association of premature emphysema in ZZ homozygotes who smoke.

S62 CHARACTERISATION OF A NOVEL "PSEUDO-Z" VARIANT OF α1-ANTITRYPSIN

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The Z (Glu342Lys) variant of α_1-antitrypsin is common in populations of North European descent. The mutation causes individual α_1-antitrypsin molecules to assemble into polymer chains in the endoplasmic reticulum of hepatocytes. Z homozygotes (PiZZ) have circulating levels of α_1-antitrypsin ~15% of normal and are predisposed to hepatic cirrhosis and severe, early-onset emphysema. The risk of clinically significant disease associated with the heterozygote PiMZ state is minimal. We describe a case phenotyped as PiZZ during family screening, but with surprisingly preserved circulating α_1-antitrypsin levels. Genotyping revealed compound heterozygosity for the Z mutation and a novel, "pseudo-Z" mutation. Biochemical and ion-mobility mass spectrometry characterisation of pseudo-Z α_1-antitrypsin showed that it readily populated a polymerogenic intermediate state under physiological conditions. Cell biological studies of a series of α_1-antitrypsin variants indicated these effects involved disruption of a hydrogen bond stabilising the F-helix-linker region of the protein structure. These data strongly support the hypothesis that stability of this region co-regulates formation of the polymerogenic intermediate. Whilst the intermediate form of pseudo-Z α_1-antitrypsin is more stable than that of the true Z variant, the resultant polymers all share a characteristic neoepitope. Pseudo-Z α_1-antitrypsin is thus a useful model for in vitro screening of potential lead compounds to bind the polymerogenic intermediate state, improving the ability to develop novel therapies to treat α_1-antitrypsin deficiency. Our data predict that the likelihood of severe disease in the PiZ/Pseudo-Z compound heterozygote state will be increased relative to the PiMZ state, but far lower than for PiZZ individuals.

S63 USE OF NMR SPECTROSCOPY AND NANOSPRAY MASS SPECTROMETRY TO CHARACTERISE BINDING OF LEAD COMPOUNDS FOR DRUG DESIGN IN α1-ANTITRYPSIN DEFICIENCY

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Pathogenic mutations in the gene for α_1-antitrypsin predispose to aberrant conformational transitions of the translated protein molecules resulting in their self-association to form polymer chains. Polymerisation causes circulating deficiency of α_1-antitrypsin while predisposing to hepatic cirrhosis and severe, early-onset emphysema. Targeting the conformational transitions underlying polymerisation via ligand binding and stabilisation of the physiological native state is therefore a goal of drug design in α_1-antitrypsin deficiency. To complement previous structure-led approaches we have developed NMR spectroscopy and nanospray mass spectrometry as medium-throughput screening tools for such ligands. The coupling of these techniques combines highly sensitive detection of ligand binding with assessment of binding sites, stoichiometry, cooperativity and binding constants. We have used the TTAI peptide, developed within an existing programme of drug design, as a test case. The data demonstrate highly co-operative, slow, tight binding of two copies of the peptide in adjacent parts of the α_1-antitrypsin molecule. TTAI peptide binding is shown to induce widespread conformational change all over the molecule with the exception of β-sheet C. These data prove the utility of NMR spectroscopy and nanospray mass spectrometry in characterising ligand binding whilst providing a highly detailed template for use in specific screening for TTAI peptide-mimetic compounds.

S64 CHANGES IN PHYSIOLOGICAL PHENOTYPES OF α-1-ANTITRYPSIN DEFICIENCY WITH TIME

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Chronic Obstructive Pulmonary Disease (COPD), even due to α-1-antitrypsin deficiency (A1AD), is recognised as having distinct radiological, physiological and clinical phenotypes. Little is known about disease progression in physiologically defined phenotypes.[1] We have identified a subgroup of patients with a reduced FEV_1 but normal gas transfer determined by the lower limit of normal (LLN), that is, with standardised residual (SR) value <-1.645. The current abstract reports the progression of these physiological measures with time in this subgroup.

Methods 533 patients with A1AD were studied of whom 43 had isolated FEV_1 abnormality at baseline and also had ≥3 years of complete annual follow-up data. These patients were followed for a mean of 5.9 (2.2 SD) years. Of these, 22 remained with isolated FEV_1 abnormality (Group A) whereas 21 had developed evidence of a reduced K,co deficiency (Group B). Group A and B data at baseline and at last follow-up were compared—see Abstract S64 Table 1.

Abstract S64 Table 1

	Group A Mean (SD) n=22	Group B Mean (SD) n=21
Age	53.1 (8.6)	50.4 (9.2)
Males (%)	91	71
Pack year history	20.0 (15.7)	18.1 (18.2)
Total SGRQ	56.5 (16.8)	40.8 (11.3)*
Follow-up, years	5.7 (2.5)	6.0 (1.9)
Baseline FEV_1 (L)	1.53 (0.5)	1.44 (0.5)
Baseline FEV_1 SR	−3.83 (1.1)	−3.87 (1.1)
Last FEV_1 SR	−3.95 (0.9)	−4.04 (1.1)
FEV_1 change (L/year)	−0.038 (0.03)	−0.036 (0.05)
Baseline K,co (mmol/min/kPa/L)	1.38 (0.2)	1.34 (0.2)
Baseline K,co SR	−0.53 (0.5)	−1.01 (0.5)**
Last K,co SR	−0.95 (0.7)	−2.19 (0.6)*
K,co change (mmol/min/kPa/L/year)	−0.034 (0.02)	−0.061 (0.03)**

*p<=0.001, **p<=0.005.

Results There were no differences in FEV_1, smoking, age or sex distribution between the groups. At baseline mean K,co SR was worse in Group B compared to Group A. However, Group A had significantly worse total Saint George's Respiratory questionnaire

score (SGRQ) at baseline. K,co SR significantly deteriorated in both groups during follow-up (p<0.001 in both cases) but this was not true for FEV_1 SR. Group B had a significantly faster decline in K,co than Group A (p=0.005) resulting in all values falling below the LLN.

Conclusion About half of the A1AD patients with an isolated FEV_1 abnormality at baseline have a decline in K,co faster than expected. Whether exacerbations, treatment or emphysema distribution relates to faster decline remains to be determined.

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NIV: the acute and domiciliary settings

S65 INTERIM DATA FROM A RANDOMISED CONTROLLED TRIAL OF AVERAGE VOLUME-ASSURED PRESSURE SUPPORT (AVAPS) VERSUS SPONTANEOUS-TIMED (ST) PRESSURE SUPPORT IN OBESITY HYPOVENTILATION SYNDROME (OHS)

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Introduction The obesity epidemic is leading to an increase in respiratory morbidity including sleep disordered breathing (SDB). The optimal ventilatory strategy in OHS is yet to be characterised. Changes in the respiratory system compliance through sleep and positional variations could compromise the effectiveness of fixed level pressure support thus the idea of varying pressure support to maintain tidal volume is appealing. Published data show improvements in nocturnal control of SDB in OHS using AVAPS mode ventilation (Storre *et al*, 2006) but also concerns regarding sleep fragmentation (Janssens *et al*, 2009). Data from these studies have been difficult to interpret as patient set up has not been set out to minimise the differences between modes.

Method Consecutive patients admitted for setup of domiciliary NIV were randomised to either ST or AVAPS mode (BiPAP Synchrony, Philips-Respironics, Murrysville, USA). NIV was titrated to improve nocturnal oximetry-capnometry using a standard setup protocol. Patients had baseline investigations including anthropometrics, health related quality of life and gas exchange. A subset of patients had sleep disruption monitored via actigraphy (AW64, Philips-Respironics, Murrysville, USA) in the week following discharge.

Results 50 patients were enrolled, mean age 55±11 years, 53% male, BMI 50±7 kg/m^2, $PaCO_2$ 6.85±0.81 kPa, PaO_2 8.91±1.55 kPa, ESS 12±6 with preliminary data available at 6 weeks for 43 patients, 13 were initiated acutely and 30 were elective admissions. No significant between group differences (Abstract S65 Table 1). Actigraphy analysis (AVAPS n=16, ST n=17) during 1st week of NIV showed total sleep time of 347±80 min in AVAPS and 348±78 min in ST with sleep efficiency of 81±6% in AVAPS and 79±12% in ST. Arterial blood gas analysis at 6 weeks showed no between group differences. However, significant improvement occurred in $PaCO_2$ in AVAPS patients, mean difference 0.63 kPa (p=0.013), that did not reach significance in ST, mean difference 0.55 kPa (p=0.053).

Abstract S65 Table 1

	AVAPS (n=22)	ST (n=21)
Age (years)	54±9	56±12
Gender (%male)	50	57
BMI (kg/m^2)	48±7	51±7
ESS (/24)	11±6	14±6
Baseline $PaCO_2$ (kPa)	6.93±0.77	6.77±0.85
Baseline PaO_2 (kPa)	9.08±1.14	8.72±1.91
Mean delivered Ipap	23±5	23±4
4%ODI	23±17	20±15
Mean nocturnal SpO_2	92±3	92±4
Mean $tcCO_2$	7.0±0.6	7.2±1.1
Δ$PaCO_2$ (kPa)	−0.63±1.1	−0.55±1.2
ΔPaO2 (kPa)	0.1±1.3	0.7±1.4

Conclusion The preliminary data indicate no significant sleep disruptive effect of AVAPS mode compared to ST following initiation of NIV for OHS. There was no clinically significant difference between groups in the primary outcome of change in $PaCO_2$, although there was only a significant fall in $PaCO_2$ in the AVAPS group. 3 months data are awaited.

S66 A RANDOMISED CROSSOVER TRIAL OF PRESSURE SUPPORT VENTILATION (PSV) VERSUS PRESSURE CONTROLLED VENTILATION (PCV) IN STABLE HYPERCAPNIC CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Introduction PSV, rather than PCV, is often the preferred mode of ventilatory support in stable hypercapnic COPD patients, although this is supported by limited data. We hypothesised that PCV would be equivalent to PSV with similar patient-ventilator synchrony, nocturnal ventilation, gas exchange and sleep quality with similar adherence to non-invasive ventilation and improvements in health related quality of life (HRQL).

Method HypercapnicCOPD patients (daytime $PaCO_2$ >6 kPa) were enrolled and randomised to PSV (low back up rate) or PCV for 6 weeks. Patients had baseline anthropometric, HRQL and gas exchange measurements, were re-assessed at 6 weeks and crossed over to the other arm with the final assessment at 12 weeks. Sleep quality was assessed using a sleep diary and nocturnal actigraphy (Actiwatch AW4, CamNTech, Cambridge, UK) for 2 weeks prior to each assessment. Subjective patient-ventilator synchrony was assessed with a questionnaire (Score 0–3, 0=good synchrony). At 6 and 12 weeks, all measurements were repeated, including ventilator adherence.

Results 12 patients were enrolled. However, three were unable to tolerate NIV and 1 failed to adhere to the study protocol. Four commenced on PSV and 4 commenced on PCV. Mean (±SD) age 72±8 years, BMI 32±9 kg/m^2, FEV_1/FVC 54±14%, FEV_1 29±11%, $PaCO_2$ 8.6±1.7 KPa and PaO_2 7.3±1.4 KPa. Mean IPAP 28±4 cm H_2O and mean EPAP 5±3 cm H_2O. Backup rate for PSV