.48 (0.74) point at 6 and 12 months, respectively, were in keeping with improvements in the SGRQ.

A responder analysis of subjects 6 and 12 months post treatment for the available data at these time points (table 3.5) shows small falls in the responder rates in the measured outcomes. Twelve months after treatment 55%, 46%, 62% and 43% of subjects still had significant benefits exceeding the MCIDs in the SGRQ, RV, 6MWD and FEV_1, respectively.

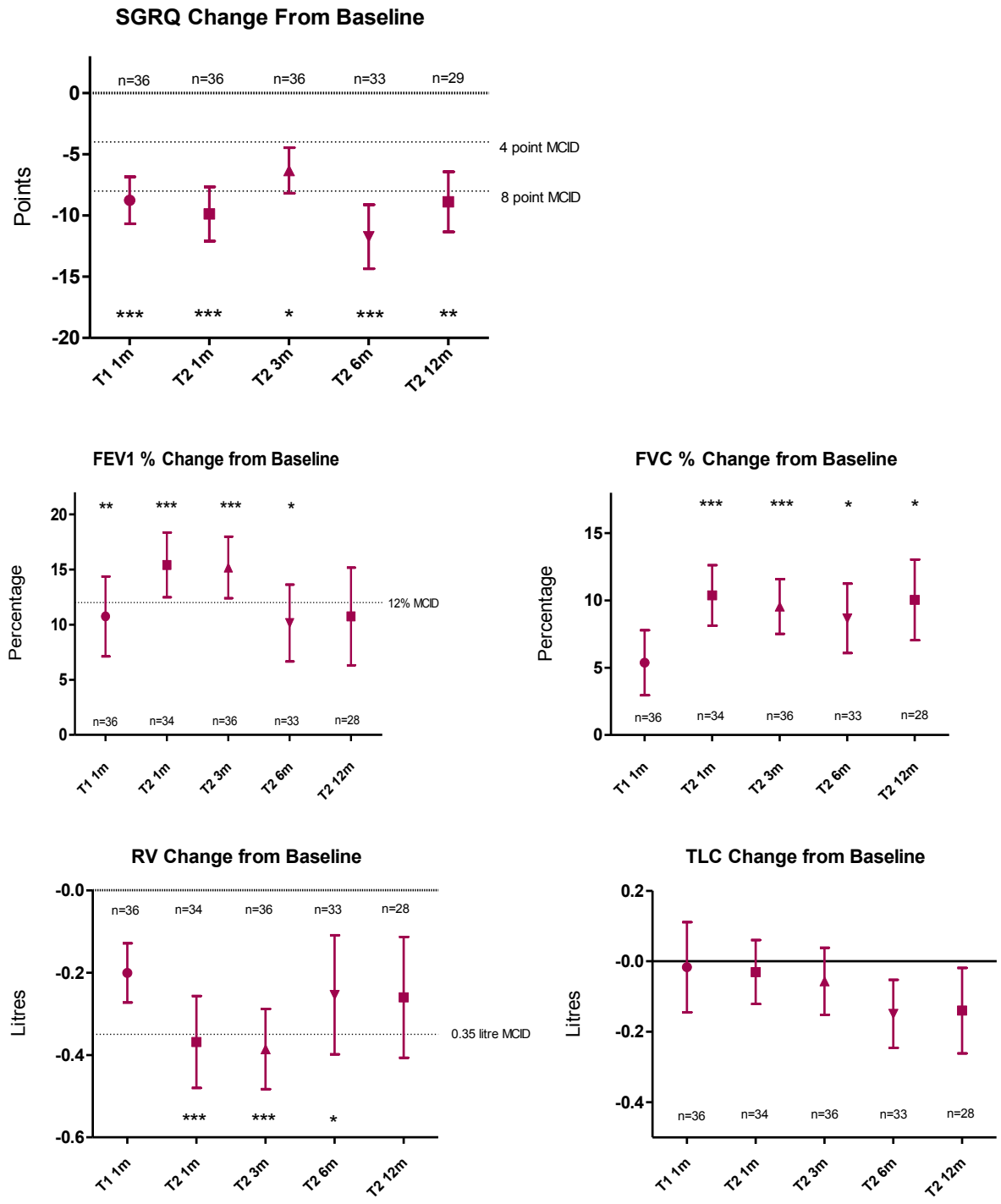


Figure 3.15: Continued with legend overleaf.

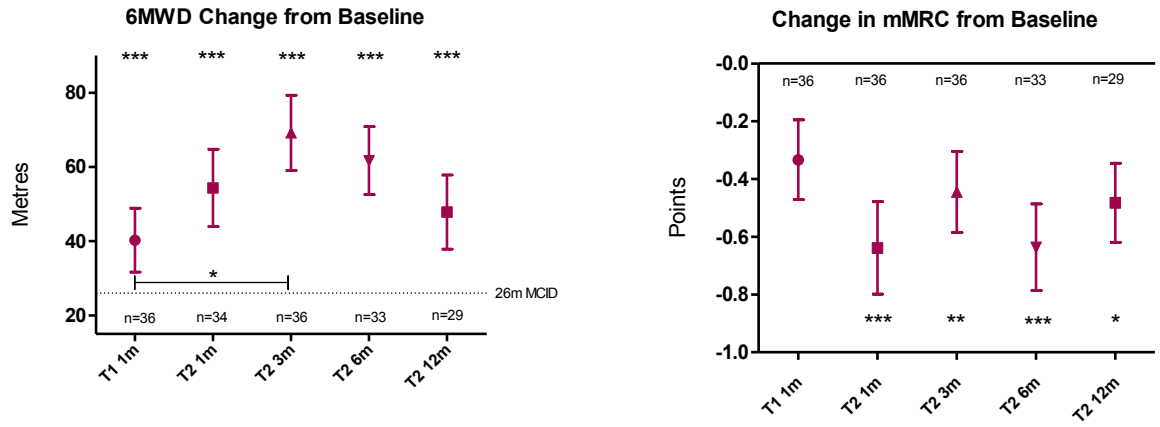


Figure 3.15: Change in outcome measures from baseline at each time point (1 month after 1st (T1 1m) and final (T2 1m) treatments, and 3 months (T2 3m), 6 months (T2 6m) and 12 months (T2 12m) after the final treatment. Repeated measures ANOVA performed with Bonferroni's multiple comparison test, or Friedman's test with Dunn's comparison of all pairs of columns as appropriate. Statistical differences from baseline marked at each time point where they occur, and highlighted with connecting bars when significant between time points. * p=<0.05, ** p=<0.01, *** p=<0.001.

	3 months post T2 *(n)*	**6 months post T2 (n)**	**12 months post T2 (n)**
Primary outcome			
SGRQ- 4 Point improvement (133)	60.0% (22/36)	66.7% (22/33)	55.2% (16/29)
SGRQ- 8 Point improvement	50.0% (18/36)	54.5.7% (18/33)	41.4% (12/29)
Secondary outcomes			
RV - 0.35 L improvement (134)	55.6% (20/36)	33.3% (11/33)	46.4% (13/28)
6-minute Walk Test- 26m improvement (126)	77.8% (28/36)	75.8% (25/33)	62.1% (18/29)
FEV_1- 12% improvement (135)	52.8% (19/36)	42.4% (14/33)	42.9% (12/28)

Table 3.7: Responder analysis of efficacy outcomes in the LVRC treatment arm 3,6 and 12 months post final treatment.

3) Adverse Events:

Table 3.6 represents the adverse events in both the treatment and control arms by interval. In the immediate post-treatment period and up to 3 months following the final treatment, there was no difference in the rate of infective and non-infective exacerbations of COPD between the 2 study arms. From 3 months post treatment up to the final 12 month follow-up visit, 20 patients suffered from an average of 3 infective exacerbations each, whilst 16 patients did not suffer any. Five patients suffered from minor haemoptysis (less than 10mls per day for more than 4 days).

Deaths: One subject developed a severe infective exacerbation secondary to H1N1 influenza during the 2009 epidemic, and passed away due to a haemorrhagic stroke whilst ventilated on the intensive care unit. One subject developed a severe infective exacerbation of his COPD approximately 10 weeks after his second treatment and passed away from respiratory failure refractive to ventilatory therapy via endotracheal tube at the end of a 2 week hospital admission. One subject died secondary to a severe infective exacerbation of COPD 7 months after his final treatment. In all three cases the LVRCs did not appear to play a role in the subject's death. One subject died from severe urinary sepsis 11 months after her treatment.

Pneumothoraces: There were eight pneumothoraces following 68 procedures (11.7%) in the treatment recovery period. Six of these occurred within 2 hours of the procedure and were picked up on the routine post-procedure chest X-ray, and one confirmed before discharge the next morning. Six of these seven patients were treated with small bore chest tube drainage and all were discharged within 72 hours. Two patients had overnight chest tube drainage and did not have a delayed discharge, hence the pneumothorax in these two cases was not considered an SAE as per the *a priori* definition of SAE set in the protocol. One subject was diagnosed with a pneumothorax during his 1 month follow-up visit (he had been symptomatic for 10 days and self medicated with antibiotics and prednisolone suspecting an infective exacerbation). He had a 14 day admission and required large bore surgical chest drain insertion and attachment to wall suction to treat a bronchopleural fistula. He proceeded with his contralateral treatment 6 weeks later without complication. One subject had a recurrence of his immediate post-procedure pneumothorax 3 months later, and was managed with small bore chest tube drainage and suction for 7 days. He was reviewed by thoracic surgeons who did not feel intervention was necessary. He remains problem free 3 years after his second pneumothorax.

Table 3.8: Adverse Events (Serious Adverse Events (SAEs)) by interval.

Adverse Events (SAEs)	**LVRC Treatment** (n=68 procedures)			**Control** (n=36 procedure equivalents)			**p-value***
	Events, n	Patients, n	Incidence (%)	Events, n	Patients, n	Incidence (%)	
Treatment Recovery Period (up to day 28 post procedure)							
Non-IECOPD	4 (0)	3 (0)	5.8	2 (0)	2 (0)	5.6	0.69
IECOPD [π]	15 (1)	8 (1)	22.1	7 (0)	7 (0)	19.4	0.81
Haemoptysis	5 (0)	5(0)	7.4	0	0	0	0.16
Pneumothorax	8 (6)	8(6)	11.7	0	0	0	**0.052**
Death	1 (1)	1 (1)	1.5	0	0	0	0.99
Adverse Events (SAEs)	**LVRC Treatment** (n=36 patients)			**Control** (n=18 patients)			**p-value***
	Events, n	Patients, n	Incidence (%)	Events, N	Patients, n	Incidence (%)	
Day 29 post each procedure up to next procedure or 90 day follow-up visit							
Non-IECOPD	3 (0)	3 (0)	8.3	2 (0)	2 (0)	11.1	0.99
IECOPD [π]	15 (2)	12 (2)	41.7	9 (1)	7 (1)	50.0	0.58
Haemoptysis	0	0	0	0	0	0	0.99
Pneumothorax	1 (1)	1 (1)	2.8	0	0	0	0.99
Death	1 (1)	1 (1)	2.8	0	0	0	0.99
90 days to 12 months post final treatment visits							
Non-IECOPD	12 (1)	4 (1)	33.3				
IECOPD [π]	60 (5)	20 (2)	166.7				
Haemoptysis	1 (0)	1 (0)	2.8				
Pneumothorax	0	0	0				
Death	2 (2)	2 (2)	5.6				

Event incidence for treatment recovery period calculated by n events/n procedures (or n procedure equivalents), and for subsequent periods by n events/n subjects.
*p-value calculated using Fisher's exact test comparing number of events.
[π]Includes pneumonia

Table 3.9: LVRC treatment arm primary, secondary and non-endpoint measures

Outcome	Baseline	T1 1m	P value	T2 1m	p value	3 months	p value	6 months	p value	12 months	p-value
SGRQ (points)	59.6 (12.8)	50.9 (16.4)	***	49.74 (17.3)	***	53.3 (16.0)	*	48.1 (17.7)	***	50.9 (14.8)	**
FEV_1 (L)	0.72 (0.17)	0.79 (0.20)	**	0.83 (0.20)	***	0.83 (0.21)	***	0.79 (0.21)	*	0.79 (0.22)	ns
FVC (L)	2.77 (0.61)	2.89 (0.63)	ns	3.04 (0.68)	***	3.02 (0.63)	***	2.98 (0.59)	*	3.08 (0.59)	*
RV (L)	5.13 (1.19)	4.93 (1.11)	ns	4.77 (1.06)	***	4.75 (1.09)	***	4.82 (1.03)	*	4.94 (1.03)	ns
TLC (L)	8.03 (1.35)	8.01 (1.41)	ns	8.00 (1.29)	ns	7.97 (1.28)	ns	7.89 (1.21)	ns	8.03 (1.29)	ns
6MWD (m)	305 (91)	346 (110)	***	360 (109)	***	375 (106)	***	365 (100)	***	349 (89)	***
mMRC (points)	2 (1-4)	2 (1-4)	ns	2 (1-3)	*	2 (1-4)	ns	2 (1-4)	*	2 (1-4)	ns
FRC (L)	6.18 (1.28)	6.04 (1.18)	ns	7.36 (8.76)	ns	5.80 (1.19)	ns	5.97 (1.07)	ns	6.09 (1.18)	ns
RV/TLC (%)	63.5 (6.41)	61.2 (6.7)	*	59.5 (7.0)	***	59.5 (6.4)	***	60.9 (6.7)	*	60.4 (6.3)	ns
TLco	2.74 (0.83)	2.73 (0.75)	ns	2.72 (0.74)	ns	2.72 (0.47)	ns	2.67 (0.76)	ns	2.67 (0.87)	ns
PaO_2 (kPa)	9.21 (1.24)					9.14 (1.16)	ns	9.26 (1.13)	ns	9.20 (1.39)	ns
$PaCO_2$ (kPa)	5.23 (0.65)					5.09 (0.63)	ns	5.08 (0.84)	ns	5.08 (0.77)	ns

Data for visits 1 month after 1st (T1 1m) and final (T2 1m) treatments, and 3 months (3m), 6 months (6m) and 12 months (12m) after the final treatment, presented as mean (SD) or median (range) as appropriate. Change from baseline compared using repeated measures ANOVA with Bonferroni's multiple test comparison, or Friedman's test with Dunn's multiple test comparison, as appropriate. * p=<0.05, ** p=<0.01, *** p=<0.001.

Table 3.10: Control arm primary, secondary and non-endpoint measures

Outcome	Baseline	T1 1m	p value	T2 1m	p value	3 months	p-value
SGRQ (points)	53.2 (12.8)	54.0 (15.3)	ns	53.2 (13.7)	ns	55.8 (14.8)	ns
FEV_1 (L)	0.75 (.019)	0.76 (0.19)	ns	0.74 (0.16)	ns	0.75 (0.19)	ns
FVC (L)	2.89 (0.70)	2.90 (0.71)	ns	2.77 (0.57)	ns	2.88 (0.68	ns
RV (L)	5.01 (1.01)	4.94 (1.03)	ns	5.00 (1.21)	ns	4.98 (0.94)	ns
TLC (L)	7.96 (1.24)	7.90 (1.25)	ns	7.95 (1.40)	ns	8.00 (1.24)	ns
6MWD (m)	339 (112)	326 (102)	ns	340 (113)	ns	328 (97)	ns
mMRC (points)	2 (2-3)	2 (1-3)	ns	2 (1-3)	ns	2 (1-4)	ns
FRC (L)	6.11 (1.19)	6.06 (1.14	ns	6.08 (1.43)	ns	6.10 (1.17)	ns
RV/TLC (%)	62.8 (7.7)	62.4 (7.3)	ns	62.4 (7.1)	ns	62.2 (6.2)	ns
TLco	2.84 (0.98)	2.86 (0.94)	ns	2.94 (0.88)	ns	2.83 (0.93)	ns
PaO_2 (kPa)	9.48 (1.17)					9.16 (1.17)	ns
$PaCO_2$ (kPa)	5.24 (0.52)					5.13 (0.52	ns

Data for visits 1 month after 1st (T1 1m) and final (T2 1m) treatments, and 3 months (3m) after the final treatment, presented as mean (SD) or median (range) as appropriate. Change from baseline compared using repeated measures ANOVA with Bonferroni's multiple test comparison, or Friedman's test with Dunn's multiple test comparison, as appropriate. * p=<0.05, ** p=<0.01, *** p=<0.001

Table 3.11: Between group differences in the mean change from baseline of primary, secondary and non-endpoint measures

Between Group Difference	T1 1m	p value	T2 1m	p value	3m	p-value
Change in SGRQ (points)	-9.5 (3.1)	**	-9.8 (3.4)	**	-8.9 (3.3)	**
% Change in FEV_1	8.4 (5.5)	ns	14.7 (4.6)	**	14.2 (4.6)	**
% change in FVC	4.4 (3.9)	ns	13.1 (3.8)	**	9.4 (3.3)	**
Change in RV (L)	-0.137 (0.113)	ns	-0.3608 (0.190)	ns	-0.359 (0.149)	*
Change in TLC (L)	-0.054 (0.146)	ns	-0.096 (0.132)	ns	-0.172 (0.107)	ns
Change in 6MWD (m)	53.2 (17.0)	**	53.2 (15.6)	**	80.0 (16.2)	***
Change in mMRC (points)	-0.17 (0.22)	ns	-0.2 (0.26)	ns	-0.39 (0.23)	ns
Change in FRC (L)	-0.091 (0.108)	ns	1.210 (2.030)	ns	-0.368 (0.164)	*
Change in RV/TLC (%)	1.9 (1.0)	ns	3.3 (1.5)	*	3.4 (1.2)	**
Change in TLco	-0.10 (0.11)	ns	-0.10 (0.13)	ns	-0.01 (0.12)	ns
Change in PaO_2 (kPa)					0.28 (0.25)	ns
Change in $PaCO_2$ (kPa)					-0.04 (0.13)	ns

1 month after the 1st (T1 1m) and final (T2 1m) treatments, and 3 months (3m) after the final treatment. Presented as mean (SD). Comparison of the means performed using unpaired t-test or Mann Whitney test as appropriate. * p=<0.05, ** p=<0.01, *** p=<0.001

3.4 DISCUSSION

In our cohort, treatment with LVRCs resulted in significant improvements in the primary outcome measure 3 months following treatment compared to controls. The data presented here is, however, comparing groups in a 2:1 assignment (36 LVRC subjects versus 18 controls), rather than the required 21 LVRCs versus 21 controls in the sample size calculation. The final independently audited and source verified results of 46 subjects randomised in 2 centres (1:1 assignment and inclusive of additional patients recruited at a different centre and not reported in this thesis) have been analysed by an independent statistician and the data was presented by the author as a late-breaking abstract at the American College of Chest Physicians Chest conference 2012 (136) and later published.(94) The results are very similar to those of our cohort which includes cross over patients at the 3 month primary time point. In this thesis I report medium term data from our cohort including cross over treatments, which reveal statistically and clinically significant improvements in quality of life and exercise capacity measures persisting up to 12 months following treatment as compared to baseline. Improvements in the FEV_1 and RV at 6 months, though statistically significant, slipped just below what is considered to be clinically significant, and lost statistical significance by 12 months post treatment (at a similar magnitude to 6 months post treatment, likely due to missing data from drop outs).

The use of a patient reported qualitative outcome measure as the primary outcome in an unblinded study is a major weakness of this trial. I was not personally involved in the study design phase of this trial, which took place soon after the VENT trial(82) results were published showing statistically significant but not clinically meaningful improvements in the primary outcome measure of % change in FEV_1. Therefore an outcome measure directly examining patient's quality of life was preferred, in keeping with requirements by the Food and Drug Administration (FDA) for a large randomised controlled trial of the intrabronchial valves (84) to include change in SGRQ as a co-primary endpoint along with CT measured volume change. Responder analyses using both the 4-point and 8-point MCID thresholds were thus performed to compensate for the unblinded nature of this study. The 8-point threshold was used in the NETT trial, chosen somewhat arbitrarily, to "*represent a degree of improvement that would be appropriate to justify the high risks associated with surgery in patients with severe emphysema*"(66). Fifty four % and 49% of LVRS patients in the NETT trial had a >8 point reduction in SGRQ 6 and 12 months post- surgery, respectively. In comparison, our cohort had a 50% and 33.3% responder rate at these time points (to allow a like for like comparison, patients

with missing data were considered non-responders, explaining the discrepancy from figures in table 3.7). Nevertheless, the changes in the outcome measures (qualitative and quantitative) experienced by subjects in the LVRC treatment arm are all consistent in the direction of benefit, with no significant change in the control arm, suggesting that the improvements in the SGRQ are a real treatment effect. Nevertheless, the placebo effect of unblinded intervention on patients with end stage disease with a naturally fluctuating symptomatic course is sizable and will not be accounted for by the measures taken here. There is disagreement as to which is the best endpoint measure to assess lung volume reduction interventions. The FDA have tended to favour % change in FEV_1 with an MCID of 12% in this population, however many feel recurrent infections and natural variations in this measure over time, as well as the small FEV_1 values in this patient population bringing this magnitude of change close to the limits of test accuracy, make it an imperfect endpoint. Furthermore, changes in FEV_1 do not necessarily correlate with changes in patient symptoms. Measures of exercise capacity are preferred by some but are dependent on factors beyond patients' respiratory status and are difficult to standardise and perform, being highly dependent on patient motivation. The 6MWD has the best guidance and evidence base in COPD and LVR, and has indeed been approved by the FDA as the primary endpoint in a new randomised controlled trial of the LVRCs. There is, however, a wide range of proposed MCIDs (section 2.7.1). The residual volume has also been proposed as a good measure of gas trapping but is subject to similar limitations to those discussed for FEV_1 above, and an MCID has not been determined. Co-primary endpoints including a test of exercise capacity and lung function would be ideal, however population size for studies employing such an approach is likely to be prohibitively large.

Another criticism of the study design is the absence of a sham procedure. The LVRCs are radiographically striking and the target patient population suffer from recurrent infections and frequently attend local hospitals acutely unwell when they are likely to have chest radiographs as part of their assessment. The chance of unblinding by a surprised and/or intrigued junior doctor or radiographer is therefore very high, minimising the scientific merit of a sham procedure. Furthermore, 8 of our 36 patients (22%) suffered from a pneumothorax (from 68 procedures). In a 1:1 randomised controlled trial with similar pneumothorax rates, pneumothorax alone could unblind between a fifth and a quarter of the treatment arm.

Three months controlled follow-up is arguably too short and perhaps should have extended to 6 months at the earliest. This is, however, the first randomised controlled trial of this device and was not designed to be a pivotal one. It is the largest treated cohort of patients with LVRCs to date. It has informed on a variety of aspects of this novel treatment approach and on the design

of a future pivotal trial. Comparison of 6 and 12 month follow-up data with baseline shows gradual return to baseline in lung function (FEV_1, RV), though improvements in exercise capacity and quality of life remained stable. In fact, there was a further improvement in the SGRQ between 3 and 6 months post treatment. This probably reflects the time needed to recover fully from the procedure and to increase regular activity levels. This in turn leads to further improvements in general conditioning and muscle strength driving further improvements in exercise capacity and quality of life. Emphysema is a progressive disease and a gradual deterioration in lung function is the norm. The VENT trial (82) reported data on a randomised, controlled population of severe emphysema patients with similar baseline characteristics, undergoing optimal medical care, providing an estimate of functional decline expected in this patient group. In these patients, median change from baseline to 6 months in 6MWD was -10·7m, and mean change in SGRQ score was +0·6 (p=0·04).(82) These small but significant reductions are expected given the compromised status of patients at randomisation and the progressive nature of the disease, and highlight the need for longer-term controlled studies to establish the true magnitude of benefit of endoscopic treatment in this patient group.

More robust guidance to ensure that recruited subjects were on optimal medical therapy would have been preferable, with clear definition of what this includes and for how long (I would recommend a minimum period of three months period prior to screening). Adding pulmonary rehabilitation within six months as an inclusion criteria is, in my opinion, an essential requirement. This was stipulated in the NETT trial and therefore not having had this as an inclusion criteria will limit from the ability to compare with this most validated form of LVR. More importantly, however, is that pulmonary rehabilitation is a categorically and incontestably one of the main pillars of optimal medical care of patients in COPD, and this should be a pre-requisite within a reasonable timeframe before considering any LVR technique, whether clinically or as part of a trial.

The SAE pneumothorax rate per procedure at our site was 8.8%, which is higher than reported in the literature and by the manufacturer's database. Our trial is the biggest to date and this may represent a more accurate representation of the true risk of pneumothorax, different patient selection criteria, or indeed a technique issue at our site. The pneumothoraces were evenly spread out amongst early, middle and late recruits, making a "learning" effect an unlikely cause. Nevertheless, taken in context, 100% of LVRS patients have a chest drain post operatively for several days, and the pneumothorax rate for successfully treated patients with endobronchial valves is likely to be higher than 20% (discussed in section 1.3.8.3.2). Pneumothorax in this patient population can be particularly serious if it occurs outside of the hospital setting or if the

patient is unable to get to hospital rapidly. The majority of the pneumothoraces (7 of 9) in our cohort occurred within 12 hours of the procedure and were therefore quickly and easily treated. Of particular concern are delayed pneumothoraces, though these did not lead to severe or life threatening situations in both episodes in our cohort. We carefully educate our patients about pneumothorax, instruct them on what symptoms to look out for, to urgently attend their local emergency department should they develop any of these symptoms, and provide a detailed information sheet with emergency contact details. It was in fact the case that subjects who suffered from a pneumothorax had better improvements in lung function than the group as a whole with a mean (SD) 16.6 (19.6) % increase in FEV1, -0.67 (0.75) litre reduction in RV, and 66.8 (81) m improvement in the 6MWD 3 months after treatment. Pneumothorax is a reflection of successful tension of the coils within the lung, and once treated this tension and compression should lead to the benefits in lung function as seen.

There was no increased risk of infective or non-infective exacerbations in the treatment recovery period or the subsequent 12 months as a result of the LVRCs. We were concerned about atypical bacterial, fungal, and non-tuberculous mycobacterial infections related to the presence of foreign bodies in a cohort already susceptible to recurrent infections. This has not been an issue in the vast majority our patients. Two patients cultured pseudomonas species for the first time, more than 6 months after treatment. Eradication was successful in one patient, and unsuccessful in another. The latter was a frequent exacerbator prior to his LVRC treatment and continues to suffer from recurrent exacerbations. Pseudomonas is a recognised coloniser in COPD and it is not possible to say whether these episodes are directly related to the LVRCs. One other patient developed an upper lobe pneumonia 8 months after treatment, leading to cavitation and ultimately an aspergilloma. There are no LVRCs in or around this cavity. He recovered fully following a 10 day admission. He continues to culture aspergillus but is otherwise well, and has not developed allergic bronchopulmonary or invasive aspergillosis. We have not seen any incidences of non-tuberculous Mycobacterial infection in this LVRC treated cohort.

Although the manufacturer states that the LVRC deployment process is reversible and the LVRCs are removable, our experience suggests that they are not. It is indeed possible (but not easy) to grasp the proximal end of a coil and advance the sheath over it, however the reality is that the vast majority of the LVRCs recoil distally once released, out of site of the bronchoscope. This makes it impossible to remove these coils with existing bronchoscope sizes. In over 200 treated patients, there was one case in Germany where an LVRC needed to be removed due to persistent coughing. It was not possible to pull the LVRC back into a catheter so it was simply pulled out, fortunately without injury. To my knowledge, there has not been another situation

where a coil needed to be removed. The LVRCs should not preclude lung transplantation should this become an option for patients as the whole lung is resected, however LVRCs may be problematic if lung volume reduction surgery is to be considered. It is likely that LVRCs will cross the intended staple line and possibly interrupt the staple gun action. The LVRCs, which are not removable endobronchially, will therefore need to be removed by dissecting the lung prior to stapling. This should not be technically difficult to perform however it would certainly require an open thoracotomy rather than a video assisted thoracoscopic surgical (VATS) procedure, according to Mr Simon Jordan, thoracic surgeon. One subject from this trial, a non-responder, was referred for LVRS two years after his LVRC treatment. A lobar resection approach to LVRS was adopted case in this case as there was very little remaining healthy parenchyma in the resected lobe. However we made attempts to staple over the LVRCs *ex vivo* post explantation and the staple gun could not successfully accomplish this.

Whereas a unilateral treatment approach has been adopted for endobronchial valve lung volume reduction, bilateral treatment has been used for LVRCs. When comparing paired data in our LVRC treatment cohort, there was no statistically significant difference in any of the outcome measures between 1 month post 1st treatment and 1 or 3 months post 2nd treatment, other than a difference between the 6MWDs 1 month post 1st treatment and 3 months post 2nd treatment. However, the between group difference for change in RV, % change in FEV_1 and % change in FVC as compared to baseline where not significant after the first treatment but significant 3 months post 2nd treatment. The small number of patients studied makes comment difficult, however it may be the case that the largest improvements occur after the first treatment as the worst affected lung was targeted first. It may be that some “retensioning” effect is transferred across the mediastinum towards the contralateral lung as gas trapping is reduced in the treated lung. It may also be the case that there is a reduction in benefit after an early peak after which the lung or LVRCs remodel to absorb the new tension. It may therefore be more optimal to spread out treatments over a longer time period (for example 3-4 months). This would also allow a longer period for recovery from any adverse events associated with the first procedure.

The optimal number of LVRCs per lung to achieve maximal benefit is not known. The first-in-man studies of the LVRCs treated each lung with six LVRCs leading to small clinical benefits.(103) The following feasibility study aimed to treat each lung with 10 coils, and results were encouraging. Inserting more than 10 LVRCs into a single lobe is technically difficult; accessing more than 10 subsegmental airways leading into distinct airways in different parts of the lobe is challenging with the required size bronchoscope. Therefore the number of LVRCs is dictated by practical issues and knowledge of the minimum number of coils needed to effect a

positive change (probably ~8 LVRCs). There was no relationship between outcomes and number of LVRCs in our cohort. Different subjects or indeed lungs probably respond differently to LVRCs and a standardised number of LVRCs for all subjects may not be appropriate. It is now possible to measure compliance endobronchially using a dedicated pressure balloon, and studies examining the effect of each individual additional LVRC on lung compliance are required to better understand the effects of the LVRCs on the lung and tailor therapy for each lung.

In our study, subjects with homogeneous emphysema were treated with LVRC implantation to both the upper and lower lobes. Unpublished data from one centre in the Netherlands, where a small number of patients with homogenous emphysema were treated with LVRCs to the upper lobe, showed benefits in outcomes on a par to patients with heterogeneous emphysema (personal communication, Dr. D-J Slebos and PneumRx representatives). It remains unclear which approach is best, and it is unfortunately difficult to make any conclusions from our cohort as only five subjects had upper and lower lobe treatments bilaterally, whilst 4 others had one homogenous and one heterogeneous lung and therefore had "mixed" distribution of treatment. The five patients with bilateral upper and lower lobe LVRC treatment had a mixed response with a mean (SD) change in the SGRQ of -2.7 (7.7) points, a reduction in the RV of -0.44 (0.71) litres, no change in FEV1 (+0.6 (12.2)%), and an increase in the 6MWD of 52.6 (54.1) metres 3 months after treatment. Although some localised atelectasis surrounding LVRCs developed in some (but by no means all) patients on their CT scans, there was no significant volume loss in the treated lobes. This is consistent with the absence of change in TLC following LVRC treatment. Hence there was no "volume reduction" per se, and therefore the reduction in gas trapping is attributed primarily to retensioning of the lung and the resultant small airway splinting and prevention of expiratory airway collapse. Crucially for patients, this leads to reductions in dynamic hyperinflation during exertion, which may explain the improvements in exercise capacity and quality of life which are proportionally larger than the changes in lung function. The target, therefore, is reducing gas trapping (RV) and it would seem sensible to deploy coils throughout the damaged lung parenchyma and not to restrict treatment to one particular lobe.

3.5 CONCLUSION

Treatment with LVRCs results in improvements in quality of life, exercise tolerance and lung function which are sustained up to 12 months following treatment. Overall, the safety profile is acceptable particularly in view of the magnitude of benefit experienced by our cohort and in comparison with surgical and other bronchoscopic lung volume reduction techniques. A larger randomised controlled trial with longer follow-up to assess longer term durability and safety of the LVRCs is required. Spreading out the sequential treatments might extend the benefits, and further studies informing on optimal LVRC number and location will help maximise the patients' response.

Chapter 4

Endobronchial autologous blood to reduce hyperinflation in advanced emphysema

4.1 BACKGROUND

Lung volume reduction surgery (LVRS) is successful at improving quality of life, exercise capacity and mortality in a subgroup of patients with severe emphysema however it is associated with high morbidity and a5.5% mortality.(66) A variety of less invasive techniques to replicate the effects of LVRS have therefore been evaluated with mixed results. Bronchoscopic lung volume reduction using endobronchial valves, lung volume reduction coils, airway bypass stents, transpleural pneumonostomy, bronchial thermal vapour and biological gels are expensive techniques costing many thousands of pounds per treatment. They require extensive training of both primary and support staff, as well as substantial technical skill and experience to execute safely and successfully. For these reasons, access to these techniques is likely to be very limited even when a solid evidence base develops to support their use. These techniques require leaving foreign material in the airways in the form of foreign implants or biological gels and sclerosants. This predisposes to a theoretical risk of infection, trauma, bleeding, device migration or expectoration, and device failure. Furthermore, it is likely that each of these techniques, similar to LVRS, will be suitable to treat small subgroups of the emphysema population depending on phenotype.

Biological lung volume reduction is based on the concept of inducing scarring of hyperinflated lung parenchyma, leading to tissue contraction and hence volume loss. In early animal studies, endobronchial trypsin-based solutions followed by fibrinogen and thrombin solutions were used to stimulate fibroblast attachment, proliferation and collagen expression, inducing scar organisation.(137) Human pilot studies of this technique followed (138, 139) and the solution has since been revised and patented as Aeris Polymeric lung volume reduction. Data from 28 patients treated with this solution demonstrate changes on cross-sectional imaging in keeping with volume loss.(101) A pivotal trial of this technique is currently underway.

Using a similar strategy Kanoh and colleagues trialled the use of autologous blood admixed a thrombin solution to achieve volume reduction, and have demonstrated significant reductions in static lung volumes and dyspnoea in a 59 year old man after infusion of a pre-prepared mixture of autologous blood with thrombin and fibrinogen into a large bulla.(105) The same group also published encouraging results in one patient with lymphangioleiomyomatosis and two with advanced heterogeneous emphysema.(140) Kanoh and colleagues suggested that blood has "*potential bioadhesive properties*", and added thrombin solution to "*enhance this blood effect*"(140). They bronchoscopically injected 4 mls of blood with 2mls of thrombin solution in up to 5 subsegments per treated lung (maximum 20mls of blood per treatment), and repeated

this treatment twice weekly for up to four treatments. The amount of thrombin used per treatment was 20,000 iu.

I investigated what volume of whole unaltered blood would contain equivalent amounts of thrombin. Discussions with Louise Tillier, consultant haematologist, and Simon Davidson, clinical scientist at our institution, informed that after a lag phase of up to 1 minute following venesection when no thrombin is measurable, thrombin generation peaks at approximately 2-4 minutes. The thrombin concentration varies between individuals and is somewhere between 200-1000nmol/ml (there is approximately 10nmol to 1iu). Therefore 180mls of whole blood contains anywhere between 36000 to 180000 iu of thrombin.

In addition to the effects of clotting factors, the induction of oxidation and reduction reactions by extracellular haeme-bound iron contained within blood, an airway and alveoli irritant, also plays an important role in triggering an inflammatory response.(141) Therefore we propose that, if delivered in sufficient quantities, unaltered autologous blood contains sufficient amounts of fibrinogen, thrombin and extracellular haeme-bound iron to induce similar effects to the Biological LVR solutions or Kanoh et al.'s reconstituted blood mixture. If safe and efficacious, this inexpensive single treatment strategy has the potential for dramatic cost savings and widespread uptake. Theoretically, it can be offered to patients with a wide variety of patterns of emphysema including bullous disease, and not only restricted to heterogeneous upper lobe emphysema. We have therefore studied this treatment approach in two phenotypes of emphysema: heterogeneous emphysema and giant bulla. Crucially, we did not manipulate the blood following venesection with 180-240mls of blood instilled within 60 seconds of being withdrawn from the subject during the procedures (up to ~10 multiples of the volumes used by Kanoh et al).

4.2 A RANDOMISED DOUBLE-BLIND SHAM CONTROLLED TRIAL OF AUTOLOGOUS BLOOD INSTILLATION IN UPPER LOBE HETEROGENEOUS EMPHYSEMA

4.2.1 METHODS

4.2.1.1 Study Design

This was a randomised double-blind sham-controlled study examining the safety and efficacy of autologous blood instilled bronchoscopically into the most emphysematous lobe in subjects with heterogeneous disease. Research ethics committee and NHS Trust R&D approval was obtained and all patients provided written informed consent. Patients were recruited between January 2010 and June 2012.

4.2.1.2 Study outcomes

Primary Endpoint

- Between group difference in the change in Residual Volume (RV) 8 weeks post- procedure

Secondary Endpoints

1) Between group difference in the percentage change in FEV_1 8 weeks post- procedure
2) Between group difference in the change in the 6MWD 8 weeks post-procedure
3) Between group difference in change in the SGRQ 8 weeks post procedure
4) Between group difference in change in the mMRC score 8 weeks post procedure
5) Evidence of new atelectasis on HRCT 8 weeks post- procedure.
6) Difference in the adverse event profiles between the two groups.

4.2.1.3 Patient Selection

Subjects with GOLD stage III-IV emphysema were recruited from the respiratory clinics at the Royal Brompton and the Chelsea and Westminster Hospitals, after discussion in the appropriate multidisciplinary meeting. Patients with severe airflow obstruction, significant hyperinflation, heterogeneous emphysema and limiting breathlessness who have no contraindications prohibiting bronchoscopy were considered. The inclusion and exclusion criteria are listed below.

Inclusion Criteria:

- Age 40-80 years.
- Moderate to severe airflow obstruction FEV_1 <50% Predicted.
- Significant dyspnoea – mMRC ≥2.
- Hyperinflation – TLC ≥100% predicted, RV ≥150% predicted.
- Heterogeneous upper lobe predominant emphysema in at least one lung
- Optimum COPD treatment for at least 6 weeks.
- No COPD exacerbation for at least 30 days.
- Fewer than 3 hospital admissions for COPD exacerbations in the preceding 12 months.

Exclusion Criteria:

- Patient unable to provide informed consent.
- TLco <15% predicted or FEV_1 <15% predicted.
- PaO_2 on air <6.0kPa or $PaCO_2$ on air >8.0kPa.
- Other major medical illness that will limit participation.
- No contraindications to bronchoscopy.
- Clinically significant bronchiectasis.
- Large bulla more than 1/3 of hemithorax volume on CT scan.
- Maintenance oral steroids greater than 10mg prednisolone daily.
- Prior LVRS or lobectomy.
- Participated in a study of investigational drug or device in prior 30 days

4.2.1.4 Study schedule

Baseline/screening visit:

- Full Informed consent.
- Full medical history and clinical examination.
- Static and dynamic lung volumes and gas transfer measurements.
- Arterial blood gas tensions.
- HRCT scanning of the chest.
- 6MWT.
- SGRQ.
- mMRC dyspnoea score.

Bronchoscopic Procedures:

The bronchoscopic procedure was performed at the earliest opportunity following fulfilment of the trial entry criteria. Subjects were randomised to either bronchoscopic autologous blood LVR or sham bronchoscopic LVR using 0.9% saline. Randomisation, blinding and the procedure are discussed in more detail below.

8 week evaluation:

Participants underwent a repeat of all the examinations, investigations and health related quality of life questionnaires performed at baseline as listed above. Assessments were performed by an investigator blinded to the patient's treatment allocation. Participants were unblinded only after completion of this 8 week assessment.

4.2.1.5 Static and dynamic lung volumes and gas transfer measurements

Lung function testing was performed at baseline and 8 weeks post- treatment. The lung function physiologists at the Royal Brompton Hospital lung function department perform all testing using the Compact Master Lab system (Jaeger, Germany). The European Coal and Steel Workers cohort is used to obtain standardised reference values(120).

4.2.1.6 Arterial blood gases

ABG analysis was performed at baseline and 8 weeks post procedure by the lung function department physiologists at the Royal Brompton Hospital. End capillary blood samples from the participant's earlobe were used. Analysis for pH and for partial pressures of O_2 and CO_2 was performed using the Rapidlab 348 analyser (Bayer, Germany).

4.2.1.7 HRCT of the chest

HRCT scanning was performed at baseline and 8 weeks post procedure. A Siemens Sensation 64, a 32 detector scanner with a rotation time of 0.33 seconds was used. Volumetric spiral acquisition with contiguous slices (1mm slice thickness on 1mm for lung windows, and 10mm on 10mm mediastinal windows) was taken with the participant in the supine position at full inspiration.

Baseline HRCTs were studied and heterogeneity independently assessed visually by two investigators using thin slice axial, sagittal and coronal reconstructions. The most heterogeneous lobe was identified for treatment. Subjects were excluded from the trial if both lungs were considered homogeneous. A joint review of the HRCT by the two investigators was performed and a consensus reached in case of disagreement between investigators. Interlobar fissures in the treated lung were considered intact if >90% of the fissure was in clear continuity in at least one axis.

For post-trial analysis, HRCT scans at baseline and 8 weeks post treatment were directly compared by an independent, blinded, radiologist asked to state whether new atelectasis had developed, and in which lobe.

4.2.1.8 6 minute walking distance

The 6MWD is a well validated test of exercise capacity in patients with COPD, and is commonly used both in clinical practice and in research. In this study patients had their 6MWD measured at baseline and at 8 weeks post-procedure. The American Thoracic Society criteria(128) for the 6MWD were followed. The test was performed in the same 30 metre long corridor at the Royal Brompton Hospital by the same blinded investigator.

4.2.1.9 St. George's Respiratory Questionnaire

The SGRQ (122) is a 76-item health status survey specific for respiratory conditions. It is designed to measure impact of the disease on overall health, daily life, and perceived well-being. The participants answered the questions considering the preceding 4 weeks at baseline and 8 weeks post procedure.

4.2.1.10 mMRC dyspnoea score

Participants in this trial completed an mMRC score at baseline and 8 weeks post procedure.

4.2.1.11 Randomisation and blinding

Subjects were randomly allocated in a one-to-one ratio to either blood LVR (treatment arm) or sham procedure using 0.9% Saline (control arm). The randomisation sequence was computer generated in random permuted blocks of 10. The generated codes were placed in sequentially numbered opaque sealed envelopes and opened in sequence in the bronchoscopy suite after the patient was sedated, by a staff member who was not part of the research team. The six 60ml syringes used during each procedure were pre-wrapped in opaque tape making the contents of the syringe unknown on external examination. Treatment and control arm patients had venesection of 180 mls of blood. At the time of instillation of solution, the staff member with the randomisation information handed the investigators a wrapped syringe containing either blood or 0.9% saline solution as per randomisation. At the end of the procedure, 5 mls of blood were injected down the bronchoscope channel in the main trachea in all subjects, such that subjects in both treatment arms had the possibility of having minor haemoptysis post- procedure. The bronchoscopists were therefore blinded throughout the procedure, as was the patient. As the instilled solution was released 4cm distal to the tip of the bronchoscope, we anticipated that the contents of the syringe will not be made known to the bronchoscopist in most cases. We were unexpectedly pleased that in none of the subjects treated with autologous blood did any blood leak or flow back proximally after instillation. The follow-up investigations (6MWD, PFTs) were performed by assessors who were blinded as to which trial arm the subject was in.

4.2.1.12 Bronchoscopic Procedures and venesection

The bronchoscopic procedures were performed at the Chelsea and Westminster Hospital endoscopy unit using moderate sedation (intravenous Midazolam and Fentanyl) as day case procedures. The participant was given a bronchoscopy information leaflet to review and relevant instructions at least 24 hours in advance of the procedure. Departmental pre-procedure and post-procedure protocols for routine bronchoscopy were followed for patients in both treatment arms.

Once in the bronchoscopy suite and sedated, a pre-sealed envelope was opened by a member of staff who was not part of the research team. This informed on the patient's randomisation to receive either blood or 0.9% saline solution. A diagnostic bronchoscopy was performed before the target segment was approached. This was determined by the investigators based on HRCT assessment as described above. An extended working channel was advanced 4 cm distally from the tip of the bronchoscope into one sub-segment (figure 4.1). Venesection of 60 mls of blood was then performed using syringes wrapped in opaque tape and the syringe handed to the assistant who opened the randomisation envelope. The bronchoscopist was then handed back a syringe (contents unknown to the bronchoscopist) by the unblinded assistant. The treatment solution was instilled within 60 seconds of venesection through the extended working channel followed by a 10mls 0.9% saline flush. After a period of 120 seconds, the extended working channel was repositioned into the next sub-segment and the process repeated. Three subsegments of the target lobe were treated.

At the end of all procedures, 5mls of blood were injected into the trachea via the bronchoscope working channel, aiming to even out the risk of minor haemoptysis post-procedure between both study arms. The rest of the blood retrieved during the procedure was discarded in accordance with infection control policies.

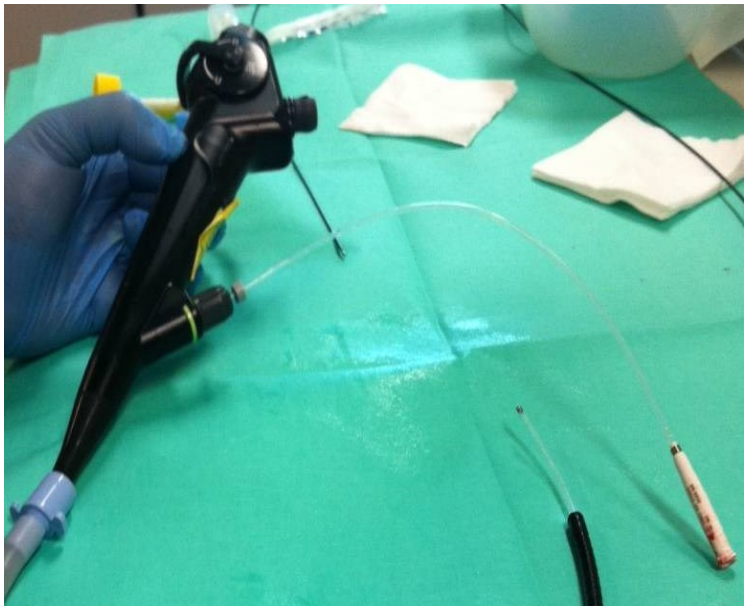


Figure 4.1: The extended working channel advanced 4cm beyond the tip of the bronchoscope.

4.2.1.13 Statistical analysis and sample size

The VENT endobronchial valve study,(82) which recruited a similar patient population, is the only published randomised controlled trial from which data for calculation of sample size can be utilised. The change in RV at 6 months in the VENT trial responder sub-group (subjects with high heterogeneity, intact fissures, and successful lobar occlusion) was Δ-56.8%. Changes in RV at earlier time-points were not published. For 80% power and a significance of 0.05, assuming a more conservative reduction in RV of 40% in the treatment arm to be clinically significant and no change in RV in the control arm, a study of 14 patients in each arm would be required. Therefore in such a pilot trial with little data to support a sample size calculation, recruiting 35 patients (assuming 20% drop outs) was sensible to pick up any signal in outcomes and safety. An efficacy and safety analysis after recruitment of approximately half the cohort was performed.

Qualitative data is presented as percentages and comparisons of these variables will be performed using Chi squared or Fishers exact test. Quantitative data was checked for normality. Data that are normally distributed are presented as mean (standard deviation) and comparisons done using the 2 sample t test. Data that are not normally distributed are presented as median (Inter quartile range) and comparisons done using the Wilcox rank-sum test.

4.2.2 RESULTS – INTERIM ANALYSIS (17 PATIENTS RECRUITED)

4.2.2.1 Baseline data, procedure details and follow-up data availability

An interim analysis was conducted after 17 patients were recruited. One patient withdrew consent before randomisation. One subject died before his procedure (sudden cardiac event) and two withdrew consent before their procedures (one no longer wished to take part, and the other was offered entry into a novel inhaler device trial). Of the remaining 14 patients, seven were randomised to the treatment arm with autologous blood LVR, and seven to the control (sham) arm using 0.9% saline.

Baseline demographics and lung function data are illustrated in table 4.1. No differences were observed between the two groups. There were no differences in procedure time, sedation requirements or target treatment lobes.

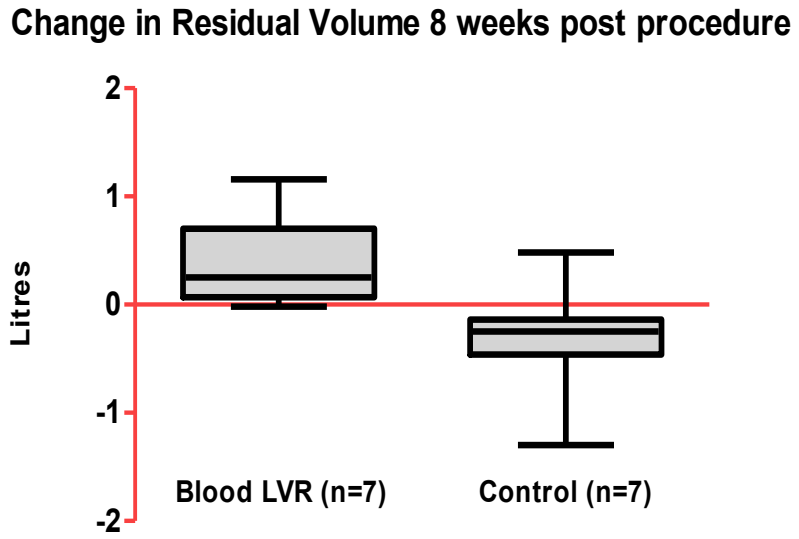
Table 4.1: Baseline and procedure data for the endobronchial blood LVR study

	Treatment	Control	p value ₸
Number	7	7	-
Age (yr.)	64.9 (4.9)	65.4 (7.9)	0.85
Male (%)	57	71	1.0 ¥
BMI	24.3 (4.4)	22.5 (4.5)	0.46
FEV1 % predicted	28.9 (8.1)	26.9(10.2)	0.99
FVC % predicted	87.3 (14.3)	76.7(19.8)	0.54
RV % predicted	229.4 (31.6)	223.3 (46.9)	0.44
TLC % predicted	135.7 (7.1)	127.1(14.0)	0.26
RV/TLC	63.7 (7.0)	64.2 (9.7)	0.80
TLco % predicted	32.4 (14.8)	31.1(10.7)	0.90
PaO_2 (kPa)	8.8 (1.3)	8.8 (1.3)	0.54
$PaCO_2$ (kPa)	5.1 (0.8)	5.1 (0.8	0.17
mMRC (points)	2.6 (0.5)	2.6 (0.5)	0.94
SGRQ (points)	55.4 (14.0)	57.1 (12.6)	0.90
6MWD (m)	264.0 (76.6)	274 (131)	0.71
Procedure data			
Procedure time (min)	23.9 (4.0)	22.6 (3.2)	0.52
Right upper lobe (%)	43	57	1.0 ¥
Midazolam (mg)	2.0 (0.58)	1.86 (0.4)	0.66
Fentanyl (mcg)	28.6 (9.5)	21.4 (9.5)	0.21

₸ All Mann-Whitney test except ¥ where Fisher's exact test was used.

4.2.2.2 Primary Endpoint

The primary endpoint visit took place 49.3 (8.9) and 50.7 (17) days following the procedure in the treatment and control arms, respectively. Tables There was a mean (SD) increase in the RV in the treatment arm of 0.384L, and a mean (SD) reduction in the control arm of 0.333L. The between group difference in the change in RV was 0.719 L (95% CI 0.019 to 1.41, p=0.011) to the detriment of the treatment arm (figure 4.2, tables 4.2 - 4.4).



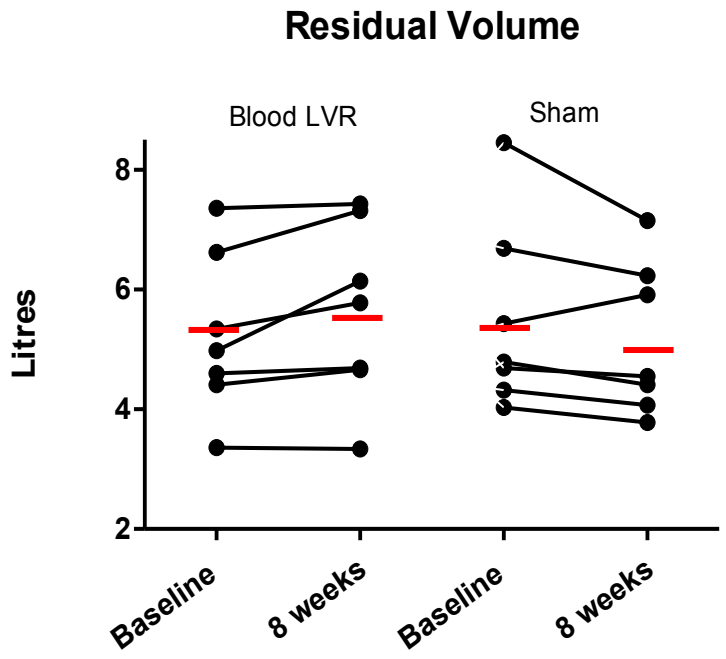


Figure 4.2: Primary outcome change in RV 8 weeks post procedure – Autologous blood LVR study. Top: Box plot; and bottom: individual and group average data.

4.2.2.3 Secondary Endpoints

Data discussed below is illustrated in figure 4.3 and detailed in tables 4.2 – 4.4.

1) ***Percent change in FEV_1:*** 8 weeks following the procedure, there was a 13.2 (5.8) % reduction in FEV1 in the treatment arm, and a 2.4 (8.2) % increase in FEV_1. The between group difference was a non-statistically significant 15.8 (10.3) % change in favour of the control arm (p=0.15).
2) ***Change in the 6MWD:*** 8 weeks following the procedure, there was a 32.9 (40.3) m reduction in the 6MWD in the treatment arm, and a 4.7 (51.1) m increase in the control arm. The between group difference was a non-statistically significant 37.6 (24.6) m in favour of the control arm (p=0.25).
3) ***Change in SGRQ:*** 8 weeks following the procedure, there was a 3.4 (7.9) point increase in the SGRQ in the treatment arm, and a 2.5 (5.0) point increase in the control arm. There was no significant difference between the groups (Δ 0.88 (3.4) points).

4) ***Change in the mMRC dyspnoea score:*** There was no change in the mMRC score in any of the treatment arm patients, and a mean 0.29 (0.49) increase in the mMRC score in the control arm patients (2 subjects had a 1 point increase).
5) ***Evidence of new atelectasis on HRCT***: Zero of seven subjects in the treatment arm and zero of seven subjects in the control arm had CT evidence of development of new atelectasis in the treated lobe 8 weeks post procedure.
6) ***Safety Analysis:*** Three of seven subjects in the treatment arm and one of seven in the control arm experienced mild infective exacerbations of COPD which resolved fully following treatment with the rescue pack of an appropriate antibiotic and 30mg daily of Prednisolone for seven days provided on discharge. None required hospital admission or medical review. Only one study patient (in the treatment arm) experienced minor haemoptysis post-procedure. There were no adverse events related to venesection of 180ml of blood in these subjects.

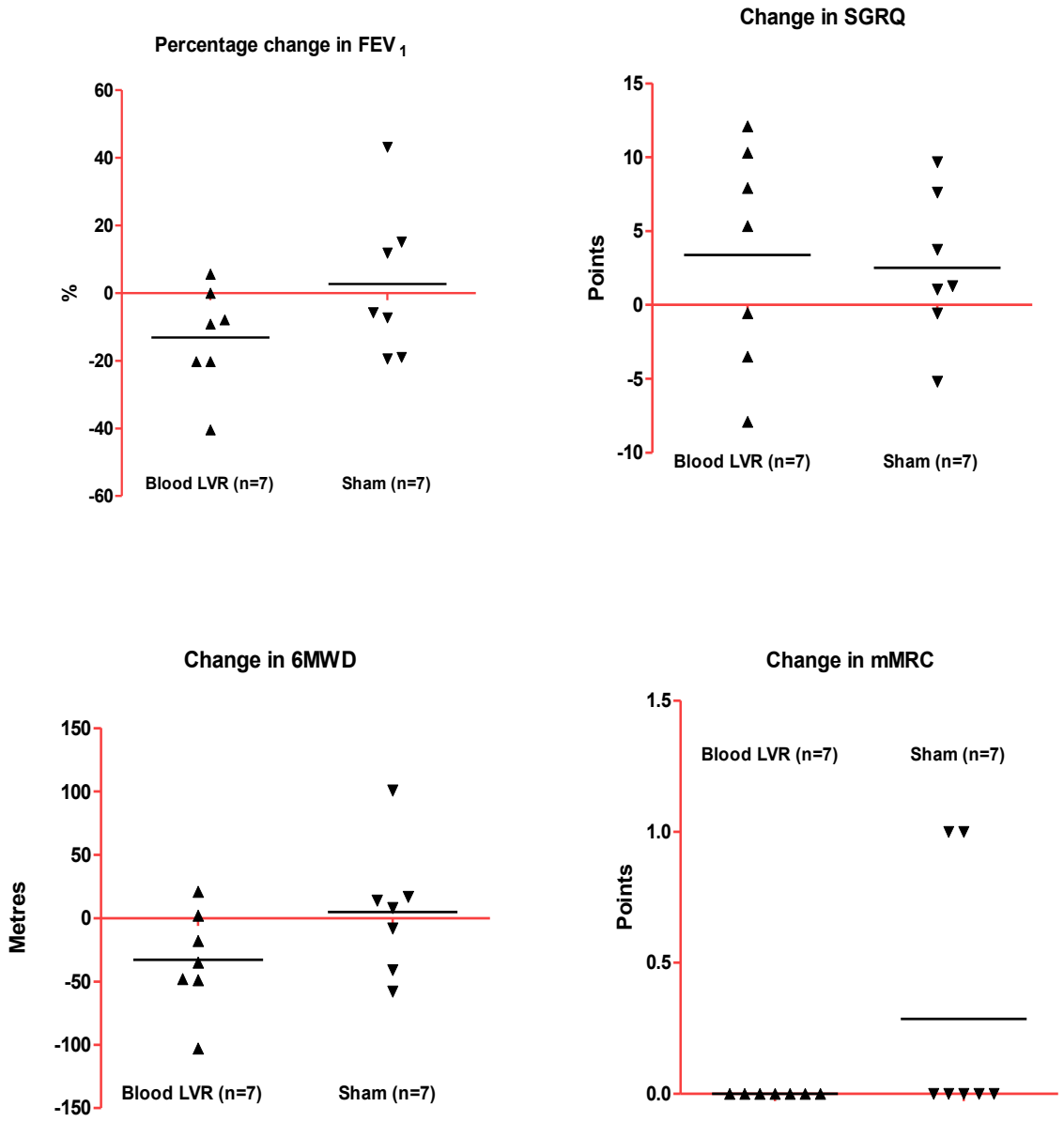


Figure 4.3: Change in secondary endpoint outcome measures 8 weeks autologous blood LVR post-procedure.

Table 4.2: Treatment arm outcome measures at baseline and 8 weeks following autologous blood LVR treatment.

Outcome	Baseline	8 weeks	Change	p-value¥
RV (L)	5.24 (1.36)	5.62 (1.50)	0.38 (0.42)	0.03
FEV_1 (L)	0.76 (0.19)	0.66 (0.20)	-0.10 (0.10)	0.48
FVC (L)	2.90 (0.46)	2.52 (0.53)	-0.37 (0.29)	0.03
TLC (L)	8.14 (1.46)	8.32 (1.52)	0.18 (0.28)	0.16
SGRQ (points)	55.4 (14.0)	58.8 (12.3)	3.39 (7.51)	0.30
6MWD (m)	264 (77))	231 (68)	-33 (40)	0.11
mMRC (points)	3 (2-3)	3 (2-3)	n/a	n/a
RV/TLC (%)	63.7 (6.95)	66.8 (8.23)	3.1 (3.4)	0.08
TLco	2.67 (1.33)	2.47 (1.22)	-0.20 (0.28)	0.18
pO_2 (kPa)	9.21 (1.24)	8.83 (1.29)	-0.37 (1.23)	0.47
pCO_2 (kPa)	5.10 (0.84)	5.36 (0.87)	0.26 (0.51)	0.22

Mean (SD) or median (range); ¥ Wilcoxon sign rank test.

Table 4.3: Control arm outcome measures at baseline and 8 weeks following sham bronchoscopy.

Outcome	Baseline	8 weeks	Change	p-value¥
RV (L)	5.49 (1.57)	5.16 (1.27)	-0.33 (0.53)	0.22
FEV_1 (L)	0.81 (0.30)	0.80 (0.27)	-0.01 (0.16)	0.80
FVC (L)	2.93 (0.68)	3.13 (0.76)	0.20 (0.30)	0.16
TLC (L)	8.44 (1.27)	8.47 (1.19)	0.02 (0.38)	0.94
SGRQ (points)	57.1 (12.6)	59.6 (11.5)	2.51 (5.02)	0.22
6MWD (m)	273 (131)	278 (103)	4.71 (51.2)	0.87
mMRC (points)	3 (2-3)	3 (2-4)	n/a	0.35
RV/TLC (%)	64.2 (9.69)	60.5 (8.56)	-3.74 (2.90)	0.03
TLco	2.72 (0.80)	2.94 (0.99)	-0.22 (0.55)	0.38
pO_2 (kPa)	8.30 (1.18)	8.60 (1.16)	-0.30 (1.19)	0.69
pCO_2 (kPa)	5.67 (0.89)	5.48 (1.06)	-0.19 (0.53)	0.38

Mean (SD) or median (range); ¥ Wilcoxon sign rank test.

Table 4.4: Between group differences in the mean change from baseline of primary, secondary and non-endpoint measures 8 weeks post- treatment.

Outcome	8 weeks following treatment	p value¥
Change in RV (l)	0.713 (0.225)	0.011
% Change in FEV_1	15.8 (10.2)	0.13
% change in FVC	20.4 (5.4)	0.002
Change in TLC (l)	0.156 (0.177)	0.53
Change in 6MWD (m)	37.6 (24.6)	0.26
Change in mMRC (points)	0.29 (0.48)	n/a
Change in SGRQ (points)	0.88 (3.4)	0.71
Change in RV/TLC (%)	6.8 (1.7)	0.002
Change in TLco	0.43 (0.23)	0.08
Change in PaO_2 (kPa)	0.67 (0.65)	0.38
Change in $pPaCO_2$ (kPa)	0.45 (0.28)	0.097

Mean (SD) or median (range); ¥ Mann Whitney test.

4.2.3 STUDY DISCONTINUATION

The study was discontinued after the interim efficacy and safety review conducted by the study team led by the chief investigator, Dr. Pallav Shah. This decision was later discussed at the advanced COPD MDT at the Royal Brompton Hospital and there was consensus that this was an appropriate course of action. The primary reason was that there did not appear to be any signal to suggest a positive response clinically, radiologically or on lung function to LVR using endobronchial segmental instillation of autologous blood. It also became apparent that the primary endpoint was inappropriate, with eight weeks too short a period for a fibrotic process to manifest, nor for full recovery from post procedure exacerbations. After commencement of the trial, data was published from other techniques utilising a similar mechanism of action (vapour(87) and PLVR(86)) showing optimal benefit at six months following treatment. We also had safety concerns with data suggesting a deterioration in the status of the treatment arm patients with a statistically significant worsening in gas trapping (RV) despite small patient numbers.

4.3 A PILOT STUDY OF BRONCHOSCOPIC INTRABULLOUS AUTOLOGOUS BLOOD INSTILLATION (BIABI) FOR THE TREATMENT OF GIANT BULLAE

4.3.1 METHODS

4.3.1.1 Study Design

This trial was a small single arm open label proof of concept pilot study examining the safety and efficacy of autologous blood instilled bronchoscopically directly into giant bullae. Subjects who were not suitable for, or had declined the offer of, surgical bullectomy and had no alternative treatment options were recruited. Research ethics committee and NHS Trust R&D approval was obtained and all patients provided written informed consent. Patients were recruited between October 2011 and May 2012.

4.3.1.2 Study Endpoints

Primary Endpoint

- Change in the RV 3 months following treatment.

Secondary Endpoints

1) Percentage change in FEV_1 3 months following treatment.
2) Change in SGRQ 3 months following treatment.
3) Change in 6MWD 3 months following treatment.
4) CT evidence of change in bulla volume 3 months following treatment.
5) Adverse event rate.

4.3.1.3 Patient Selection

Subjects with giant bullae who were not suitable for, or had declined the offer of, surgical bullectomy and had no alternative treatment options were recruited from the respiratory clinics at the Royal Brompton and the Chelsea and Westminster Hospitals, after discussion in the appropriate multidisciplinary meeting. Patients with a giant bulla, airflow obstruction, significant hyperinflation, and limiting breathlessness who have no contraindications prohibiting bronchoscopy were considered. The inclusion and exclusion criteria are listed below.

Inclusion Criteria:

- Age > 40 years.
- Hyperinflation – TLC ≥100% predicted, RV ≥150% predicted.
- Giant bulla (>30% of hemithorax).
- Exertional breathlessness (mMRC ≥1).
- Bullectomy contraindicated or is actively avoided.
- Optimum COPD treatment for at least 6 weeks.
- No COPD exacerbation for at least 6 weeks.
- Fewer than 3 admissions for infective exacerbations in the preceding 12 months.

Exclusion Criteria:

- Inability to obtain informed consent
- Co-morbidities that would render bronchoscopy or sedation unsafe.
- Anaemia or other reasons precluding venesection.
- pO_2 on air <6.0kPa or pCO_2 on air >8.0kPa.
- Clinically significant bronchiectasis.
- Subject taking clopidogrel, warfarin, or other anticoagulants and unable to stop. treatment for 5 days pre-procedure.
- Maintenance oral steroids greater than 10mg prednisolone a day.

4.3.1.4 Study schedule

The study schedule is summarised in table 4.5.

Baseline/screening visit:

- Full Informed consent.
- Full medical history and clinical examination.
- Static and dynamic lung volumes and gas transfer measurements.
- Arterial blood gas tensions.
- High resolution computed tomography (HRCT) scanning of the chest.
- 6 minute walking test (6MWT).
- St. George's Respiratory Questionnaire (SGRQ).
- Modified Medical Research Council (mMRC) dyspnoea score.

Table 4.5: Summary of BIABI trial study schedule

	Baseline	Procedure	3 months post treatment
Clinical History	X		X
Examination	X		X
PFTs	X		X
mMRC	X		X
SGRQ	X		X
HRCT scan	X		X
6MWT	X		X
Bronchoscopy		X	

Bronchoscopic Procedures:

The bronchoscopic procedures were performed at the Chelsea and Westminster Hospital endoscopy unit as day case procedures using mild sedation (intravenous Midazolam). The participant was given a bronchoscopy information leaflet to review and relevant instructions at least 24 hours in advance of the procedure. Departmental pre-procedure and post-procedure protocols for routine bronchoscopy were followed.

A diagnostic bronchoscopy was performed before the bronchial segment containing the giant bulla was approached. This was determined by the investigators based on careful examination of the bronchial anatomy on HRCT along with real time fluoroscopic imaging. An extended working channel was passed bronchoscopically into the giant bulla and fluoroscopy was used to guide and confirm the positioning of the tip of the extended working channel inside the giant bulla (figure 4.4). Venesection of 60 mls of blood was then performed and the blood was instilled through the extended working channel within 60 seconds of being withdrawn, followed by a 10ml normal saline flush. The process was repeated and a total of 180mls-240mls of the patient's blood was instilled.

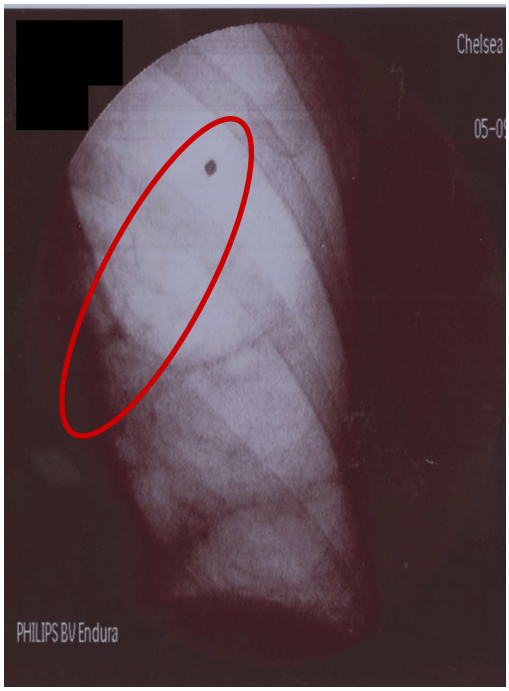


Figure 4.4: Fluoroscopic image exhibiting the tip of an extended working channel inside a giant bulla.

3 month evaluation:

Participants underwent a repeat of the examinations, investigations and health related quality of life questionnaires performed at baseline as listed above.

4.3.1.5-9 Static and dynamic lung volumes and gas transfer measurements, arterial blood gases, 6MWD, SGRQ, and mMRC

As in sections 4.2.1

4.3.1.10 HRCT of the chest

HRCT scanning was performed at baseline, 3 and 6 months following treatment. A Siemens Sensation 64, a 32 detector scanner with a rotation time of 0.33 seconds was used. Volumetric spiral acquisition with contiguous slices (1mm slice thickness on 1mm for lung windows and 10mm on 10mm for mediastinal windows) was taken with the participant in the supine position at full inspiration.

HRCT scans were studied and the presence of a giant bulla was independently assessed visually by two investigators using thin slice axial, sagittal and coronal reconstructions. Fissures in the treated lung were considered intact if >90% of the fissure was in clear continuity in at least one axis. The location of the bulla and the sub-segmental airways leading into it were noted.

For post-trial analysis, HRCT scans at baseline and 3 months post treatment were directly compared by an independent, blinded, radiologist who were asked to state whether there is bullae volume change of >20%, and whether there is evidence of scarring/fibrosis in the bullae lining.

4.3.2 RESULTS

4.3.2.1 Baseline data and procedure details

Five subjects (three male and two female) were recruited (age range 43 – 78 years). Table 4.6 details the baseline demographics, lung function, CT characteristics, and procedure specifics. The cohort had severe airway obstruction (mean (SD) FEV_1 36.4 % (6.8) predicted) with severe gas trapping and hyperinflation (mean RV 218 % (53.3) predicted). Mean (SD) procedure time was 25 (6.6) minutes. There was successful deposition of the blood with no back-spill seen in any of the cases. The mean dose of Midazolam required for the procedures was 2.25 (0.62) mg.

4.3.2.2 Primary Endpoint

The primary endpoint visit took place 95.4 (5.8) days following the procedure. The cohort experienced a clinically significant reduction in the primary outcome measure of change in RV of Δ-0.73 (0.50) L three months following BIABI treatment (p=0.06) (figure 4.6, table 4.6).

4.3.2.3 Secondary Endpoints

The secondary endpoints are illustrated in figure 4.6 and detailed in table 4.7.

1) There was a mean (SD) % increase in FEV_1 of 17.3 (17.8) % 3 months post treatment.
2) There was a mean (SD) reduction in SGRQ of 11.1 (13.3) points 3 months post treatment.
3) There was a mean (SD) increase in the 6MWD of 88 (69.9) m 3 months post treatment.
4) There was significant reduction in the CT size of the bulla as evidenced by displacement of the interlobar fissures and the development of new scarring within the bulla lining in 3 of 5 subjects (60%) as determined by an independent blinded radiologist 3 months following treatment.
5) Adverse events: discussed in section 4.2.3.4 below.

Table 4.6: Baseline demographics, lung function, CT characteristics (including fissure integrity), and procedure details of subjects in the BIABI study.

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Mean	SD
Sex	F	M	M	M	F	-	-
Age (yr.)	61	60	68	43	78	63.7	8.7
FEV1 (% predicted)	39	41	13	30	59	36.4	16.8
FVC (% predicted)	102	69	39	96	91	79.4	25.8
TLco (% predicted)	32	48	-	68	26	43.6	18.8
RV (% predicted)	214	185	283	253	149	216.7	53.3
TLC (% predicted)	146	104	127	144	118	127.8	17.7
RV/TLC (%)	57.8	59.2	79.2	52.6	57.9	61.3	10.3
PaO2 (kPa)	8.62	9.88	6.98	10.3	6.75	8.51	1.62
PaCO2 (kPa)	4.58	4.32	5.61	4.79	3.85	4.63	0.65
mMRC (points)	3	2	4	1	4	2.8	1.3
SGRQ (points)	74.9	56.4	72.6	28	66	59.6	19.1
6MWD (m)	90	144	-	411	63	177	160
Fissures >90% intact (treated lobe)	Yes	No	Yes	No	Yes	-	-
Treated bullae	RLL apical segment	RUL anterior segment	RML	LUL apical segment	LLL apical segment	-	-
Procedure time (min)	25	19	33	30	18	25.0	6.6

RLL, right lower lobe; RUL, right upper lobe; RML, right middle lobe; LUL, left upper lobe; LLL, left lower lobe.

Table 4.7: Change in efficacy outcomes three months after treatment.

Subject number	1	2	3	4	5	No. of Responders	Mean change	SD
RV (L)	***-1.23***	***-0.98***	-0.23	***-1.06***	-0.17	3/5	-0.73 &	0.50
FEV_1 (%change)	***27.1***	***33.1***	-11.1	***22.4***	***14.9***	4/5	17.30	17.28
SGRQ (points)	0.9	***-22.5***	2.2	***-8.8***	***-27.5***	3/5	-11.1	13.25
RV/TLC ratio (%)	***-12.1***	***-19.3***	3.6	***-14.9***	0.9	3/5	-8.39	10.39
6MWT (m)	***53***	***177***	-	***106***	16	3 /4	88	69.90
Number of MCID endpoints	4/5	5/5	0/4	5/5	2/5			
Change on HRCT	Yes	No	No	Yes	Yes			

&p=0.06 Wilcoxon matched pair test. Improvements beyond the minimal clinically important differences (MCIDs) of FEV_1 improvement of >12%,(135) RV reduction of >0.35L,(134) SGRQ reduction of >4 points,(133) increase in the 6MWD of >26m,(126) and RV/TLC ratio reduction >10% highlighted in ***bold/italics***)

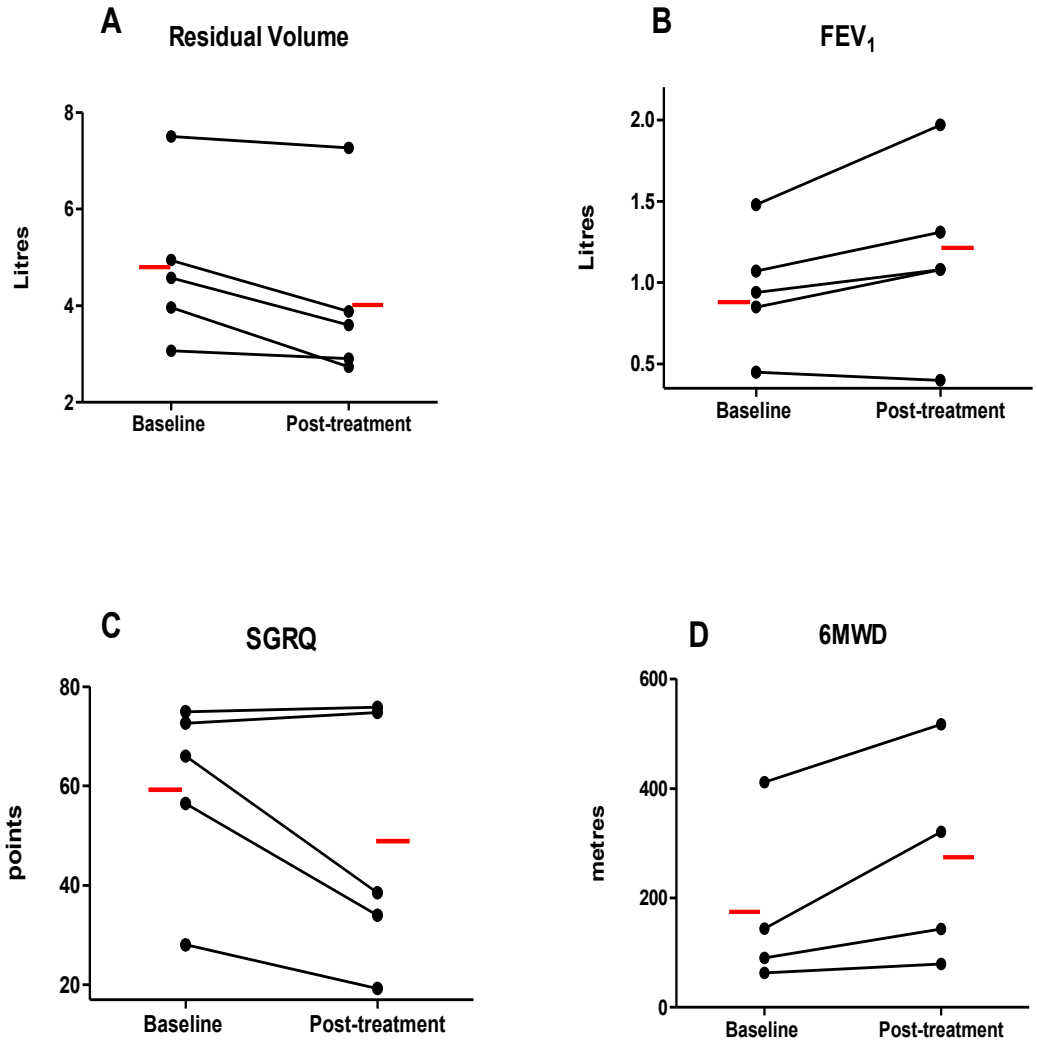


Figure 4.5: Primary and secondary outcomes before and 3 months following BIABI treatment. 6MWD was not available for one subject.

4.3.2.4 Safety Analysis

Subject 1 was admitted to her local hospital eight days after her procedure with symptoms and chest radiograph appearances of pneumonia. She improved with nebulised bronchodilators and intravenous antibiotics for three days and was discharged home five days after admission, with subsequent complete resolution of the adverse event. Two of the other four patients experienced infective exacerbations of their COPD at days 4 and 9 following their procedures, respectively. Both took their seven day rescue pack of antibiotics and prednisolone provided to them on discharge, after discussion with the research team. Both episodes fully resolved. No other adverse events were reported by the subjects. There were no adverse events noted related to venesection of 180-240mls of blood in these subjects.

4.4 DISCUSSION

These two pilot studies demonstrate the safety of bronchoscopically instilled endobronchial autologous blood using moderate sedation in patients with severe COPD. The adverse event profile was acceptable with the only adverse events experienced involving an inflammatory reaction – a desired outcome in terms of inflammation leading to scarring.

The optimal volume of blood instilled to cause the desired effect is unclear, and likely depends on the location and method of instillation. Our data reveals that 180-240mls is sufficient to trigger a response when concentrated inside a confined space (a bulla), but probably not when instilled in 60mls aliquots as in subsegmental airways of emphysematous parenchyma. This volume of venesected blood was not sufficiently large to cause side effects of hypotension in our studies. Venesection of 440mls is routinely undertaken for blood donation and other medical reasons.

The patients with heterogeneous disease having lobar blood instillation had a significant deterioration in lung function compared to the sham control group 8 weeks following treatment in this small cohort. Mean reduction in FEV_1 of 13% and increase in RV of 380mls are above the MCIDs for these outcomes, but these are likely skewed by one subject in the treatment arm who had recovered from an exacerbation only 3 days before her follow-up visit and had a 40% reduction in FEV1 and 1.16L increase in her RV. Similarly, the control group had a mean 330ml increase in the RV, driven by one subject's 1.3L reduction 8 weeks following a sham

bronchoscopy. This highlights a major limitation of such small underpowered trials from which one should not draw conclusions.

It may be that there remains subtle parenchymal inflammation in the treated lobes 8 weeks following lobar blood instillation, and that the patients had not fully recovered from post-procedure exacerbations. The follow up period may be inadequate to detect a benefit as trials with Ariseal and thermal ablation with steam have shown that maximal benefit occurs after six months.(85, 142) However five of the seven patients in the treatment arm group (two received other non-medical therapy soon after completing trial follow-up) did not demonstrate any symptomatic or lung function improvements at routine clinical review 9 - 12 months following treatment. It may be that a more concentrated instillation of the full volume of blood in one subsegment or repeated treatments would be more effective at inducing scarring, rather than small volumes of blood interspersed throughout the treated lobe.

Stopping randomised controlled trials early for apparent benefit or lack thereof is controversial and may have ethical considerations. Conducting frequent or unplanned interim analyses runs a risk of capturing the data at a time of a random extreme, usually representing an overestimation of benefit, though an underestimation is equally possible but less likely to be acted upon in terms of stopping a trial early.(143) In an explanation and elaboration to the CONSORT 2010 statement on guidelines of reporting parallel RCTs,(144) possibilities why trials may be stopped early are reviewed: "*RCTs can stop earlier than planned because of the result of an interim analysis showing larger than expected benefit or harm on the experimental intervention. Also RCTs can stop earlier than planned when investigators find evidence of no important difference between experimental and control interventions (that is, stopping for futility). In addition, trials may stop early because the trial becomes unviable: funding vanishes, researchers cannot access eligible patients or study interventions, or the results of other studies make the research question irrelevant".* Whatever the cause, RCTs must clearly indicate why trials came to an end and who made the decision, disclosing extrinsic factors including the funding sponsor's role in the decision to stop the trial. Section 4.2.3 details this information for the autologous blood LVR study, and several of the reasons reviewed by Moher *et al.* contributed to the decision to discontinue this trial. However one must comment on the fact that there was no pre-appointed safety and data monitoring committee for this interventional study and the decision was made by the chief investigator and study team. This was a small single centre study with very limited funding nevertheless it would have been preferable to have an independent committee in a trial involving an intervention which risks serious adverse events. The decision was later discussed with members of the COPD MDT to obtain a consensus, but this was not mandated in the

protocol. The timing of the interim analysis was appropriate as the follow up period was short such that follow-up data was available for all patients enrolled onto the study at the time of the decision to discontinue the trial. This meant there was no unblinding of patients still awaiting follow-up at the time of trial discontinuation, and no "relaxation" of the best medical care offered to patients in both study arms. However as discussed previously there is little data in the literature to give an accurate sample size calculation and patient numbers were small with data skewed by patients with outlying results. There are ethical obligations to trial participants who provided informed consent at the time of recruitment, and all subjects were informed of the trial discontinuation and offered other treatments if suitable. It is important that results of this trial are published as this may guide other researchers to adjust trial protocols avoiding other patient exposure to this unsuccessful technique. The results have been submitted to several respiratory journals but unfortunately editors did not find the study of sufficient interest for publication. We hope to successfully publish this data in an open access journal in the near future.

The post-BIABI treatment data are very encouraging and show large improvements in lung function, exercise capacity, and respiratory related quality of life in 3 out of 5 patients. Crucially, this was accompanied by clear reduction in bullae size on CT in 3 of the 5 patients. Subjects 1, 2 and 4 had dramatic and almost universal improvements across the outcome measures, exceeding the minimally clinically important differences (MCIDs) by large margins (table 4.6). All three described their symptomatic improvements as "life-changing". Subject 5 had strong responses in 2 of the 5 outcome measures with trends in the direction of benefit in RV change. CT scans performed at the follow-up visit demonstrated noticeable reductions in the size of the bullae in subjects 1, 4 and 5, with evidence of new fibrotic reactions in the bullae lining (figure 4.6). The patients had further follow-up assessments six months post- BIABI treatment outside the trial protocol, and the mean reduction in RV diminished slightly but was still improved compared to baseline (Δ-0.27 (0.47)L), whilst improvements in FEV1 (Δ+16.4 (23.7)%), 6MWD (Δ+60.5 (42.4) m), and SGRQ (Δ- 11.7 (10.7) points) were maintained. FVC increased further as compared to baseline (Δ+16.2 (30.2)%). These encouraging results after five treated patients informed the design of a larger feasibility and safety study of BIABI treatment for giant bullae in patients unsuitable for bullectomy. The protocol was written by the author and favourable Ethics and local Research and Development opinions obtained (NCT 01727037). Ten of a target 30 patients have already been treated and early results are thus far consistent with data presented in this thesis.

The health and symptom status of the BIABI cohort was relatively heterogeneous, with two of the three “responders” suffering from end-stage inoperable disease with very poor exercise tolerance, whilst the third subject was relatively young and active but had declined the offer of a bullectomy. Nevertheless all three had similarly large benefits from this minimally invasive treatment. Subject 3, the non-responder in this cohort, had had two previous pleurodeses for pneumothoraces which may have restricted lung remodelling explaining his lack of response.

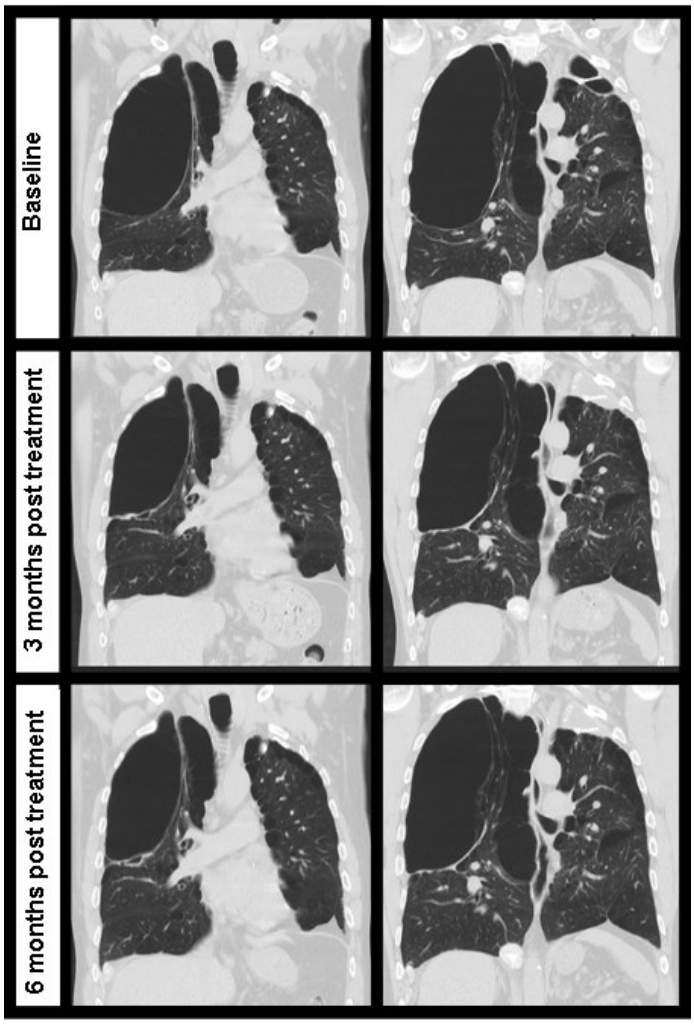


Figure 4.6: Coronal HRCT scan images from subject 2 at baseline, 3, and 6 months following BIABI treatment. There is a reduction in bulla size 3 months after treatment and new thickening and fibrosis of the inferior bulla lining can be appreciated. No subsequent change was seen between 3 and 6 months following treatment.

We also observed that, when successful at instigating an inflammatory reaction, remodelling and scarring continues to develop beyond three months. Figure 4.7 illustrates images from subject 1's HRCT scans at baseline, 3, 6 and 12 months following treatment. The shrinking of the bulla is progressive and dramatic. This subject's lung function and quality of life score improvements have been maintained 12 months following treatment. Trials with other sclerosants and profibrotic agents such as Aeriseal and thermal ablation with steam have shown that maximal benefit occurs after six months.(85, 142)

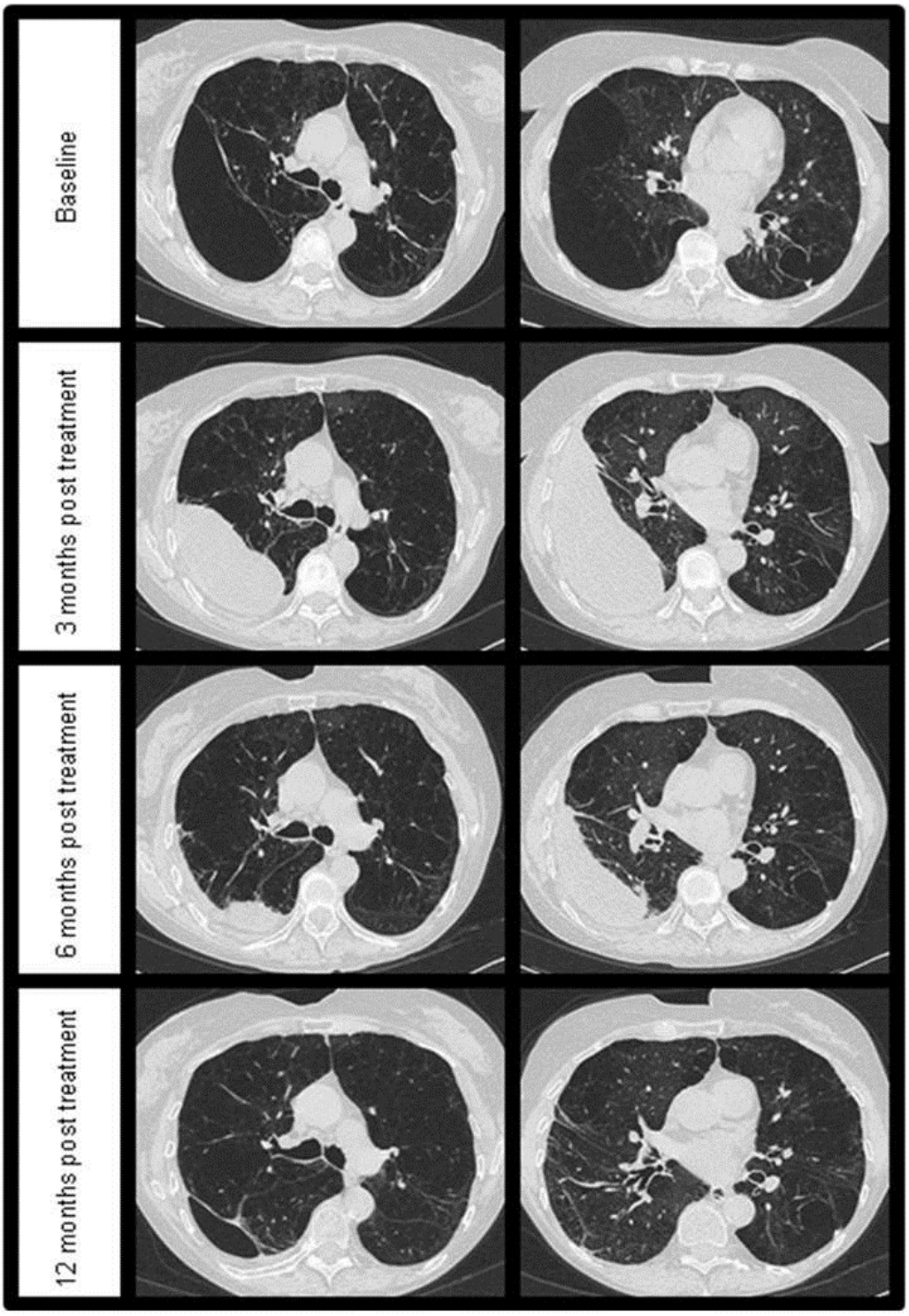


Figure 4.7: Axial CT scan images of Subject 1 at the levels of the T4 (carina) and T6 vertebrae at baseline, 3, 6 and 12 months following BIABI treatment. There is progressive and dramatic shrinking in the size of the bulla.

It is likely that repeat intrabullous blood instillation (perhaps 3-6 months after the first treatment) can lead to further shrinkage of bullae. However this was not necessary in subject 1 as described above. We repeated subject 5's BIABI treatment as she showed a partial response three months after her first treatment. Three months after her second BIABI treatment (nine months after the first treatment) the patient had further improvements in lung function, quality of life, exercise capacity (table 4.7), along with a major reduction in bulla size on HRCT scanning (figure 4.8). Repeat treatment decisions should be made on an individual basis.

Table 4.8: Outcome measures for subject 5 three months after the first and second treatments.

	Baseline	**3 months post 1st treatment**	**Change (%change) from baseline**	**3 months post 2nd treatment**	**Change (%change) from baseline**
RV (L)	3.07	2.90	-0.17 (-5.5%)	2.45	-0.62 (-20.2%)
FEV1 (L)	0.94	1.08	0.14 (14.9%)	1.41	0.47 (50.0%)
SGRQ (points)	66	38	-28	37	-29
RV/TLC ratio (%)	57.9	52.4	-5.51 (-9.5)	46.1	-11.8 (-20.3)
6MWT (m)	63	79	16 (25.4)	101	101 (60.3)

Although essential for successful lung volume reduction using endobronchial valves,(82, 83) success of techniques which reduce lung volume by inducing scarring and fibrosis should not be influenced by the presence or absence of collateral ventilation. Hence fissure integrity (as a surrogate for the absence of collateral ventilation) is not a factor in the success of these treatment approaches.(101, 145) We can therefore deduce that fissure integrity should not influence the success of bronchoscopic intrabullous autologous blood instillation. In our cohort, two of the five patients BIABI patients had incomplete fissures in the treated lobe, both being strong responders.

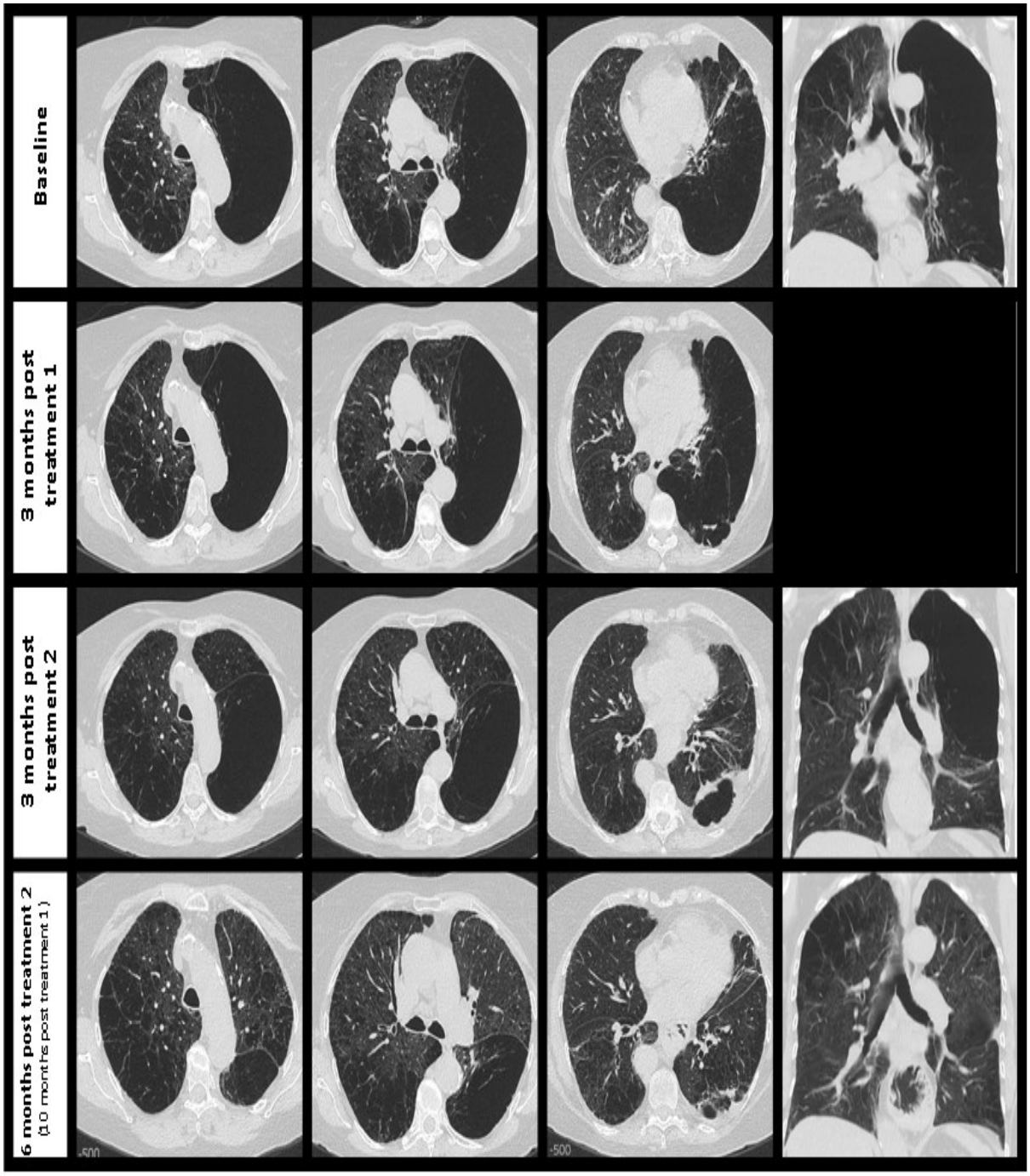


Figure 4.8: HRCT scan images for subject 5 at the levels of the aortic arch, the carina and T7 vertebra, as well as coronal views 3 months after the first, and 3 and 6 months after the second treatment (10 months after the first treatment). These demonstrate shrinkage of the giant bulla with re-expansion of the upper lobe and shifting of the mediastinum towards the treated lung.

4.5 CONCLUSION

The results from these studies using endobronchially instilled autologous blood suggest that BIABI treatment into giant bullae can induce shrinkage of the bullae leading to clinically meaningful improvements in lung function, exercise capacity and quality of life in some patients. This treatment represents a cheap, minimally invasive and safe technique to reduce bulla volume. It may serve as an adjunct to surgical bullectomy, by postponing the need for surgery or indeed as a precursor to surgery. It may also be considered in the treatment of frail patients on maximal medical therapy who are not fit for surgical intervention when no other treatment options are available. Further basic science research is required but the patient responses in the BIABI pilot study are sufficiently impressive to warrant a larger clinical trial.

Autologous blood instilled in aliquots of 60mls per lobar segment is ineffective at inducing atelectasis and reducing lung volumes. Success of autologous blood instillation in giant bullae suggests that, in principle, the technique may be successful but the technique requires refinement and further study is required.

Chapter 5

Optoelectronic Plethysmography in the assessment of advanced emphysema and the effects of lung volume reduction

5.1 BACKGROUND

Optoelectronic plethysmography (OEP) is a system for indirectly measuring lung volumes based on an automatic motion analyser which detects 89 passive markers composed of a thin film of retro-reflective paper on plastic hemispheres (5-10mm diameter). Six-eight cameras surrounding the patient record non-invasively real time breath-by-breath images of the markers and their movement (figure 1.8). Dedicated software uses the data received from the cameras to compute 3-dimentional co-ordinates of the markers by stereo-photogrammetric techniques. The principles, history, validation and applications of OEP were discussed in Section 1.4.

A particularly useful characteristic of OEP is that the software can be programmed to divide chest wall volumes into any desired combination of different compartments or subdivisions once the raw data has been accrued. This technology has not been used to study the effect of lung volume reduction in the treatment of emphysema, and in particular I was interested to examine the effect of unilateral treatment on changes in chest wall measured lung volumes with a view to informing physiological mechanisms of benefit following lung volume reduction. Specifically, does reduction in hyperinflation lead to changes in chest wall movements? Is any improvement limited to the treated side or is there bilateral change? In which compartment does this change in chest wall volumes predominate (pulmonary rib cage (RC,p), abdominal rib cage (RC,a) or abdomen(Ab))?

In health, the expansion and contraction of the rib cage and abdominal compartments during inspiration and expiration occurs in tandem as the straightened diaphragm pushes abdominal contents downwards (and thus abdominal wall outwards), and the intercostal and accessory muscles of respiration work to expand the ribcage. The diaphragm apposed part of the rib cage (RC,a) is subjected to different pressures than the upper rib cage (RC,p) which is apposed to the visceral pleurae. The flattened straightened diaphragm in COPD alters this dynamic and uncoordinated or asynchronous expansion of the rib cage compartment can occur, with negative impacts on ventilatory mechanics.(146, 147) Aliverti and colleagues used ultrasonography to delineate the area of apposition of the diaphragm to the chest wall, and then to measure diaphragm fibre length.(109) They demonstrated a linear relationship between OEP measured abdominal compartment volume displacement and diaphragm length, and concluded that this highly repeatable measure can be used to estimate diaphragm length. The same group used OEP to demonstrate the effect of within breath asynchrony on dynamic hyperinflation in

patients with COPD, with lower rib cage paradox associated with earlier dynamic hyperinflation than in COPD patients without chest wall asynchrony at baseline.(119) This did not influence exercise capacity or dyspnoea, but leg fatigue was higher in early hyper inflators. In contrast, Bruni *et al.* did not find that rib cage paradox influenced exercise capacity or the degree of dynamic hyperinflation in 10 COPD patients.(148) It has been proposed that returning the length of the diaphragm back to a more natural shape is one of the mechanisms of benefit of LVRS (section 1.3.8.3.1), but this has not been quantified. Here, the author hypothesised that OEP can demonstrate that reductions in hyperinflation and the accompanied return of the diaphragm to a more normal physiological length results in improvements in chest wall asynchrony or diaphragmatic paradox. Whether the presence of asynchrony at baseline can predict the response to lung volume reduction was also of interest.

In terms of direct comparison of volumes obtained with spirometry and those using OEP, small discrepancies were reported during quiet tidal breathing,(108) slow expiratory manoeuvres,(149) tidal breathing during submaximal (150, 151) and peak exercise (152) in patients with COPD and healthy controls. However there is general agreement that OEP measured dynamic chest wall volumes during forced or maximal manoeuvres are different to the volumes of air being expired from the mouth. This is due to factors relating to changes in intrathoracic pressures (blood shift out to the extremities and gas compression),(153) and increased movement artefact.(151) In patients with severe airflow obstruction, the author hypothesised that gas compression may play a leading role in the discrepancy between spirometric and OEP measured volumes during forced expiratory manoeuvres as exit out of the thorax through narrowed and collapsible airways is severely restricted, compared to patients without airflow obstruction. Do improvements in airflow obstruction lead to reduction in discrepancies between spirometric and OEP measured volumes during forced expiratory manoeuvres?

Thus the aims of this study are to:

1) Assess compartmental chest wall volume changes following lung volume reduction in patients with emphysema.
2) Assess whether improvements in airways obstruction following LVR lead to reduction in the discrepancy between spirometry and OEP measured volumes during forced expiratory manoeuvres.
3) Assess changes in chest wall asynchrony following lung volume reduction.

I also included in the study protocol cardiopulmonary exercise testing to examine whether OEP can be used, reliably and non-invasively (without a mouth piece), to assess the effect of lung volume reduction on dynamic hyperinflation in patients with severe COPD, though this was beyond the scope of this thesis.

5.2 METHODS

5.2.1 STUDY DESIGN

This was a prospective study recruiting patients with COPD undergoing lung volume reduction procedures at the Royal Brompton Hospital as part of routine clinical care or clinical trials. This included patients having both LVRS and BLVR (LVR coils, endobronchial valves, and endobronchial/intrabullous autologous blood instillation). Research ethics committee and NHS Trust R&D approval was obtained and all patients provided written informed consent. Patients were recruited between July 2011 and March 2013. After fulfilling the enrolment criteria, subjects had baseline assessments and these were repeated 3 months following treatment.

This is a pilot study with no data in the literature to guide a sample size calculation. We obtained ethics committee approval to assess 20 patients undergoing lung volume reduction, aiming to study 8-10 LVRS and 10-12 BLVR subjects, as well as 20 control COPD patients preferably undergoing a sham bronchoscopy as part of a clinical trial.

5.2.2 STUDY ENDPOINTS

1) Change in static and dynamic compartmental chest wall volumes 3 months post LVR, compared to controls.
2) Change in FEV_1 and FVC measured by OEP post LVR, and the change in the difference between OEP and spirometry measured values after LVR compared to baseline.
3) Change in chest wall asynchrony 3 months post lung volume reduction compared to controls.

5.2.3 PATIENT ENROLMENT

Participants were recruited at the Royal Brompton Hospital. Patients already scheduled to undergo LVRS as part of routine clinical care where identified from the thoracic surgical outpatient clinics, the advanced COPD MDT and ward admissions lists. Patients enrolled onto BLVR clinical trials were identified from the advanced COPD MDT and research fellows in our department. BLVR trials ongoing at time of recruitment for this study included randomised controlled trials of endobronchial valves, lung volume reduction coils, and autologous endobronchial blood instillation. Subjects were also recruited from a single arm pilot study of bronchoscopic intrabullous autologous blood instillation for giant bullae. The control phase of the endobronchial valve and the endobronchial autologous blood instillation trials involved a sham bronchoscopic procedure.

The enrolment criteria were as follows:

Inclusion Criteria

- COPD patient scheduled for a lung volume reduction procedure
- Age > 18 years
- Written informed consent

Exclusion Criteria

- Inability to obtain informed consent
- Contraindications or inability to perform cycle ergometry

5.2.4 SUBGROUP DEFINITIONS

Not all patients are expected to have a positive outcome following BLVR, and the implication this has on possible OEP findings is clear; if there is no “lung volume reduction” then we do not expect to find any change on OEP measured chest wall volumes. In this study, we sought to identify changes in thoraco-abdominal chest wall movements as a result of successful lung volume reduction, specifically compartmental volume change and chest wall asynchrony after unilateral procedures. Therefore those with a positive outcome were separated from those with unsuccessful treatment for the purpose of data analysis. BLVR patients were divided into

subgroups depending on whether lung volume reduction was achieved or not; termed "responders" and "non-responders". Patients were deemed to be responders if there was:

(1) Clear radiological evidence of significant volume reduction (i.e. lobar or segmental collapse with displacement of the interlobar fissures on HRCT, or significant reduction in the size of a giant bullae causing interlobar fissure displacement or adjacent parenchyma re-expansion); and

(2) Improvements in spirometry or hyperinflation on pulmonary function testing exceeding the MCIDs in % change in FEV_1 of reduction in RV.

5.2.5 STUDY SCHEDULE

Baseline assessments were performed within 2 weeks of the planned procedure, and in conjunction with other assessments if treatment was performed as part of another clinical trial. The data collected included:

- Demographic data
- Pulmonary function tests (static and dynamic lung volumes and gas transfer)
- SGRQ
- mMRC Dyspnoea Score
- HRCT of the thorax
- 6MWD
- Arterial blood gas analysis
- Incremental cycle ergometry to maximum achievable workload.
- Endurance submaximal cycle ergometry exercise test at 75% of maximal workload achieved during the Incremental test.
- OEP recordings were made simultaneously during spirometry and endurance cycle ergometry.

Three months after the procedure (LVR or sham), subjects had a repeat assessment as listed above without repeating the incremental cycle ergometry test.

5.2.6 OEP: TECHNICAL ASPECTS AND PATIENT TESTING

The OEP system at the Royal Brompton Hospital is the latest from BTS Bioengineering (2011) and uses eight cameras. This maximises reflective yield from the markers and improves stability of the geometric model, especially if there is excessive movement during the recording. After the first few cases and a couple of system "crashes", we operated the infrared cameras at 30Hz rather than 60 Hz to minimise the chance of system malfunction and loss of data from excessively large data files.

This study was the first to utilise the OEP system at the Royal Brompton Hospital. Simon Ward, head of the lung function department at the Royal Brompton, and Chris Nelson, senior physiologist, had received training on how to calibrate and use the OEP system by BTS Bioengineering engineers upon installation of the system. They in turn kindly trained me, and Chris and I performed the first 20 patient assessments together. A steep learning curve and technical difficulties were expected in the early stages. The majority of OEP tests were performed by both operators present together to ensure consistency, and I was personally present for all but two patient assessments.

5.2.6.1 Room preparation

Before each test, the cameras were mounted on their dedicated tripod stands or wall brackets and connected in the correct numbered order to the OEP system (the equipment is kept secure when not in use). Blinds were closed as natural light (but not indoor incandescent light) can disturb infrared light detection. All reflective material in the room was covered with drapes (e.g. metal taps, oxygen cylinders, coat hooks, computer screens, PhD candidate's belt buckle) and the patient and other staff instructed to remove watches, rings, necklaces and any item that can reflect light.

5.2.6.2 Infrared cameras

Experience following the first few cases suggested that the optimal camera positioning when patients are on a cycle ergometer (often leaning forwards and with arms out straight on the handlebar) is not the standard setup with eight cameras on wall brackets at head height. For subsequent tests we placed six of the cameras on wall mounted brackets at a height of 2.5m and the other two cameras were positioned on tripods at chest level (Figure 5.1). This enabled

marker detection from an angle below the outstretched arms. Before each OEP assessment, the camera positions were adjusted for every patient with the patient sitting on the cycle ergometer seat after adjusting the seat height. The camera views on the computer screen guided camera positioning ensuring that the whole torso is within each camera's the field of vision (Figure 5.1).

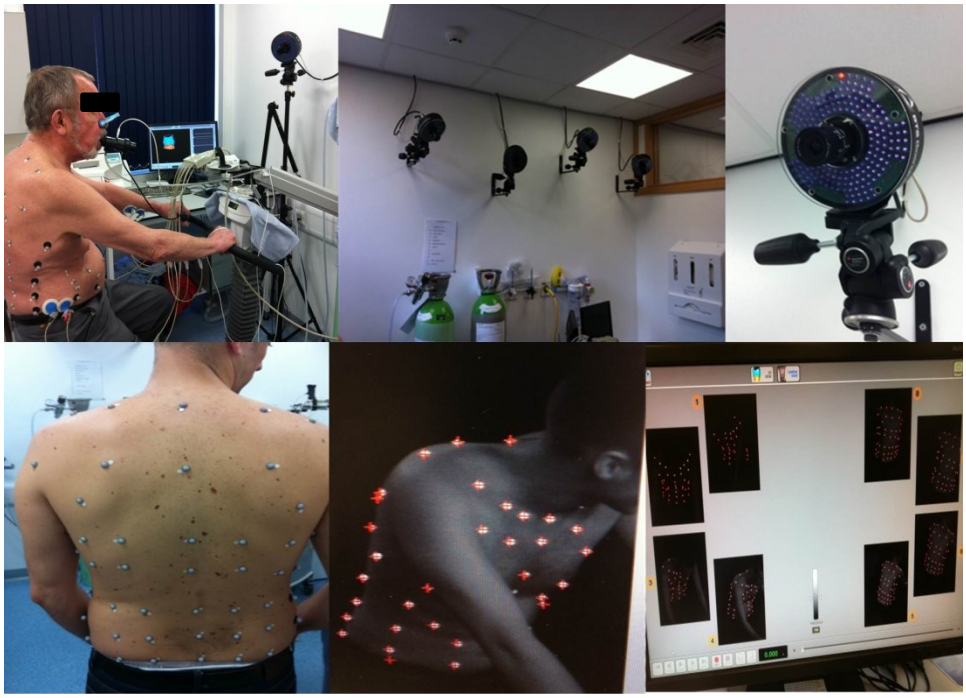


Figure 5.1: OEP system setup at the Royal Brompton. Top panel, camera positioning anteriorly; Bottom panel, reflective marker positioning; camera view for optimisation of camera positioning and focus level to ensure all markers are within view and detectable by each infrared camera.

5.2.6.3 Calibration

A triangular shaped calibration tool ("Reference Frame Assembly" including a "wand") with inbuilt reflective material was used to perform a two part calibration of the system (Figure 5.2). The tool was placed on the cycle ergometer seat, and 3-dimensional positions in the *x*, *y*, and *z* axes were calculated during a 5-10 second recording. Each camera has to recognise all three axes in the first part of the calibration process. In the second part, the wand is moved around within the space above the cycle ergometer seat which the subject will occupy for approximately 90 seconds. The calibration is complete and accurate when the cameras are able to detect the wand as it moves through the given space. If the wand is not detected, part 1 of the

calibration needs to be repeated, and the cameras may need to be manipulated. Once calibration is complete, the system is immediately ready to measure breath by breath volumes.

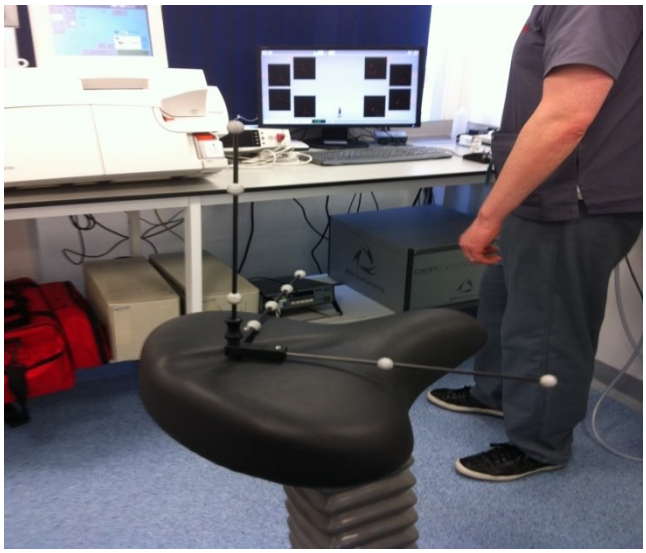


Figure 5.2: Step 1 of the OEP system calibration using the Reference Frame Assembly tool.

5.2.6.4 Reflective markers

With the cameras and cycle seat position optimised and the OEP system calibrated, OEP recordings may commence. The 89 reflective markers were carefully positioned on the subject's torso in a grid following a specific protocol (BTS biomedical engineering handbook 2001, see figure 5.3). This was done using two-sided hypoallergenic circular adhesive tape. Anteriorly, the grid consists of seven horizontal rows between the clavicles and the anterior superior iliac crest with additional bilateral columns in the mid-axillary line. Posteriorly there are also seven horizontal rows between the C7 vertebra and the posterior axillary lines. All markers were 6mm in diameter. Guidance is for 79 hemi-spherical markers and the 10 markers in the mid-axillary lines being spherical protruding off their base to improve detection by the cameras which are positioned anteriorly and posteriorly relative to the cycle ergometer. However we found that, due to the camera views being restricted by outstretched arms holding the cycle ergometer handlebar, as well as other equipment in a relatively small room, views of the lower left anterior abdominal markers were frequently lost. Our solution was to place spherical markers in these positions, and also at the horizontal line at the level of the xiphisternum, to improved marker detection and accuracy.

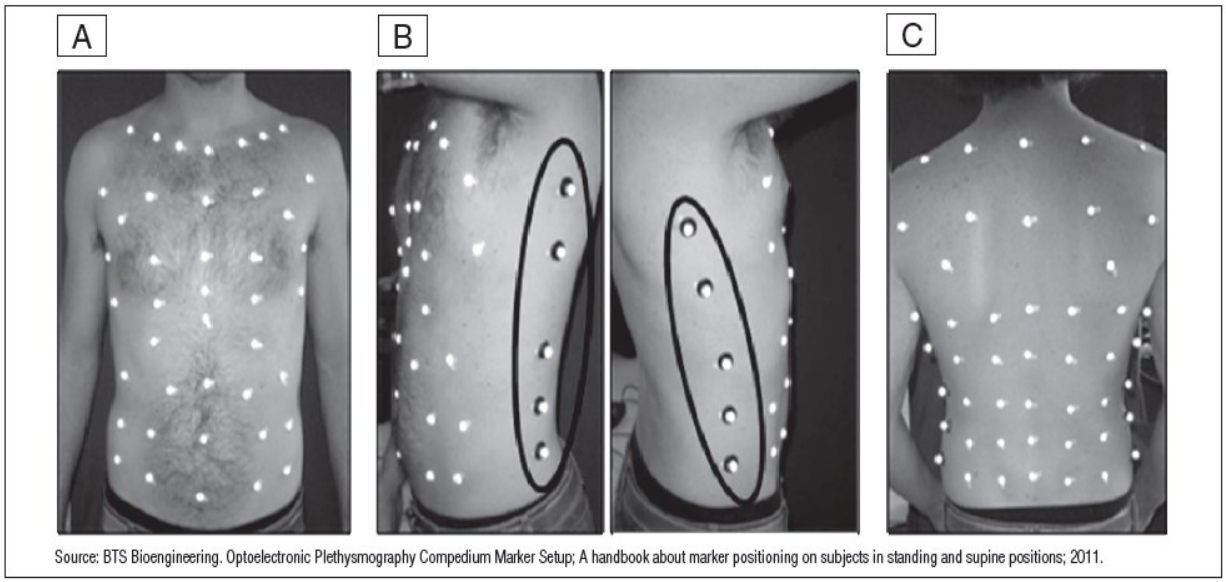


Figure 5.3: 89 marker configuration setup.

5.2.6.5 OEP patient testing

Before the start of each OEP recording, the subject was positioned optimally with all markers facing each camera completely within the camera's field of vision. The OEP screen was then switched from "camera view" to "3D view" and the "refresh" command used to prompt the OEP system to automatically connect the 89 markers matching the predefined geometric model, thus assigning each marker a label (1-89). The system can only create a model if all 89 markers are detected, and additional transient "phantom" markers from reflections off other objects in the room are common. If the resultant geometric model was incorrect, the system was refreshed repeatedly whilst subtle changes in the rotation and angulation of the torso were made until the geometric model was recognised by the OEP system. Labels can be re-tracked after the recordings are made and so if the automatic labelling system is not "connecting the dots" perfectly, this could be corrected at a later stage provided there is no error in marker placement on visual inspection of the model in the 3-D view. On occasions, repositioning of some markers was necessary to improve image capture. Once happy with a stable geometric model, recording was commenced. For each OEP test, two sets of OEP recordings were performed:

- Three forced expiratory manoeuvres were performed with the patient seated on the cycle ergometry seat with simultaneous recording of spirometry via a pneumotacograph with a mouthpiece and a nose clip applied.
- OEP measurements were then obtained simultaneously whilst cycle ergometry testing took place, including a five minute rest phase with inspiratory capacity manoeuvres performed every minute, as detailed in section 2.7.2.

The OEP and the metabolic cart recordings were started simultaneously to synchronise timelines and allow breath by breath lung volume measurement comparisons between the two systems.

Standing or sitting up straight provides the best views and putting arms out to the side or on one's hips kept them from interfering with the cameras' marker capture. During cycling, however, subjects were asked to grab hold of the handlebars to enable them to cycle effectively and safely. Leaning forward alters thoraco-abdominal chest wall shape and volume, and the outstretched arms in particular interfered with the camera views especially of the lower anterior abdominal markers. Layton *et al.* reported difficulties ensuring all their healthy study subjects maintained adequately upright torso position and they were unable to analyse 3 of 30 studies due to impeded camera views. (152) However, cycling upright is not the natural cycling position and likely influences exercise tolerance which is particularly limited in patients with severe emphysema. Therefore we asked patients to cycle holding the handlebars and, only if safe to do so, subjects were asked to sit up straight with their arms out to the side or on their hips supported by investigators for the 10 seconds before and 5 seconds after each inspiratory capacity manoeuvre (figure 5.4).

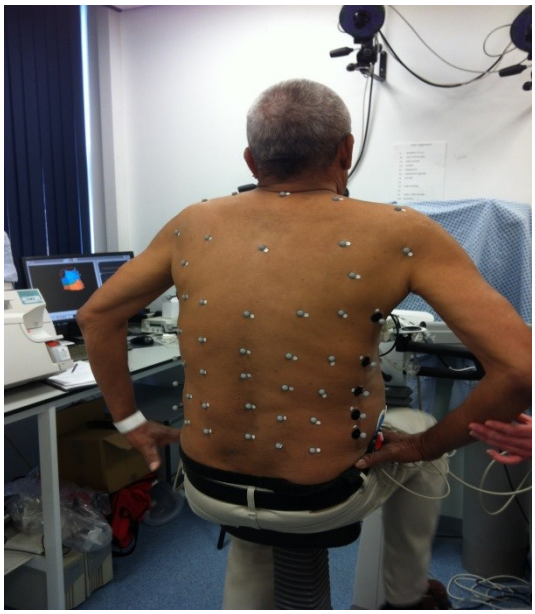


Figure 5.4: Arm positioning during inspiratory capacity manoeuvres to optimise marker detection by the infrared cameras.

Early experience of cycle ergometry testing with OEP recording revealed that ECG electrodes were problematic, with limited room on the chest wall for the electrodes and 10 wires repeatedly impeding camera views of the markers markedly diminished the quality of the OEP recordings. Having had an incremental cycle ergometry test to maximal workload without cardiovascular strain, we took the view that it was safe to perform submaximal steady state exercise without ECG monitoring, and subsequently the ECG electrodes were placed either on the forearms or lower back below the level of the lowest reflective markers (required for cardiac pulse rate measurements) (figure 5.1).

It became clear early on that performing reliable OEP recordings of women is much more challenging, specifically with maintaining adequate camera vision of markers below the breast line. In fact it was near impossible particularly during cycling with the patients leaning forward. Furthermore, following strict anatomical guidelines for marker positioning is essential in this study of measuring compartmental chest wall volumes and chest wall asynchrony, and several studies of female patients were thus technically inadequate for analysis. However recruitment was dictated by patient availability and I continued to recruit females having LVRS (limited numbers) but restricted female recruits to those with a normal/low BMI.

5.2.6.6 Thoraco-abdominal chest wall volume analysis

The standard OEP software protocol divides thoraco-abdominal lung volumes (Vcw) measurements into three compartments: pulmonary rib cage (Vrc,p), abdominal rib cage (Vrc,a) and abdomen (Vab). The upper border of Vrc,p is at the clavicles and jugular notch and terminates inferiorly at the horizontal line at the level of the xiphoid. This line is the superior border of Vrc,a which has its inferior borders at the lower costal margins. Vab extends from the lower costal margin to the level of a horizontal line connecting the anterior superior iliac crests (figure 5.5). For the purpose of our study and with the assistance of the technical department at the manufacturer BTS Bioengineering and the team at the Politecnico di Milano (Andrea Aliverti and Antonella Lo Mauro), we devised protocols to divide the chest wall volumes into six compartments; i.e. left and right for each of Vrc,p, Vrc,a and Vab.

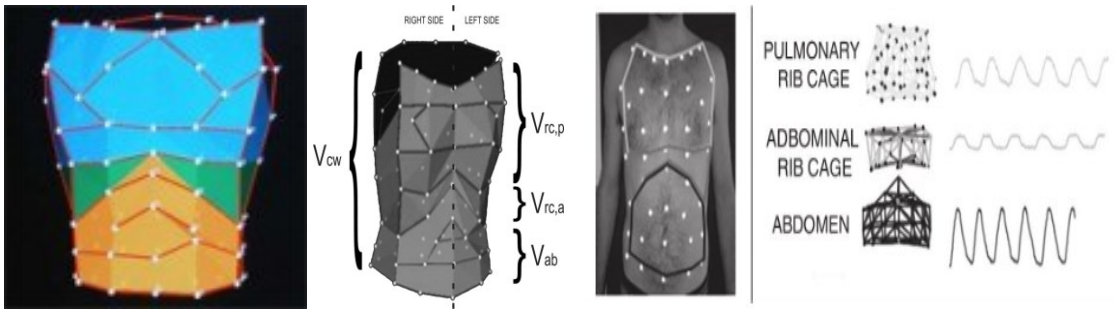


Figure 5.5: Thoraco-abdominal chest wall volumes (Vcw) and its separation into six compartments. (Adapted from the BTS Bioengineering OEP handbook 2011).

After raw data accrual, the following process was followed:

- For each recording, dedicated OEP software (OEPtracker, OEPanalyzer, and OEPtdfInspector (BTS Bioengineering, Milan)) enabled frame-by-frame review of all markers for correction of anomalous reflections, re-labelling of markers, and reconstruction of missing markers if feasible, to create a geometric model as complete as possible (ideally 89 markers for the duration of the recording) (figure 5.6). Some cycle ergometry recordings were very long (lasting up to 20 minutes at 30 or 60 frames/second) and the resultant OEP files being extremely large (>300MB). Splitting these recordings into smaller and easier to manage parts was performed to facilitate analysis.

- Once marker tracking was completed and the models “cleaned up”, the OEPtracking software was used to calculate the frame by frame volumes of the recordings.
- The volume data files were then viewed by dedicated software kindly provided by Andrea Aliverti and the team from the Politecnico di Milano (DIAMOV). A protocol splitting volumes into six compartments, as well as the standard three compartments (Vrc,p, Vrc,a and Vab) and Vcw was devised specifically for this study (figure 5.7).
- The volume traces on DIAMOV were then used to identify points of interest on the time-volume trace, and these were saved in the appropriate format: (1) for forced spirometry manoeuvres, the FRC, TLC, and RV points were highlighted for the largest of the three manoeuvres (figure 5.7).(2) For chest wall volume and asynchrony measurements, a run of between 5-10 stable tidal volume breaths was identified and the end expiratory (FRC) and maximum volumes of these tidal breaths (TV) was highlighted (figure 5.8). For the IC manoeuvre, TLC was highlighted and the end expiratory (FRC) volume obtained from the 5-10 tidal breaths (figure 5.8). The Vcw trace was used to identify the start and end of each breath or manoeuvre (rather than compartmental traces).
- Matlab (version 7.11.0.584, Mathworks, Naticks, Massachusetts, USA), a mathematical analysis software, was then used to extract and export the data from the highlighted points of interest using DIAMOV, calculating volumes for each compartment and transferring this to a Microsoft Excel spreadsheet for analysis.

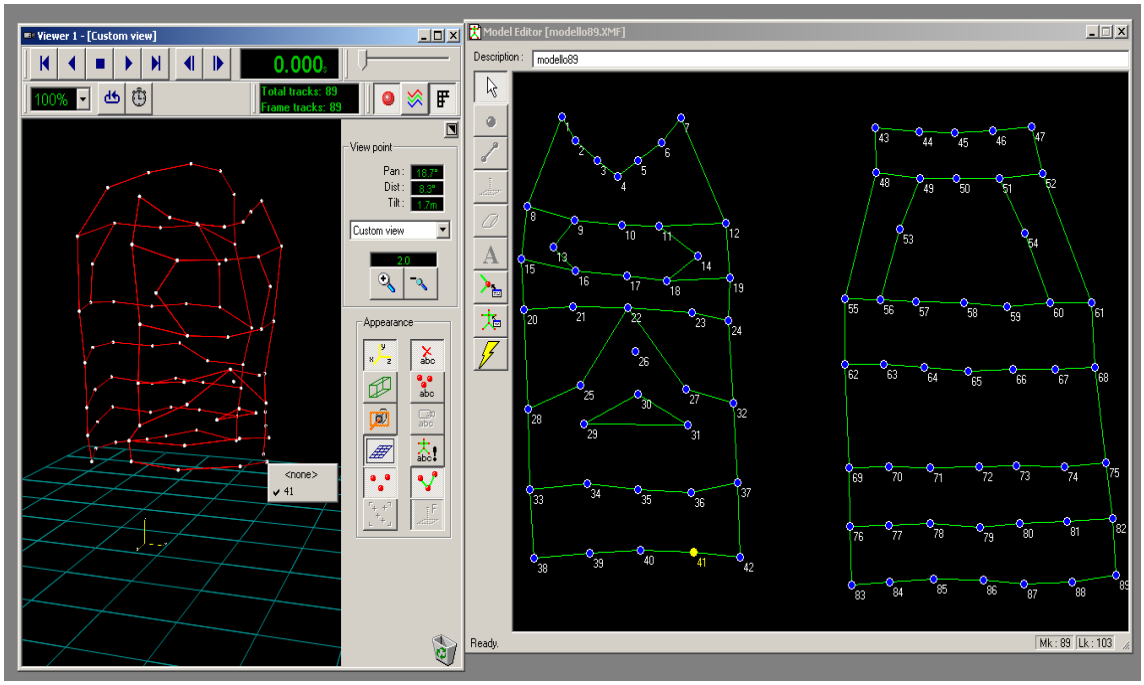


Figure 5.6: Geometric model marker labelling using OEPtracker software.

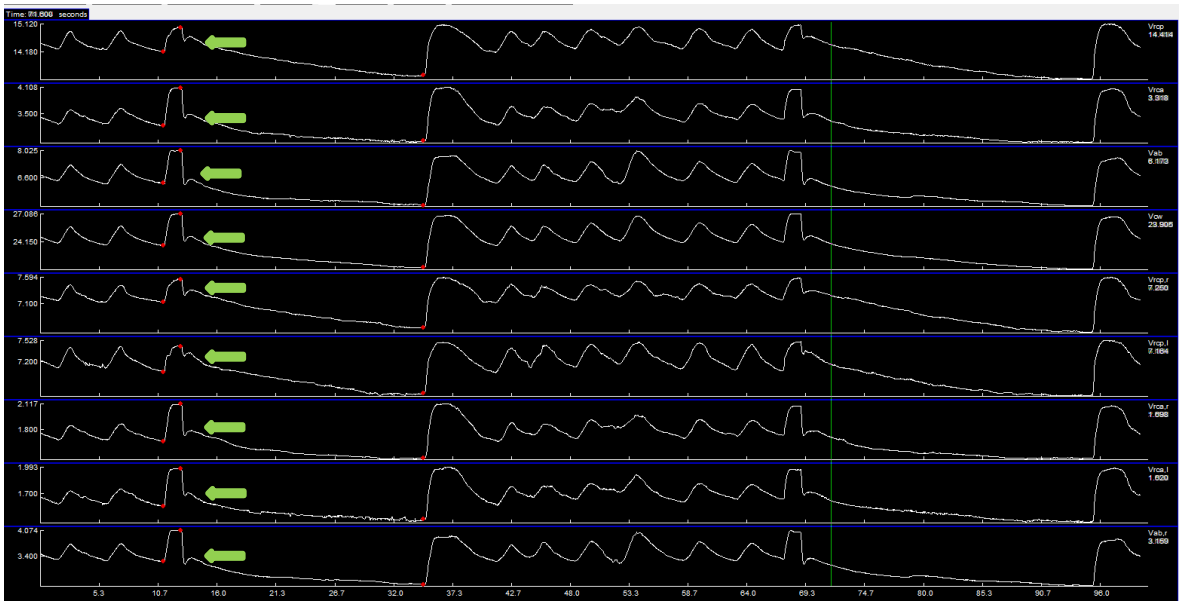


Figure 5.7: Volume-time trace of 9 compartments (labelled on right of screen), with the points of interest during the forced expiratory manoeuvre (FRC, TLC, RV) highlighted (red dots) for data extraction. A transient expansion of the chest wall compartments was seen in most patients within the first second of the forced expiratory manoeuvres in our cohort (green arrows), despite continuous expulsion of air from the mouth.

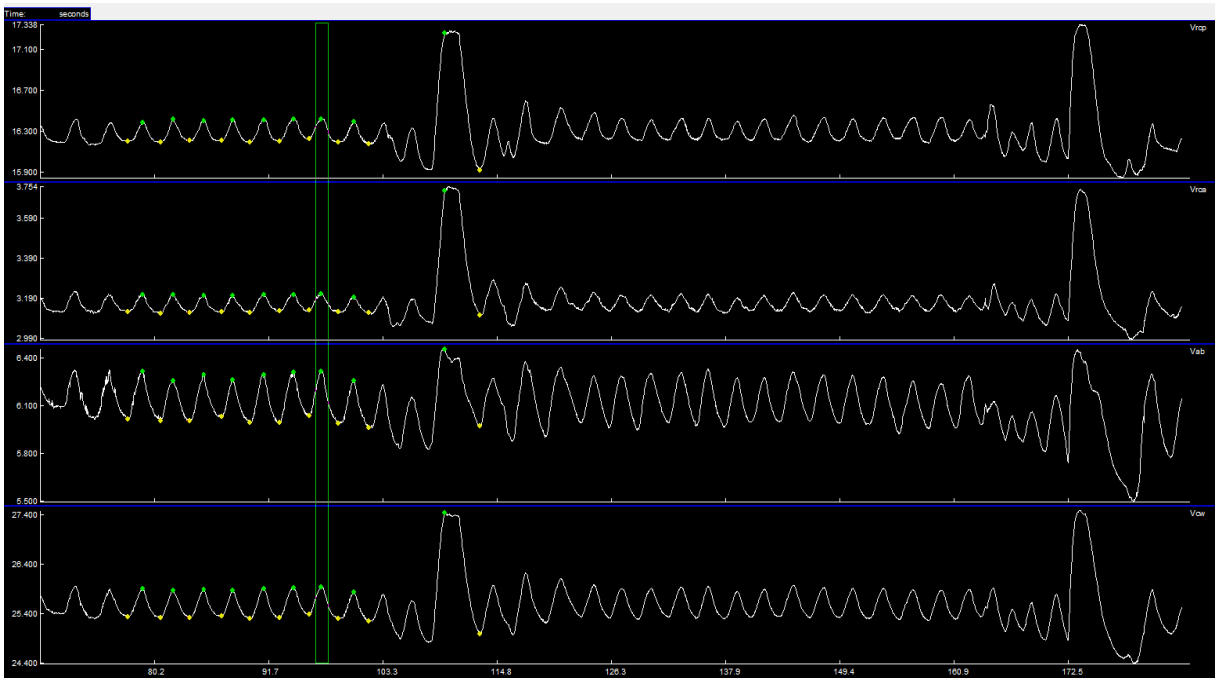


Figure 5.8: Volume-time trace of Vcw, Vrc,p, Vrc,a and Vab during quiet breathing and an inspiratory capacity manoeuvre. Tidal volumes and IC points of interest highlighted (green and yellow dots) for extraction.

5.2.6.7 Analysis of thoraco-abdominal wall asynchrony

Five to 10 stable tidal breaths during quiet breathing were averaged to obtain a typical respiratory cycle during quiet breathing (figure 5.8). This and the best of five resting IC manoeuvres were used to measure compartmental chest wall asynchrony using an approach first used to assess asynchrony by Bloch *et al.,* and later by other groups (78, 148, 154-156) as follows:

The time courses of the change in volume of the two compartments being examined for phase shift Θ (see below) were plotted against each other creating a Lissajou figure (figure 5.9). The degree of opening of the Lissajou figure corresponds to the phase shift angle(Θ). Θ was determined by the ratio of the distance delimited by the intercepts of the two compartmental volumes' dynamic loops on a line parallel to the x-axis at 50% of the tidal volume of the first compartmental volume (*m*), divided by the second compartmental tidal volume (*s*) (figure 5.9), as:

$$\boldsymbol{\theta = sin^{-1}\,(ms^{-1})}$$

In this system, a phase angle of zero represents a completely synchronous movement of the compartments and 180˚ total asynchrony. The phase shift angle Θ was calculated separately for both quiet breathing and inspiratory capacity manoeuvres.

Aliverti *et al.* (154) and Bruni *et al.* (148) both examined asynchrony between the pulmonary and abdominal rib cages in their respective studies of COPD patients during exercise. However there are other possible asynchronous chest wall movements particularly when investigating the effect of unilateral interventions. Therefore, a Matlab protocol was kindly prepared by Antonella Lo Mauro of the Politecnico di Milano to extract the phase shift angles between the following compartments to enable the assessment of these various potential forms of chest wall asynchrony:

- ΘRC; Phase shift angle between RC,p and RC,a.
- ΘDIA; Phase shift angle between RCa and Ab.
- ΘRC and ΘDIA for the treated (or worst affected side in sham treated patients) and non-treated sides.
- ΘRC,p; Phase shift angle between treated and untreated sides of RC,p.

- ΘRC,a; Phase shift angle between treated and untreated sides of RC,a
- ΘAb; Phase shift angle between treated and untreated sides of Ab
- All phase shift angles above were calculated during tidal breathing and inspiratory capacity manoeuvres.

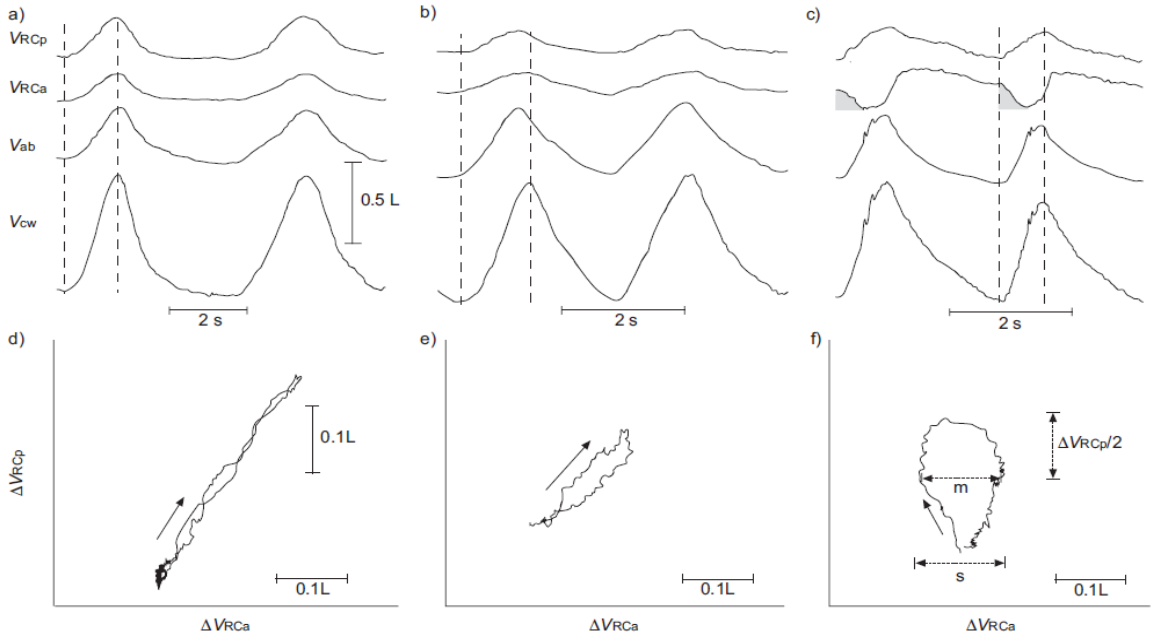


Figure 5.9: (a-c) Time courses of Vrc,p, Vrc,a, Vab and Vcw during two consecutive breaths at rest. (d-f) Lissajou figures of the dynamic loops of ΔVrc,p versus ΔVrc,a during quiet breathing, averaged in respiratory cycle time of a (d) healthy subject, (e) a patient with COPD without asynchrony between Vrc,p and Vrc,a, and (f) a patient with COPD and asynchronous rib cage movement. Period of inspiratory paradoxical movement; m, line parallel to the x-axis at 50% of RCp tidal volume; s; RCa tidal volume. Phase shift is calculated as $\Theta = \sin^{-1}(ms^{-1})$. Adapted from (119) and reproduced with permission of the European Respiratory Society © Eur Respir J 2009 33:49-60;2008 (see appendix for permission letter).

Aliverti *et al.* studied 14 normal subjects and used a difference of at least 2 standard deviations above the mean value in normal subjects (99% confidence interval) to obtain a threshold for the upper limit of normal of 14˚ for ΘRC.(154) Bruni *et al.* used in the same method to obtain a threshold for the upper limit of normal of 18˚ for ΘRC (this is mentioned in their manuscript (148) but not formally reported in the literature). The upper range of normality for ΘDIA is not known, but is likely higher than ΘRC in view of the much more compliant abdominal wall as compared to the rib cage. Using an upper limit of normal of 18˚ for both ΘRC and ΘDIA in this study is conservative and reasonable based on the limited available evidence.

5.2.7 STATISTICAL ANALYSIS

Data are presented as mean (1 standard deviation(SD)) or mean ± SD in tables for continuous variables. The normality test applied was the Shapiro-Wilk test. The differences between groups for continuous variables were studied using either unpaired T-tests or the Mann-Whitney U test depending on the normality of their distribution, or when comparing more than one group the one way analysis of variance with bonferroni's multiple comparison test or Kruskal-Wallis test with Dunn's multiple comparison test depending on normality of distribution. The differences between groups for categorical variables were tested using the Chi-square test. Comparisons of repeated measures were performed using paired T-tests or Wilcoxon matched pairs test depending on normality of distribution. Between group comparisons were presented as mean change with 95% confidence intervals (CIs). A level of $p<0.05$ was considered significant.

5.3 RESULTS

5.3.1 OVERVIEW

The technical quality of the first 10-12 recordings was poor, and most were inadequate for analysis. We were still in the process of identifying the optimal camera positions for the purpose of our recordings, and had lost several recordings at the "save recording" stage due system malfunction as some data files were too large. The body habitus of some patients made detection of markers in certain positions (e.g. under the breast line in women) very poor. Improvements were made in our technique and also in patient selection, and advice sought from BTS Bioengineering. Recording quality and efficiency improved as we became more experienced. Thus to account for technically inadequate studies and subjects who did not proceed to have a treatment or follow-up assessment, we continued recruitment beyond the initial target of 40 patient and ultimately 52 patients were recruited and assessed at baseline, with 43 having follow-up assessments. The flow diagram in figure 5.10 illustrates subject numbers in the trial and reasons for drop outs. Nine patients had LVRS, 12 LVR with endobronchial valves, eight LVR coils, eight sham bronchoscopy and five autologous blood LVR.

A total of 104 OEP assessments were performed (LVR coil and two BIABI subjects had two treatments and hence two follow-up OEP assessments each). The primary follow-up assessment visit for LVR coil patients was the one after the first treatment as our interest is in unilateral changes. Mean (SD) time between baseline and the primary follow-up assessment was 107 (50) days.

For the purpose of data analysis, patients were categorised in the following groups: 1) LVRS (n=9); 2) BLVR responders (n=9); 3) Controls (sham controls (n=8) and BLVR non-responders (n=9)); and 4) LVR coils (n=8).

The reasons for unsuccessful treatment in the BLVR non-responders were as follows: two expectorated valves; three had positive interlobar collateral ventilation and would thus not be expected to benefit from valve treatment; one had endobronchial anatomy which precluded complete lobar exclusion; and three had no response to autologous blood LVR. It is reasonable to consider this group as effectively having had the equivalent of sham procedures for the purpose of this study, and thus their data was used with that of the sham bronchoscopy patients in the group labelled "controls".

All eight LVR coil patient assessments where in the first 12 tests performed, and five were female. As a result only two subjects have technically satisfactory assessments. This was disappointing as this group was the only cohort to have bilateral sequential treatments, of great interest from a unilateral assessment perspective. Although some had positive responses clinically the mechanism of benefit does not involve volume reduction per se, rather restoring lung elasticity and reductions in dynamic airway collapse (Chapter 3). Therefore responders from this cohort were not added to the BLVR responder group.

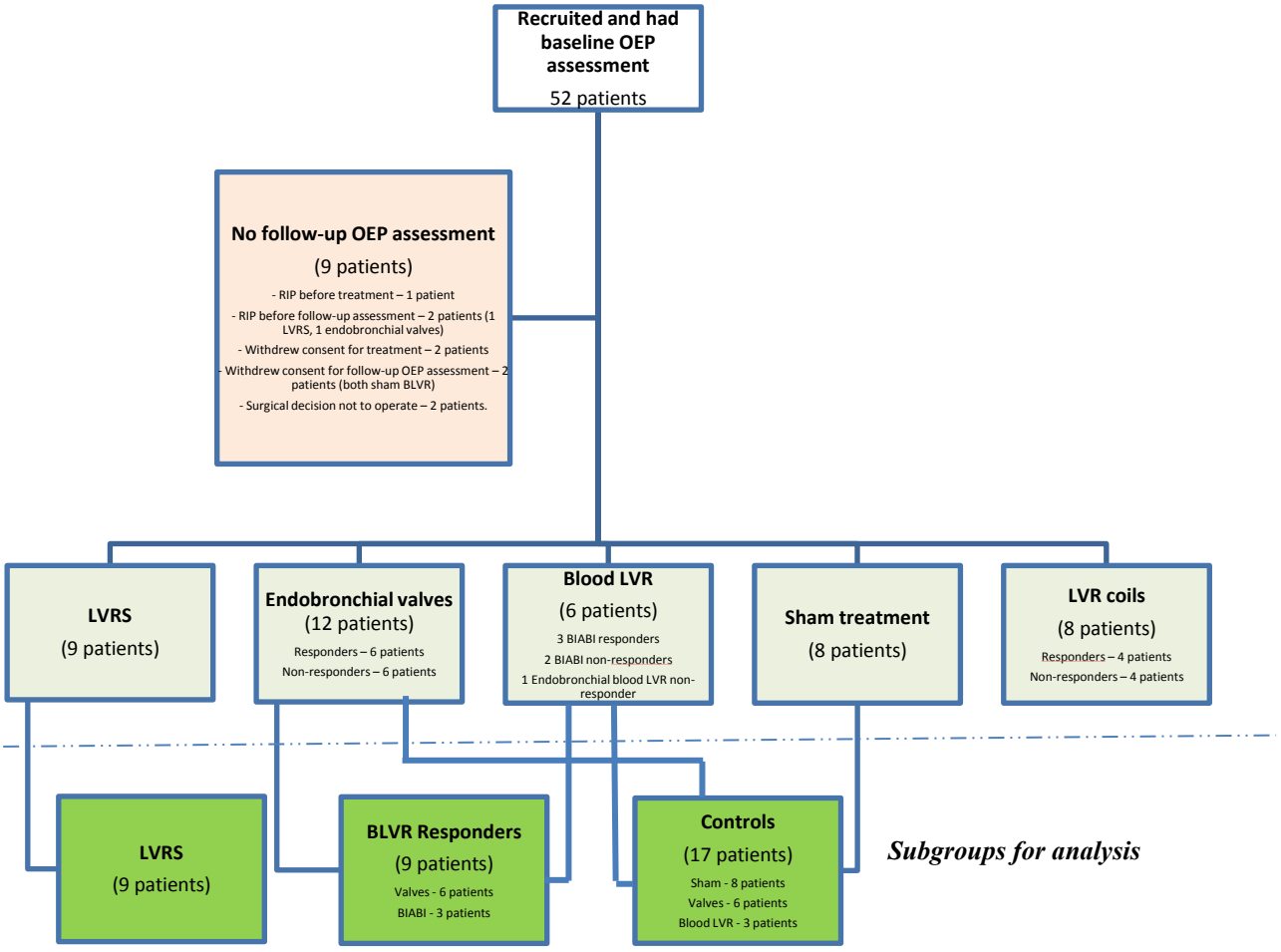


Figure 5.10: Flow diagram of subjects in the OEP study

For measurements of TVs, ICs and chest wall asynchrony, both baseline and 3 month OEP studies of sufficiently good technical quality for assessment were available for 9 LVRS patients, 7 BLVR responders, and 10 controls. For forced expiratory manoeuvres, pre- and post- studies of adequate quality for assessment were available for 8 LVRS patients, 7 BLVR responders, and 11 controls.

5.3.2 CLINICAL CHARACTERISTICS AND VALUES AT BASELINE

Baseline characteristics for the whole cohort and the subgroups are detailed in Table 5.1. There was no significant difference between the any of the groups.

Table 5.1: Baseline characteristics of all subjects and the different subgroups.

		All subjects (n=52)	LVRS (n=9)	BLVR responders (n=9)	BLVR non-responders (n=9)	Sham (n=8)	Control (n=17)	Coils (n=8)	No follow-up (n=9)	p-value ¥
Age (years)	mean	62.7	58.6	62.2	62.4	64.0	63.2	65.4	63.8	ns
	SD	7.6	9.2	10.1	5.7	5.4	5.5	6.0	7.9	
BMI (kg/m^2)	mean	24.8	23.0	27.4	24.9	25.5	25.2	24.8	23.3	ns
	SD	4.0	4.5	2.9	3.4	3.9	3.5	4.0	4.2	
Males (%)		83	89	78	100	75	88	38	89	n/a
FEV_1 (L)	mean	0.94	1.07	1.04	0.94	0.97	0.95	0.76	0.85	ns
	SD	0.30	0.39	0.26	0.29	0.23	0.26	0.20	0.34	
FEV_1 % predicted	mean	34.6	46.4	42.4	29.3	32.1	30.6	29.6	27.1	ns
	SD	17.7	33.4	14.0	11.5	7.5	9.6	9.6	7.6	
FVC (L)	mean	3.40	3.57	3.55	3.49	3.59	3.54	2.87	3.27	ns
	SD	0.88	1.18	0.91	0.76	0.95	0.83	0.57	0.79	
FVC % predicted	mean	95.2	103.0	113.4	85.3	97.3	90.9	87.9	83.8	ns
	SD	33.6	47.9	53.4	26.2	18.5	23.0	12.8	13.2	
RV % predicted	mean	217.8	214.3	194.3	229.5	229.0	229.3	212.3	227.9	ns
	SD	41.8	43.1	40.4	53.6	23.4	41.0	47.6	35.6	
TLC % predicted	mean	139.5	140.5	137.8	134.3	144.5	139.1	149.8	132.0	ns
	SD	26.5	31.5	21.8	10.2	10.4	11.2	52.3	13.6	
FRC % predicted	mean	182.2	181.1	170.4	192.2	190.0	191.1	195.8	167.6	ns
	SD	36.2	32.6	20.8	23.3	19.9	21.1	31.3	65.9	
Raw % predicted	mean	406.3	291.5	329.5	350.5	439.3	392.2	524.9	519.0	ns
	SD	192.0	151.6	138.7	108.1	195.9	157.2	212.0	232.2	
$TLco_c$ % predicted	mean	36.4	33.1	39.1	35.5	43.1	39.3	37.6	30.6	ns
	SD	11.0	11.7	12.1	10.2	7.1	9.3	11.1	11.3	
RV/TLC (%)	mean	60.2	58.1	56.7	60.7	60.0	60.4	63.6	62.8	ns
	SD	6.9	7.1	5.1	9.3	4.9	7.3	5.7	7.4	
SGRQ (points)	mean	59.3	59.1	64.4	56.7	59.2	57.8	58.8	57.2	ns
	SD	15.1	12.1	16.1	17.8	13.9	15.7	17.5	15.7	
6MWD (m)	mean	330.1	390.6	297.9	350.0	353.3	351.6	317.4	281.4	ns
	SD	101.2	82.7	137.3	82.7	94.3	85.7	53.0	114.4	
mMRC (points)	mean	2.6	2.7	2.9	2.8	2.3	2.6	2.4	2.6	ns
	SD	0.8	0.7	0.6	1.0	0.8	0.9	0.9	0.5	
PaO2 (kPa)	mean	9.3	10.0	9.1	9.0	9.7	9.4	8.9	9.0	ns
	SD	1.2	1.4	1.3	1.1	0.7	0.9	1.4	1.1	
PaCO2 (kPa)	mean	5.1	5.0	4.9	4.7	5.3	5.0	5.4	5.3	ns
	SD	1.0	0.7	1.0	0.6	1.7	1.1	0.8	1.0	

¥ Kruskal-Wallis test with Dunn's multiple comparison test.

5.3.3 CLINICAL OUTCOMES

LVRS patients and the BLVR responders had clinically and statistically significant improvements in lung function, exercise capacity and quality of life as detailed in table 5.2, which accompanied the radiological evidence of volume loss. Controls (patients who had sham bronchoscopy and patients who did not derive benefit from BLVR) did not exhibit any significant change in the clinical outcome measures.

Table 5.2: Change from baseline in clinical outcome measures in the whole cohort and subgroups.

		All subjects (n=43)	LVRS (n=9)	BLVR responders (n=9)	Coils (n=8)	All LVR responders (n=18)	Controls (n=17)	p-value¥
ΔFEV$_1$ (L)	mean	0.16	0.38	0.25	0.07	0.32	0.02	0.01
	SD	0.33	0.61	0.21	0.10	0.43	0.14	
FEV$_1$ %change	mean	15.3	33.6	26.9	9.8	30.3	1.6	0.003
	SD	28.0	48.1	19.9	14.6	34.9	14.4	
ΔFVC (L)	mean	0.25	0.21	0.58	0.20	0.39	0.11	ns
	SD	0.59	0.82	0.36	0.26	0.63	0.66	
ΔRV (L)	mean	-0.49	-0.77	-1.16	-0.34	-0.96	-0.03	<0.0001
	SD	0.66	0.71	0.32	0.61	0.55	0.42	
ΔFRC (L)	mean	-0.34	-0.50	-0.82	-0.31	-0.66	0.05	<0.0001
	SD	0.54	0.47	0.36	0.60	0.43	0.42	
ΔTLC (L)	mean	-0.29	-0.57	-0.79	0.23	-0.68	-0.13	0.001
	SD	0.69	0.58	0.52	1.10	0.53	0.36	
ΔRV/TLC	mean	-5.1	-6.3	-9.3	-3.4	-7.8	0.5	0.0004
	SD	11.0	10.5	2.8	3.6	7.4	4.3	
TLCOc %change	mean	3.9	10.1	9.8	0.8	10.0	-0.9	ns (0.057)
	SD	15.9	20.0	17.6	11.9	17.8	13.4	
ΔSGRQ (points)	mean	-7.4	-15.7	-12.4	-8.3	-14.1	0.1	0.01
	SD	16.0	13.5	19.0	8.6	15.6	16.1	
Δ6MWD (metres)	mean	40.9	30.5	60.6	85.5	46.4	6.8	ns
	SD	70.8	49.4	41.6	49.9	47.3	82.9	
ΔmMRC (points)	mean	-0.40	-0.78	-0.67	-0.25	-0.72	-0.18	ns
	SD	0.86	0.83	0.87	0.71	0.82	0.95	

¥Unpaired t-tests or Mann Whitney test comparing the change from baseline between all LVR responders (LVRS and BLVR responders) vs. controls. No significant difference was seen between LVRS and BLVR responder groups.

5.3.4 OEP RESULTS

5.3.4.1 Static chest wall volumes

5.3.4.1.1 Baseline

Five to ten continuous stable tidal breaths during quiet breathing at rest with the patient sitting on the cycle ergometer were used to extract the end expiratory lung volume (Vcw at FRC), and the volume at the end of the inspiratory capacity manoeuvre was used to calculate the maximal total thoraco-abdominal chest wall volume (Vcw at TLC), and their compartments.

There was no significant difference between the groups in static Vcw at TLC or at FRC at baseline, though there is a 7.7 L difference between the mean Vcw at TLC of the LVRS and BLVR responder groups at baseline. This may in be attributable to the difference in the mean BMI (23.0 (4.5) kg/m^2 in the LVRS group vs. 27.4 (2.9) kg/m^2 in the BLVR responder group). Vcw of the treated (or worst affected in the control arm) side as a proportion of the total Vcw was similar between the groups at both TLC and FRC.

Table 5.3: Baseline OEP measured static thoraco-abdominal chest wall volumes.

		All subjects (n=26)	LVRS (n=9)	BLVR responders (n=7)	Controls (n=10)	p-value¥
Vcw at TLC (L)	mean	31.30	28.10	35.80	31.03	ns
	SD	6.47	6.03	6.53	5.43	
Vcw at TLC treated side (L)	mean	14.73	13.11	16.80	14.73	ns
	SD	3.26	2.89	3.41	2.88	
Vcw TLC treated side % of total Vcw	mean	46.94	42.52	46.83	47.34	ns
	SD	1.55	18.77	1.50	1.70	
Vcw at FRC (L)	mean	29.47	26.21	33.66	29.47	ns
	SD	6.47	6.01	6.29	5.80	
Vcw at FRC treated side (L)	mean	14.79	13.13	16.91	14.79	ns
	SD	3.27	2.90	3.40	2.86	
Vcw FRC treated side % of total Vcw	mean	50.20	50.21	50.16	50.23	ns
	SD	1.15	0.93	0.92	1.54	

¥ Kruskal-Wallis test with Dunn's multiple comparison test.

5.3.4.1.2 Change in static total chest wall volumes at 3 months

There were non-statistically significant reductions in Vcw at TLC of 0.71(2.89) L and at FRC of 0.79 (2.7) L in the LVRS group 3 months following treatment (table 5.4). The reduction was evenly distributed between the treated and non-treated sides. There were no changes seen in the BLVR responder or control groups at 3 months (Table 5.4). Between group comparisons in the change in Vcw at both FRC and TLC at 3 months did not reveal any significant between group differences.

Table 5.4: Change in Vcw at TLC and FRC and change in proportion of Vcw from treated side.

		LVRS (n=9)	BLVR responders (n=7)	Controls (n=10)
Change in Vcw at TLC (L)	mean	-0.71	0.35	0.06
	SD	2.89	1.91	2.80
% change in Vcw at TLC (L)	mean	-2.6	0.97	0.89
	SD	9.3	5.05	8.76
Change in proportion of treated side to total Vcw at TLC (%)	mean	-0.52	-0.18	-0.25
	SD	1.18	1.44	1.41
Change in Vcw at FRC (L)	mean	-0.79	-0.02	0.51
	SD	2.7	2.70	7.92
% change in Vcw at FRC (L)	mean	-0.39	0.78	-0.07
	SD	1.27	8.43	2.53
Change in proportion of treated side to total Vcw at FRC (%)	mean	-0.97	0.36	0.32
	SD	1.28	0.91	0.86

Wilcoxon matched pairs test comparing baseline and 3 months for each group, all non-significant. Kruskal Wallis with Dunn's multiple comparison comparing change between the groups, non-significant.

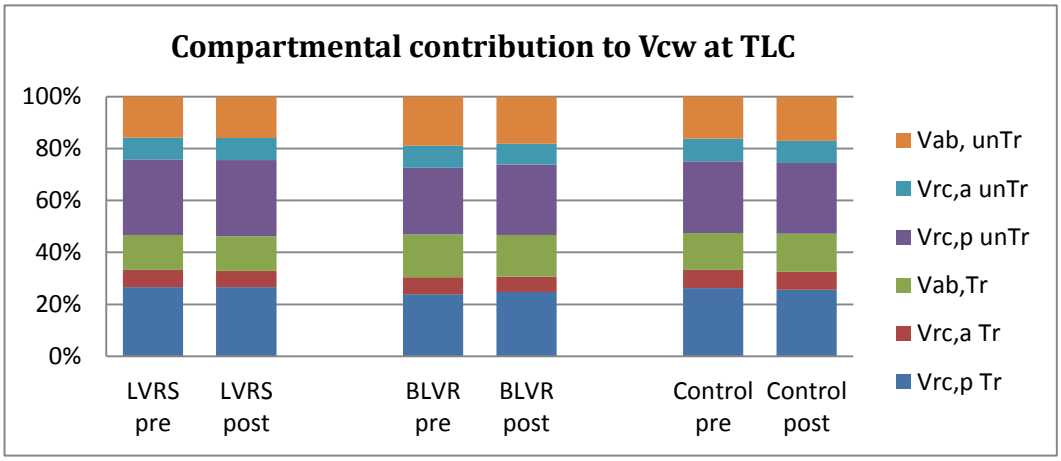
5.3.4.1.3 Static compartmental chest wall volumes and proportions to Vcw

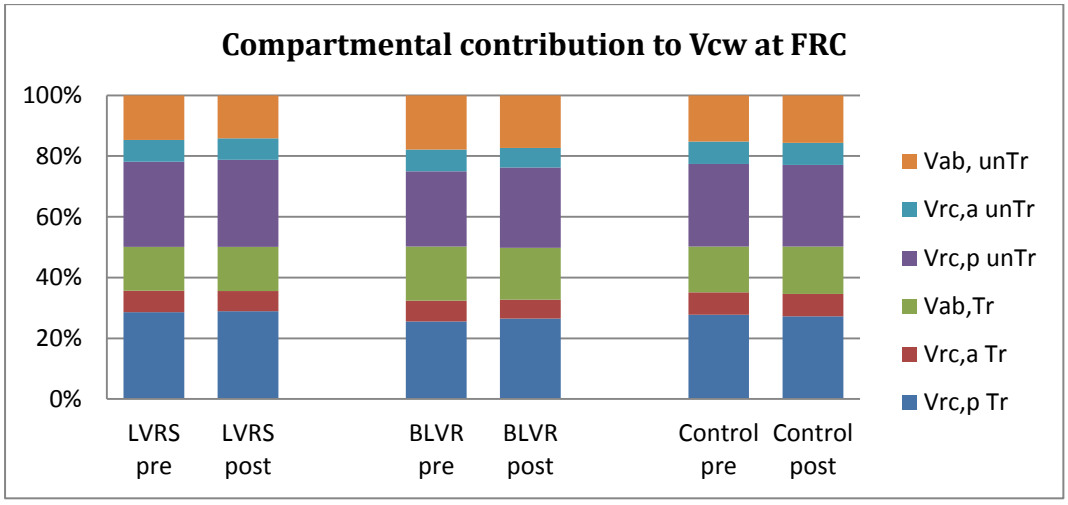
There was no significant change in compartmental volumes nor to their contribution to Vcw at TLC or FRC at 3 months in any of the groups (figure 5.12, table 5.5), though there was a trend towards a small reduction in Vrc,a post LVRS on the treated side (ΔVcw at TLC - 0.17L , p=0.08; Vcw at FRC -0.17L, p=0.09). There was no between group difference in the change in compartmental chest wall volumes at 3 months.

Table 5.5: Static compartmental lung volumes at baseline and 3 months post procedure.

		LVRS pre	LVRS post	p-value¥	BLVR pre	BLVR post	p-value¥	Control pre	Control post	p-value¥
Vcw at TLC (L)	Vrc,p Tr	7.47	7.29	0.48	8.54	9.15	0.17	8.14	7.96	0.65
	Vrc,a Tr	1.87	1.70	0.08	2.34	2.19	0.66	2.16	2.17	0.97
	Vab,Tr	3.77	3.67	0.68	5.92	5.90	0.91	4.42	4.54	0.62
	Vrc,p unTr	8.17	8.01	0.48	9.16	10.03	0.17	8.56	8.49	0.65
	Vrc,a unTr	2.36	2.35	0.55	3.07	2.95	0.66	2.70	2.63	0.97
	Vab, unTr	4.45	4.35	0.68	6.77	6.69	0.91	5.04	5.30	0.62
Vcw at FRC (L)	Vrc,p Tr	7.49	7.35	0.58	8.58	9.20	0.17	8.19	8.00	0.63
	Vrc,a Tr	1.87	1.70	0.09	2.32	2.18	0.64	2.17	2.18	0.98
	Vab,Tr	3.77	3.70	0.73	6.02	5.90	0.80	4.43	4.56	0.63
	Vrc,p unTr	7.35	7.29	0.58	8.33	9.23	0.17	8.01	7.89	0.63
	Vrc,a unTr	1.87	1.79	0.09	2.41	2.23	0.64	2.18	2.15	0.98
	Vab, unTr	3.86	3.59	0.73	6.00	6.00	0.80	4.49	4.59	0.63

¥Wilcoxon matched pairs test. Tr, treated (or worst affected) side; unTr, untreated side. LVRS n=9, BLVR responder n=7, controls n=10.





Figures 5.11 and 5.12: Compartmental contribution to Vcw at TLC (Fig 5.11 top) and FRC (Fig 5.12 bottom). Tr, treated (or worst affected) side; unTr, untreated side.

5.3.4.2 Dynamic chest wall volumes (TV, IC, FEV_1, FVC)

There was a reduction in the change in Vab during quiet breathing (TV) on the non-treated side in the LVRS group, and an increase in Vrc,a on the treated side in the BLVR responder group (table 5.6). No changes were seen in chest wall volumes during quiet breathing in the control group, and there were no significant between group differences in the above mentioned changes when comparing with the change in the control group. There were no changes in any of the groups in the compartmental volumes during inspiratory capacity manoeuvres (table 5.6).

Table 5.6: Compartmental contributions to volume change during quiet breathing (TV) and IC at baseline and at 3 months. Presented as means.

		LVRS pre	LVRS post	p-value¥	BLVR pre	BLVR post	p-value¥	Control pre	Control post	p-value¥
TV (L)	Vrc,p Tr	0.152	0.127	0.21	0.090	0.050	0.14	0.062	0.098	0.08
	Vrc,a Tr	0.023	0.052	0.13	0.005	0.017	***0.01***	0.018	0.012	0.57
	Vab,Tr	0.200	0.214	0.52	0.353	0.304	0.53	0.359	0.367	0.38
	Vrc,p unTr	0.149	0.138	0.53	0.205	0.157	0.27	0.185	0.226	0.13
	Vrc,a unTr	0.067	0.064	0.56	0.070	0.107	0.50	0.119	0.104	0.51
	Vab, unTr	0.222	0.148	***0.04***	0.207	0.186	0.29	0.224	0.251	0.89
IC (L)	Vrc,p Tr	0.413	0.287	0.24	0.305	0.350	0.95	0.201	0.205	0.81
	Vrc,a Tr	0.110	0.142	0.91	0.186	0.234	0.52	0.150	0.157	0.54
	Vab,Tr	0.420	0.296	0.18	0.320	0.184	0.28	0.196	0.317	0.11
	Vrc,p unTr	0.425	0.476	0.36	0.548	0.516	0.79	0.372	0.414	0.51
	Vrc,a unTr	0.383	0.408	0.22	0.471	0.486	0.83	0.376	0.402	0.88
	Vab, unTr	0.167	0.513	0.10	0.571	0.497	0.39	0.343	0.498	0.95

¥Wilcoxon matched pair test. LVRS n=9, BLVR responder n=7, controls n=10.

Table 5.7: Compartmental contributions to FEV_1 and FVC at baseline and at 3 months.

		LVRS pre	LVRS post	p-value¥	BLVR pre	BLVR post	p-value¥	Control pre	Control post	p-value¥
FEV_1 (L)	Vrc,p Tr	0.20	0.19	ns	0.19	0.16	ns	0.16	0.19	ns
	Vrc,a Tr	0.18	0.19	ns	0.19	0.25	ns	0.25	0.20	ns
	Vab,Tr	0.25	0.35	ns	0.35	0.25	ns	0.25	0.37	ns
	Vrc,p unTr	0.23	0.21	ns	0.21	0.17	ns	0.17	0.17	ns
	Vrc,a unTr	0.21	0.22	ns	0.22	0.22	ns	0.22	0.20	ns
	Vab, unTr	0.30	0.36	ns	0.36	0.23	ns	0.23	0.36	ns
	Vcw	1.37	1.58	ns	1.50	1.42	ns	1.40	1.47	ns
FVC (L)	Vrc,p Tr	0.71	0.44	ns	0.44	0.51	ns	0.51	0.52	ns
	Vrc,a Tr	0.43	0.36	ns	0.36	0.48	ns	0.48	0.42	ns
	Vab,Tr	0.72	0.86	ns	0.86	0.66	ns	0.66	0.86	ns
	Vrc,p unTr	0.70	0.45	ns	0.45	0.51	ns	0.51	0.48	ns
	Vrc,a unTr	0.40	0.40	ns	0.40	0.46	ns	0.46	0.39	ns
	Vab, unTr	0.73	0.90	ns	0.90	0.62	ns	0.62	0.82	ns
	Vcw	3.69	1.35	ns	3.50	1.25	ns	3.29	3.37	ns

¥Wilcoxon matched pair test. LVRS n=8, BLVR responder n=7, controls n=11.

In terms of the forced expiratory manoeuvres, there were no significant changes at 3 months in OEP measured chest wall volumes of FEV_1 or FVC in any of the groups compared to baseline. None of the compartments, treated or non-treated sides, had a statistically significant change at 3 months as compared to baseline (table 5.7).

5.3.4.3 Correlation between spirometry and OEP measured volumes

As expected and for the reasons discussed in section 5.1, the correlation between spirometry and OEP measured volumes during forced respiratory manoeuvres was moderate at best. (figure 5.13). Bias was small but 95% limits of agreement were wide for both FEV_1 and FVC. FEV_1 measured by spirometry was lower than OEP measured FEV_1 (Bland Altman FEV_1 figure 5.13) due to gas compression and blood shift. Total chest wall volume should equal the sum of volume at mouth (spirometry), volume of compressed gas and volume of blood shifted out of trunk to the extremities.(151) As expected this was less pronounced for FVC. For FEV_1, the relationship between OEP and spirometry measurements is stronger when looking at the change at 3 months compared to baseline with r^2 value of 0.58, $p<0.001$. There was no significant reduction in the discrepancy between OEP and spirometry measured forced expiratory volumes following LVR which may have suggested reduction in gas compression following LVR due to reduced airways obstruction. In this context, OEP measured expiratory volumes should be higher than spirometry measured volumes, but this was not always the case with some OEP measures smaller than spirometry measured values.

Agreement in the % change in the FEV_1/FVC ratio measured by spirometry and that measured by OEP was poor (r^2 value of 0.02), with a bias of 4.4% and 95% limits of agreement from -99.1% to 107.8%. The change in OEP measured forced expiratory volumes 3 months post-treatment did not correlate with clinical and functional outcome assessments.

During quiet breathing, agreement between OEP and spirometry measured TV was strong (r^2 value of 0.62, $p<0.001$), though there was a relatively wide 95% limit of agreement (-0.50 to 0.60 L) (figure 5.14). Much stronger agreement was reported in the literature (r^2 values >0.90 for measurements of tidal volume at rest (154) as well as during exercise (148) in patients with COPD. The patterns are similar for IC and minute ventilation (VE) (figure 5.14)

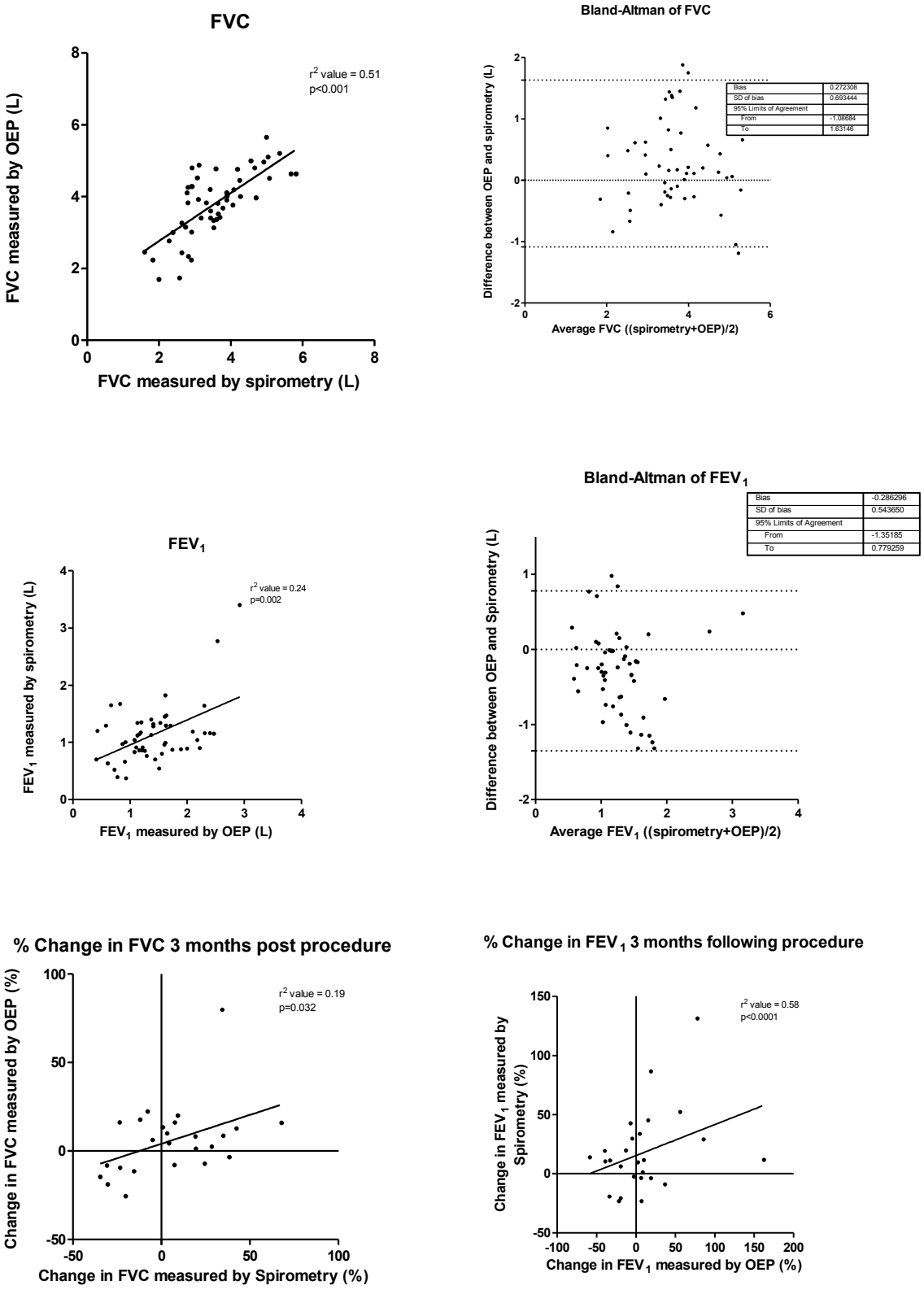


Figure 5.13: Agreement between spirometry and OEP measured volumes during forced respiratory manoeuvres.

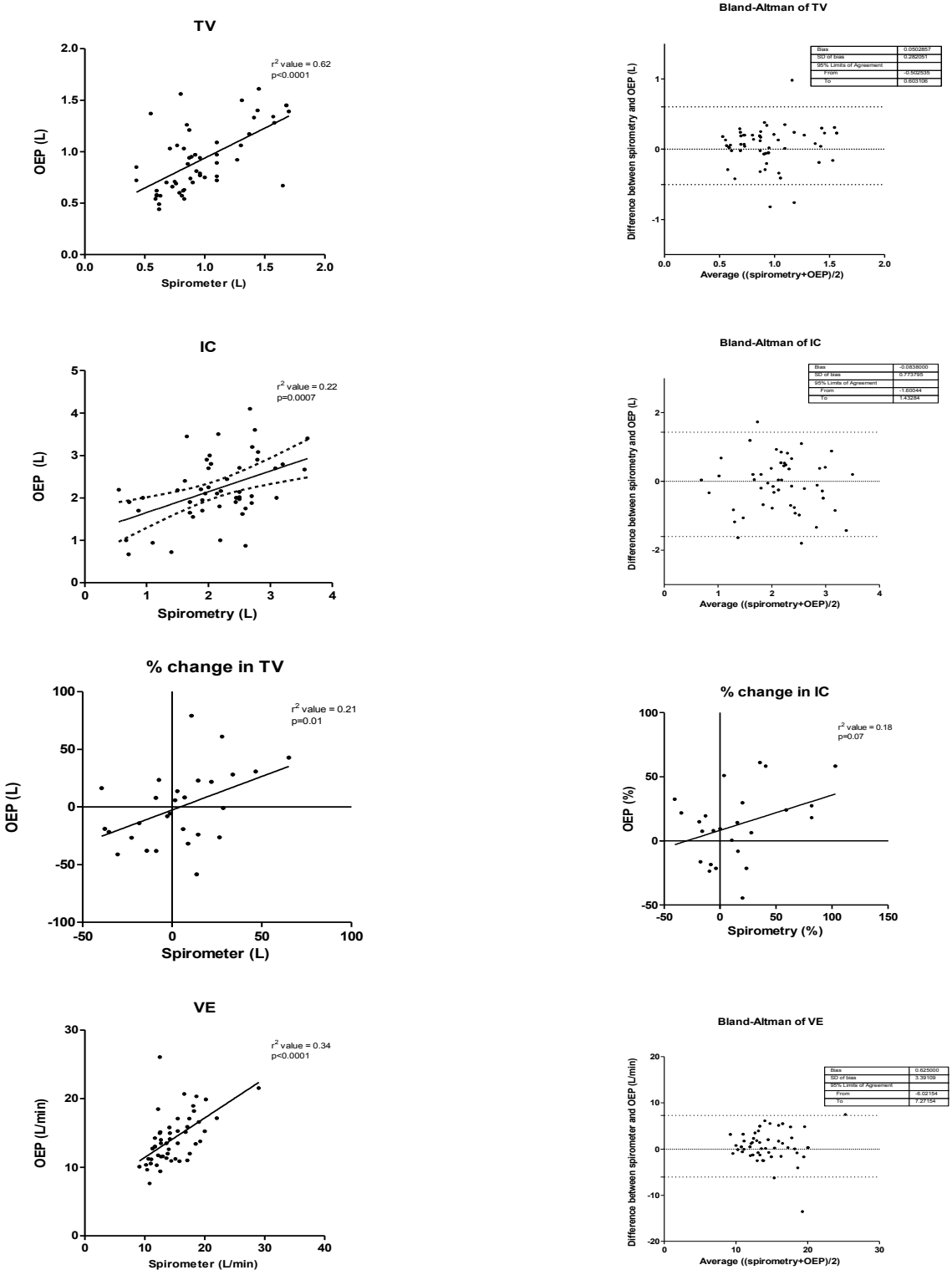


Figure 5.14: Agreement between spirometry and OEP measured volumes during quiet breathing and inspiratory capacity manoeuvres.

5.3.4.4 Chest wall compartmental asynchrony

5.3.4.4.1 Baseline Phase shift angles (θ)

There was no difference in phase shift angles between any of the groups at baseline, in any of the phase shifts angles measured as detailed in table 5.7. The following phase angle shifts were assessed: θRC, θDIA, θRC treated and non-treated, θDIA treated and non-treated θRC,p, θRC,a, θAb.

Table 5.8: Phase shift angles at baseline

Tidal breathing		All subjects (n=26)	LVRS (n=9)	BLVR responders (n=7)	Controls (n=10)	p-value¥
θRC (°)	mean	31.3	28.2	50.1	20.9	
	SD	38.4	31.5	42.2	40.3	ns
θRC Treated (or worst affected) side (°)	mean	34.2	36.2	51.6	20.2	
	SD	39.9	33.8	47.4	38.2	ns
θRC Untreated side(°)	mean	29.6	24.0	46.1	23.1	
	SD	37.3	30.6	35.7	43.6	ns
θDIA (°)	mean	-38.7	-36.2	-54.4	-30.1	
	SD	36.3	29.7	44.7	35.4	ns
θDIA Treated (or worst affected) side (°)	mean	-38.8	-42.1	-51.4	-27.0	
	SD	36.8	31.1	45.3	35.4	ns
θDIA Untreated side (°)	mean	-39.6	-32.8	-55.7	-34.3	
	SD	36.1	28.5	42.6	37.5	ns
IC manoeuvre						
θRC (°)	mean	5.1	9.9	-25.0	22.0	
	SD	58.0	55.1	44.8	65.2	ns
θRC Treated (or worst affected) side (°)	mean	-5.4	9.7	-8.7	-10.1	
	SD	55.3	60.6	43.7	53.8	ns
θRC Untreated side(°)	mean	35.3	13.8	67.0	32.6	
	SD	59.2	41.1	64.1	65.2	ns
θDIA (°)	mean	-1.0	8.3	-33.8	13.6	
	SD	57.9	49.8	52.6	64.1	ns
θDIA Treated (or worst affected) side (°)	mean	24.0	17.9	65.0ñ	0.7ñ	
	SD	58.5	15.0	54.3	73.4	ns
θDIA Untreated side (°)	mean	23.7	18.7	54.8≠	6.5≠	
	SD	47.0	10.1	45.6	59.7	ns

¥ Kruskal-Wallis test with Dunn's multiple comparison test. ≠ p=0.09; ñp=0.08 Mann Whitney test; θRC, phase shift angle between RC,p and RC,a; θDIA, phase shift angle between RCa and Ab.

5.3.4.4.2 Change in Phase shift angles (θ) at 3 months

In the LVRS group, there was a significant improvement in θDIA from -36.2 (31.5)˚ to -7.3 (16.1)˚ 3 months after surgery (p=0.004) during quiet breathing (Table 5.9). The change in θDIA was statistically significant in the treated but not untreated side. The BLVR responders saw a mean 28 (30.1)˚ reduction in θDIA during tidal breathing but this change did not reach statistical significance.

θRC reduced from 50.1 (42.2) ˚ to 7.7 (17.1) in the BLVR responders 3 months after the procedure (p=0.002) during quiet breathing. The improvement was statistically significant in the treated but not untreated side. The LVRS group also saw improvements in θRC but these did not reach statistical significance (Table 5.9).

When assessing change at 3 months from baseline of all successful LVR patients as a single group, there were statistically significant improvements in θRC and θDIA, as well is in θRC and θDIA on the treated sides (but not untreated sides) during quiet breathing (table 5.9). The changes in θDIA and θRC seen here can be considered clinically relevant as it brings the all LVR group means of θDIA and θRC to within the presumed "normal" ranges (based on published data on θRC) of within 0 to 18˚ (-44.1 (36.8) ˚ to -15.7 (16.5) ˚, p=0.002 for θDIA; and 37.8 (37.0 to 9.5 (17.8) ˚, p=0.004 for θRC).

There were no differences in θRC or θDIA during inspiratory capacity manoeuvres at 3 months in any of the groups, though there was less asynchronous chest wall movement at baseline during these manoeuvres (table 5.10). There was no change in θRC,p, θRC,a or θAb before and 3 months after the intervention in any of the groups.

Table 5.9: Phase shift during quiet breathing (TV).

θ during Quiet Breathing		**θRC (°)**				**θRC Treated (or worst affected) side (°)**				**θRC Untreated side (°)**			
		Pre	**Post**	**change**	**p-value**	**Pre**	**Post**	**change**	**p-value**	**Pre**	**Post**	**change**	**p-value**
LVRS	mean	28.2	11.0	-17.3	0.10	36.2	10.8	-25.4	0.13	24.0	12.1	-11.9	0.43
	SD	31.5	19.1	40.5		33.8	19.3	42.5		30.6	21.6	41.1	
BLVR	mean	50.1	7.7	-42.4	***0.02***	51.6	2.0	-49.6	***0.02***	46.1	20.8	-25.3	0.22
	SD	42.2	17.1	30.3		47.4	14.0	36.2		35.7	35.5	47.0	
All LVR	mean	37.8	9.5	-28.2	***0.004***	42.9	6.9	-36.0	***0.005***	33.6	15.9	-14.7	0.10
	SD	37.0	17.8	37.5		39.6	17.2	40.5		33.7	27.8	42.8	
Control	mean	20.9	36.9	16.1	0.16	20.2	38.0	17.8	0.16	23.1	35.4	12.3	0.77
	SD	40.3	37.5	45.1		38.2	36.5	38.1		43.6	40.2	54.9	
		θDIA (°)				**θDIA Treated (or worst affected) side (°)**				**θDIA Untreated side (°)**			
		Pre	**Post**	**change**	**p-value**	**Pre**	**Post**	**change**	**p-value**	**Pre**	**Post**	**change**	**p-value**
LVRS	mean	-36.2	-7.3	28.9	***0.004***	-42.1	-9.3	32.8	***0.004***	-32.8	-19.4	13.5	0.25
	SD	29.7	16.1	24.1		31.1	20.7	22.6		28.5	31.2	51.2	
BLVR	mean	-54.4	-26.4	28.0	0.11	-51.4	-21.4	30.0	0.11	-55.7	-39.4	16.4	0.47
	SD	44.7	10.0	38.6		45.3	10.1	45.3		42.6	27.9	44.7	
All LVR	mean	-44.1	-15.7	28.5	***0.002***	-46.1	-14.6	31.6	***0.003***	-42.9	-28.1	14.8	0.16
	SD	36.8	16.5	30.1		36.9	17.6	33.1		36.0	30.6	46.9	
Control	mean	-30.1	-36.0	-6.0	0.49	-27.0	-38.2	-11.2	0.32	-34.3	-39.6	-5.4	0.38
	SD	35.4	36.4	51.9		35.4	40.8	47.7		37.5	38.6	59.1	

Wilcoxon matched pair s test. θRC, phase shift angle between RC,p and RC,a; θDIA, phase shift angle between RCa and Ab.

Table 5.10: Phase shift during inspiratory capacity manoeuvre.

θ during IC manoeuvre		**θRC (°)**				**θRC Treated (or worst affected) side (°)**				**θRC Untreated side (°)**			
		Pre	**Post**	**change**	**p-value**	**Pre**	**Post**	**change**	**p-value**	**Pre**	**Post**	**change**	**p-value**
LVRS	mean	9.9	-23.3	-33.1	0.16	9.7	-5.6	-15.4	0.51	13.8	22.7	8.9	0.15
	SD	55.1	42.8	52.9		60.6	36.8	67.3		41.1	54.8	50.1	
BLVR	mean	-25.0	8.4	33.4	0.11	-8.7	11.8	20.5	0.38	67.0	-17.3	-84.3	0.06
	SD	44.8	14.3	42.3		43.7	21.6	36.4		64.1	79.5	88.4	
All LVR	mean	-5.4	-9.4	-4.0	0.93	-10.1	-17.3	-7.2	0.84	1.7	2.0	-0.3	0.62
	SD	52.4	36.3	58.1		53.8	48.4	68.8		53.0	31.5	57.3	
Control	mean	22.0	17.1	-4.0	0.85	-16.7	18.6	35.3	0.19	32.6	24.2	-8.3	0.92
	SD	65.2	60.2	52.2		59.8	59.5	78.1		65.2	59.8	64.6	
		θDIA (°)				**θDIA Treated (or worst affected) side (°)**				**θDIA Untreated side (°)**			
		Pre	Post	change	p-value	Pre	Post	change	p-value	Pre	Post	change	p-value
LVRS	mean	8.3	-35.7	-44.0	0.16	17.9	19.2	1.3	0.93	18.7	14.9	-3.7	0.78
	SD	49.8	58.4	59.1		15.0	48.7	42.7		10.1	37.1	41.0	
BLVR	mean	-33.8	6.4	40.2	0.08	65.0	39.2	-25.8	0.69	54.8	40.6	-14.2	0.79
	SD	52.6	12.0	50.3		54.3	80.0	126.3		45.6	89.7	130.9	
All LVR	mean	38.5	28.0	-10.6	0.45	37.1	5.2	-31.9	0.46	34.5	26.2	-8.3	0.39
	SD	43.4	62.7	86.7		57.3	67.5	81.2		35.1	64.2	88.2	
Control	mean	13.6	5.0	-8.6	0.77	0.7	9.5	8.8	0.70	6.5	-4.7	-11.2	0.56
	SD	64.1	60.8	48.8		73.4	70.1	57.0		59.7	56.7	63.4	

Wilcoxon matched pairs test. θRC, phase shift angle between RC,p and RC,a; θDIA, phase shift angle between RCa and Ab.

5.3.4.4.3 Between group comparisons in the change in Phase shift angles (θ)

Between group differences in the change in θ were significantly different for θRC and θDIA including θRC and θDIA on the treated (but not untreated) side in the direction of benefit (towards zero°) favouring the LVRS group when compared to control groups (table 5.11). Similar results are seen when comparing the change in θRC and θDIA between the BLVR and control groups (table 5.12) (except the between group difference in the change in θDIA on treated side which did not reach statistical significance), and all successful LVR subjects as compared to the control group (Table 5.13).

Table 5.11: Difference in the change in Phase shift angle (θ) during quiet breathing between the LVRS and Control groups.

Mean change in θ	LVRS (n=9)	Control (n=10)	Between-Group Difference in Change from Baseline	P-value¥
	Number ± SD or *(95% confidence interval)*			
θ RC	-17.3 ± 13.5	16.1 ± 14.3	-33.3 (-75.0 to 8.4)	***0.03***
θ RC treated side	-25.4 ± 14.2	17.8 ± 12.0	-43.2 (-82.2 to -4.3)	***0.04***
θ RC untreated side	-11.9 ± 13.7	-5.4 ± 18.7	-6.5 (-56.4 to 43.4)	0.96
θ DIA	28.9 ± 8.0	-6.0 ± 16.4	34.8 (-5.1 to 74.8)	***0.008***
θ DIA treated side	32.8 ± 7.5	-11.2 ± 15.1	44.0 (7.2 to 80.8)	***0.008***
θ DIA untreated side	13.5 ± 17.1	-1.2 ± 4.4	14.7 (-20.7 to 50.1)	0.11

¥Mann Whitney test. θRC, phase shift angle between RC,p and RC,a; θDIA, phase shift angle between RCa and Ab.

Table 5.12: Difference in the change in Phase shift angle (Θ) during quiet breathing between the LVRS and Control groups.

Mean change in Θ	BLVR (n=7)	Control (n=10)	Between-Group Difference in Change from Baseline	P-value¥
	Number ± SD or *(95% confidence interval)*			
Θ RC	-42.4 ± 11.5	16.1 ± 14.3	-58.4 (-100.3 to -16.6)	***0.003***
Θ RC treated side	-49.6 ± 13.7	17.8 ± 12.0	-67.40 (-106.6 to -28.2)	***0.001***
Θ RC untreated side	-25.3 ± 17.8	-5.4 ± 18.7	-19.9 (-77.3 to 37.4)	0.31
Θ DIA	28.0 ± 14.6	-6.0 ± 16.4	34.0 (-15.4 to 83.3)	***0.05***
Θ DIA treated side	30.0 ± 17.1	-11.2 ± 15.1	41.2 (-7.8 to 90.3)	0.07
Θ DIA untreated side	16.4 ± 16.9	-1.2 ± 4.4	17.6 (-14.2 to 49.4)	0.131

¥Mann Whitney test. ΘRC, phase shift angle between RC,p and RC,a; ΘDIA, phase shift angle between RCa and Ab.

Table 5.13: Difference in the change in Phase shift angle (Θ) during quiet breathing between the all successful LVR patients and the control group.

Mean change in Θ	LVR (n=16)	Control (n=10)	Between-Group Difference in Mean Change from Baseline	P-value¥
	Number ± SD or *(95% confidence interval)*			
Θ RC	-28.2 ± 9.4	16.1 ± 14.3	-44.3 (-78.0 to -10.6)	***0.003***
Θ RC treated side	-36.0 ± 10.1	17.8 ± 12.0	-53.8 (-86.8 to -20.9)	***0.003***
Θ RC untreated side	-17.7 ± 10.7	-5.4 ± 18.7	-12.4 (-53.6 to 28.9)	0.62
Θ DIA	28.5 ± 7.5	-6.0 ± 16.4	34.5 (1.42 to 67.5)	***0.007***
Θ DIA treated side	31.6 ± 8.3	-11.2 ± 15.1	42.8 (10.2 to 75.4)	***0.008***
Θ DIA untreated side	14.8 ± 11.3	-1.2 ± 4.4	16.0 (-15.7 to 47.6)	0.13

¥Mann Whitney test. ΘRC, phase shift angle between RC,p and RC,a; ΘDIA, phase shift angle between RCa and Ab.

5.4 DISCUSSION

Successful lung volume reduction with radiological evidence of volume loss resulted in statistically and clinically significant improvements in lung function, exercise capacity and quality of life. This study showed that: (a) OEP measured static chest wall volumes did not change in tandem with lung volumes measured by body plethysmography; (b) Agreement between OEP measured dynamic chest wall volumes and spirometry measured volumes was stronger in quiet breathing than in forced manoeuvres (as expected), but with a weaker correlation and wider 95% limits of agreement than previously reported in the literature; (c) Change in the discrepancies between OEP and spirometry measured forced expiratory volumes was variable and did not correlate with clinical outcomes; and (d) Successful lung volume reduction resulted in significant improvements in phase shift angles ϴRC (asynchrony between Vrc,p and Vrc,a) and ϴDIA (asynchrony between Vrc,a and Vab) at 3 months compared to baseline, and compared to controls.

Almost 15 years ago, Bloch and colleagues studied 19 patients before and after LVRS, and reported reductions in phase shift between the rib cage (as one compartment) and the abdomen.(78) They used respiratory inductive plethysmography (RespitracePT:Non-invasive Monitoring Systems, Florida, USA), a system using inductive bands which measure in 2 dimension the lateral and antero-posterior dimensions of the rib cage and abdomen. This is the first study to use OEP, a system integrating 3-dimentional volume measurements from multiple markers accurately placed to delineate the areas of interest, to demonstrate highly significant improvements in respiratory asynchrony following lung volume reduction (both surgical and bronchoscopic) compared to matched controls. OEP demonstrated this effectively (figure 5.16). Our findings may be different to those of Bloch and others who used RIP to measure asynchronous respiration, as only two measures were taken with RIP: abdominal and rib cage cross sectional areas. The rib cage was considered a single entity, however our OEP data demonstrates that the RC,p moved in tandem with Ab, but it is RC,a that was moving paradoxically. Hence for RIP to detect this change would require the thoracic band to be placed over the lower rib cage. Bloch reported placing the thoracic band 3cm below the nipple line, and whether this was above or below the level of the xiphisternum or the caudal limit of the zone of apposition would depend on patient height and degree of hyperinflation. OEP is thus much more accurate at assessing thoracoabdominal chest wall asynchrony.

The improvements in ΘRC and ΘDIA are strongly significant, more so on the treated side. Although improvements were seen in the non-treated side, these did not reach statistical significance. Mean ΘRC during quiet breathing reduced from 38.8 (37.0) to 9.5 (17.8) 3 months post treatment ($p<0.004$) in 16 patients who had successful LVR. Using an upper limit of normal of 18˚ for ΘRC, 9 of 16 patients had asynchronous rib cage inspiratory movements during quiet breathing at baseline, and only 4 at 3 months post procedure. Similarly, large improvements in ΘDIA were seen (change of 28.5(38.6) towards zero˚, $p=0.002$) with 12 patients before and 8 patients after having a ΘDIA of <-18 ˚ (note upper limit of normal unknown for ΘDIA).

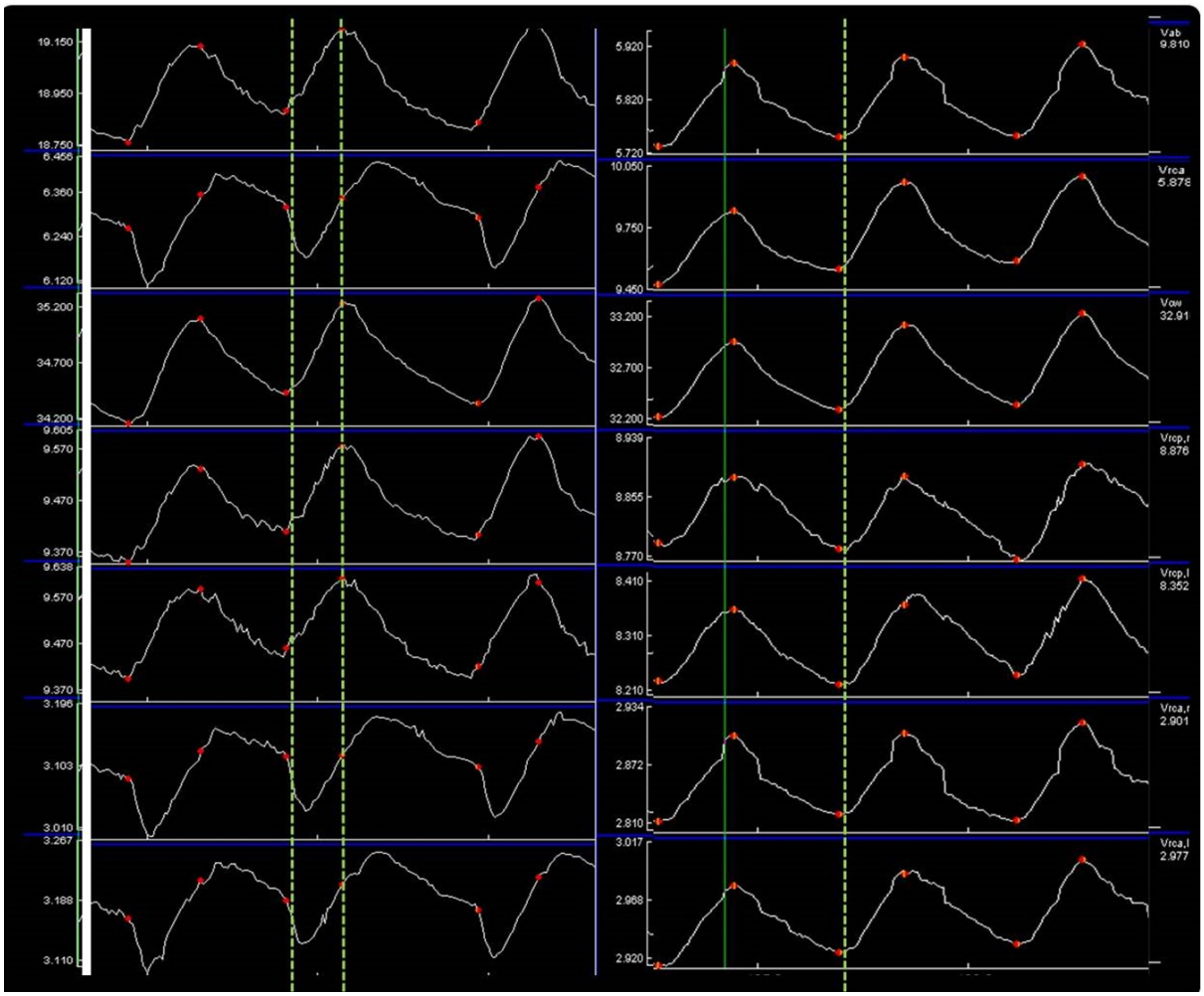


Figure 5.15: Volume-time traces of a representative patient before (left) and after (right) LVRS. Asynchrony of the Vrc,a compartment (Vrc,a second panel from top; Vrc,a left and right bottom 2 panels) on both treated and non-treated sides is almost completely corrected post LVRS. ΘRC and ΘDIA pre LVRS were 87.5˚ and 92.3˚, and post LVRS -4.0˚ and 12.2˚, respectively.

Chest wall asynchrony during quiet breathing was predominantly due to asynchronous movements of the portion of the rib cage apposed to the flattened diaphragm, Vrc,a. Thus ΘRC (phase shift angle of Vrc,p in relation to Vrc,a) correlated extremely strongly with ΘDIA (phase shift angle of Vrc,a in relation to Vab) at baseline (r^2 =0.94, p<0.0001) (figure 5.15). The degree of asynchrony at baseline for both ΘRC and ΘDIA correlated strongly with the degree of improvement in the same measure, and in improvement in asynchrony of the other phase shift angle (figure 5.15). Hence the worse the asynchrony at baseline, the larger the improvement in asynchrony following lung volume reduction. I could not identify any relationship between the degree of chest wall asynchrony at baseline and the magnitude of improvements in various clinical parameters: change in FEV_1, change in RV/TLC, change in FRC, change in TLCOc, change in SGRQ, and change in 6MWD. Therefore the degree of chest wall asynchrony at baseline did not predict clinical response to LVR. This may suggest that LVR is effective irrespective of whether there is chest wall asynchrony at baseline. On the other hand, it has previously been reported that abdominal paradoxical breathing is not associated with increased dyspnoea or a reduced exercise tolerance,(78, 157) and this was shown again in the two recent OEP studies of exercising COPD patients,(119, 148) though Aliverti's study demonstrated earlier dynamic hyperinflation in those with chest wall asynchrony at rest as well as increased leg fatigue during exercise (but not dyspnoea) compared to those without paradoxical chest wall movements at rest. However if we consider the 9 LVR patients in our cohort who had significant improvements in asynchrony (defined arbitrarily as improvements in ΘRC by >30˚, or from above the upper limits of normal (18˚) to within normality), and compare their clinical responses with those who did not improve (no change post procedure or no asynchrony at baseline), we find that the benefits in clinical outcomes in those improvers are almost twice as large in most parameters than in the non-improvers (table 5.13). Statistical significance is reached only for the change in RV and change in RV/TLC, though in a larger group these differences may reach statistical significance.

Table 5.14: Change from baseline in clinical outcome measures comparing patients with improvements in rib cage asynchrony and those without.

	ϴRC Improvers (n=9)	**ϴRC non-improvers (n=7)**	**Between-Group Difference in Mean Change from Baseline**	**P-value¥**
	Mean ± SD or *(95% confidence interval)*			
% change in FEV_1	34.9 ± 38.7	21.9 ± 38.2	13.2 (-28.7 to 54.7)	ns
Change in RV (L)	-1.24 ± 0.50	-0.62 ± 0.55	0.61 (-1.18 to -0.04)	***0.02***
Change in RV/TLC (%)	-10.9 ± 4.6	-3.4 ± 5.9	7.4 (-15.3 to 0.43)	***0.04***
Change in FRC (L)	-0.76 ± 0.44	-0.51 ± 0.47	0.26 (-0.74 to 0.23)	ns
% Change in TLCOc	16.3 ± 20.3	2.0 ± 12.57	14.3 (-4.5 to 33.1)	ns
Change in 6MWD (m)	56.0 ± 45.6	32.3 ± 56.5	23.7 (33.3 to 80.7)	ns
Change in SGRQ (points)	-19.4 ± 17.6	-7.3 ± 12.2	12.0 (-28.8 to 4.8)	ns

¥Mann Whitney test. ϴRC, phase shift angle between RC,p and RC,a.

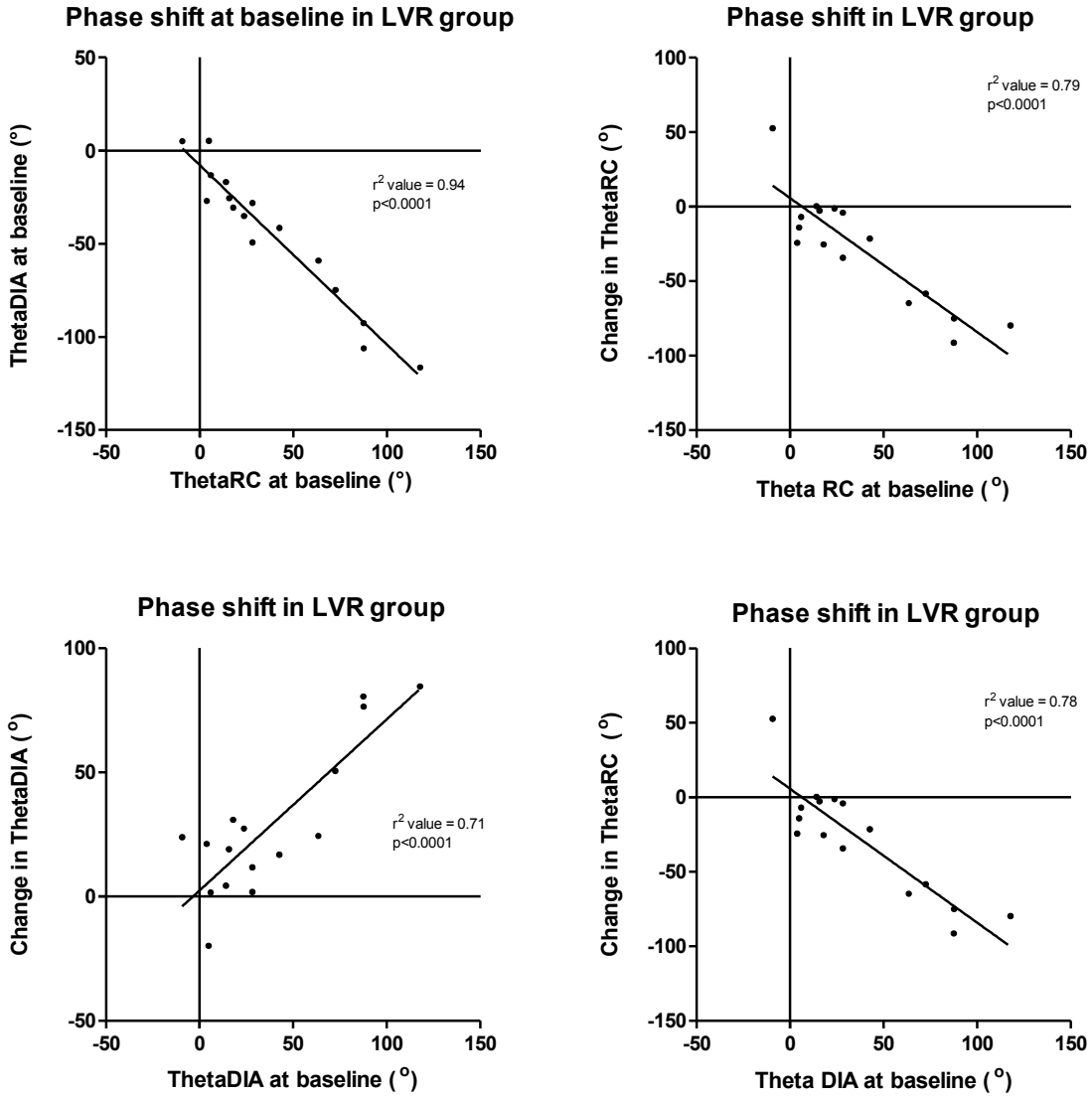


Figure 5.16: Phase shift in the lung volume reduction cohort at baseline and correlation with improvements in phase shift following treatment.

Static thoraco-abdominal volumes measured using OEP did not change significantly, nor in tandem with lung volumes measured using body plethysmography, and there were no changes in compartmental volumes nor contributions to total Vcw after LVR. The pulmonary and abdominal rib cages are relatively fixed and not much volume change in these compartments is expected as a result of loss of lung volume, but theoretically diaphragm elevation should be accompanied by change in abdominal volume. However, reduced intra-abdominal pressures from diaphragm repositioning may well be accompanied by upwards shift in pelvic contents potentially counteracting any loss in lung volume.

Patient numbers in each group were relatively small, but this is the only study to use OEP to assess the effects of LVR to date. In fact, no published study has examined more than 30 patients with COPD using OEP in any context. The small numbers probably contributed to the large deviations from the group means in the change in static chest wall volumes (TV, IC, FEV_1, FVC) at 3 months compared to baseline. Although OEP measures a different entity to body plethysmography, one would expect to see similar trends. Reasons for this discrepancy may reflect technical issues: We attempted to minimise differences in marker positioning by limiting this task to two individuals strictly following recognised anatomical landmarks, but exact marker placement may have differed between the two assessments. Differences in subject positioning during testing may also impact on compression of the chest wall (e.g. leaning forward or backwards), and to address this concern we sat patients down on the cycle ergometer seat adjusted at the same height for both tests, and ensured both legs were in a neutral position. During post-test preparation and optimisation of the geometric models, some markers had to be reconstructed using geospatial relationship with other adjacent markers. This served to improve the quality of the geometric model for analysis by "filling in the gaps" when camera views of markers was impeded, but may have reduced accuracy of measurement of specific compartmental volumes. Thus reconstructing markers which lay at the compartmental borders was avoided unless absolutely necessary. We sent raw data files and volume time traces to the team at Politecnico di Milano for quality control purposes, and we were reassured that technically the recordings and geometric models were of very high quality.

Significant weight loss or weight gain will have an impact on total thoraco-abdominal chest wall volumes, and several subjects had fluctuations in weight. Specifically, three LVRS patients had extended hospital admissions (> 4 weeks, one having suffered a cerebrovascular accident), and two others had intercostal chest drains in situ for over 6 weeks restricting activity levels. These patients reported significant weight loss (not accurately measured for all patients and therefore not reported here). On the other hand, two other subjects in the BLVR group had gained a significant amount of weight. Weight reduction or gain may have augmented or reduced, respectively, any benefits from LVR as measured by OEP.

We used OEP to attempt to detect a change in overall static lung volumes of around 0.68 (0.59) L (change in TLC as measured by body plethysmography in all LVR patients), however this as a proportion of the OEP measured total chest wall volume Vcw of 31.6 (6.5) L in the cohort is very small indeed. A very large number of patients would be required to detect such small changes (~2% of the total Vcw). Furthermore, minor marker positioning differences (e.g. 1 cm superiorly or inferiorly of the lower most horizontal line connecting the superior iliac crests) on

serial testing could conceivably significantly alter volume measurements by a few hundred mls. For this reason and other factors that can change chest wall and abdominal dimensions, OEP may not be a suitable technique for serial static total (and compartmental) chest wall volume measurements. However in the assessment of asynchrony between different chest wall compartments, the effect of minor marker positional changes is unlikely to significantly alter phase shift angles and hence the analysis of asynchrony. Here it is the direction of movement of different chest wall compartments in relation to each other that is assessed, and this is largely uninfluenced by exact marker positioning. Furthermore, the lower costal margin is very easy to identify and delineate anatomically, as is the xiphisternum, making it easier to replicate identical marker positioning on serial testing.

Physiological reasons which may contribute to why Vcw did not correlate well with changes in plethysmographic lung volumes during dynamic manoeuvres include the effect changes in thoracic and abdominal pressures on the circulatory system (the role of blood shift (153)), on volume of solid organs, and on gas compression. Total thoracoabdominal chest wall volume should equal the sum of volume at mouth (spirometry), volume of compressed gas and volume of blood shifted out of trunk to the extremities.(151)Figure 5.7 illustrates how chest wall volumes do not necessarily correlate with air being expired from the mouth, with gas compression likely a major factor particularly in early phases of forced expiratory manoeuvres in patients with severe airways obstruction. In their study of six healthy adults exercised with expiratory flow limitation using a starling resistor, Iandelli and colleagues reported a mean (SE) difference of 489 (74) mls in tidal volume between OEP and spirometry at resistance of 30% of peak expiratory flow. Oesophageal and gastric pressure balloons were used to calculate intrathoracic and abdominal pressures and Boyle's law was used to determine the proportion of this discrepancy due to gas compression (163 (24) mls) and the remaining was thus attributed to blood shift (326 (66.3) mls).(151)

The effect of chest wall asynchrony itself on overall chest wall volumes is likely to be significant as the asynchronous portion of the chest wall counteracts some of the overall chest wall volume changes being measured by OEP. Changes in the amount of asynchrony will thus influence the change in static and dynamic OEP measured chest wall volumes. Furthermore, a theoretical limitation of OEP in assessing relative changes between Vrc,p and Vrc,a, previously described by Romaglioni *et al.,*(155) is that in patients with severe hyperinflation, the superior margin of the zone of apposition of the diaphragm to the rib cage is likely more caudal than normal, and therefore the proportion of the abdominal rib cage exposed to abdominal pressures may be smaller. Reductions in hyperinflation following LVR certainly shifts diaphragm positioning and

this may have an impact on changes in static Vrc,a in particular. Also, the horizontal line at the level of the xiphisternum used as the border between RC,p and RC,a may not exactly correspond to the true zone of apposition in our cohort with severe COPD, that is the portion of the rib cage exposed to muscles which act in a different manner to those in contact with the upper rib cage. Nevertheless, Iandelli and colleagues monitored the cephalic border of the area of apposition (i.e. border between RC,p and RC,a) with ultrasound during exercise and they demonstrated stability in this zone after inducing dynamic hyperinflation.(151) In the case of this study, we seek to identify any change in chest wall movements that can result from lung volume reduction, irrespective of possible changes in the zone of apposition. Thus if there is such a change in our cohort, it is unlikely to influence the outcomes or interpretation of data presented here.

It is worth noting that several LVRS patients still had intercostal chest drains in situ at the time of discharge from hospital, and in two patients remained in place for over 6 weeks. Intercostal nerve injury is common following LVRS and neuropathic pains were reported by 5 of 9 LVRS patients at the time of their follow-up assessment. Pain, as well as incomplete recovery of the chest wall from the trauma of surgery, may well have reduced chest wall movements and thus total and dynamic chest wall volumes. Furthermore, patients may not have fully recovered back to their baseline levels of activity and fitness by 3 months, and a longer follow-up period may have been preferable for the LVRS group.

The agreement between OEP and spirometry when measuring dynamic lung volumes and change over time was variable, with stronger relationships during quiet compared to forced manoeuvres (as expected). Different entities are being measured by the two systems, however other published data reveals much higher rates of agreement than that seen in this study suggesting that improvements can be made to our testing techniques. Improvements I believe need to be implemented to the OEP system at the Brompton include:

1) A larger room allowing distancing further the infrared cameras from the subjects being tested, enabling greater freedom of movement of the subject being tested without risk of loss of marker detection.
2) Alternative support system to the standard cycle ergometer handlebars as these markedly reduce quality of OEP marker recordings by both the impedance of camera views by outstretched arms, and by encouraging the subjects to lean forward. The hospital trust health and safety regulations precluded the use of temporary stabilisation devices on each side of the patient allowing the patient to sit up straighter and have

their arms to the side, because of the risk of falls. Securing such devices to the floor was prohibited by the infection control department. Suspending handlebars from the ceiling was not possible for similar reasons.

3) OEP recordings should be restricted to short intervals (90-120 seconds) to minimise data loss and ease analysis.
4) More meticulous marker positioning around anatomical landmarks by trained and experienced individuals.

The effect of chest wall asynchrony on exercise before and change in this after lung volume reduction needs to be studied. All patients had exercise testing as part of this study protocol. This occurred beyond the remit of this thesis and is the logical next step in furthering the analysis of this data. The data could also be used to assess OEP in the measurement of dynamic hyperinflation before and after LVR, which has not previously been reported. But first, substantial input will be required to improve the quality of the recorded geometric models during exercise which are on first look significantly degraded by movement artefact and marker loss. Comparing spirometry and OEP measured flow volume loops and time-volume traces to further scrutinise the discrepancy between OEP and spirometry during forced manoeuvres is possible with the available data, and will be of interest in clarifying the reasons for this difference. Studies of a larger number of patients undergoing LVR procedures are needed before the effects of chest wall asynchrony at baseline and improvements in chest wall asynchrony can identify phenotypes most suitable for specific LVR techniques.

5.5 CONCLUSION

OEP is a novel and unique tool which enables 3D assessment of the mechanics of ventilation in patients with emphysema undergoing lung volume reduction. This study demonstrated that in experienced hands, the setup and patient testing process is feasible and reasonably straight forward, though slightly time consuming. However considerable training and experience of a team of investigators is required before the technique can be mastered. In particular, data on unilateral chest wall volume change and on chest wall asynchrony is unique and informative. In this study, we found that statistically significant improvements in chest wall asynchrony occurred following successful lung volume reduction, particularly in the treated side, and these benefits were largest in those with the highest degrees of asynchrony at baseline and correlated with a range of clinical outcomes. OEP is an ideal tool to make assessments of chest wall asynchrony, however the clinical relevance of chest wall asynchrony in advanced COPD is yet unclear. How improvements in asynchrony correlate with clinical benefit is also unknown. Therefore further studies of larger cohorts of emphysema patients undergoing LVR are needed before this can be determined, and any change in asynchrony during exercise assessed. Although helpful with this respect, this study also reveals that OEP is not helpful in assessing change in static lung volumes following LVR especially as currently available techniques are reliable, easy to perform, cheaper, well validated and yield accurate and reproducible results. Movement during exercise markedly degrades recording quality and thus for the time being, it is likely that OEP will remain a tool for the researcher and is unlikely to come into regular clinical use in the context of LVR until the clinical relevance of chest wall paradoxical movements is established.

Chapter 6
General discussion and future directions

6.1 SUMMARY OF FINDINGS

This thesis reviews the current status of lung volume reduction for the treatment of severe emphysema. Studies of two novel techniques to achieve lung volume reduction are presented, as well as a study of the use of a novel 3D measurement system to shed light on the physiological mechanism of benefit from both surgical and bronchoscopic LVR. The trial of the LVR coils demonstrates, for the first time in a randomised controlled setting, that treatment with LVR coils results in statistically and clinically meaningful improvements in quality of life, lung function and exercise capacity compared with controls, and that benefits are largely maintained up to 12 months post treatment compared to baseline. The use of 180-240 mls of autologous blood instilled directly into a giant bullae is very promising, but appears ineffective when the volume is spread over 3 subsegments of emphysematous lung. The most interesting novel finding from the OEP study was the confirmation that lower rib cage paradoxical inspiratory movements in patients with hyperinflation improve significantly after lung volume reduction when compared to control patients undergoing a sham bronchoscopy, as assessed using 3D chest wall volume measurements. The improvements are statistically significant on the treated but not untreated sides.

6.2 CRITIQUE OF METHOD AND FUTURE WORK

6.2.1 LUNG VOLUME REDUCTION COILS

The LVRC study had several inherent weaknesses. The first is the absence of a sham bronchoscopy and the unblinded nature of the treatments, which links directly to the second major weakness; the use of a self reported quality of life assessment tool as the primary outcome. Thirdly, the short controlled phase of the trial reduces the confidence with which firm conclusions can be drawn from the longer term data, especially that, finally, the small patient numbers under-power the statistical analyses. The not insignificant rate of pneumothoraces complicating LVRC treatment needs to be highlighted, and taken into account when considering the most appropriate lung volume reduction technique, whether bronchoscopic or surgical, to offer a particular patient. Nevertheless, the data is very encouraging with improvements in

quality of life correlating with changes in objective measures such as lung function and the 6MWD, and this study with its weaknesses have informed the design and protocol of a larger (commercially funded) pivotal trial which is currently recruiting patients across North America and Europe; the Lung Volume Reduction Coil Treatment in Patients with Emphysema (RENEW) study (NCT01608490).

Much is yet unknown about the mechanisms of action of the LVRCs, which do not cause lung volume reduction in the same manner as LVRS and other bronchoscopic techniques. It is hypothesised that increases in lung elasticity and a retensioning effect improves maintenance of airway patency preventing dynamic expiratory airway collapse, but this has not been directly studied. The optimal number of coils required per lung, the distribution of coil implantation (whether to restrict to one lobe or not), and longer term safety and efficacy information are needed, and in the author's opinion should have preceded a large pivotal trial. The pressure on medical device manufacturers to generate income is understood, but perhaps optimising the treatment regime would in the long run improve yield from a treatment that is more effective. Trials investigating the following aspects of LVRCs should be considered:

- Assessments of the effect of LVRC treatment on dynamic hyperinflation using cycle ergometry, to support the circulating notion that LVRCs improve dynamic hyperinflation and hence exercise tolerance in a degree which is out of proportion with improvements in lung function and on cross sectional imaging.
- A study measuring lung compliance after the implantation of each coil to determine the relationship between the number of coils implanted and change in lung compliance. This will likely differ between individuals but may suggest loss of benefit after a certain number of coils are implanted, may establish a threshold after which the risk of pneumothorax increases, may help determine whether larger changes in compliance result from lobar or whole lung treatment, may be useful to perform during procedures to determine whether each coil is implanted in the optimal location, may help determine how proximal or distal the coils should ideally be placed, and inform the degree of segmental emphysematous destruction on HRCT which would preclude any benefit from LVRCs. The compliance measurements could be performed using dedicated endobronchial blocking pressure measuring balloons akin to the Chartis catheter designed to measure collateral ventilation (section 1.3.8.3.2), or in patients under general anaesthesia as measured by the ventilator.
- A study comparing the effectiveness of LVRC distribution (lobar or whole lung) in each of heterogeneous and homogeneous disease phenotypes.

- An assessment of the role any collateral ventilation may play in the efficacy of LVRC treatment. This could be retrospective using data from the study presented here.
- A cost effectiveness study.
- If proven effective in the pivotal trial, a trial randomising patients to LVRCs or other bronchoscopic LVR techniques such as endobronchial valves will ultimately be needed, to clarify the best treatment to offer patients who in theory could benefit from more than one technique.

6.2.2 AUTOLOGOUS BLOOD LUNG VOLUME REDUCTION

The expense and risks associated with the commercially funded bronchoscopic lung volume reduction techniques currently under development will restrict availability to a limited number of centres worldwide, and hinder patient access to LVR. We sought to investigate whether a simple inexpensive approach which does not involve leaving foreign bodies or material inside a patient's airways could be successful. The two pilot studies presented in this thesis demonstrate the safety of bronchoscopically instilled endobronchial autologous blood using moderate sedation in patients with severe COPD, with proof of concept that intrabullous autologous blood can indeed cause significant reductions in the size of giant bullae leading to clinical benefit in selected patients. We have not treated enough patients to establish baseline predictors of who is most likely to respond, and indeed whether an intense inflammatory reaction (and adverse event) is a pre-requisite. Laboratory based studies examining the nature and amount of pro-fibrotic contents contained in autologous blood is needed to guide volumes of blood to be instilled. The heterogeneous response to BIABI treatment may be at least partially explained by the varying amount of thrombin per ml of blood between individuals (anywhere between 20 iu and 100 iu as discussed in section 4.1). Personalising the treatment by studying each patient's blood sample pre-procedure can guide therapy by informing autologous blood volume requirements for each person depending on thrombin content, and this may also help to predict response to treatment. Animal models could be used to assess whether varying concentrations of thrombin have different clinical effects, and establish whether there is a relationship between bulla size and the optimum volume of blood which should be instilled to instigate a response.

Longer term follow-up data on efficacy and safety of BIABI treatment is needed. The natural course of bulla remodelling after BIABI treatment is unknown, as is the effect of repeat treatments and their timing. A larger safety and feasibility trial designed by the author is

currently underway, the Bronchoscopic Intrabullous Autologous Blood Instillation (BIABI) for Emphysema trial (NCT01727037), with 10 of 30 patients already treated. The primary outcome time point is 6 months on this occasion, and early results have shown positive responses in several patients which is reassuring and complements the results seen in the pilot study presented here. In our small group we have seen progressive reductions in bulla size taking place beyond 6 months post treatment in one patient, but whether a repeat treatment could have amplified the effect or accelerated the speed of bulla shrinkage is unknown.

6.2.3 OEP FOR THE ASSESSMENT OF LVR

The OEP techniques used to measures chest wall volumes as presented in this thesis are unlikely to be a useful assessment tool for measuring changes in static total and compartmental volumes following LVR, due to the inherent variability of the measurements and dependence on exact marker positioning. OEP may be useful in measuring changes in dynamic volumes during respiration and has indeed been used accurately for measuring unforced manoeuvres by others. However we were unable to detect the changes seen on conventional lung function testing in our study with a degree of confidence or significance, though with a larger patient group this may have been different. Where the OEP system was of most interest was in measuring movements of different compartments of the chest wall in relation to each other. This is not reliant on precise marker placement and inspiratory paradoxical movement of the lower rib cage was clearly illustrated in this cohort with severe hyperinflation and flattened diaphragms. For the first time, improvements in these paradoxical movements following lung volume reduction and the return of the diaphragm to a more superior and natural position, were demonstrated to have occurred, and to a more significant extent on the treated side of the chest wall. Patients with the highest degree of asynchronous chest wall movements at baseline had the largest improvements in chest wall asynchrony, and those who had sizeable improvements in asynchrony had larger improvements in lung function, exercise capacity and quality of life compared to patients without asynchrony or any change thereof. Patient numbers were too small to draw firm conclusions on whether the degree of asynchrony at baseline predicts whether a patient is likely to respond more of less to LVR, or indeed to guide LVR treatment options. A large number of patients undergoing a variety of LVR procedures will be needed to establish whether a specific approach is more suited to, or likely to be more beneficial for, patients with varying degrees of chest wall asynchrony. More work is needed to clarify normal ranges for phase shift angles in normal subjects and patients with COPD, and how this correlates

with clinical parameters. Changes in phase shift angles during exercise following lung volume reduction is also of great interest. Ultimately the goal would be to improve patient selection and matching with the most appropriate LVR technique, discussed in more detail below.

6.5 OVERALL LUNG VOLUME REDUCTION SUMMARY

This thesis reviews the literature and presents the evidence behind the various lung volume reduction techniques currently available and/or under development, four of which are studied and presented here. The data in chapters 3, 4 and 5 clearly demonstrate that some patients with severe emphysema derive significant clinical benefit from LVRC treatment, intrabullous blood, and LVRS and endobronchial valves, respectively. However, at the time of writing the only established therapy with Grade A evidence of reduced mortality and cost effectiveness in patient with severe emphysema should be considered LVRS which is indicated for hyperinflated patients with heterogeneous upper zone disease, who exceed the NETT safety criteria, who experience symptoms despite pulmonary rehabilitation. Novel longer acting bronchodilators currently under development and some now available for clinical use appear to be more effective than their predecessors, and so ensuring that medical care of patients with COPD is optimised is essential before LVR is considered. LVR should remain a last resort for patients who remain significantly symptomatic despite best therapy including pulmonary rehabilitation, and although more minimally invasive techniques are becoming available they are likely to be associated with a not insignificant risk of complications and benefit will be limited by the usually markedly diseased remaining lungs.

In trials of the BLVR techniques published thus far, including those presented in this thesis, there is large heterogeneity of response with a significant proportion of patients gaining no benefit. Maximising patient response rates is thus of critical importance moving forward, with optimal matching of patients with specific BLVR techniques being essential, particularly as there is overlap in emphysema subgroups or phenotypes that can potentially gain from more than one LVR approach. Future patient selection and matching with specific LVR techniques will be heavily reliant on detailed analysis of HRCTs, with focus not only on lobar heterogeneity and integrity of the interlobar fissures, but also on the degree of emphysematous destruction and bullae size, paraseptal vs. panacinar distribution, as well as the differing degree of segmental emphysema within lobes. Measures of chest wall asynchrony may also come into play along with the varying thresholds in lung function parameters for severity of gas trapping and airway

obstruction which are currently in flux. In the next three to five years, the pivotal randomised controlled trials currently underway should highlight the most favourable characteristics for a good response to each of the bronchoscopic LVR techniques as well as overall efficacy and safety. Long term efficacy and safety data for these novel bronchoscopic techniques, including the effect any implants may have on future thoracic surgery or lung resection, is limited but will emerge in the near future as further follow-up data is reported.

Figure 6.1 includes a recommended algorithm to be followed when considering LVR, and is broadly in line with current practice at our institution. All non-surgical LVR should be offered as part of clinical trials until stronger evidence emerges to support their use, and the author has concerns regarding the proliferation of centres offering BLVR in Europe including the UK, under the cheery encouragement of the medical device manufacturers. The risk is to expose the wrong patients to inappropriate treatments which are inadequately performed, managed by physicians without the expertise to deal with the complications. These along with poor outcomes may reverberate to negatively impact the popularity of BLVR with both physicians and patients alike, akin to the negative image LVRS has attained from over exuberant use in the 1990s which it has not been able to recover from despite such a strong supportive evidence base. Furthermore, as the success of BLVR increases with improved patient selection, so too will complication rates. It is therefore best, at least for the time being, that LVR is offered through specialist centres able to adopt a multidisciplinary approach and carefully match patients with the optimal treatment from a range of surgical and non-surgical techniques, crucially with the ability to manage the complications.

In the future, randomised controlled trials of LVRS versus BLVR techniques will be needed, and there will develop a need for trials randomising specific phenotypes or subgroups of emphysema patients to the different bronchoscopic techniques under development in order to the demonstrate superiority of certain approaches.

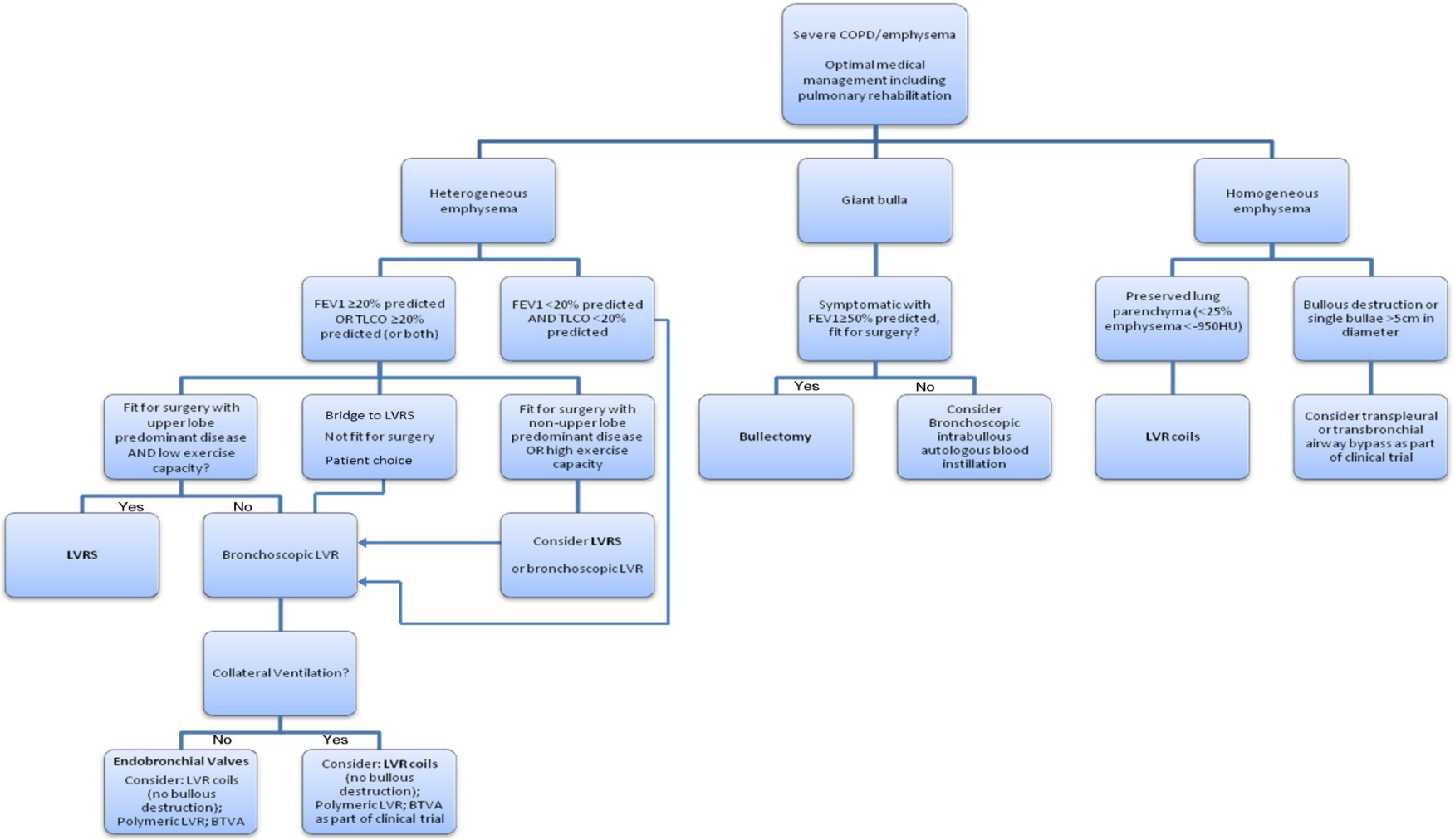


Figure 6.1: Treatment Algorithm for lung volume reduction. (Author's own work adapted with permission from Clinics in Chest Medicine (68))

Publications arising from work in this thesis

- Zoumot Z, Kemp SV, Caneja C, Singh S, Shah PL. *Bronchoscopic intrabullous autologous blood instillation; a novel approach for the treatment of giant bullae.* Ann Thorac Surg. 2013 Oct;96(4):1488-91.
- Shah PL, Zoumot Z, Singh S, Bicknell SR, Ross ET, Hopkinson NS, Kemp SV for the RESET trial Study Group. *Randomised Control Trial of Endobronchial Coils for the Treatment of Severe Emphysema with HyperinflaTion (RESET).* Lancet Resp 2013: 1(3):233-240.
- Zoumot A, Kemp SV, Singh S, Bicknell S, McNulty W, Hopkinson NS, Ross ET Shah PL. *Lung Volume Reduction Coils for emphysema are effective up to 12 months following treatment: medium term and cross-over results from a randomised controlled trial.* (submitted).
- Zoumot Z, Lo Mauro MA, Aliverti A, Nelson C, Ward S, Hopkinson NS, Shah PL. *The assessment of the effect of lung volume reduction on inspiratory chest wall asynchrony in severe emphysema using Optoelectronic Plethysmography.* (In prep)

Abstracts arising from work in this thesis

Oral slide presentations

- Zoumot Z, Kemp SV, Ross E, et al. *Outcomes from the Randomised Controlled Trial of RePneu (LVRC) Endobronchial Coils for the Treatment of Severe Emphysema with HyperinflaTion (RESET)*. BTS winter meeting Dec 2012, London.
- Zoumot Z, Kemp SV, Caneja C et al. *Randomised Controlled Trial of RePneu Endobronchial Coils for the Treatment of Severe Emphysema with HyperinflaTion (RESET)*. ***Late-breaking abstract*** session at the ACCP Chest meeting, Atlanta Oct 2012.

Poster oral presentations

- Zoumot Z, KempSV, Caneja C, Hopkinson NS, Singh S, Shah PL . *Preliminary medium-term follow-up data from a single centre experience of a randomised controlled crossover study of the lung volume reduction coils*. ATS conference Philadelphia 2013. ***ATS Abstract Scholarship Award, presented by the ATS Assembly on Clinical Problems.***
- Zoumot Z, Faisal A, Polkey M. *Bronchoscopic lung volume reduction improves exercise capacity but not oxygen uptake kinetics in patients with severe emphysema.* ERS congress Barcelona 2013.
- Kemp SV, Zoumot Z, , Caneja C, Singh S, Ross E, Bicknell S, Hopkinson NS, Polkey MI, Shah PL. *Randomised Controlled Trial of RePneu Endobronchial Coils for the treatment of Severe Emphysema with Hyperinflation (RESET Study).* ATS conference San Francisco 2012.

Poster thematic presentations

- Zoumot Z, Kemp S, Caneja C, et al. *Bronchoscopic intrabullous endobronchial autologous blood instillation (BIABI) for the treatment of giant bullae*. ERS Barcelona 2013.
- Zoumot Z, Kemp S, Caneja C, et al. *6 and 12 month outcomes following RePneu bronchoscopic lung volume reduction coil treatment.* ERS congress Barcelona 2013.

Recently submitted

- Zoumot Z, Lo Mauro MA, Aliverti A, Nelson C, Ward S, Jordan S, Davey C, McNulty W, Polkey I, Shah PL, Hopkinson NS. *Successful lung volume reduction improves inspiratory paradoxical movement of the lower rib cage at rest as measured by optoelectronic plethysmography.* (Submitted ERS congress Munich 2014).

Details of contributions of others to work presented in this thesis

The LVRC trial and autologous blood LVR studies were already recruiting on January 2011 when I commenced my fellowship. I was however an assigned study researcher assisting in the bronchoscopic procedures and post-procedure care on both these studies since April 2010 in my capacity as the respiratory specialist registrar at the Chelsea and Westminster Hospital where these procedures were performed. I also performed several follow-up assessments for the blood LVR study as a member of the blinded assessment team. In January 2011 I became study coordinator for all trials, subsequently recruiting all patients and conducting all follow-up assessments. Below are details of contributions of others and my own input into each of the studies:

LVRC trial: The protocol was written by Dr. Pallav Shah (chief investigator and primary supervisor) in conjunction with the sponsor (PneumRx Inc.). Dr. Samuel Kemp (research fellow) obtained favourable ethics opinion, recruited the first 15 patients and performed ~20% of follow-up assessments. I recruited the remaining 21 patients and performed ~80% of all follow-up visits. I assisted Dr. Pallav Shah and the team in all but the first 2 bronchoscopic procedures which took place before I joined the team at Chelsea and Westminster hospital, and can perform the procedure independently without supervision.

Autologous blood LVR trial: The protocol was written by Dr. Samuel Kemp (research fellow) who obtained favourable ethics opinion and recruited the first 8 patients. I recruited the remaining 9 patients and performed 20% of the follow-up visits as the blinded assessor before becoming study coordinator in January 2011. Cielito Caneja (research nurse) performed the remaining blinded follow-up assessments. I assisted Dr. Pallav Shah as part of the bronchoscopy team in all but the first 4 bronchoscopic procedures and can perform the procedure independently without supervision.

BIABI study: I conceived the study in conjunction with Dr. Shah, wrote the protocol, recruited all subjects, performed all bronchoscopic procedures and conducted all follow-up visits.

OEP study: I conceived the study in conjunction with Drs. Nicholas Hopkinson and Pallav Shah, wrote the protocol, obtained favourable ethics opinion, recruited all patients, and conducted all but 2 of 104 OEP assessments. I performed all marker tracking, model reconstructions, data extraction and analysis. Antonella LoMauro designed the Matlab protocol enabling data extraction, and provided technical advice and assistance along with Andrea Aliverti, both of the Politecnico di Milano.

For all studies, I personally collated all data from the source documents, inserted into spreadsheets and performed all the data and statistical analyses presented in this thesis.

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