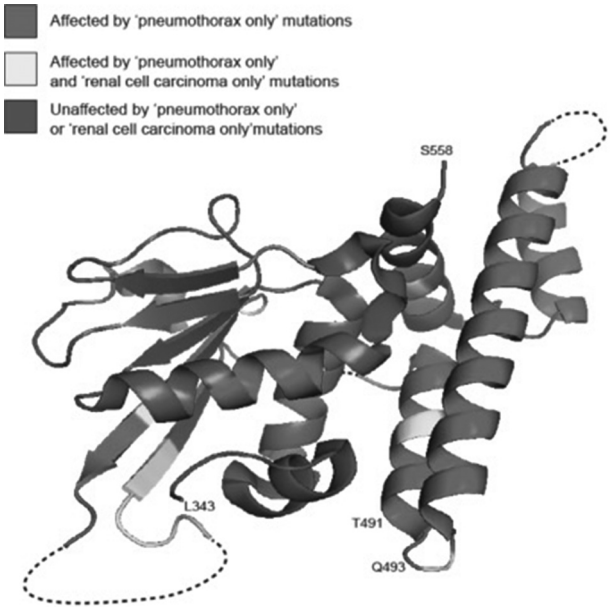

Abstract S59 Figure 1 FLCN mutations within cDENN & dDENN domains. Mutations of *FLCN* within the DENN domain L343-S558 mapped onto the crystal structure. Red indicates regions affected by mutations said to cause only pneumothorax. Yellow indicates mutations said only to cause RCC and yet fall within 'red' regions

Conclusion No bias was identified in the locations of mutations reported to cause only pneumothorax. Individuals with pneumothorax-only mutations were significantly younger than other patients with BHD. Large deletions and truncating mutations are common in both typical and 'pneumothorax-only' BHD suggesting that folliculin loss-of-function explains the pathogenesis in both instances. These observations suggest that pneumothorax-only *FLCN* mutations likely reflect ascertainment bias. We recommend that all patients with a *FLCN* mutations should be offered renal surveillance.

S60 **NON-INVASIVE MEASUREMENT OF LUNG INHOMOGENEITY FOLLOWING RECOVERY FROM PRIMARY SPONTANEOUS PNEUMOTHORAX**

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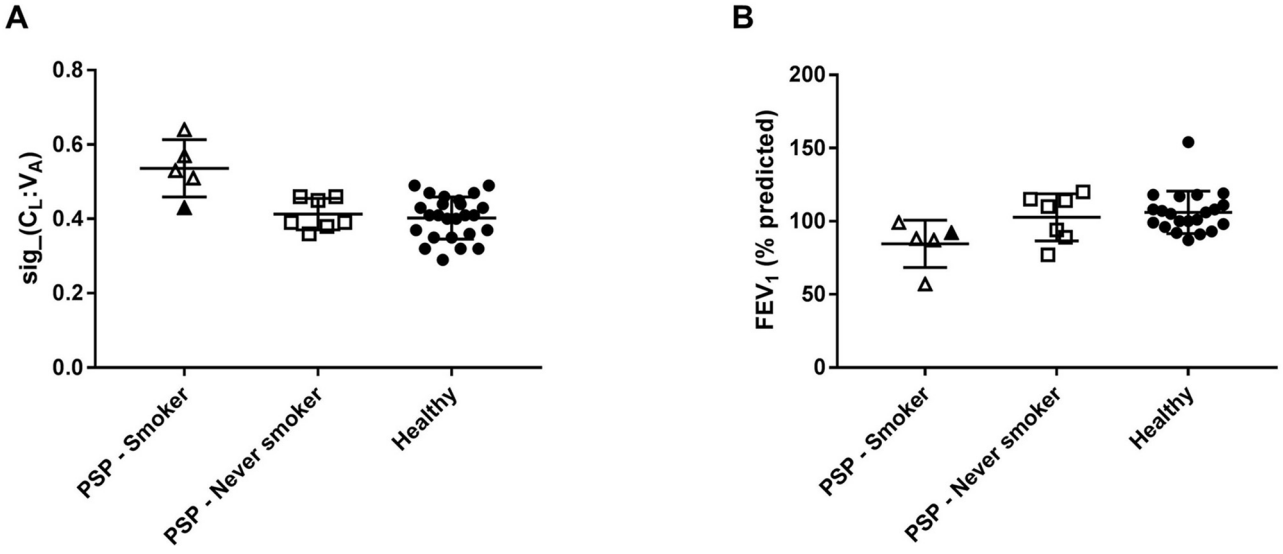
Background There is some evidence that patients with Primary Spontaneous Pneumothorax (PSP) have subtle emphysema-like change (ELC) and regional airway inflammation. These abnormalities may not be evident using standard lung function testing. We hypothesized that a novel non-invasive method for quantifying lung inhomogeneity (LI) would reveal lung abnormalities in patients following PSP.

Methods Twelve patients were enrolled following PSP, along with 25 healthy volunteers. All participants gave written informed consent and each underwent a standard nitrogen washout test (10 min breathing air, 5 min breathing O_2), using a novel gas analyser that precisely measures respired gases using laser absorption spectroscopy. A mathematical model of the lung was fitted to the data to estimate LI parameters, including the distribution of lung compliance relative to alveolar volume (σCL:VA).[1]

Results The PSP and healthy volunteer groups were well-matched for age (29.8±8.4 vs 26.4±7.3 years, mean ±SD, respectively) and height (181±9 vs 179 ±7 cm). In the pneumothorax group, five patients were smokers (four current and one former; mean 9±4 pack years). In the healthy group, all participants were never-smokers.

In the PSP group as a whole, σCL:VA was significantly elevated, compared with healthy volunteers ($p<0.03$, Student's t-test). However, further analysis (ANOVA) revealed that the elevation in σCL:VA was due to the effects of smoking history ($p<0.001$), with no significant independent effect



Abstract S60 Figure 1 Panel A: σCL:VA in healthy volunteers (filled circles), never-smokers in the PSP group (squares), and those in the PSP group with a smoking history (triangles; filled triangle represents the former-smoker). Panel B: FEV_1 in the same groups

of pneumothorax status (p>0.4; figure 1A). The former smoker had the lowest value for σCL:VA in the smoker group.

Importantly, despite the clear effect of smoking on σCL:VA within the PSP group, neither smoking history (p>0.3) nor pneumothorax status (p>0.1) had any significant effect on forced expiratory volume in 1 s (FEV_1), the standard method of detecting airways disease (figure 1B).

Conclusion This study shows that it is possible to demonstrate statistical differences in LI between a small group of PSP patients and controls, mainly due to modest smoking history in the PSP group. However, such differences were not apparent using FEV_1. Although controls were not matched for age or smoking, this study nevertheless suggests that measures of LI may provide a sensitive method for exploring possible parenchymal abnormalities.

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S61 NOVEL ASSESSMENT OF VENTILATION ABNORMALITIES IN PRIMARY SPONTANEOUS PNEUMOTHORAX USING XENON-ENHANCED MRI

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Background There is increasing evidence in patients with Primary Spontaneous Pneumothorax (PSP) of emphysema-like change (ELC) and inflammation. Pulmonary function tests are global metrics, not sensitive to subtle disease. Computed tomography scans can provide detailed structural, but not direct functional, information. Hyperpolarised ^{129}Xenon magnetic resonance imaging (MRI) allows functional assessment of ventilation.

Methods Patients underwent ^{129}Xe MRI ventilation scan with a single breath-hold of 1L ^{129}Xe with ~10% hyperpolarisation. Percentage ventilation of lung receiving ^{129}Xe hyperpolarized gas were analysed by lobe using a semi-automated software package.[1]

Results Of 10 PSP patients, 8 (80%) were male, (median age 28.6 years), 5 (50%) were current or ex-smokers. Mean overall%Ventilation was 88.0% (SD 4.8%) and was correlated with forced expiratory volume in 1 s, (R2 0.41, p 0.045) and diffusing capacity, (R^2 0.77, p<0.001). Regional differences were demonstrated between lobes. Smokers had a reduced%Ventilation (overall 3.9%), which was particularly marked in the upper lobes: right 9.0%, left 4.8%.

Conclusion This study demonstrates reduced% ventilation on ^{129}Xe MRI in patients post-PSP. These areas may represent the ELC, known to be associated with PSP, and were more marked in smokers. ^{129}Xe MRI is a non-ionising technique with the potential to visualise and characterise important subtle structural abnormalities. On-going work will assess pulmonary microstructure and gas transfer capacity to provide a comprehensive functional/structural evaluation on a regional basis, and its correlation with risk of PSP recurrence.

REFERENCE

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Signal failures: mechanisms of lung disease

S62 MYCOBACTERIAL ESCAPE BY NON-LYTIC EGRESS

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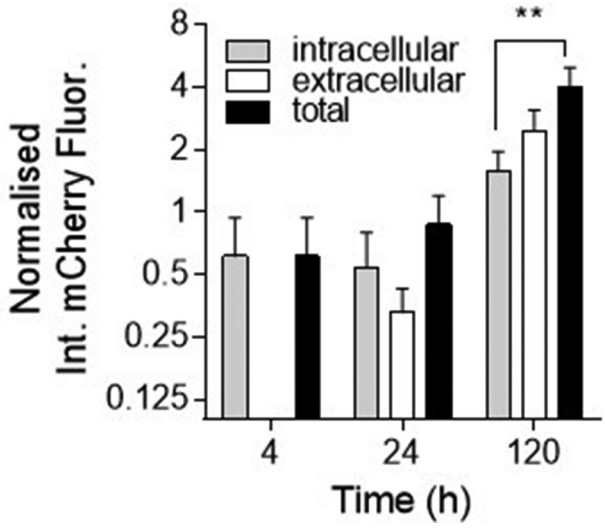
Mycobacterium tuberculosis (*Mtb*) is a highly efficient facultative intracellular pathogen circumventing attempts by the immune system to eradicate it. Alveolar macrophages are the primary target for intracellular invasion, and central to its pathogenesis is *Mtb*'s remarkable capacity to survive and proliferate within the hostile environment of these professional phagocytic cells. Despite its status as an intracellular pathogen, numerous extracellular bacteria can be found in caseating granulomas, the histopathological hallmark of TB disease. *Mycobacterium marinum*, the closest genetic relative to *Mtb*, thrives extracellularly in the absence of macrophages in zebrafish.

Extracellular *Mtb* seen in histopathological lesions are likely to arise, at least in part, from macrophage necrosis which is associated with outer membrane damage and release of nuclear and cytoplasmic contents into the extracellular space. But several organisms, including other mycobacteria, have versatile strategies for escape into the extracellular environment, both by triggering cell lysis and leaving the host cell intact.

The exit of intracellular organisms is a crucial stage of pathogenesis since cellular escape facilitates spread of infection to neighbouring cell, tissue invasion and onward transmission to new hosts. However, our understanding of the exit of *Mtb* from human macrophages is limited. Because studies examining mycobacterial control in various *in vitro* and *in vivo*



Abstract S62 Figure 1 Extracellular Mtb accumulate following co-culture with macrophages. Human monocyte derived macrophages were infected with H37Rv mcherry for 4 hours. Cultures were washed extensively to remove all extracellular bacteria. Fresh media was added for the times specified. At the relevant time point exctracellular bacteria in the supernatant were collected. Intracellular bacteria were harvested by washing and lysing cells. Bacteria were fixed in 4% PFA and analysed by flow cytometry. Mean±SEM 8 separate experiments conducted in duplicate or triplicate