largest cohort study focusing on cardiovascular manifestations in COPD.

Methods Spirometry, haemodynamic measures (aortic pulse wave velocity (aPWV), augmentation index (AIx), peripheral and central blood pressure (BP)) and CIMT (ultrasound measure of carotid artery intima-media layer thickness) were performed in 729 COPD subjects aged ≥40 years. COPD severity was classified by BODE Index [BMI, Obstruction (FEV1), Dyspnoea (mMRC score), Exercise tolerance (6-minute walk distance)], a validated score based on clinical variables and predictor of mortality in COPD.

Results Mean aPWV was 10.3 (SD 2.6) m/s, AIx 27 (10)%, brachial BP 144/82 (18/11) mmHg, central BP 131/82 (18/11) mmHg, CIMT 0.86 (0.4) mm.

BODE correlated with aPWV ($p < 0.0001$) and this was maintained when adjusted for study site, age, supine heart rate (HR) mean arterial pressure (MAP), years smoked and cardiovascular comorbidities (MI, stroke, diabetes, peripheral vascular disease), $p < 0.0001$. BODE was also associated with AIx when adjusted for site, age, seated HR and MAP, years smoked and cardiovascular comorbidities, $p < 0.01$. The constituent variables of BODE did not have the same significant association with both aPWV and AIx, Table 1.

Abstract S124 Table 1 Comparison of linear regression models of BODE constituent variables, cardiovascular comorbidities and established predictors of arterial stiffness

Dependent variable	aPWV (m/s)		Augmentation Index (%)	
	β coefficient	p-value	β coefficient	p-value
Age (years)	0.4	<0.0001	-0.01	0.7
MAP (mmHg)*	0.2	<0.0001	0.26	<0.0001
HR (bpm)*	0.2	<0.0001	-0.49	<0.0001
TPYs	-0.001	0.98	0.02	0.63
BMI (kg/m^2)	0.09	0.01	-0.17	<0.0001
FEV1 (%)	-0.06	0.09	0.05	0.14
mMRC (0–4)	0.07	0.09	0.003	0.94
6MWD (m)	-0.03	0.5	-0.01	0.002
MI	-0.01	0.7	-0.08	0.02
Stroke	-0.01	0.7	-0.02	0.46
Diabetes	0.07	0.03	-0.08	0.02
PVD	0.1	0.004	0.01	0.78
Study site	-0.06	0.09	-0.03	0.45

*Supine for aortic pulse wave velocity (aPWV), seated for Augmentation Index.
TPYs: Total pack years smoked, mMRC dyspnoea scale, 6MWD: 6-minute walk distance, MI: Myocardial Infarction, PVD: Peripheral Vascular Disease.
Cardiovascular comorbidities: self-reported on questionnaire.

An inverse correlation of BODE with central systolic BP ($p = 0.003$) was observed and this was maintained after adjustment for study site, age and HR $p = 0.03$. There was no significant relationship between BODE and CIMT.

Conclusions BODE is associated with arterial stiffness in COPD, independent of traditional risk factors. Its negative relationship with systolic pressure suggests increasing arterial stiffness with COPD severity, is independent of blood pressure. The BODE Index composite variables are not on the causal pathway for vascular stiffness, so its positive association likely reflects patient susceptibility to injury from smoke or other irritants in the lungs and vasculature. BODE may also enhance cardiovascular risk stratification in COPD, since its relationship with stiffness was independent of self-reported cardiovascular comorbidities.

S125 RELATIONSHIP OF RIGHT HEART ECHO PARAMETERS TO FUNCTIONAL STATUS AND PULMONARY FUNCTION IN SEVERE COPD

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Introduction COPD is associated with structural and functional cardiac changes, particularly the right heart. There is little evidence as to whether right heart echo parameters are associated with QOL, health status and pulmonary function.

Methods We looked at the relationship of right heart function to QOL (SGRQ) and health status (SF-36) and to pulmonary function (spirometry and DLCO) in patients with severe COPD.

Results 120 patients were included in the analysis: 82 men and 38 women; mean age 69 years; mean FEV_1 41%; mean FEV1/FVC 0.38; mean PAP 29 mmHg; mean $Sa0_2$ 95%. Pulmonary vascular resistance was related to 6MW distance ($p = 0.008$), BODE Index ($p = 0.01$) as well as FVC% ($p = 0.03$). RV ejection time (RVET) was related to SGRQ ($p = 0.02$), SF-36 scores for limitations due to physical problems (PL) ($p = 0.03$), social functioning (SF) ($p = 0.04$) and general health perceptions (GH) ($p = 0.02$) as well as FVC% ($p < 0.001$) and DLCO ($p = 0.001$). When comparing pulmonary acceleration time (PAT) <100 ms ($n = 68$) vs PAT ≥ 100 ms ($n = 51$), we found a difference in mean SGRQ 59.3 vs 52.1 ($p = 0.01$) and mean RVET 262 vs 286 ms ($p = 0.001$). Dynamic lung volumes as FEV_1%, FVC% and FEV_1/FVC were significantly related to SGRQ and SF-36 scores for physical function (PF), PL, SF and GH. There were significant differences between GOLD 2 vs GOLD 4 groups for: mean PAP ($p = 0.05$), mean RVET ($p = 0.001$) and mean SF-36 scores for PF ($p < 0.001$), PL ($p = 0.009$), SF ($p = 0.01$) and GH ($p = 0.001$).

Conclusion In patients with severe COPD, right heart echocardiographic parameters are associated with functional status and dynamic lung volumes.

Basic mechanisms of airways disease

S126 MEASURING ER PROTEIN MOBILITY DURING ER FRAGMENTATION IN ALPHA-1-ANTITRYPSIN DEFICIENCY

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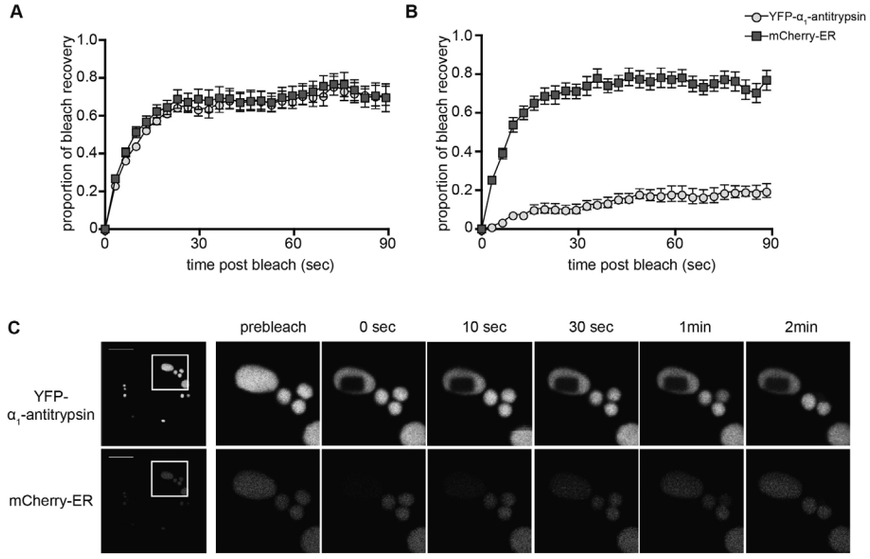
Introduction and objectives Alpha-1-antitrypsin is a serine protease inhibitor produced in the liver that is responsible for the regulation of pulmonary inflammation. The commonest pathogenic gene mutation yields Z-alpha-1-antitrypsin, which has a propensity to self-associate into polymers that become entrapped within inclusions of endoplasmic reticulum (ER). This predisposes to the development of cirrhosis, while the resulting paucity of circulating alpha-1-antitrypsin leads to early-onset emphysema. It is unclear whether intracellular inclusions are physically or functionally connected to the main ER network in Z-alpha-1-antitrypsin expressing cells. In this study, we sought to clarify the behaviour of proteins within inclusion bodies to further our



Abstract S126 Figure 1 Assessing ER chaperone mobility in cells expressing wild-type and polymerogenic AAT using 2-colour FRAP. Cells expressing WT (A) or polymerogenic Z (B) AAT were subjected to 2-colour FRAP. Note the ER protein ER-mCherry remains mobile even in the presence of immobile Z-AAT. (C) 2-colour bleaching of a single ER inclusion containing Z-AAT confirms immobility of Z-AAT but free movement of ER-mCherry through the immobile AAT lattice. (AAT; al-antitrypsin)

understanding of the consequences of Z-alpha-1-antitrypsin expression on cellular dysfunction.

Methods We created YFP tagged wild-type and Z-alpha-1-antitrypsin constructs and expressed them in a cell model along with other fluorescently tagged proteins of interest. Using live-cell imaging including photobleaching techniques, we assessed the relative mobilities of alpha-1-antitrypsin and other ER resident proteins. We further assessed the nature of inter-inclusion protein trafficking by creating a permeabilised cell system in which the cytosol could be manipulated or removed.

Results We have shown that inclusions are translationally active ER fragments in which polymerisation occurs. Using fluorescence recovery after photobleaching (FRAP), we observed that despite inclusions containing immobile polymeric alpha-1-antitrypsin, small ER resident proteins including the ER chaperone BiP are able to diffuse freely within them (Figure 1). We observed that inclusions are physically separated from the tubular ER network but despite this, cargo is transported between inclusions in a cytosol-dependent fashion that is dependent on vesicular trafficking components and may involve the ER-Golgi intermediate compartment (ERGIC).

Conclusions We propose that protein movement between physically separated ER inclusions via ER-ERGIC recycling acts to minimise ER heterogeneity in Z-alpha-1-antitrypsin expressing cells. This may reduce the toxic effects of polymer accumulation via increased availability of, for example, ER chaperones within inclusions and is consistent with *in vivo* observations of a striking lack of toxicity in cells expressing Z-alpha-1-antitrypsin.

S127 GENE THERAPY FOR ALPHA-1-ANTITRYPSIN DEFICIENCY USING A PSEUDOTYPED LENTIVIRUS VECTOR

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Introduction and objectives A protease/anti-protease imbalance is a characteristic feature of inflammatory lung diseases such as cystic fibrosis (CF) and alpha-1-antitrypsin deficiency related emphysema. A recent trial of alpha-1-antitrypsin (hAAT) enzyme replacement therapy (ERT) suggested that hAAT can slow the progression of lung density loss in alpha-1-antitrypsin deficiency (Chapman *et al*, Lancet 2015). However, the results are modest and ERT is expensive, so gene therapy may be a more appropriate treatment strategy.

The UK Cystic Fibrosis Gene Therapy Consortium has pseudotyped a simian immunodeficiency viral vector with the Sendai virus F and HN proteins (rSIV. F/HN) for efficient transduction of airway epithelial cells.

Results Mice were transduced with rSIV. F/HN-hAAT (1.4e8 TU/mouse) by nasal instillation and culled 10 days post-transduction. hAAT levels in lung tissue homogenate and epithelial lining fluid (ELF) were 3 logs above controls ($p < 0.05$), and hAAT concentration in ELF was 92 ± 28 μg/ml, similar to the therapeutic hAAT level in ELF of 70 μg/ml (Figure 1). For comparison, transfection of mouse lung with cationic lipid GL67A, used in the recent Phase IIb trial of non-viral gene therapy for cystic fibrosis, complexed to plasmids carrying hAAT only led to 0.4 ± 0.1 μg/ml in ELF.

A neutrophil elastase (NE) activity assay showed that the recombinant hAAT successfully neutralised NE activity ($p < 0.05$). In a separate experiment, mice were treated with a single dose of rSIV. F/HN-hAAT (4e7 TU/mouse) and quantification of hAAT one year post-transduction showed that expression was stable over this period. Here, we also demonstrate for the first time that rSIV. F/HN transduction of lung generates significant ($p < 0.05$) levels of recombinant hAAT protein in serum.

Conclusion In conclusion, rSIV. F/HN produces therapeutically relevant and long-lasting levels of hAAT in murine lung and may offer advantages over enzyme replacement therapy. In addition, we showed that hAAT escapes from the lung into the circulation which may be relevant for a range of diseases including diabetes and graft vs. host disease.