Understanding Pneumothorax: Epidemiology, Physiology and Predicting Outcome

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Abstract

Contrary to traditional teaching, patients with Primary Spontaneous Pneumothorax (PSP) do not have normal lungs. Emphysema-like change (ELC) and inflammation are common. However, the natural history of ELC and its significance in terms of future disease is not known. Current management of pneumothorax is generic and not personalised.

This thesis updates the UK epidemiology of pneumothorax, describes the use of two novel methods to examine the lungs, a method of predicting early treatment failure, the association of CT findings and recurrence, and a systematic review of chemical pleurodesis to reduce recurrence.

Analysis of fifty years' data on ~150,000 admissions demonstrated that the incidence of pneumothorax is increasing, and established a method to identify primary from secondary pneumothoraces and their relative risk of recurrence.

Reduced ventilation of hyperpolarised Xenon on enhanced-Magnetic Resonance Imaging (MRI) was seen in those PSP patients with greater low attenuation areas on Computed Tomography (CT) and with reduced pulmonary function. A model of lung inhomogeneity found that metrics of lung ventilation distinguished pneumothorax patients from healthy volunteers and Chronic Obstructive Pulmonary Disease (COPD) patients. This may represent subtle or mild disease, not identified on standard testing, which may be exacerbated by smoking.

CT scanning found that mild emphysema and cystic airspaces were common in PSP patients. Ex- or current smokers had more (and larger) cysts. Emphysema was more common in smokers and patients with a history of previous pneumothorax: who were at higher risk of recurrence. However, variation in number and size of cysts were seen in both those patients with and without recurrence. As such, no single algorithm to predict recurrence was identified.

Airflow measurement early in the patient pathway has the potential to identify those likely to fail treatment, potentially allowing early triage to surgery. The addition of talc or minocycline as an adjunct to surgery provides the lowest recurrence rates, but physician-led talc poudrage may be similarly effective. Those in whom surgery is not suitable, chemical pleurodesis could be offered via chest drain.

Data presented in this thesis thus provides insights into the underlying abnormalities in PSP and lays the groundwork for strategies to fundamentally alter the management paradigm.

Abbreviations

Abbreviation	Meaning
%LAA	Percentage Low Attenuation Areas
^{129}Xe	Xenon-129 gas
^{3}He	Helium-3 gas
ACCP	American College of Chest Physicians
ADC	Apparent diffusion capacity
ATS	American Thoracic Society
BHD	Birt–Hogg–Dubé syndrome
BMI	Body mass index
BTS	British Thoracic Society
CF	Cystic Fibrosis
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CXR	Chest radiograph
DLCO	Diffusing capacity for carbon monoxide
ELC	Emphysema-like change
ERS	European Respiratory Society
FBN1	Fibrillin 1 gene
FEV_1	Forced expiratory volume in 1 second
FLCN	Folliculin gene
GP	General Practice/Practitioner
GPRD	General Practice Research Database
HES	Hospital Episode Statistics (database)
HRCT	High resolution computed tomography
HIV	Human Immunodeficiency Virus
ICD	International Coding and Diagnostics (codes)
kCO	Diffusing capacity for carbon monoxide (DLCO) normalised for lung volume
MBW	Multiple breath washout

MRI	Magnetic resonance imaging
MMP	Matrix metalloproteinases
MFS	Molecular flow sensor
N_2	Nitrogen
NA	Needle aspiration
Nrf2	Nuclear factor erythroid 2-related factor 2
O_2	Oxygen
ONS	Office for National Statistics
OX-RAMPP	Oxford Sub-study of Randomised Ambulatory Management of Primary Pneumothorax
PAL	Prolonged air leak
PFT	Pulmonary function test
PSP	Primary spontaneous pneumothorax
RAMPP	Randomised Ambulatory Management of Primary Pneumothorax study
RB	Respiratory bronchiolitis
RCT	Randomised controlled trial
SP	Spontaneous pneumothorax
SSP	Primary spontaneous pneumothorax
TB	Mycobacterium Tuberculosis
TLC	Total lung capacity
VATS	Video-assisted thoracoscopic surgery
VC	Vital capacity

Table of Contents

1. Introduction 1

1.1. Historical perspective 1

1.2. Aetiology of Primary Spontaneous Pneumothorax (PSP) 3

1.3. Imaging of Pneumothorax 12

1.4. Lung function assessment in PSP 20

1.5. Epidemiology of PSP 25

1.6. Management of pneumothorax 30

1.7. Summary 48

2. Epidemiology of Spontaneous Pneumothorax in England: Record-linked database studies, 1968-2013 51

2.1. Background 51

2.2. Aims and Hypothesis 51

2.3. Methods 52

2.4. Results 57

2.5. Discussion 70

2.6. Conclusions 75

2.7. Future directions 76

3. Novel Imaging Assessment – ^{129}Xe MRI 78

3.1. Background 78

3.2. Aims and Hypothesis 83

3.3. Methods 84

3.4. Results 93

3.5. Ventilation results 98

3.6. ADC results 103

3.7. Quantitative CT results 104

3.8. Sensitivity analysis - PFTs and smoking 109
3.9. Adverse Events 110
3.10. Discussion 111
3.11. Conclusions 114
3.12. Future directions 115

4. Novel Functional Assessment – Lung inhomogeneity 118
4.1. Background 118
4.2. Aims and hypothesis 123
4.3. Methods 123
4.4. Results 132
4.5. Compliance distribution 133
4.6. Comparison with PFTs 134
4.7. Sensitivity Analysis 138
4.8. Discussion 140
4.9. Conclusions 143
4.10. Future directions 144

5. Predicting Outcomes – Air leak and treatment failure 146
5.1. Background 146
5.2. Aims and hypothesis 158
5.3. Methods 159
5.4. Results 163
5.5. Prediction by absolute airflow 164
5.6. Prediction by threshold value for airflow 165
5.7. Discussion 168
5.8. Conclusions 173
5.9. Future directions 174

6. Systematic Review: Chemical Pleurodesis in Spontaneous Pneumothorax Recurrence Prevention 176

6.1. Background 176

6.2. Aim 178

6.3. Methods 178

6.4. Results 182

6.5. Talc 188

6.6. Tetracycline 196

6.7. Blood 200

6.8. Minocycline 202

6.9. Other agents 205

6.10. Discussion 206

6.11. Conclusions 212

6.12. Future directions 212

6.13. Addendum 214

7. Predicting Outcomes - CT scoring 215

7.1. Background 215

7.2. Bleb Scoring Systems 220

7.3. Lung density assessment 222

7.4. Recurrence rates 224

7.5. Aims & Hypothesis 225

7.6. Methods 225

7.7. Results 231

7.8. Agreement between radiologists 231

7.9. CT findings 232

7.10. Patient factors and recurrence 236

7.11. CT findings and recurrence 237

7.12. CT score and recurrence – developing a model 240
7.13. Discussion 243
7.14. Conclusions 248
7.15. Future directions 248

8. Conclusions 250
8.1. Pathophysiology of PSP 250
8.2. Epidemiology and risk factors for recurrence 252
8.3. Initial management and predicting short term outcomes 255
8.4. Optimising management 255
8.5. What key questions remain in PSP? 257
8.6. Future work 258
8.7. Final thoughts 261

9. References 262

1. Introduction

1.1. Historical perspective

The pleural cavity is a potential space that is devoid of any material except for a tiny layer of plasma filtrate that facilitates its function as a gliding membrane for the lung it surrounds. Any collection of fluid (liquid or gas) within this cavity is thus pathological. Air in the pleural space is termed pneumothorax.

One of the earliest accounts of a case of pneumothorax probably dates back to the fifteenth century A.D. when an Ottoman surgeon described a case of pneumothorax complicating traumatic fracture of the ribs[1]. Later descriptions of pneumothorax appear in 19th century medical literature by Laennec who referred to many pneumothoraces complicating Mycobacterium Tuberculosis (TB) infection. He also acknowledged the occurrence of spontaneous pneumothorax which he termed “pneumothorax simple”[2].

Spontaneous pneumothorax can occur without any preceding trauma or iatrogenic injury. Therefore, the air present in the pleural space must have arisen from an abnormal communication between the air containing alveolar spaces of the lung and the pleura. Spontaneous pneumothoraces are further subdivided into primary spontaneous pneumothorax (PSP) that occurs in apparently normal lungs, and those arising in patients with lungs known to be abnormal which are termed secondary spontaneous pneumothoraces (SSP). In PSP, the exact pathogenesis of the abnormal communication between alveoli and pleura is not clear. In SSP, it is presumed to be a result of the pathological process in the underlying lung disease. In the past, TB was the most commonly recognised causes of SSP. Although TB is still the most common cause in the worldwide

world, many different airway and lung diseases can be complicated by SSP. In the UK, the commonest of these is Chronic Obstructive Pulmonary Disease (COPD)[3]. Other common causes include cystic fibrosis (CF), lung cancer, necrotising pneumonias and HIV-related *Pneumocystis jiroveci* lung infection. Two rare infiltrative lung diseases associated with SSP are Pulmonary Langerhans cell histiocytosis and lymphangioleiomyomatosis (with or without other features of tuberous sclerosis). Pleural endometriosis is a recognised cause for recurrent pneumothorax in women of childbearing age (known as catamenial pneumothorax).

This introduction will describe the current understanding of the aetiology and epidemiology of PSP, and evidence behind existing management strategies. This will set the scene for the work undertaken in this thesis to:

- Improve and update the epidemiology of PSP (Chapter 2)
- Explore novel methods of imaging the lung (^{129}Xe MRI, Chapter 3) and assessing functional abnormalities (Lung Inhomogeneity, Chapter 4)
- Develop a model to predict treatment failure (Predicting Outcomes – Air Leak, Chapter 5)
- Review the literature to assess most effective agent for medical recurrence prevention (Systematic review of Chemical Pleurodesis, Chapter 6)
- Develop of model of radiological appearance to predict long term outcomes (Predicting Outcomes – CT scoring, Chapter 7)

1.2. Aetiology of Primary Spontaneous Pneumothorax (PSP)

The classical definition of PSP is that occurring in the absence of underlying lung disease. The current British Thoracic Society (BTS) guidelines suggest categorising patients who are older than 50 or with significant smoking history as SSP category (along with those with known lung disease) because of the presumed likelihood of having pathological lung changes even in the presence of a normal chest radiograph[4], although there is no evidence behind these cut-off values for age or smoking history.

However, there is evidence that patients with PSP have macroscopic and microscopic structural abnormalities characterised by microscopic evidence of distal airways inflammation, "pleural porosity" and emphysema-like changes (ELCs). ELCs are subpleural blebs and bullae, commonly seen in patients with PSP on surgical inspection and on CT scans[5-11], but also in healthy volunteers (both smokers and non-smokers)[5, 12]. However, it cannot be assumed that these abnormalities are the sole cause of pneumothorax, as they are not present in all patients with PSP, and may be present in healthy individuals without PSP.

1.2.1. Blebs and Bullae

The anatomical lesion known as a bleb was first described in 1947 by Miller, as distinct from a bulla (or bullous emphysema)[13]. A bleb can be defined as an outpouching (or vesicle) of the visceral pleura caused by air in the interstitium, forming between the lamina elastica interna and externa of the pulmonary pleura, typically <1cm in diameter (see Figures 1.1 and 1.2). Whereas, a bulla (i.e. subpleural emphysematous bulla) is an airspace measuring >1cm, which is sharply demarcated by a thin wall (no greater than 1mm in thickness). In 1967, Reid further subdivided bulla into three types: type I, a small amount of hyper-inflated lung tissue

that is narrow (pedunculated) and contains no lung parenchyma; type II, a relatively smaller amount of hyper-inflated lung tissue that is broad (sessile) and usually contains vanishing lung; and type III, a large amount of hyper-inflated lung tissue extending to the pulmonary hilum, with ill-defined margins and vanishing parenchyma in each bulla[14].

Figure 1.1. Schematic illustration of the anatomy of emphysematous lung lesions, representing a bleb and a bulla(from Lyra *et al* [15])

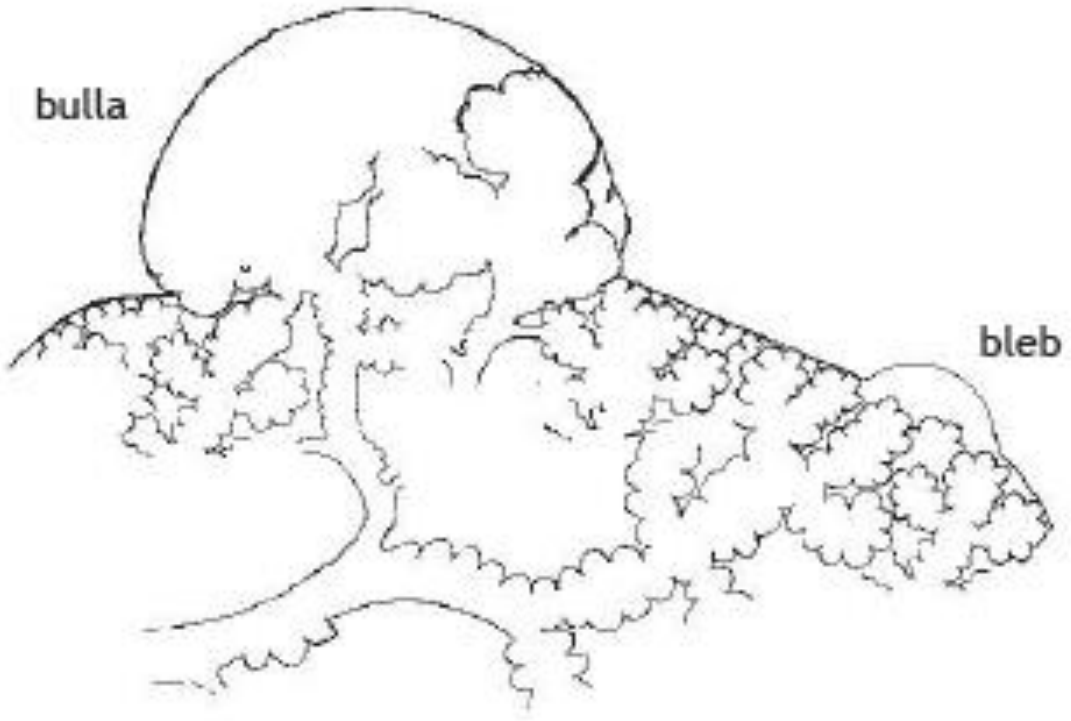
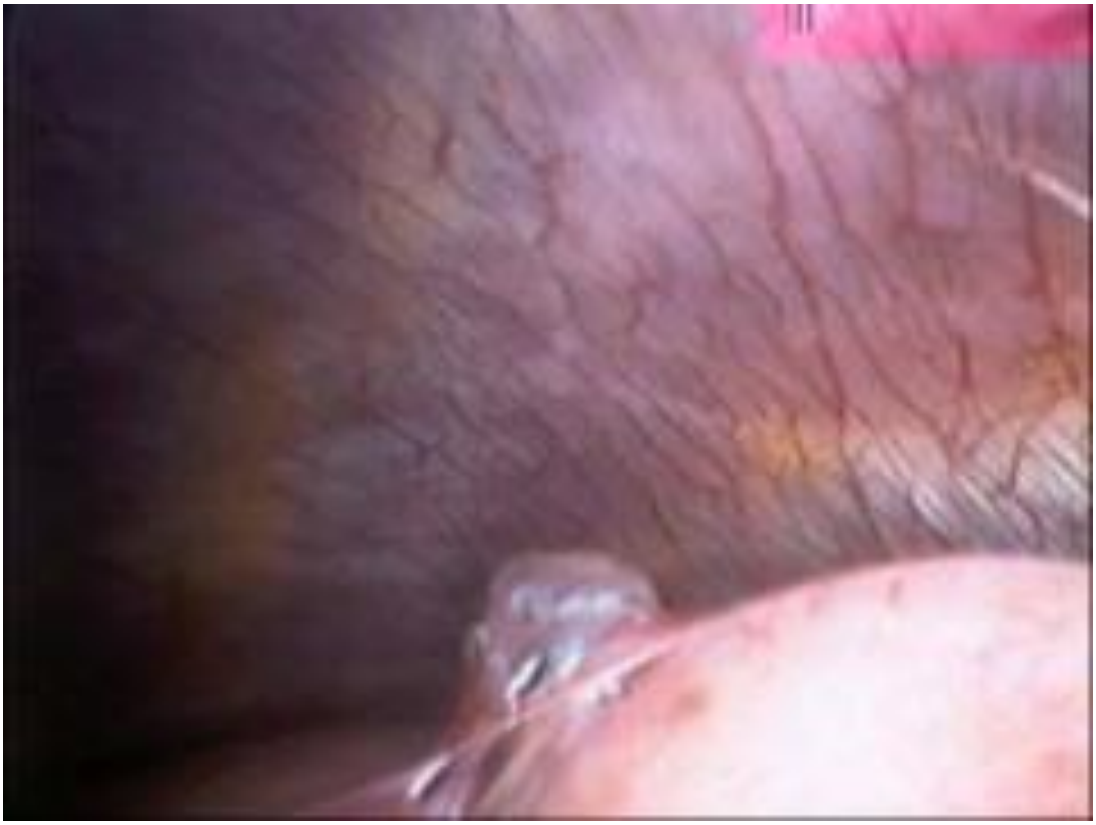


Figure 1.2: Thoracoscopic view of a bleb on the visceral pleural surface (Courtesy of M Noppen)



The use of the term bleb by radiologists is discouraged by Fleischner guidelines as it is thought to be of little clinical importance[16]. However, there is evidence that different types of bullae may have differing microscopic abnormalities[17].

1.2.2. Microscopic abnormalities – Inflammation, elastofibrosis and pleural porosity

Microscopic examination of lung parenchyma from 20 young patients with PSP who had undergone surgical resection in a study from 1971 showed features of chronic distal airway inflammation with lymphocyte and macrophage infiltration alongside fibrotic changes[18]. This chronic inflammation could lead to the formation of ELCs in otherwise healthy lungs. However, this has not been proven. Another surgical study of 79 patients with PSP found histopathologic evidence of respiratory bronchiolitis (RB) on surgical biopsy in 88.6%[19]. RB is the accumulation of pigmented macrophages in the lumen and walls of bronchioles.

Unfortunately, all the patients in this study were smokers, a known cause of RB; so whether RB is a causal step in the development of pneumothorax, or simply a marker of smoking status remains unclear. A subsequent study of 126 surgical cases found that RB was only present in 50%[17]. In the same patients, light microscopic assessment found thickening and elastofibrosis of the pleura. Reid type I bulla were found to have microscopic changes in keeping with that originally described by Miller with respect to blebs, i.e. formation of small air containing space between lamina elastic interna and externa that contains no lung parenchyma (Figure 1.1) [14, 17]. Electron microscopic examination showed further differences between Reid type I and type II bullae: Type I bullae showed marked absence of mesothelial cells, with underlying collagen fibres clearly seen and pores of 10-20μm in diameter were noted; Type II bullae (and giant bullae) have relatively well preserved mesothelial cells with short microvilli[17]. Therefore, it could follow that these smaller "blebs" (consistent with Reid Type I bulla), with absence of mesothelilal cells and nearby pores, are at greater risk of air leaking than the often larger Reid Type II bullae with intact mesothelial cells. These areas of disrupted mesothelial cells at the visceral pleural (replaced by an inflammatory elastofibrotic layer), along with observed small pores, may contribute to a more general "pleural porosity".

It was historically postulated that rupture of ELCs creates direct communication between the alveolar air and the pleural space thus creating a pneumothorax. This view was contested by the observation that the presence of visible air leaks from ELCs at thoracoscopy or thoracotomy is highly variable[20] with many blebs or bullae remaining intact and, in some cases, no macroscopic lesions seen at all. The idea that pleural porosity, as described above (rather than ELC rupture), may be critical in pneumothorax formation was elegantly

demonstrated in an experiment by Noppen et al[12]. Twelve patients with PSP were compared to 17 control subjects at thoracoscopy using fluorescein-enhanced autofluorescence. The control subjects were undergoing sympathectomy and did not have any lung disease, or previous pneumothorax. This study demonstrated, for the first time, areas of parenchymal abnormality (areas of subpleural fluorescence or visible fluorescence leak when inspected under ultraviolet light) at regions of the lung which otherwise appeared normal on plain white light thoracoscopy. High grade lesions were seen in PSP patients only. Two patients with ELC demonstrated air leak, but the leakage was not directly at the site of the macroscopic blebs or bullae[12].

1.2.3. Abnormal elastolysis

The reason why airways inflammation should result in degradation of elastic fibres, and hence formation of a porous elastofibrotic layer, is not clear. One theory is that there is an imbalance in the protease-antiprotease and oxidant-antioxidant systems. Matrix metalloproteinases (MMP) are a group of zinc- and calcium dependent endopeptidases that can damage the basement membrane (between pulmonary epithelium and alveloli)[21]. MMP-2 and MMP-9, two interstitial collagenases, have been postulated to be pathogenic in other lung diseases[22], including asthma and COPD[23]. Two Taiwanese groups examined of surgical resection specimens for patients undergoing surgery for PSP and demonstrated overexpression of MMPs[21, 24]. The first compared lung tissue from 15 PSP patients with that from 20 patients with stage I non-small cell lung cancer who were used as controls[21]. Immunohistochemistry showed overexpression of MMP-2, MMP-7 and MMP-9 in the tissue of PSP patients compared to controls[21]. The second non-comparative study of 91 patients also found high MMP-2 and MMP-9 expression and that higher levels were more frequent in

those patient presenting with a recurrence of their pneumothorax compared to those with first episode[24]. The same group of patients were examined for expression of nuclear factor erythroid 2-related factor 2 (Nrf2) in alveolar type I pneumocytes. NrF2 is a regulator of redox homeostasis and inflammatory response. It is believed to play a cytoprotective role in detoxification and chemoprevention[25]. High Nrf2 expression was seen in those patients without previous recurrence, suggesting a protective effect[25]. However, recurrence was not defined by prospective collection of actual recurrence events post-surgery, but retrospectively by their prior clinical course. The recurrence group consisted of patients "with radiological proof of relapse of pneumothorax after the first episode of PSP" (presumably not surgically treated), and non-recurrence group were patients "who underwent surgery during their first admittance with PSP and had no recurrence during a 2-year follow-up period". Therefore, the two patient groups could be fundamentally different. As most patients presenting with first episode are not treated surgically, and the recurrence rates after surgery are very low, this is not a valid comparison of "risk of recurrence".

Nevertheless, these studies provide interesting insight in the potential pathogenic overexpression of MMPs and the role of oxidative stress response in PSP. Further prospective work is required to confirm these findings and determine its clinical applicability in terms of risk stratification of patients or potential treatment options.

1.2.4. Other risk factors

Ectomorphic body type

The classic morphology of a patient with PSP is the young, tall male[26-28]. Sadikot *et al* studied risk of recurrence in 153 PSP patients over a four year period and found that height was significantly associated with greater risk of recurrence, but only in males[26]. In this

study, female height, and lower body mass index (BMI) in either sex, was not associated with increased risk. Large-scale data of 5,604 cases of pneumothorax in Japan, compared their height and weight with that of healthy individuals[27]. The authors found a significantly lower weight:height ratio (using Kaup index) in individuals with pneumothorax. Another interesting study from Japan looked retrospectively at national growth records for 31 patients surgically treated for PSP[28]. Compared to national standard values, the PSP patients were ectomorphic (i.e. tall and thin) from childhood, but their height showed a marked increase from 11-14 years[28]. The expected increase in height gain per year in adolescence started 2 years earlier in patients than their increase in weight (in the standard group this peak occurred simultaneously). It is postulated that as pleural pressures increase from base to apex of the lung, taller individuals experience higher distension pressures at the lung apex which may predispose them to bleb and bullae formation. However, this speculative hypothesis has never been proven and other mechanisms (discussed above) seem more likely.

Aluminium

Aluminium has been known to be associated with asthma and COPD in patients exposed to aluminium dust in industry. Whether aluminium is implicated in the pathogenesis of PSP is not clear. Two case-control studies have conflicting results. Thirty PSP patients in Turkey had significantly higher blood plasma aluminium concentrations (18.43µg/dl ,SD 0.63) than a control group of 30 healthy volunteers (2.66µg/dl, SD 0.81)[29]. However, a smaller French study of 10 patients and 10 matched controls from hospital laboratory found no difference in aluminium levels: 3.83 µg/l (SD1.21) vs 4.57µg/l (SD 1.8)[30]. None of the patients in either study had occupational exposure to aluminium.

Familial pneumothorax and genetic predisposition

A significant proportion of patients with PSP will report a family history. This is often quoted at being 11.5% from a retrospective study (from 1991) of males who served in the Israeli Defense Forces, in which 33 of 286 patients surveyed reported a family history of PSP[31]. Of these 33, family pedigrees for 15 families were examined (along with constructed pedigrees from an available literature search). The pattern of inheritance was complex but the authors concluded that it was most likely that PSP predisposition is due to more than one gene: with some familial cases inherited as an X-linked recessive disorder; and others as an autosomal dominant trait with incomplete penetrance, with penetrance being higher in males (50%) than females (35%)[31].

Since this study, mutations in a number of the genes have been identified in patients with heritable diseases associated with spontaneous pneumothorax. Mutations in the folliculin gene (FLCN) are known to cause a rare skin disease, Birt–Hogg–Dubé (BHD) syndrome[32], an autosomal-dominantly inherited disease characterized by benign skin tumours, diverse types of renal cancer, pulmonary cysts, and spontaneous pneumothorax[33]. Mutations in Fibrillin 1 (FBN1) gene cause Marfan syndrome: the major manifestations include increased height, disproportionately long limbs and digits, subluxation of the lens of the eye, and dilation of the aortic root[34]. Apical blebs and spontaneous pneumothorax have been described as one of the minor diagnostic criteria for Marfan syndrome[34]. Whether mutations in the FBN1 gene predispose individuals to PSP in the absence of Marfan syndrome is not clear. An analysis of two pedigrees of patients with a strong family history of spontaneous pneumothorax (in keeping with autosomal dominant inheritance with variable penetrance) did not find associated mutations in the FBN1 gene[35].

Although rare, familial patterns of inheritance of spontaneous pneumothorax, particularly autosomal dominance, should be investigated as they may herald an unrecognised connective tissue disorder (Marfan syndrome or Ehlers–Danlos syndrome), metabolic disorder (Homocystinuria) or skin disease (BHD) with the need for potential lifelong surveillance for severe extra-pulmonary complications (e.g. renal cancer or aortic rupture).

It seems likely that minor mutations in FBN1 or FLCN genes could be predisposing factors in the development of PSP, without causing full clinical manifestation of BHD or Marfan syndrome. This is an area requiring large scale prospective studies collecting genetic and clinical data. If successful in identifying causative genetic mutation(s), this data could determine a patient's individualised risk of recurrence; as long as this data is applicable on the individual level, and not simply associated with familial pneumothorax as discussed in a recent review article[36].

At present, there appears to be a link between inflammation, perhaps as a result of protease-antiprotease and oxidant-antioxidant system imbalance, with possible (multi-locus) genetic predisposition and environmental exposure, which causes subpleural structural abnormalities. These abnormalities consist of pleural porosity and ELCs, but these changes can be present in individuals who haven't suffered with pneumothorax episodes. Likewise, some patients with pneumothorax will have no macroscopic abnormalities seen. Further work is required to determine the exact pathological mechanism predisposing some individuals to pneumothorax.

1.3. Imaging of Pneumothorax

ELCs are cystic air spaces and lower density areas of lung parenchyma. Cystic air spaces contiguous with the pleura are arbitrarily called blebs if ≤1cm and bullae if >1cm[16]. At present, the data on true recurrence rates for patients who have been treated for PSP are poor. Low radiation dose Computed Tomography (CT) has been proposed as a method of risk stratification for recurrence through identification of these lung abnormalities, either ipsilaterally or in the contralateral lung, assuming that ELCs are associated with recurrence.

1.3.1. Computed Tomography and PSP

A number of studies of varied design have been conducted which investigate CT scan findings in patients with PSP. An early study of CT in patients with PSP in 1990 (called Idiopathic SP at the time) described findings in 20 patients with PSP and 20 age-, sex- and smoking-history matched controls[5]. Emphysematous lesions were more commonly found in the PSP group. Three of the 20 had normal CT scans, but subpleural emphysema was noted in 16 patients, centrilobular emphysema in 11, thickened bronchial walls in 10 and bullae in 5 patients[5]. Lesions were most common in the upper third of the lung. Interestingly, the CT scans were abnormal in six of the 20 patients in the control group (two with bullae, two with subpleural emphysema and two with centrilobular emphysema). It should be noted that 17 of 20 patients in both groups were smokers with a mean consumption of 6 pack-years. This suggests that these ELCs may be present in general population who may never suffer with a pneumothorax episode, particularly those who smoke.

ELCs and pneumothorax course

Another study of 26 consecutive patients with PSP assessed the number of blebs found on CT scan during treatment for their pneumothorax and whether they had a "complicated pneumothorax"[37]. The "complicated" group were defined as those patients who either had a prior pneumothorax, recurrent pneumothorax on follow-up, or need for chest tube drainage. The 15 "uncomplicated" patients, i.e. patients with first episode treated conservatively, had a fewer blebs, both ipsilateral and contralateral[37]. The authors calculated a "bleb score" by assigning a numeric value to different ranges of bleb sizes: blebs ranging in size from 0 to 5 mm were each assigned a value of 1, a value of 2 was given to each bleb between 6 and 10 mm, 3 for blebs between 11 and 21 mm, 4 for blebs between 21 and 30 mm, and 5 for any bleb greater than 31 mm. The bleb score for each lung was determined by multiplying by number of blebs in each size category by the numeric value assigned to that category[37]. This study suggested that a higher "bleb score" (see Chapter 7) based on size and number of blebs could identify patients at risk of recurrence or need for chest tube treatment, but the numbers in this study were small and there was no comparator group.

Another small prospective study of by Mitlehner *et al* examined CT scans of 35 patients with PSP[7]. 88.6% (31/35) had lesions identified on CT scan. Of the 32 patients followed up (for a mean of 32 months), 8 had recurrence but there was no difference between the number, size and distribution of bleb/bullae between patients with and without recurrence[7].

Smit *et al* assessed whether incidence of blebs or bullae was different between patients presenting with first or recurrent PSP[6]. They hypothesized that if bullae were a pre-disposing factor for PSP, then one would expect a higher prevalence in those with recurrent

PSP than those with first episode. 101 cases of PSP underwent CT scan. Bullae (>2cm) were identified in 59% of patients. However, the proportion of patients with bullae was not significantly different between those presenting with first PSP (56%) and those with recurrent PSP (64%). A limitation of this early paper could be the resolution of the CT scanners, which at the time may not have been sufficient to identify lesions smaller than 2cm.

Are ELCs incidental findings?

Although ELCs have been identified in patients with PSP, these findings may simply be common in the general population, particularly in those who smoke. A large study of 250 healthy individuals undergoing thoracoscopic investigation (being treated with thoracoscopic sympathectomy) with no prior history of pneumothorax or pleural disease demonstrated a 6% incidence of apical blebs on visual inspection of the lung[38]. These were more prevalent in slim individuals (BMI <22kg/m2) who smoked[38].

In order to determine whether ELCs were related to smoking *per se*, Bense et al conducted a small case-control study of 27 non-smoking patients with PSP and ten, healthy non-smoking volunteers[39]. ELCs were found 81% patients with PSP, more frequently in the upper zones, but not in any of the healthy controls[39]. Therefore, ELCs were present in patients with PSP even in the absence of smoking as a risk factor, but the number of patients in this study was small.

Association of CT findings and recurrence

A Spanish study, prospectively collected data on 55 patients treated for PSP and performed CT scan after resolution[8]. Importantly, the authors excluded patients who had persistent

air leak for more than 5 days (as they were sent for surgery). In these 55 patients successfully managed with chest tube drainage, 26 (47.3%) had bullae on CT and 29 (52.7%) did not. There was no difference in recurrence between the two groups: 6 of 26 with bullae recurred, compared to 7 of 29 without bullae[8]. In this group, not requiring surgery, presence of bullae was not predictive of recurrence.

Risk of contralateral recurrence

Three surgical studies investigated whether the presence of ELC or blebs on CT scanning could predict recurrence in the contralateral lung (i.e. the lung not being operated upon). These studies, of patients having undergone surgery for pneumothorax, elegantly prospectively assess the risk of subsequent pneumothorax in a defined population, all of whom had undergone CT scanning. Firstly, Sihoe *et al* conducted a small prospective cohort study of 28 patients[9]. Pre-operative CT scan was assessed for presence or not of blebs or bullae in the contralateral lung. Contralateral blebs were seen in 15 patients (53.6%). Four of the 15 (26.7%) had recurrence within 22 months, compared to none in the 13 patients who did not have contralateral blebs[9]. The authors originally calculated that this difference was statistically significant (p 0.04). However, this was a mistake as pointed out by Noppen[40]. As a response, Sihoe *et al*, updated their dataset by contacting all their patient again (after one year more follow-up had occurred). They reported that two additional patients with contralateral blebs had suffered with pneumothorax recurrence, but none in the group without contralateral blebs, thereby making the difference significant (p 0.02).

Huang *et al* conducted a large retrospective review of 231 patients treated for PSP, with a long follow-up period of an average of 92 months[10]. All patients were managed initially with chest tubes and had high resolution CT (HRCT) when the lung had re-expanded. 77.1%

went on to have surgery (178/231); indications being persistent air leak, tension pneumothorax at first presentation, haemopneumothorax, occupations of patient (such as diver or pilot), and ipsilateral or contralateral recurrences. 148 patients had contralateral blebs. 33 patients (14.3% of total, 22.3% of those with blebs) went on to have contralateral recurrence [10]. All of those with recurrence had contralateral blebs, compared to 48% in the group, none of which had recurrence ($p<0.001$, <0.007 after Bonferroni correction) [10]. On multiple logistic regression for risk factors for recurrence (in 128 patients with contralateral blebs), low BMI ($<18.5 kg/m^2$) was found to be an independent predictor of recurrence. The high prevalence of blebs (48%) in patients who did not go on to have recurrence is striking. Therefore, the argument for early surgical intervention on the contralateral lung on the basis of CT bleb findings alone has not been made.

In a similar more recent study, Noh et al followed up 262 patients who had undergone CT scan after being referred for surgery (due to persistent air leak for >3 days)[11]. Contralateral bullae were found in 32 patients (12.2%). After a long follow-up period, 12 of these 32 (37.5%) had a contralateral pneumothorax recurrence (median interval to recurrence 52 months). Contralateral recurrence was seen in 6.1% (12/230) of patients without contralateral bullae[11]. The authors suggest that “single-stage bilateral surgery might be beneficial for young patients with recurrent pneumothorax and patients with contralateral bullae”. However, their own data suggest that they would be operating unnecessarily upon the 63.5% of patients with contralateral bullae who will not recur.

Summary view of data

Given the presence of blebs and bullae on CT scans in healthy volunteers and patients who do not have a contralateral pneumothorax recurrence, the simple metric of the presence or absence of blebs or bullae is likely to be too crude a measure of abnormalities in the lung.

Scoring systems in pneumothorax

A number of studies have investigated whether a "scoring" system of number, size and distribution of cystic air spaces might provide value in predicting those patients at high risk of recurrence. These will be discussed in Chapter 7, along with analysis of new data from the RAMPP trial. The aim is to assess the CT characteristics of patients with PSP with good quality prospectively-collected data to determine whether a CT scoring system based upon ELC and lung density can predict 12 month pneumothorax recurrence rates.

1.3.2. Magnetic resonance imaging (MRI) of lungs

Limitations of CT

CT scans performed at high resolution can provide more detailed structural lung parenchymal information than conventional CT. However, it does not provide information on ventilation defects. In addition, HRCT requires higher levels of ionising radiation, making it less favourable for young patients (as in this population with PSP) and also limits its use in follow-up when repeated scanning will be required.

Benefits of MRI

MRI uses no ionising radiation and is thus attractive for potential risk assessment in a young healthy population, such as seen in PSP. However, as the signal in conventional MRI

originates principally from the protons in water molecules of tissues, it is therefore not particularly useful in assessing the lungs, as they are composed largely of air spaces rather than water. The use of hyperpolarized noble gases, helium (^{3}He) and xenon (^{129}Xe) overcomes this problem of using MR for lung imaging, as they have a nuclear spin of ½ which generates a signal on MRI.

Ventilation imaging

Ventilation imaging using ^{3}He has demonstrated utility in detecting functionally abnormal areas of lung in patients with obstructive lung diseases, e.g. chronic obstructive pulmonary disease (COPD), CF [41, 42], asthma [43-45] and bronchiolitis obliterans [46, 47]. More recently, ventilation imaging has been safely performed with ^{129}Xe[48-50].

Diffusion analysis

As well as allowing visualisation of the ventilation of lung areas, hyperpolarized gas imaging can measure the diffusion of the gas within the lung. The diffusion coefficient of a gas determines the distance the atoms will move in a given time period. Analogous to the information on the microscopic motion of water molecules in tissue using standard proton MRI, diffusion-weighted hyperpolarised gas MRI can provide a measurement of the movement of the gas when restricted within the lung microstructure. This measure, the Apparent Diffusion Capacity (ADC), assessed the distance moved by the random motion of the Xe gas particles and hence a measure of the size of the lung microstructure (e.g. alveolar spaces and small airways) [51, 52]. Typical ADC values for healthy lung parenchyma using ^{129}Xe are ~0.04cm^{2}/s, which is substantially smaller than the corresponding diffusion coefficient of the gas in an unrestricted space (~0.14cm^{2}/s)[51]. A study using hyperpolarised

^{3}He imaging to measure ADC in eleven symptomatic smokers and eight healthy non-smokers[53]. ADC values were significantly higher in smokers, and were correlated with total number of pack-years. The authors also showed that ADC was correlated with Pulmonary Function Tests (PFTs: Forced Expiratory Volume in 1 second, FEV_1, and diffusing capacity), concluding that subclinical smoking–related emphysematous changes might be revealed with ADC measurements before they are demonstrated on high resolution CT [53]. This technique has the potential to identify subtle or early changes in lung parenchyma, which could be of particular use in pneumothorax patients.

A recent study by the group in Oxford showed that ^{129}Xe imaging can assess lobar contributions to lung function using ventilation and ADC values [54]. Twenty two patients with COPD underwent hyperpolarized ^{129}Xe imaging, quantitative CT scan and PFTs. Percentage ventilated volume and average ADC by lobe showed correlation with percentage emphysema on quantitative CT and whole lung average ADC values correlated with PFT results [54].

Utility in pneumothorax patients

Patients with PSP may have subtle disease or ELCs which are more prevalent in some regions (e.g. upper lobes) of the lung parenchyma. Hyperpolarized ^{129}Xe could be a powerful non-ionising method of assessing these abnormalities. This novel method of assessing ventilation and diffusion has been used for the first time in pneumothorax for the purpose of this thesis. The results will be discussed in Chapter 3.

1.4. Lung function assessment in PSP

The functional assessment of the lungs in patients who have had PSP has not been well studied. The assessment of lung function focuses on overall measures of function: measurement of gas flow through the larger airways (spirometry) and diffusion of inhaled gas into the blood (diffusion capacity). In 1965, Williams and Kane performed lung function tests on 14 patients who had "recovered uneventfully from SP and did not show evidence of other cardiopulmonary disease"[55]. In 5/14 patients the diffusing capacity was <73% of normal, but only one patient (who was asymptomatic) had evidence of emphysema on the basis of marked reduction in diffusing capacity in association with increased compliance and low lung retractive force[55]. This small study suggests that mild abnormalities in PFTs can be found in PSP patients, but is not convincing evidence given its small size. In 1987, Pawlowicz et al reported the PFTs in 56 young adults after PSP, compared to control group of 20 age- and smoking habit-matched healthy participants[56]. Only four (7%) of the 56 patients had evidence of emphysema, based on PFT measurements.

1.4.1. Is pneumothorax associated with spirometrically abnormal lungs?

In 1988, Lange et al reported an impressive long-term follow-up study of PFTs 22 to 35 years after a PSP event, either treated with talc pleurodesis or by simple drainage[57]. 75 of 114 patients fully completed the study (others having died from unrelated causes, emigrated or failed to respond). The mean values for FEV_1, vital capacity (VC) and total lung capacity (TLC) were lower than predicted (by standardised values) but the "impairment was slight and in most subjects were within the normal range" [57]. The group treated with talc pleurodesis (n=46) showed a mild restrictive impairment of lung function (with a mean TLC of 89% predicted); whereas the group treated with drainage alone had a mean TLC 96% predicted

(n=29) [57]. Interestingly, those patients with recurrent pneumothorax, the mean TLC was significantly lower (88% predicted) than that in those with no recurrence (95% predicted) [57]. However, this finding may be confounded by the fact that they are more likely to have received talc (for recurrence prevention). Having suffered with a pneumothorax in early life (all under 41 years old) did not appear to predispose this group to emphysema. Fourteen (19%) of the 75 patients demonstrated airflow obstruction (with five being severe FEV_1<50% predicted); but 12 of these were lifelong heavy smokers[57].

Shramel et al assessed PFT findings along with CT and surgical assessments of ELC[58]. 85 patients had PFTs six weeks after video-assisted thoracoscopic surgery (VATS) for pneumothorax (indications not listed) [58]. ELCs were graded from a score of 0 (no ELCs) to 3 (extensive ELCs) by combining CT and VATS findings. They found no significant differences in PFTs between those with ELC score <2 and ELC score ≥2, except for TLC: 88.1% vs 99.0% predicted, respectively. 67% of the patients were smokers. In this subgroup, the diffusing capacity (normalised for lung volume, kC0) was significantly lower in patients with ELC score ≥2 (70.4 %) compared to an ELCs score <2 (78.8%)[58]. However, it is difficult to draw firm conclusions from this data as the surgical treatment undertaken at VATS was determined by the macroscopic findings of blebs and bullae; thereby directly influencing (and hence confounding) the results.

PFTs are well-established, validated and routinely used in the diagnosis and on-going monitoring of many pulmonary diseases. However, they do have a number of limitations. Spirometry is effort- and technique-dependent, which can be a particular problem for patients with significant breathlessness or advanced respiratory disease. In addition, PFTs may be are relatively insensitive to changes in early lung disease, which may be the case in

patients with PSP. They provide global measures of lung function, and relatively little information about regional pathology and heterogeneity in the lungs[59-61].

The abnormalities in patients with PSP may be regional (e.g. at the lung apices), inhomogeneous, or subtle enough not to be easily distinguished on these global assessments.

1.4.2. Ventilation and Perfusion assessment

In most respiratory diseases, the primary physiological mechanism limiting efficient gas exchange is ventilation-perfusion (V:Q) mismatch: i.e. discrepancy between the distribution of blood flow through the lung (perfusion) and the distribution of gas flow within the lung (ventilation)[62]. Measuring these distributions would provide additional information in the assessment of gas exchange in the lungs, and may be useful in the diagnosis and management of patients with established or suspected respiratory disease[60, 63].

Applicability for pneumothorax patients

Parenchymal structural abnormalities of ELCs or underlying small airways inflammation in patients with PSP may be associated with subtle V:Q mismatch. This may be due to regional differences disease, leading to inhomogeneity within the lung.

Current methods of measuring V:Q mismatch

Methodology for measuring blood and gas distributions in the lung was developed in the 1970s, e.g. the multiple inert gas elimination technique (MIGET). This is a well-validated method of determining ventilation and perfusion distributions but has a number of limitations. It is invasive, requiring a systemic arterial catheter in place for a prolonged

intravenous infusion and sampling of arterial blood, and time-consuming[64]. MIGET is therefore unsuitable for use in routine clinical practice.

Novel techniques to measure and model V:Q and inhomogeneity

A new methodology developed by the Department of Physiology (University of Oxford) uses non-invasive means of making similar measurements to MIGET that involves simply breathing through a mouthpiece for 15 minutes. During that period, the participant initially breathes air for 10 minutes and then 5 minutes of pure oxygen (O_2) both at normal tidal breathing. Therefore, the test is simple to conduct and uses inexpensive gases.

This new methodology has been made possible by two recent advances. Firstly, a new molecular flow sensor (MFS) has been developed for the measurement of the composition of inspired and expired gases. The concentrations of oxygen, carbon dioxide (CO_2), and water vapour within the chamber are measured every 10 milliseconds using highly accurate laser absorption spectroscopy, while the flow of gas is measured contemporaneously using a modified pneumotachograph[65, 66]. Secondly, the increased precision of gas analysis has facilitated the development of the novel mathematical model of inhomogenity in the lung[67].

1.4.3. Multiple breath washout

Measurement of the change in respiratory gas exchange from breathing air to pure O_2 in this new model is the same concept as multiple breath washout (MBW) assessments using an insert gas (e.g. Nitrogen, N_2), which was described as early as the 1960s. MBW can assess the efficiency of ventilation distribution and hence potential lung inhomogeneity [68]. The concept of “slow” and “fast” compartments corresponding to differential ventilation defects

within the lung has been shown using N_2 washout in patients with cystic fibrosis[59, 60]. However, MBW has been hampered in its utility by the limited accuracy of existing technologies and lack of robustly validated commercial washout systems, and is not routinely used in clinical practise. A combined European Respiratory Society (ERS) and American Thoracic Society (ATS) consensus statement on this provided recommendations for inert gas washout system characteristics[68]. These characteristics are more than met by the MFS used in this study[65]. The new methodology, by providing significant accuracy improvements, allows the model of lung inhomogeneity to be used to provide a number of determined parameters including “compliance”, alveolar volume and “deadspace”.

The aim of this study is to utilise this new methodology to determine estimates of lung inhomogeneity in patients who have had a PSP, in comparison with patients with COPD and healthy volunteers (young and old). The results are presented and discussed in Chapter 4.

1.5. Epidemiology of PSP

The true incidence of PSP has been poorly studied. Frequently quoted estimates of incidence are based on two small out-dated single-centre studies from the USA[69] and Sweden[70], and only two epidemiological studies: one from the UK in 2001[71], and a more recent study from France[72]. Since these first studies were published there have been significant changes in rates of smoking in western populations, and patients with chronic diseases are living longer. Changes in the long-term incidence of pneumothorax over this period have not been studied.

1.5.1. Single-centre studies

Melton et al reported the incidence of pneumothorax in Olmsted County (Minnesota, USA) between 1950 and 1974 through retrospective medical record review[69]. Of 318 cases of pneumothorax, only 141 were spontaneous and only 77 of those were deemed primary. Incidence rates for PSP were calculated (on the basis of person-years at risk using population data) as 7.7 cases per 100,000 person-year for males and 1.3 for females[69].

Bense et al studied incidence in the County of Stockholm (Sweden) over ten years from 1975 to 1984[70]. During this time period 138 patients were admitted with their first spontaneous pneumothorax. The patients were not subdivided into PSP and SSP. The overall annual incidence of first spontaneous pneumothorax was 18 and 6 per 100,000 per year for men and women, respectively[70]. However, given the small number of cases in these two single-centre studies, these estimates could be inaccurate.

1.5.2. National dataset studies

The first epidemiological study to use national datasets was by Gupta *et al*[71]. Two datasets were used: from 1991 to 1995 patients consulting primary care with a diagnosis of pneumothorax were identified from the General Practice Research Database (GPRD); and from 1991 to 1994 emergency hospital admissions for pneumothorax were identified from the Hospital Episode Statistics (HES) data. The overall rate of persons consulting with pneumothorax (both primary and secondary combined) in the GPRD was 24.0 per 100 000 per year for men and 9.8 per 100 000 per year for women[71], which is higher than the previous single-centre studies[69, 70]. The overall annual incidence of emergency hospital admissions for pneumothorax was 16.7 per 100 000 per year and 5.8 per 100 000 per year for men and women, respectively[71]. Gupta *et al* presented data split into two age groups: 15-34 and ≥55 years, the presumption being that the 15-34 year olds were PSP and ≥55 years were SSP, but this was not tested on concurrent records of co-morbidities. In reality, the distinction is likely to be more complex that a simple age cut-off.

More recently, Bobbio *et al* [72] conducted a study using the French national dataset, equivalent to HES in the UK, collects information on all hospital stays in French public and private hospitals, over a four-year period (2008-2011). They identified 60,000 cases where spontaneous pneumothorax was the main diagnosis leading to hospitalisation, with additional data available including associated comorbidities, hospital stay and some treatment modalities. This data found an annual rate of admission of 22.7 per 100,000 population per annum (95% CI 22.4-23.0)[72]. However, taking into account rehospitalisation, the rate was 16.2 per 100,000 which may be a more accurate reflection of the incidence of pneumothorax. The male to female ratio of 3.3 to 1. Mean age at

presentation was higher in women than men (41 (SD 19) vs. 37 (SD 19) years; p<0.0001). The peak incidence was in men <20 years; whereas in women the peak was delayed and stayed stable until 40 years[72].

Hospital stay for SSP was significantly longer (median 8 days (IQR 5–14) vs. 5 (3–7) days) and patients with SSP were more likely to need surgical treatment than those with PSP (33% vs. 23%; p<0.0001)[72].

1.5.3. Pros and cons of national datasets

Use of national datasets allows the analysis of large number of patients; far larger than any individual cohort study could achieve. This type of study, therefore, has the potential to identify risk factors and associations that could otherwise be missed. The French data represents the largest published epidemiological dataset to date, providing a snapshot of pneumothorax incidence around 2010[72]. Pneumothorax episodes are identified using ICD (International Coding and Diagnostics) codes. Helpfully, spontaneous pneumothorax has one discrete code (J93 in ICD version 10) and therefore can be easily identified as the main reason for admission (unlike some other diagnoses which rely on a combination of ICD codes).

The limitations of using national admissions datasets are the fact that they only report patients who are admitted to hospital. This will not include those individuals managed without hospitalisation, for example, those managed conservatively or with a needle aspiration and discharged home from the Emergency Department. This may be a significant underestimate of the true incidence as patients with small and minimally symptomatic pneumothoraces can be managed conservatively, and a proportion of patients requiring treatment may be adequately treated with a needle aspiration of their pneumothorax,

thereby avoiding admission. Good quality data on the proportion of patients being managed conservatively is lacking. A small historical retrospective study of 117 patients in Scotland suggested that 32% of episodes did not require chest drain insertion, and so did not require admission[73]. Patients may be successfully managed by needle aspiration alone (and discharged home). A summary of the data on success rates of needle aspiration is presented below (see Management of Pneumothorax).

The GPRD rates are determined by a record of "significant events" that could include a referral but also the receiving of a hospital letter. It is unclear whether these data could distinguish initial GP consultations, hospital correspondence and follow-up consultations, which could potentially be recorded as "pneumothorax events", and may, therefore actually overestimate the true incidence.

Both of the above studies only cover four-year periods and therefore were not able to provide longitudinal data on trends in incidence over time.

1.5.4. Distinguishing PSP from SSP

The ICD codes do not distinguish between primary (i.e. no known lung disease) and SSP. Therefore, researchers must rely on co-morbidities also being coded. Gupta *et al* did not attempt to distinguish PSP from SSP, instead sampling presenting rates by age group[71]. The method for distinguishing SSP in the study by Bobbio *et al* was not well described. The proportion of SSP (15% of cases) was surprisingly low in this paper[72], with previous data suggesting SSP should make up around 50% of the total [69]. Therefore, it is unclear whether these differences represent different populations or a problem with the nature of hospital coding.

1.5.5. Need to update the epidemiology of pneumothorax

Data presented in this thesis (Chapter 2) uses the HES and related datasets from 1968 to 2013, to provide data on trends in incidence in England over two generations – far greater than any previous epidemiological study. Record-linked data is available from 1999-2013, enabling detailed analysis of comorbid diagnoses to more accurately distinguish PSP from SSP: Use of episode-based (non-linked) data only allows SSP to be defined using comorbidities listed on that admission, which could be incomplete or inaccurate. In contrast, record-linked data allows analysis of prior diagnoses and future diagnoses, capturing a greater proportion of patients who have a respiratory comorbidity. In addition, over a decade of record-linked data provides the opportunity to generate reliable data on how many patients have a recurrence, and the risk factors for recurrence.

1.6. Management of Pneumothorax

1.6.1. Why treat pneumothorax?

Tension pneumothorax

Tension pneumothorax, in which the hole in the visceral pleura forms a one-way valve, can lead to progressively increasing intra-pleural pressure. In turn, this will lead to reduced venous return, hypotension and haemodynamic compromise. These patients should be treated as an emergency with urgent decompression with a standard 14 gauge cannula[4]. Thankfully, tension is thought to be a rare occurrence in PSP, typically occurring in the context of trauma or ventilated patients in intensive care units[74]; although true incidence in not clear.

Non-tension pneumothorax

The vast majority of PSP patients will not be haemodynamically compromised. The aim of physician treatment is to safely manage the patient while the lung heals and air leak resolves. However, the optimal initial treatment regime for treatment of PSP is not defined.

1.6.2. Initial Management of PSP

The first choice to make is whether any intervention is required ("Do something" approach) or whether the patient can be managed conservatively with observation ("Do nothing" approach). In 1966 two studies were published in the same edition of the respiratory journal Thorax. The first was a case series of 119 patients over 10 years, which describes a mainly "Do nothing" approach in which 83% of PSP and 55% of SSP were managed conservatively[75]. The authors concluded that this success rate justified a general policy of non-intervention and outpatient management". Conversely, the second was another case

series over 10 years including 242 cases largely managed with intervention ("Do something"): 194 patients had chest tube drainage, 49 had thoracotomy, and only 11 were conservatively managed[76]. They concluded that these data "outline the case for active surgical management" for all pneumothorax cases. Clearly these cannot both be the case. There continue to be advocates of both approaches, and over 50 years after these two studies, the debate continues. A randomised controlled trial (RCT) of conservative versus active management of PSP has just completed recruitment in Australia and New Zealand, the results of which are eagerly awaited[77].

The British Thoracic Society (BTS) guidelines suggest treatment is required in patients with large pneumothorax and/or symptomatic[4]. However, International guidelines and expert consensus statements vary[4, 78, 79]. The very definition of what constitutes a "large" pneumothorax is not consistent. The BTS definition is >2 cm measured from the visible visceral pleura to lateral chest wall at the level of the hilum on CXR[4]. The American College of Chest Physicians (ACCP) consensus statement suggests using the distance from the lung apex to the ipsilateral thoracic cupola at the parietal surface, with large being ≥3cm[78]. The Belgian Society of Pneumology (BSP) use evidence of lung dehiscence over the whole length of lateral chest wall to define a large pneumothorax[80]. A study of 49 pneumothorax episodes compared the classification of pneumothorax size across these 3 guidelines and found that there was agreement in only 47% of cases[81]. In addition to the lack of consensus on size definitions, there is an acknowledgement that large size does not always correspond to worse symptoms. The BTS guidelines include the caveat that "in some patients with a large pneumothorax but minimal symptoms, conservative management may be appropriate". Therefore, the decision to treat or not largely lies in the hands of the

treating clinician: patients with a small pneumothorax but severe symptoms may well require intervention; whereas a stable patient with a pneumothorax classified as large may be initially managed conservatively with observation only. It may be that the air leak was a transient event, which deflated the lung, but has already healed. These patients may be those with minimal symptoms that can be managed conservatively. Conversely, on-going air leak will lead to progressive collapse or non-resolution of the pneumothorax, thereby requiring intervention to drain the pneumothorax and control air leak.

1.6.3. Needle aspiration vs Chest drain

If a decision is made to intervene, the choice of initial management is needle aspiration (NA) or insertion of small-bore chest drain. NA (using 16-18G cannula) of up to 2.5L of air is recommended as initial treatment. If aspiration is unsuccessful, then chest tube insertion is required. These recommendations are based upon a number of small RCTs showing equivalence of NA and chest drainage in terms of initial success rates: varying between 59-80%[82-85]. There were significant differences between the studies in terms of design and definition of “initial success” (Table 1.1).

Table 1.1: Randomised controlled trials of needle aspiration vs chest drain: Initial success rates (%)

Author	Year	n	Aspiration success rate %	Chest drain initial success rate %	p value	Note
Harvey*[82]	1994	73	80%	100%	ND	1st or 2nd episode
Andrivet*[83]	1995	61	67%	93%	0.01	Late aspiration
Noppen[84]	2002	60	59%	64%	0.9	1st episode
Ayed†[85]	2006	137	62%	68%	0.4	1st episode
Ho$^{\Delta}$[86]	2011	48	48%$^{\Delta}$	72%$^{\Delta}$	ND	1st episode
Parlak$^{\delta}$ [87]	2012	56	68%	81%	0.3	1st episode
Thelle$^{\mu}$[88]	2017	77	74%	38%	0.001	1st or 2nd episode

*Excluded from original (2007) Cochrane review (as included 2nd episode SP). † Both arms placed on suction initially. Δ % discharged home after initial Rx (chest drain with Heimlich valve). δ Included traumatic (22/56). μ PSP data only. ND: not done

In 1994, Harvey *et al* randomised 73 patients to either NA or chest drain[82]. NA was performed manually up to a maximum permitted volume of aspirated air of 3.0L, with "success" defined as not requiring intercostal chest tube insertion. 28 (80%) of 35 patients were treated with NA alone, although five patients did require two aspirations. Little detail was provided on the 38 patients randomised to chest tube, other than they were managed according to "usual practice". However, the chest tube group had a longer hospital stay and were more likely to have a pleurectomy (surgery) within 1 year[82]. The explanation for why treatment with chest tube rather than NA would lead to greater need for surgery is not clear.

In 1995, Andrivet *et al* performed a study comprising an RCT of chest tube insertion vs "delayed" NA (61 patients), followed by a series of another 35 patients treated with immediate NA [83]. The patients were mainly PSP (with 8 patients were secondary, but results were not presented separately). In this study, all patients were connected to negative pressure (i.e. "suction"). The 28 patients randomised to the chest tube arm were treated immediately after being randomised, and placed on suction (-20 to -25 cmH_20). NA was performed using a 16 of 18 gauge plastic catheter, which was then connected to a one-bottle water seal vacuum system (-10 to -15 cmH_2O) until cessation of bubbling or for a maximum of 30mins. However, the NA was only performed immediately if the patients were showing "signs of poor clinical tolerance". This occurred in 7 of 33 patients. The remaining 26 patients had "delayed NA" after 3 days of bed rest. The authors state the "arbitrary delay of 72 hours was chosen to facilitate healing of the parenchymal tear", without any evidence as to why a lack of re-inflation would be helpful in healing the lung. Indeed, the "initial success" of lung re-expansion (>=80%) with no recurrence in 24 hours occurred in 66.7%

(22/33) of the delayed NA group, which was identical to the success rate in the subsequent series of immediate NA (68.6%, 24/35) [83]. The authors' rationale of waiting 3 days with the lung "down" to promote for the lung to healing before NA, did not provide any additional benefit to initial success. The success rate in the chest tube arm was 92.9% (26/28)[83]. However, the criteria for failure of chest tube was persistent bubbling after 10 days or short-term recurrence requiring insertion of a second chest tube; which is much longer than most clinicians (and the current BTS guidelines[4]) would suggest is appropriate to wait. Therefore, the success rate of chest tube at 3-4 days is likely to be lower than 92.9% (data at early time points were not presented by the authors).

These two studies[82, 83] were not included in the first Cochrane review of this topic as they failed to exclude patients with prior pneumothorax[89], which was disappointing as patients, at least initially, are managed in same way, regardless of prior pneumothorax episode. Patients with one or more recurrence episodes can be referred to surgery for consideration of recurrence prevention, but this can be planned electively after treatment for their current episode. Patients with non-resolving pneumothorax (see Treatment Failure section below) can be referred for surgery as an in-patient, regardless of whether this was the patients first or second episode. As a result of these excluded trials, the Cochrane review published in 2007, only included one RCT, limiting its evidence base[89]. This RCT was conducted by Noppen *et al* in 2002[84]. Sixty patients with first episode of PSP were randomised to NA or chest tube. NA was performed until resistance was felt and air was no longer aspirated. Patients could be aspirated twice if required. Failure of NA was defined as any aspiration of ≥4.0L (without signs of re-expansion) or if second aspiration attempt was unsuccessful, at which point a chest tube was inserted. In contrast to 10 day criteria for chest tube failure in

the study by Andrivet[83], Noppen *et al* defined success for chest tube drainage as complete lung expansion, absence of air leakage, and chest drain removal within 72 hours after tube placement[84]. With these more realistic definitions of success: the NA and chest tube arms were equally effective: 16 out of 27 (59.3%) in NA group, and 21 out of 33 (63.6%) in chest tube group[84].

Ayed *et al* published the largest RCT of initial management of PSP to date in 2006[85]. 137 patients with first episode of PSP were randomised to NA or chest tube insertion as initial management. They used sensible, practical definitions of immediate success. For NA group: complete, or nearly complete, lung expansion following aspiration; and for the chest tube group: absence of air leak, complete lung expansion and chest tube removal within 3 days of the insertion of the tube (as per Noppen *et al*[84]). However, both groups were placed on suction, either via chest tube (-20 cmH_20) or NA catheter (-10 to -15 cmH_20) as in the trial by Andrivet et al[83]. This is not advised in the current BTS guidance and has no evidence base at present. Nevertheless, the reported immediate success rates were similar in both groups; 61.5% (40/65) and 68.1% (49/72) patients for NA and chest tube, respectively[85]. These results are also similar to those reported by Noppen *et al*, when suction was not routinely used. Therefore, it is not clear if there is any benefit in the use of immediate suction in initial treatment of PSP.

In 2017, Carson-Chahhoud *et al* updated the Cochrane review[90], this time including Harvey[82], Andrivet[83], and Ayed[85] alongside Noppen[84], with the addition of a trial by Parlak[87], which also included traumatic pneumothoraces, as well as spontaneous. The authors concluded that immediate success rates were higher in the chest tube group than the NA group[90]. However, it should be noted that there was heterogeneity in the

definitions of immediate success. Recurrence rates were no different between the groups. Hospital stay was shorter in the NA group (see below) as were the complication rates for NA (in a narrative synthesis) compared to the chest tube group[90].

More recently, Thelle *et al* conducted another similar RCT enrolling both PSP (n=79) and SSP (n=48) patients[88]. A maximum permitted volume of air aspirated at each attempt was 3.5L. Immediate success in the NA arm was defined as a pneumothorax size less than 20% and no reported breathlessness (after up to two NA), followed by persistent stable condition on subsequent chest radiographs. In the chest tube group, immediate success was defined as cessation of bubbling with no visible pneumothorax or a pneumothorax size less than 10%, and a stable clinical condition (for a minimum of 12 h prior to chest tube removal) within 72 hours of initial treatment. This corresponds to the definition in the studies by Ayed[85] and Noppen[84]. Overall, they found NA to be more effective than chest tube drainage for initial treatment success (68.8% vs 31.8%), although 37.5% (24/36) required a second aspiration [88]. NA remained significantly different when analysing PSP (73.8% vs 37.8%) and SSP separately (59.1% vs 23.1%). This is the first study to specifically include sufficient numbers of patients with SSP to report the results separately. The authors suggest the guidelines should be changed to treat SSP in the same way as PSP (i.e. with NA initially)[88]. However, it should be noted the low success rate of the chest tube drainage in all patient groups (31.8%). The definition of immediate success was reportedly identical to that of previous studies, whose corresponding rates were 68.1%[85] and 63.6%[84]. The reason for this discrepancy is unclear. Disappointingly the authors do not comment on this inconsistency with published data, but do report that the “success at one-week” was the same in both treatment arms, as per previous studies.

Time to change the BTS guidelines?

Despite the most recent Cochrane review concluding higher immediate success rates in the chest tube group compared to NA, this recommendation should be viewed with caution[90], and is not convincing enough to change the current BTS guidelines of attempted NA first. There were significant differences in the definitions of immediate success across the studies. Early failure rates and recurrence rates were not different between the groups, and hospital stay was shorter for the patients in the NA groups. In addition, the recent study by Thelle *et al* again reports a high success rate for patients treated initially with NA[88].

1.6.4. Duration of hospital stay

Patients being treated for PSP who require a chest drain are managed as inpatients in hospital, attached to an underwater seal, waiting for the lung to heal. They are reviewed daily to assess for resolution: lung re-expansion with chest radiograph (CXR) and no on-going air leak (by looking for a lack of bubbling through the underwater seal). Therefore, length of stay is a surrogate for the natural resolution history of the pneumothorax.

Good quality large-scale prospective data on the duration of hospital stay for patients with PSP is lacking. Prospective data from the RCTs (of NA vs chest tube) are shown in Table 1.2. A synthesis of these data shows an overall mean hospital stay for those patients initially randomised to NA was 2.7 days compared to 4.1 days for those randomised to chest tube (difference 1.3 days). However, the length of stay for the NA group in the study by Andrivet *et al* was very long as a result of the policy of delayed aspiration[83]. Excluding that study provides mean hospital stays of 2.0 and 3.7 days, respectively (difference 1.7 days). The study by Ho *et al* was not included in this hospital stay analysis as it was designed as an ambulatory management study with the chest tube group having small bore drain with

Heimlich valve attached to allow discharge home, rather than staying in hospital (as would be standard care)[86]. Although the authors report number of patients requiring re-admission, they did not provide overall hospital stay data.

Table 1.2: Randomised controlled trials of needle aspiration vs chest drain: Mean hospital stay (days)

Author	Year	n	Aspiration stay (days)	Chest drain stay (days)	p value	Note
Harvey[82]	1994	73	3.2	5.3	ND	1st or 2nd episode
Andrivet[83]	1995	61	7.0	7.0	0.01	Late aspiration
Noppen[84]	2002	60	3.4	4.5	0.9	1st episode
Ayed†[85]	2006	137	1.9	4.0	0.4	1st episode
Parlak$^{\delta}$ [87]	2012	56	2.4	4.4	0.3	1st episode
Thelle$^{\mu}$[88]	2017	79	2.2	4.1	0.001	1st or 2nd episode

† Both arms placed on suction initially. Δ All discharged home after initial Rx (chest drain with Heimlich valve). δ Included traumatic (22/56). µ PSP data only. ND: not done

The only large scale epidemiological study which provides information on hospital stay was the French study by Bobbio *et al*[72]. From a dataset of nearly 60,000 hospital admissions with pneumothorax the average duration of hospital stay was reported by sex, age group and pneumothorax type (PSP, SSP), using a combination of means and medians, interchangeably. The mean was 7.0 days (SD 9.0): slightly longer duration for women (7.2 days, SD 9.7) than men (6.9 days, SD 8.8) [72]. The median hospital stay was significantly greater for SSP, 12.2 days (IQR 14.5) than PSP 6.1 days (IQR 7.2). Stay was longer for the

older patients group (50-65 years) compared to the younger group (18-30 years), but this may be confounded by the fact that a larger proportion of older patients were classified as SSP (35% men and 23% women) compared to the younger group (6% for both sexes).

The burden of in patient admission for PSP is significant. The data from the RCTs suggest a mean stay of between 2 and 4 days, depending on initial treatment option, which will include those never admitted to hospital. Epidemiological data from France, including only those patients admitted to hospital, suggests that PSP patients stay for 6 days.

1.6.5. Treatment failure and surgical referral

"Treatment failure" in terms of pneumothorax can be divided into three components:

1) initial failure of NA to successfully re-inflate the lung and for the lung to remain inflated (as discussed above)
2) failure of subsequent chest tube to re-inflate the lung
3) prolonged air leak (PAL)

Treatment failure will inevitably lead to non-optimal care, with prolonged hospitalisation and/or additional invasive procedures. Although a number of studies have attempted to stratify patients (e.g. by age, co-morbidities or size of pneumothorax), there currently exists no robust method of determining those at high risk of initial failure. These studies will be discussed in detail in Chapter 5 alongside the novel use of digital airflow measurement as a tool to predict treatment failure (Predicting outcomes – Air leak).

Failure of lung re-inflation

Failure of the lung to re-inflate with a patent chest tube in place can be due to two scenarios: either there is such a large air leak (from a hole in the visceral pleura), that the air

in the pleural space is not evacuated fast enough by the presence of the chest drain to allow the lung to passively re-expand; or there is visceral pleural thickening (without air leak) that is "trapping" the lung, not allowing re-expansion. Visceral pleural thickening would be unusual in patients with PSP, but if present will require surgical intervention.

Prolonged air leak (PAL)

In the presence of a very large air leak some physicians may also advocate replacing a small-bore tube with a large-bore one to allow a greater total flow rate of air, or placing using high-volume low-pressure suction attached to the chest tube. The larger chest tube allows greater flow rate as it is proportional to the fifth power of the radius of the tube, as described by the Fanning equation: $v = \pi^2 r^5 P/fl$ (v: flow, r: radius, l: length, P: pressure, and f: friction factor). The theory in both cases being that the air can be removed from the pleural cavity at a rate exceeding the egress of air through the breach in the visceral pleura, thereby re-inflating the lung. This theory would seem rational if there is clear evidence of insufficient drainage of air (i.e. subcutaneous emphysema, increasing pneumothorax size, major bubbling or worsening clinical condition). However, there is no good trial evidence to support this theory, and is not advocated in the use of larger drains or suction in stable patients with PAL.

Lung healing

In most cases, the visceral air leak will stop when the lung "heals" itself. There exist two theories as to how to best promote lung healing: Firstly, that the lung may heal more quickly if the lung is not re-inflated – perhaps due to reduced stretch on the visceral pleura. Indeed this was the rationale behind the "delayed" aspiration group in the study by Andrivet *et al*,

who waited 3 days with the lung “down” to promote for the lung to healing before NA. However, their findings did not support this theory, as initial success rates in the delayed group were identical to those in the group aspirated immediately[83]. Conversely, some physicians believe that by fully re-inflating the lung, healing of visceral air leak may be promoted by apposition of the visceral and parietal pleural layers, but this has not been proven either.

Use of suction

Suction is application of negative pressure to the intra-pleural space via the chest tube. Its routine use is not recommended by the current guidelines[4]. However, suction is advocated by some physicians in cases of non-resolution of pneumothorax (i.e. PAL and/or failure of lung re-inflation). In this situation applying high volume (up to 15-20 L/min) and low pressure suction (to prevent fast lung re-expansion and injury) is suggested[4]. The theory behind the use of suction is that it helps remove air in the pleural cavity a rate faster than it leaks through the visceral pleural breach, thus facilitating pneumothorax resolution.

Despite this guidance, there is no evidence for the use of suction. There have been two RCTs: the first comprised of 53 patients (23 PSP and 30 SSP) randomised to either suction (initially -8cmH_20, up to -20cmH_20). or standard underwater seal[91]. They found no difference in success rates (defined as re-expansion by 10 days and no re-collapse after chest rube removal): 57% in suction and 50% in underwater seal groups[91]. The second was a small study which randomised 29 patients (17 spontaneous and 12 iatrogenic pneumothoraces) to either: -20cmH_20 suction, -10cmH_20 suction or underwater seal (no suction)[92]. After 48 hours, the patients were reassessed and chest tubes removed if the lung had re-expanded and there was no evidence of air leak. Although the numbers of spontaneous pneumothorax

patients in each group were small, there was no significant difference in success at 48hours: 57% (95%CI 18-90%) with -20cmH_20, 73% (95%CI 39-94%) with -10cmH_20, and 45% (95%CI 17-77%) with no suction. However, the small study size meant that it was grossly underpowered to detect a difference.

Furthermore, the application of suction is not without risk: specifically that of precipitating re-expansion pulmonary oedema or exacerbating the hole in the visceral pleura, so its use should be carefully considered. Further studies are required to set more defined and reliable criteria for using suction, particularly for patients with PAL

Duration of attempted drainage

There is some data to suggest that if one waits long enough, most PSP patients with PAL will eventually resolve. A study by Chee *et al* found that 100% of patients with PSP with PAL for >7 days had resolved by 14 days[93]. Therefore, any decision to define failure has to be a balance between allowing time for the visceral pleura to heal (and PAL to cease spontaneously) and the practical limitations of patients remaining in hospital for up to 14 days.

Current BTS guidelines suggest that (if NA fails) drainage with chest tube should be attempted for at least 3 days, and a thoracic surgical opinion should be sought “early” at 3-5 days[4]. Presumably this surgical opinion recommendation is to make plans for possible intervention as they state that indications for surgery are PAL (despite 5-7 days of chest tube drainage) or failure of lung re-expansion[4]. The authors of the guidelines acknowledge that there is no evidence on which to base the ideal timing for thoracic surgical intervention in cases of PAL and that the cut-off point of 5 days is arbitrary.

In the clinical trials of initial management (NA vs chest tube), the rates of PAL resolution (and hence referral for surgery) vary. Many trials reported indication for surgical treatment was persistent air leak for "more than 7 days". Noppen *et al* found that 5 (15.2%) of 33 in the chest drain group, and 2 (7.4%) of 27 in the aspiration group, required thoracoscopy or thoracotomy for PAL [84]. Likewise, Ayed *et al* referred patients for surgery if PAL lasted 7 days: this occurred in 9 (12.5%) of 72 in chest tube group and 7 (10.8%) of 65 in aspiration group[85]. Both Thelle and Andrivet did not report their surgical rate during initial pneumothorax episode[83, 88]. Although, Thelle *et al* reported "one-week success" of discharge from hospital within 7 days, suggesting that even in the PSP patients a high failure rate of 21.6% in chest tube group and 14.3% in the NA group[88]. This variation may in part be due to differences in practice over time and across different countries. However, there is also likely to be inter-clinician discrepancy based on their experience and belief, given a lack of clear evidence-based guidance.

1.6.6. Surgical treatment options

Surgical treatment for PAL is typically undertaken by VATS, which has replaced open thoracotomy as the approach of choice. The aims of surgery are to identify and seal any areas of air leakage, and to resect any visible blebs or bullae on the visceral pleura. As discussed above, air leakage may well occur from areas of ELC or pleural porosity close to the surface of the visceral pleura. Therefore, resection of macroscopically abnormal areas of the visceral pleura needs to be combined with a method of pleurodesis. This will also reduce future recurrence risk. Pleurodesis can be performed by pleural abrasion, pleurectomy or chemical pleurodesis.

Elective surgery for recurrence prevention can be considered for patients deemed at high risk of recurrence. At present, international guidelines recommend elective recurrence prevention after a second ipsilateral (or first contralateral) occurrence of pneumothorax; unless their profession means that the patient would be an increased risk if a recurrence event occurred (e.g. pilot or deep-sea diver), who may be offered surgery after their first episode[4, 78, 80]. The rationale for these criteria is that having had a second pneumothorax episode, the patient is then at higher risk of subsequent episodes. Recurrence prevention is not deemed suitable for patients at their first episode because the majority of these patients would not recur and so would be operating on them unnecessarily.

As well as being a vital adjunct to surgical resection, chemical pleurodesis can be performed in patients who are not fit for surgery by instillation via the chest tube.

1.6.7. Choice of Chemical pleurodesis agents

There exist numerous agents which have been used as pleurodesis agents. However, there are few direct comparative studies and there is no consensus as the most efficacious agent. The BTS make reference to tetracycline as the previous first line agent for PSP and SSP, but with decline in usage through difficulties in supply in favour of graded talc, with passing mention of minocycline and doxycycline efficacy in animal models[4].

Historically there have been numerous different agents used intrapleurally to induce pleurodesis in patients with recurrent symptomatic malignant pleural effusions as well as in pneumothorax. The principle mechanism of all the agents is to stimulate an inflammatory response within the pleural cavity to promote artificial symphysis of the pleural layers. Each agent induces pleurodesis in different ways. Additionally, choice of agent differs between countries, at least in part driven by limited availability in some parts of the world.

1.6.8. Mechanism of action

Talc

Talc is hydrated magnesium silicate with varying amounts of calcium, aluminium and iron, according to the origin of the formulation. Introduction of talc into the pleural cavity causes an acute pleural injury. Original animal models involving histological analysis of the pleura at between 2 and 16 weeks post infiltration of talc, showed pleural thickening with fibroblast proliferation, macrophage infiltration and foreign body reaction[94].

Tetracycline/Minocycline

Tetracycline and its derivatives (minocycline and doxycycline) are principally antibiotic agents with broad spectrum of anti-microbial activity. Upon instillation into the pleural cavity they induce an inflammatory reaction in the pleural surfaces. The pathophysiology is thought to include stimulation of fibroblast proliferation, mesothelial sloughing, pleural fluid clotting, and inhibition of fibrinolysis, all contributing to fibrosis of the pleural surfaces[95].

Iodopovidone

The commercial medicated form of talc is not only expensive but is also difficult to obtain in India. Therefore, Iodopovidone is often the chemical pleurodesis agent of choice. The precise mode of action of iodopovidone is not clear, but it is thought to be related to its low pH (2.97), or to the oxidative and cytotoxic properties of iodine, producing an inflammatory response[96].

Blood

Historically the instillation of blood into the pleural cavity is performed with the aim of a blood "patch" for patients with on-going air leak. The theory being that coagulated blood seals the site of the air leak. Whether the clotted blood has an additional pleurodesis effect is still the subject of some debate[97]. It seems likely that blood is primarily sealing the air leak, given that, when successful air leak appears to cease within a few days, a much shorter time period than that for pleurodesis to occur. Furthermore, in an animal model, gross inspection of rabbit pleura revealed no difference in degree of pleurodesis between blood instillation and chest tube control when assessed after 30 days[98].

Silver nitrate

Silver nitrate is an oxidant which can have a caustic effect on tissue as high concentration. Intrapleural injection of silver nitrate solution in an animal model found a greater degree of inflammation and pleural fibrosis than talc[99]. In the same study, silver nitrate also produced more collagen at the pleural surface [99].

In this thesis, a systematic review and meta-analysis of the literature regarding chemical pleurodesis was conducted to determine the relative effect of different agents on recurrence rates (see Chapter 6).

1.7. Summary

Epidemiological studies of spontaneous pneumothorax to date are either old single centre studies, or larger national database studies which only cover 4-year periods, limiting time-trend analysis. The last study in England used data from over 20 years ago.

- Chapter 2 in this thesis will bring this up to date, using the HES datasets from 1968 to 2013, to provide data on trends in incidence in England over two generations. In addition, record-linked data available from 1999-2013, enables detailed analysis of comorbid diagnoses to more accurately distinguish PSP from SSP and generate data on risk of recurrence.

The idea that PSP occurs in patients with normal lungs, as described in some textbooks, is no longer correct. Abnormalities have been identified macroscopically, microscopically, biochemically and genetically. Yet the true histopathological cause and time course is not understood. Macroscopic changes of ELC are readily identified in patients with PSP, but also in control subjects (without pneumothorax), and, as yet, do not clearly predict recurrence of another pneumothorax episode. Microscopic findings of respiratory bronchiolitis are common on surgical resection specimens, but are also found in other patients who smoke. There is evidence of an absence of mesothelial layers on some smaller ELCs (blebs); whereas on other larger bulla, the mesothelial cells (although thin) remain intact. In additional, pleural porosity has been identified as a potential site of visceral leak, which does not necessarily co-locate with ELCs.

This thesis will examine two new methodologies to examine the lungs of patients with PSP. ^{129}Xe-enhanced MRI scanning is a non-ionising imaging modality which can assess ventilation and diffusion.

- Chapter 3 will describe the use of ^{129}Xe MRI for the first time in patients with pneumothorax. The results will be discussed in comparison with those from patients with COPD and healthy volunteers.

Functional assessment of the lungs traditionally relies on PFTs which are global measures of lung function, and are not good at identifying subtle abnormalities or inhomogeneity.

- Chapter 4 describes the use of a novel methodology, developed in Oxford, combining a highly precise Molecular Flow Sensor with mathematical model of inhomogeneity. Estimates of lung inhomogeneity will be determined for the first time in PSP patients, and compared with patients with COPD and healthy volunteers (young and old).

Patients with spontaneous pneumothorax are treated as per a generic, non-personalised, management paradigm. There is no model as yet to stratify patients by risk into those who will respond to treatment (i.e. the lung re-expand and air leak cease) and those that fail. Treatment failure will inevitably lead to non-optimal care, with prolonged hospitalisation and/or additional invasive procedures.

- Chapter 5 will investigate whether digital airflow measurement, early in the treatment pathway, can be a useful tool to predict treatment failure.

Patients failing treatment will typically be referred for surgical intervention, which includes apical resection of the lung and application of a chemical pleurodesis agent, as will those

patients presenting with recurrent pneumothoraces. Those not fit for surgery can have chemical pleurodesis via the chest tube.

- Chapter 6 is a systematic review and meta-analysis of the literature regarding chemical pleurodesis to determine the relative effect of different agents on recurrence rates.

Patients who present with their first pneumothorax are currently not considered for recurrence prevention. However, a system to predict likelihood of recurrence could allow a more personalised approach and allow informed discussion between clinician and patient. A number of studies have investigated whether use of CT scanning to develop a "scoring" system of number, size and distribution of cystic air spaces, but this remains controversial.

- Chapter 7 describes a new CT scoring system based upon CT findings and their associate with pneumothorax recurrence rates.

Work in this thesis will bring to light new understanding about the epidemiology of pneumothorax, imaging and functional abnormalities, and methods of predicting short term treatment failure (using airflow measurements) and long term recurrence (by choice of chemical pleurodesis agent, and by CT findings).

2. Epidemiology of Spontaneous Pneumothorax in England: Record-linked database studies, 1968-2013

2.1. Background

Estimates of the incidence of spontaneous pneumothorax are based on studies which are often small, many years old and from single centres[69, 70], and two national databases each covering 4 years[71, 72]. These have reported an overall incidence of SP of 17-24 per 100,000 population per annum for men and 1-6 per 100,000 for women[69-72].

Recurrence estimates for spontaneous pneumothorax are based upon mostly retrospective case series data, which report a recurrence risk anywhere between 21 and 54% within 1-2 years[26, 76, 100-104].

2.2. Aims and Hypothesis

The aim of this study was to determine the contemporary and historical incidence of spontaneous pneumothorax in England, and its recurrence, using longstanding datasets of hospital records.

HES and related datasets were available from 1968 to 2013, providing data on trends in incidence in England over two generations – far greater than any previous epidemiological study. Record-linked data were available from 1999-2013, enabling detailed analysis of comorbid diagnoses to more accurately distinguish PSP from SSP, and provide reliable data on risk of recurrence.

2.3. Methods

2.3.1. Data sources

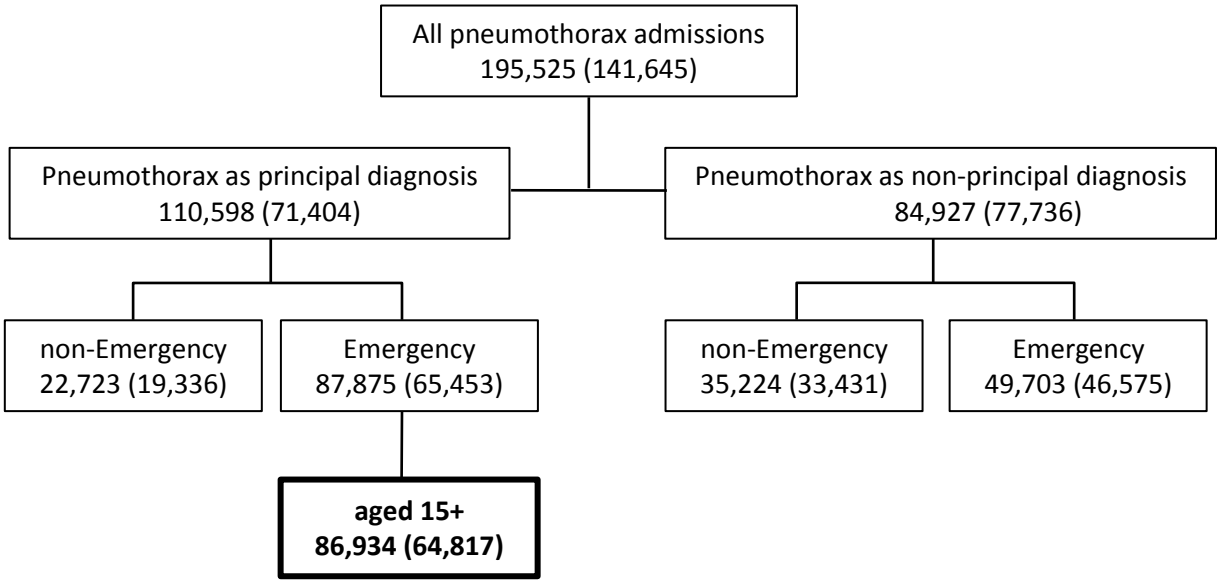
The English national dataset comprised records from the Hospital In-Patient Enquiry (HIPE) 1968-1985 and HES 1990-2013. HIPE was a random 1 in 10 sample of all hospital discharge records in England, which were collected as statistical abstracts by all English hospitals and collated nationally by the National Office of Population Censuses and Surveys from 1968 to 1985. This sample was intended to be representative of NHS hospital care throughout England. Hospital statistics were not collected nationally between 1986 and 1989. Since 1990, statistical abstracts of every day case and inpatient admission from every National Health Service (NHS) hospital in England have been collected in the form of HES. The proportion of missing data in both datasets is very low (0.2%). Migration data was not available.

The English national data were compared with regional data from the Oxford Record Linkage Study (ORLS) 1968-2013. The ORLS dataset comprises statistical abstracts of all NHS day case and inpatient admissions occurring within what was formerly the Oxford NHS regional health authority area.

In all datasets, each discharge record contains a field for the principal reason for the admission (the "primary diagnosis"), along with other secondary/subsidiary diagnoses, coded using the International Classification of Diseases (ICD). The ICD codes used to identify spontaneous pneumothorax from the discharge records were ICD10 J93 (1995-current), ICD9 512 (1979-1995) and ICD8 512 (1968-1979). Pneumothorax admissions were divided according to whether the pneumothorax was recorded as the primary or non-primary diagnosis, and according to whether the episode was an emergency or non-emergency

admission. All data analysis was based on emergency admissions and where pneumothorax was the primary diagnosis on the hospital record, unless otherwise specified (see Figure 2.1).

Figure 2.1: Flowchart to illustrate how the 86,934 pneumothorax admissions in English HES 1999-2013 were derived for analysis; numbers of unique people in brackets (derivations for other datasets not shown)



2.3.2. Distinguishing PSP and SSP

The ICD does not distinguish between PSP and SSP. Therefore, a methodology was established to attempt to define SSP in the most robust, but manageable way. The most straightforward method would be to use the other ICD codes listed as secondary diagnoses on that admission (where pneumothorax was the primary diagnosis). However, previous experience with hospital coding and the HES datasets suggested that the coding of comorbidities may not always been 100% accurate: for example, there may be chronic lung diseases diagnosed in the past, which were not listed on that particular admission. This could significantly underestimate the proportion of SSP. Therefore, it seemed prudent to utilise the record-linked dataset to identify diagnoses of chronic respiratory diseases listed on any previous hospital admission prior to the index pneumothorax admission.

In addition, the pneumothorax episode itself may have triggered further investigations into underlying lung disease, which may not have been formally diagnosed before. Therefore, if a diagnosis of chronic lung disease was made within 12 months of the admission, the patient was also defined as being SSP. The rationale being that chronic disease, such as COPD or pulmonary fibrosis would not have developed de novo within 12 months, and so was likely to be present at the time of the pneumothorax.

Therefore, SSP was defined as the presence of any chronic lung disease (defined as any one of the 73 ICD codes listed in Table 2.1) coded either on the same pneumothorax record or, using record linkage, on any known previous hospital record or any record within the next 12 months. PSP was defined simply as any SP admission that was not SSP.

Although this model of distinguishing SSP and PSP is not ideal, for example the dataset does not provide information on smoking history or functional tests (such as spirometry), it provides a more robust method of capturing underlying lung disease than any study have attempted previously. Gupta *et al* simply divided individuals into two broad age groups (15-34 and ≥55years old)[71]. Bobbio *et al* did not describe how they defined SSP, but presumably they used the other ICD codes on the same admission[72].

Table 2.1: List of ICD-10 codes for chronic lung disease used to define Secondary Spontaneous Pneumothorax

Group	ICD-10 codes
Tuberculosis	A150, A151, A152, A153, A155, A156, A157, A158, A159, A160, A161, A162, A164, A165, A168, A169, B909
Malignancy	C340, C341, C342, C343, C348, C349, C780, D020, D022, D023, D143, D381, D382, Z851, Z852
Sarcoidosis	D860, D861, D862, D863, D868, D869
Cystic Fibrosis	E840, E841, E848, E849
COPD/Emphysema	J40X, J410, J411, J42X, J430, J431, J432, J438, J439, J440, J441, J448, J449
Asthma	J450, J451, J458, J459, J47X
Interstitial lung disease	J700, J701, J703, J704, J708, J709, J840, J841, J848, J849, J961, J991, J998

2.3.3. Incidence

The 2012 rates were considered to be the most reliable single year estimates, as they are the most contemporary and take into account the longest patient-history of prior recorded comorbidity, while also allowing for inspection of records occurring up to 12 months subsequently. The data was split by age, sex, and pneumothorax type (PSP vs SSP) as defined above. Historical hospitalisation rates per 100,000 population aged 15 and over were calculated for each year going back to 1968 in England and ORLS. Population counts were obtained from the Office for National Statistics (ONS). Age-specific rates were calculated in 5-year age groups. Rates for broader age-groups (15-34, 35-49, 50-64, 65+) and all-ages combined were directly standardised to the European Standard Population 1976. Analyses using record-linkage were undertaken to identify multiple pneumothorax records per person. Record-linkage enabled distinction between “admission-based” annual rates (where every day case or inpatient record for pneumothorax was counted, regardless of how many pneumothorax records each individual had) and “person-based” annual rates (where only

one pneumothorax record per individual was counted and allocated to the first known year of occurrence, regardless of how many subsequent admissions that individual had over the whole study period). Admission-based rates indicate whether hospital admissions for pneumothorax, which include both hospital transfers and re-admissions for the same disease event, are increasing/decreasing over time; person-based rates indicate whether pneumothorax is affecting more or fewer individuals in any one year compared with another. Within the ORLS, the data were linkable throughout the period of coverage. Nationally, the data only became linkable from 1999 onwards. Details of the record-linkage methods are reported elsewhere[105]. Where visual inspection of the annual rates indicated a linear (or curvilinear) trend, annual percentage change (APC) was calculated with associated 95% confidence intervals by fitting a regression model to the logarithms of the annual rates assuming Poisson variance.

2.3.4. Recurrence

Episode-based (non-linked) data does not allow identification of repeated admissions for the same person. Therefore, the national record-linked data (1999-2013) were used for recurrence analysis. The probability of a second pneumothorax was determined at various time-points: 30 days, 90 days, one year and five years by age and sex. Recurrence probabilities were calculated using a cumulative time-to-failure analysis, censoring individuals for death using mortality records obtained from the ONS. Entry date was defined for each individual as the date of discharge on their first known pneumothorax record that did not indicate an inter-hospital transfer on discharge. 'Failure date' was defined as the date of admission for the earliest known recurrence event. A recurrence event was defined as a subsequent admission where spontaneous pneumothorax was again recorded as the

principal diagnosis and where the patient was admitted as an emergency. Multivariable Cox proportional hazards models were developed to assess the independent effects of sex, age group, SP type and calendar period of first pneumothorax admission on the risk of recurrence within specified follow-up time intervals: <30 days, 30-89 days, 90-364 days, and 365-1825 days.

The linked datasets were built by the Unit of Health-Care Epidemiology, University of Oxford, with ethical approval for a multi-purpose programme of work from the Central and South Bristol Multi-Centre Research Ethics Committee (04/Q2006/176).

2.4. Results

During the periods of HIPE (1968-1985, 10% national sample) and unlinked HES (1990-1998), there were 7,178 and 48,213 eligible pneumothorax admissions respectively. During the period of record-linked HES (1999-2013), there were 86,934 eligible pneumothorax admissions pertaining to 64,817 individuals. Figure 2.1 demonstrates the derivation of these data for the record-linked HES period. In the ORLS region 1968-2013, there were 9,063 eligible pneumothorax admissions pertaining to 6,954 individuals.

2.4.1. Annual incidence

In 2012, there were 6,339 eligible pneumothorax admissions in England pertaining to 4,445 patients aged 15 and over in a corresponding total population of 44,008,900 individuals, giving an admission-based rate of 14.4 per 100,000 population (95% CI 14.1-14.8) and a person-based rate of 10.0 per 100,000 population (95% CI 9.8-10.4). Pneumothorax admissions were more common among males than females. There was a bimodal age-

distribution with a first peak aged 15-34 years and an increasing incidence with age beyond 60 years (Figure 2.2) in both males and females. Overall admission-based rate was 21.7 (95%CI 21.1-22.3) for men and 7.5 (95%CI 7.1-7.8) for women per 100,000 respective populations aged 15 and over (Table 2.2).

Figure 2.2: Number of spontaneous pneumothorax admissions per 100,000 age-specific population in England, 2012

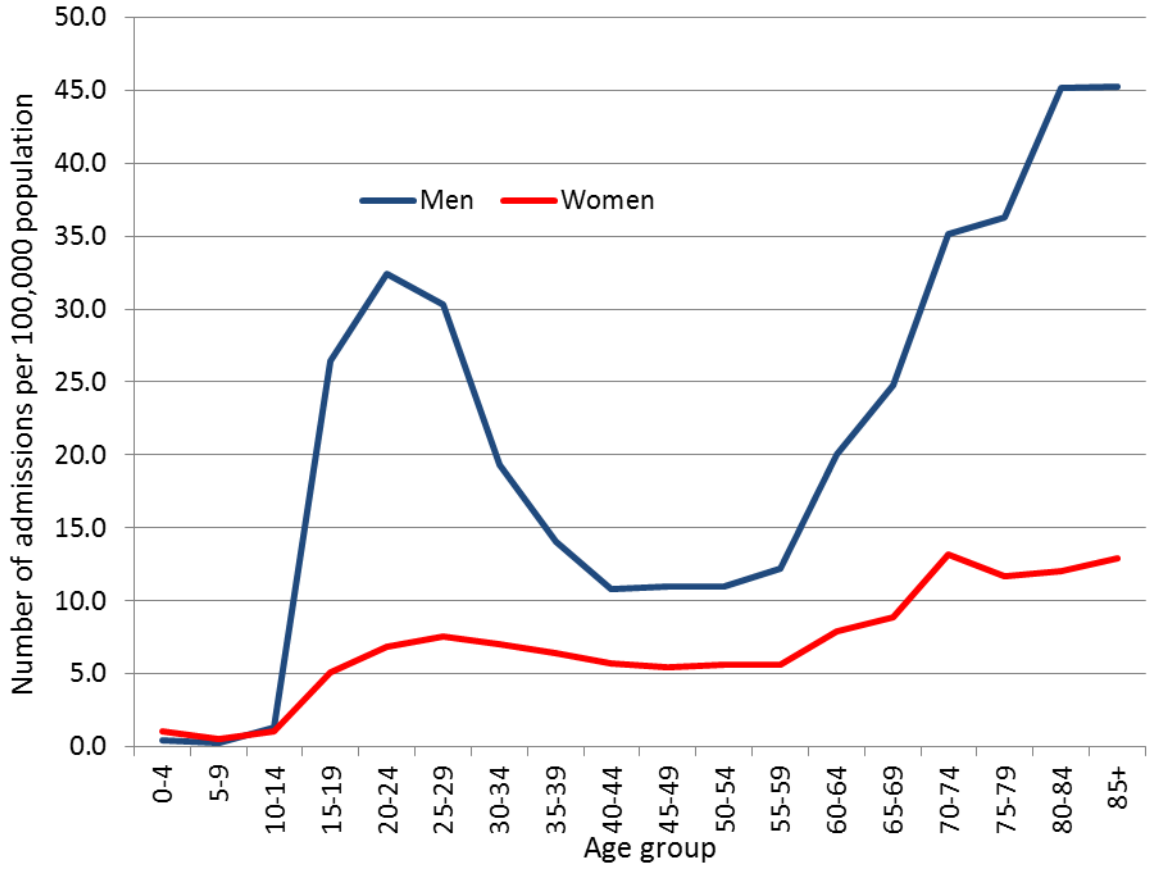


Table 2.2: Numbers of pneumothorax admissions in 2012, and rates per 100,000 population, by age group and sex

	Overall SP		PSP		SSP		
	Number of admissions	**Rate per 100,000 pop (95% CI)**	**Number of admissions**	**Rate per 100,000 pop (95% CI)**	**Number of admissions**	**Rate per 100,000 pop (95% CI)**	**Population, 2012**
Men, by age group							
15-34	1,941	27.2 (26.0-28.4)	1,185	16.6 (15.7-17.6)	756	10.6 (9.8-11.4)	7,142,600
35-49	658	11.9 (11.0-12.8)	341	6.1 (5.5-6.8)	317	5.7 (5.1-6.4)	5,548,000
50-64	672	14.2 (13.1-15.3)	183	3.9 (3.3-4.5)	489	10.3 (9.4-11.3)	4,734,500
65+	1,388	34.2 (32.5-36.1)	246	6.1 (5.3-6.9)	1,142	28.2 (26.6-29.9)	4,053,100
All ages 15+	**4,659**	**21.7 (21.1-22.3)**	**1,955**	**9.1 (8.7-9.5)**	**2,704**	**12.6 (12.1-13.1)**	**21,478,200**
Women, by age group							
15-34	471	6.7 (6.1-7.3)	279	4.0 (3.5-4.5)	192	2.7 (2.4-3.1)	7,032,100
35-49	329	5.8 (5.2-6.5)	151	2.7 (2.3-3.1)	178	3.2 (2.7-3.7)	5,639,600
50-64	308	6.3 (5.7-7.1)	81	1.7 (1.3-2.1)	227	4.7 (4.1-5.3)	4,855,600
65+	572	11.4 (10.5-12.4)	131	2.6 (2.2-3.1)	441	8.8 (8.0-9.7)	5,003,400
All ages 15+	**1,680**	**7.5 (7.1-7.8)**	**642**	**2.8 (2.6-3.1)**	**1,038**	**4.6 (4.3-4.9)**	**22,530,700**

Figure 2.3A shows a rise in the rate of PSP in the over 80 year age group. By definition, these patients had no chronic respiratory condition coded before their first pneumothorax event or up to one year after. Further investigation of this group revealed that other comorbidities were very common; 88% had a diagnosis of cardiovascular disease coded elsewhere on their records.

From 1968 to 2013, age-standardised admission-based rates in England (Figure 2.4) increased significantly both for men (APC 0.79, 95%CI 0.66-0.92, p<0.001) and women (APC 1.54, 95%CI 1.25-1.84, p<0.001). Analysis of the record-linked Oxfordshire data from 1968 to 2013, where multiple admissions per person were excluded, demonstrated a small but significant increase in the rate of *new* people admitted for pneumothorax across the whole time period for women (APC 1.22, 95%CI 0.82 to 1.61, p<0.001) while the increase in men was marginal (APC 0.26, 0.01 to 0.52, p=0.05) (Figure 2.4).

Figure 2.3: Number of PSP (Figure 2.3A) and SSP (Figure 2.3B) admissions per 100,000 age-specific population in England, 2012 (Note: different scales used for males and females to emphasise similarity of age-distributions by PSP and SSP)

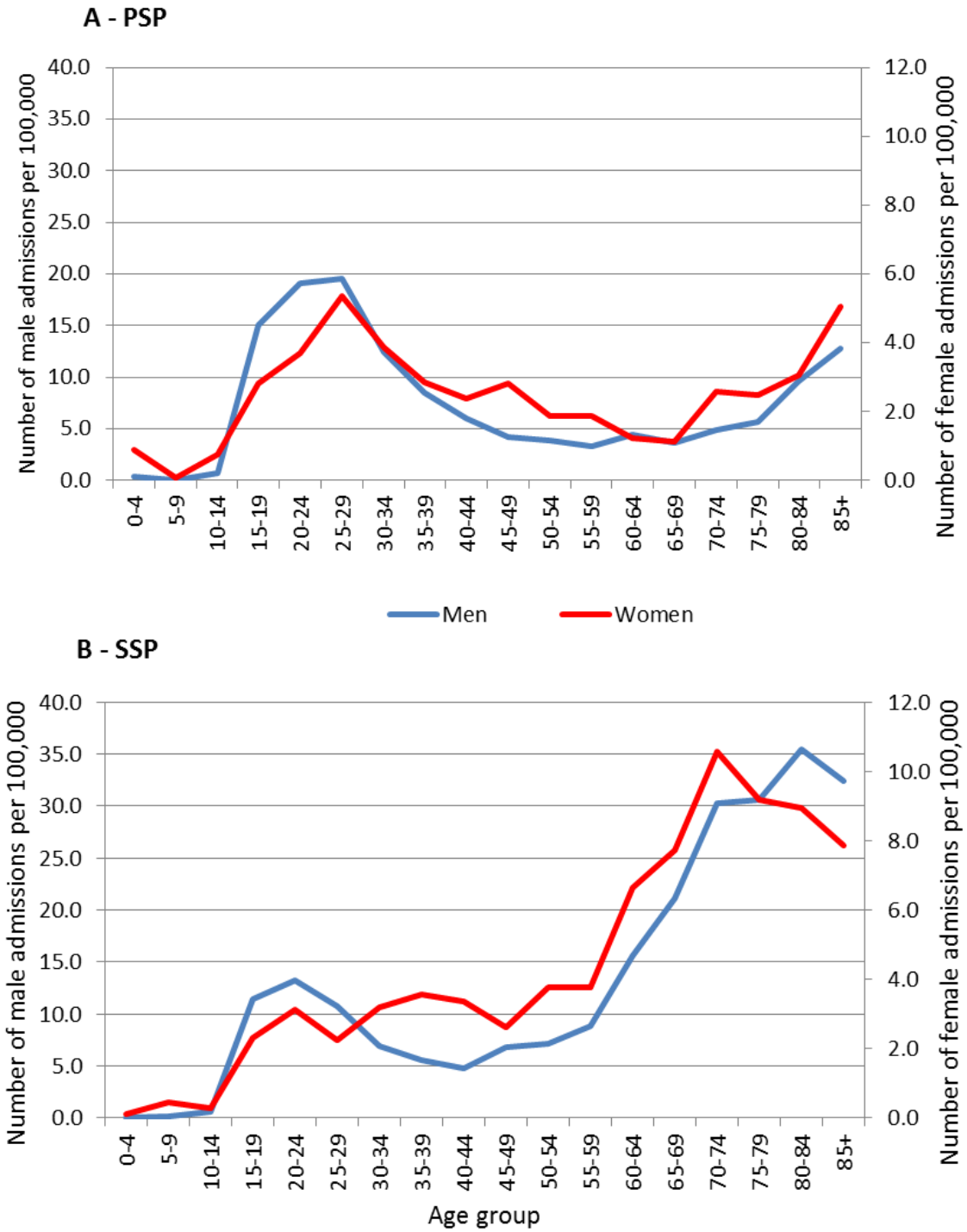
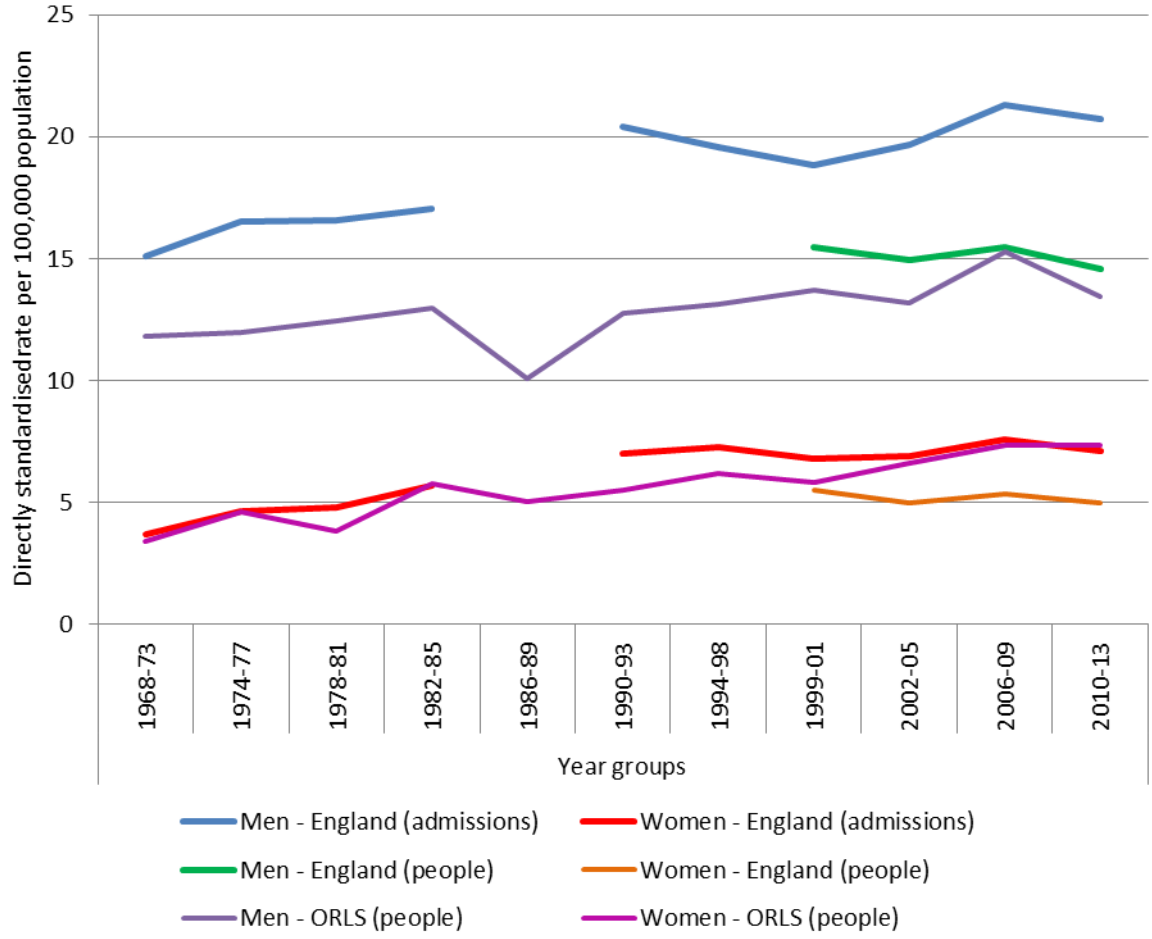
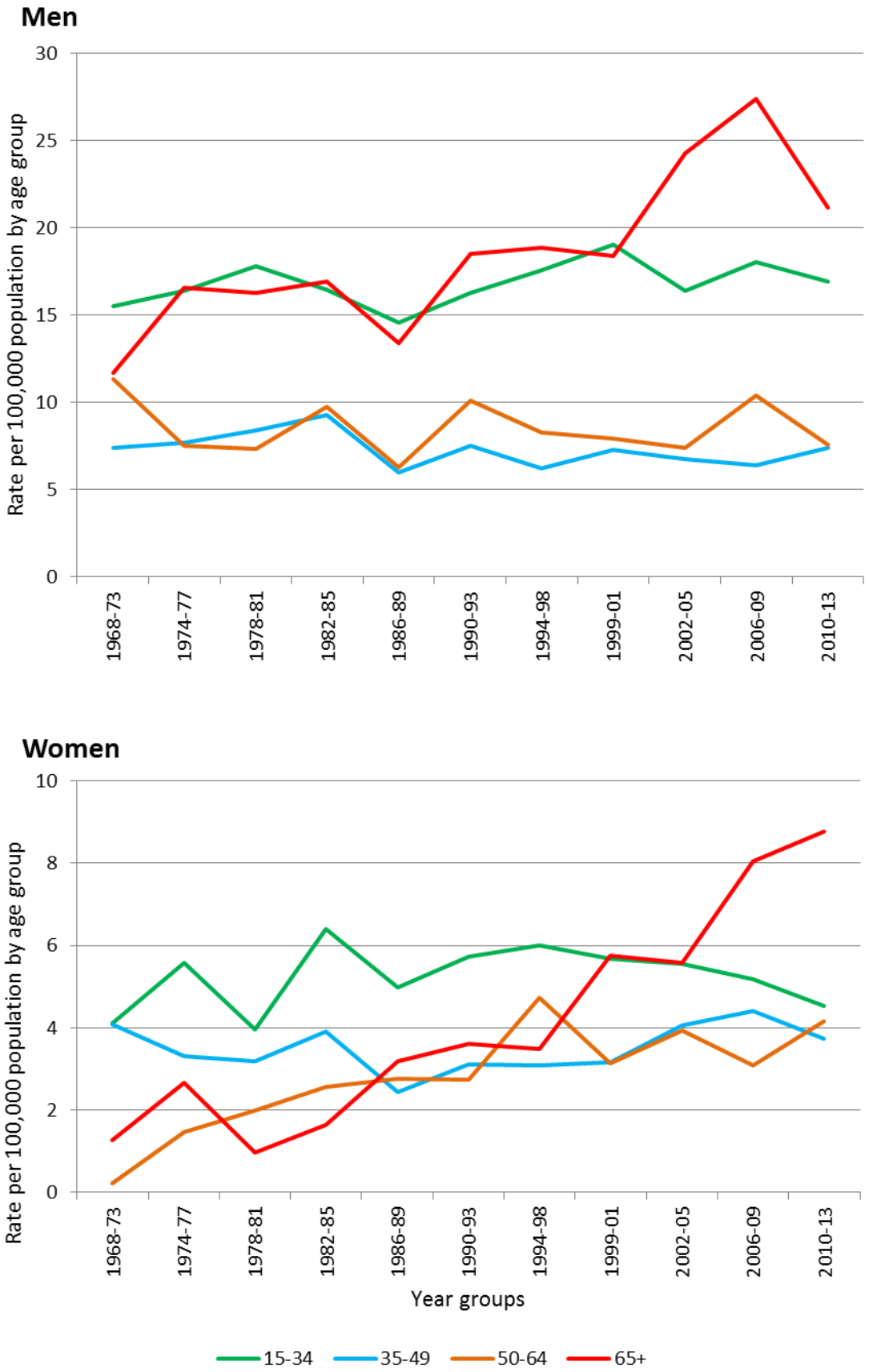


Figure 2.4: Age-standardised hospitalisation rates for pneumothorax per 100,000 sex-specific population aged 15+ in England, 1968-2013



The change in age profile over the decades based on person-based rates in ORLS is illustrated in Figure 2.5. In women, pneumothorax became significantly more common since 1968 among age groups 50-64 and 65+ (respectively, APC 1.89, 95%CI 0.81-2.99 and APC 3.94, 95%CI 3.09-4.79). In men, significant increases since 1968 were confined to ages 65+ (APC 1.13, 95%CI 0.67-1.60, $p<0.001$) (Figure 2.5).

Figure 2.5: Person-based hospitalisation rates for pneumothorax per 100,000 population by age group in ORLS, 1968-2013



Analysis by age group of the shorter but higher powered linked national data from 1999-2013 (Figure 2.6) demonstrated that in more recent years, person-based rates have increased significantly since 1999 for women aged 65+ (APC 2.05, 95%CI 1.43-2.67, $p<0.001$), but have decreased significantly in women aged 15-34 (APC -2.28, 95%CI -3.49 to -1.06, $p<0.001$). Among men, person-based rates have not increased or decreased significantly in any broad age group since 1999 (Figure 2.6).

Figure 2.6: Person-based hospitalisation rates for pneumothorax per 100,000 population by age group in England, 1999-2013



2.4.2. Recurrence

Analysis of linked national data from 1999-2013 (Table 2.3) demonstrates the cumulative probability of pneumothorax recurrence within 30 days, 90 days, one year and five years, by age, sex and SP type.

The cumulative probability of recurrence within one year was 18.5% (95%CI 18.1-18.8) for men and 19.3% (95%CI 18.6-19.9) for women, and within 5 years was 25.2% (95%CI 24.7-25.6) and 25.8% (95%CI 25.1-26.6) respectively. This probability of recurrence ranged between 15%-33% at 1 year, and 21-39% at 5 years, depending on age group and presence of chronic lung disease (SSP). The presence of a chronic lung condition significantly increased the probability of recurrence in every age group ($p<0.001$), but particularly in younger age groups where the cumulative probability of recurrence within five years was 39% (Table 2.3).

A Cox proportional hazards model (Table 2.4) demonstrated that, after adjustment for sex and calendar period of index admission, patients with SSP were significantly more likely to suffer recurrence than those with PSP in every age group at nearly every stage of follow-up. There was a significant interaction between SSP and age (hence adjusted hazard ratios (aHR) displayed by age group). The effect of SSP was most marked in the 15-34 year age group: aHR (compared to PSP) of 2.14 (95%CI 1.96-2.33) within 30 days, 3.22 (95%CI 2.79-3.71) between 30-89 days, and 3.00 (95%CI 2.67-3.38) between 90-365 days.

Table 2.3: Probability (expressed as %) of spontaneous pneumothorax (SP) recurrence within 30 days, 90 days, one year and five years

	Time interval			
	<30 days	**<90 days**	**<365 days**	**<=1826 days**
Men				
All SP by age group				
15-34 (n=18,574)	9.0 (8.6-9.4)	12.1 (11.6-12.6)	17.4 (16.8-17.9)	25.2 (24.6-25.9)
35-49 (n=6,032)	9.5 (8.7-10.2)	12.2 (11.4-13.1)	15.6 (14.7-16.5)	21.4 (20.3-22.5)
50-64 (n=5,660)	12.5 (11.7-13.4)	16.9 (16.0-18.0)	21.2 (20.2-22.3)	26.7 (25.5-28.0)
65+ (n=10,034)	11.1 (10.5-11.7)	15.7 (15.0-16.4)	20.7 (19.9-21.6)	26.1 (25.1-27.2)
Overall (n=40,300)	10.1 (9.8-10.4)	13.7 (13.3-14.0)	18.5 (18.1-18.8)	25.2 (24.7-25.6)
SSP by age group				
15-34 (n=3,518)	16.1 (14.9-17.3)	22.8 (21.5-24.3)	33.3 (31.7-34.9)	39.3 (37.6-41.0)
35-49 (n=1,572)	14.9 (13.2-16.7)	20.4 (18.5-22.5)	27.2 (25.0-29.5)	33.5 (31.1-36.1)
50-64 (n=3,064)	15.4 (14.2-16.8)	21.7 (20.3-23.2)	27.8 (26.2-29.5)	33.7 (31.9-35.6)
65+ (n=6,952)	12.3 (11.5-13.1)	17.3 (16.4-18.3)	23.5 (22.4-24.5)	29.0 (27.7-30.4)
Overall (n=15,106)	14.1 (13.5-14.7)	19.9 (19.2-20.5)	27.2 (26.4-27.9)	33.0 (32.2-33.9)
Women				
All SP by age group				
15-34 (n=5,002)	11.0 (10.1-11.9)	15.3 (14.4-16.4)	20.8 (19.7-21.9)	28.9 (27.6-30.2)
35-49 (n=3,121)	11.5 (10.5-12.7)	15.0 (13.8-16.3)	20.3 (18.9-21.7)	26.3 (24.8-28.0)
50-64 (n=2,457)	10.8 (9.7-12.1)	14.6 (13.2-16.1)	18.4 (16.9-20.0)	23.4 (21.6-25.3)
65+ (n=4,177)	8.3 (7.5-9.2)	12.9 (11.9-13.9)	17.1 (16.0-18.4)	22.2 (20.7-23.7)
Overall (n=14,757)	10.3 (9.8-10.8)	14.5 (13.9-15.0)	19.3 (18.6-19.9)	25.8 (25.1-26.6)
SSP by age group				
15-34 (n=1,245)	16.3 (14.3-18.5)	24.1 (21.8-26.6)	32.9 (30.3-35.6)	39.4 (36.6-42.3)
35-49 (n=1,037)	15.2 (13.2-17.6)	21.3 (18.9-24.0)	28.3 (25.6-31.2)	34.8 (31.8-37.9)
50-64 (n=1,412)	12.0 (10.4-13.8)	17.2 (15.3-19.2)	22.7 (20.6-25.1)	29.3 (26.7-32.1)
65+ (n=2,805)	9.7 (8.6-10.8)	15.3 (14.0-16.7)	20.7 (19.2-22.4)	27.2 (25.2-29.4)
Overall (n=6,499)	12.3 (11.6-13.2)	18.4 (17.5-19.4)	24.8 (23.8-25.9)	31.4 (30.1-32.7)

Table 2.4: Cox proportional hazards model showing adjusted hazard ratios (aHR) for first SP recurrence by sex, SP type (PSP and SSP), age group and calendar period, split by time since index SP event

	Time since index SP event							
	<30 days		30-89 days		90-364 days		365-1826 days	
Potential risk factor (comparing…)	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**	**aHR**	**95% CI**
Sex:								
Women to Men	0.98	0.92-1.04	1.08	0.98-1.19	0.99	0.91-1.09	1.03	0.94-1.12
SP type, by age group:								
SSP to PSP, among ages 15-34	2.14	1.96-2.33	3.22	2.79-3.71	3.00	2.67-3.38	0.95	0.83-1.10
SSP to PSP, among ages 35-49	1.86	1.63-2.12	3.28	2.58-4.17	2.77	2.24-3.42	1.35	1.09-1.67
SSP to PSP, among ages 50-64	1.58	1.39-1.81	2.83	2.20-3.63	3.19	2.46-4.15	1.50	1.19-1.88
SSP to PSP, among ages 65+	1.53	1.35-1.73	1.71	1.41-2.07	2.50	2.01-3.10	1.33	1.07-1.66
Age group, by SP type:								
35-49 to 15-34, among PSP patients	1.08	0.97-1.19	0.77	0.63-0.94	0.70	0.60-0.82	0.66	0.59-0.75
50-64 to 15-34, among PSP patients	1.20	1.06-1.35	0.92	0.73-1.17	0.52	0.41-0.66	0.55	0.46-0.66
65+ to 15-34, among PSP patients	0.98	0.87-1.11	1.30	1.08-1.58	0.64	0.52-0.79	0.53	0.44-0.64
35-49 to 15-34, among SSP patients	0.93	0.83-1.06	0.79	0.65-0.96	0.65	0.54-0.77	0.94	0.75-1.18
50-64 to 15-34, among SSP patients	0.89	0.80-0.99	0.81	0.69-0.95	0.56	0.47-0.65	0.87	0.71-1.06
65+ to 15-34, among SSP patients	0.70	0.64-0.77	0.69	0.60-0.80	0.53	0.47-0.61	0.74	0.62-0.89
Calendar period:								
2004-2008 to 1999-2003	1.14	1.07-1.22	1.10	0.99-1.23	1.02	0.92-1.12	1.04	0.95-1.13
2009-2013 to 1999-2003	1.15	1.07-1.23	1.03	0.92-1.15	0.92	0.83-1.02	-	-

* The Cox proportional hazards model contained the following terms: sex, SP type (PSP and SSP), age group, SP type*age group (interaction), calendar period

Older age was associated with a significantly lower risk of recurrence independently of sex, SP type and calendar period of index admission (Table 2.4). Individuals who had their first (index) pneumothorax admission in 2004-2008 or 2009-2013 were about 15% more likely to have a recurrent event within the first 30 days of follow-up than those who had their first admission in 1999-2003 ($p<0.001$; Table 2.4). However, in this model, the risk of recurrence beyond 30 days did not appear to vary by calendar period. Sex was not a significant predictor of recurrence at any period of follow-up.

As recurrence results were potentially biased by cases where the only knowledge of a relevant comorbidity came from subsequent records (e.g. if post-presentation investigations identified previously unrecognised lung pathology), a sensitivity analysis was undertaken. Reclassifying these cases as PSP led to an attenuation of the apparent effect of chronic lung disease on recurrence risk, but the margin of change was small and the pattern of strong associations in younger people with SSP persisted; the relative risk of recurrence over five years of follow-up, comparing SSP with PSP in men aged 15-34, dropped from 2.0 (1.9-2.2) in the main analysis to 1.9 (1.8-2.1) in sensitivity analysis.

2.5. Discussion

2.5.1. Incidence

This analysis of all hospitalisations for spontaneous pneumothorax in England represents the largest study in the published literature of its kind, with national estimates of incidence and recurrence by age group, sex, and presence or absence of chronic lung disease, set in a historical context. The data demonstrate that the admission-based rates of spontaneous pneumothorax have increased over the period 1968-2013 both for men (APC 0.79, 95%CI 0.66-0.92, p<0.001) and for women (APC 1.54, 95%CI 1.25-1.84, p<0.001). The measures of admission-based rates are useful because these are the commonest available measures in hospital admission statistics in many countries, against which these data can be compared, and provide information on the hospital 'burden of care' for pneumothorax. Data from the record-linked datasets suggest that the annual rates of new people admitted for pneumothorax have remained steady overall, but these are significantly higher in recent years than they were in previous decades for women aged over 50 years and men aged over 65 years. Data from 2012 show an annual admission-based rate of 21.7 for men and 7.5 for women with a ratio of 2.9. These admission-based rates and ratios are consistent with previous smaller epidemiological studies from the UK (m:f ratio 2.7)[71] and France (m:f ratio 3.3)[72].

The bimodal nature of the age distribution for spontaneous pneumothorax has again been demonstrated in this dataset. Although described previously[72, 73, 76] this data shows for the first time on a large scale that the first peak (15-34 years) predominately comprises those with no known lung disease (PSP) with the latter peak mainly due to those with SSP. In 2012, nearly 60% of hospital admissions for pneumothorax were due to SSP. The increase in

the ratio of PSP:SSP among those aged over 80 (Figure 2.3A) is perhaps surprising. This could be attributed to a survivor effect, as those with chronic lung disease are known to die younger[106], or may be explained by chronic respiratory conditions being less reliably recorded in the very elderly, where there is often multi-morbidity leading to greater misclassification. Catamenial pneumothorax is pneumothorax resulting from thoracic endometriosis in women of child-bearing age. The true incidence is unclear but is often thought to be underreported. This is also likely to be the case in our dataset: the ICD10 code for Endometriosis (N80) was only present in 0.04% of pneumothorax episodes (data not shown). Case series report an incidence of 3-6%[107] of pneumothoraces in young women, but may be as high as 30-40%[108] in those patients requiring surgery (for recurrence or on-going air leak).

2.5.2. Recurrence

Previous data on recurrence risk for spontaneous pneumothorax are poorly defined for specific age groups, by sex and pneumothorax type. Numerous small and mostly retrospective case series report recurrence risk (i.e. number of recurrences divided by the total population with SP) of between 21 and 54% at 1-2 years[26, 76, 100-104]. Data from control or non-interventional arms of RCTs show a range of risk of recurrence of 21-49%[82-85, 109, 110].

This population-based data, using cumulative failure analysis with longer follow-up and much larger numbers of cases than previous studies, found no difference by sex. This is surprising given the marked difference in the respective rates of first occurrence per 100,000 sex-specific population. For both men and women, around a quarter of pneumothorax patients will experience a recurrence within 5 years, but around three-quarters of these will

occur within the first year. However, the probability of recurrence varies markedly by age group and presence of chronic lung disease (SSP).

Previous small and retrospective studies have suggested a higher rate of recurrence in patients with pre-existing lung disease (SSP) compared to those without (PSP)[102, 111]. Our study confirms the increased risk, and for the first time quantifies the varying risks of recurrence among SSP patients across age-groups. The probability of recurrence is particularly marked in younger patients with SSP (around 3-fold increase within one year of follow-up), which may be a marker of disease severity of differing aetiology. For example, cystic fibrosis is known to be a risk factor for recurrent pneumothorax, which will affect younger populations[112].

Analysis of recurrence by calendar year indicates that recurrence has become more common in recent years. However, this is only true of recurrence within 30 days (aHR 1.15, 95%CI 1.07-1.23). The potential statistical noise of increased multiple admissions for the same pneumothorax event was minimised by excluding hospital transfers, and by defining recurrence restrictively as a subsequent admission where pneumothorax was recorded as the principal diagnosis where the patient was admitted as an emergency. The increased risk of recurrence within 30 days in more recent years may be a real effect, reflecting a change in clinical practice. For example, if physicians are treating an increasing proportion of patients conservatively, or simply with needle aspiration with shorter hospital stay rather than chest drain and prolonged admission, this might lead to the observed higher readmission rate.

Current UK guidelines suggest that patients over the age of 50 years old should be treated as an SSP[4]. Although this cut-off was relatively arbitrarily chosen, our data suggests that this age limit coincides with the nadir between the two bimodal peaks, and captures the majority

of patients with SSP. However, the data shows that there is an overlap of the age ranges for PSP and SSP, and there is an additional peak (albeit lower) of SSP in patients aged <50 years. The probability of recurrence appears highest amongst this group, and it is therefore important to consider the evidence of underlying lung disease in younger populations when counselling on probability of recurrence.

The risk of recurrence has been shown to peak within the first 90 days. If the underlying pathological changes in the lung are persistent, and not reversible, one would expect the risk of recurrence to be fixed over time (i.e. the risk in year one to be the same as year two etc.). However, it is evident that this is not the case. Although the cumulative risk increasing up to five years, the risk per year reduces from year two onwards: for example, probability recurrence in men overall is 18.5% at 1 year, but 25.2% cumulatively at 5 years – suggesting only 6.7% probability of recurrence in years 2 to 4. This reduction could be due to a number of factors: the index pneumothorax event may prompt a change in lifestyle leading to a reduction in behaviour known to be associated with recurrence, for example tobacco and marijuana smoking; or an alteration in the underlying pathology. As discussed in the Introduction, histological samples of lung in patients with PSP have shown inflammation and respiratory bronchiolitis at surgical biopsy. It could be that this inflammation is a precursor to emphysema-like change and pleural porosity which predispose to air leak and subsequent pneumothorax. If this inflammation and subsequent parenchymal changes are transient, then this may be driving the reduction in probability of recurrence over time. However, there have been no longitudinal studies in pneumothorax investigating the natural history of ELC to determine whether the changes are progressive or any components are reversible.

In the future, the clinical distinction between PSP and SSP may become less important in favour of risk-stratifying all patients based on specific comorbidities, likely outcomes and potential management options. Further epidemiological and prospective clinical studies are required to convert these findings into clinical practice. Given the reduction in probability of recurrence after 1 year, should clinical advice be different for those patients who survive to 1 year without recurrence? Are there better diagnostic tools available to identify those at risk on an individual, rather than a population, basis?

2.5.3. Strengths and limitations of the study

This is the largest study of its kind in the literature and has compared two long-standing datasets, including an English national population of 52 million. The record-linked ORLS dataset (1968-2013) and the record-linked era of the national dataset (1999-2013) allow follow-up of individual patients to assess recurrence and its relationship to admission-based and person-based incidence.

Limitations to this study include that the data only provide information on patients admitted to hospital. Patients who may be managed in the community or conservatively without admission, and patients admitted to hospitals outside the study region, are not included. This data may therefore underestimate the true incidence and recurrence of spontaneous pneumothorax. Analysis is reliant on the accuracy of the coding for each hospital episode; reassuringly, spontaneous pneumothorax is covered by relatively few ICD codes. However, other diagnoses listed alongside pneumothorax may be less reliably recorded. Whilst the primary diagnosis (i.e. the principal reason for admission to hospital) has been well recorded over time, the reliability and consistency of recording secondary/subsidiary diagnosis codes is less clear. SSP was defined as having a chronic lung condition coded on either the same

pneumothorax record, any known previous hospital record, or up to 12 months afterwards using record-linkage. This method was chosen to capture those patients whose coding may have been incomplete on their index pneumothorax episode, but who did in fact have an underlying lung disease. Pneumothorax recurrence risk may be related to smoking and body mass index. Unfortunately, HES datasets do not include these data to allow assessment in our model.

2.6. Conclusions

This is the largest epidemiological study of pneumothorax to date. These data cover hospitalised pneumothorax only, and therefore may be a conservative estimate of the true burden of disease. Pneumothorax admission rates are increasing. The increase is attributable partly to an increase in readmissions, and partly to a modest increase in first-known admissions among older age groups. The findings provide clinically useful data on true short and long term recurrence rates that can be used in practice to advise PSP and SSP patients and their clinicians.

Personalising risk of pneumothorax recurrence

Epidemiological studies can provide valuable insight into disease specific risk and uncommon disease associations. However, on an individual patient level, there may be new techniques to determine personalised probability of pneumothorax recurrence.

Novel techniques in this thesis have the potential to examine the lungs in new ways. ^{129}Xe-enhanced MRI scanning can assess ventilation and diffusion of gas within the lungs (see Chapter 3). This may provide a method of identifying abnormalities in the lung without the

use of ionising radiation (unlike CT scanning) making repeated scanning acceptable in a young population such as those with PSP.

Abnormalities in the lungs of patients with PSP may be subtle or inhomogeneous. A new method combining a highly precise Molecular Flow Sensor with mathematical model can estimate of lung inhomogeneity in a simple, non-invasive way. This technique has the potential to identify patients with disease which may otherwise be missed on global, non-specific measures of lung function. Chapter 4 will describe its use the first time in PSP patients.

2.7. Future directions

The relative risk of pneumothorax associated with specific lung conditions has not been well studied. To date, these have consisted of case series of patients with disease.

2.7.1. Disease specific risk of pneumothorax

As well as determining incidence in those with specific diseases, the record-linked HES dataset can be used to generate a cohort of matched individuals without disease to assess relative risk. The plan is to conduct this analysis for a number of chronic respiratory diseases: including asthma, COPD, cystic fibrosis, and lung cancer.

2.7.2. Future consequences of pneumothorax episode

The long-term sequelae of pneumothorax in early adulthood (PSP) are not known. The long duration of the linked datasets (HES 1999-2013 and ORLS 1968-2013) provides a powerful tool to conduct follow-up studies looking at the likelihood of developing other respiratory disease, cardiovascular disease or malignancy can be assessed. In addition, as discussed in the Introduction, familial pneumothorax is relatively common in patients presenting with

presumed PSP. Some familial conditions, such as Birt–Hogg–Dubé syndrome and Marfan syndrome require surveillance to assess for serious complications. The linked HES dataset will allow identification of other potentially unrecognised associations with PSP, which could have important implications for screening of patients with pneumothorax.

Combining disease specific risk with using new and emerging functional and imaging techniques will provide an opportunity to personalise risk and better inform discussions between patients and physicians.

Author contribution:

The study design, including the definition of PSP vs SSP, was conceived by R Hallifax. The data used in this chapter is held and managed securely by the Unit of Health-Care Epidemiology, Big Data Institute, University of Oxford. As such, Raph Goldacre performed the raw data analysis, including recurrence probability and APC analysis. R Hallifax performed the literature search, additional data manipulation and manuscript preparation.

3. Novel Imaging Assessment – ^{129}Xe MRI

3.1. Background

PSP is traditionally defined as a spontaneous event in a patient with no apparent lung disease. However, as discussed in the Introduction, structural abnormalities have been identified: ELCs, pleural porosity and lower density areas of lung parenchyma. Computed tomography (CT) scans may be able to identify these areas of ELC, but do not provide information on the extent or impact of these abnormalities on ventilation or pulmonary function. The standard methods of assessing pulmonary function provide crude measures of global function. Defects or abnormalities in patients who have had PSP may be regional or subtle and hence poorly characterised by traditional methods.

Hyperpolarized xenon-129 magnetic resonance imaging (^{129}Xe MRI) of the lungs is a technique in use in a limited number of centres world-wide, including Oxford. It has the advantage of involving no ionising radiation. Previous studies have been carried out in animals, and in small numbers of healthy volunteers and patients. ^{129}Xe MRI has the potential to characterise functional abnormality relating to areas of ELC and areas of reduced lung density on CT. Inhalation of hyperpolarized helium and xenon gas has been demonstrated to be safe and well-tolerated by cohorts of healthy volunteers and patients with lung disease [48, 49, 113-116].

3.1.1. Limitations to current imaging and functional studies in pneumothorax

Currently, PFTs rely upon spirometry and/or diffusing capacity. These parameters are well-established and validated for monitoring of many pulmonary diseases. However, PFTs may be are relatively insensitive to changes in early lung disease, and so may not detect

mild/early abnormalities in patients with PSP. PFTs provide global measures of lung function, and relatively little information about regional pathology and heterogeneity in the lungs[59-61].

CT scans performed at high resolution (HRCT) can provide more detailed structural lung parenchymal information than conventional CT. However, it does not provide functional information. Correlation between CT measures and PFTs, and most importantly patient symptoms are very inconsistent. Xenon offers the potential for detailed regional functional information. In addition, HRCT requires higher levels of ionising radiation, limiting its use in follow-up when repeated scanning will be required. MRI uses no ionising radiation.

3.1.2. Hyperpolarized gas MRI

Conventional MRI is good for assessment of thoracic structure in terms of chest wall/soft tissues/diaphragmatic movement, as the MRI the signal originates principally from the protons in water molecules of tissues. Xenon is required for assessment of lung function, as it allows direct imaging of ventilation – almost equivalent to a contrast medium. The hyperpolarized noble gases, helium (^{3}He) and xenon (^{129}Xe) overcome this problem of using MR for lung imaging, as they have a nuclear spin of ½ which generates a signal on MR imaging. The low signal at the equilibrium due to the low density of the xenon gas can be increased approximately 10,000 times using a polarizer device based on spin exchange optical pumping (hence “hyperpolarized”). As a result, the MR signal is easily detected with a standard MRI scanner and radiofrequency coils that are tuned to the resonance frequency of xenon.

Hyperpolarised gas MRI images were first obtained using ^{129}Xe in excised mouse heart-lung specimens in 1994[117] and in human lungs using ^{3}He in 1996[118]. ^{3}He has a higher

gyromagnetic ratio than ^{129}Xe, thereby providing a stronger MR signal. However, the ability polarise ^{129}Xe has improved and it is now possible to produce the high levels of polarization required for high quality imaging. In addition, ^{3}He has become more difficult to obtain. Therefore, ^{129}Xe has become the focus of most hyperpolarized gas research. This study used hyperpolarized ^{129}Xe.

3.1.3. ^{129}Xe

Xenon (Xe) is an inert, non-toxic noble gas. Atmospheric air contains approximately 0.04 mol% of xenon. The xenon isotope ^{129}Xe is employed for hyperpolarized xenon MR imaging, that is to say that the nuclear spin within the atoms will be increased artificially using a polarizer device (Model 9300, Polarean, Durham, NC). The natural abundance of ^{129}Xe in atmospheric Xenon is 26%, and can be extracted relatively easily. The study used nuclear-enriched xenon with 86% ^{129}Xe. Following inhalation, hyperpolarized ^{129}Xe gas permits direct visualisation of the airspaces. The rapid Brownian motion of ^{129}Xe gas atoms may be exploited to probe the lung microstructure and detect regions of emphysematous tissue destruction using ^{129}Xe diffusion-weighted MRI. Additionally, ^{129}Xe readily dissolves in blood, where it emits different MR signal characteristics. Thus ^{129}Xe MRI enables information regarding airflow, diffusion and gas transfer to be evaluated.

3.1.4. Ventilation imaging

Ventilation imaging using ^{3}He has demonstrated utility in detecting functionally abnormal areas of lung in patients with obstructive lung diseases, e.g. COPD, CF [41, 42], asthma [43-45] and bronchiolitis obliterans [46, 47]. More recently, ventilation imaging has been safely performed with ^{129}Xe[48-50]. Driehuys *et al* performed hyperpolarized ^{129}Xe MRI scans on 44 patients: 24 healthy volunteers, 10 patients with COPD and 10 age-matched controls[48].

Likewise, Shukla *et al* successfully imaged 12 healthy volunteers, 10 with patients with COPD, 7 with asthma, and one with radiation-induced lung injury[49]. In both studies mild transient symptoms were noted: typically dizziness, paraesthesia, euphoria and hypoesthesia[48, 49]. No hypoxic or serious adverse events were observed.

3.1.5. Diffusion weighted imaging (ADC)

As well as allowing visualisation of the ventilation of lung areas, hyperpolarized gas imaging can measure the diffusion of the gas within the lung. The diffusion coefficient of a gas determines the distance the atoms will move in a given time period. Analogous to the information on the microscopic motion of water molecules in tissue using standard proton MRI, diffusion-weighted hyperpolarised gas MRI can provide a measurement of the movement of the gas when restricted within the lung microstructure. This measure, the Apparent Diffusion Capacity (ADC), can be assessed by lung region to provide a map of lung microstructure (e.g. alveolar spaces)[51, 52]. Typical ADC values for healthy lung parenchyma using ^{129}Xe are ~0.04cm^2/s, which is substantially smaller than the corresponding diffusion coefficient of the gas in an unrestricted space (~0.14cm^2/s)[51]. A study using hyperpolarised ^{3}He imaging to measure ADC in eleven symptomatic smokers and eight healthy non-smokers[53]. ADC values were significantly higher in smokers, and were correlated with total number of pack-years. The authors also showed that ADC was correlated with PFTs (FEV_1, and diffusing capacity) concluding that subclinical smoking–related emphysematous changes might be revealed with ADC measurements before they are demonstrated on high resolution CT [53].

3.1.6. Applicability to pneumothorax patients

Patients who have had a PSP are likely to have a range of severity of ELC in their lungs. Some patients will have demonstrable cystic airspaces on CT scan, but these are also present in young patients who have not suffered with pneumothorax (particularly those who smoke) and have not yet been shown to be predictive of severity of disease or likelihood of recurrence[5, 9-11, 38] (See Chapter 7). Others may have subtle or early changes in lung parenchyma, which could be identified using hyperpolarized ^{129}Xe in this study.

^{129}Xe MRI has been shown to be able to identify regional differences in ventilation and ADC.

3.1.7. Lobar analysis

To date, studies of hyperpolarized gas imaging to identify regional differences has been confined to patients with COPD, who may benefit from localised targeted treatments, such as lung volume reduction surgery or endobronchial valve therapy. However, the feasibility of assessing regional and lobar ventilation using ^{3}He has been demonstrated in healthy volunteers and patients with asthma[119, 120]. A recent study in Oxford showed that ^{129}Xe imaging can assess lobar contributions to lung function using ventilation and ADC values[54]. Twenty two patients with COPD underwent hyperpolarized ^{129}Xe imaging, quantitative CT scan and PFTs. Percentage ventilated volume and mean ADC by lobe showed correlation with percentage emphysema on quantitative CT and whole lung average ADC values correlated with PFT results[54]. The patients in this study had established clinically significant COPD. It has yet to be shown whether ^{129}Xe MRI imaging can identify lobar abnormalities in early stage disease, or those smokers with minimal symptoms[115].

3.1.8. Evidence for regional nature of disease in PSP

There is some evidence that ELC may have a preference for upper lobes. A number of studies describe most lesions being in the upper third of the lung[5] or that “mostly apical” blebs were identified[37] [121]. More detail was provided by Mitlehner *et al* who found apical blebs in 28, and “extra-apical” blebs (defined as anywhere below the upper quarter of the lung) in 16 of 35 patients with PSP[7]. Both central and sub-pleural blebs were found by Smit *et al* [6]and although most had blebs in the upper half of the lung (divided horizontally at the carina), 5% had blebs solely in the lower half [6].

Therefore, the ability of ^{129}Xe MRI to provide detail on lobar differences in ventilation and ADC will be of particular interest in PSP patients.

3.1.9. Quantitative CT

Quantitative CT can provide reliable measures of lung structure including parenchymal attenuation, and air trapping. The threshold for abnormal lung density (low attenuation) has been established at -950HU and used routinely in the quantification of emphysema in patients with COPD[122, 123]. This value was chosen to balance the sensitivity and specificity of CT to identify emphysema[124].

The combination of Quantitative CT and ^{129}Xe MRI will provide comprehensive and quantitative assessment of both lung structure and function. There is no established “gold standard” of imaging in patients with pneumothorax. These data will provide novel metrics, which may be more sensitive in the detection of changes that might be relevant to PSP.

3.2. Aims and Hypothesis

The aim is to use ^{129}Xe MRI to objectively and quantitatively describe regional and structural lung changes for the first time in patients who have had a primary spontaneous pneumothorax.

The hypothesis is that ^{129}Xe MRI imaging can provide evidence of abnormal lung ventilation and pulmonary microstructure (ADC). These results will be compared to quantitative CT and PFTs

3.3. Methods

3.3.1. Patients

Patients were enrolled into the OX-RAMPP (Oxford Sub-study of Randomised Ambulatory Management of Primary Pneumothorax) trial, specifically designed to explore the novel imaging and lung function assessment techniques detailed in this thesis. All patients were initially enrolled into the parent study (RAMPP), then offered inclusion in OX-RAMPP at completion of their treatment for their pneumothorax. The trial was approved by NHS Research Ethics Committee (Ref 16/SC/0412) and funded by a Medical Research Council (MRC) Clinical Research Training Fellowship (Ref MR/L017091/1).

Inclusion Criteria

1. Recruited into RAMPP study through the Oxford or Reading sites (both interventional and observational cohort patients).
2. Able to give informed consent for participation in the study.

3. Female participants of child bearing potential must agree to take appropriate steps to avoid pregnancy in the three months following the hyperpolarized xenon lung MRI scan.

Exclusion Criteria

1. Inability to lie flat for procedures.
2. Contraindication to MRI examination (e.g. indwelling pacemaker, non-MRI compatible metallic implant, severe claustrophobia, intra-ocular foreign body).
3. Female participants who are pregnant, lactating or planning pregnancy during the course of the study.
4. Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the trial, or the participant's ability to participate in the study.
5. Epilepsy requiring on-going medical treatment, or a seizure within the past year.

Timing of Visits

After completion of treatment for their index pneumothorax episode (ideally within the first 3 months), patients will be asked to attend for ^{129}Xe MRI scan and PFTs. In order to minimise the number of visits, the trial team endeavoured to schedule all of the appointments on the same day as pre-arranged RAMPP CT scan and follow-up visit.

3.3.2. Hyperpolarized ^{129}Xe MR Imaging

Hyperpolarized ^{129}Xe – Manufacture and storage

^{129}Xe was polarized via spin exchange optical pumping, using the Polarean Xenospin. ^{129}Xe was then frozen to isolate it from other gases (gas mixture of 1.0% xenon, 10% nitrogen and 89% helium) and sublimated into Tedlar plastic bags for administration to participants via inhalation.

^{129}Xe MR Image Acquisition

The MRI images were obtained with a 1.5-T whole-body system (Signa HDx; GE Healthcare). Subjects were fitted with a flexible lightweight containing twin Helmholtz quadrature transmit-receive coil (Clinical MR Solutions, Brookfield, Wis) resonating at the ^{129}Xe Larmour frequency (~17.7MHz). Images were acquired with patients in the supine position. Scans were performed at approximate 1 hour intervals as it takes this period of time to manufacture a 1L bag of hyperpolarised ^{129}Xe gas.

Before the first ^{129}Xe MRI scan involving inhalation of up to 1L of xenon, patients breathed in a small volume of xenon of approximately 100mL mixed with medical grade nitrogen (i.e. ~10% ^{129}Xe and ~90 nitrogen), for the proton MRI required for co-registration purposes. The patient performed a standard breath hold for a short period of time (approximately 2 seconds). This set-up procedure enables optimization of ^{129}Xe MRI parameters according to patient height and weight, and acts as practice run for the patient. The output from calibration (flip angle measurement) allowed optimisation of the ^{129}Xe MRI images for each individual and were not be used to evaluate the study endpoints.

For the actual ^{129}Xe MRI scan, the patient was asked to breathe out (to functional residual capacity, FRC), and then breathe in from a bag containing up to 1L of xenon, balance nitrogen. The total volume of gas participants inhaled for ^{129}Xe MRI scans was 1L with

polarisation levels of approximately 10%. The patient received a bag full of air or oxygen to practice this breathing manoeuvre before breathing xenon.

The image acquisition strategy was:

- Short echo proton MRI for co-registration purposes.
- Static ventilation – conventional 3D gradient echo based pulse sequences with small flip angles to produce static ventilation images of the lung. Parameters: repetition time 10ms, echo time 5ms, flip angle ~5^{o}, section thickness 15mm, matrix 128 x 256, field of view 32-50cm.
- Diffusion-weighted imaging - interleaved two-dimensional gradient-echo sequence with two b values (b = 0, 20.855 sec/cm2) to generate ADC values. Parameters were as follows: 30-mm coronal sections covering the whole lung in the anteroposterior direction, 40x40-cm field of view, 96 x 96 matrix resolution, 4-kHz bandwidth, TR/TE=20/13.2, and 7° flip angle.

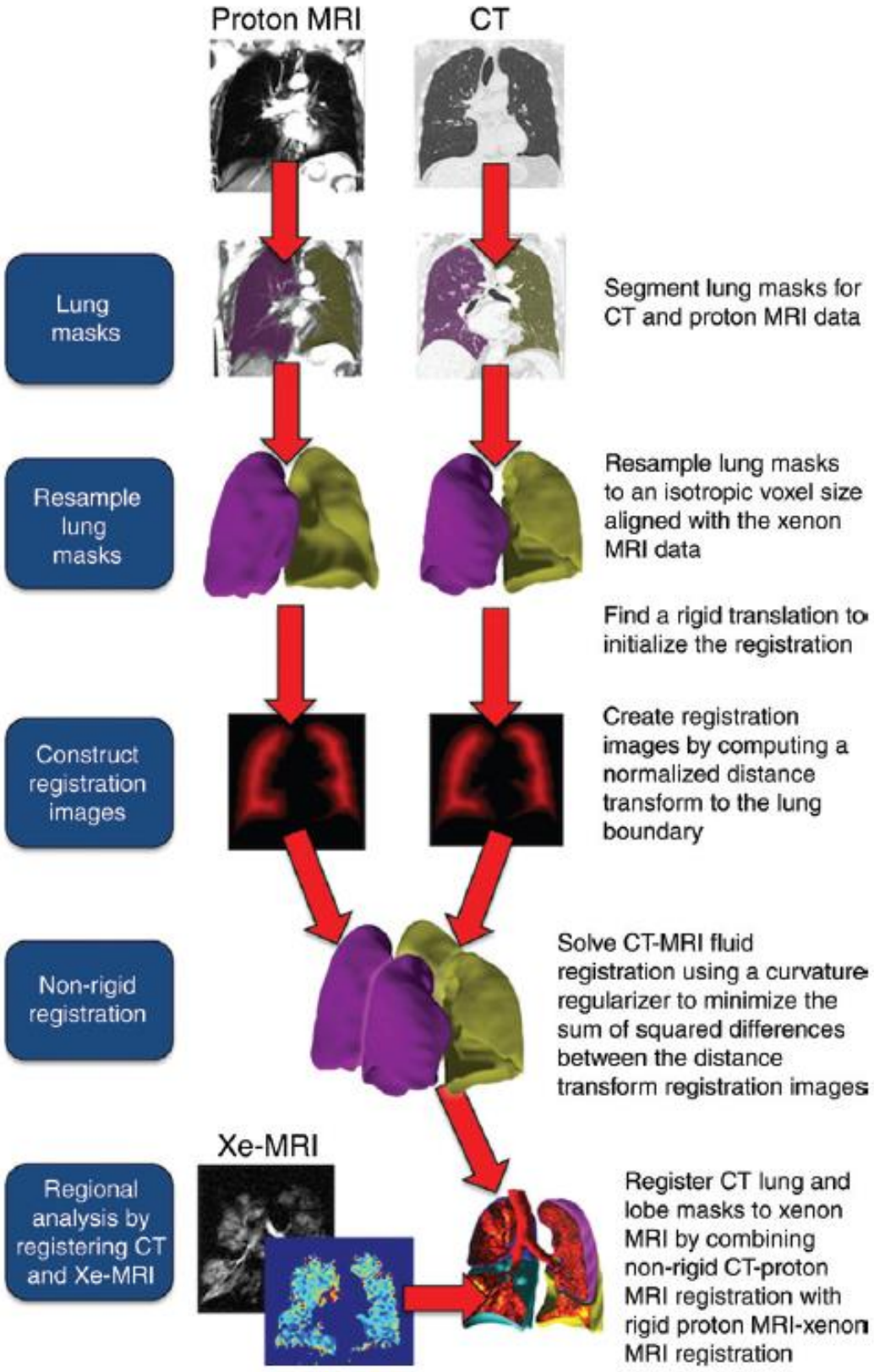
A separate inhalation of hyperpolarised xenon gas is required for acquisition of each scan sequence. Patients were consented to perform this manoeuvre up to five times to enable acquisition of all ^{129}Xe MRI sequences. However, all patients in this study only required two scans each to acquire the two sequences (ventilation and ADC imaging).

^{129}Xe MR Imaging - Analysis

All analyses were performed blinded to clinical data and all other investigation results to avoid bias. Analysis of the images was performed using a methodology developed by the group in Oxford for analysis of COPD patients[54]. The methodology uses Pulmonary Toolkit (PTK, version 0.4) [125, 126], which is an open-source image processing kit that runs in the

Matlab environment (MathWorks, Natick, Mass). This analysis is capable of semi-automated lobar analysis of ^{129}Xe MRI ventilation and diffusion-weighted imaging. The key steps in the analysis pathway involving PTK are summarised in Figure 3.1.

Figure 3.1: Schematic of key steps in regional image analysis using PTK. Regional analysis is performed by registering lobar boundaries from CT to proton MR imaging by combining a non-rigid method from CT to proton MR imaging with a rigid translation from proton MR imaging to ^{129}Xe MR imaging. (Reproduced with permission[54])



The first step involves the co-registration of the proton MRI and CT images to apply lung and lobar boundaries. PTK performs an automated segmentation of the lungs (on CT and proton MRI) and the lobes (on CT image). Automated rigid registration of Xe-MRI and conventional MRI is performed, followed by rigid and fluid registration of CT to Xe-MRI[54]. The accuracy of the image registration was ensured by confirming the volume overlap index (DICE index) of greater than 0.8.

ADC analysis was undertaken via PTK in Matlab. The ADC value for each pixel is calculated from segmented source images according to this equation:

$$ADC = \frac{1}{b}\, ln\left(\frac{S_0}{S_1}\right)$$

where S_1 is the signal intensity of the diffusion-weighted image pixel, and S_0 is the intensity of the pixel without weighting (i.e. with a b value of zero), and b is the diffusion-weighted factor that depends on the strength and timing of the gradients used to generate diffusion-weighted image (i.e. S_1), calculated using the following formula:

$$b = (\gamma G)^2 . \left[\tau^2 \left(\Delta - \frac{\tau}{3}\right) + \tau \left(\delta^2 - 2\Delta\delta + \Delta\tau - \frac{7}{6}\delta\tau + \frac{8}{15}\tau^2\right)\right]$$

Where γ is gyromagnetic ratio of the xenon nuclei, G is the gradient magnitude, τ is ramp (or rise) time, Δ is diffusion time, and δ is the lobe duration. These values are specified prior to each MRI scan and will determine the signal intensity, and hence ADC. It is therefore important to note the b values when comparing ADC values of ^{129}Xe scans undertaken on different MRI scanners or under different conditions.

3.3.3. ^{129}Xe MR Imaging - Safety & Monitoring

Patients were observed and monitored throughout the study, including direct visual observation, heart rate, respiratory rate and arterial oxygen saturations. During each scan there was at least two trained staff in attendance including a doctor or allied health care professional such as a nurse or radiographer, responsible for patient monitoring, and safety. Any adverse events were recorded on dedicated reporting forms. Procedures were in place such that should patients have experienced severe reactions, physicians were available to review the patients. Follow-up was available for any persistent reactions via telephone calls or clinic visits as deemed necessary by the clinician.

3.3.4. CT imaging

Patients underwent a CT scan either before or on the same day as their MRI scans. All patients had a low dose CT scan of the chest with 4 HRCT slices at the apices. The low dose scan was a full helical scan with the following parameters: rotation time 0.5s, detector coverage 40mm, helical thickness 0.625mm, speed 39.37, 120kV voltage, 60mA current, and 0.984 beam pitch. The HRCT was a full helical scan with the following parameters: rotation time 0.8s, detector coverage 1.25mm, axial thickness 1.25mm, 120kV voltage, 200mA current, with one image per rotation.

The low dose, thin slice (0.625mm) CT scans were analysed using PTK to determine percentage emphysema (defined as less than -950HU) on a whole lung and lobar basis, presented as percentage low attenuation area (%LAA).

3.3.5. Pulmonary Function Testing (PFTs)

On the same day as the Xe-MRI imaging, patients completed PFTs in the accredited Churchill Hospital Pulmonary Function laboratory. Spirometry (FEV_1, FVC) was performed using a compact plus flowmeter pulmonary function testing station (Hypair; Medisoft Group, Sorinnes, Belgium) and a body plethysmography system (MasterScreen Body; Carefusion, Hoechberg, Germany). Individual data were compared with predicted values from Global Lung Function Initiative[127].

3.3.6. Comparison with COPD patients

A cohort of 22 COPD patients studied in Oxford underwent CT and 129Xe MRI scanning[54]. Their results were used as a comparator group in this thesis to identify similarities and differences with the PSP patient group – many of whom may have early or mild emphysema or ELC.

3.3.7. Data & Statistical Analysis

Ventilation data derived from the PTK analysis above were expressed as percentage ventilation by lobe and presented with overall calculated whole lung mean (and standard deviation). ADC data is presented as absolute values (cm^2/s) by lobes, right and left lungs and whole lung. Quantitative CT data is presented at percentage low attenuation area (%LAA) by lobe and whole lung. Pulmonary function tests are analysed as absolute values by individual (for FEV_1, FVC, kCO) and percentage of predicted values.

Data were tested for normality by plotting histograms and assessing the skewedness of the distribution. The results were expressed as means and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for skewed (non-

normally distributed data) and frequency (%) for categorical variables. Comparison of means of two groups were conducted using unpaired t-tests, whereas for multiple groups (for example inter-lobar analysis) was conducting used a one-way ANOVA (Analysis of Variance) test with Bonferroni correction. Proportions between groups were compared using Chi-squared test. All statistical analyses were conducted using Excel as part of Microsoft Office 2010 (Microsoft Corp, USA) and Stata v14.1 (Stata Corp, USA). Statistical significance was assumed at p value <0.05.

3.4. Results

3.4.1. Patient demographics

From February 2016 to December 2017, 19 patients enrolled into the RAMPP study in Oxford were screened for inclusion. Ten (53%) were enrolled. 4 declined for personal reasons (did not want additional time off work, were out of the country at the scheduled scan timings, or were going on prolonged holiday); 5 had undergone surgery, or were due to have surgery within the follow-up period. These latter four patients were deemed unsuitable as surgical intervention would have firstly altered the lung architecture (surgery usually involves apical resection or "bullectomy") and secondly altered the recurrence risk of the patients (which will be the subject of future follow-up work comparing ^{129}Xe MRI findings with recurrence risk).

The ten patients' results are presented. Eight (80.0%) of the patients were male. The median age was 28.6 years (Interquartile range, IQR, 9.9 years), and median BMI was 20.0kg/m^2 (IQR

3.9 kg/m^2). Three (30.0%) had experienced a previous pneumothorax episode. None had a family history (either first or secondary degree relative) of pneumothorax.

Four (40.0%) were current smokers at the time of their pneumothorax episode, one (10.0%) was an ex-smoker, and the remaining five (50.0%) were never smokers. The mean smoking pack-years was 4.6 overall, or 9.2 amongst ex- or current smokers.

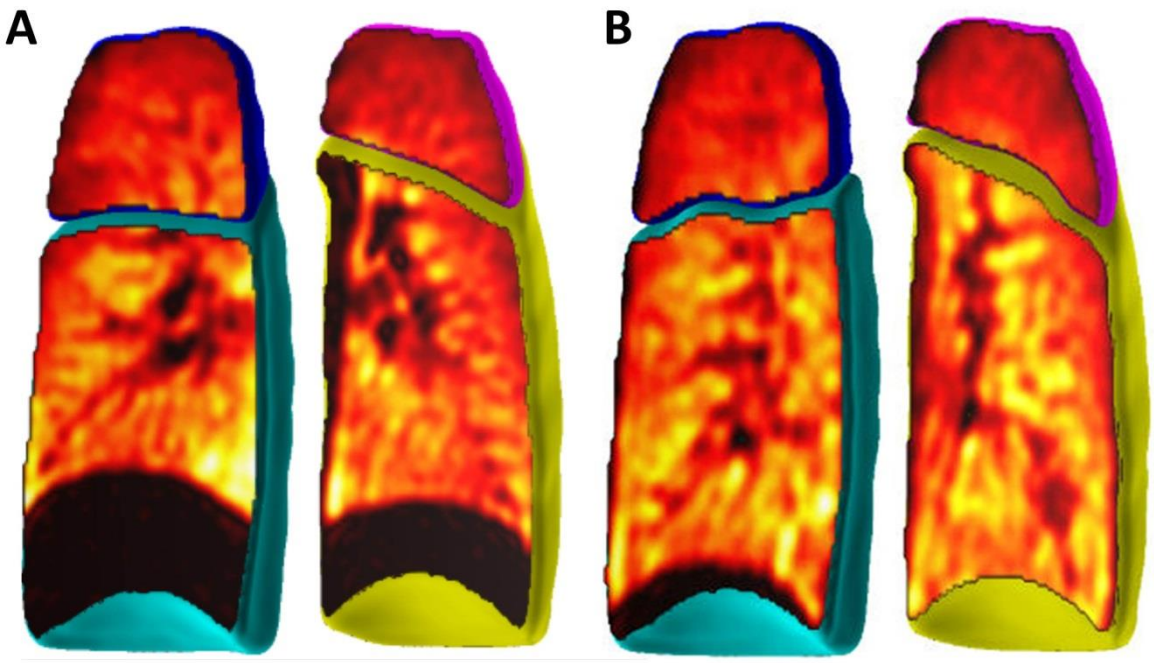
The 22 COPD patients comprised 15 males (68%) and seven females (32%) with mean age of 66.6years (SD 7.3) and mean pack-years of 66.3 years (SD 47.3). The majority were GOLD (Global Initiative for Chronic Obstructive Lung Disease) Stage II or III (Stage II 59.1%, stage III 36.4% and stage IV 4.5%).

3.4.2. ^{129}Xe MRI Analysis Trouble-shooting

Ventilation analysis issues

Manual inspection of the co-registration of CT and MRI identified errors in mapping in three cases in which registration had not produced an accurate fit (see Figure 3.2A). Transformation of the Xe-MRI images was undertaken to better fit the CT image. For example, if the diaphragm position was not correctly mapped from Xe-MRI to CT, then it would appear that the basal portions of the lower lobes were not being ventilated. In these cases, the ^{129}Xe MRI image was linearly transformed to fit the CT thorax size (see Figure 3.2B).

Figure 3.2 Three-dimensional hyperpolarized ^{129}Xe imaging derived ventilation maps showing inaccurate co-registration (3.2A) which, after correction, better fitted the thorax (3.2B).



ADC analysis issues 1) –data corruption

Unfortunately, in three of the ten patients, the ADC data files (to allow matching to MRI image) were corrupted and not usable. Therefore, seven patients data were used.

ADC analysis issues 2) – b values

Initial ADC values generated using the PTK Matlab program were of the order of 30-50cm^2/s, which is three orders of magnitude greater than previously reported[51-53]: e.g. 0.04cm^2/s in healthy lung parenchyma to 0.06cm^2/s in those with COPD. Root-cause analysis was undertaken to determine the discrepancy. Firstly, the units of measurement were rechecked to note any difference: For example, if ADC calculations used milliseconds (ms) rather than seconds, then values would be rescaled by factor of 1000 – i.e. values actually 0.03-0.05 cm^2/s. However, analysis of the Matlab code with an academic radiologist, found no such

unit correction. In addition, the ADC values of previous COPD patients (calculated for comparison), were of the order of 150-600 cm^2/s, which could not be explained by unit errors.

In the original PTK code, the *b* value formula (see Methods) appeared to be incorrect. Therefore the code was corrected and ADC values recalculated. As discussed above, the ADC is calculated from the ratio of signal intensities and adjusted according to the *b* value (the diffusion-weighted factor): $ADC = \frac{1}{b}\, ln\left(\frac{S_0}{S_1}\right)$

As such, as S_0 and S_1 generated independently, a difference in ADC values could potentially be corrected by adjusting for the difference in b values (i.e. dividing by b_{new} and then multiplying by b_{old}). This process will be used in the near future to compare the ADC findings for the pneumothorax patients with the COPD cohort, once the ADC values and calculations have been rechecked.

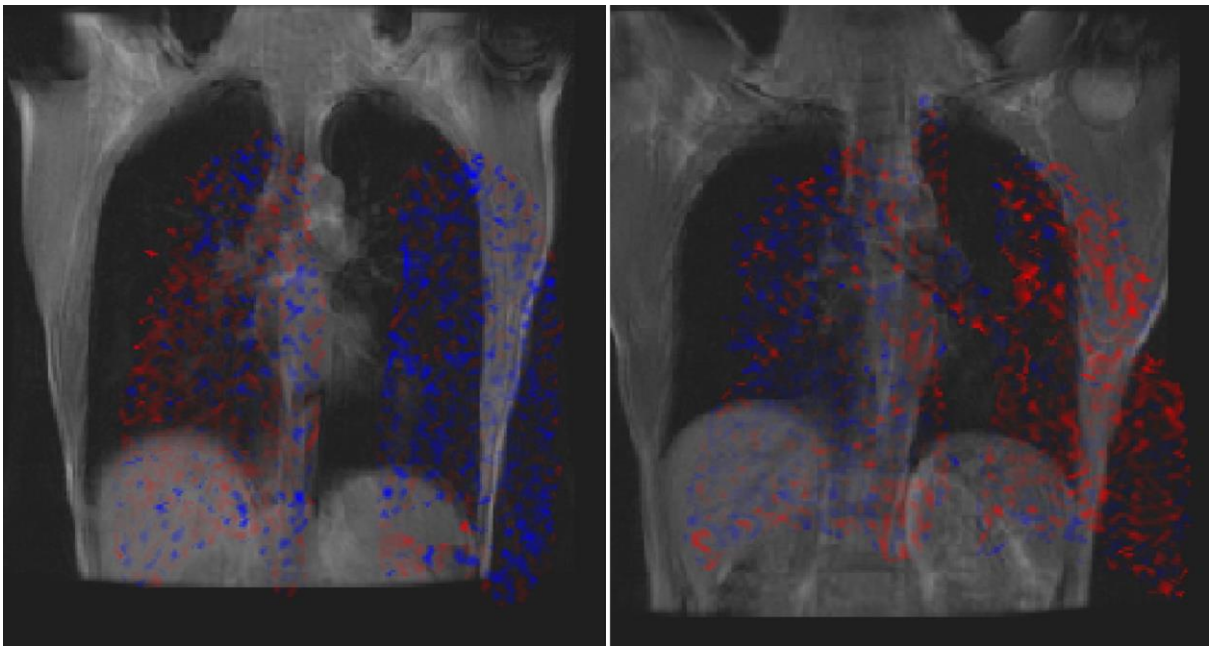
ADC analysis issues 3) Co-registration issues

In a similar manner to the Ventilation analysis, ADC requires co-registration of images (in case the proton MRI and Xenon MRI) and alignment with ADC values. Unfortunately, in three of the seven patients the co-registration did not effectively align the images (see Figure 3.3 for two examples). This is due to the intrinsic factors not adequately corrected for when converting the ADC data from data "p" files into digital images. Although a correction step was introduced into the Matlab code, it was not sufficient in these 3 cases. Clearly this could affect the results, but perhaps less than the co-registration issue in the ventilation analysis. The ventilation analysis uses a count of the presence (or not) of Xenon in voxels over the volume of the entire lobe, thus if only half of the lobe is incorrectly aligned the mean

ventilation will be half (or less). However, the lobar ADC value is simply a mean of the ADC values assigned that lobe, thus if half of the lobe does not have ADC readings, the mean will not be affected. This is demonstrated by the fact that despite these issues the ADC values for patient #8 and #10 are broadly in line with the other patients (see below)

During this study, it was not possible to correct all of the ADC misalignment, but this is a work in progress (see Future Directions).

Figure 3.3: Two examples of misaligned co-registration of ADC analysis (Patient Trial #8 and #10)



The pneumothorax ADC values are presented in this thesis, but as a result of these ADC issues, comparison has not been made with the COPD patients yet.

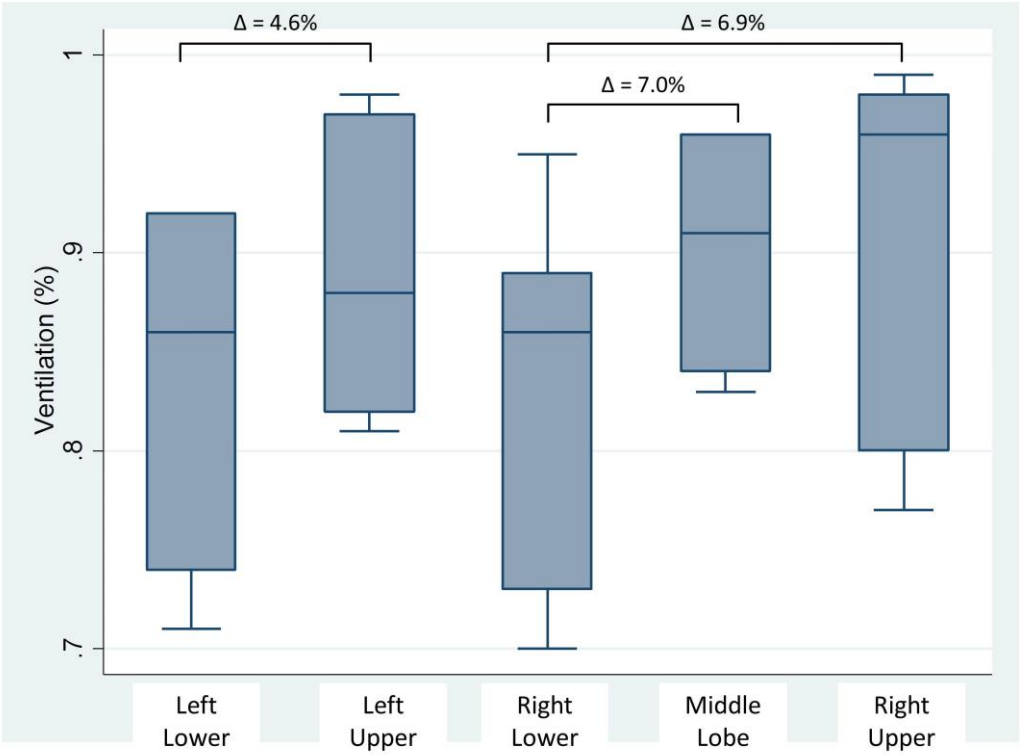
3.5. Ventilation results

For the ten patients, the mean overall percentage ventilation of lung receiving ^{129}Xe hyperpolarized gas (% ventilation) was 88.0% (SD 4.8%). There was variation both between lobes within the same patient and between patients (see Table 3.1 and Figure 3.4). However, the mean differences between lobes were not statistically significant.

Table 3.1 Percentage ^{129}Xe MRI ventilation by lobe for seven PSP patients

	% Ventilation with ^{129}Xe MRI by lobe						
Participant	**Right Upper**	**Middle lobe**	**Right Lower**	**Left Upper**	**Left Lower**	**Mean (Whole Lung)**	**SD (Whole Lung)**
1	92.4%	82.4%	88.3%	88.1%	91.2%	88.5%	3.9%
2	98.0%	83.5%	85.2%	98.2%	83.3%	89.6%	7.7%
3	96.5%	82.9%	94.8%	82.6%	92.1%	89.8%	6.6%
4	95.9%	96.2%	89.1%	93.1%	91.6%	93.2%	3.0%
5	77.1%	96.4%	73.3%	87.9%	74.4%	81.8%	10.0%
6	99.4%	93.9%	86.6%	97.3%	92.0%	93.8%	5.0%
7	86.6%	89.5%	70.0%	80.8%	70.7%	79.5%	8.9%
8	80.0%	90.8%	85.9%	82.2%	86.2%	85.0%	4.1%
9	81.4%	95.1%	83.1%	86.8%	88.1%	86.9%	5.3%
10	79.3%	94.5%	95.5%	94.5%	97.1%	92.2%	7.3%
Mean	**88.7%**	**90.5%**	**85.2%**	**89.2%**	**86.7%**	**88.0%**	
SD	8.7%	5.7%	8.2%	6.3%	8.4%	4.8%	

Figure 3.4 Box plot of median (and IQR) for %Ventilation by lobe. Δ = difference in means. p values calculated on differences between means not significant (using ANOVA with Bonferroni correction)



3.5.1. Ventilation: By smoking status

Smokers (current or ex) had a lower % ventilated volume than non-smokers (Table 3.2). Over all of the lobes, the mean % ventilated volume was lower: difference of 3.9% (95%CI -0.3 – 8.0%); but was particularly marked in the upper lobes: right 9.0% (95%CI -0.2 – 20.2%) and left 4.8% (95%CI -4.0 – 13.6%).

Table 3.2 Mean % ^{129}Xe MRI ventilation by lobe by smokers (current or ex) vs non-smokers. p values calculated using t test.

	% Ventilation with ^{129}Xe MRI by lobe						
Smoking status	**Right Upper**	**Middle lobe**	**Right Lower**	**Left Upper**	**Left Lower**		**Mean (All lobes) (95%CI)**
Non-smoker (n=5)	93.0%	89.4%	87.0%	91.6%	88.8%		90.0% (87.6% - 92.3%)
Smoker/Ex (n=5)	84.0%	91.8%	83.4%	86.8%	84.4%		86.1% (82.5% - 89.7%)
Overall (n=10)	88.5%	90.6%	85.2%	89.2%	86.6%		88.0% (85.9% - 90.2%)
Difference	9.0%	-2.4%	3.6%	4.8%	4.4%		3.9% (-0.3% - 8.0%)
p value	0.10	0.53	0.52	0.24	0.43		0.06

3.5.2. Ventilation: Comparison with PFTs

The mean percentage ventilated volume on ^{129}Xe MRI (mean for whole lung) was strongly correlated with standard PFTs by patient (Figures 3.5 and 3.6): FEV_1, R^2 0.41 (p 0.045) and kCO, R^2 0.77 (p <0.001).

Figure 3.5: Mean percentage ventilated volume (whole lung) vs forced expiratory volume in 1s (FEV_1).

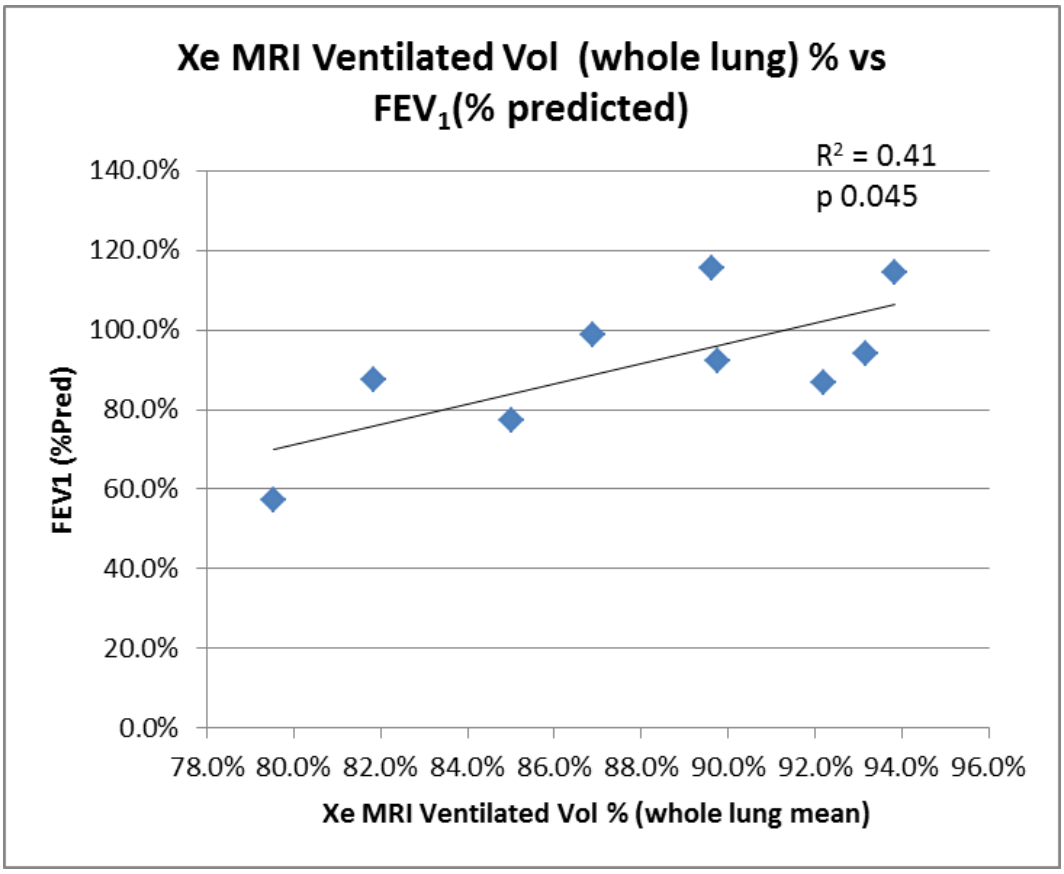
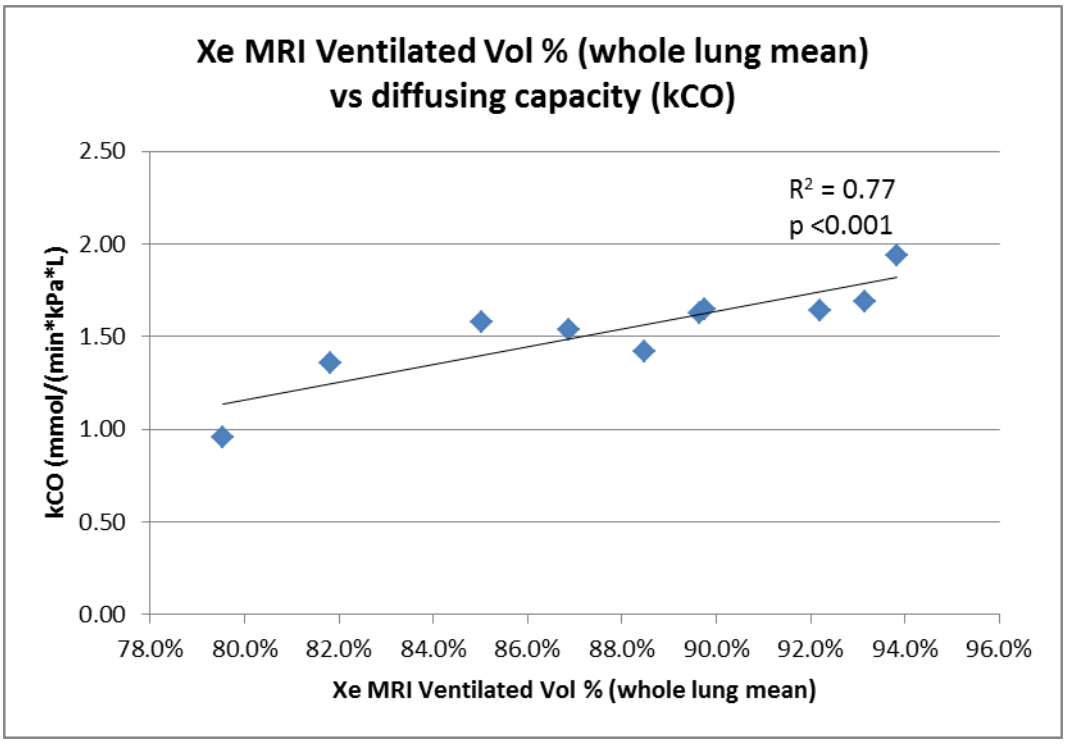


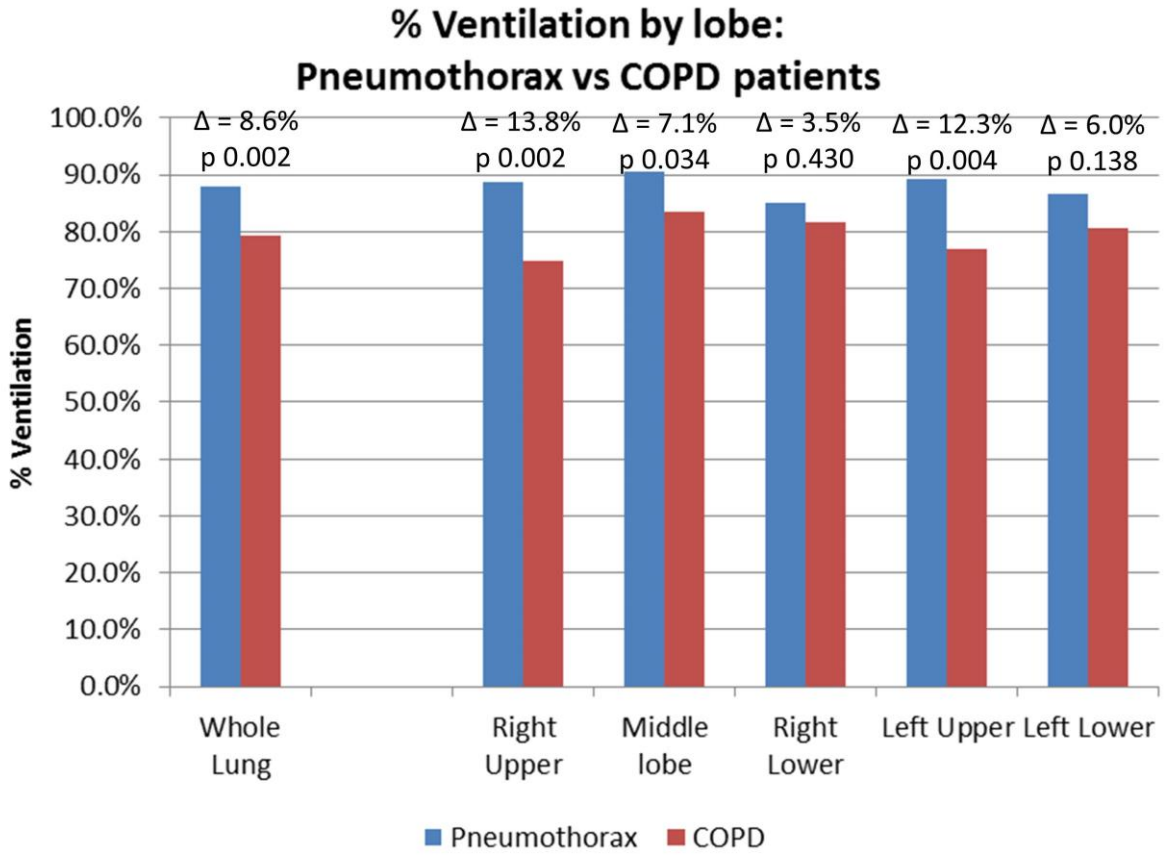
Figure 3.6: Mean percentage ventilated volume (whole lung) vs diffusing capacity, normalised to lung volume (kCO).



3.5.3. Ventilation: Comparison with COPD patients

Comparison was made with 22 COPD patients (Figure 3.7). The % ventilation on ^{129}Xe MR imaging was significantly lower in patients with COPD than those with pneumothorax: the overall mean (all lobes) difference was 8.6% (p 0.002), this was particularly marked in the upper lobes (right 13.8% and left 12.3%) – i.e. patients with COPD had significantly less ventilation as measured by presence of ^{129}Xe than pneumothorax patients.

Figure 3.7: Mean % Ventilation by lobe comparing pneumothorax patients (n=10) with COPD patients (n=22). p values calculated by t test.



3.6. ADC results

Mean ADC values were calculated in seven patients. The mean whole lung ADC for all patients was 0.040cm^2/s (95%CI 0.037-0.042). There was some variation across the patients (Table 3.3).

Table 3.3 Mean ADC (cm^2/s) for pneumothorax patients by lobe

	ADC (mean) cm^2/s						
Trial Number	**Whole Lung**		**Right Upper**	**Middle lobe**	**Right Lower**	**Left Upper**	**Left Lower**
Pneumothorax group (n=7)							
4	0.051		0.044	0.052	0.055	0.050	0.044
5	0.039		0.040	0.036	0.044	0.039	0.034
6	0.045		0.050	0.042	0.051	0.046	0.037
7	0.033		0.033	0.030	0.041	0.033	0.031
8	0.047		0.055	0.049	0.051	0.044	0.038
9	0.030		0.035	0.028	0.032	0.033	0.025
10	0.032		0.037	0.035	0.034	0.032	0.026
Mean	**0.040**		**0.042**	**0.039**	**0.044**	**0.040**	**0.034**
SD	0.008		0.008	0.009	0.009	0.007	0.007

3.6.1. ADC: By smoking status

The mean ADC was significantly lower for smokers than for non-smokers in all lobes (Table 3.4): overall difference for whole lung was 0.013cm^2/s (95%CI 0.010-0.017), p <0.001.

Table 3.4: Mean ADC by lobe by smokers (current or ex) vs non-smokers. p values calculated using t test.

	ADC (mean) cm^2/s						
Smoking status	**Right Upper**	**Middle lobe**	**Right Lower**	**Left Upper**	**Left Lower**		**Mean whole lung (95%CI)**
Non-smoker (n=3)	0.050	0.048	0.052	0.047	0.040		0.047 (0.044 - 0.050)
Smoker/Ex (n=4)	0.036	0.032	0.038	0.034	0.029		0.034 (0.032 - 0.036)
Overall (n=7)	0.042	0.039	0.044	0.040	0.034		0.040 (0.037 - 0.042)
Difference	0.013	0.015	0.015	0.012	0.011		0.013 (0.010 - 0.017)
p value	0.009	0.006	0.009	0.004	0.019		<0.001

3.6.2. ADC: Comparison with PFTs

Mean overall ADC values showed poor correlation with PFTs: FEV_1, r2 0.07 (p 0.54) and kCO, r2 0.22 (p 0.28). Data not shown.

3.7. Quantitative CT results

The mean overall (whole lung) %LAA for the ten pneumothorax patients was 8.6% (SD 4.1%), however there was marked variation both between patients and by lobe within patients (see Table 3.5).

Table 3.5: Quantitative CT analysis of % Low Attenuation Area (defined < -950HU) by lobe

	% LAA (<-950HU) by lobe						
Participant	**Right Upper**	**Middle lobe**	**Right Lower**	**Left Upper**	**Left Lower**		**Whole Lung**
1	8.7%	7.1%	3.6%	9.0%	4.1%		6.2%
2	10.5%	10.8%	5.9%	11.4%	7.1%		8.6%
3	15.1%	14.8%	13.5%	13.7%	12.3%		13.5%
4	12.5%	16.1%	10.4%	13.3%	9.4%		11.7%
5	8.8%	8.2%	9.3%	9.8%	11.8%		10.0%
6	3.5%	3.5%	3.0%	4.0%	2.7%		3.3%
7	4.3%	3.0%	3.2%	5.9%	4.0%		4.3%
8	4.9%	6.6%	4.7%	6.6%	3.7%		5.3%
9	6.9%	7.1%	7.1%	8.0%	7.4%		7.3%
10	17.2%	17.0%	13.6%	18.4%	14.2%		15.8%
Mean	**9.2%**	**9.4%**	**7.4%**	**10.0%**	**7.7%**		**8.6%**
SD	4.6%	5.0%	4.1%	4.3%	4.1%		4.1%

3.7.1. Quantitative CT: By smoking status

The %LAA was higher for smokers than non-smokers (Table 3.6). Overall mean %LAA for the whole lung was significantly different: 10.2% in smokers and 7.3% for non-smokers (difference 2.9% (95%CI 0.5-5.2%), p 0.01).

Table 3.6: % LAA by lobe; Comparison of smokers with non-smokers. p values calculated using t test

	% LAA (<-950HU) by lobe						
Smoking status	**Right Upper**	**Middle lobe**	**Right Lower**	**Left Upper**	**Left Lower**		**Mean whole lung (95%CI)**
Non-smoker (n=5)	8.0%	8.8%	5.5%	8.9%	5.4%		7.3% (5.8% - 8.9%)
Smoker/Ex (n=5)	10.5%	10.0%	9.3%	11.2%	9.9%		10.2% (8.3% - 12.1%)
Overall (n=10)	9.2%	9.4%	7.4%	10.0%	7.7%		8.6% (7.5% - 10%)
Difference	2.4%	1.2%	3.8%	2.3%	4.5%		2.9% (5.2% - 0.5%)
p value	0.43	0.73	0.14	0.43	0.07		0.01

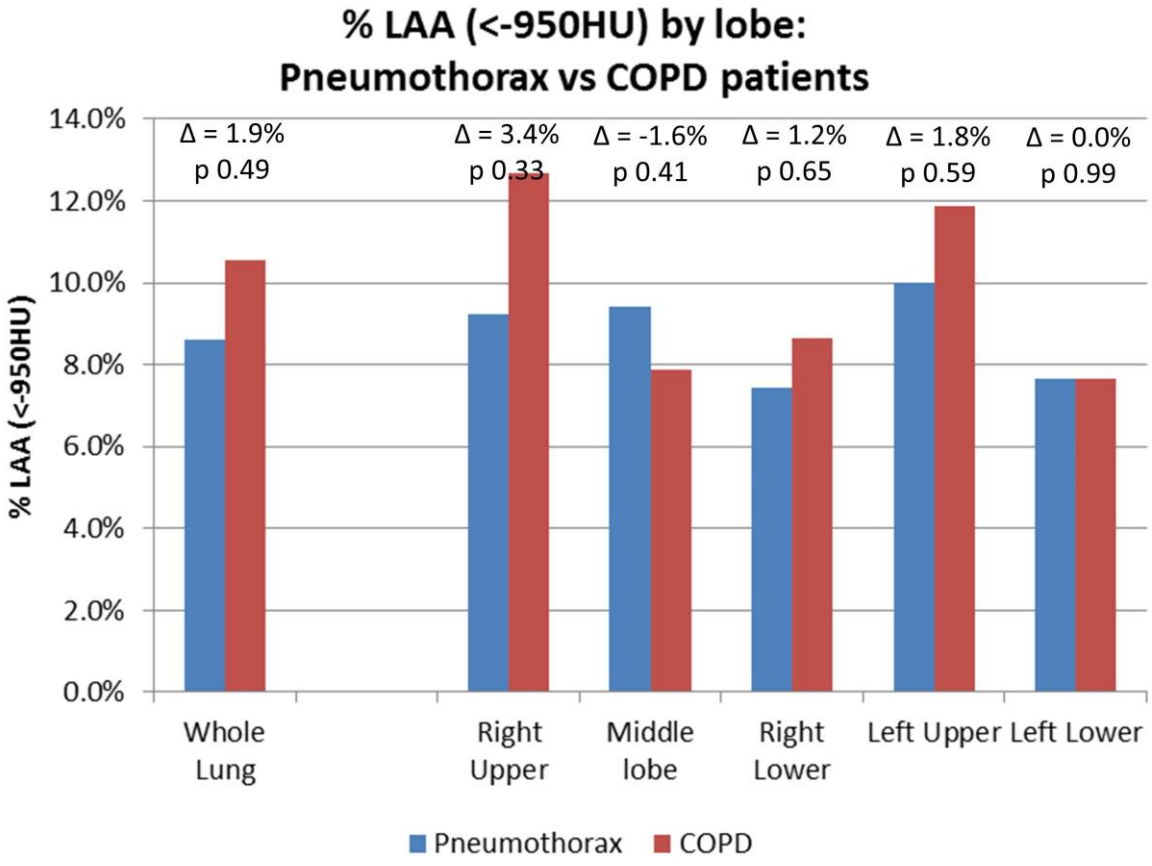
3.7.2. Quantitative CT: Comparison with PFTs

The %LAA on quantitative CT scan analysis showed no correlation with PFTs. Mean % LAA for whole lung correlation: FEV1, r^2 0.002 and kCO, r^2 0.04. Data not shown.

3.7.3. Quantitative CT: Comparison with COPD patients

The mean %LAA in the 22 COPD patients was slightly higher than the pneumothorax patients: particularly in the upper lobes: right 3.4% and left 1.8% (Figure 3.8). However, the differences were not statistically significant.

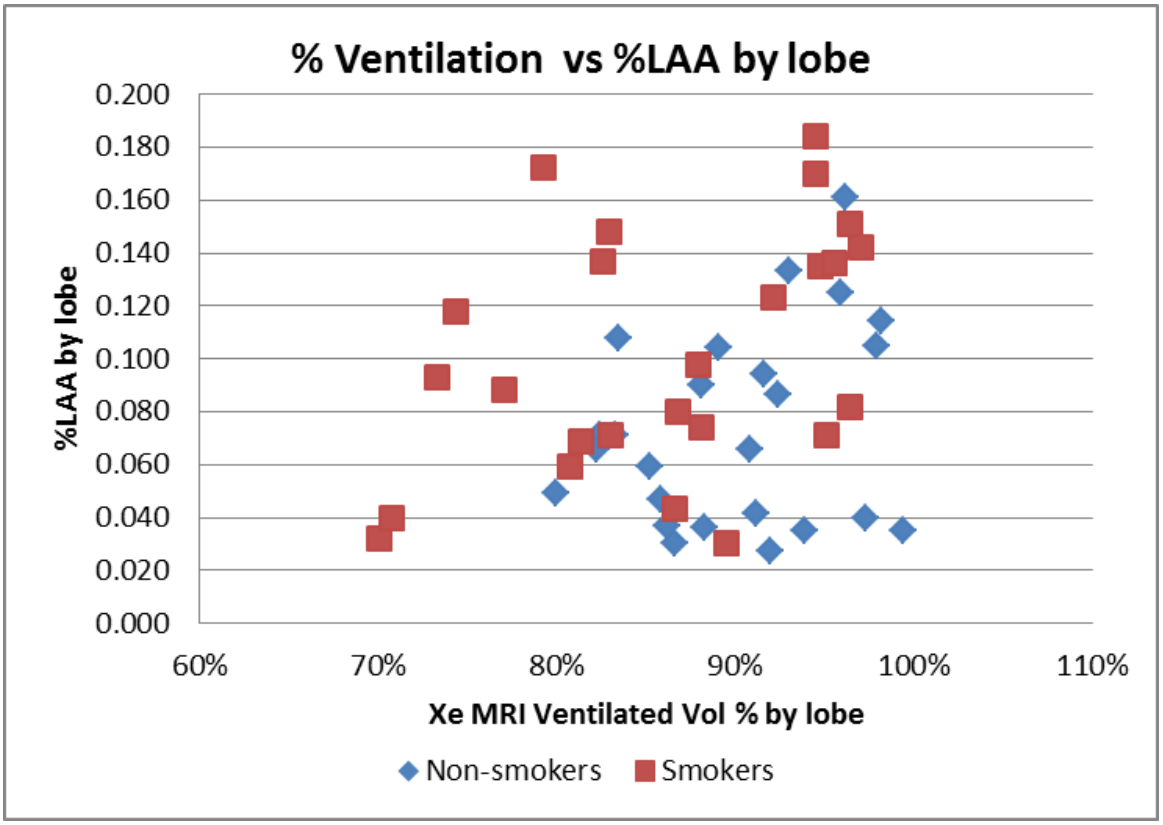
Figure 3.8: %LAA by lobe comparing pneumothorax patients (n=10) with COPD patients (n=22).



3.7.4. Comparison of Ventilation with Quantitative CT

Analysis of the percentage ventilated volume ^{129}Xe MRI did not show good correlation with %LAA on quantitative CT scan (Figure 3.9): r^2 0.12. The effect was not modified when stratified by smokers and non-smokers.

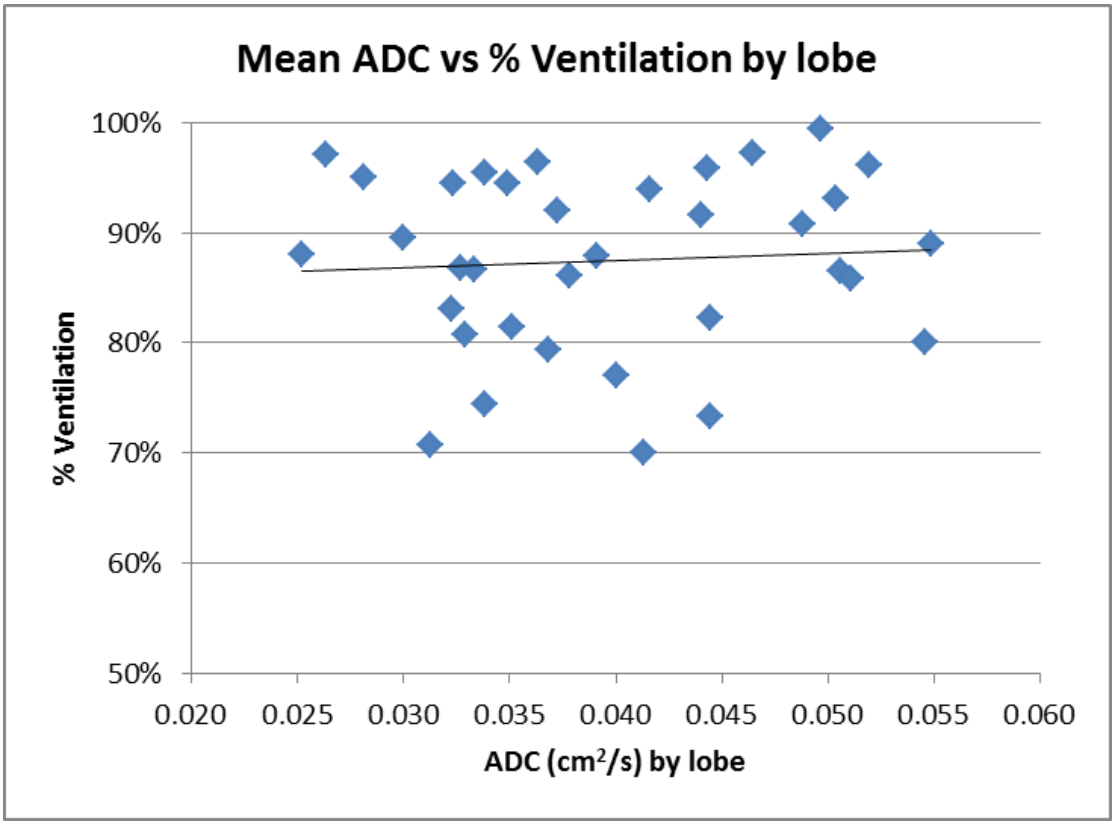
Figure 3.9: % ventilated volume vs %LAA on quantitative CT scan by lobe. Smokers and non-smokers highlighted separately.



3.7.5. Comparison of Ventilation with ADC

The percentage ventilated volume ^{129}Xe MRI showed no correlation with mean ADC (Figure 3.10): r^2 0.001.

Figure 3.10: Mean ADC vs % ventilated volume by lobe.



3.7.6. Comparison of ADC with Quantitative CT

The mean ADC per lobe showed no correlation with %LAA on quantitative CT scan: r^2 0.01 (p 0.56). Data not shown.

3.8. Sensitivity analysis - PFTs and smoking

As a result of the unexpected finding of lower ADC values in smokers than non-smokers, a sensitivity analysis was conducted to determine whether other factors were driving the differences. There were no difference in age or BMI between smokers and non-smokers. The

two female pneumothorax patients were both non-smokers. As expected, the PFTs of the smokers were lower than that of the non-smokers (Table 3.7). The difference was sustained when analysing just the 7 patients who had ADC data available (data not shown).

Table 3.7: Difference in PFTs between smokers and non-smokers

	FEV_1 (% predicted)			**DLCO (mmol/(min*kPa))**			**kCO (mmol/(min*kPa*L))**		
Pneumothorax	Mean	SD	n*	Mean	SD	n*	Mean	SD	n*
Non-smoker	104.2	18.1	5	9.0	1.8	5	1.4	0.3	5
Smoker	84.4	16.0	5	10.6	1.6	5	1.7	0.2	5
Difference	**-19.78**	**10.80**	**10**	**1.55**	**1.08**	**10**	**0.22**	**0.15**	**10**
p value**	0.10			0.19			0.19		

*n = number of participants, ** p value = between groups ANOVA

3.9. Adverse Events

Mild transient adverse events were common after administration of the ^{129}Xe. All ten patients experienced some form of reaction. Over the two scans, all but one patient experienced 2 or more reactions. The most common were deep voice (32.5%), euphoria (22.5%), dizziness (17.5%), and dysaesthesia (12.5%). However, the mean duration of all effects was less than 30seconds (See Table 3.8). No patients experienced long term side effects. The maximum duration of any effect in any patient was 3 minutes (deep voice and euphoria). All patients were happy to continue with their second ^{129}Xe MRI scan despite these effects.

Table 3.8: Total adverse events occurring in 20 scans (2 per patient) and duration(s)

Adverse Event	Number of events	%	Mean duration (s)
Deep Voice	13	32.5%	29.4
Euphoria	9	22.5%	38.9
Dizziness	7	17.5%	21.4
Dysesthesia	5	12.5%	19.0
Impaired hearing	2	5.0%	7.5
Light headedness	2	5.0%	25.0
Tingling	2	5.0%	20.0
Total	**40**	**100.0%**	**27.1**

3.10. Discussion

Exploratory results described in this thesis represent the first reported use of ^{129}Xe MRI to assess patients who have suffered with PSP.

3.10.1. Ventilation and %LAA

There was variation in the percentage ventilation both between patients and by lobe in the same patients. % Ventilation was greater in the five non-smokers than the five current or ex-smokers, particularly in the upper lobes. This is corroborated by the findings of greater percentage of low attenuation areas (%LAA <-950HU) in the upper lobes of pneumothorax patients who were smokers. These findings are in keeping with previous CT findings of a preference for ELC to occur in the upper zones. Therefore, the reduced ventilation in smokers could represent structural abnormalities (ELC) or early emphysema, known to be associated with PSP, but exacerbated by smoking. Comparison with the COPD patients confirmed that those patients (who have established emphysema) had significantly lower %

ventilation than the pneumothorax. This could represent more severe emphysema and/or gas trapping in the small airways.

Reassuringly, the % ventilation results in the pneumothorax patients (mean over all lobes) were correlated with PFTs: both spirometry (FEV_1) and diffusing capacity (kCO), suggesting a functional as well as imaging based abnormality; even though many of the pneumothorax patients had PFTs within the normal range. It may be that the ^{129}Xe ventilation analysis can highlight functional abnormalities in patients which would otherwise be classified as normal.

%LAA was not correlated with PFTs in this patient group, unlike the COPD patients[54]. This may be because the established threshold of -950HU, defined for COPD, is not suitable for PSP patients. The pattern of ELC in pneumothorax could be isolated to the peripheries (subpleural) or could be patchy. In which case ^{129}Xe MRI ventilation analysis may be a more sensitive way of identifying structural abnormalities in PSP patients than CT scanning.

3.10.2. ADC

ADC data purport to demonstrate airspace enlargement, defined as the distance diffused by the inhaled gas. A recent study attempted to validate the ADC measurement with that made histologically at lung resection[128]. The authors took recently explanted lungs (transplant rejections) from five patients with severe COPD and two with idiopathic pulmonary fibrosis (IPF). They found good correlation between the ADC values of airspace size with that measured histologically (r^2 0.59) for both the COPD patients (with enlarged airspaces) and those with IPF (with smaller airspaces, as a result of excess accumulation of collagen and elastin) [128]. Data on the 22 COPD patients from Oxford, showed good correlation mean ADC and %LAA on quantitative CT and PFT results[54].

The mean ADC value in the PSP patients (0.040cm^2/s) is consistent with previous literature in healthy patients[51, 52]. This is suggestive that any airspace enlargement (emphysema) may be mild or patchy. However, there was variation between patients: with four of seven patients having mean ADC of <0.040cm^2/s and remaining three were ≥0.045cm^2/s; None had mean ADC values in the region of 0.06cm^2/s, as had been previously reported in COPD patients[51, 52].

The ADC results for the pneumothorax patients were not consistent with other metrics: there was no correlation between mean ADC and % ventilation or %LAA. The difference between smokers and non-smokers is not easily explained. PSP smokers had greater %LAA on quantitative CT scanning and reduced % ventilation, which is in keeping with early emphysema or ELC. However, the ADC values were lower in smokers than non-smokers – the opposite of the expected result, given previous literature comparing older never-smokers and COPD patients[115]. However, further work is required to correct the issues with the ADC analysis and comparison with healthy volunteers and COPD patients (see below).

3.10.3. Limitations

The small number of patients in this exploratory study, and in the comparison groups, may mean that any genuine difference in the ^{129}Xe ventilation or ADC values may not be statistically significant, due to lack of statistical power.

Neither the volume of inhaled Xe, nor the ADC values, were normalised to the total lung volume across the patients. Each subject inhaled a fixed 1-L volume of gas from functional reserve capacity. As a result, differences in alveolar volume related to body size and lung volume rather than to disease may be reflected in the ADC value. This may reduce the

precision of the mean ADC measurements because of different alveolar inflation volumes across subjects.

The co-registration process in the ventilation and ADC analysis was not perfect and on a number of occasions required manual adjustment of images to better fit the ^{129}Xe MR image to the CT and proton MR images. Therefore, although effort was made to optimise the co-registration, there may still be consistencies within the analysis between patients.

Half of the pneumothorax patients were ex- or current-smokers. Therefore, there is a possibility that the some of the defects seen are an effect of smoking, rather than an intrinsic lung abnormality, but this in itself an important finding.

3.11. Conclusions

These data are the first reported use of ^{129}Xe MRI in patients post-pneumothorax. This analysis shows that there is variability in ventilation and ADC values both between patients and by lobes within the same patient. Reduced % ventilation was correlated with greater %LAA on quantitative CT scanning and with reduced pulmonary function. These areas of reduced ventilation may represent the ELC or early emphysema known to be associated with PSP, and were more marked in smokers than non-smokers. The reduction in ventilation for smokers was greatest in the upper lobes, suggesting that although underlying abnormalities may be present in all patients, they may be exacerbated by smoking. When compared to a COPD cohort, the pneumothorax results were consistent with milder but identifiable abnormalities.

The mean ADC of pneumothorax patients was lower than described in COPD patients, as expected, assuming that ADC is truly a measure of the dilatation of the small airways and gas trapping (as seen in emphysema). However, unexpectedly, the mean ADC values for the pneumothorax non-smokers were significantly greater than the smokers. Even though all the patients were not symptomatic, the PFTs of the non-smokers were found to be worse than that of the smokers. Although this may be have occurred by chance (small sample size), the ADC measure could be a useful measure of sub-clinical lung function impairment.

^{129}Xe MRI has the potential to be a technique using non-ionising radiation to visualise and characterise important structural abnormalities of ventilation.

3.12. Future directions

The utility of the Xenon enhanced MRI scanning in the clinical assessment of PSP requires further prospective clinical work, which is on-going.

3.12.1. Comparison with healthy volunteers

Recruitment is continuing for a cohort of healthy volunteers to undergo ^{129}Xe MRI scanning (ventilation and ADC) as a control group for comparison with pneumothorax (and other patient groups). This work is vital particularly when analysing patient with mild or early disease (which may be the case with many patients with pneumothorax).

3.12.2. Reconciliation of ADC calculations and mis-alignment

As discussed in the Results section, the issues with the ADC value calculations for pneumothorax and COPD patients will be reconciled and double-checked, to allow accurate

comparison. Work is also in-progress to implement a better inter-modal (CT-MRI) registration and pulmonary lobar segmentation using pulmonary vasculature-derived fissure completion method.

3.12.3. Recurrence risk prediction

If ventilation or ADC defects, for example, can highlight patients at greater risk of long term recurrence, better than standard PFTs or without the need for ionising radiation (CT scan), then this technique could be used to stratify patients at risk. At present there is no robust method of identifying patients at high risk of recurrence. Studies of CT "bleb scores" have to date not been convincing (see Chapter 7).

Recruitment for additional pneumothorax patients is on-going. These patients will be prospectively followed-up for 12 months in total to capture recurrence data. Future work will incorporate this data to assess whether those patients who recur form a distinct subgroup in terms of ^{129}Xe MRI ventilation or ADC values.

3.12.4. Evolution over follow-up

These current analyses are of patients scanned within 1-3 months of their pneumothorax. Do the changes persist or are they transient? Many patients with PSP are current smokers. Does smoking cessation have an effect on an individual which can be measured with ^{129}Xe MRI? Ethical approval will be sought to perform additional testing on the ten patients in this study in 12-24 months' time. Of particular interest will be those current smokers, who have managed to quit smoking in the interim period.

Author contribution:

R Hallifax recruited patients, downloaded raw data, performed data analysis (Matlab) on all PSP patients, and manuscript preparation. Training in these methods was provided by Tahreema Matin and Mitch Chen (Academic Radiologists from the Department of Radiology).

4. Novel Functional Assessment – Lung inhomogeneity

4.1. Background

The traditional definition of patients with PSP having "no underlying lung disease" is being challenged (see Introduction). There is increasing evidence of ELC in the lung parenchyma, bronchial inflammatory and abnormalities at the sub-parietal pleural layer (pleural porosity)[12, 14, 17-19].

Methods of imaging the lungs of patients who have had a PSP are discussed in detail in Chapter 3 (^{129}Xe MRI) and Chapter 7 (CT scoring).

This chapter will discuss the limitations of current PFTs, particularly with respect to the potentially subtle disease found in patients with PSP, and describe the use of a new novel method of measuring lung inhomogeneity using highly precise measurements of respiratory gas exchange (the Molecular Flow Sensor, MFS) and a new mathematical model. These have been developed as a collaborative project between the Department of Chemistry and the Department of Physiology, Anatomy and Genetics at the University of Oxford.

4.1.1. Pulmonary Function Tests (PFTs) in Pneumothorax

The functional assessment of the lungs in patients who have had PSP is not well studied. PFTs focus on overall measures of function: measurement of gas flow through the larger airways (spirometry) and diffusion of inhaled gas into the blood (diffusion capacity). In 1965, Williams and Kane performed lung function tests on 14 patients who had "recovered uneventfully from SP and did not show evidence of other cardiopulmonary disease"[55]. In 5/14 patients the diffusing capacity was <73% of normal, but only one patient (who was asymptomatic) had evidence of emphysema on the basis of marked reduction in diffusing

capacity in association with increased lung compliance and low lung retractive force[55]. This small study suggests that mild abnormalities in PFTs can be found in PSP patients. In 1987, Pawlowicz *et al* reported the PFTs in 56 young adults after PSP, compared to control group of 20 age- and smoking habit-matched healthy participants[56]. Only four (7%) of the 56 patients had evidence of emphysema, based on PFT measurements.

In 1988, Lange *et al* reported an impressive long-term follow-up study of PFTs 22 to 35 years after a PSP event, either treated with talc pleurodesis or by simple drainage[57]. 75 of 114 patients fully completed the study (others having died from unrelated causes, emigrated or failed to respond). The mean values for FEV_1, vital capacity (VC) and total lung capacity (TLC) were lower than predicted (by standardised values) but the "impairment was slight and in most subjects were within the normal range" [57]. The group treated with talc pleurodesis (n=46) showed a mild restrictive impairment of lung function (with a mean TLC of 89% predicted); whereas the group treated with drainage alone had a mean TLC 96% predicted (n=29) [57]. Interestingly, those patients with recurrent pneumothorax, the mean TLC was significantly lower (88% predicted) than that in those with no recurrence (95% predicted) [57]. However, this finding may be confounded by the fact that they are more likely to have received talc (for recurrence prevention). Having suffered with a pneumothorax in early life (all under 41 years old) did not appear to predispose this group to emphysema, as defined at the time. Our definitions of chronic lung impairment are now more subtle. Fourteen (19%) of the 75 patients demonstrated airflow obstruction (with five being severe FEV_1<50% predicted); but 12 of these were lifelong heavy smokers[57].

Shramel *et al* assessed PFT findings along with CT and surgical assessments of ELC, which they defined as blebs or bullae[58]. 85 patients had PFTs six weeks after VATS for

pneumothorax (indications not listed) [58]. ELCs were graded from a score of 0 (no ELCs) to 3 (extensive ELCs) by combining CT and VATS findings. They found no significant differences in PFTs between those with ELC score <2 and ELC score ≥2, except for TLC: 88.1% vs 99.0% predicted, respectively. 67% of the patients were smokers. In this subgroup, the kC0 was significantly lower in patients with ELC score ≥2 (70.4%) compared to an ELCs score <2 (78.8%)[58]. However, it is difficult to draw firm conclusions from this data as the surgical treatment undertaken at VATS was determined by the macroscopic findings of blebs and bullae; thereby directly influencing (and hence confounding) the results.

PFTs are well-established, validated and routinely used in the diagnosis and on-going monitoring of many pulmonary diseases. However, they do have a number of limitations. Spirometry is effort- and technique-dependent, which can be a particular problem for patients with significant breathlessness or advanced respiratory disease. In addition, PFTs are relatively insensitive to changes in early lung disease, which may be the case in patients with PSP. A recent large observational study involving 2,736 current or former smokers and controls who had never smoked found that clinically significant respiratory symptoms were present in 50% of current or former smokers with preserved PFTs (i.e. within the normal range)[129]. PFTs are a tool to detect the severity of established and significant damage. However, once abnormalities are detected, it may be “too late” to intervene. In addition, PFTs provide global measures of lung function, and relatively little information about regional pathology and heterogeneity in the lungs[59-61].

The abnormalities in patients with PSP may be regional (e.g. at the lung apices) or subtle enough not to be easily distinguished on these global assessments.

4.1.2. Ventilation and Perfusion assessment

In most respiratory diseases, the primary physiological mechanism limiting efficient gas exchange is ventilation-perfusion mismatch: i.e. discrepancy between the distribution of blood flow through the lung (perfusion) and the distribution of gas flow within the lung (ventilation)[62]. Measuring these distributions would provide additional information in the assessment of gas exchange in the lungs, and may be useful in the diagnosis and management of patients with established or suspected respiratory disease[60, 63].

Methodology for measuring blood and gas distributions in the lung was developed in the 1970s, e.g. the multiple inert gas elimination technique (MIGET). This is a well-validated method of determining ventilation and perfusion distributions but has a number of limitations. It is invasive, requiring a systemic arterial catheter in place for a prolonged intravenous infusion and sampling of arterial blood, and time-consuming[64]. MIGET is therefore unsuitable for use in routine clinical practice.

4.1.3. New techniques

The new methodology developed in Oxford uses non-invasive means of estimating the regional variability of ventilation and perfusion in the lung that involves simply breathing through a mouthpiece for 15 minutes. During that period, the participant initially breathes air for 10 minutes and then 5 minutes of pure oxygen (See Methods), both at normal tidal breathing. Therefore, the test is simple to conduct and uses inexpensive gases.

This new methodology has been made possible by two recent advances. Firstly, a new gas analyser (MFS) has been developed for the measurement of the composition of inspired and expired gases. The concentrations of oxygen (O_2), carbon dioxide (CO_2), and water vapour within the chamber are measured every 10 milliseconds using highly accurate laser

absorption spectroscopy, while the flow of gas is measured contemporaneously using a modified pneumotachograph[65, 66]. Secondly, the increased precision of gas analysis has facilitated the development of the novel mathematical model of inhomogenity in the lung[67].

4.1.4. Multiple breath washout

Measurement of the change in respiratory gas exchange from breathing air to pure O_2 in this new model is the same concept as Multiple Breath Washout (MBW) assessments using an insert gas (e.g. Nitrogen, N_2), which was described as early as the 1950s. MBW assesses how efficiently N_2 is washed out of the lung by oxygen. The efficiency of ventilation distribution, and hence potential lung inhomogeneity can be estimated on the assumption that the more homogenous the lung, the quicker the washout will be [68]. The concept of “slow” and “fast” compartments corresponding to differential ventilation defects within the lung has been shown using N_2 washout in patients with cystic fibrosis[59, 60]. However, MBW has been hampered in its utility by the limited accuracy of existing technologies and lack of robustly validated commercial washout systems, and is not routinely used in clinical practise. A combined European Respiratory Society (ERS) and American Thoracic Society (ATS) consensus statement on provided recommendations for inert gas washout system characteristics[68]. These characteristics are more than met by the MFS used in this study[65]. The new methodology, by providing significant accuracy improvements, allows the model of lung inhomogeneity to be used to provide a number of determined parameters including “compliance distribution”, alveolar volume and “deadspace distribution”(see Methods).

4.2. Aims and hypothesis

The aim of this study is to utilise this new methodology to determine estimates of lung inhomogeneity in patients who have had a PSP, in comparison with patients with COPD and healthy volunteers (young and old).

The hypothesis is that patients who have suffered with PSP do not have "normal" lungs, and the derived metrics of lung inhomogeneity, determined by this new methodology, will be distinct from health volunteers and patients with established COPD. The findings will be compared to standard PFTs, but functional abnormalities in patients with pneumothorax may be too "early" or subtle to be detected by standard testing.

4.3. Methods

4.3.1. Participants

Pneumothorax patients

Pneumothorax patients were enrolled into the OX-RAMPP (see Chapter 3 – Methods).

Healthy volunteers and COPD patients

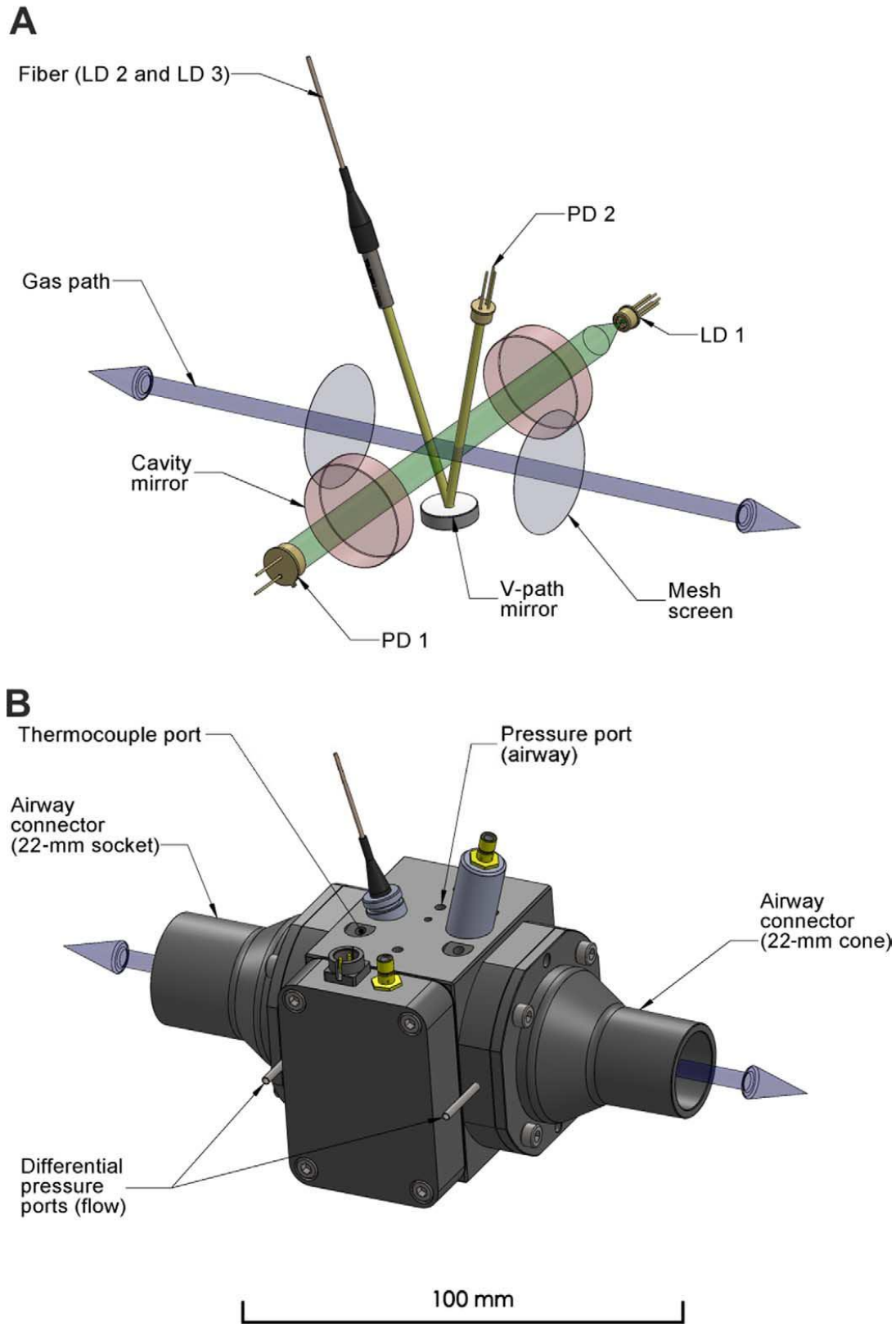
Data from healthy volunteers and COPD patients used in this study were obtained from the authors of the recent study describing the methodology and validation of the MFS and mathematical model[67]. That study was conceived and undertaken by the Department of Physiology, Anatomy and Genetics (University of Oxford). Ethical approval for this original study was granted by NHS Research Ethics Committee (Ref 11/SS/0091). These participants

comprised of three groups: six healthy young individuals (20-30 years old), six healthy older individuals (60-80 years) and six participants with mild or moderate COPD.

4.3.2. Novel measurement device

The MFS was developed to provide rapid, highly accurate measures of gas exchange[65]. This technique uses laser absorption spectroscopy to measure the concentration of O_2, CO_2 and water vapour every 10ms. The respiratory mass spectrometer is recognised by some as the "gold standard gas analyser"[130]. However, this inline laser absorption technology provided simultaneous time-aligned measurements of concentration and flow (by being in-line with airflow, rather than a side port), had faster response time and is capable of measuring water vapour[65]. Other systems have to calculate or estimate water vapour, which is less accurate. O_2, CO_2 and water vapour all have different optical absorption frequencies. In order to measure all three simultaneously, three laser diodes were mounted together to produce a single multichannel absorption spectrometer (see Figure 4.1). For CO_2 and water vapour the transition strengths are similar and large enough to be measured using direct absorption spectroscopy. Therefore, two lasers (LD2 and LD3) could share the same simple V-shaped optical path of ~5cm in the MFS head[65]. For O_2, the transition strength is much weaker, so a much greater optical path is required. In order for this path to be contained within the MFS an optical cavity was constructed with a pair of highly reflective mirrors to allow multiple reflections prior to radiation collection.

Figure 4.1 Design of MFS head. A: simplified diagram showing the gas path (inspiratory and expiratory). Radiation from Laser Diode (LD) 1 was injected into an optical cavity constructed from a pair of highly reflective mirrors (red) and collected by photodiode (PD) 1 in order to measure O_2. LD2 and LD3 were used to measure CO_2 and water vapour, respectively. B: Three-dimensional CAD model. (Reproduced with permission [65])



The MFS head is contained within a protective canister. Participants breathe through a mouthpiece directly attached to the device (Figure 4.2).

Figure 4.2: Photograph of healthy participant breathing through the mouthpiece attached to the MFS. (Reproduced with permission[67])



4.3.3. Study procedure

Participants were provided with information leaflets along with verbal explanation of the technique. Written consent was taken in every case. The participants were seated in a chair during the test. The height and angle of the rubber mouthpiece were adjusted to the patient's height for comfort. A nose-clip was provided to ensure that all gas exchange occurred through the mouth, via the device. Participants were asked to breath normally through the mouthpiece. After a few minutes of familiarisation, the study period

commenced, with real-time partial pressures being recorded every 10ms, whilst breathing air. After 10 minutes of normal breathing, the gas supply was changed to medical-grade pure O_2 for a further 5 minutes. Each pneumothorax participant was asked to undertake this test twice, with a break of at least 15 minutes. In the previous study of the healthy volunteers and COPD patients, each participant underwent six tests[67]. Out of the 108 in total (18 participants, 6 repeats each), only 4 failed to "converge" to provide realistic model parameters (see below). In addition, the six repeat runs showed good repeatability[67]. This high success rate of convergence and repeatability meant two datasets per participant were deemed sufficient in these patients. In six patients, the model converged in both datasets, so the mean values of the two models were used. In two case, one dataset for each patient did not converge (#5, due to irregularities in the first washout phase; #2, the model converged at a physiologically unfeasible position), so data presented is that of the successfully convergent model.

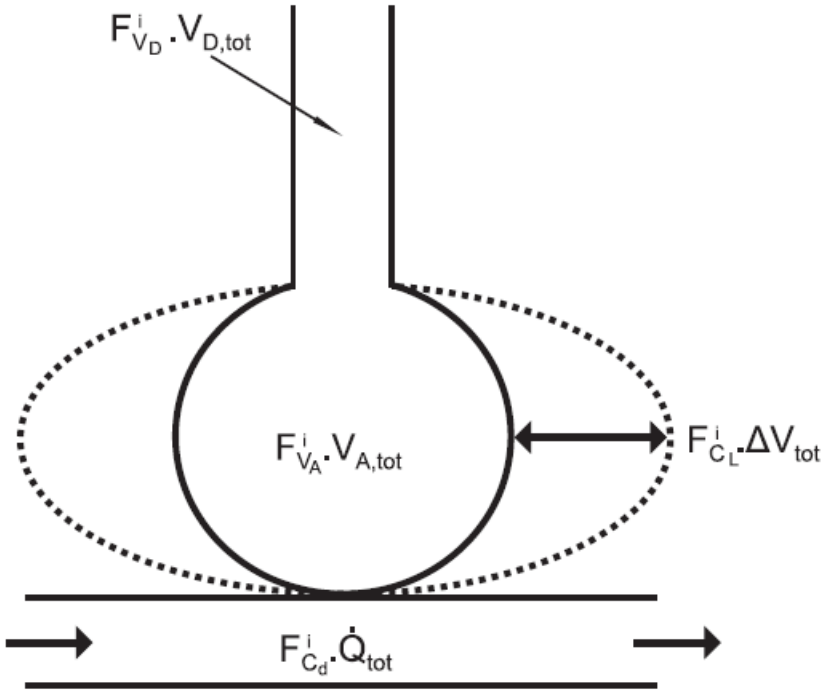
The measured partial pressures in initial breathing phase and during washout were saved under the participant's trial number (anonymously) onto a laptop computer attached to the MFS. Data were then fed into the mathematical model on high performance computers in the Oxford Advanced Research Computing Facility.

4.3.4. Mathematical Modelling

The basis of the mathematical model is that the inhomogeneity in any individual's lungs can be expressed through a set of parameters that describe a model based on the behaviour of 125 lung compartments[67]. Each lung compartment is assumed to have: equal fractional share (FV_A) of the total alveolar volume ($V_{A,tot}$) at functional residual capacity (FRC), equal fractional share (FC_L) of the total lung compliance ($C_{L,tot}$), equal fractional share (FC_d) of total

pulmonary vascular conductance ($C_{d,tot}$), and equal fractional share (FV_D) of total anatomical deadspace ($V_{D,tot}$) as shown in Figure 4.3. The deadspace fraction relative to alveolar volume fraction is assumed to be normally distributed, whereas C_L and C_d form a bivariate log-normal distribution of FC_L and FC_d relative to FV_A [67].

Figure 4.3: Model of lung inhomogeneity. Schematic of a single lung unit of the model, illustrating the fractional changes in alveolar volume (FV_A), lung compliance (FC_L), pulmonary vascular conductance (FC_d) and anatomical deadspace (FV_D). Q_{tot} is total pulmonary flow. (Reproduced with permission[67])



In the previous publication, the use of fractional lung compliance and fractional pulmonary vascular conductance in preference to ventilation and perfusion to ensure that the model of lung inhomogeneity was constructed from properties that are *intrinsic* to the lung. Ventilation and perfusion will vary dependent upon the nature of breathing (i.e. will differ by respiratory effort and depth of breathing) and cardiac output. However, in these patients, measured at rest (at normal breathing with no change in cardiac output), the term

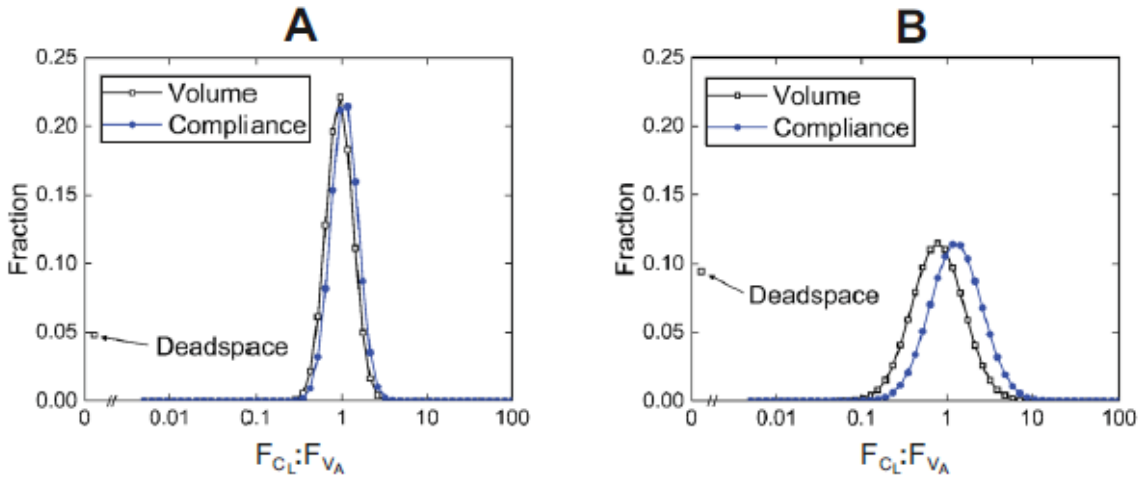
"compliance distribution" in this case can be used as a surrogate for the distribution of ventilation in the lung.

The model parameters are determined using non-linear regression to find those that produced the closest fit of the model output to the experimental data gathered for each individual: i.e. the model is provided with inspiratory gas fractions and flows; the model then predicts the expiratory gas fractions, which are evaluated iteratively against the measured gas fraction data. For each dataset, the model was run four times to assess the reproducibility of the model's regression.

4.3.5. Primary model parameters

Modelled expiratory gas profiles closely matched the measured values in the human participants[67]. Model parameters were thought to represent intrinsic characteristics of the lung. Therefore, the distributions of these parameters were assessed between the groups. For example, Figure 4.4 compares a healthy participant (left hand panels) with a COPD (right hand panels). Panels A and B, show the distributions of the fractional lung compliance, normalised to fractional alveolar volume (FC_L:FV_A), which is much wider for the participant with COPD[67]. Greater variability in the parameters is suggestive of disease, with some lung compartments affected more than others, i.e. greater inhomogeneity. Therefore the standard deviation of the normalised fractional lung compliance (see Figure 4.4) and deadspace (not shown) were important metrics to compare between groups, along with derived measure of total alveolar volume.

Figure 4.4. Example of distributions of the fractional lung compliance, normalised to fractional alveolar volume (FC_L:FV_A). A: healthy participant. B: COPD. The distributions have been illustrated in a discretised form, with 50 points evenly spaced on a logarithmic scale from 0.005 to 100. (Reproduced with permission[67])



In this thesis, the model parameters will be defined as follows:

- "Compliance distribution" or "SigmaC_L" ($\sigma \ln C_L$): the standard deviation of the natural logarithm of the fractional lung compliance, normalised to fractional alveolar volume, i.e. SD(ln(FC_L:FV_A)
- Alveolar volume: $V_{A,tot}$
- "Deadspace distribution" (σV_D): the standard deviation of the fractional deadspace, normalised to fractional alveolar volume, i.e. SD(FV_D:FV_A)

These parameters are referred to as compliance distribution, alveolar volume and deadspace distribution from now on in this analysis. They are presented for the pneumothorax patient group and then in comparison with the findings in the healthy volunteer and COPD patient groups from the previous study[67].

4.3.6. Pulmonary Function Testing (PFTs)

On the same day as the assessment with the MFS, patients completed PFTs in the accredited Churchill Hospital Pulmonary Function laboratory. Spirometry (FEV_1, FVC) was performed using a compact plus flowmeter pulmonary function testing station (Hypair; Medisoft Group, Sorinnes, Belgium) and a body plethysmography system (MasterScreen Body; Carefusion, Hoechberg, Germany). Individual data were compared with predicted values from predicted values from Global Lung Function Initiative[127].

4.3.7. Data analysis

Primary model parameters were derived using the mathematical model as described above. Values presented are means of multiple outputs: In the pneumothorax group, the test was repeated twice; the participants in the other groups each had six tests (three tests performed on two visits). PFTs are analysed as absolute values by individual (for FEV_1, kCO, DLCO) and percentage of predicted values.

Data were tested for normality by plotting histograms and assessing the skewedness of the distribution. The results were expressed as means and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for skewed (non-normally distributed data) and frequency (%) for categorical variables. Comparisons of means between groups were conducted using one-way ANOVA (Analysis of Variance) test with Bonferroni correction. Proportions between groups were compared using Chi-squared test. All statistical analyses were conducted using Excel as part of Microsoft Office 2010 (Microsoft Corp, USA) and Stata v14.1 (Stata Corp, USA). Statistical significance was assumed at p value <0.05.

4.4. Results

4.4.1. Participants

The ten pneumothorax patients had a median age of 28.6 years (IQR 10). 50.0% were current or ex-smokers. None of the healthy volunteers were current or ex-smokers: the six healthy young participants had median age of 22.5 years (IQR 3); the six healthy older participants had median age 71.5 years (IQR 5). The six participants with mild or moderate COPD were all current or ex-smokers with a median age of 67.0 years (IQR 6).

4.4.2. Model parameters by group

The results of the model parameters by group are shown in Table 4.1. There were significant differences between groups for the Compliance distribution and Deadspace distribution, which were further assessed.

Table 4.1: Primary model parameters comparing groups with p value of difference

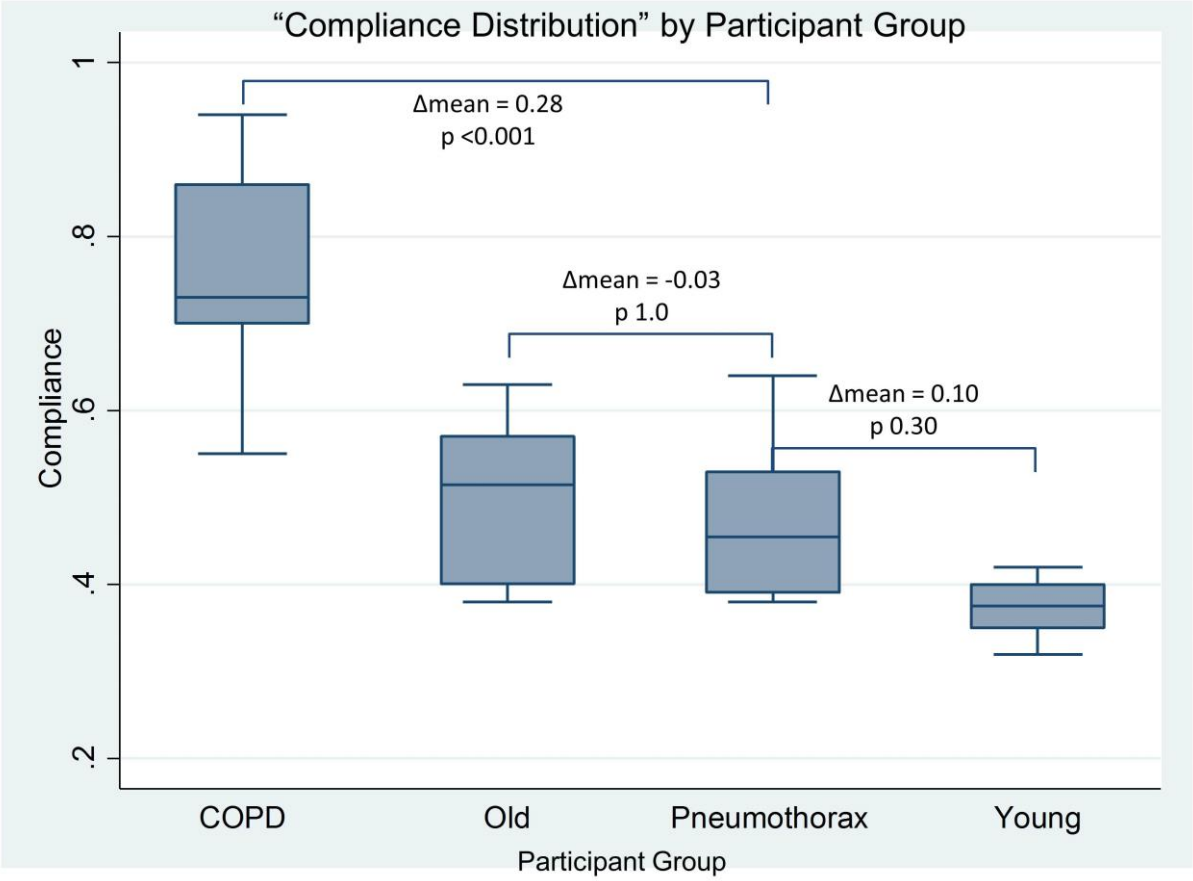
	Compliance distribution			**Alveolar Volume (L)†**			**Deadspace distribution (L)†**		
Group	Mean	SD	n*	Mean	SD	n*	Mean	SD	n*
Young	0.37	0.04	6	3.38	0.85	6	0.023	0.005	6
Pneumothorax	0.47	0.09	10	3.22	0.58	10	0.019	0.003	10
Old	0.50	0.10	6	3.94	1.27	6	0.022	0.008	6
COPD	0.75	0.14	6	3.11	1.32	6	0.042	0.010	6
Overall	**0.52**	**0.16**	**28**	**3.38**	**0.98**	**28**	**0.025**	**0.011**	**28**
p value**	<0.001			0.463			<0.001		

*n = number of participants, ** p value = between groups ANOVA.
†estimated at BPTS: Body Temperature and Pressure, Saturated.

4.5. Compliance distribution

The measure of “Compliance distribution” in the pneumothorax group was greater than the young healthy participants and less than the older healthy, but the differences between the mean values were not statistically significant: 0.10 (p 0.30) and -0.03 (p 1.0), respectively. However, the difference in mean compliance distribution between pneumothorax and COPD participants, 0.28, was significant (p <0.001)(see Table 4.1 and Figure 4.5).

Figure 4.5: Box plot of medians (and IQR) for Compliance distribution by participant group. Δmean = difference in means between groups. p value (ANOVA with Bonferoni correction)



4.5.1. Alveolar volume

The measure of alveolar volume showed no significant difference between participant groups (p 0. 463, see Table 4.1) and marked within group variation.

4.5.2. Deadspace distribution

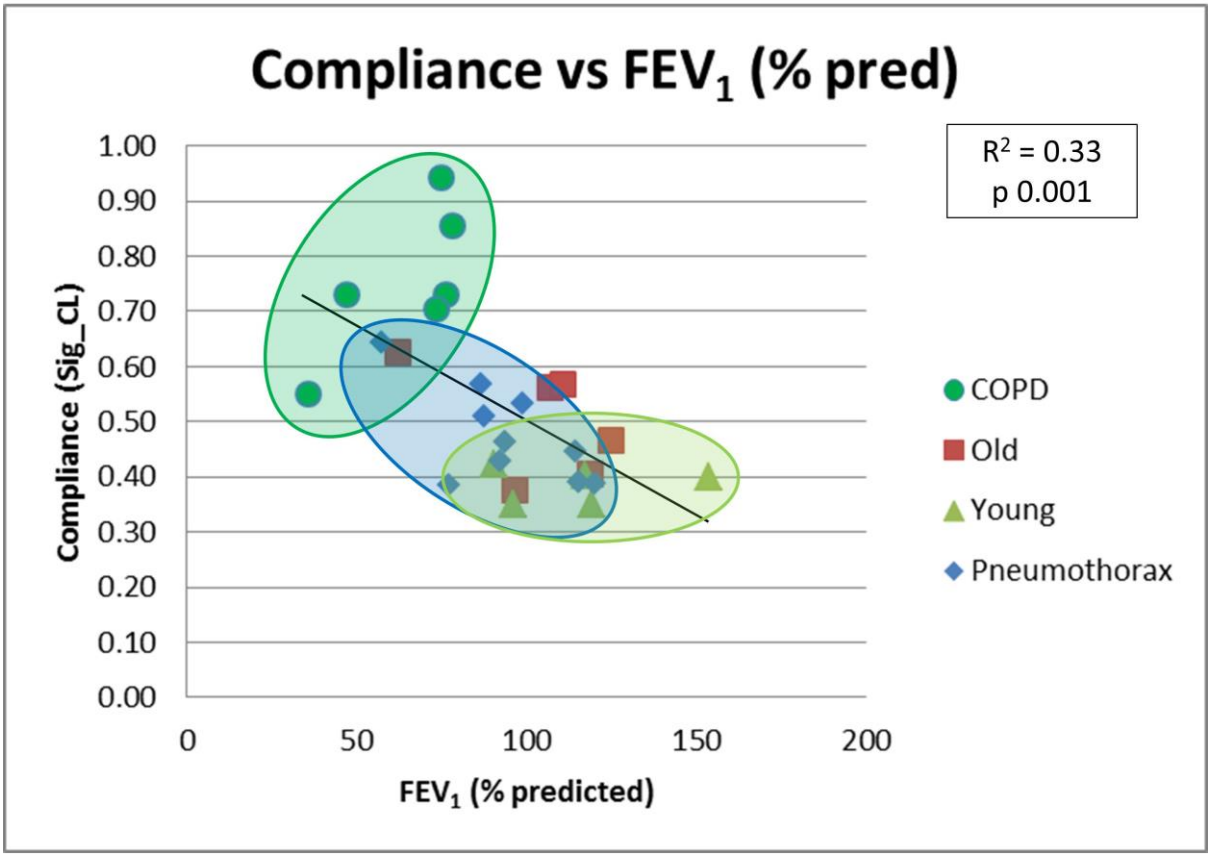
The measure of "Deadspace distribution" was remarkably similar in the pneumothorax, young healthy, and older healthy groups; but was significantly greater in COPD participants (mean difference 0.023, p <0.001) (see Table 4.1).

4.6. Comparison with PFTs

In order to determine whether the derived model parameters of inhomogeneity were related to lung function as measured by current standard assessment, a comparison was made with PFTs: FEV_1, DLCO and kCO.

Compliance distribution showed moderate correlation with FEV_1 (% predicted): overall Pearson's R^2 0.33, with corresponding p 0.001 (Figure 4.6). However, plotting groups separately (Figure 4.6) shows the pneumothorax as distinct from the young healthy group (with lower compliance distribution) but not as severe as that in the COPD group (with greater compliance distribution and lower FEV_1 (% predicted)). The data for the older healthy group also lies between the young and COPD groups.

Figure 4.6: Plot of compliance distribution vs FEV_1 (% predicted) for all groups (highlighted separately). p value calculated by t test of Pearson's correlation coefficient for the whole group



There were also moderate but significant correlations between compliance distribution and DLCO and kCO, with some group separation (Figures 4.7 and 4.8).

Figure 4.7: Plot of compliance distribution vs DLCO for all groups (highlighted separately). p value calculated by t test of Pearson's correlation coefficient for the whole group

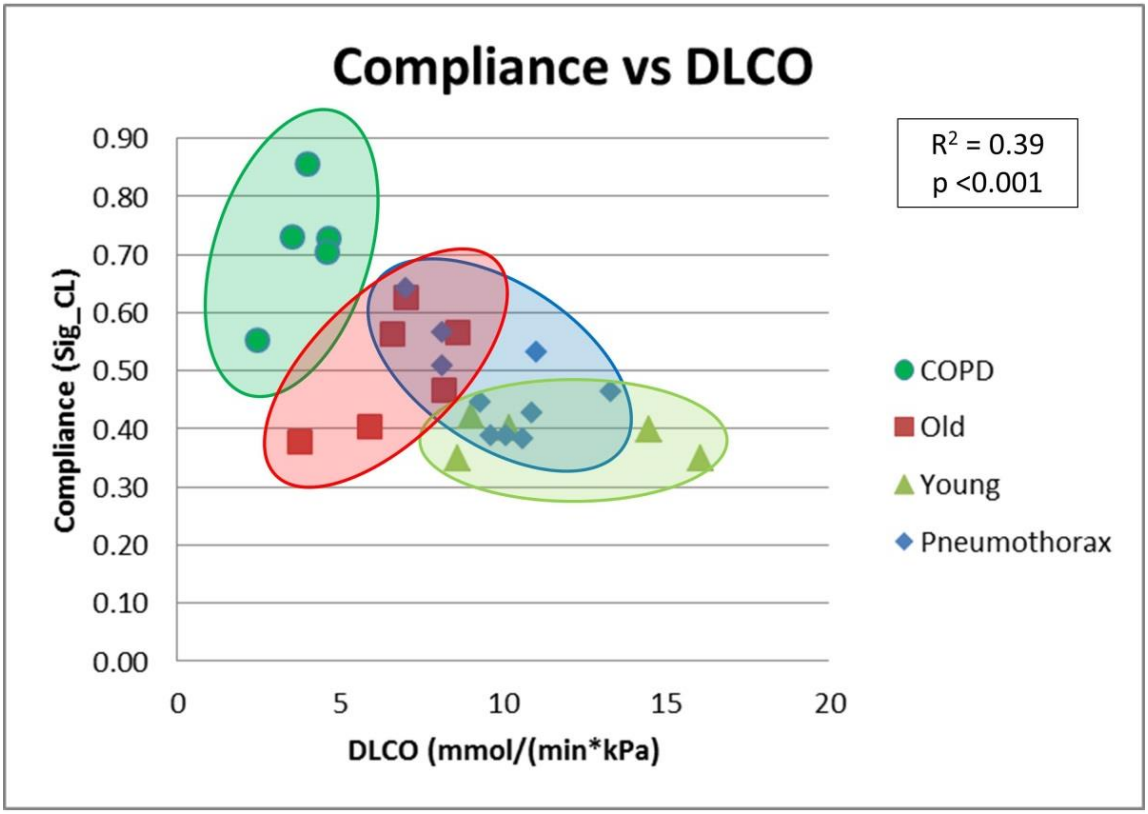
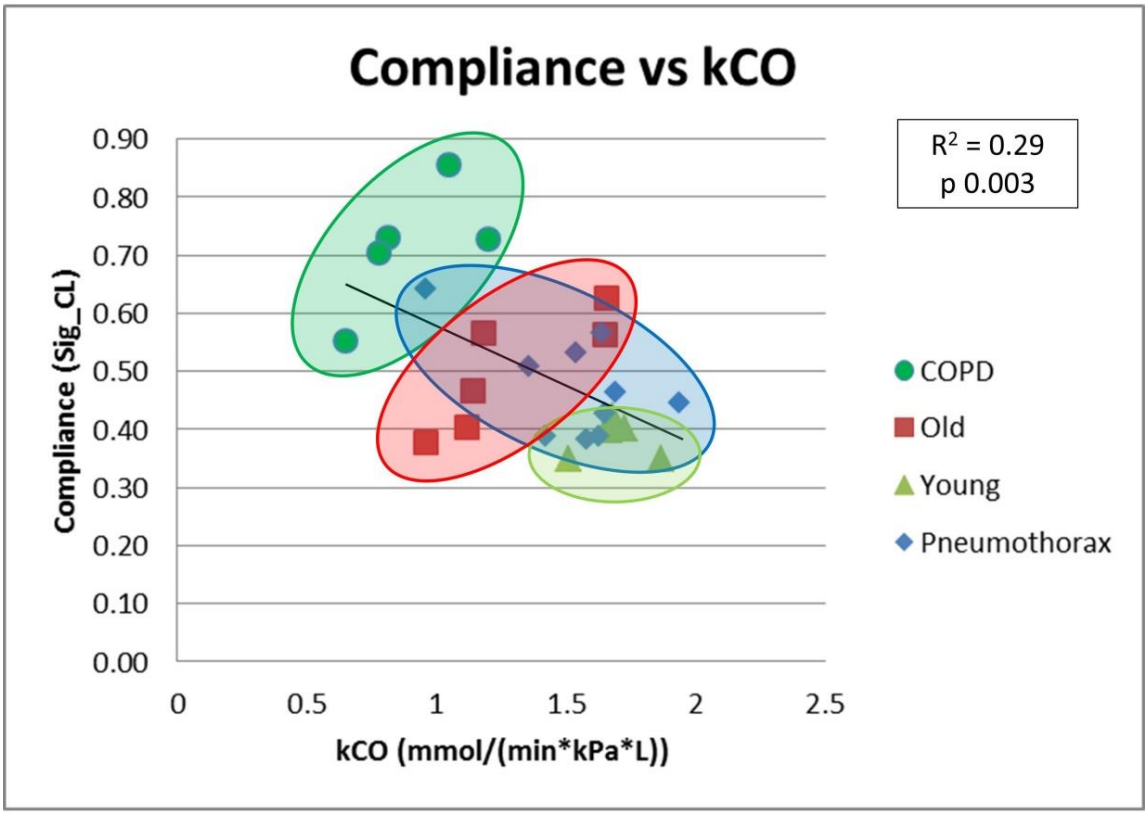


Figure 4.8: Plot of compliance distribution vs kCO for all groups (highlighted separately). p value calculated by t test of Pearson's correlation coefficient for the whole group



There was no correlation between Alveolar volume and PFTs (data not shown), as indicated by the similar values in Table 4.1.

The deadspace distribution was significantly greater in the COPD participants compared to the other groups (Table 4.1). The deadspace distribution did not differentiate between the young healthy, old healthy and pneumothorax participants, despite a range of FEV_1 (% predicted) (see Figure 4.9) and DLCO (Figure 4.10).

Figure 4.9: Plot of deadspace distribution vs FEV_1 (% predicted) for all groups (COPD group highlighted separately). p value calculated by t test of Pearson's correlation coefficient for the whole group.

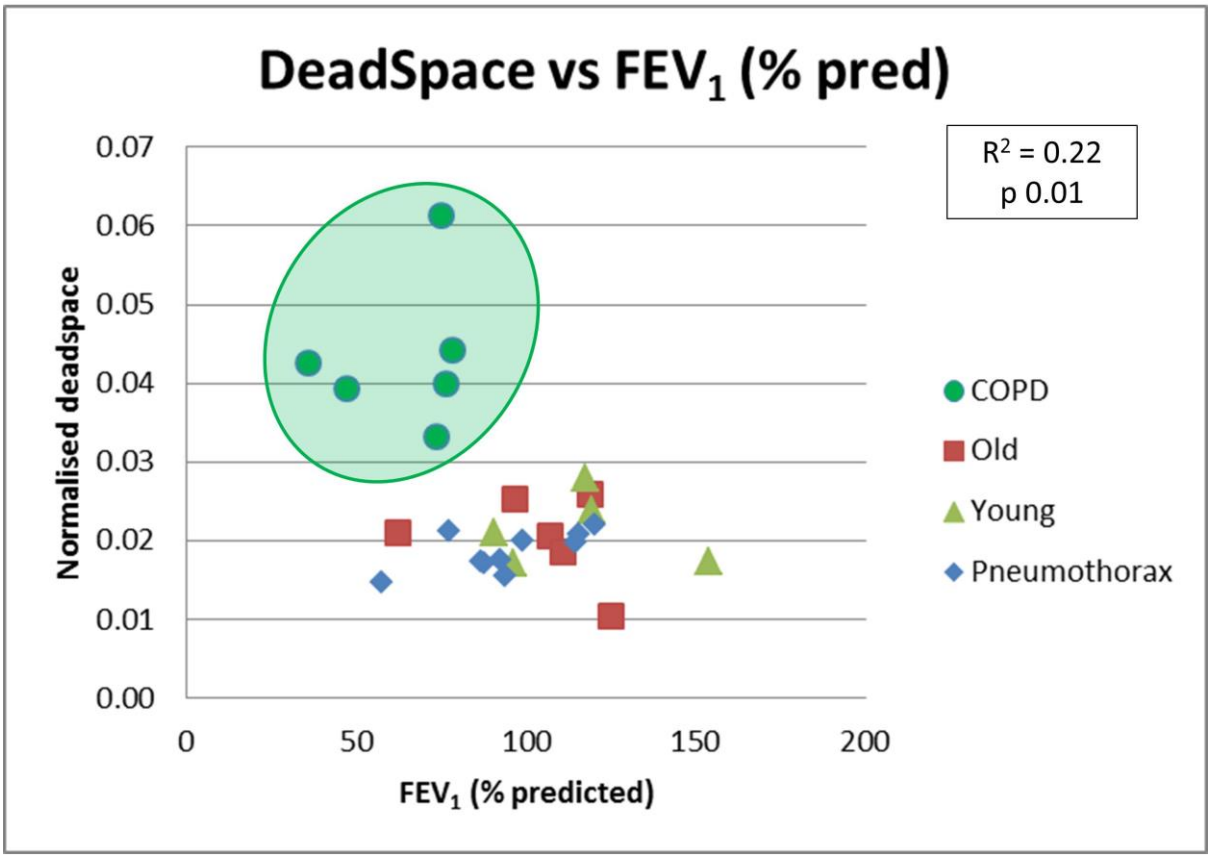
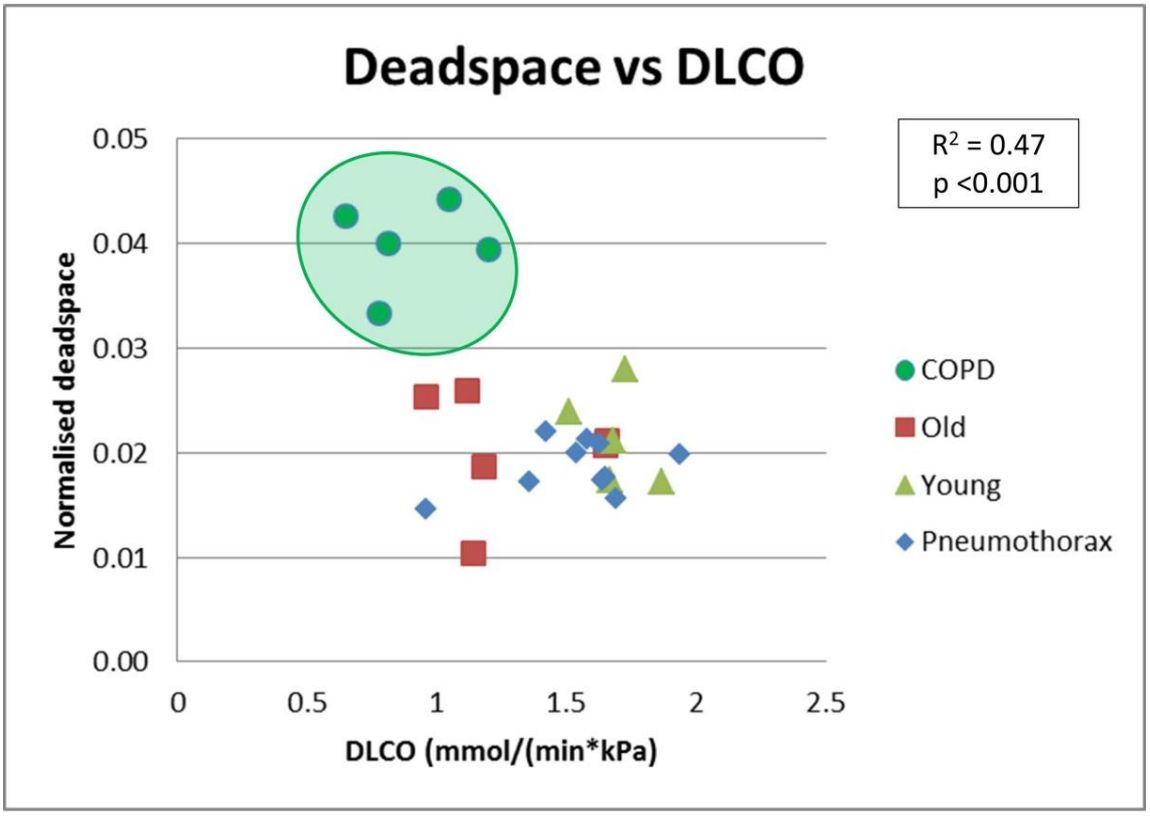


Figure 4.10: Plot of deadspace distribution vs DLCO for all groups (COPD group highlighted separately). p value calculated by t test of Pearson's correlation coefficient for the whole group.



4.7. Sensitivity Analysis

Effect of smoking on pneumothorax patients

Amongst the pneumothorax group, 50% were ex- or current-smokers. In order to assess whether this smoking history affected the results within the pneumothorax group a sensitivity analysis was conducted.

Smokers had significantly higher measures of compliance distribution compared to never smokers (difference in mean values 0.12, SD 0.04, p 0.01), see Table 4.2. The alveolar volume and deadspace distribution were not significantly different.

Table 4.2: Primary model parameters of pneumothorax patients comparing ex- and current-smokers to never smokers, with p value of difference

	Compliance distribution			Alveolar Volume (L)†			Deadspace distribution (L)†		
Pneumothorax	Mean	SD	n*	Mean	SD	n*	Mean	SD	n*
Non-smoker	0.41	0.04	5	2.97	0.50	5	0.020	0.000	5
Smoker	0.54	0.08	5	3.46	0.59	5	0.018	0.004	5
Difference	**-0.12**	**0.04**	**10**	**-0.49**	**0.35**	**10**	**0.002**	**0.002**	**10**
p value**	0.013			0.199			0.347		

*n = number of participants, ** p value = between groups ANOVA
†estimated at BPTS: Body Temperature and Pressure, Saturated.

Table 4.3 shows the difference in PFTs between smokers and never smokers in the pneumothorax group. Although there was a reduction in the FEV_1 (% predicted) in the smoking group (84.4% vs 104.2%), this was not statistically significant (p 0.10). The clustering of the groups as described in Figures 4.7-4.10 were not affected.

Table 4.3: PFTs of pneumothorax patients comparing ex- and current- smokers to never smokers, with p value of difference

	FEV_1 (% predicted)			**DLCO (mmol/(min*kPa))**			**kCO (mmol/(min*kPa*L))**		
Pneumothorax	Mean	SD	n*	Mean	SD	n*	Mean	SD	n*
Non-smoker	104.2	18.1	5	9.0	1.8	5	1.4	0.3	5
Smoker	84.4	16.0	5	10.6	1.6	5	1.7	0.2	5
Difference	**-19.78**	**10.80**	**10**	**1.55**	**1.08**	**10**	**0.22**	**0.15**	**10**
p value**	0.10			0.19			0.19		

*n = number of participants, ** p value = between groups ANOVA

4.7.1. Adverse events

The patients were carefully observed throughout the two testing periods, with O_2 saturations being measured continuously. No adverse events were reported in these patients, although some patients found the nose-clip uncomfortable (but tolerable) to wear.

4.8. Discussion

This study represents the first use of a highly precise measurement of gas exchange, utilising a novel technique of in-airway MFS[65] and a mathematical model of lung inhomogeneity[67], in patients who have had PSP. This technique was shown to obtain highly repeatable estimates for parameters reflecting inhomogeneity in a non-invasive measurement of gas exchange.

4.8.1. What can measures of inhomogeneity tell us about PSP?

Compliance distribution

Comparison with data from other participant groups have highlighted that model-derived lung parameters of the pneumothorax patients are not the same as either young healthy, old healthy or COPD participants. The compliance distribution (i.e. the measure of variability of compliance, as a surrogate for variability of ventilation) in the pneumothorax group was greater than the young healthy participants and less than the older healthy and COPD participants (see Table 4.1 and Figure 4.6). Although the differences in compliance distribution were only statistically significant compared to the COPD patients, the findings are in keeping with the hypothesis that patients with PSP (who were young) do not have "normal" lungs, and are therefore not the same as young healthy volunteers.

Why is increased variability of compliance seen in patients with pneumothorax? As a surrogate for increased inhomogeneity of ventilation, this may represent a measure of abnormalities which may be causative, such as early emphysema or ELC, or may simply represent a marker of patients who have experienced a pneumothorax. Longer-term follow-up will allow assessment of whether greater variability is an indicator of increased risk of recurrence (see Future Directions).

Deadspace distribution

Interestingly, the measure of deadspace distribution, which appears to differentiate patients with established COPD to healthy participants[67], does not distinguish pneumothorax patients from healthy volunteers. Therefore, the pathological process in the lungs of patients with pneumothorax, which gives rise to the (small) difference compared to healthy volunteers, may be subtle, or different from the pathology related to smoking, and the deadspace measurement may be marker of established (or more severe) emphysema.

4.8.2. Sensitivity Analysis

Half of the pneumothorax patients were current or ex-smokers at the time of their pneumothorax. In fact, four of the smokers had the largest compliance distribution values. There was a significant difference in the model measure of compliance distribution, with the non-smokers resembling the young healthy volunteers and the smokers being more similar to the older volunteers. However, this difference was not replicated in alveolar volume or deadspace distribution. Interestingly, PFT analysis showed a trend towards reduction in FEV_1 the smoking group compared to the never smokers, but this was not significant. Therefore, the compliance distribution may be a useful metric in identifying a functional difference in patients with pneumothorax who smoke, which is not reflected in PFTs. What proportion of

this difference is reversible with smoking cessation, and whether these differences correspond to a greater risk of recurrence, remains to be determined. It is possible that greater compliance distribution is an early marker of long term structural damage (prior to that identified on other imaging or functional testing), or it could simply be an effect of smoking.

4.8.3. Utility of methodology

These data from this exploratory group of patients demonstrates that this technique is well tolerated and safe for patients who have had a pneumothorax. Unlike CT scanning there is no ionising radiation involved, which lends itself to use in younger patients with the possibility of repeat testing at future intervals, without putting patients at additional risk. The test is simple and non-invasive unlike MIGET. It is simple, easy for the patient to undertake, and unlike standard PFTs, does not require any forced expiratory manoeuvres which may be difficult in some patient groups, and limits its use in patients with on-going or very recent spontaneous pneumothorax. Hyperpolarised gas MRI (such as ^{129}Xe MRI) imaging have been shown to highlight inhomogeneity within the lung (see Chapter 3), but the equipment required for these scans is expensive.

4.8.4. Limitations

This novel technique combining MFS with mathematical model of lung inhomogeneity does have some limitations, as discussed in a recent paper[67]. Ideally, all of the model parameters could have been derived by the model fitting process. However, this was not possible for all parameters. Sensitivity analysis showed that the model parameters used in this study were essentially independent of these fixed parameters[67]. The use of pure O_2 during the "washout" phase potentially alters the patient's physiology as pure O_2 reduces

cardiac output and causes pulmonary vasodilatation (hence changing the properties of the lung in this period), and some O_2 will dissolve in the blood, the effect of which is not currently measured[67].

The small number of patients in this exploratory study, and in the comparison groups, means that any difference in the model parameters may not be statistically significant, despite there being a real effect (a Type II (false negative) error): For example, the difference in compliance distribution between pneumothorax and healthy volunteers. Larger sample size is required to assess this.

Half of the pneumothorax group were ex- or current-smokers, whereas the healthy volunteers were all never-smokers. Therefore, there is a possibility that the differences seen between groups could be a smoking effect, rather than an intrinsic lung abnormality. However, it seems likely that there is inhomogeneity within the lungs of patients who have experienced a pneumothorax, which may be exacerbated by greater or lesser extent by the fact that they also smoke.

4.9. Conclusions

In a small group of patients (post-pneumothorax), this novel technique combining MFS with a mathematical model of inhomogeneity has been shown to be safe and well tolerated.

Data supports the hypothesis that these pneumothorax patients do not have normal lungs, and may lie on a spectrum between that of young healthy volunteers and patients with established COPD; although the small participant numbers were unable to show statistical significance. The compliance distribution may be a useful metric in identifying a functional difference in patients with pneumothorax who smoke, which is not reflected in PFTs.

This simple, quick, non-invasive test has many advantages to existing techniques but requires validation in further, larger patient groups with follow-up data.

4.10. Future directions

The utility of the combined MFS and lung inhomogeneity model requires further prospective clinical work, which is on-going.

4.10.1. Recurrence risk prediction?

If compliance distribution, for example, can highlight patients at greater risk of long term recurrence, better than standard PFTs or without the need for ionising radiation (CT scan), then this technique could influence patient care. At present there is no robust method of identifying patients at high risk of recurrence. Studies of CT "bleb scores" have to date not been convincing (see Chapter 7).

Recruitment for additional pneumothorax patients is on-going. These patients and the ten involved in this study, and will be prospectively followed-up for 12 months in total to capture recurrence data. Future work will incorporate this data to assess whether those patients who recur form a distinct subgroup in terms of the model parameters.

4.10.2. Lung changes over time?

The model parameters have been shown to be highly reproducible for the same patient[67]. Are the model parameter findings fixed, or do they change over time? Are the abnormalities seen on testing within 1-3 months of pneumothorax transient? Many patients with PSP are current smokers. Does smoking cessation have an effect on an individual which can be measured with the technique described in this thesis? Ethical approval will be sought to perform additional testing on the ten patients in this study in 12-24 months' time, in order

to determine whether parameters have changed. Of particular interest will be those current smokers, who have managed to quit smoking in the interim period.

4.10.3. Implications of mild abnormalities?

The long-term implications of having a pneumothorax early in life, in terms of lung health, are not known. Will mild inhomogeneity or "early" disease translate into clinically significant respiratory disease in the future for these patients? Will they go on to develop significant airways disease (e.g. asthma or COPD) earlier than a cohort with similar smoking history? Large scale cohort studies of patients with long term follow-up and PFTs found that a substantial proportion of patients with an eventual diagnosis of COPD have a low FEV1 in early adulthood, so do not have to experience the traditionally described "rapid decline" in PFTs before meeting the criteria for significant COPD[131]. Are these pneumothorax patients similarly predisposed to future airways disease? Further longitudinal studies of pneumothorax patients are required to assess the risk of future disease and, importantly, identify if early intervention can influence the natural history.

Author contribution:

R Hallifax recruited and assisted in data collection for the PSP patients, performed the statistical analysis and manuscript preparation. The raw data processing (via the mathematical model) was undertaken by the high performance computers in the Oxford Advanced Research Computing Facility, coordinated by Nicholas Smith (Department of Physiology, Anatomy and Genetics (University of Oxford).

5. Predicting Outcomes – Air leak and treatment failure

5.1. Background

The optimal initial treatment regime for treatment of PSP is not yet defined. Options include conservative management, NA or insertion of small-bore chest drain. International guidelines and expert consensus statements vary[4, 78, 79]. The BTS guidelines suggest treatment is required in patients with large pneumothorax (>2 cm at the level of the hilum) and/or symptomatic[4]. NA (using 16-18G cannula) of up to 2.5L of air is recommended as initial treatment. If aspiration is unsuccessful, then chest tube insertion is required.

Ideally, removal of the air in the pleural cavity will allow the lung to re-expand. This relies on the air leak from a hole in the visceral pleura (i.e. an alveolar-pleural fistula) to have ceased. If the air leak causing the pneumothorax is a one-off event, collapsing the patient's lung, then simple NA or drainage of air via chest tube over a short period of time should be sufficient. However, if the air leak continues, the lung may re-collapse after initial NA, or continue to drain air via the chest tube. Continued air leak is described as a "bubbling chest drain" due of the appearance of the air leaving the chest tube via the underwater seal which acts as a one-way valve, allowing air to escape but not be drawn back into the chest. However, this is a crude measure of air leak at that time-point and is not used as a predictor of treatment failure.

5.1.1. What is treatment failure?

Failure of the lung to re-inflate can therefore be due to two scenarios:

1) Prolonged air leak (PAL): there is such a large air leak that the air re-accumulates in the pleural space thereby not allowing the lung to passively re-expand, despite patent chest tube.
2) Healed lung, with no (or minimal) air leak, but there is visceral pleural thickening "trapping" the lung, not allowing re-expansion. Visceral pleural thickening would be unusual in patients with PSP, but if present will require surgical intervention.

Treatment failure will inevitably lead to a prolonged need for treatment which, as a result of current treatment pathway requires inpatient stay, will prolong hospitalisation and/or additional invasive procedures. A different ambulatory pathway of pneumothorax management, after appropriate identification of patients in terms of safety and suitability, could allow for prolonged drainage, without the extended hospital stay (see Conclusion).

5.1.2. Predictors of treatment failure

In the case of PAL, the key to predicting failure is to understand factors which might lead to a failure of healing of the site of air leak in the visceral pleura. There currently exists no robust method of determining those at high risk of initial failure, but previous studies have suggested that presence of underlying lung disease, older age, large volume of initial aspiration and size of pneumothorax may be important. Underlying lung disease such as COPD or ILD, may understandably cause a structural differences or differences in healing rates. However, these pneumothoraces will be defined as SSP rather than PSP. That withstanding, in patients with PSP, visceral leak can occur from areas of pleural porosity or ELC. The true aetiology and natural history of these lesions is not well known. It seems likely that a larger hole will take longer to heal, but there may be other factors relating to the

nature of the alveolar-pleural fistula which are determined by the integrity of the underlying lung.

Size of pneumothorax could be a surrogate for the amount of air leak. Large initial size of pneumothorax (on CXR) could be the result of a greater (or prolonged) air leak, and it follows that a larger pneumothorax will have a greater volume on initial NA.

A direct measurement of the air leak from the lung could provide a surrogate for the physical characteristic of the alveolar-pleural fistula and thereby could be predictive of future failure. Historically, the only metric of air leak has been the presence (or not) of bubbling via chest tube. More recently quantification of airflow has been made possible by the use of digital suction devices. The evidence behind these markers of potential treatment failure will now be reviewed.

5.1.3. Size of pneumothorax and failure of NA

In a small series of 30 patients, investigators found that NA was more likely to be successful in patients <50 years old and "<50% lung collapse", having aspirated up to 4.0L of air [132]. However, eight of the 11 patients who failed NA treatment had pre-existing lung conditions (i.e. SSP). Pneumothorax size was only estimated "by eye" in this study, which was not quantified or qualified in any way. Analysing the results of the 18 PSP patients only, shows no significant difference in age or estimated size of pneumothorax.

Retrospective case series of 91 patients treated with aspiration, found that patients with >40% pneumothorax more likely to fail NA[133]. All patients were initially treated with NA. Failure was defined as those patients in whom a chest tube was ultimately required: Criteria for insertion were aged >50 years, had bilateral pneumothorax, previous ipsilateral

pneumothorax recurring more than once, presence of pleural effusion, or if more than 2.5 L of air was aspirated. The authors did not provide a breakdown of which patient met the criteria. Therefore, there will be a number of patients in whom NA was not attempted classified as “failures”. Nevertheless, pneumothorax size was estimated based upon the Rhea criteria[134] and patients categorised groups: ≤20%, 21-39% or more than 40%. Failure rates were statistically different between the groups: found an 84.6% (22/26) failure in >40% compared to 38.2% (13/34) in the 21-39% pneumothorax size group[133]. Although the authors report conducting a stepwise logistic regression model, it is not clear which other factors were considered. Therefore, the conclusion that pneumothorax size was the only factor that was predictive of the outcome should be viewed with caution.

Tsai *et al* recently conducted a retrospective review 253 patients with PSP who were treated with small-bore (8-French pigtail) chest tube drainage[135]. After chest tube insertion, air was aspirated until resistance felt (the maximum volume of air was not specified). The chest tube was then attached to suction (-10cmH_20), presumably for the remainder of the patient’s treatment. The authors used Light’s index to determine the size of pneumothorax[136] and thereby divided the patients into tertiles by percentage size of pneumothorax. Massive pneumothorax was defined as >62.6%, with 38–62.6% being moderate and <38% being mild. Treatment failure occurred in 28.1% (71/253) patients. The failure group consisted of 60 patients with persistent air leak at 72hours, and 11 cases which showed enlargement of the pneumothorax on chest radiograph after small bore chest tube removal. Failure rates were greater with larger pneumothoraces: 42.9% (36/84), 25.9% (22/85) and 15.5% (13/84), respectively[135]. A multivariate logistic regression was performed using a “classification and regression tree” method. Age, BMI and smoking status

were not associated with treatment failure, but pneumothorax with 92.5% collapse was predictive of failure (with odds ratio of 4.23 (p 0.009). However, they do not describe how many patients in their study met this hypothetical cut-off of very large lung collapse. For example, in a patient with 10cm hemithorax would require a 5.8cm pneumothorax as measured by interpleural distance at the level of the hilum (as per BTS guidelines[4]). If this only applies to a small proportion of pneumothorax patients then it is not a useful cut-off value.

5.1.4. Volume of air aspirated and failure of NA

Larger pneumothoraces on initial CXR (i.e. with greater lung collapse) will have a larger amount of air in the pleural cavity. It follows that a larger volume of air aspirated on initial NA may also be a surrogate for large air leak or on-going fistula.

Harvey *et al* found that the amount of air aspirated during first aspiration was significantly different in successful and unsuccessful aspirations (1.59L vs 2.52 L) [82]. In this study, clinicians aspirated a maximum of 3.0L of air, after which a chest drain was inserted. Therefore, failure in the group with larger volume aspirated is not surprising. This either is a result of the initial volume of air being significantly greater than 3.0L (and so full re-expansion would not be expected after 3L aspiration), or there is on-going visceral air leak. However, further logistic regression found no significant association with failure (including previous pneumothorax episodes or "radiographic features"). This implies that, once accounting for other clinical features, volume of air aspirated does not predict outcome. Non-significance could be a result of the small number of patients failing NA, or there being too many clinical parameters being assessed in the regression model: predictive modelling

typically require a minimum of 10 events per variable to formulate predictive criteria robustly. The authors do not expand on this any further in their paper.

5.1.5. Direct detection or measurement of on-going air leak

In 1991, Seaton et al devised a method of testing for on-going leak into the pleural cavity[137]. In a pilot study, 25 patients were asked to breathe air from a Douglas bag that contained chlorofluororcarbon (CFC) gas from a metered dose inhaler while their pneumothorax was aspirated. Presence of the CFC gas was detected (by passing the aspirated air through a flame ioniser) in patients who went on to require chest tube insertion[137]. A larger follow-up study of 119 patients (84 of whom were PSP, 35 SSP) found that after NA: if the CXR had improved and the no CFC gas was detected, 96% required no further treatment; whereas if CFC gas was detected, even if the CXR has improved, only 51% avoided further treatment[138]. These studies are the first (and only) to use a direct clinical measure of air leak to devise a treatment algorithm to stratify patients. Unfortunately, this technique has not been adopted clinically (partly because the lack of availability of CFC inhalers and the ioniser, and impracticality of use at the bedside in hospitals). Therefore, guidelines advise generic management paradigm for those failing treatment.

5.1.6. Digital suction device – quantitative measure of air leak

Rather than counting bubbles of air from a chest drain, digital suction devices can provide a quantitative measure of airflow through the drain. This provides real-time data and trends over time on air leak, providing more information to the clinician.

The most commonly used digital suction device used in the UK, and the one used in this study, is the Thopaz+ device (Medela Ltd, Switzerland). The Thopaz+ device (Figure 5.1) uses a diaphragm pump to generate negative pressure set by the operator. The pressure is measured over each breathing cycle and will only provide suction if the average pressure is greater (more positive) than the set pressure.

Figure 5.1: Thopaz+ device (Medela Ltd, Switzerland)



In this study, the aim is to passively measure the airflow at normal physiological state, rather than actively sucking air out. As such, the digital suction device is set to “gravity” or “physiological” mode, of negative -0.4kPa pressure. -0.4kPa was chosen in order to mimic physiological intra-pleural pressure, which at functional residual capacity is -0.3 to -0.5kPa in health[139].

5.1.7. Digital suction device – accuracy

Each device is quality checked at manufacture to ensure that all average and minimum and maximum pressures are within +/-10% of the set pressure (tested at -2, -5 and -10kPa). The pressure sensors are recalibrated each time the device is turned on. The airflow is measured using a revolutions per minute counter to ensure accuracy at flows <100ml/min. Other devices use heating element-based airflow sensors which are less accurate at low flow rates. Flow rates are also calibrated and checked to be within +/-10% of a certified flowmeter at rates of 100, 1000 and 5000 ml/min[140].

5.1.8. Learning from PAL in thoracic surgery

Patients undergoing thoracic surgical procedures will have chest drains inserted to re-inflate their lung after surgery. PAL is also one of the main complications of post-operative surgical management. In these cases, the lung has usually been cut (e.g. wedge resections, lobectomies or pneumonectomies) and the remaining parenchyma surgically repaired using sutures, staples or electrocautery. The intention is to have completely repaired the lung, or to have minimal residual leak, which can heal itself after the operation. Therefore, it is expected that the lung will have re-inflated and air leak will cease within the first few days.

There are data in the thoracic surgical literature which investigate clinical predictors of PAL and the increase use of digital suction devices, which provide insight into the concept developing of clinical predictors and will have parallels with work presented here on pneumothorax patients.

5.1.9. Use of digital suction device in surgery

RCTs in surgical patients comparing digital suction devices to standard underwater seal and wall-mounted suction have shown that digital suction can reduce chest drain duration and hospital stay[141-144]. These studies were well conducted RCTs. Patients had undergone post-lung resection for suspected or proven non-small cell lung cancer[141], pulmonary lobectomies for lung cancer[142, 143], or pulmonary lobectomy or segmentectomy[144]. All four studies showed a significant difference in drain duration and hospital stay of around 1 day. The premise behind these studies is that digital airflow measurement can more easily or more quickly identify when air leak (from the visceral pleura) has ceased, compared to the standard method of assessing a lack of air bubbling through the underwater seal.

However, these surgical studies used a range of different thresholds to determine when air leak has ceased using the digital suction device, and hence chest tube can be removed. Cerfolio *et al* removed chest tubes if there was "no presence of a discernible air leak" on either digital device or standard underwater seal[141]. In their 2010 RCT, Brunelli *et al* used a convoluted criteria either: zero air leak over the last 6 hours; or <15ml/min in last 6 hours, then clamping for 12-24hours, after which no further air leak was detected[142]. In a consensus statement, the definition was refined as a result of "clinical experience from different centres" to <40ml/min for last 6-8hours (or "sloping downward trend"). However, in 2013, the same group, used the definition of <20ml/min "continuously" to determine cessation of air leak[143] and, in 2014, Pompili *et al* used <30ml/min in last 8 hours[144].

5.1.10. What is the minimum airflow required to safely remove the drain?

These above data provide interesting examples of using a digital suction to determine when to remove chest tube after thoracic surgery. However, there was no consistent definition of

the minimum airflow measured by digital device to define cessation of air leak, and hence remove the chest drain. Only one surgical study has attempted to use the air leak measurement early in the post-operative period to predict PAL. Bille *et al* retrospectively analysed the airflow data from 142 patients post-lobectomy, or wedge resection (via thoracotomy, not VATS)[145]. PAL, defined as air leak on >day 5 post-operation, occurred in 13 patients. 32 patients had a measured air leak on Day 2 ≥180ml/min. 11 (34.4%) of these 32 had PAL on Day 5, compared to 4 (3.1%) of the 130 who had air leak on Day 2 <180ml/min (p 0.0001)[145]. The authors did not give a physiological rationale as to why this threshold was chosen. It seems likely that in retrospective analysis, this value provided the most statistically significant result. Nevertheless, the hypothesis that a clinical measurement undertaken within the first few days of treatment can predict future outcomes in interesting and provides the rationale for use in the pneumothorax patients in this study.

The direct applicability of this data (and thresholds) to medical patients with pneumothorax is not clear. Patients in the above studies have undergone thoracic surgery in which the lung has been cut or manipulated. They are fundamentally different to the patient population with PSP, in which an air leak has spontaneously occurred as a result of pleural porosity of ELC.

5.1.11. Other surgical clinical predictors of PAL

PAL, in surgical patients, is clinically defined as air leak at day five post-thoracic surgery. Retrospective studies of patients post-thoracic surgery have been undertaken to determine clinical risk factors for PAL[146-148].

Petrella *et al* [146] reported a retrospective review of 121 patients who had undergone lobectomy for lung cancer. 58 patients had PAL (at ≥5 days post-operation). They assessed

CT scans and clinical parameters to “predict” PAL. The clinical parameters were sex, age, side, intensive care stay, histology, cancer stage, and whether they had been pre-treated with chemotherapy. Multivariate analysis was performed. Male sex, right side of thorax and age were identified as statistically significant risk factors for PAL. However, the biological plausibility of these is questionable. The authors comments that this finding may be the effect of a more complex right-sided operation due to there being two fissures requiring a more extensive parenchymal dissection, and that complete fissure is more common on the left side. However, the finding of male sex was not commented upon and is not easily explained physiologically. In addition, the degree of emphysema (as measured by CT scan) was greater in those with PAL[146]. Emphysema is destruction of lung tissue around the small airways leading to over-inflation of the alveolar airspaces, often associated with smoking, leading to COPD. Surgical resection of damaged emphysematous lung may be more technically difficult to manipulate and seal (e.g. with sutures or staples), and the lung may take longer to heal. Therefore, the degree of emphysema predicting PAL is reasonable.

Brunelli *et al* developed a scoring system for predicting PAL post-lobectomy[147]. The used data from 658 patients for the derivation set, and then a further 233 patients in a validation set. PAL was defined as day 5 post-operation. The clinical factors considered in their multivariate analysis were: sex, age, albumin, haemoglobin level, FEV_1, ratio FEV_1/FVC, BMI, DLCO), smoking history (pack years), diabetes mellitus, side and site of lobectomy, and the presence of adhesions at surgery. In their model the risk factors significantly associated with PAL were: age >65 years, adhesions, an FEV_1 of <80% of the predicted value and BMI <25.5[147]. This is the only study to report older age as an independent risk factor for PAL, and, although the authors hypotheses that elderly patients “may have a more fragile lung

parenchyma with reduced healing capacity", this finding was not validated elsewhere. A reduction in FEV_1 is usually a marker of underlying lung disease, which could predispose to poor healing and hence PAL, particularly in the context of emphysema or COPD. However, smoking history (which is the most common cause of COPD) was not reported as an independent risk factor. Low BMI seems to be a physiologically reasonable predictor of PAL as it may be a marker for poor nutritional status of the patient, which would also reduce healing capacity.

Recently, Pompili *et al* conducted the largest retrospective study to date using the European Society of Thoracic Surgeons database[148]. They included 5069 patients having undergone VATS lobectomies. 504 patient had PAL (>5 days leak). The risk factors assessed were: age, BMI, sex, FEV_1, FEV_1/FVC ratio, DLCO, performance status (ECOG score), coronary artery disease, neoadjuvant chemo, side and site of resection. Logistic regression found an association with just three variables: male sex, an FEV_1 <80% predicted, BMI <18.5. The reduced FEV_1 and low BMI (this time at a lower threshold) seem to be consistent risk factors across these studies. The association between male sex and PAL is not clear. Pompili et al suggest that male sex may actually represent a surrogate for other unaccounted variables, such as smoking history or COPD, which were not available in their database[148]. However, previous studies did include these factors, which were not identified as significantly associated with PAL.

These studies, with large patient numbers, demonstrate the potential for risk factors for early treatment failure can be retrospectively identified. However, the results were inconsistent and difficult to directly translate to the pneumothorax population. The biological plausibility of male sex being a risk factor for PAL is questionable. Reduced lung

function (FEV_1) may be useful in patients with known COPD but may be of limited use in PSP patients. Reduced BMI would be compatible with the classically described ectomorphic body shape of PSP patients[26-28].

The next step should be to use these risk factors to influence behaviour to reduce post-operative complications including PAL. To date, a study of this kind has not been reported in thoracic surgical patients or medical patients with pneumothorax. This study intends to be the first to identify risk factors in prospectively collected data in PSP.

5.2. Aims and hypothesis

The aim of this study is to determine whether initial airflow measurement (using a digital device) can be predictive of treatment failure in pneumothorax. Air leak from the visceral pleura will need to cease in order for the lung to successfully re-expand. Standard management currently involves monitoring for on-going bubbling of the chest tube as a marker of on-going leak. If a chest tube is removed whilst there is on-going leak, air will re-accumulate in the pleural space and the lung will collapse again. Therefore, the monitoring for bubbling of the chest tube occurs each day, and if present, the patient will remain in hospital for another day, and reassessed the following day. This management strategy is unsatisfactory for patient and clinician. Bubbles via the chest drain are not precise (they are not consistently present), and are a binary measure (either bubbles or not), which do not show whether air leak is increasing or decreasing.

The natural history of resolution of air leak is poorly understood. However, a quantifiable measure of airflow seems preferable to the existing unreliable binary measure of bubbles or

not. The minimum measured airflow required to demonstrate resolution is not known. What does 50, 100 or 500ml/min airflow mean for the patient, in terms of diagnosis of on-going air leak or resolution time?

In this study airflow will be measured on the first day (Day 0) and the next 4 days of treatment. On Day 0, initial measurements will be the primary drainage of the pneumothorax, so these values are likely to be large. However, after 24/48hrs one would expect the lung to be re-expanded and any airflow measurement to be more to representative of on-going air leak. Therefore, determining how airflow measures evolve over the first 2 days of treatment could be critical.

Being able to predict PAL early in the patient's treatment pathway would potentially remove the uncertainty and enable early triage to surgery if the likelihood of PAL is high. This is only clinically important if this prediction could be made on Day 1 or 2 after chest tube insertion.

Hypothesis

The hypothesis is that airflow (either absolute values, or change over time) on Day 0, 1 and 2, can successfully predict which patients eventually require surgical referral, according to pre-specified criteria.

5.3. Methods

Data was used from patients who were enrolled into the RAMPP trial (Randomised Ambulatory Management of Primary Pneumothorax, ISRCTN 79151659) trial. RAMPP compares the use of the Pleural Vent (Rocket Medical, UK) to standard care (as per BTS

guidelines) in patients with PSP requiring treatment. The trial was approved by NHS Research Ethics Committee (Ref 15/SC/0240) and funded by a Research for Patient Benefit grant from the National Institute for Health Research (NIHR).

5.3.1. Airflow measurement

As part of trial protocol, airflow measurements were undertaken after initial insertion of Pleural Vent or chest drain (Day 0) and on each subsequent day until day 4, or until the drainage device (Pleural Vent or chest drain) was removed. The digital airflow measurement was made using the Thopaz+ digital suction device as per trial protocol. Based upon clinical experience in Oxford to date, use of the Thopaz device on patients post-thoracoscopy has demonstrated that the airflow can change significantly over the initial 10 minutes. Therefore, to maximise the useful data collected in this study, airflow measurements (in ml/min) were recorded manually from the digital display at 1, 5 and 10 minutes.

Training in use of Thopaz+ device was given by a local Medela representative and RAMPP trial coordinator (the author) at site initiation visits and on subsequent occasions as required.

5.3.2. Clinical outcome data

Clinical data was collected at baseline and at each daily review thereafter until Day 4. Patient demographics included sex, age, height, weight, BMI, history of prior pneumothorax, and smoking history.

The decision to remove the drainage device was made clinically by the treating clinician based upon the following guidance: In the Pleural Vent group, if the CXR showed full resolution and no air could be aspirated manually (using syringe attached to device); In

standard care group, if the CXR shows full resolution and no bubbling evident on under-water seal (as per standard management).

5.3.3. Criteria for surgical referral

The objectivity of the outcome measure (surgical referral) was determined by the use of pre-specified criteria for referral, which were:

> *"At Day 4 post-insertion of chest drain, persistent air leak as measured by "bubbling" chest drain attached to underwater seal, or evidence of on-going air leak through an ambulatory device; and/or persistent pneumothorax on CXR."*

Data on surgical referral, duration of chest drainage, total treatment period (days) and need for further pleural intervention were recorded. The size of the pneumothorax (< or >=4cm measured at the level of the hilum) was recorded at randomisation. This data was uploaded onto dedicated web-based clinical trial database designed for remote electronic data capture. Blinded interim data download for patients having completed treatment was conducted on 28th September 2017 for use in this thesis.

5.3.4. Data analysis

Airflow measurements were compared. Both absolute values, and the change in absolute values over Days 0 to 1 and 0 to 2; and threshold values of greater or less 50ml/min, 100ml/min and 150ml/min at Days 0, 1 and 2 were used. If an absolute value or threshold level were identified, this could be directly applicable at the bedside, as the airflow can be read directly from the digital device. As discussed above, the surgical studies have multiple different criteria for "no air leak" (i.e. from zero, 30 or 40ml/min over 6 to 8 hours), with little evidence behind the choice in each case.

Determining air leak thresholds

As discussed above, there was no consistent definition in the surgical studies of minimum airflow required to define cessation of air leak. Therefore, pilot work was carried out in Oxford using the Thopaz+ device after thoracoscopy and use in selected pneumothorax patients on the respiratory ward. This clinical work demonstrated that when initial airflow post-thoracoscopy reduces to a low level, the flow often varies between zero and 50ml/min. Therefore, 50ml/min was chosen as the lower threshold. Conversely, airflow of >150ml/min had previously been observed in pneumothorax patients with on-going leak, and so chosen to be the upper threshold. 100ml/min was chosen as a mid-point between these values, to add granularity to the model, to assess whether there is a "dose effect" (i.e. is ≥150ml/min more likely to predict PAL than ≥100ml/min?).

The proportions of patients reaching the thresholds were compared between two groups of those who eventually required surgery for PAL and those who spontaneously resolved. The duration of treatment (days) was compared between those reaching airflow thresholds at Days 0-2.

Data were tested for normality by plotting histograms and assessing the skewedness of the distribution. The results were expressed as means and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for skewed (non-normally distributed data) and frequency (%) for categorical variables. Means of groups were compared with two-sample t-tests. Proportions between groups were compared using Chi-squared test. For binary outcome variables, univariate odds ratios were calculated using Mantel-Haenszel technique, and logistic regression was performed for multivariate odds ratios. All statistical analyses were conducted using Excel (Microsoft Office 2010, Microsoft

Corp, USA) and Stata v14.1 (Stata Corp, USA). Statistical significance was assumed at p value <0.05.

5.4. Results

At data download, 115 patients data entered onto the trial database. 81 (70.4%) patients had air leak data recorded and were analysed in this study.

Airflow measurement and length of stay data were not normally distributed ("positively skewed" with outliers with high airflow or long length of stay).

5.4.1. Baseline data

74.1% (60/81) patients were male. The mean age was 30.0 years (standard deviation, SD, 7.9). 51.9% (42/81) were current smokers at time of enrolment, 22.2% (18/81) were ex-smokers and 25.9% (21/81) never smokers. The mean cumulative pack-years for current and ex- smokers was 7.5 (SD 5.2) and 6.2 (SD 4.9) years, respectively. 51.9% (42/81) were current or former smokers of marijuana. The mean heights were 182.7cm (SD 4.7) and 164.2cm (SD 4.5) for males and females, respectively, and the corresponding BMI were 21.1kg/m^2 (SD 2.6) and 20.8kg/m^2 (SD 2.4).

At presentation with their pneumothorax, the majority (70.4%, 57/81) had a large pneumothorax of >=4cm at the level of the hilum (as measured by the local clinician). There was a trend towards larger pneumothoraces being more common in females than males (85.7% vs 65.0%, p 0.07). The mean duration of treatment was 5.2 days (SD 5.2) overall.

5.4.2. Outcome data

Twenty patients (24.7%) were referred for surgery during their inpatient stay. Patients with large pneumothoraces were slightly more likely to be referred (26.3% vs 20.8% with small pneumothoraces, OR 1.36) and have marginally longer treatment duration (mean 5.4 days (SD 5.5) vs 3.6 days (SD 4.7)), but these differences was not statistically significant (p 0.19 and p 0.20, respectively). Rates of referral for surgery were also slightly higher for underweight patients (BMI <18.5kg/m^2), female sex, and for non-smokers (Table 5.1).

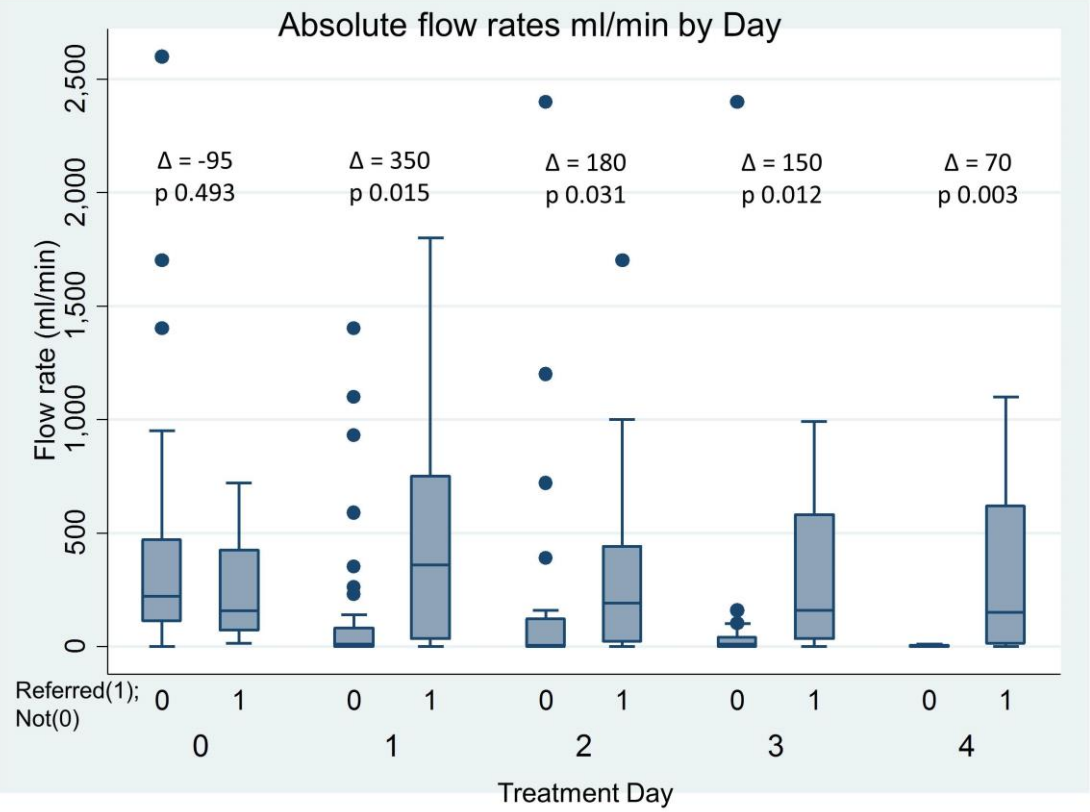
Table 5.1: Odds ratios of referral for surgery by patient characteristics: univariate and multivariate

	Risk of referral for surgery		
Factor	Odds ratio	95%CI	p
Univariate			
Sex (F:M)	1.81	(0.6 - 5.5)	0.29
Size (large:small)	1.36	(0.4 - 4.3)	0.60
Smoker (ever:never)	0.41	(0.1 - 1.2)	0.10
BMI (<=18.5:>18.5)	3.07	(0.7 - 13.7)	0.12
Multivariable			
Sex (F:M)	2.52	(0.6 - 11.1)	0.22
Size (large:small)	1.11	(0.2 - 5.3)	0.89
Smoker (ever:never)	0.39	(0.1 - 1.5)	0.16
BMI (<=18.5:>18.5)	3.63	(0.8 - 17.4)	0.11
_cons	0.35		

5.5. Prediction by absolute airflow

The median airflow measurements (at 1 minute) are shown in Figure 5.2. Immediately after Pleural Vent or chest drain insertion (Day 0), the absolute values for airflow were similar; whereas, on subsequent days (1-4) the median airflow was significantly greater in those who were eventually referred for surgery (as per pre-specified criteria).

Figure 5.2: Absolute airflow values (at 1min) on treatment days 0-4 by whether or not patient eventually required surgical referral



Δ= Difference in Medians, p value calculated using Mann-Whitney U test

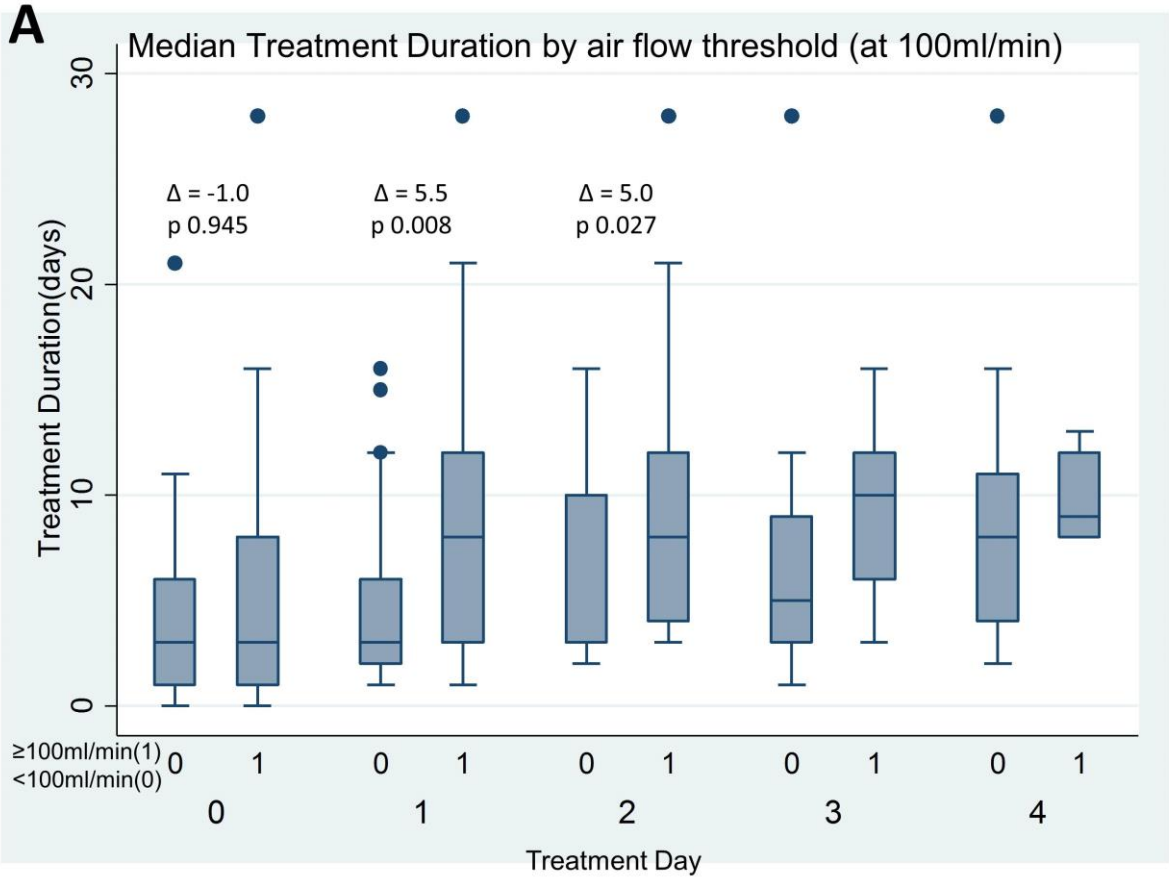
5.6. Prediction by threshold value for airflow

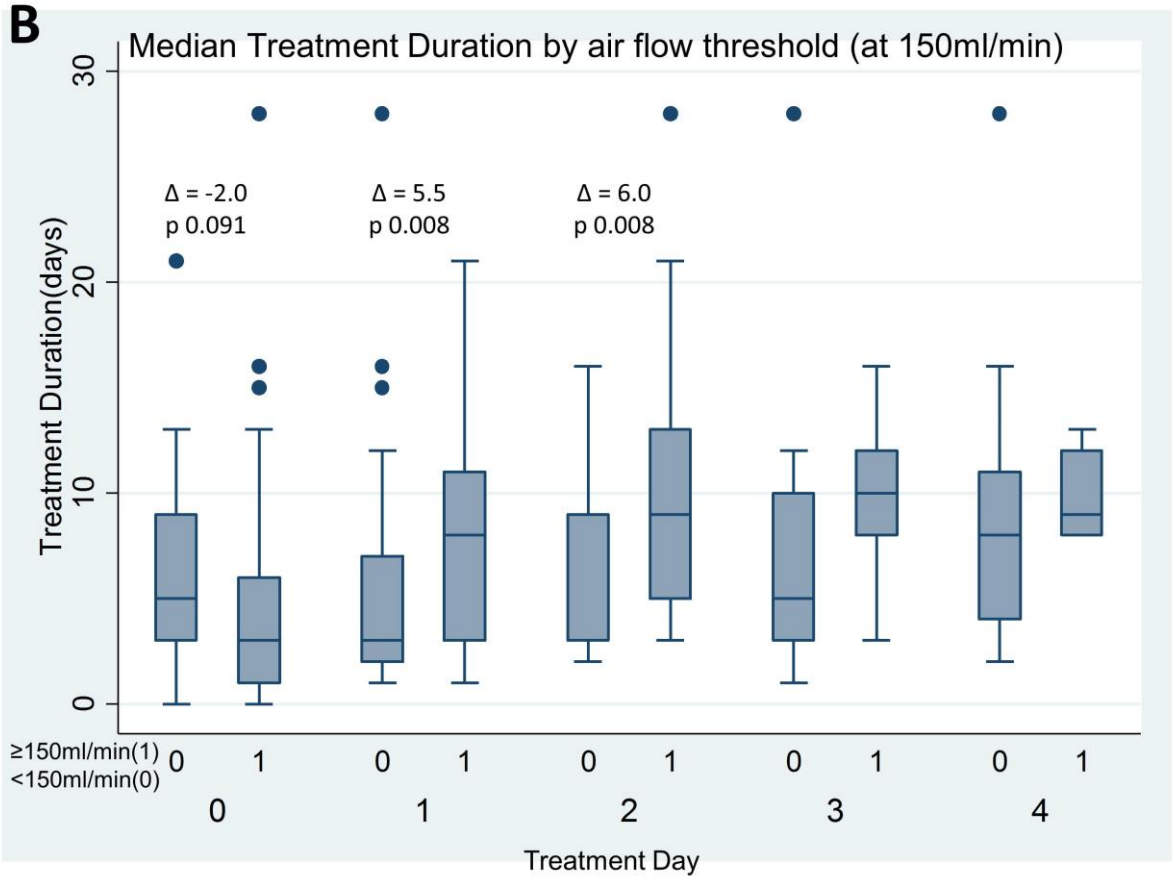
A threshold airflow measurements of ≥100ml/min or ≥150ml/min on Days 1 or 2 were associated with significantly longer duration of treatment (Figure 5.3). The median treatment duration for patients with airflow <100ml/min on day 1 was 3.0 days (IQR 3.0), compared to 8.5 days (IQR 9.0) if >100ml/min (p 0.003). On Day 2, the duration <100 and >=100ml/min were 3.0 days (IQR 6.0) and 8.0 days (IQR 8.0), respectively (p 0.027).

The odds ratio of patient requiring referral for surgery were 5.2 (95%CI 1.34-19.95, p 0.008) if the airflow measurement was ≥100ml/min (vs <100ml/min) on Day 1 and 2.9 (95%CI 0.74-

10.97, p 0.110) on Day 2. At a higher threshold (150ml/min), the odds of referral surgery were 4.8 (95%CI 1.24-18.67, p 0.012) on Day 1 and 4.5 (95%CI 1.04-19.52, p 0.028) on Day 2. The negative predictive value (NPV) of having airflow <100ml/min on Day 1 is 80.6% in predicting spontaneous resolution (i.e. no need for referral for surgery); correspondingly for <150ml/min on Day 1 is value 78.9%.

Figure 5.3: Number of days of treatment by airflow threshold by treatment day: 5.3A shows the 100ml/min threshold; 5.3B shows the 150ml/min threshold

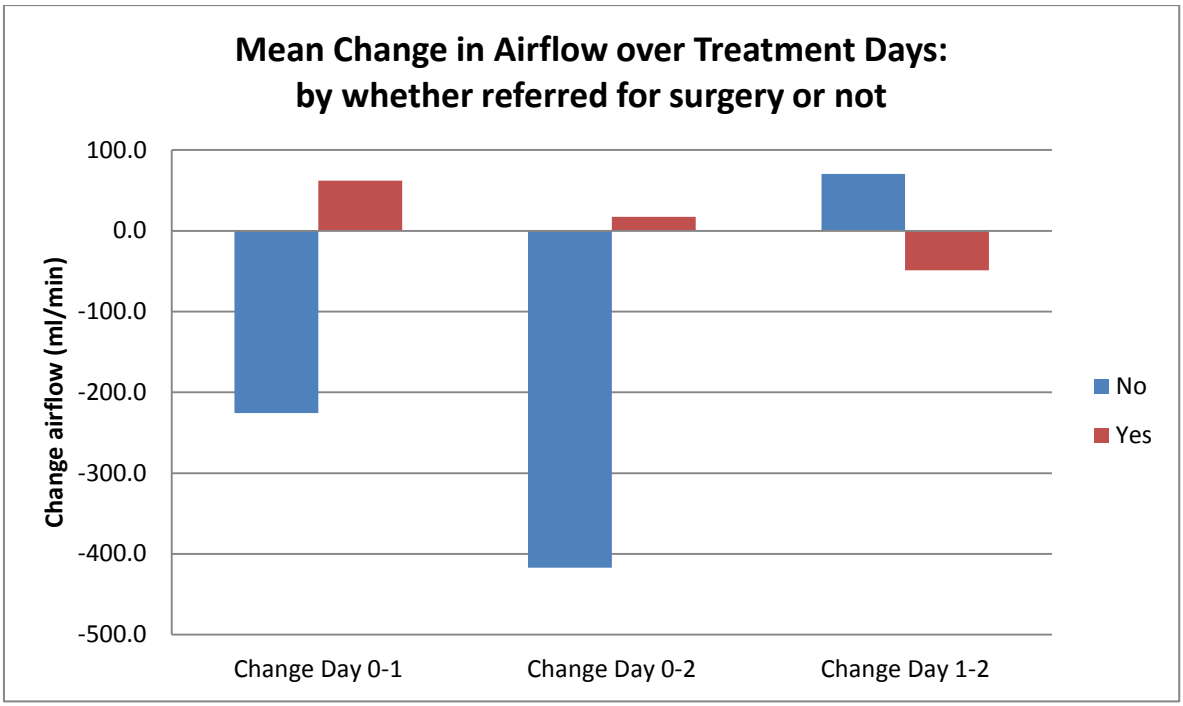




Δ= Difference in Medians, p value calculated using Mann-Whitney U test

Changes in absolute airflow values in individual patients over treatment Days 0 to 2 show that the largest reduction in airflow occurred in those patients resolving spontaneously compared to those being referred to surgery (Figure 5.4). The airflow reduced between Days 0 and 1 in most patients: Mean change in airflow between Day 0-1 was -153.6ml/min. However, the reduction was greater in those in those resolving spontaneously (-225.6ml/min) compared to those referred for surgery (+63.3ml/min). On Day 0-2 was difference was greater (-452.6ml/min and +17.2ml/min, respectively). However, these differences did not reach statistical significance.

Figure 5.4: Mean change in airflow measurement over treatment periods: Day 0-1, Day 0-2 and Day1-2: by whether referred for surgery or not.



5.7. Discussion

The optimal management strategy for patients with PSP is controversial and is not well defined. Treatment guidelines are not consistent in their definition of who to treat (in terms of size definition) and initial management [4, 78, 80]. Treatment failure for patients with pneumothorax (i.e. failure of lung to re-expand and/or PAL) will inevitably lead to non-optimal care, uncertainty about expected length of hospital stay and likely referral for surgical management. This will occur in a significant proportion of patients. Data from previous RCTs suggest that at 7 days between 7 and 15% of patients will have PAL[84, 85].

5.7.1. Risk factors for PAL

As discussed in above, large volume of initial aspiration and size of pneumothorax on CXR may be important in determining failure of NA[82, 132, 133, 135]. These findings are understandable physiologically. At onset of the spontaneous pneumothorax (which is presumed to coincide with the patient's symptoms of chest pain), air must leak from a breach of the visceral pleura. A small pneumothorax may occur if the air leak is small, or if there was a moderate initial air leak which spontaneously ceased. Conversely, a large amount of air will accumulate if either the initial air leak is large or there is a prolonged moderate air leak. The resulting pneumothorax will appear large on CXR, and a larger pneumothorax will by definition have a larger volume of air aspirated (usually up to a pre-specified maximum volume). Therefore, it would seem likely that patients with larger size pneumothoraces could have increased rate of treatment failure (PAL). However, previous studies have not found useful predictors of PAL or prolonged treatment duration. This may be because other studies did not have sufficient patient numbers to show a difference, or because there are other clinical factors which are more important.

Other risk factors to consider are sex, age, BMI and smoking status. These were evaluated in this study. The patient population was representative of the population likely to suffer with PSP: majority (74.1%) male, with a mean age of 30.0 years and 74.3% were current or ex-smokers. Interestingly, there was a trend towards current or ex-smokers being slightly less likely to be referred for surgery (OR 0.41). This result is surprising as historically smoking has been linked to higher rates of initial pneumothorax and of second recurrence[70]. The patient's age did not affect the rate of referral. Previous studies have suggested older age (>50 years) is a risk factor for PAL[132], but patients in this study with PSP were all younger.

Underweight patients (BMI <18.5kg/m^2) showed a trend towards being more likely to be referred for surgery. Likewise, patients with large pneumothoraces (>=4cm at level of the hilum) at presentation were slightly more likely to be referred and have marginally longer treatment duration, but these differences not statistically significant. These results may be due to insufficient sample size (a Type II (beta) error) and that with a larger patient group, a significant difference may be detected.

5.7.2. Airflow measurement

This study is the first to use sequential digitally measured airflow measurements along with clinical data and is based on interim analysis of prospectively collected data as part of a multi-centre trial. Initial absolute airflow measurements were high in both those eventually referred for surgery (median 155ml/min, IQR 355ml/min) and those not referred (median 220ml/min, IQR 360ml/min). As these measurements were taken immediately after insertion of a catheter to re-inflate the lung (i.e. Day 0, after insertion of either a chest tube or Pleural Vent device), they are likely to represent air flowing out of the pleural cavity as the lung attempts to re-expand. As such the lack of difference between the groups is not surprising.

Measurements taken on subsequent days (≥Day 1) are more likely to be measuring any on-going air leak from the lung, if present. Figure 5.1 shows that the difference in median airflow rates was significantly different between those eventually referred and those not referred by Days 1 and 2. Considering the mean treatment duration was 5.2 days, use of data at Day 1 or 2 to predict eventual outcomes could be clinical useful in reducing days of patient and clinician uncertainty and potentially allow triage to a different treatment strategy. However, demonstrating a difference may be less useful than providing a threshold

value which predicts treatment success (i.e. spontaneous resolution rather than requiring surgical referral).

On this basis, data showed that utilisation of an airflow threshold of 100 or 150ml/min on Day 1 or 2 could indicate the likelihood of patient failing treatment: Patients with an airflow measurement on Day 1 of >=100ml/min have an odds ratio of 5.1 for referral for surgery; whilst those with <100ml/min have a NPV of 80.6%. In other words, only 1 in 5 patients with <100ml/min will fail to resolve spontaneously.

5.7.3. Physiological implications

Patients who have a pneumothorax as a result of a one-off air leak event, which subsequently heals, are likely to resolve quickly. On-going air leak at a low level (e.g. 100ml/min) might suggest that the alveolar-pleural fistula is starting to repair itself, and thereby less likely to require further intervention. Large size of initial pneumothorax on CXR (and hence large volume of initial aspiration) may not be good indicators of likelihood failure, as it could be due to large initial air leak (which has now stopped), or a low level leak of long duration (some patients present after many days of symptoms). These two different scenarios will have different clinical courses.

5.7.4. Limitations

The relatively small sample size (81 patients) and the short sampling method of 10 minute airflow measurements are limitations to the study. Ideally the digital devices would have been continuously attached to the patient in order to provide greater longitudinal data. However, the practicalities of use in a busy emergency department (in which the patients were recruited) or on a medical/respiratory ward, where clinical staff are unfamiliar with the

device, meant that this was not practical. Airflow measurements were therefore only taken by trained research staff. Air leak data were available for 70% of patients, but data were not always recorded for every treatment day. This is likely to be due to the practical considerations listed above, but it is possible that the patients whom have airflow data recorded are not representative of the whole patient group.

In this study, the digital airflow measurement was conducted using Thopaz+ device (Medela, UK). Providing active suction to re-inflate the lung in patients with pneumothorax is controversial and not currently recommended due to lack of sufficient evidence[4]. The digital suction device was set to negative 0.4kPa, at which point the device should be attempting to reduce any more positive intra-pleural pressure back to a physiological small negative pressure. It is possible be that even at this low level suction the digital suction device is providing enough suction to be influencing the natural course of the resolution of the pneumothorax (rather than passively observing). It is hoped that 10min period every 24hours would have minimal effect, but if patients were continuously attached to the digital device this may be more pronounced, or even detrimental. However, at present there exists no alternative "non-suction" method of quantifying air leak – the method described by Seaton *et al*[137, 138] provides a binary "leak or not" reading rather than a quantitative airflow measure and is not currently commercially available. As such, despite these limitations, digital airflow measurement is the most promising method of air leak detection and measurement.

The size of pneumothorax in this analysis was determined from the initial assessment by the treating clinician (i.e. < or >=4cm measured at the level of the hilum). This binary description may not be as sensitive as a continuous measurement of pneumothorax size (using one of

the techniques described above), which will be conducted in the final analysis of the entire RAMPP dataset.

5.8. Conclusions

At present, management of patients with pneumothoraces involve daily monitoring of the underwater seal connected to their chest drains, looking for swinging (indicative of change in intra-pleural pressure when breathing) or bubbling (suggestive of on-going air leak). Patients with bubbling drains will remain as inpatients and be reviewed again the following day. This binary system of "bubbling or not" does not seem satisfactory and has not been shown to provide any predictive information about likely length of stay.

Data presented in this study, the first of its kind in medical patients with pneumothorax, suggest that airflow measurements in the early stages of PSP management may be predictive of failure of treatment at Day 4 (and hence surgical referral). On-going prospective data is being collected. If validated, early prediction of treatment failure could lead to an alternative treatment pathway: patients at higher risk of failure could be triaged to an early preventative treatment pathway (i.e. thoracic surgery), rather than waiting with daily reviews until Day 4, with associated cost of inpatient stay as well as the patient distress at the uncertainty. This new treatment paradigm will need to be assessed prospectively in a controlled trial, but it has the potential to change the management strategy for pneumothorax for the first time in decades.

5.9. Future directions

Recruitment to the RAMPP trial is on-going. Once recruitment is complete, the remaining dataset will be analysed. This could provide up to 165 patients' data in total (assuming 70% air leak data capture from total target 236 predicted patients). Once all the data is present, data completeness will be assessed to ensure that there is no bias in the capture and recording of the airflow measurements: For example, to check that particular recruiting sites or patient types (either by treatment group or time of admission) were equally likely to have measurements undertaken.

The data will be reassessed with larger patient numbers in order to determine whether the thresholds of 100 and 150ml/min robustly distinguishes patients resolving spontaneously within 5 days and those requiring referral for surgery. In addition, risk factors of sex, age, smoking history, and, importantly, initial size of pneumothorax will be re-examined.

This current dataset shows a trend towards larger pneumothorax being predictive of surgical referral on a crude binary measure of large (≥4cm at the level of the hilum) or not. At the end of the trial, patient CXRs will be available, so a continuous measure of size (for example, Rhea criteria or Light's index) can be used, which may provide more statistical power to detect a difference.

A future tool using easily identifiable clinical factors (including size of initial pneumothorax, bedside airflow measurement) early in the treatment pathway (e.g. Day 1 or 2) to predicting treatment failure is a step closer. If validated in a prospective cohort of patients, such a tool could change the current treatment paradigm of unselected, daily review to one involving

informed discussion about likelihood of treatment failure, and for those as high risk potential targeted early referral for surgery.

5.9.1. Plans for the next trial

Validation will require an RCT. The trial would include patients with PSP who require chest tube insertion (either standard chest drain or ambulatory device), with a pneumothorax that has not resolved after 24 hours of drainage. They would then be randomised into two groups: an intervention group using a new treatment decision pathway based upon digital airflow measurement at day 1 or 2; compared to a control group using standard care (daily assessment of bubbling from chest drain and CXR appearance). The primary outcome will be overall length of treatment.

The hypothesis is that use of the new pathway, involving early referral for surgery (e.g. if airflow is >100ml/min on Day 2) reduces length of stay by removing the requirement to "wait until day 4 or 5" before referring for surgery. In this current dataset, the mean total treatment duration for those referred for surgery was 11.9 days (SD 5.4). Any strategy which can successfully identify and triage patients likely to fail could significantly lessen time to surgery, thereby overall treatment time.

6. Systematic Review: Chemical Pleurodesis in Spontaneous Pneumothorax Recurrence Prevention

6.1. Background

Patients with who have failure initial treatment (i.e. PAL) will require intervention to seal the hole in the visceral pleura (See Chapter 1: Introduction and Chapter 5: Air Leak). In addition, patients may opt to undergo elective treatment to reduce their recurrence risk (if they have a second ipsilateral, first contralateral episode). At present this elective treatment is undertaken by thoracic surgeons, during which any visible blebs or bullae will be resected by apical pleurectomy or bullectomy using resection, staplers, suturing or electrocoagulation. Historically, open thoracotomy was performed. However, a systematic review of RCTs concluded that Video Assisted Thoracoscopic Surgery (VATS) was superior to thoracotomy in terms of pain relief, duration of hospital stay and atelectasis following the procedure[149]. Therefore, surgeons will typically now undertake VATS.

6.1.1. Surgical recurrence rates without pleurodesis

Surgical bullectomy alone is associated with a relatively high rate of pneumothorax recurrence (6–14%)[20, 150, 151], suggesting that resection of bullae alone is not sufficient. Surgical series showing poorer rates of recurrence prevention with simple bullectomy compared with bullectomy and pleurectomy or pleurodesis confirm that it is necessary to also undertake diffuse treatment of the visceral pleura. This can take the form of a surgical technique (pleural abrasion or pleurectomy) or instillation of a chemical agent to induce pleurodesis. One series of 453 patients undergoing VATs for PSP found that the recurrence rate after talc poudrage (1.8%) was significantly lower than that of patients treated with subtotal pleurectomy (9.2%)[152]. However, this was a non-randomised historical

comparison over a period in which surgical practice changed from pleurectomy (1992-1995), to talc poudrage (1995-1998), so should be not be viewed as conclusive.

Moreover, one may argue that it is the pleurodesis achieved by pleural synthesis, either by chemical agent or abrasion/pleurectomy, rather than the surgical bullectomy or resection, which drives the low recurrence rates. In addition, patients who are unfit or unwilling to undergo surgery can be offered pleurodesis.

6.1.2. Choice of chemical pleurodesis agents

There exist numerous agents which have been used as pleurodesis agents. However, there are few direct comparative studies and there is no consensus as to the most efficacious agent. The BTS make reference to tetracycline as the previous first line agent for PSP and SSP, but with decline in usage through difficulties in supply in favour of graded talc, with passing mention of minocycline and doxycycline efficacy in animal models[4]. The mechanism of action of chemical agents is discussed in the Introduction.

6.1.3. The evidence gap

There are no studies to date which synthesize data on all of the chemical pleurodesis agents with respect to the efficacy in pneumothorax management. As such, it is not clear what clinicians should expect in terms of recurrence rates when considering pleurodesis agents. Further data is required to allow informed discussions with patients about risk of recurrence and with colleagues regarding the generation of local guidelines.

6.2. Aims

This study aims to systematically review the existing literature regarding the efficacy of chemical pleurodesis for recurrence prevention in pneumothorax.

6.3. Methods

In light of this evidence gap, a systematic review of the literature was undertaken to identify relevant studies to allow comparison of agents. Ideally all agents would have been assessed robustly in a randomised, blinded fashion as part of RCTs. However, it was known that there was a dearth of these trials in chemical pleurodesis, so the review was expanded to include case control studies and case series (without comparator groups). Whilst these studies would not allow direct comparison, well-conducted studies could still provide useful data across similar patient groups.

6.3.1. Eligibility criteria

Therefore, the following criteria were devised. Studies considered eligible for inclusion consisted of:

- Adult patients with any spontaneous pneumothorax (PSP and SSP) were included so as not to limit the evidence base. SSP patients are more likely to be unfit for surgery, due to their respiratory and other comorbidities, and thereby undergo chemical pleurodesis instead.
- Undergoing pleurodesis at first occurrence or subsequent recurrence: although most guidelines recommend pleurodesis at secondary occurrence, some trials exist of intervention at first occurrence, which should be included.

- Patients being treated for persistent air leak, by instillation via chest tube or in addition to surgical procedure.
- Intervention using chemical pleurodesis with any agent.

Comparators included were any of: chest tube drainage alone (no pleurodesis), other pleurodesis agent and surgical procedures (e.g. mechanical abrasion, bleb/bullectomy, pleurectomy). The outcome was pneumothorax recurrence rate (ideally, after at least one year of follow up).

Studies were excluded if they were animal models (as they cannot be considered to have directly transferrable results) or paediatric studies. Studies which did not contain any new information, such editorials, letters and review articles, were excluded so as to not double count primary data. The other main indication for pleurodesis is in patients with recurrent malignant pleural effusion. However, the mechanism for fluid re-accumulation is different from that of pneumothorax recurrence, and therefore pleurodesis efficacy may be different, so pleural effusion studies were excluded.

Surgical studies in which only surgical procedures were undertaken (i.e. no chemical agent was inserted) were not included. Likewise, patients undergoing pleurodesis for post-operative air leak only (after thoracic surgery for other indications) were not considered as the reason for the air leak was likely to be due to the intervention on the lung, rather than the cause of the pneumothorax.

Any studies with insufficient data to allow adequate comparison (e.g. no data on agent or technique used) were not considered. There needed to be reasonable follow-up period to capture all potential recurrence events, so studies with a follow-up period of less than 3

months were excluded. Although case series were eligible, case reports and small case series with less than 10 cases were not included because of the high risk of reporting bias.

Papers were also excluded if they were not available on paper or online via the University of Oxford's extensive library access collections.

6.3.2. Search strategy

Literature searches of multiple databases (including PubMed, Embase, Medline, Web of Science, Cochrane Library) were performed up to and including June 2016. Results were not restricted by year of publication. Combinations of search terms were used adapted for each database as appropriate, including "pleurodesis", "spontaneous", "pneumothor*", "chemical", "talc", "tetracycline", "minocycline", "iodopovidine", and "blood". In addition to electronic database searches, reference lists, relevant textbooks and review articles were hand-searched and back-referenced (i.e. reference lists of review articles examined for additional studies not appearing in initial searches). Abstracts were independently reviewed for relevance by two respiratory registrars. Any discrepancies were resolved by discussion (with two further respiratory consultants) with a low threshold for review of the full article. Relevant full journal articles were subsequently assessed again for eligibility.

6.3.3. Data extraction

Data were extracted from the full articles separately by two authors using a pre-specified extraction form (Excel 2010, Microsoft, USA). Extracted information included: lead author, year, geographical area, nature of pneumothorax (primary or secondary, where available), number of participants, intervention agent(s), control/comparator measures, recurrence rate for each arm, follow-up timescale (mean or median when described), study type, and

quality. In those with mixed populations (for example, including patients with pleural effusions or post-operative air leak), only data pertaining to spontaneous pneumothorax was extracted. Where available, data on number of episodes of pneumothorax (rather than number of patients) were extracted. Early pleurodesis failures which required further procedure or surgical referral were included in the calculated recurrences rates.

6.3.4. Quality and risk of bias assessment

Risk of bias of the included RCTs was assessed using the Cochrane Risk of Bias tool [153]. This tool addresses seven domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'.

Case control studies or case series are not suitable for assessment using this tool as there is no randomisation or blinding. Although not formally assessed, the risk of selection and reporting bias in these studies was high.

6.3.5. Data analysis

Ideally, if a significant number of similar studies with comparable design, pleurodesis agents, control groups and outcomes were identified, a formal data synthesis via meta-analysis would be conducted. However, if there were heterogeneity in studies, precluding formal meta-analysis, a narrative synthesis would be conducted, presenting similar studies side by side to allow some comparison, whilst including detail of how studies differ. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated, where possible, as a measure of the effectiveness in reducing pneumothorax recurrence relative to a control. Recurrence was defined as another pneumothorax event within a set time period, typically 1 year. Estimates

of the pneumothorax recurrence rate were calculated, including a 95% CI (calculated on the log scale), using the following formulae:

$$95\%\ CI = \exp[\ln(\text{recurrence rate}) +/- 1.96*(\text{standard error})]$$

However, when a low number of events (recurrences) occur in one arm (i.e. <5), the above formula for calculating the upper limit of the CI is not valid. For zero or low number of events, the Cochrane Handbook for Systematic Reviews of Interventions[153] recommend estimating the upper limit using the formula 3/n, where n is the sample size([153] section 16.9.4). The value 3 coincides with the upper limit of a one-tailed 95% CI form the Poisson distribution (equivalent to a two-tailed 90% CI). In addition, zero values preclude the calculation of ORs, so the standard approximation of adding 0.5 to all cell counts before calculating ORs and their CIs was also applied ([153] section 16.9.2).

6.4. Results

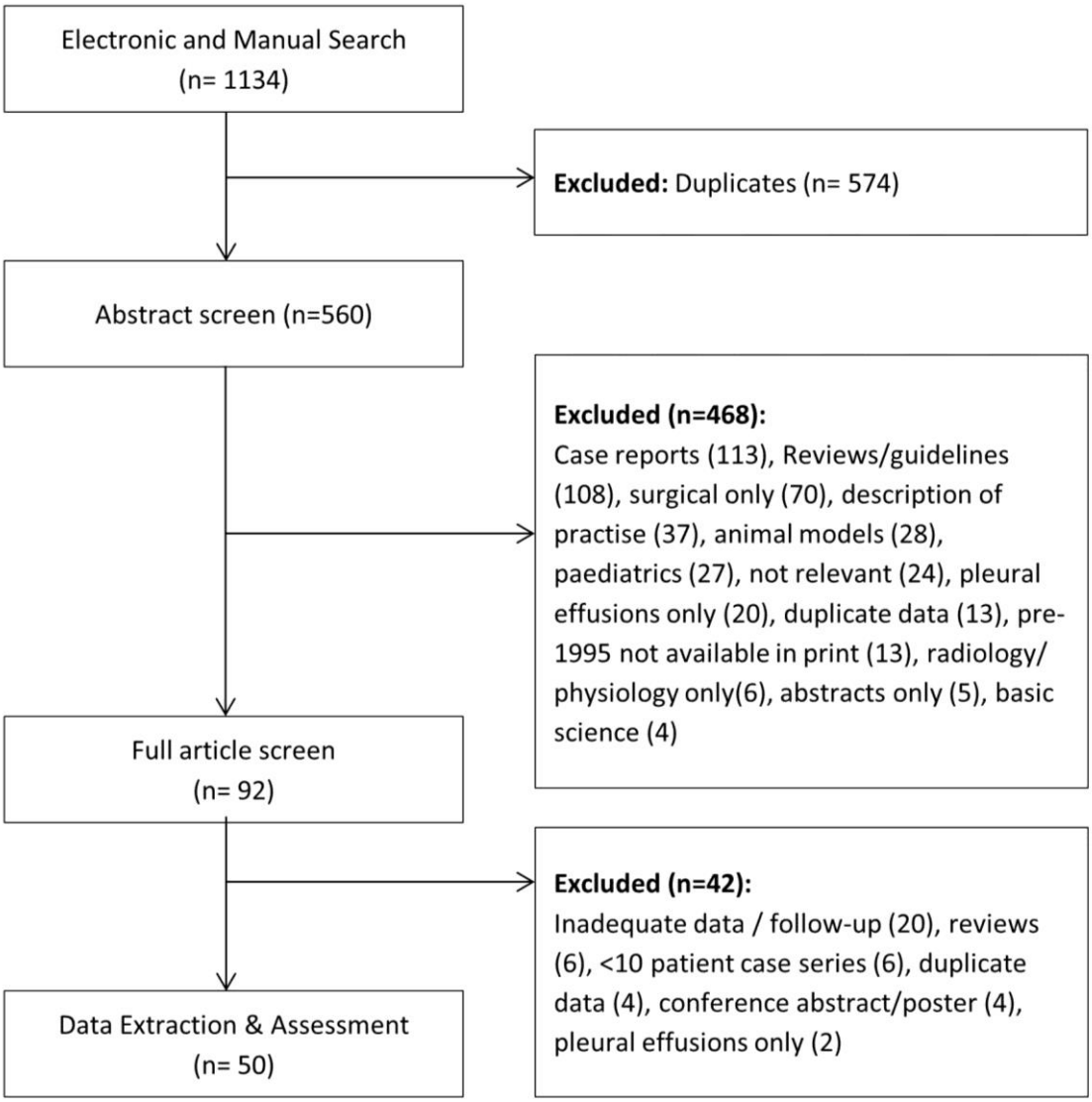
6.4.1. Search results

After de-duplication of search results, 560 abstracts were reviewed (see Figure 6.1). 468 were excluded as not eligible for our review at this stage (case reports, reviews, surgical series or description of practise, animal models, paediatric cases, pleurodesis for pleural effusions only, duplicate data or basic science articles) and full text copies of 13 papers published prior to 1995 were not available. Of the remaining 92 potentially eligible papers, an additional 42 studies were identified as not being eligible for data extraction (20 with inadequate data or no long term follow-up data, 6 reviews, 6 with <10 cases, 4 duplicate data from other publications, 4 conference posters or abstracts only and 2 only related to

pleural effusion management) when full texts were screened. Hence 50 relevant studies were identified and the results summarised.

These 50 studies varied in size, quality and study design: 9 RCTs, 10 prospective case series (3 with non-randomised comparator groups) and 31 retrospective case series (10 with non-randomised comparator groups). The indication for pleurodesis varied; 16 (32%) studies stated an indication of pneumothorax recurrence or on-going air leak, seven (14%) enrolled only those at first occurrence, six (12%) assessed patients with on-going air leak, five (10%) studied recurrent pneumothorax only and three studies (6%) enrolled a mixture of first occurrence, recurrent pneumothorax and on-going leak or haemothorax. The remaining 13 studies (26%) did not specify the indication for recurrence prevention precisely enough to categorise this further.

Figure 6.1: PRISMA flow diagram of study selection.



6.4.2. Assessment of bias

Assessment of bias of the RCTs showed a low risk of reporting, detection or attrition bias as the outcomes of pneumothorax recurrence were well reported and the loss to follow-up was low (see Table 6.1). The randomisation process was generally well described and adequate, with the exception of some of the older studies which did not describe the process[109, 154] and a more recent study which appeared to be alternating treatment arms based upon trial number[155]. Alternating treatment arms is not adequate as clinicians enrolling patients

would be able to predict the next allocation and could thereby alter their behaviour or recruitment accordingly. None of the studies were blinded, some providing explanation of why this was not attempted: difficulties of matching colour of agent or that the expected pain associated with minocycline instillation would be likely to unmask the blinding.

6.4.3. Study heterogeneity

As discussed above, there was heterogeneity in terms of study design, indications for pleurodesis, multiple different pleurodesis agents, variation in the availability of a control group (either historical or concurrent randomised or non-randomised) and differences in the outcomes across identified studies. Therefore, formal data synthesis via meta-analysis was not conducted.

Instead, data on recurrence rates by each agent will be presented by study population: for example, talc was used as a pleurodesis agent in the largest number of studies (24), data is presented for PSP patients who had underdone thoracoscopy, who, by definition, did not have any intervention on the lung (Table 6.2), separately from those in surgical studies who had surgical intervention (Table 6.3); studies in which it was not possible to separate the results for PSP and SSP were presented together (Table 6.4).

In terms of quality of the studies, RCTs were considered the most robust, hence presented first, followed by prospective studies, then retrospective case series (with and without comparator groups).

Table 6.1: Risk of Bias Assessment of RCTs

						Assessment of Bias				
Study Author [Ref]	**Year**	**Setting**	**Participants**	**Intervention**	**Outcome**	**Randomisation & Concealment (Selection Bias)**	**Blinding (Performance bias)**	**Blinding of outcomes (detection bias)**	**Data completion (attrition bias)**	**Selective reporting (reporting bias)**
Agarwal [96]	2011	Single centre, India	4 PSP 23 SPP	Iodopovidone vs talc via chest drain	Recurrence	Low risk: Computer generated sequence	High risk: not blinded to allocation	Low risk: pneumothorax recurrence	Low risk: no loss to follow-up	Low risk: all outcomes reported
Alayouty [155]	2011	Single centre, Egypt	82 PSP	Minocycline vs abrasion (after VATS Bullectomy)	Recurrence	High risk: odd or even trial number	High risk: not blinded to allocation	Low risk: pneumothorax recurrence	Low risk: no loss to follow-up	Low risk: all reported
Almind [154]	1989	Single centre, Denmark	71 PSP 25 SSP	3 arms: talc, tetracycline or chest drainage alone	Recurrence	Unclear: no details given	Unclear: no details given	Low risk: pneumothorax recurrence	Moderate:7% loss to follow-up	Low risk: all outcomes reported
Chen [156]	2006	Single centre, Taiwan	202 PSP	Minocycline vs no agent via chest drain (after VATS Bullectomy)	Recurrence	Low risk: by chart number assigned before work-up (odd or even)	High risk: not blinded as pain with minocycline expected to unmask blinding	Low risk: pneumothorax recurrence (patient reported)	Low risk: no loss to follow-up	Low risk: all outcomes reported
Chen [110]	2013	Two centres, Taiwan	214 PSP	Minocycline vs no agent via chest drain	Recurrence	Low risk: Computer generated sequence	High risk: not blinded to allocation	Low risk: pneumothorax recurrence	Low risk: no loss to follow-up	Low risk: all outcomes reported

Chung [157]	2008	Multi-centre, Korea	144 PSP	3 arms: talc & dextrose, dextrose vs no agent (after VATS + bleb resection or electro-coagulation	Recur-rence	Unclear: no details given	Unclear: no details given	Low risk: pneumothorax recurrence	Low risk: no loss to follow-up	Low risk: all outcomes reported
Light [109]	1990	Multi-centre, USA	46 PSP 183 SSP	Tetracycline vs chest drainage alone	Recur-rence	Low risk: Sequentially numbered sealed envelopes	High risk: not blinded as pain unable to match yellow colour of tetracycline	Low risk: pneumothorax recurrence	Low risk: 3% loss to follow-up	Low risk: all outcomes reported
Tschopp [158]	2002	Multi-centre (across Europe)	144 PSP	Talc poudrage vs no agent (after thoracoscopy)	Recur-rence	Low risk: sealed envelopes	Unclear: no details given	Low risk: pneumothorax recurrence	Low risk: 1% loss to follow-up	Low risk: all outcomes reported
Wied [159]	1983	Single centre, Denmark	41 PSP	Tetracycline vs silver nitrate (after thoracoscopy)	Recur-rence	Low risk: sealed envelopes	Unclear: no details given	Low risk: pneumothorax recurrence	Low risk: no loss to follow-up	Low risk: all outcomes reported

6.5. Talc

Twenty four studies used talc as a chemical pleurodesis agent. Twelve assessed the efficacy of talc poudrage for the treatment of PSP: 4 in which talc poudrage was performed at medical thoracoscopy with no associated intervention on the lung (Table 6.2) and 8 in which talc poudrage was administered post-VATS with bleb electrocoagulation, bleb resection or apical bullectomy (Table 6.3).

Of the 4 studies in which talc poudrage was performed without intervention on the lung (Table 6.2), only 1 was an RCT. It demonstrated a lower recurrence rate among those receiving talc poudrage compared with those treated with drainage alone (talc 5.1% vs drainage 34.0%, OR = 0.10, 95% CI 0.03-0.38)[158]. A case series study with a (non-randomised) control arm provided similar estimates: talc 2.6% vs drainage 26.1%, OR = 0.08 (95% CI 0.01-0.69)[160]. Two case series, without comparators, estimated 10.2% recurrence in patients presenting with recurrent PSP or on-going air leak (including early failures)[161] and 9.5% in combination of first episode (62%) and recurrent (38%) PSPs[162]. All 4 studies had follow-up periods of at least 24 months (Table 6.2).

In the eight surgical studies evaluating talc poudrage for PSP post-VATS with bleb electrocoagulation, bleb resection or apical bullectomy the follow-up period was variable from 10 to 62 months (Table 6.3). There was only one RCT, which was carried out in 141 patients undergoing VATS with bleb resection or electrocoagulation. The recurrence rate among patients receiving talc and dextrose was 2.4%, compared with 6.0% in the control arm of surgery only. However, the confidence interval for the OR was very wide, indicating that the uncertainty related to this finding: OR 0.38 (95%CI 0.04-3.82)[157]. Further, similar results were also seen by simply introducing dextrose without talc[157]. Observed

recurrence rates across the other seven surgical studies were between 0.0% and 3.2%[163-169]. Only two of these had (non-randomised) comparator groups[166, 169] one of which provided statistical evidence for a reduced recurrence rate in those receiving talc compared with pleural abrasion: talc 1.5% vs pleural abrasion 4.0%, OR = 0.38 (95% CI 0.15-0.97)[166].

The remaining twelve studies used talc to treat both PSP and SSP patients (Table 6.4). One RCT estimated a reduction in recurrence rates by performing talc pleurodesis via chest drain compared to drainage alone, OR 0.16 (95%CI 0.03-0.85)[154]. Two small studies insufflated talc under local anaesthetic and reported 0% recurrence in 24 patients [170] and 20 patients[171], respectively. However, four larger series including 521 patients undergoing talc poudrage at thoracoscopy found recurrence rates of 5.6 to 16.1% (including early failures)[172-175]. One study comparing talc to autologous blood pleurodesis found lower recurrence in the talc group (OR 0.48) but wide confidence intervals (0.10-2.24)[176]. A retrospective case series of 122 patients using talc pleurodesis via chest drain found a similar recurrence rate of 13.3%[177]. A further three retrospective surgical studies, including 317 patients undergoing VATS bullectomy and talc poudrage for PSP and SSP found recurrence rates of 1.1-4.5%[178-180]. The (non-randomised) comparator groups of the two studies (n=312) found the recurrence rate for talc via chest drain for SSP to be 2.9%[178] and 30.8%[180]. Although the difference in the latter study was statistically significant, the two patient groups were very different: patients receiving talc via chest drain were those not deemed fit for VATS[180].

Table 6.2: Efficacy of Talc Pleurodesis for PSP at thoracoscopy (No intervention on lung): presented by study size by trial design

Study Author [Ref]	Year	Study Design	n	Intervention (n)	Co-Intervention	Intervention Recurrence rate (95% CI)	Control/ Reference Arm (n)?	Control/ Reference Recurrence rate (95% CI)	Follow-up period (months)	Odds ratio (vs control) (95%CI)
Randomised Controlled Trial (RCT)										
Tschopp [158]	2002	RCT	108	Talc poudrage (61)	Thoracoscopy only	5.1% (1.6-16.2%)	Drainage only (47)	34.0% (18.6-62.2%)	61[MN]	0.10 (0.03-0.38)
Retrospective Case Series (with comparator group)										
Verschoof [160]	1988	Retrospective Case series	61*	Talc poudrage (38)	Thoracoscopy only	2.6% (0.4-19.2%)	Drainage only (23)	26.1% (10.3-66.2%)	48[MN]	0.08 (0.01-0.69)
Retrospective Case Series (no comparator group)										
Gyorik [161]	2007	Retrospective Case series	59†	Talc poudrage (59)	Thoracoscopy ‡	10.2%† (4.4-23.7%)	-	-	118[MD]	-
Adewole[162]	2015	Retrospective Case series	21*	Talc poudrage (21)	Thoracoscopy only	9.5% (2.2-40.9%)	-	-	24[MN]	-

CI: Confidence Interval. MN: Mean. MD: Median. † Includes 3 early failures in recurrence rates. ‡ Electrocoagulation performed in 4 cases. * PSP patients only.

Table 6.3: Efficacy of Talc Pleurodesis for PSP – Post surgery (Intervention on Lung): presented by study size by trial design

Study Author [Ref]	Year	Study Design	n	Intervention (n)	Co-Intervention	Intervention Recurrence rate (95% CI)	Control/ Reference Arm (n)?	Control/ Reference Recurrence rate (95% CI)	Follow-up (months)	Odds ratio (vs control) (95%CI)
Randomised Controlled Trial (RCT)										
Chung [157]	2008	RCT (3 arms)	141	Talc & Dextrose (42)	VATS + bleb resection or electrocoag	2.4% (0.3-17.3%)	Drainage only (50)	6.0% (1.9-19.3%)	24 MN, 20 MN	0.38 (0.04-3.82)
				Dextrose only (49)	"	2.0% (0.3-14.8%)			18 MN	0.33 (0.03-3.25)
Prospective Series										
Ramos-Izquierdo[163]	2010	Prospective series	133	Talc poudrage (133)	VATS +/- bleb electrocoag	3.2% (1.2-8.7%)	-	-	36 MN	-
Dubois [164]	2010	Prospective series	72	Talc poudrage (72)	VATS + apical bullectomy	0% (0.0-4.2%)	-	-	12 MN	-
Retrospective Case Series (with comparator group)										
Moreno-Merino [166]	2012	Retrospective Case series	787	Talc poudrage (388)	VATS + bullectomy	1.5%* (0.7-3.5%)	Abrasion** (399)	4.0%* (2.4-6.6%)	unclear	0.38 (0.15-0.97)
Janssen [169]	1994	Retrospective Case series	44	Talc poudrage (21)	VATS +/- bleb resection or electrocoag‡	0% (0.0-14.3%)	VATS-Bullectomy (23)‡	8.7% (2.0-37.1%)	>18	0.20 (0.01-4.42)
Retrospective Case Series (no comparator group)										
Cardillo [165]	2006	Retrospective Case series	861	Talc poudrage (861)	VATS +/- bullectomy	1.7%† (1.0-3.0%)	-	-	53 MN	-
Margolis [167]	2003	Retrospective Case series	156	Talc poudrage (156)	VATS + bleb resection	0% (0.0-1.9%)	-	-	62 MD	-
Mármol Cazas [168]	2011	Retrospective Case series	130	Talc poudrage (130)	VATS +/- bullectomy	3.1% (1.1-8.3%)	-	-	10 MN	-

CI: Confidence Interval. MN: Mean. MD: Median. Electrocoag = Electrocoagulation *Includes early treatment failures requiring re-intervention. **Historical comparison. †Excluded 56 lost to follow-up. ‡Thoracoscopic talc poudrage was performed in patients with normal pleura or bullae <2cm diameter, bullectomy was performed in those with bullae>2cm.

Figure 6.2: Graphical representation of recurrence rates after talc pleurodesis for PSP only at thoracoscopy (no intervention on lung) and surgical intervention: presented by number of patients receiving intervention (n)

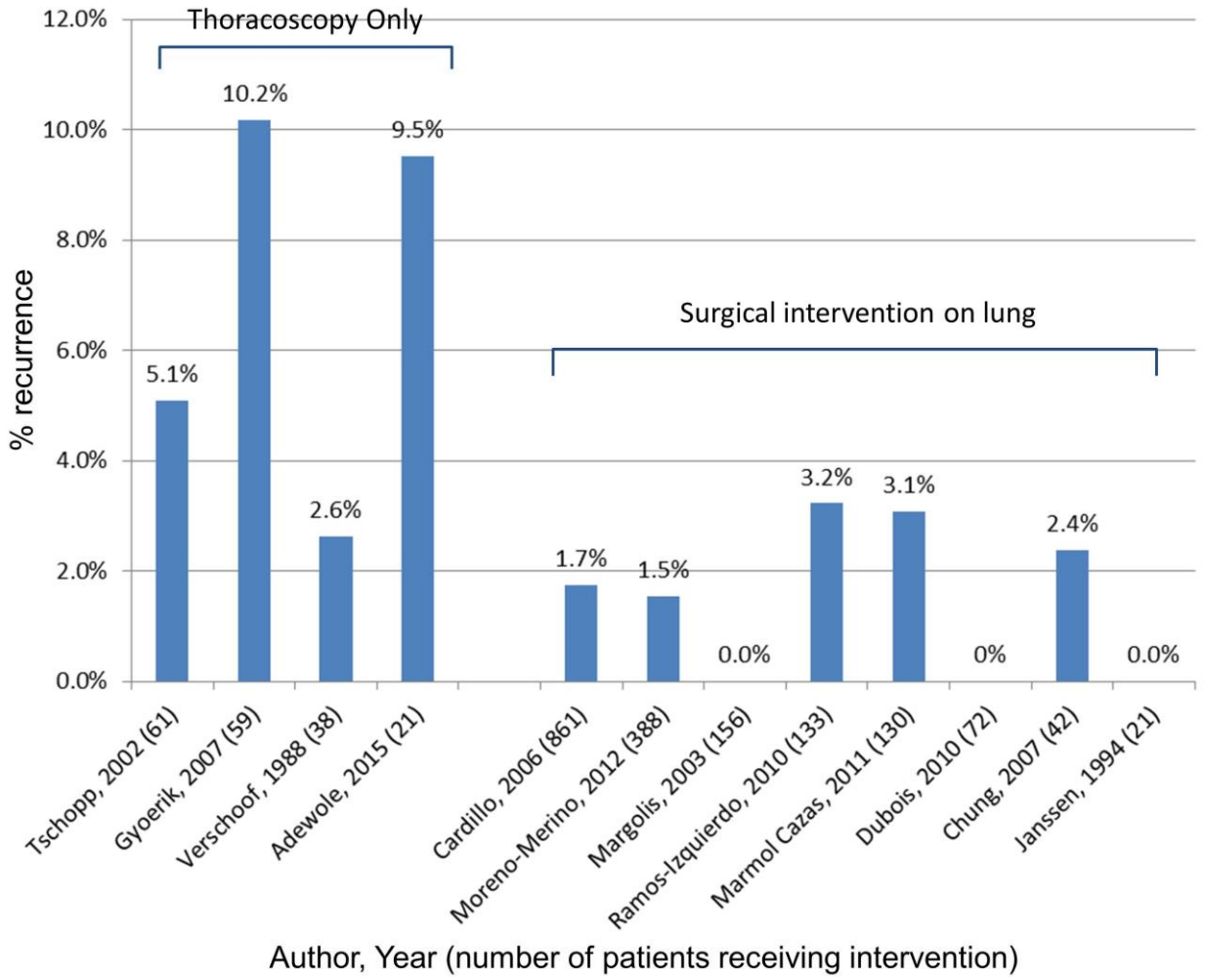


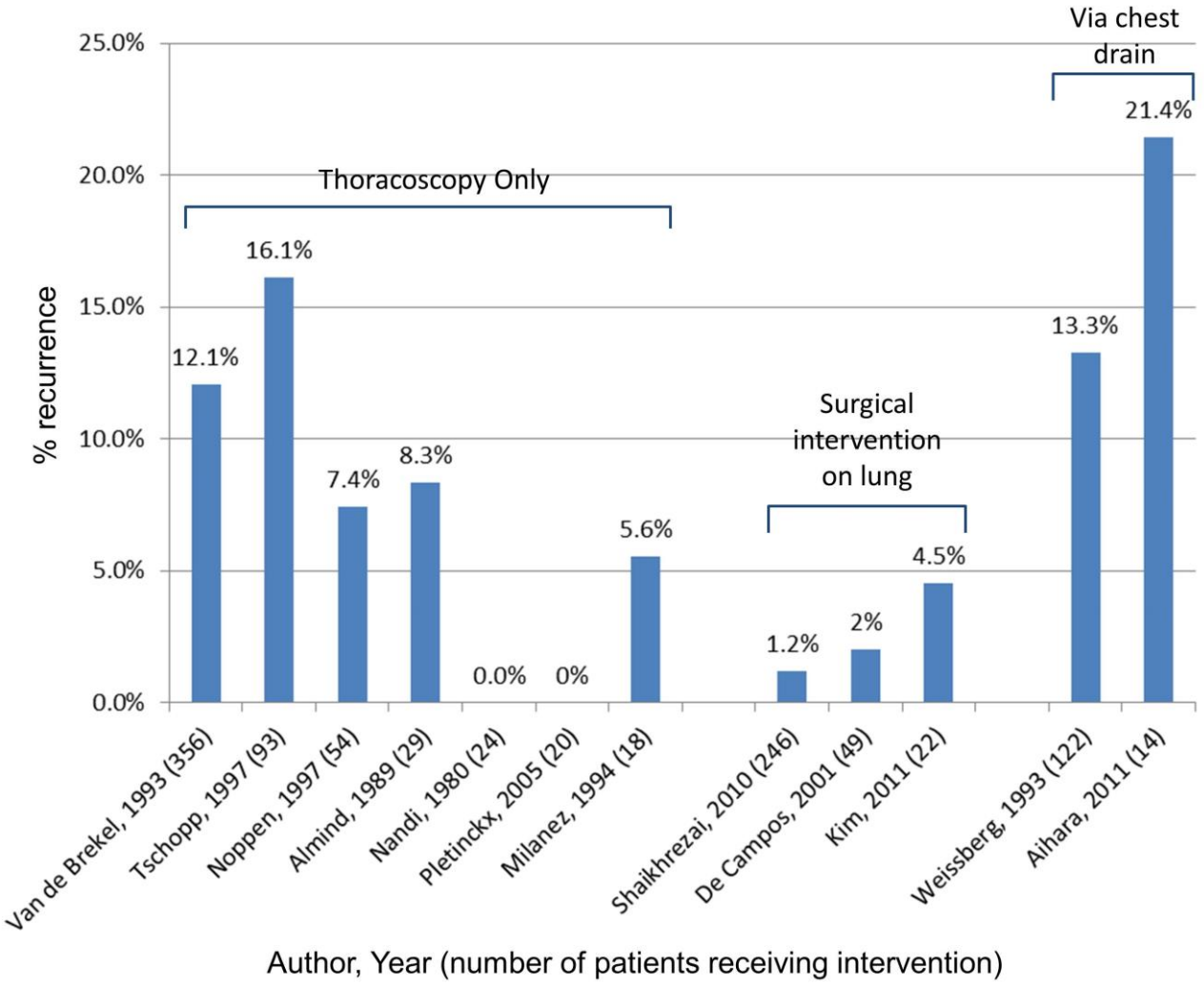
Figure 6.4: Efficacy of Talc Pleurodesis on Spontaneous Pneumothorax (both PSP & SSP) by intervention medically & surgically treated: presented by study size by trial design

Study Author [Ref]	Year	Study Design	n	PSP or SSP? (n)	Intervention (n)	Intervention Recurrence rate (95% CI)	Control/ Reference Arm (n)?	Control/ Reference Recurrence rate (95% CI)	Follow-up period (months)	Odds ratio (vs control) (95%CI)
Randomised Controlled Trials (RCT) - medical										
Almind [154]	1989	RCT[Δ]	96[Δ]	PSP (71) SSP (25) [Δ]	Talc at thoracoscopy (29)	8.3% (2.0-35.4%)	Drainage only (34)	36.0% (15.9-81.5%)	55 [MN]	0.16 (0.03-0.85)
Prospective Series – medical										
Noppen [172]	1997	Prospective Case series	54	PSP (31) SSP (23)	Talc at thoracoscopy (54) +/- bleb electrocoag	7.4% (2.7-20.5%)	-	-	18 [MN]	-
Milanez [173]	1994	Prospective Case series	18	PSP (15) SSP (3)	Talc at thoracoscopy (18)	5.6% (0.7-41.7%)	-	-	38.5 [MN]	-
Retrospective Case Series – medical (with comparator group)										
Aihara [176]	2011	Retrospective Case series	36	PSP (0) SSP (36)	Talc via chest drain (14)	21.4% (6.0-76.8%)	Blood (22)	36.4% (15.3-86.7%)	15 [MN]	0.48 (0.10-2.24)
Retrospective Case Series – medical (no comparator group)										
Van de Brekel [174]	1993	Retrospective Case series	356†	Unclear	Talc at thoracoscopy (356)	12.1% (8.8-16.6%)	†	†	12-240	-

Weissberg [177]	1993	Retrospective Case series	122	Unclear	Talc via chest drain (122)	13.3% (7.7-22.9%)	-	-	Unclear	-
Tschopp [175]	1997	Retrospective Case series	93	PSP (65) SSP (28)	Talc at thoracoscopy (93)	16.1% (9.3-28.0%)	-	-	60	-
Nandi [170]	1980	Retrospective Case series	24	PSP (0) SSP (24)	Talc at thoracoscopy (24)	0% (0.0-12.5%)	-	-	2-24	-
Pletinckx [171]	2005	Retrospective Case series	20	PSP (5) SSP (15)	Talc at thoracoscopy (54) +/- bleb resection	0% (0.0-15.0%)	-	-		-
Retrospective Case Series – surgical (with comparator group)										
Shaikhrez [178]	1984	Retrospective Case series	322	PSP (550) SSP (94)	VATS + bullectomy + talc poudrage (246)	1.2% (0.4-3.8%)	VATS + bullectomy + abrasion (273)	2.9% (1.5-5.9%)	73 [MD]	0.41 (0.11-1.56)
Kim [180]	2011	Retrospective Case series	61	PSP (0) SSP (61)	VATS + bullectomy + talc (22)	4.5% (0.6-33.8%)	Drainage + talc via drain (39)	30.8% (15.6-60.7%)	Unclear	0.11 (0.01-0.89)
Retrospective Case Series – surgical (no comparator group)										
De Campos [179]	2001	Retrospective Case series	49	Unclear	VATS + bullectomy + talc (49)	2.0% (0.3-14.8%)	**-**	**-**	24-60	**-**

CI: Confidence Interval. MD: Median. MN: Mean. Follow-up range shown if no average given. † Thoracotomy & bullectomy was performed in those with bullae>2cm at thoracoscopy – not included in analysis. [Δ]RCT had 3 arms (total numbers include tetracycline arm, n=33)

Figure 6.3: Graphical representation of recurrence rates after talc pleurodesis for all spontaneous pneumothorax (where unable to distinguish PSP & SSP) by intervention medically & surgically treated: presented by number of patients receiving intervention (n)



6.6. Tetracycline

Nine studies evaluated the efficacy of tetracycline pleurodesis for spontaneous pneumothorax via chest drains or thoracoscopy without intervention on the lung (Table 6.5 and Figure 6.4). These were of variable quality including both PSP and SSP but comprised 3 RCTs including a total of 366 patients. Two RCTs, from 1990 and 1989, randomised patients to either tetracycline vs chest drain or drainage only[109, 154]. Both reported lower rates in the tetracycline arm but only one study was statistically significant OR 0.48 (95%CI 0.27-0.85)[109]. The other small RCT of tetracycline vs silver nitrate at thoracoscopy found recurrence rate of 0% in both arms[159]. Four non-randomised retrospective studies of tetracycline vs drainage alone all estimated reduced recurrence rates in the tetracycline group. However, all but one had wide CIs crossing the null value of one: OR 0.50 (95%CI 0.23-1.09), 0.25 (95% CI 0.09-0.73), 0.43 (95% CI 0.07-2.68) and 0.14 (95% CI 0.01-2.53)[103, 181-183]. It should be noted that four studies included only patients with first occurrence of SP[154, 159, 181, 183], with the remaining five studies not specifying indication for recurrence prevention. One surgical study of tetracycline after VATS bullectomy reported no recurrences (0.0%) in contrast to 10.9% in a group treated non-surgically with chest tube drainage alone[184]. However, another older prospective surgical series found showed a recurrence rate of 9.4% with no control group[185].

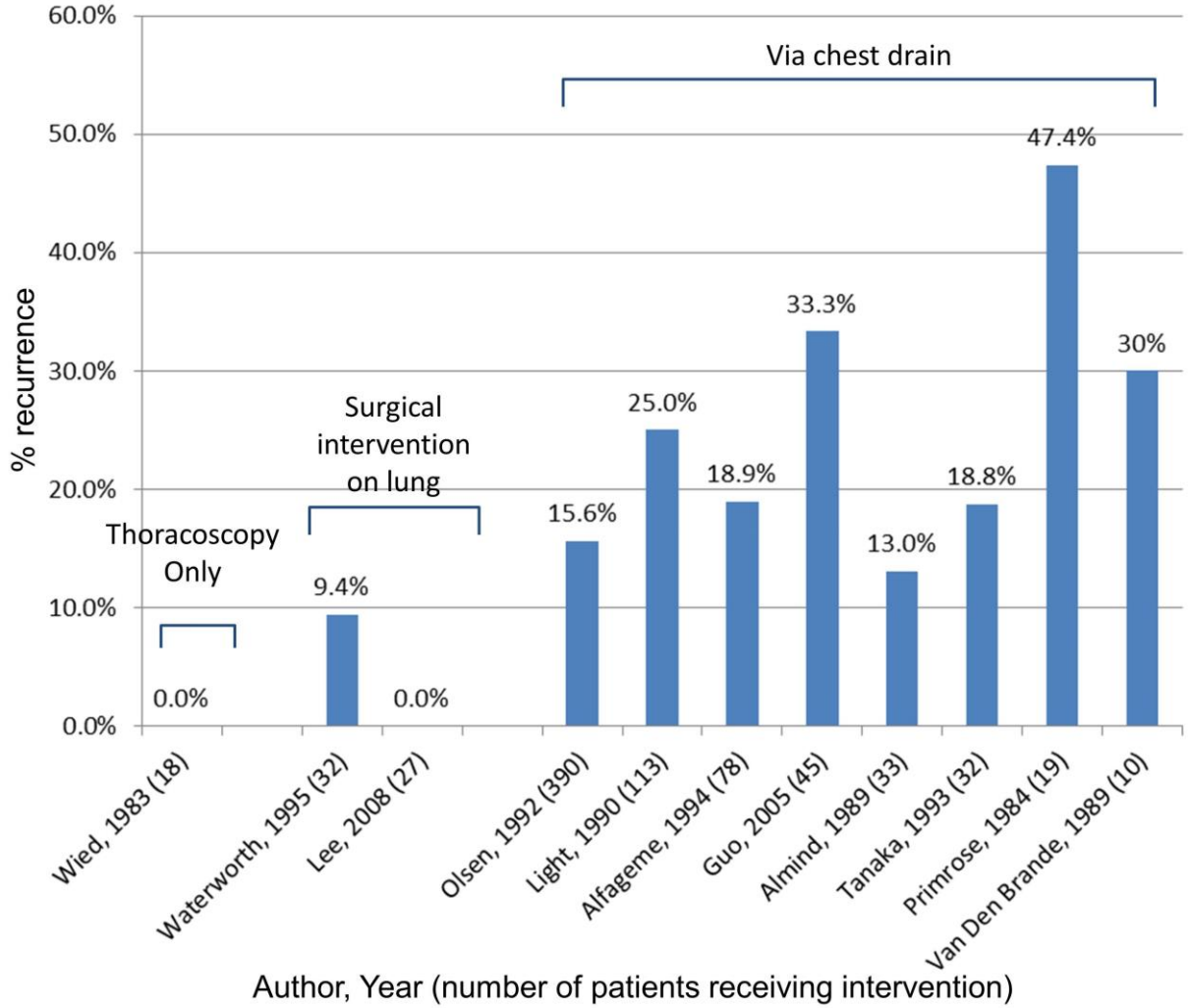
Table 6.5: Efficacy of Tetracycline Pleurodesis for Spontaneous Pneumothorax (no intervention on lung): presented by study size by trial design

Study Author [Ref]	Year	Study Design	n	PSP or SSP? (n)	Intervention (n)	Intervention Recurrence rate (95% CI)	Control/ Reference Arm (n)?	Control/ Reference Recurrence rate (95% CI)	Follow-up period (months)	Odds ratio (vs control/ reference) (95%CI)
Randomised Controlled Trials (RCT) – Medical										
Light [109]	1990	RCT	229	PSP (46) SSP (183)	Tetracycline via chest drain (113)	25.0% (16.2-38.0%)	Drainage only (116)	40.7% (28.0-58.7%)	29-34 [MN]	0.48 (0.27-0.85)
Almind [154]	1989	RCT[Δ]	96[Δ]	PSP (71) SSP (25) [Δ]	Tetracycline via chest drain (33)	13.0% (3.9-43.9%)	Drainage only (34)	36.0% (15.9-81.5%)	55 [MN]	0.27 (0.06-1.15)
Wied [159]	1983	RCT	41	PSP (41)	Tetracycline at thoracoscopy (18)	0% (0.0-16.7%)	Silver nitrate (22)	0% (0.0-13.6%)	14 [MD]	-
Prospective Series – medical										
Alfageme [103]	1994	Prospective Case series	146	PSP (96) SSP (50)	Tetracycline via chest drain (78)	18.9%‡ (10.6-33.8%)	Drainage only (68)	35.3% (19.9-62.7%)	45 [MN]	0.43 (0.19-0.97)
Prospective Series - Surgical										
Waterworth [185]	1995	Prospective series	32	PSP (32)	VATS + bullectomy + tetracycline (32)	9.4% (2.9-30.8%)	-	-	19 [MD]	-
Retrospective Case Series – Medical (with comparator group)										
Guo [181]	2005	Retrospective Case series	138		Tetracycline via chest drain (45)	33.3% (17.9-62.0%)	Drainage only (70)	50.0% (31.3-79.9%)	6-69	0.50 (0.23-1.09)

Tanaka [182]	1993	Retrospective Case series	78*	SSP (78)	Tetracycline via chest drain (32)	18.8% (7.7-45.6%)	Drainage only (46)	47.8% (26.8-85.3%)	48 [MN]	0.25 (0.09-0.73)
Van den Brande [183]	1989	Retrospective Case series	20	PSP (86) SSP (52)	Tetracycline & 30% Glucose via chest drain (10)	30.0% (7.8-100%)	Drainage only (10)	50.0% (14.5-100%)	26 [MN] (intervention) and 18 [MN] (control)	0.43 (0.07-2.68)
Retrospective Case Series – Surgical (with comparator group)										
Lee [184]	2008	Retrospective Case series	91	PSP (91)	VATS + bullectomy + tetracycline (27)	0.0% (0.0-11.1%)	Drainage only (64)	10.9% (5.0-24.0%)	16 [MN]	0.14 (0.01-2.53)
Retrospective Case Series – Medical (no comparator group)										
Olsen [186]	1992	Retrospective Case series	390 †	PSP (390)	Tetracycline at thoracoscopy (390)	15.6% (11.9-20.6%)	†	†	43 [MD]	-
Primrose [73]	1984	Retrospective Case series	19**	Unclear	Tetracycline via chest drain (19)	47.4% (19.2-100%)	-	-	Unclear	-

CI: Confidence Interval. MD: Median. MN: Mean. Follow-up range shown if no average given. † Thoracotomy & bullectomy was performed in those with bullae>2cm at thoracoscopy – not included in analysis. ‡Includes 8 early treatment failures. *Excluding patients being observed or aspirated only and those having thoracotomy. **Small subgroup of patients undergoing pleurodesis. [Δ]RCT had 3 arms (total numbers include talc arm, n=29)

Figure 6.4: Graphical representation of recurrence rates after tetracycline pleurodesis for all spontaneous pneumothorax (PSP & SSP) by intervention: presented by number of patients receiving intervention (n)



6.7. Blood

Five studies of blood patch pleurodesis were included in the analysis (n=270, Table 6.6). There were no RCTs compared to drainage alone. Two studies prospectively enrolled patients after spontaneous pneumothorax with persistent air leak. One non-randomised study estimated an OR of 0.47 (95%CI 0.17- 1.32) for recurrence in patients following autologous blood pleurodesis compared with drainage alone (15.6% blood pleurodesis, including early failures requiring surgery, vs 28.1% drainage)[187].

As noted in the Talc section above, a small retrospective comparison study of talc via chest drain vs blood patch was inconclusive[39]. Two further small retrospective series of patients unfit for surgery with recurrence or persistent air leak found long term recurrence of 16.0%[188] and 16.1%[189] with no comparator groups.

Table 6.6: Efficacy of Blood Pleurodesis for Spontaneous Pneumothorax (PSP and SSP) via chest drain: presented by study size by trial design

Study Author [Ref]	Year	Study Design	n	PSP or SSP? (n)	Intervention (n)	Intervention Recurrence rate (95% CI)	Control/ Reference Arm (n)?	Control/ Reference Recurrence rate (95% CI)	Follow-up (months)	Odds ratio (vs control/ reference) (95%CI)
Prospective Series										
Cagirici [187]	1998	Prospective series	167	PSP (116) SSP (51)	Blood via chest drain (32)	15.6% (6.0-40.6%)	Drainage only (135)	28.1% (19.3-41.0%	12-48	0.47 (0.17-1.32)
Ando [190]	1999	Prospective series	11	SSP (11)	Blood via chest drain (11)	18.2% (3.9-84.1%)	-	-	2-24	-
Retrospective Series										
Aihara [176]	2011	Retrospective Case series	36	SSP (36)	Blood via chest drain (22)	36.4% (15.3-86.7%)	Talc (14)	21.4% (6.0-76.8%)	15 MN	2.10 (0.45-9.81)
Evman [189]	2016	Retrospective Case series	31	SSP (31)	Blood via chest drain (31)	16.1%* (6.2-42.0%)	-	-	29 MN	-
Robinson [188]	1987	Retrospective Case series	25	Unclear	Blood via chest drain (25)	16.0% (5.5-46.6%)	-	-	24-132	-

CI: Confidence Interval. MN: Mean. Follow-up range shown if no average given. * Includes early treatment failures.

6.8. Minocycline

Three RCTs in patients with PSP (n=498) found recurrence rates of 0%[155] and 1.9% after the instillation of minocycline after lung re-expansion post-VATS procedure[156] but 29.2% after instillation via chest drain only (i.e. medical management, no intervention on the lung) in patients with first presentations of PSP[110] (Table 6.7). This RCT provided evidence of a reduction in recurrence compared with drainage only in non-surgical patients (minocycline 29.2% vs drainage only 49.1%, OR = 0.43, 95% CI 0.24-0.75) [110]. Among surgical patients, Chen *et al* also observed a reduced recurrence rate compared with patients receiving saline, but the strength of statistical evidence was weak (minocycline 1.9% vs saline 8.1%, OR = 0.23, 95% CI 0.05-1.09) [156]. The third surgical RCT, comparing minocycline vs mechanical abrasion, was small and inconclusive (minocycline 0.0% vs mechanical abrasion 5.0%, OR = 0.18, 95% CI 0.01-3.89) [155].

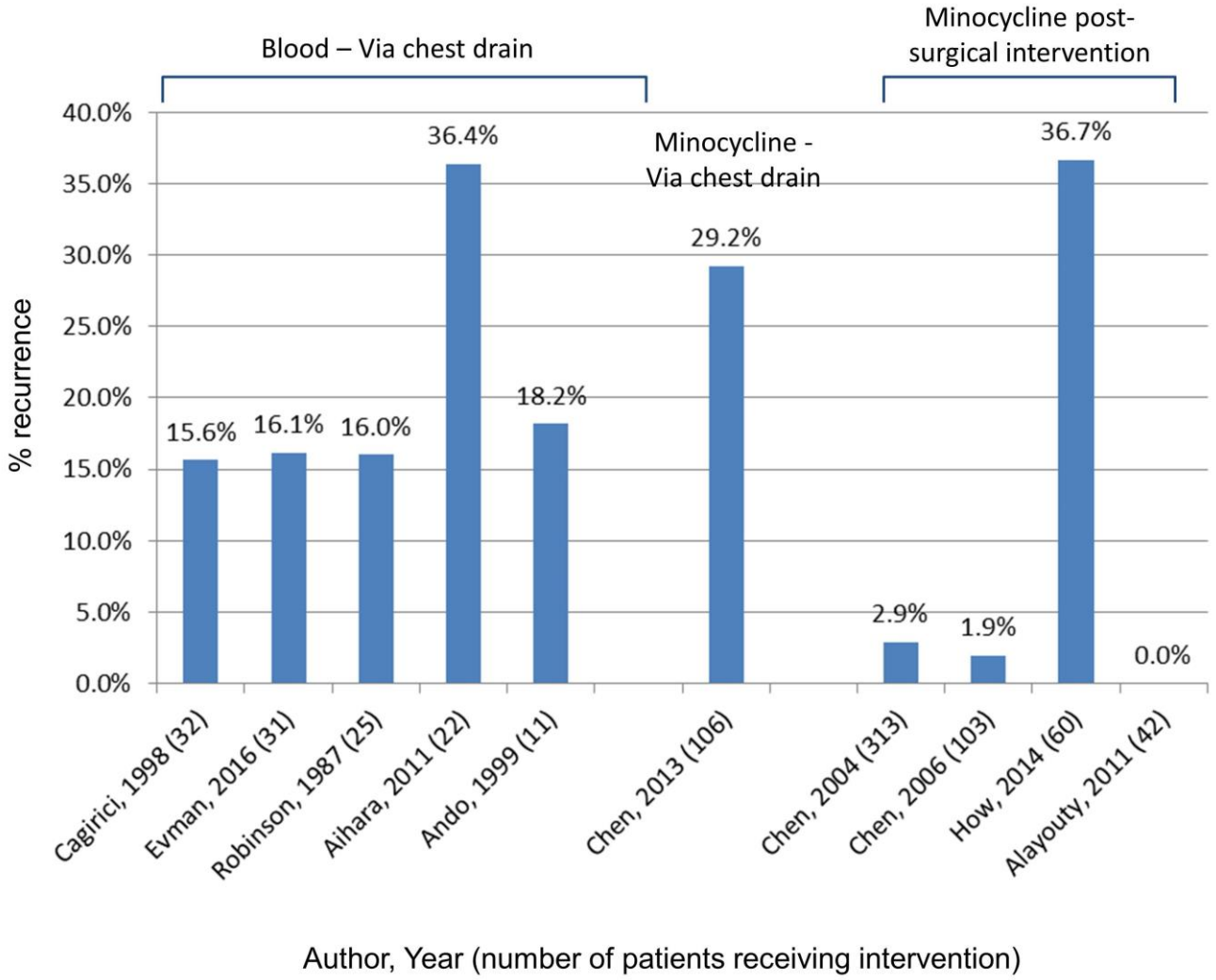
There were also two retrospective non-randomised studies with control arms. One suggested that minocycline significantly reduced recurrence rates with minocycline post-VATS compared with saline (minocycline 2.9% vs 9.8% saline, OR 0.27 (95%CI 0.09-0.85)) in a historical comparison[191]. The other comparative study, found markedly increased recurrence rates in the minocycline group compared to OK-432 (estimated failure rate 36.7% minocycline vs 5.3% OK-432, OR = 10.42 (95% CI 1.30-83.5)[192]. This high failure rate may well be due to the inclusion of a number of patients with prolonged air leak post-VATS for pneumothorax.

Table 6.7: Efficacy of Minocycline Pleurodesis for PSP: presented by study size by trial design and medical/surgical management

Study Author [Ref]	Year	Study Design	n	Intervention (n)	Co-Intervention	Intervention Recurrence rate (95% CI)	Control/ Reference Arm (n)?	Control/ Reference Recurrence rate (95% CI)	Follow-up (months)	Odds ratio (vs control/ reference) (95%CI)
Randomised Controlled Trial (RCT) – Medical										
Chen [110]	2013	RCT	214	Minocycline via chest drain (106)	Nil	29.2% (19.2-44.4%)	Drainage only (108)	49.1% (33.7-71.6%)	19 MN	0.43 (0.24-0.75)
Randomised Controlled Trial (RCT) – Surgical										
Chen [156]	2006	RCT	202	Minocycline via chest drain (103)*	VATS + bullectomy	1.9% (0.5-7.9%)	No agent (99)	8.1% (3.9-16.6%)	29 MN	0.23 (0.05-1.09)
Alayouty [155]	2011	RCT	82	Minocycline via chest drain (42)*	VATS + bullectomy	0% (0.0-7.1%)	Mechanical Abrasion (40)	5.0% (1.2-20.7%)	36 MN	0.18 (0.01-3.89)
Retrospective Case Series – Surgical										
Chen [191]	2004	Retrospective Case series	364	Minocycline via chest drain (313)*	VATS + bullectomy	2.9% (1.5-5.6%)	Saline (51)†	9.8% (3.9-24.7%)	48 MN	0.27 (0.09-0.85)
How [192]	2014	Retrospective Case series	79 **	Minocycline via chest drain (60)	VATS + bullectomy	36.7% (21.7-62.0%)	OK-432 (19)	5.3% (0.7-39.4%)	16 MN	10.42 (1.30-83.50)

*Minocycline introduced post-surgery once lung had re-expanded. †Historical comparison. **Only patients with post-op air leak after VATS were Included.

Figure 6.5: Graphical representation of recurrence rates after "blood patch" or minocycline pleurodesis for all spontaneous pneumothorax (PSP & SSP) by intervention: presented by number of patients receiving intervention (n)



6.9. Other agents

A retrospective surgical series of 81 cases reported a recurrence rate of 6.2% when using iodopovidone during VATS, despite only 37% undergoing bullae resection. Two small studies in India assessed the efficacy of iodopovidone via chest drain. One randomised trial (n=35) had no recurrence in either the iodopovidone or talc pleurodesis arms[96] and a retrospective review of 27 cases found a recurrence rate of 7.4%[193].

Two studies used silver nitrate as a chemical pleurodesis agent: One RCT (see Table 6.5) reported 0% recurrence after instillation at thoracoscopy but described increased pleural fluid production and longer hospital stay than using tetracycline[159]. A retrospective surgical study (n=184, 3 years follow-up) used silver nitrate after VATS bullectomy with a recurrence rate of 1.1%, but had no comparison group[194]. A retrospective series reviewing recurrence prevention at first occurrence found a significant recurrence rate using gentamicin via chest drain, although this was more efficacious than drainage alone (3 year recurrence rates 26.1% and 50.0% respectively (OR 0.35 (95%CI 0.12-1.00), with a reported p value <0.05)[181]. A small study including 17 spontaneous pneumothoraces found only one recurrence (5.9%) after administration of quinacrine[195]. In a group of 57 patients with SSP deemed too high risk for surgery with on-going air leak, diluted fibrin glue was instilled via chest drain. The long term (60 months) recurrence rate was 10.5%[196]. The addition of acromycin post-VATS bullectomy reportedly reduced recurrence to 3.8% from 20.0%, in a non-randomised historical comparison group, but CI were wide (OR 0.16, CI (95%CI 0.02-1.48), despite the authors stating a p value <0.05[151].

6.10. Discussion

This is the first study attempted to systematically review the evidence for the effectiveness of pleurodesis in recurrence prevention for all chemical pleurodesis agents in cases of spontaneous pneumothorax, in both “medical” pleurodesis (i.e. no intervention on the lung) and as an adjunct to surgical procedures.

6.10.1. Quality of the studies

There was considerable heterogeneity across studies in terms of study design, indications for pleurodesis, different comparative agents, variation in term of the availability of a control group (either historical or concurrent randomised or non-randomised) and differences in the outcomes across identified studies. As such, formal data synthesis via meta-analysis was not conducted as the results would be clinically meaningful. Only 9 of 50 studies were RCTs. 13 of the 41 other studies (case series) provided comparator groups but these were historical comparisons or non-randomised comparator groups. The lack of head-to-head comparisons limits the ability to formally compare relative effectiveness of different agents in this systematic review. This is in contrast to a recent Cochrane Review of pleurodesis agents in malignant pleural effusion, in which a network meta-analysis of pleurodesis agents was possible with 62 RCTs identified [197].

6.10.2. What is the best agent/technique?

The recurrence rates for pneumothorax without intervention are best estimated by studies in which the control arms were drainage with a chest drain only (i.e. no other agent). These suggest recurrence rates of 26.1-50.1% at 1-2 years.

The lowest rates of recurrence are achieved when chemical pleurodesis is an adjunct to surgical intervention. The control arms of 3 surgical RCTs presented here suggest that VATS bullectomy with or without abrasion alone provide recurrence rates of 2.9 to 10.9% [166, 169, 184]. When talc poudrage is performed in addition, the recurrence rate appears to be reduced even further (to between 0.0% and 3.2%, See Figure 6.2) [157, 163-169, 184]. Minocycline appears to be the agent of choice in Taiwan and produces a similarly low recurrence if instilled via chest drain once the lung has re-expanded post-VATS bullectomy results (between 0.0-2.9%) [155, 156, 191]. The only exception to this success with minocycline was from a study, which comprised mainly patients with post-operative air leak, with an estimated failure rate of 36.7% in the minocycline group [192]. This high failure rate is not adequately explained by the authors but is likely to be due to the differing patient group.

Therefore, talc and minocycline pleurodesis agents as an adjunct to surgical intervention provide the best reduction in recurrence rates. There have been no direct comparisons of VATS bullectomy and pleurectomy to VATS bullectomy and talc pleurodesis.

6.10.3. Non-surgical options

VATs requires a general anaesthesia and although complication rates are low, may not be suitable for all patients. Local anaesthetic ("medical") thoracoscopy, performed under conscious sedation, is an option for some patients. The majority of thoracoscopy studies have used talc. Talc appears to be effective at reducing recurrence for PSP when used via poudrage at thoracoscopy (Figure 6.2), with two studies with comparator arms give recurrence rates of 5.1% and 2.6% with OR 0.10 and 0.08, respectively, when comparing talc

poudrage to drainage alone[158, 160]. However, more recent case series data suggested higher recurrence rates (9.5%[161] and 10.2%[162]).

It would appear that these excellent results for PSP patients are not replicated in the studies of general spontaneous pneumothorax population (i.e. where both PSP and SSP patients were enrolled): talc poudrage at thoracoscopy in these patients appear to be between 5.6-16.1% in larger case series. However, these studies without comparator arms could be subject to significant selection and reporting bias.

6.10.4. Pleurodesis via chest drain

In those patients not suitable for VATS or thoracoscopy, chemical pleurodesis agents can be instilled via the chest drain. The majority of these studies involve tetracycline. The higher quality studies (RCTs) would suggest a recurrent rate of between 13% and 25%, which is significantly better than those receiving drainage only (OR 0.27 and 0.61)[109, 154].

Minocycline via chest drain without surgical intervention in patients with first presentation of PSP also seems to provide a significant reduction in recurrence in a high quality RCT (OR 0.43)[110] although intervention at first occurrence is not generally considered and not advised in the current guidelines[4].

No studies of talc slurry pleurodesis for SP alone were found, except two studies with small comparator groups of 14 and 10 patients, which gave 21.4% and 0.0% recurrence rates respectively[96, 176]. A previous systematic review of talc pleurodesis of 22 studies in 1994 found an overall success rate of 91%; however, 6 of 15 studies assessing talc poudrage and the 4 studies assessing talc slurry were small (≤10 patients) such that estimated rates are very imprecise[94].

There are numerous other pleurodesis agents with potential efficacy. Iodopovidone is widely available in India with one small RCT demonstrating equivalent success rates to talc[96]. The case for widespread use of acromycin, gentamycin, or quinacrine via chest drains, and silver nitrate or diluted fibrin glue post-VATS is still to be made.

These results are consistent with recent network meta-analysis of pleurodesis for malignant pleural effusions which found that talc poudrage was highly effective, followed by talc slurry, mepacrine, iodine, bleomycin and doxycycline; although this is clearly a different patient population[197].

6.10.5. Persistent air leak

Blood patch pleurodesis for persistent air leak in those patients not fit for surgery (mainly those with SSP and significant comorbidities) seems to deliver a recurrence rate of around 16%[188, 189]. An RCT assessing the short term efficacy of autologous blood patch pleurodesis at varying doses found that administration of 1 or 2 mL/kg was more successful at ceasing air leak by 13 day (both 82%) than 0.5 mL/kg or saline (27% and 9%, respectively)[198].

6.10.6. Intervention at first occurrence?

The indication for pleurodesis in the vast majority of studies was recurrence prevention at second occurrence or on-going air leak, as per guideline recommendation. However, one study assessed early surgical intervention at first occurrence[167]. This group was controversially managed without aspiration or chest tube drainage, undergoing VATS with bleb resection and talc poudrage pleurodesis within 12 hours of first presentation. While none of these patients had a subsequent recurrence, it is likely that a significant proportion

were unnecessarily operated upon as many will have resolved with conservative management and not recurred.

6.10.7. Limitations of systematic review

There are a number of limitations to this systematic review. Firstly, the review is limited by the quality of the available data. Although a few well conducted RCTs were identified, the majority of identified studies were observational, many of which were non-comparative. Many included studies were also retrospective, with a high risk of reporting bias. Thirteen papers published pre-1995 which were not available electronically or in print and so were not included. Indications for pleurodesis varied across the studies including those solely assessing patients at first occurrence, those with recurrent pneumothorax or air leak patients, and those with on-going air leak only. Size of pneumothorax at presentation and details of previous treatment were not always provided. There was variation both within, and across, surgical studies as to the specific co-incident procedure being undertaken (alongside chemical pleurodesis). The exact procedure was often determined on visual inspection of the lung (e.g. bleb/bullae resection or electrocoagulation only performed if visible blebs and bullae seen) but results usually only reported as overall recurrence rates. This results in significant clinical heterogeneity in the published data, and therefore interpretation of results across study types should be guarded.

6.10.8. Learning from the best studies

Many of the limitations of this systematic review are driven from discrepancies in trial design. RCTs are the ideal design for comparing interventions, as they minimise selection bias. Robust objective outcomes are required to avoid detection bias: recurrence of pneumothorax as reported by treating clinician is a good outcome as chest radiographic

evidence of a pneumothorax is not subjective (as opposed to patient symptoms, for example). Loss to follow-up should be minimised to avoid attrition bias. Registration of the RCT prior to commencement of the study allows transparency of reporting – i.e. reporting predetermined metrics, rather than post-hoc, avoids reporting bias.

A number of RCTs identified in this systematic review did meet these criteria. Tschopp *et al* conducting a pan-European multicentre RCT of thoracoscopy with or without talc poudrage[158]. This study showed the additional talc poudrage significantly reduced recurrence (talc 5.1% vs drainage alone 34.0%, OR = 0.10, 95% CI 0.03-0.38)[158]. The mean follow-up period was 5 years, which is commendable but perhaps longer than required as the majority of patients will recur within one year (see Chapter 2 - Epidemiology). Disappointingly, blinding of allocation was not commented upon in this study[158]. Blinding of both patient and clinician would be ideal as knowledge of which trial arm allocation to could potentially change the behaviour of the team and (unwittingly) alter the way in which they are treated.

A further two well conducted RCTs also failed to provide evidence of blinding. Both trials were conducted by Chen *et al* using minocycline [110, 156]. The first studied the addition of minocycline via chest drain after surgical intervention and showed a trend towards reduced recurrence rate (minocycline 1.9% vs saline 8.1%, OR = 0.23, 95% CI 0.05-1.09) [156]. The second randomised patients with PSP at first occurrence to minocycline (via chest drain, without surgical intervention) or drainage alone, and found evidence of a reduction in recurrence (minocycline 29.2% vs drainage only 49.1%, OR = 0.43, 95% CI 0.24-0.75) [110]. Neither trial stated if the patient was blinded to treatment allocation. However, if seems unlikely as the minocycline was administered on a separate occasion after the lung had re-

expanded, without any description of a “sham” saline administration. Otherwise these trials were robustly conducted, reporting their outcomes at 1 year, which is appropriate. Future trials in pleurodesis for pneumothorax could be modelled upon this design with the addition of true blinding of allocation (for example, with sham administration in the control group).

6.11. Conclusions

This comprehensive systematic review of the literature demonstrates that numerous agents have been used for chemical pleurodesis for recurrence prevention in spontaneous pneumothorax.

The most effective method of chemical pleurodesis is the addition of talc or minocycline alongside surgical treatment (i.e. bullectomy or apical resection), followed by thoracoscopic talc poudrage but this is not suitable for all patients. In these cases, the instillation of talc, tetracycline or minocycline via the chest drain will provide some reduction in the recurrence rate, but data on the true degree of improvement is not clear given the retrospective nature of most of the studies. Evidence for relative success rates between agents is significantly limited by the small number of randomised and prospective comparative trials.

6.12. Future directions

Direct head-to-head well controlled RCTs of different pleurodesis agents are required to assess choice of agent in SP recurrence prevention. Moreover, the optimal management of when and in whom to use these agents has not been defined. Surgical “fitness of surgery” is

often poorly defined and may vary by local practise as well as individual surgeon's preference.

The optimal trial

As discussed above, the ideal trial of chemical pleurodesis agents in PSP would be an RCT, with blinding of allocation, clear outcome of evidence of clinically significant pneumothorax – i.e. chest radiograph showing new pneumothorax after patients presented with symptoms consistent with recurrence), with follow-up for one year. This follow-up period will capture the majority of the recurrences, whilst being pragmatic in terms of the overall length of study (although 5 years would capture a few more recurrence events, the benefit would not be outweighed by the additional workload in conducting and following up a clinical trial for that length of time).

Which agents/intervention to test?

The present evidence base suggests that talc and minocycline are both effective adjuncts to surgery or administered at thoracoscopy. Therefore, unless a novel agent with potentially improved efficacy becomes available and requires testing, these should be the agents of choice.

The key question for the next clinical trial is whether risk stratification can identify those patients at risk of treatment failure or early recurrence who should undergo pleurodesis earlier than currently recommended (i.e. at first occurrence or as inpatient with prolonged leak).

Predictive modelling described elsewhere in this thesis may alter the treatment paradigm for these patients:

- Use of clinical parameters, including airflow (Chapter 5), early in treatment to predict patients at high risk of treatment failure (e.g. PAL), thereby allowing triage to early treatment, which could include chemical pleurodesis agents
- Use of imaging to predict future recurrence (Chapter 7) could allow a stratified approach: offering preventative treatment (chemical pleurodesis or surgery) to those at high risk of recurrence after their first episode, rather than having to wait for recurrence.

6.13. Addendum

This chapter is adapted from published work (with permission from co-authors):

Hallifax RJ, Yousuf A, Jones HE, Corcoran JP, Psallidas I, Rahman NM, "Effectiveness of chemical pleurodesis in spontaneous pneumothorax recurrence prevention: a systematic review". *Thorax*. 2017 Dec;72(12):1121-1131

7. Predicting Outcomes - CT scoring

7.1. Background

PSP is traditionally defined as a spontaneous event in a patient with no apparent lung disease. However, structural abnormalities (ELCs and lower density areas of lung parenchyma) have been identified. Cystic air spaces contiguous with the pleura are arbitrarily called blebs if ≤1cm and bullae if >1cm[16]. At present, the data on true recurrence rates for patients who have been treated for a single episode of PSP is poor. Low radiation dose CT has been proposed as a method of risk stratification for recurrence through identification of these lung abnormalities, either ipsilaterally or in the contralateral lung.

7.1.1. First use of CT Computed in PSP

An early study of CT study in patients with PSP in 1990 (called Idiopathic SP at the time) described findings in 20 patients with PSP and 20 age-, sex- and smoking-history matched controls[5]. Emphysematous lesions were more commonly found in the PSP group. Three of the 20 had normal CT scans, but subpleural emphysema was noted in 16 patients, centrilobular emphysema in 11, thickened bronchial walls in 10 and bullae in 5 patients[5]. Lesions were most common in the upper third of the lung. Interestingly, the CT scans were abnormal in six of the 20 patients in the control group (two with bullae, two with subpleural emphysema and two with centrilobular emphysema). It should be noted that 17 of 20 patients in both groups were smokers with a mean consumption of 6 pack-years. This suggests that these ELCs may be present in general population who may never suffer with a pneumothorax episode, particularly those who smoke.

A concurrent study of 26 consecutive patients with PSP assessed the number of blebs found on CT scan during treatment for their pneumothorax and whether they had a “complicated pneumothorax”[37]. The “complicated” group were defined as those patients who either had a prior pneumothorax, recurrent pneumothorax on follow-up, or need for chest tube drainage. The 15 “uncomplicated” patients, i.e. patients with first episode treated conservatively, had a fewer blebs, both ipsilateral and contralateral[37]. The authors calculated a “bleb score” by assigning a numeric value to different ranges of bleb sizes: blebs ranging in size from 0 to 5 mm were each assigned a value of 1, a value of 2 was given to each bleb between 6 and 10 mm, 3 for blebs between 11 and 21 mm, 4 for blebs between 21 and 30 mm, and 5 for any bleb greater than 31 mm. The bleb score for each lung was determined by multiplying the number of blebs in each size category by the numeric value assigned to that category[37]. This study suggested that a higher “bleb score” (see below) based on size and number of blebs could identify patients at risk of recurrence or need for chest tube treatment, but the numbers in this study were small and there was no have a comparator group.

Another small prospective study of by Mitlehner *et al* examined CT scans of 35 patients with PSP[7]. 88.6% (31/35) had lesions identified on CT scan. Of the 32 patients followed up (for a mean of 32 months), 8 had recurrence but there was no difference between the number, size and distribution of bleb/bullae between patients with and without recurrence[7].

7.1.2. Difference between first or recurrent pneumothoraces

Smit *et al* assessed whether incidence of blebs or bullae was different between patients presenting with first or recurrent PSP[6]. They hypothesized that if bullae were a pre-disposing factor for PSP, then one would expect a higher incidence in those with recurrent

PSP than those with first episode. 101 cases of PSP underwent CT scan. Bullae (>2cm) were identified in 59% of patients. However, the proportion of patients with bullae was not significantly different between those presenting with first PSP (56%) and those with recurrent PSP (64%). A limitation of this early paper could be the resolution of the CT scanners, which at the time may not have been sufficient to identify lesions smaller than 2cm.

7.1.3. Prevalence of blebs in control groups

A larger study of 250 healthy individuals undergoing thoracoscopic investigation (being treated with thoracoscopic sympathectomy) with no prior history of pneumothorax or pleural disease demonstrated a 6% incidence of apical blebs on visual inspection of the lung[38]. These were more prevalent in slim individuals (BMI <22kg/m^2) who smoked[38].

In order to determine whether ELCs were related to smoking *per se*, Bense *et al* conducted a small case-control study of 27 non-smoking patients with PSP and ten, healthy non-smoking volunteers[39]. ELCs were found 81% patients with PSP, more frequently in the upper zones, but not in any of the healthy controls[39]. Therefore, ELCs were present in patients with PSP even in the absence of smoking as a risk factor, but the number of patients in this study was small.

7.1.4. Recurrence in patients managed without surgery

A Spanish study, prospectively collected data on 55 patients treated for PSP and performed CT scan after resolution[8]. Importantly, the authors excluded patients who had persistent air leak for more than 5 days (as they were sent for surgery). However, in these 55 patients successfully managed with chest tube drainage, 26 (47.3%) had bullae on CT and 29 (52.7%)

did not, and there was no difference in recurrence between the two groups: 6 of 26 with bullae recurred, compared to 7 of 29 without bullae. In this group, not requiring surgery, presence of bullae was not predictive of recurrence.

7.1.5. Contralateral recurrence post-surgery

Three surgical studies investigated whether the presence of ELC or blebs on CT scan could predict recurrence in the contralateral lung (i.e. the lung not being operated upon). Firstly, Sihoe *et al* conducted a small prospective cohort study of 28 patients who were undergoing surgery for definitive treatment for PSP[9]. The indications for surgery were recurrent PSP (17), tension pneumothorax at first presentation (6), persistent air leak (6), or patient occupation (e.g. flight crew) (n=2). Pre-operative CT scan was assessed for presence or not of blebs or bullae in the contralateral lung. Contralateral blebs were seen in 15 patients (53.6%). Four of the 15 (26.7%) had recurrence within 22 months, compared to none in the 13 patients who did not have contralateral blebs[9]. The authors originally calculated that this difference was statistically significant (p 0.04). However, this was a mistake as pointed out by Noppen[40]. As a response, Sihoe *et al*, updated their dataset by contacting all their patient again (after one year more follow-up had occurred). They reported that two additional patients with contralateral blebs had suffered with pneumothorax recurrence, but none in the group without contralateral blebs, thereby making the difference significant again (p 0.02).

Huang *et al* conducted a large retrospective review of 231 patients treated for PSP, with a long follow-up period of an average of 92 months[10]. All patients were managed initially with chest tubes and had HRCT when the lung had re-expanded. 77% of the patients went on to have surgery (178/231); indications being persistent air leak, tension pneumothorax at

first presentation, haemopneumothorax, occupations of patient (such as diver or pilot), and ipsilateral or contralateral recurrences. 148 patients had contralateral blebs. 33 patients (14.3% of total, 22.3% of those with blebs) had contralateral recurrence [10]. All of those with recurrence had contralateral blebs, compared to 48% in the group who did not have recurrence ($p<0.001$, <0.007 after Bonferroni correction) [10]. On multiple logistic regression for risk factors for recurrence (in 128 patients with contralateral blebs), low BMI ($<18.5 kg/m^2$) was found to be an independent predictor of recurrence. The high prevalence of blebs (48%) in patients who did not go on to have recurrence is striking. Therefore, the argument for early surgical intervention on the contralateral lung on the basis of CT bleb findings alone has not been made.

In a similar more recent study, Noh *et al* followed up 262 patients who had undergone CT scan after being referred for surgery (due to persistent air leak for >3 days)[11]. Contralateral bullae were found in 32 patients (12.2%). After a long follow-up period, 12 of these 32 (37.5%) had a contralateral pneumothorax recurrence (median interval to recurrence 52 months). Contralateral recurrence was seen in 6.1% (12/230) of patients without contralateral bullae[11]. The authors suggest that "single-stage bilateral surgery might be beneficial for young patients with recurrent pneumothorax and patients with contralateral bullae". However, their own data suggest that they would be operating unnecessarily upon the 62.5% of patients with contralateral bullae who will not recur.

Given the presence of blebs and bullae on CT scans in healthy volunteers and patients who do not have a contralateral pneumothorax recurrence, the simple metric of the presence or absence of blebs or bullae is likely to be too crude a measure of abnormalities in the lung.

A number of studies have investigated whether a "scoring" system of number, size and distribution of cystic air spaces might provide a prognostic tool to predict risk of recurrence.

7.2. Bleb Scoring Systems

The first "bleb score" was proposed by Warner *et al* in 1991, taking into account the number and size of blebs in each lung. Ouanes-Besbes *et al*, in 2007, based their "dystrophic lesion" score on the same criteria based upon size (1 point for bleb (≤1cm), 2 for 1-3cm, 3 for >3cm), number (1 point for 0-2 lesions, 2 for between 3 and 9 lesions, and 3 points for 10 or more) and distribution (1 point for unilateral, 2 for bilateral) [121]. For example, a patient with 4 blebs (2 points), both <1cm (1 point), only on one side (1 point) would score 4 points.

The authors (in neither paper) explain why the thresholds for number of lesions were set at 2 and 10, or why 1cm and 3cm for cystic air space size was used. Another limitation is that the minimum score is 3, rather than zero. This would therefore classify both the patient with no blebs or bullae, and the patient with two unilateral <1cm blebs as a score of 3. In reality these patients may behave differently. Ouanes-Besbes *et al* prospectively enrolled 80 patients being treated for their first PSP[121]. An HRCT was performed within 2 weeks of completion of their treatment for pneumothorax. 72.5% (58/80) had dystrophic lesions identified on their CT scan. Patients were followed up for a mean of 34 months. Fifteen of the 80 patients (19%) had a recurrence of their pneumothorax. However, the proportion of patients with lesions on CT scan were actually lower in the group with recurrence (60%, 9/15) than those who did not recur (75%, 49/80). Likewise the corresponding dystrophic scores were 3.47 and 4.88, respectively, i.e. a lower score in those who recurred[121]. This is contrary to the expected outcome and not statistically different, but questions the validity and utility of this scoring system.

In spite of the negative results of Ouanes-Besbes *et al*, a retrospective study was conducted by Casali *et al*, using a similar dystrophic severity scoring system but with larger number of patients (n=176) [199]. Their simplified score was based upon size, number and distribution of lesions (See Table 7.1).

Table 7.1: Simplified dystrophic lesion score as used by Casali [199].

Score	1 point	2 points
Number of Blebs	Single	Multiple
Size	≤1cm	>1cm
Distribution	Unilateral	Bilateral

The minimum score of 3 was described as “low grade”, 4-5 “intermediate grade” and the maximum of 6 was “high grade” [199]. Importantly, patients with no ELC on CT scan were classified separately and were not classified as “low grade”. All the patients had been treated for their first episode of PSP, excluding those who underwent surgery (e.g. for on-going air leak for more than 4 days, haemopneumothorax, or for occupational reasons).

Using the simple definition of presence or absence of ELC, the authors report that the risk of recurrence was significantly related to the presence of ELC on HRCT: 79 (44.8%) of the 176 patients had ipsilateral recurrence. Of these, 75 patients had ELC, and only 4 did not. Overall, 110 patients had ELC: 75 had recurrence, 35 did not[199]. Therefore the positive predictive value (PPV) for ipsilateral recurrence was 68.1%. Conversely, the risk of ipsilateral recurrence for patients without ELC on HRCT was 6.1% (4/65), with a negative predictive value (NPV) of 93.9% for recurrence[199]. Univariate analysis of CT scan findings showed that higher dystrophic score was correlated with risk of both ipsilateral and contralateral recurrence. A Kaplan-Meier analysis found that recurrence-free survival significantly decreased from patients without ELC (93%), to those with low-grade dystrophic score (i.e. a single unilateral

bleb) (54%) and to intermediate-grade (31%) score; but no significant difference between intermediate- and high-grade scores[199].

The major limitation of this study is its retrospective nature, which only included patients who had undertaken HRCT scans. In the UK, it is not routine practise to perform CT scans on all patients. It is not clear to what proportion of the overall population being treated for pneumothorax this applies, and what was the indication for the scan. Nonetheless, this study highlights the fact that the presence of ELC is common in PSP, but also that not all patients with ELC will recur, and their results show a very good NPV for ipsilateral recurrence. Ouanes-Besbes *et al* also assessed contralateral recurrence in the same study[199]. They found that the risk of contralateral recurrence (19%), in line with that of the previous studies (24% and 28%)[9, 10].

CT scoring systems to date have all been retrospective. There is no agreed scoring system or consensus as to which components of the "score" are actually predictive of important clinical outcomes. Therefore, the utility of CT in predicting recurrence of pneumothorax has not been established and requires prospective assessment and validation.

7.3. Lung density assessment

The above studies describe description of the cystic airspaces (blebs and bullae) and their relation (or not) to recurrence. An alternative radiographic predictor may incorporate the objective quantification of low density areas within the lung, which could be a marker for early gas trapping or inflammation, or correspond to ELC and thereby predispose to recurrent episodes. An early study by Lesur *et al* looked at mean lung density in 20 patients

with PSP and 20 matched controls (as well as description of any emphysematous lesions, see above)[5]. Lung density values (in Hounsfield Units, HU) were calculated using a computer programme according to its radio-density, in intervals of 25HU. The mean lung density in both groups were in the normal range, but the mean density was significantly lower (shifted toward air density) in the PSP group: -743HU (SD 57.5HU) vs -713HU (SD 59.5HU) in the control group ($p < 0.01$). The authors defined lung density lower than -900HU as being abnormal. The percentage of lung volume below -900HU was slightly greater in the PSP than in the control group: 8.75% (SD 8.27%) vs 6.75% (SD 5.75%), but not statistically significantly different.

Since then, the threshold for abnormal lung density has been established at -950HU and used routinely in the quantification of emphysema in patients with COPD[122, 123]. This value was chosen to balance the sensitivity and specificity of CT to identify emphysema[124].

More recently, Bintcliffe *et al* retrospectively assessed lung density on CT in 20 patients with PSP, as compared with 20 patients with SSP and a matched control group of 40 patients who had undergone a CT scan for other "clinical indications"[200]. Automated software was used to assess lung parenchyma above the level of the carina and a percentage of low attenuation area (%LAA) was calculated. The median %LAA in PSP patients was low (0.25%), but significantly different between those PSP patients who smoked (0.7%) and those who did not smoke (0.1%,p 0.034), and the control group (0.0%, p 0.019)[200].

Each patient was assigned a modified Goddard score (based on an arbitrary categorisation of proportion of lung affected by Goddard et al in 1982[201]): 0, no emphysema/LAAs; 1, 1-25% affected; 3, 50-75% affected; and 4, >75% affected. The patients with SSP had

significant emphysema (median %LAA was 16.2%) and a range of modified Goddard scores. However, this classification was less useful in PSP. Seven PSP patients had zero %LAA, 12 had Goddard score of 1, and only one patients had >25% LAA. Therefore, the authors subdivided the Goddard score 1 based upon the presence and number of blebs. In this study, the classification was based upon thresholds of 20 or 40 blebs: 1a: <20; 1b 20-40 blebs and 1c with >40 blebs. These thresholds are significantly higher than those used in previous studies[121, 199] and the rationale for choosing these thresholds is not clear.

This study was limited by its retrospective design, lack of follow-up data to determine whether %LAA is predictive of recurrence and the fact that only patients who happen to have CT scans as part of their usual clinical care were included. This is likely to introduce significant selection bias (as acknowledged by the authors) to patients with a complicated treatment course, a persistent air leak, or those that required surgery. These patients may well represent a more severe cohort of PSP patients. As such, is yet to be determined if %LAA is correlated with risk of recurrence.

7.4. Recurrence rates

Previous data on recurrence risk for spontaneous pneumothorax are poorly defined for specific age groups, by sex and pneumothorax type. Numerous small and mostly retrospective case series report recurrence risk (i.e. number of recurrences divided by the total population with SP) of between 21% and 54% at 1-2 years[26, 76, 100-104]. Data from control or non-interventional arms of RCTs show a range of risk of recurrence of 21-49%[82-85, 109, 110]. More recent epidemiological data from France, which covered 4 years' hospital episode, found that 28% of patients have recurrence within 4 years[72]. Data

presented in this thesis from the HES database shows 19% recurrence rates at 1 year, and 25% at 5 years (See Chapter 2).

These data present overall risk for the PSP population and is not personalised to the individual patient. CT evidence of ELC and its severity could enable risk stratification in this patient group.

7.5. Aims & Hypothesis

This study aims to assess the CT characteristics of patients with PSP with good quality prospectively-collected data to determine whether a CT scoring system based upon ELC and lung density can predict 12 month pneumothorax recurrence rates.

7.6. Methods

7.6.1. Patients

Data was used from patients who were enrolled into the RAMPP trial comparing the use of the Pleural Vent (Rocket Medical, UK) to standard care (as per BTS guidelines) in patients with PSP requiring treatment.

7.6.2. CT parameters

Patients underwent a CT scan at least 2 weeks after their completion of treatment for their pneumothorax (to ensure resolution). All recruiting sites performed low dose CT scan of the chest with 4 HRCT slices at the apices, as per the study protocol. The low dose scan was a full helical scan with the following parameters: rotation time 0.5s, detector coverage 40mm,

helical thickness 0.625mm, speed 39.37, 120kV voltage, 60mA current, and 0.984 beam pitch. The HRCT was a full helical scan with the following parameters: rotation time 0.8s, detector coverage 1.25mm, axial thickness 1.25mm, 120kV voltage, 200mA current, with one image per rotation.

CT scans from patients in other centres around the UK were transferred to Oxford via the Image Exchange Portal (IEP, Sectra, Sweden), where they were anonymised with patient trial number and stored on a research server.

7.6.3. CT scoring system

The CT scoring system was developed in light of the above previous studies, in collaboration with two experienced thoracic radiologists in Oxford (Table 7.2). The radiologists were blinded to patient demographics, treatment and recurrence episodes. In cases where there was disagreement, final decisions were made on a consensus basis.

Table 7.2: CT scoring system: visual assessment conducted by experienced radiologists

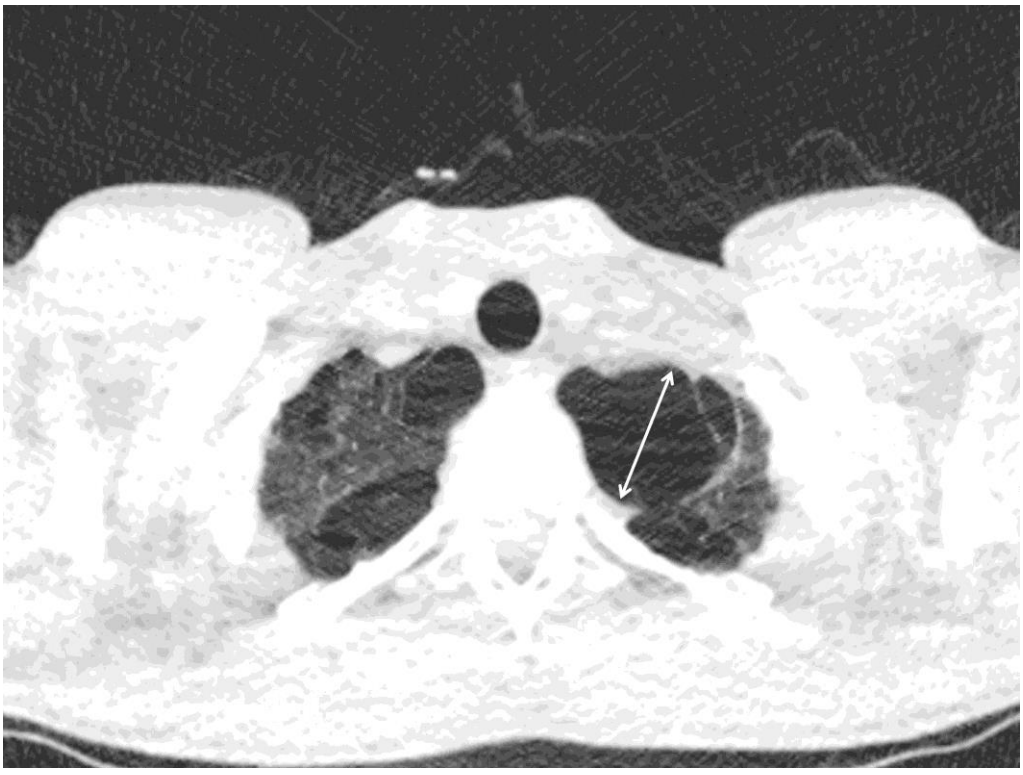
	Answer	**Detail**
Emphysema?	Yes/ No	
If yes which subtype:	Paraseptal	If yes: mild/moderate/severe
	Centrilobular	If yes: mild/moderate/severe
	Panacinar	If yes: mild/moderate/severe
	Zonal predominance	Upper/middle/lower
Bronchial wall thickening	None/Mild or Moderate/Severe	
Cystic Airspaces?	Yes/ No	<10 cysts or > 10 cysts (i.e. paraseptal emphysema)
	If <10 cysts	How many in total?
	Size of largest cyst	Largest diameter in axial or coronal section (cm)
Pleural thickening?	Yes/ No	
Other pleural abnormality	Yes/ No	If yes, specify
Thorax size	Distance from peak of apex to diaphragmatic dome (cm)	
Other finding	Yes/ No	If yes, specify

The description (Table 7.2) is modified from the Fleichner definitions[16]. Grading of severity of emphysema will be determined by the extent of the lung involved: mild (<25%), moderate (25-50%) and severe (>50% of lung). Lung parenchyma with more than 10 cystic airspaces was defined as paraseptal emphysema (rather than try to count cysts within an area of emphysema – see Figure 7.1). The size of the largest cystic space will provide information on whether one (or more) would be classically referred to as bullae (see Figure 7.2).

Figure 7.1: CT image showing paraseptal emphysema. Arrows show 3 contiguous cystic areas. If >10 cystic airspaces present, then mark as “paraseptal emphysema”, and the absolute number of blebs does not need to be recorded.



Figure 7.2: CT image showing cystic airpaces. In addition to noting the presence of cystic airspaces, the largest diameter of largest cyst was be recorded, as shown (in either axial or coronal images)



7.6.4. Quantitative CT scans – emphysema

Quantitative CT scan analysis can be used to percentage emphysema (defined as less than -950HU) on a whole lung and lobar basis, presented as percentage low attenuation area (%LAA). This was conducted using Pulmonary Toolkit (PTK), which is an open-source image processing kit that runs in the Matlab environment (MathWorks, Natick, Mass). The same methodology is described in the ^{129}Xe MRI chapter, in which the quantitative CT %LAA was compared to the hyperpolarised Xenon MRI findings.

Unfortunately, despite the CT protocol (above) being approved by Research & Development departments at each RAMPP recruitment site, the quality of the scans was variable. The protocol made allowance for the fact that some patients may have a CT thorax as part of their clinical care. In these instances, patients were not asked to have another CT scan for research purposes (to minimise their radiation dose). Therefore, a number of patients had CT scans when their initial treatment was failing (i.e. PAL) and they were referred as an inpatient for surgery. In these cases, the lung may not have been fully re-inflated (usually with a chest drain in place), which may affect the ability of the radiologists to accurately assess the lung for the components of the CT score (Table 7.2). In addition, in some centres, only a High Resolution CT scan (HRCT) was performed (not the low dose volumetric scan), or only the reformatted 2.5mm sections were not uploaded to the Picture Archiving and Communication System (PACS) at the site (rather than the raw 0.625mm files).

The quantitative CT analysis requires the thin slice (0.625mm) CT data to accurately calculate %LAA. Therefore, as %LAA could not be calculated in all cases, this was not incorporated into the full CT scoring analysis. Instead, a subgroup of those patients with the correct CT sequence was analysed with respect to the visual assessment or emphysema by the two

radiologists, for example, would mild, moderate or severe (centrilobular or paraseptal) emphysema correlate with %LAA.

7.6.5. Patient data

Patients who had completed a CT scan and completed either 6 or 12 months follow-up were included. Blinded interim data for these patients was downloaded from the online database on 27th September 2017 for use in this thesis.

7.6.6. Data analysis

The results were expressed as means and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for skewed (non-normally distributed data) and frequency (%) for categorical variables. Means of groups were compared with two-sample t-tests. Proportions between groups were compared using Chi-squared test (two-tailed), unless the sample size is one or more group is small (less than five), in which case Fisher's exact test will be used. All statistical analyses were conducted using Excel as part of Microsoft Office 2010 (Microsoft Corp, USA) and Stata v14.1 (Stata Corp, USA). Statistical significance was assumed at p value <0.05.

7.7. Results

7.7.1. Baseline data

61 patients were analysed: 78.7% (48/61) patients were male. The median age was 27.2 years (IQR, 11.7). 42.6% (26/61) were current smokers at time of enrolment, 23.0% (14/61) were ex-smokers and 34.4% (21/61) never smokers. The mean cumulative pack-years for current and ex- smokers was 7.4 (SD 5.9) and 6.0 (SD 5.6) years, respectively. 36.1% (22.61) were current or former smokers of marijuana.

Nineteen (31.1%) patients had suffered with a pneumothorax in the past: the majority of which were ipsilateral (78.9%, 15/19).

Five patients had recurrence within the first 7 days of follow-up. These were regarded as initial treatment failure rather than true recurrence. During the 12 months follow-up period, 16 (26.2%) patients had a recurrence of their pneumothorax. All recurrences were ipsilateral to the index presentation (i.e. no contralateral recurrences occurred). The median time to recurrence was 36 days (IQR 146).

7.7.2. CT scan quality

Six of the 61 patients had their CT scans conducted as part of their clinic care, and as such were not as per protocol. All six had chest drains in place; in one case the pneumothorax was large. Another four patients had HRCT scans only.

7.8. Agreement between radiologists

Two expert thoracic radiologists scored the scans independently. Generally agreement was good between the two scorers: Presence (or absence) of emphysema was agreed in 99

(81.1%) of 122 hemi-thoraces (kappa 0.54, p <0.001), Presence (or absence) of cysts was agreed in 96 (78.7%) of 122 (kappa 0.58, p <0.001). Discrepancies were subsequently all agreed on consensus. The majority of the differences lay in the interpretation of minor pleural abnormalities at the apices or very mild emphysema. For clinical measurements (cyst number and size), the mean value between the two radiologists was used.

7.9. CT findings

In all 61 patients, both hemithoraces were assessed (i.e. 122 hemithoraces in total). On both ipsilateral and contralateral sides, nineteen of the 61 patients (31.1%) had emphysema present on CT scan – all of which were deemed mild and virtually all upper lobe predominant (see Table 7.3). Of the 19, Six (31.6%) patients had both paraseptal and centrilobular emphysema, seven (36.8%) had paraseptal only, and six (31.6%) had centrilobular emphysema only.

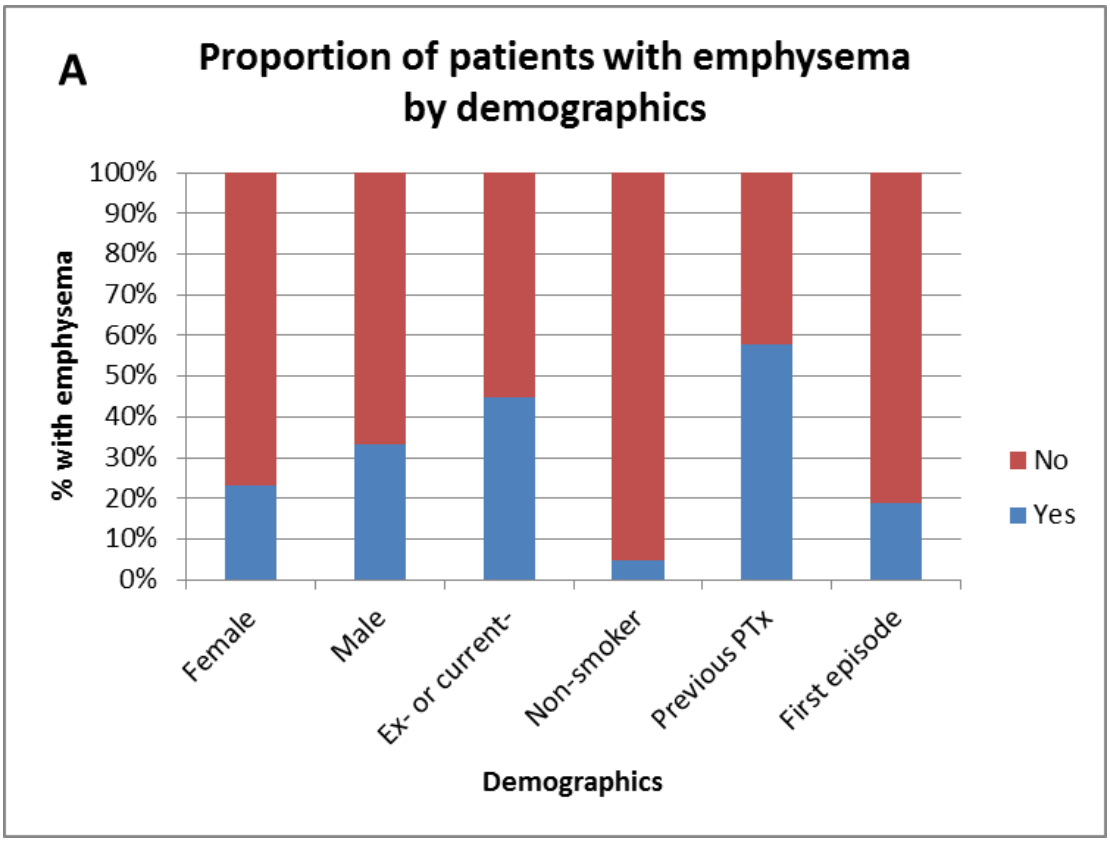
7.9.1. Comparing hemithoraces

Many patients had cystic airspaces present: 41.0% in ipsilateral, and 32.8% contralateral lung. Of those, the majority of patients had fewer than 10 cysts (lung with >10 cysts was defined as paraseptal emphysema), which was consistent across the two lungs. The maximum size (diameter) of the largest cystic airspace was usually <1cm, although there was a larger proportion of cysts of 1-2cm in size in the ipsilateral (14.8%) vs contralateral lung (11.5%); with similar median maximum cyst size: 1.2cm (IQR 1.1) and 1.1cm (IQR 1.0), respectively.

7.9.2. Comparing CT findings by Demographics

Mild emphysema was more common in males, ex- or current smokers or patients who had suffered with a previous pneumothorax (prior to their index event) (See Figure 7.3): this difference was significant in smoking status ($p < 0.001$), and previous pneumothorax (p 0.01), but not sex (p 0.48). These patients were also more likely to have cystic airspaces, but the difference was less marked (Table 7.3). Ex- or current smokers had significantly more cysts and the maximum size of cysts was greater compared to non-smokers (p 0.003). All 13 patients with >10cysts (i.e. paraseptal emphysema) were ex- or current smokers.

Figure 7.3: Proportion of patients with emphysema (7.3A) and cystic airspaces (7.3B) findings on CT by sex, smoking status and previous pneumothorax or not



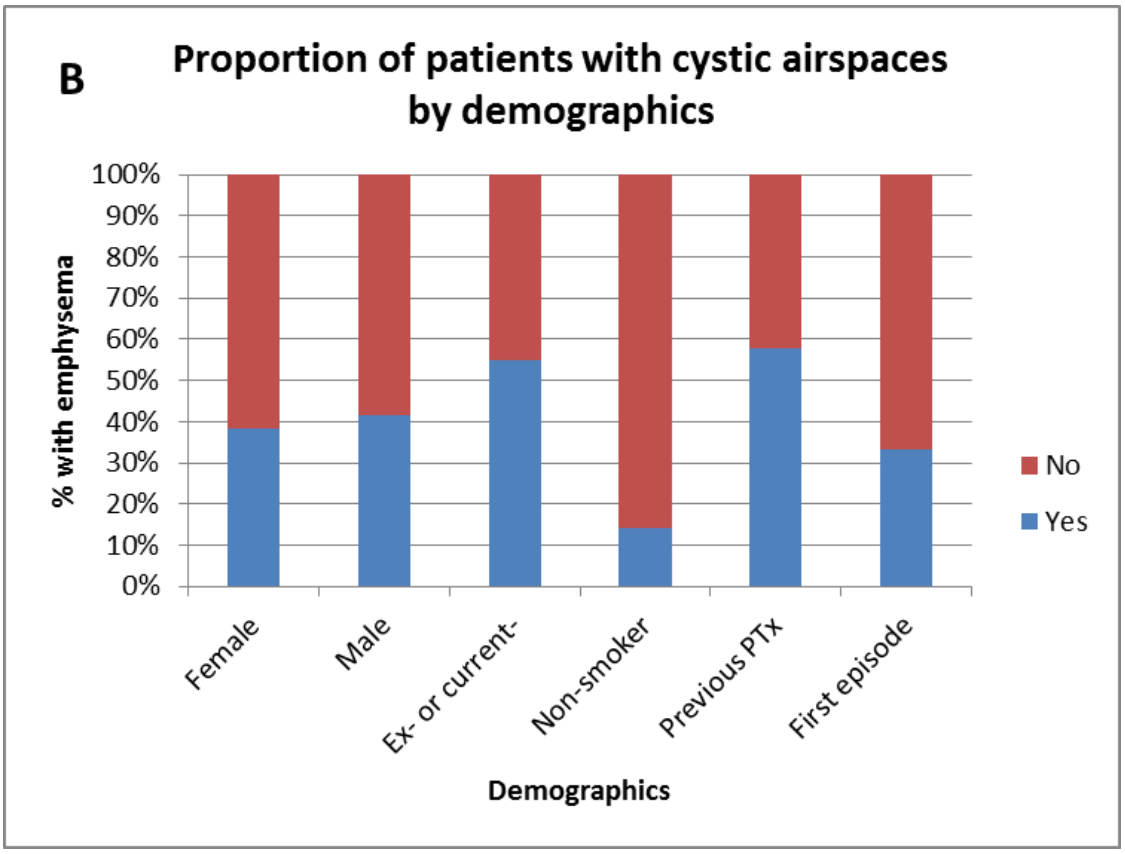


Table 7.3: CT findings by patient sex, smoking status and previous pneumothorax. p value using Chi-squared or Fisher's exact test

	CT findings by sex: n (%)		CT findings by smoking status: n (%)		CT findings by pneumothorax history: n (%)	
CT Findings	**Female (n=13)**	**Male (n=48)**	**Ex- or current (n=40)**	**Non-smoker (n=21)**	**Previous PTx (n=19)**	**First episode (n=42)**
Emphysema						
Yes	3 (23.1%)	16 (33.3%)	18 (45%)	1 (4.8%)	11 (57.9%)	8 (19%)
No	10 (76.9%)	32 (66.7%)	22 (55%)	20 (95.2%)	8 (42.1%)	34 (81%)
p value	0.48		0.001		0.01	
Cystic airspaces						
Yes	5 (38.5%)	20 (41.7%)	22 (55%)	3 (14.3%)	11 (57.9%)	14 (33.3%)
No	8 (61.5%)	28 (58.3%)	18 (45%)	18 (85.7%)	8 (42.1%)	28 (66.7%)
p value	0.84		0.003		0.09	
Number of cysts						
None	18 (69.2%)	59 (61.5%)	18 (45%)	18 (85.7%)	8 (42.1%)	28 (66.7%)
1-2	2 (7.7%)	4 (4.2%)	4 (10%)	1 (4.8%)	2 (10.5%)	3 (7.1%)
3-10	0 (0%)	14 (14.6%)	5 (12.5%)	2 (9.5%)	2 (10.5%)	5 (11.9%)
>10 cysts	6 (23.1%)	19 (19.8%)	13 (32.5%)	0 (0%)	7 (36.8%)	6 (14.3%)
Max size of cysts (cm)						
None	18 (69.2%)	59 (61.5%)	18 (45%)	18 (85.7%)	8 (42.1%)	28 (66.7%)
<1	5 (19.2%)	14 (14.6%)	7 (17.5%)	3 (14.3%)	4 (21.1%)	6 (14.3%)
1-2	3 (11.5%)	14 (14.6%)	9 (22.5%)	0 (0%)	5 (26.3%)	4 (9.5%)
>2	0 (0%)	9 (9.4%)	6 (15%)	0 (0%)	2 (10.5%)	4 (9.5%)
Median maximum size (cm)(IQR)	0.95 (0.4)	1.3 (1.2)	1.3 (1.25)	0.95 (0.1)	1.1 (0.85)	1.2 (1.25)

7.10. Patient factors and recurrence

Female patients were more likely to recur: six (37.5%) of the sixteen patients who recurred were female, compared to only 15.6% in the non-recurrence group (See Table 7.4), with an odds ratio (OR) of 3.3 (95%CI 0.9-12.5). Similarly current or ex-smokers were more likely to recur than non-smokers (68.8% vs 62.2%, OR 1.2 (0.4-4.2)); as were patient who had a previous history of pneumothorax (37.5% vs 28.9%, OR 1.5 (0.4-5.0)). However, none of these results were statistically significant (Table 7.4). There was no evidence of interaction between the variables.

Table 7.4: Patient demographics and recurrence. p values calculated using Chi-squared test

	Demographics and recurrence status: n (%)				
Demographics	**Recurrence (n=16)**	**No recurrence (n=45)**	**Overall (n=61)**	**Odds ratio (95%CI)**	**p value**
Sex					
Female	6 (37.5%)	7 (15.6%)	13 (21.3%)	3.3 (0.9-12.5)	0.07
Male	10 (62.5%)	38 (84.4%)	48 (78.7%)	Ref	
Smoker (Current or Ex)					
Yes	11 (68.8%)	29 (64.4%)	40 (65.6%)	1.2 (0.4-4.2)	0.76
No	5 (31.3%)	16 (35.6%)	21 (34.4%)	Ref	
Previous Pneumothorax					
Yes	6 (37.5%)	13 (28.9%)	19 (31.1%)	1.5 (0.4-5)	0.53
No	10 (62.5%)	32 (71.1%)	42 (68.9%)	Ref	

7.11. CT findings and recurrence

Emphysema and cystic airspaces were more common in patients who had a recurrence of their pneumothorax. Emphysema was present in 6/16 (37.5%) and cystic airspaces 8/16 (50.0%), compared to 13/45 (28.9%) and 17/45 (37.8%), respectively, in those without recurrence (See Table 7.5 and Figure 7.4). The corresponding odds ratios (OR) were 1.5 (95%CI 0.4-4.9) for the presence of emphysema and 1.6 (0.5-5.2) for cystic airspaces, which were not statistically significant.

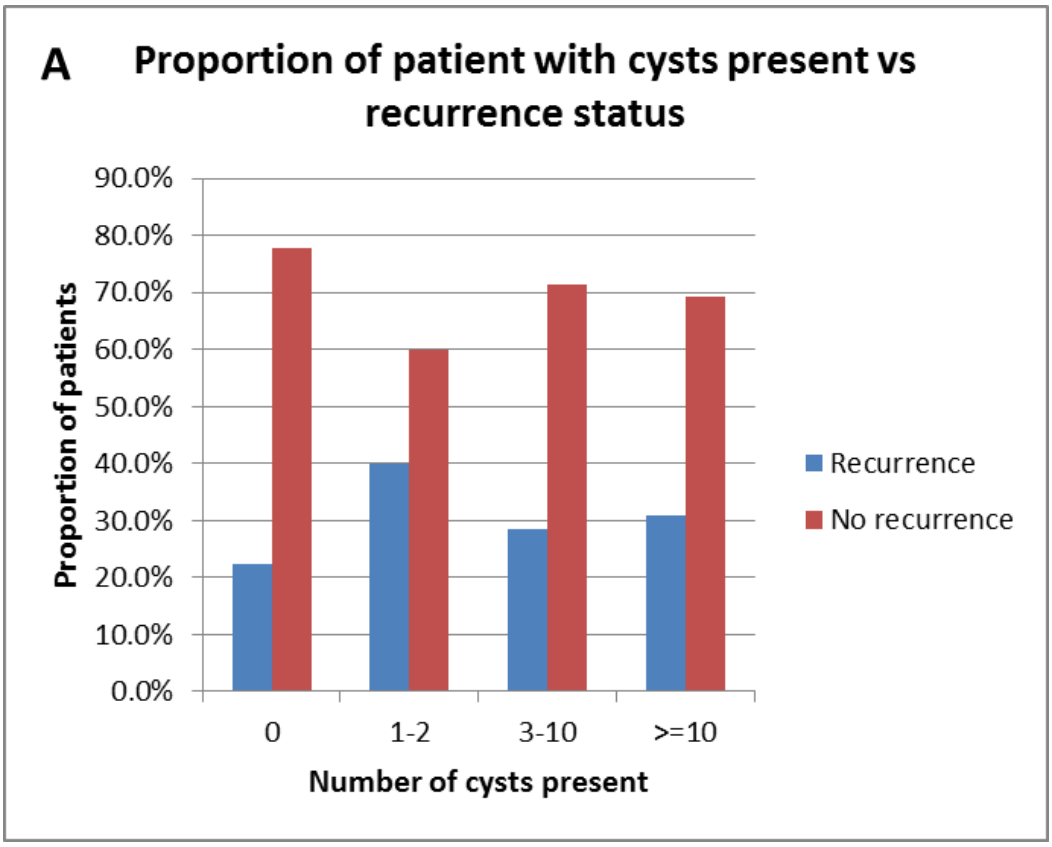
The distribution of number of cystic airspaces on ipsilateral side by recurrence status is shown in Table 7.5 and Figure 7.4. A large proportion of patients had >10 cysts (i.e. paraseptal emphysema) present on ipsilateral lung (21.3% overall), which was consistent in patients both with (25.0%) and without recurrence (20.0%). Interestingly, the group of patients with 1 or 2 cysts had the highest odds of recurrence: OR 2.3 (0.3-16.5).

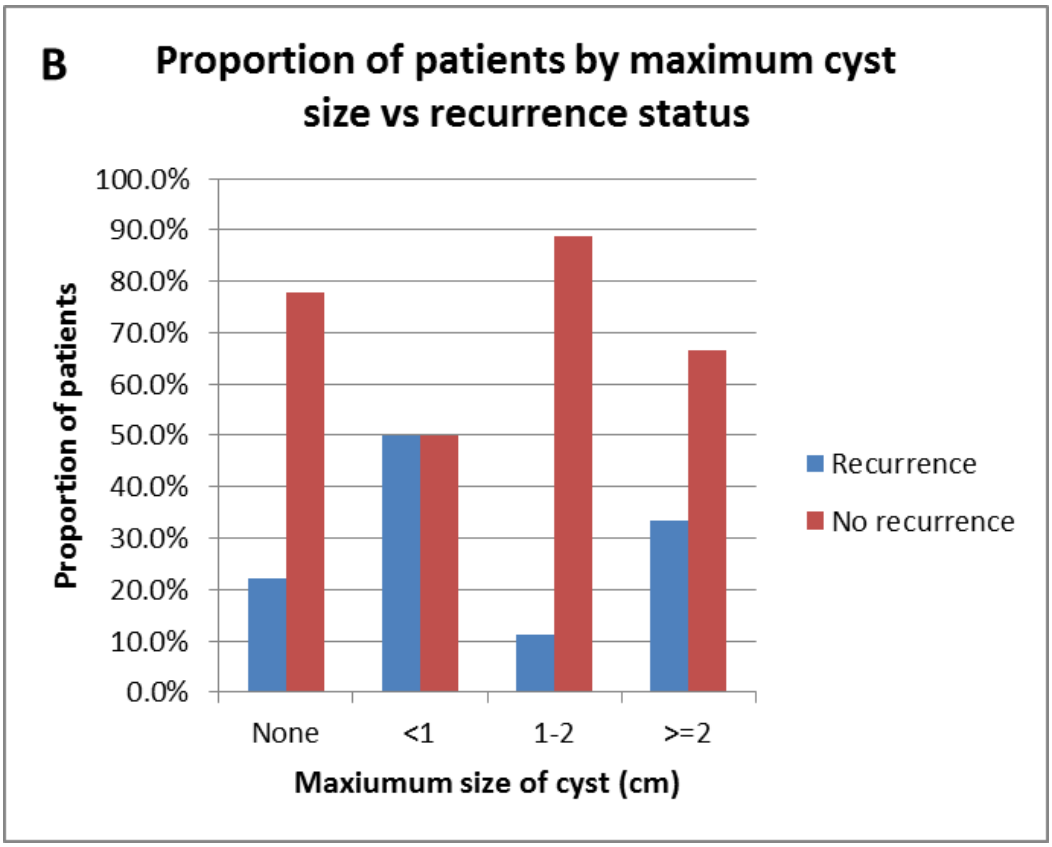
Most patients with cystic airspaces had cysts of maximum size of less than 1cm. The median size of the largest cyst was smaller in those with recurrence, 1.0cm (IQR 0.5cm), compared to those without recurrence, 1.4cm (IQR 1.0cm); although the difference was not statistically significant. Five patients had very large cysts (≥4cm), but only one of those patients had a recurrence).

Table 7.5: CT findings and recurrence. Odds ratios and p values calculated using logistic regression

	CT findings by recurrence status: n (%)				
CT Findings	**Recurrence (n=16)**	**No recurrence (n=45)**	**Overall (n=61)**	**Odds ratio (95%CI)**	**p value**
Emphysema present					
Yes	6 (37.5%)	13 (28.9%)	19 (31.1%)	1.5 (0.4-4.9)	0.52
No	10 (62.5%)	32 (71.1%)	42 (68.9%)	Ref	
Cystic airspaces present					
Yes	8 (50%)	17 (37.8%)	25 (41%)	1.6 (0.5-5.2)	0.40
No	8 (50%)	28 (62.2%)	36 (59%)	Ref	
Number of cysts					
None	8 (50%)	28 (62.2%)	36 (59%)	Ref	
1-2	2 (12.5%)	3 (6.7%)	5 (8.2%)	2.3 (0.3-16.5)	0.40
3-10	2 (12.5%)	5 (11.1%)	7 (11.5%)	1.4 (0.2-8.6)	0.72
>10 cysts	4 (25%)	9 (20%)	13 (21.3%)	1.6 (0.4-6.4)	0.54
Max size of cysts (cm)					
None	8 (50%)	28 (62.2%)	36 (59%)	Ref	
<1	5 (31.3%)	5 (11.1%)	10 (16.4%)	2.6 (0.8-15.2)	0.09
1-2	1 (6.3%)	8 (17.8%)	9 (14.8%)	0.5 (0.0-4.0)	0.47
>2	2 (12.5%)	4 (8.9%)	6 (9.8%)	1.7 (0.3-11.4)	0.56

Figure 7.4: Proportion of patients with recurrence within 12 months by: 7.4A - number of cysts, 7.4B - maximum cyst size.





7.12. CT score and recurrence – developing a model

As described above, cystic airspaces were commonly seen in both those with and without recurrence. There is also marked variation within each group in terms of the number and size of cystic airspaces. As such, developing a single scoring system was challenging.

Firstly, comparison was made with the scoring system proposed by Casali *et al* (see Table 7.1)[199]. In these 61 patients, their dystrophic severity score failed to distinguish between those at high risk of recurrence (See Table 7.6). Of the 36 patients with no cystic lung disease (hence "none" on dystrophic score), 22.2% of patients recurred. No patients were classified as Low grade, and although 45.5% of the 11 patients with Intermediate grade had recurrence, only 3 of 11 patients with High grade recurred.

Table 7.6: Comparison of Recurrence and Dystrophic Score Grade proposed by Casali *et al*[199]

	Recurrence		
Dystrophic grade (score)	**Yes (n, %)**	**No (n, %)**	**Overall (n,%)**
High (6)	3 (21.4%)	11 (78.6%)	14 (100%)
Intermediate (4 or 5)	5 (45.5%)	6 (54.5%)	11 (100%)
Low (3)	0 (0%)	0 (0%)	0 (100%)
None (0)	8 (22.2%)	28 (77.8%)	36 (100%)
Overall	**16 (26.2%)**	**45 (73.8%)**	**61 (100%)**

In this patient population, the Casali Dystrophic grade appears simply to distinguish those with cysts or not, but this did not reach statistical significance (p 0.28).

Refinement of this score was hampered by the heterogeneity of number and size of cysts across the groups. As a result, five models were developed (see Table 7.7):

1. Initial model of sequentially higher scores by number and maximum size of cyst
2. Binary score based on presence of cysts or not (i.e. No cysts = 0, ≥One cyst = 1)
3. As model 2, plus point for contralateral cystic disease
4. As 3 but reduce score for large and numerous cysts
5. As 4, plus remove score for emphysema

Table 7.7: CT scoring model input parameters (and descriptors)

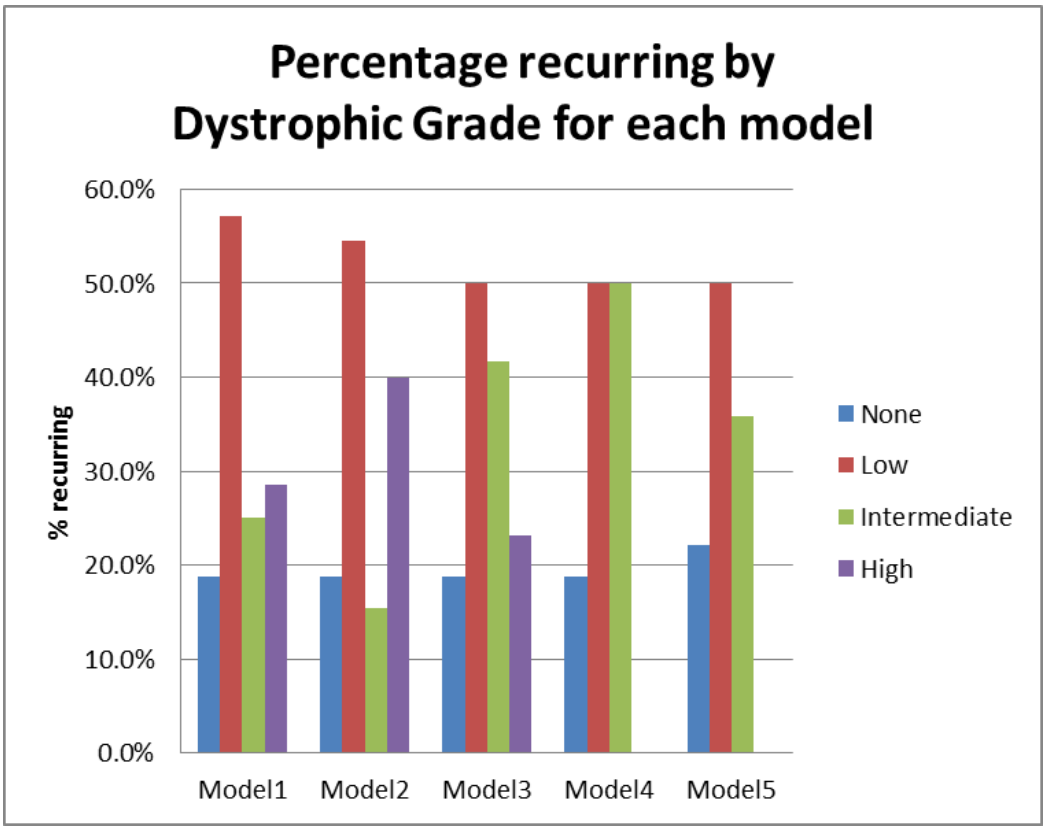
		Model1	**Model2**	**Model3**	**Model4**	**Model5**
CT Finding	**Category**	Initial Model	Binary by number of cysts	As 2, plus contra-lateral disease	Reduce score for large/ numerous cysts	As 4, plus remove emphysema
Emphysema present?	**Yes**	1	1	1	1	0
	No	0	0	0	0	0
Number of cysts	**0**	0	0	0	0	0
	1-2	1	1	1	3	3
	3-10	2	1	1	2	2
	>10	3	1	1	1	1
Max size of cyst (cm)	**<1**	0	0	0	0	0
	1-2	1	1	1	2	2
	>2	2	2	2	1	1
Contralateral Disease	**Present**	0	0	1	1	1
	Absent	0	0	0	0	0
Grade by total score	None	0	0	0	0	0
	Low	1	1	1	1	1
	Low	1	1	1	2	2
	Intermediate	2	2	2	3	3
	Intermediate	3	3	3	4	4
	High	4	4	4	5	5
	High	5	4	5	6	6
	High	6	4	5	6	6

Each model was run on the 61 patients. Risk of recurrence by Grade for each model is shown in Table 7.8 and Figure 7.6. Across all models, patients assigned the Low grade group consistently had the highest recurrence rates. Models 2 and 3 showed the highest recurrence rates in the Intermediate, rather than the High grade patients. Even increasing the scores for fewer and smaller cysts, (model 4 or 5) did not the model's improve the ability predict higher recurrence in those as classified as High grade.

Table 7.8: Model Outputs: number of patients categorised by Dystrophic Grade and percentage recurring within each grade, with mean score

	Number of patients by Grade (% recurring)				
Grade	**Model1**	**Model2**	**Model3**	**Model4**	**Model5**
High	14 (28.6%)	5 (40.0%)	13 (23.1%)	11 (9.1%)	4 (0.0%)
Intermediate	8 (25.0%)	13 (15.4%)	12 (41.7%)	14 (50.0%)	19 (36.8%)
Low	7 (57.1%)	11 (54.5%)	4 (50.0%)	4 (50.0%)	2 (50.0%)
None	32 (18.8%)	32 (18.8%)	32 (18.8%)	32 (18.8%)	36 (22.2%)
Total	61 (26.2%)	61 (26.2%)	61 (26.2%)	61 (26.2%)	61 (26.2%)
Mean score					
Recur	1.8	1.2	1.7	2.0	1.6
Not recur	1.5	1.0	1.4	1.7	1.4

Figure 7.5: Model Outputs: number of patients categorised by Dystrophic Grade and percentage recurring within each grade.



7.13. Discussion

7.13.1. CT findings and demographics

Cystic airspaces (ELC) are common in patients who present with spontaneous pneumothorax, in the absence of known respiratory comorbidities or significant smoking history – i.e. PSP. In this study of 61 patients, cystic airspaces were present in 41.0% in the ipsilateral lung (same side as index pneumothorax event) and 32.8% in the contralateral lung, slightly lower than previous CT studies [8-10, 121, 199]. Mild paraseptal or centrilobular emphysema was also common, particularly in patients who were ex- or current-smokers at the time of their pneumothorax. The link between smoking and

emphysema is well established, but it is noteworthy that the mean cumulative pack years of smoking for these patients was only 6.8, less than one might consider sufficient to cause clinically significant emphysema.

Patients with more extensive ELC could be at higher risk of recurrence. Nineteen (31.1%) patients had suffered with a pneumothorax in the past (78.9% ipsilateral). These patients were more likely to have emphysema or cystic airspaces on CT than those whose pneumothorax was their first episode.

7.13.2. Recurrence

Sixteen (26.2%) patients had a recurrence of their pneumothorax within the 12 month follow-up period. Univariant analysis found a trend towards greater risk of recurrence in females, ex- or current smokers, or patients with previous pneumothorax (OR 3.3, 1.2 and 1.5, respectively), which was not statistically significant. These findings are in keeping with the hypothesis that more severe disease are at greater risk of recurrence, although it is unclear why females should be at greater risk.

However, analysis of the CT findings was not conclusive. As expected, the patients with emphysema and those with cystic airspaces were more likely to have a recurrence (OR 1.5 and 1.6, respectively), but the risk of recurrence did not increase with worsening disease, as defined as number and size of cysts. Although a number of patients had >10cysts (paraseptal emphysema) present on their CT scan, the group with the highest risk of recurrence was in those patients with 1 or 2 cysts (OR 2.3, p 0.40). Similarly, those patients with maximum cyst size of <1cm (OR 2.6, p 0.09); rather than those with larger cysts >2cm (OR 1.7, p 0.56). Five patients had very large ipsilateral cysts (≥4cm), but only one of those patients had a recurrence.

7.13.3. CT scoring model

In light of the variation in number and size of cysts, no single model showed a linear increase in risk with higher model score. The mean score was higher in patients with recurrence compared to those without for each model (Table 7.8). However, as a result of many patients with either multiple cysts or large cysts not having a recurrence, the patients who had been given a “high” grade did not have a corresponding high recurrence risk.

Previous dystrophic scoring studies have had varying success: Sihoe *et al* found no association between score and recurrence risk[9]; although Casali *et al* using an almost identical scoring system (on a larger cohort) found good separation of recurrence-free survival on Kaplan-Meier analysis between those as low and intermediate/high risk[199] However, when applied to data in this current study, the Casali model did not sufficiently distinguish risk of recurrence (see Table7.6).

7.13.4. Biological plausibility

The idea of patients with spontaneous pneumothorax, in the absence of known lung disease (i.e. PSP), having normal lungs is out-dated. Physiologically normal parietal pleura does not leak air. However, the degree to which the ELC commonly seen on CT studies of PSP are the direct source of the air leak is still debated. ELC could be a marker of underlying pathology which, even if mild in severity, predisposes an at risk population of air leak and hence PSP.

If ELC is a marker of pre-disposition, then it follows intuitively that more extensive disease, i.e. larger number or larger size of cystic airspaces, would be expected to impart higher risk of recurrence. This was tested in scoring Model 1, with linearly increasing score for greater number of cysts and size of largest cyst (Table 7.7). However, the corresponding recurrence risks were similar across low, intermediate and high risk. Model 2 was a simplified version,

giving a binary score of presence or not of cystic airspaces; and Model 3 was identical with the addition of a point for contralateral disease. Neither model 2, nor 3, improved the differentiation; and in fact simply divided the patients with cysts into either intermediate or high grade but the risk of recurrence was greatest in the low grade group.

The recurrence rates were high in patients with 1 or 2 cysts of <1cm in size. Could it be that paraseptal emphysema (>10 peripheral cysts) or a few large cysts is actually a more stable pathological state than a few isolated cysts? To compensate for this, Models 4 and 5 were developed with a reduced score for patients with >10 cysts or cysts >2cm in size. The accuracy of risk prediction actually reduced, with more patients being classified as intermediate. There is no previous published clinical data to suggest that the more numerous or larger cysts impart any "protective" effect. However, as discussed in the Introduction, there is evidence on electron microscopy that smaller blebs (consistent with Reid Type I bulla) have an absence of mesothelilal cells and nearby pores, which may mean they are more likely to leak. Whereas, larger blebs may be consistent with Reid Type II bullae with intact mesothelial cells and thereby be more stable. Equally, given the relatively small sample size in this study, the differences in recurrence rates could have occurred by chance (given no statistical significant difference was seen between groups).

Although cystic lung disease was prevalent in both ipsilateral and contralateral lung, recurrence only in this patient group only occurred ipsilaterally. If presence of cysts or emphysema alone were sufficient for pneumothorax occurrence, one would predict an almost equal number of ipsilateral and contralateral occurrences.

7.13.5. Strengths

The strengths of this study include the prospective nature of the data collection (in contrast to many previous CT scoring publications which relied on retrospective data). As RAMPP is a multi-centre RCT, patients were recruited from across the UK rather than being from single centres. The patients recruited included both those requiring intervention (randomised group) and those managed conservatively (observational group), as opposed to only patients who either have had (or are referred for surgery). The two radiologists undertook the CT scoring were thoracic experts, and their agreement was generally good.

7.13.6. Limitations

Sample size in this initial analysis of the RAMPP patient group was relatively small (n=61). Therefore, small but significant differences in initial CT findings by patient characteristics or by recurrence could be missed by lack of statistical power. Due to a lack of consistency in CT regime undertaken at different sites, quantitative CT analysis of %LAA could not be calculated for all patients, and as such was not included in the model. Although, having expert radiologists scoring the scans maximises the chance of identifying relevant disease, it may limit the applicability of the findings to patients treated and managed in smaller centres whose radiologists may be not be thoracic experts.

7.13.7. Implications for clinical practice

Patients who are successfully treated for the first episode of PSP (i.e. those without PAL and fully re-expanding lung) are not routinely referred for surgical recurrence prevention. To date, there are no clinical or radiological parameters identified to robustly identify those patients at high enough skill to alter this standard pathway of waiting until second occurrence (i.e. first recurrence) before referral. Previous retrospective studies have attempted to identify radiological features which correspond to high recurrence risk, the

largest study of which was undertaken by Casali *et al*[199]. However, in this study, using Casali's simple dystrophic score did not distinguish patients sufficiently. Additional modelling was undertaken including a measure of the presence of emphysema and more detailed scoring of size and number of cystic airspaces, but no single model adequately differentiated those a highest risk.

7.14. Conclusions

Stratification of risk recurrence in pneumothorax remains elusive. This study confirmed that mild emphysema and ELC are common in patients with PSP. Ex- or current smokers had more cysts and the maximum size of cysts was greater compared to non-smokers. All 13 patients with more that 10cysts (i.e. paraseptal emphysema) were ex- or current smokers. Emphysema was more common in males, ex- or current smokers or patients who had suffered with a previous pneumothorax. These patients were at slightly higher risk of recurrence, but there was considerable variation in the extent and size of cystic airspaces in both those patients who recurred and those who did not. As a result, in this group of 61 patients, no single model of CT findings sufficiently accurately predicted recurrence.

7.15. Future directions

Recruitment to the RAMPP trial is on-going. Once recruitment is complete, the remaining dataset will be analysed. This will provide over 400 patients' data in total, including all 236 patients requiring intervention, and assuming at least 167 patients in the observational cohort.

The data, as presented in this thesis for 61 patients, will be reassessed with larger patient numbers in order to determine whether the trends towards differences in recurrence risk by patient demographics and CT findings are significant with greater statistical power. Any prediction model generated by this subsequent analysis will require external validation, but it would have the potential to allow a personalised assessment of a patient's risk. This would enable a more informed discussion regarding future risk and the pros and cons of recurrence prevention measures.

In addition, given the high prevalence of contralateral disease, but relatively low occurrence of contralateral pneumothorax, further microscopic understanding of the pathology is required. What occurs in the one affected lung to cause a pneumothorax which is not occurring in the other lung (with equally severe disease radiologically)?

8. Conclusions

This conclusion will summarise the state-of-play in the knowledge of PSP prior to this thesis, the new understandings gleaned from the data presented within it, what further questions it raises, and where this leads in terms of future directions for pneumothorax research.

8.1. Pathophysiology of PSP

8.1.1. What we thought we knew

The idea that PSP occurs in patients with normal lungs, as described in some textbooks, is not correct. Abnormalities have been identified macroscopically, microscopically, biochemically and genetically. Yet the true histopathological cause and time course is not understood. Macroscopic changes of ELC are readily identified in patients with PSP, but also in control subjects (without pneumothorax). Microscopic findings of respiratory bronchiolitis are common on surgical resection specimens, but are also found in other patients who smoke. There is evidence of an absence of mesothelial layers on some smaller ELCs (blebs); whereas on other larger bulla, the mesothelial cells (although thin) remain intact. In additional, pleural porosity has been identified as a potential site of visceral leak, which does not necessarily co-locate with ELCs.

The degree to which the cystic airspaces (ELC) commonly seen on CT studies of PSP are the direct source of the air leak is still debated. ELC could be a marker of underlying pathology which, even if mild in severity, predisposes an at risk population to air leak and hence PSP. Little is known of the functional implications in terms of ventilation defects or inhomogeneity.

8.1.2. What this thesis adds

This thesis describes two new methodologies to examine the lungs of patients, both of which were used for the first time in patients with PSP: Hyperpolarised ^{129}Xe-enhanced MRI, and Molecular Flow Sensor with mathematical model of inhomogeneity.

^{129}Xe MRI

^{129}Xe MRI scanning is a non-ionising imaging modality which can assess ventilation and diffusion. Data presented in Chapter 3 show that, although there is variability by patient (and by lobe), reduced percentage ventilation was seen in PSP patients with greater %LAA on quantitative CT scanning and with reduced pulmonary function. These areas of reduced ventilation may represent the ELC or early emphysema known to be associated with PSP, and were more marked in smokers than non-smokers. The reduction in ventilation for smokers was greatest in the upper lobes, suggesting that although underlying abnormalities may be present in all patients, they may be exacerbated by smoking. When compared to a COPD cohort, the pneumothorax results were consistent with milder but identifiable abnormalities.

^{129}Xe MRI has the potential to be a technique to visualise and characterise important structural abnormalities of ventilation in PSP. If proven to identify an at-risk sub-population of patients, particularly those with early disease, they this could alter the management paradigm for these patients (see below).

Lung inhomogeneity assessment

Functional assessment of the lungs traditionally relies on PFTs which are global measures of lung function, and are not good at identifying subtle abnormalities or inhomogeneity.

Chapter 4 describes the use of a novel methodology, developed in Oxford, combining highly precise MFS measurements of gas exchange with a mathematical model of inhomogeneity, for the first time in PSP patients.

Comparison with data from other participant groups have highlighted that model-derived lung parameters of the pneumothorax patients are not the same as either young healthy, old healthy or COPD participants. The compliance distribution (a surrogate for variability of ventilation) in the pneumothorax group was greater than the young healthy participants and less than the older healthy and COPD participants. Although the differences in compliance distribution were only statistically significant compared to the COPD patients, the findings in patients with PSP (who were young) are not the same as young healthy volunteers. There is inhomogeneity within the lungs of patients who have experienced a pneumothorax, which may be exacerbated by greater or lesser extent by smoking.

The findings from these two new techniques will require longitudinal testing and clinical follow-up. Both tests are quick and simple for the patients to perform. The non-ionising nature of MRI allows repeated assessments of young patients without the risks of exposure to radiation (as would be the case for CT scanning).

8.2. Epidemiology and risk factors for recurrence

8.2.1. What we thought we knew

Epidemiological studies of spontaneous pneumothorax to date are either old single centre studies, or larger national database studies which only cover 4-year periods, limiting time-trend analysis. The last study in England used data from over 20 years ago. Previous epidemiological studies had limited data on recurrence rates for PSP, so data are mostly

based upon retrospective case series data, which report a recurrence risk anywhere between 21 and 54% within 1-2 years.

Patients who present with their first pneumothorax are currently not considered for recurrence prevention. However, a system to predict likelihood of recurrence could allow a more personalised approach and allow informed discussion between clinician and patient. A number of studies have investigated whether use of CT scanning to develop a "scoring" system of number, size and distribution of cystic air spaces, but this remains controversial.

Pleurodesis is required for treatment of PAL or for effective recurrence prevention. Thoracic surgery is generally considered first line option for elective recurrence prevention and typically consists of VATS apical bullectomy or wedge resection. However, it is increasingly acknowledged that to achieve a truly low recurrence rate, the additional of a chemical agent is required. (Pleurectomy also provides a pleurodesis but has greater side effects.) In patients who are unfit for surgery, chemical pleurodesis can be considered via a chest drain. There was no good evidence synthesizing the data on the efficacy of chemical pleurodesis agents in pneumothorax. As such, it was not clear what clinicians should expect in terms of recurrence rates when considering pleurodesis agents.

8.2.2. What this thesis adds

Epidemiological study

Using the HES and ORLS datasets from 1968 to 2013, including over 150,000 admissions, analysis in this thesis represents the largest epidemiological study of pneumothorax to date. This shows that pneumothorax admission rates are increasing. The increase is attributable partly to an increase in readmissions, and partly to a modest increase in first-known

admissions among older age groups. In addition, record-linked data (available from 1999-2013) allowed the development of a robust method to distinguish between PSP from SSP, and generation of probability of recurrence data.

Data from 2012 show an annual admission-based rate of 21.7 for men and 7.5 for women per 100,000 population with a ratio of 2.9. Probability of recurrence at 1 year was between 17.4% and 33.3% depending on age and respiratory comorbidity (PSP vs SSP), quantifying for the first time the increased risk for patients with SSP, particularly in younger patients.

CT scoring

Stratification of recurrence risk in pneumothorax by CT findings remains elusive. Data in this thesis confirmed that mild emphysema and cystic airspaces are common in patients with PSP. Ex- or current smokers had more cysts and the maximum size of cysts was greater compared to non-smokers. 13 patients had more than 10 cysts in each hemithorax (i.e. paraseptal emphysema), all of whom were ex- or current smokers. Emphysema was more common in females, ex- or current smokers or patients who had suffered with a previous pneumothorax. These patients were at slightly higher risk of recurrence, but there was considerable variation in the extent and size of cystic airspaces in both those patients who recurred and those who did not. As a result, in this group of 61 patients, no single model of CT findings sufficiently accurately predicted recurrence.

Chemical pleurodesis

Systematic review of the literature found that the most effective method of chemical pleurodesis is the addition of talc or minocycline alongside surgical VATS, followed by thoracoscopic talc poudrage. Surgery is not suitable for all patients. In these cases, the

instillation of talc, tetracycline or minocycline via the chest drain will provide some reduction in the recurrence rate, but data on the true degree of improvement is not clear given the retrospective nature of most of the studies.

8.3. Initial management and predicting short term outcomes

8.3.1. What we thought we knew

Patients with spontaneous pneumothorax are treated as per a generic, non-personalised, management pathway. Treatment failure will inevitably lead to prolonged hospitalisation with a chest drain waiting for air leak to cease. There is no model as yet to stratify patients by risk into those who will respond to treatment and those who will fail.

8.3.2. What this thesis adds

Airflow measurements in the early stages of PSP management may be predictive of failure of treatment at Day 4. On-going prospective data is being collected. If validated, early prediction of treatment failure to lead to an alternative paradigm: patients at higher risk of failure could be triaged to an early preventative treatment pathway (i.e. thoracic surgery), rather than waiting with daily reviews until Day 4, with associated cost of inpatient stay as well as the patient distress at the uncertainty.

8.4. Optimising management

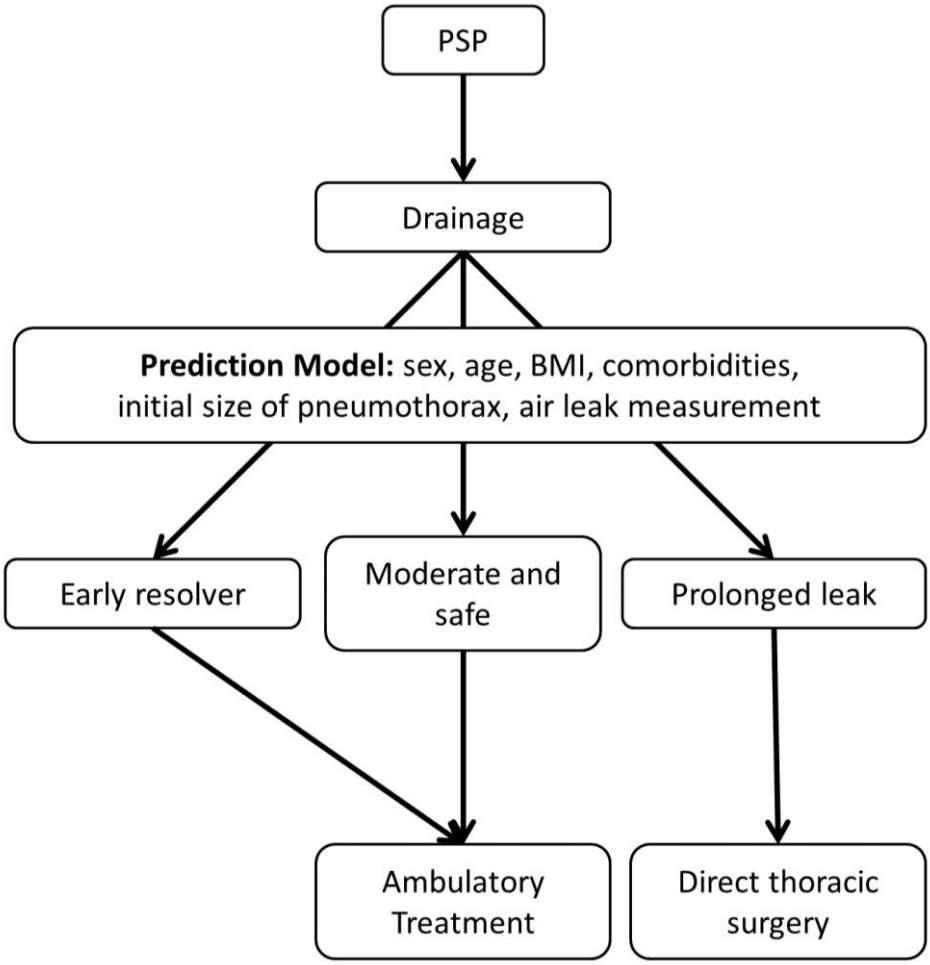
8.4.1. New treatment paradigm

There needs to be a move away from a generic, non-personalised treatment pathway to one which incorporates clinical measurable parameters and allows informed discussion of risk of treatment failure and recurrence (Figure 8.1). Patients with high risk of treatment failure (identified by clinical characteristics including digital airflow), can be triaged to early

preventative treatment (at present, VATS). Patients identified as “early resolvers” could be reviewed within 1-2 days. Those identified as “moderate risk but safe” will be those with a low level air leak, who could be managed safely as an outpatient with an ambulatory device and reviewed less often, but should resolve after 3-4 days

This new treatment paradigm will need to be assessed prospectively in an RCT (see below), but it has the potential to change the management strategy for pneumothorax for the first time decades.

Figure 8.1: Schematic for optimal new treatment paradigm for PSP incorporating a prediction model to triage patients at high risk of PAL direct to early surgery; whilst the rest are managed on an ambulatory pathway



8.4.2. Ambulatory management

The established dogma of prolonged hospital inpatient management of PSP patients with few (if any) comorbidities is being challenged. Therefore, alongside the new risk-based treatment pathway (Figure 8.1), patients deemed early resolvers or safe for discharge could all be managed out of hospital.

The ambulatory management strategy of PSP is being currently assessed in the RAMPP study - an on-going RCT (designed and coordinated by the author). If this study proves ambulatory management is safe and effective in PSP, then the outpatient management could become the default option.

8.5. What key questions remain in PSP?

- What is the natural history of ELC in patients with and without pneumothorax?
- To what degree do ELC identified in lungs of patients with PSP actually correspond to risk of pneumothorax?
- Can digital airflow measurement-based treatment paradigms be shown to improve patient outcomes?
- Can the novel non-invasive/non-ionising tests provide reliable metrics of pathology or quantifiable risk of recurrence?
- What does subtle or early disease mean for long term lung health?
- What are the long-term sequelae of PSP in young patients in terms of respiratory and other diagnoses?
- Is thoracoscopic talc as effective as surgical intervention for recurrence prevention? (Can the physicians take over from the surgeons?)

- What is the genetic component of pneumothorax risk?

8.6. Future work

8.6.1. Better understanding pathophysiology

Blebs, bullae and pleural porosity all seem to be associated with PSP formation. However, to what degree each abnormality is pathogenic remains unknown. Historically surgical intervention has focussed on resection of blebs or bullae, but we now know that the surrounding parietal pleura is not normal. The seminal research by Noppen *et al* using fluorescein-enhanced autofluorescence thoracoscopy in patients with PSP and control subjects, demonstrated areas of parenchymal abnormality[12]. These areas of subpleural fluorescence or visible fluorescence leak occurred at regions of the lung which otherwise appeared normal on plain white light thoracoscopy. Why are those areas of pleura affected and others not? What are the histological, chemical and proteomic differences?

Fluorescein-targeted pleural biopsies

These questions will be investigated by combining expertise: respiratory physicians, surgeons, anaesthetists and histopathologists. Patients who are undergoing elective PSP recurrence surgery will be consented to undergo fluorescein-enhanced autofluorescence during their operation. This is straightforward and simply involves asking the anaesthetist to use of a different gas source for a short period whilst the patient is under a general anaesthetic (GA). During the period of inspection under ultraviolet light, areas of lung highlighted with fluorescein will be marked for closer histological inspection. Apical or wedge resection is common surgical technique for PSP, and therefore any marked areas within the resected specimen can be specifically assessed by the histologists. Findings can be

compared to the bleb/bullae and to non-fluorescein enhancing regions. Control subjects will be recruited from age- and smoking-history matched patients with early stage lung cancer (i.e. isolated small tumours) being treated with curative intent with wedge resection or lobectomy. They will also undergo fluorescein-enhanced autofluorescence to highlight areas of pleural abnormalities, despite no history of pneumothorax.

Samples will assessed histologically for evidence of respiratory bronchiolitis thickening and elastofibrosis of the pleura, formation of small air containing space between lamina elastic interna and externa, and absence of mesothelial cells, and/or underlying collagen fibres.

Prior to setting the samples in formalin, a small sample could be taken for proteomic analysis. The analysis of the protein expression in different lung regions may provide novel insight in the pathophysiology and natural history of ELC.

8.6.2. Digital air leak & predicting early failure

As a result of work in this thesis, a tool using easily identifiable clinical factors (including size of initial pneumothorax, bedside airflow measurement) early in the treatment pathway (e.g. Day 1 or 2) to predict treatment failure is a step closer.

Validation will require an RCT. The patients would include patients with PSP who require chest tube insertion (either standard chest drain or ambulatory device), with a pneumothorax that has not resolved after 24 hours of drainage. They would then be randomised into two groups: an intervention group using a new treatment decision pathway based upon digital airflow measurement at day 1 or 2; compared to a control group using standard care (i.e. daily assessment of bubbling from chest drain and CXR appearance). The primary outcome would be overall length of treatment.

The hypothesis is that use of the new pathway, involving early referral for surgery (e.g. if airflow is >100ml/min on Day 2) reduces length of stay by removing the requirement to "wait until day 4 or 5" before referring for surgery. In this current dataset, the mean total treatment duration for those referred for surgery was 11.9 days (SD 5.4). Any strategy which can successfully identify and triage patients likely to have PAL could significantly lessen time to surgery, thereby overall treatment time.

8.6.3. Long-term consequences of PSP

The long-term sequelae of pneumothorax in early adulthood (PSP) are not known. The long duration of the linked datasets (HES 1999-2013 and ORLS 1968-2013) provides a powerful tool to conduct follow-up studies looking at the likelihood of developing other respiratory disease, cardiovascular disease or malignancy can be assessed. This analysis will allow identification of other potentially unrecognised associations with PSP, which could have important implications for screening of patients with pneumothorax. For example, are young patients, who have a pneumothorax in their 20s at greater risk of early diagnosis of COPD, cystic lung disease, connective tissue disorders, or cardiovascular disease? Identification of individuals at risk could allow informed debate regarding early intervention (e.g. smoking cessation), and regular screening for serious complications.

8.6.4. Physician-led recurrence prevention

The systemic review found that the most effective method of chemical pleurodesis for recurrence prevention is the addition of talc or minocycline alongside surgical treatment (i.e. bullectomy or apical resection), but this was closely followed by thoracoscopic talc poudrage. Thoracoscopies are performed by physicians under conscious sedation and do not

require GA and intubation of the patient. With evidence that it is the pleurodesis aspect which is key, should recurrence prevention be undertaken by physicians?

An RCT comparing physician-led thoracoscopic talc poudrage vs standard surgical management (i.e. possible bleb/bullae resection followed by talc poudrage or pleurectomy) could answer this question. The primary outcome would be recurrence rates at 1 year. A successful trial would only need to prove non-inferiority to potentially change practise: thoracoscopy would be quicker than VATS with no need for GA induction and shorter patient recovery time. Therefore, thoracoscopic management may also reduce overall time in hospital. Given the low recurrence rates, a large multi-centre trial would be required. With the established network of experienced centres already recruiting to the RAMPP study around the UK, this could be achievable.

8.7. Final thoughts

Primary spontaneous pneumothorax is a condition which presents regularly to emergency departments and medical teams across the country every day. Data presented in this thesis provides an insight into the underlying abnormalities in PSP and lays the groundwork for potentially fundamentally altering the management paradigm. With many questions unanswered, much work remains to be done, but it is an exciting time to be involved in pneumothorax research.

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