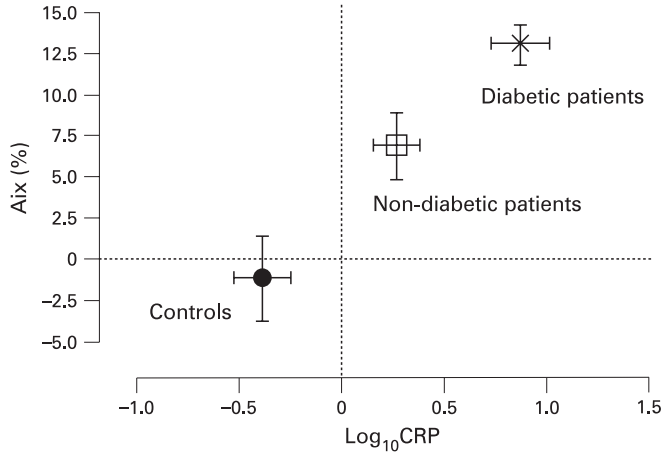

Abstract S84 Figure Relationship between Log_{10} CRP and AIx in controls (•), non-diabetic patients (□) and diabetic patients (×). Symbols represent mean values with error bars representing ±1 SEM.

inversely related to glomerular filtration rate ($r = -0.55$, $p<0.001$) but did not relate to lipid profile.

Conclusions: Adult patients with CF have evidence of premature vascular aging, as indicated by increased AIx compared with controls. This relates to systemic inflammatory mediators and diabetic status.

S85 PREDICTORS OF OUTCOME IN CYSTIC FIBROSIS PATIENTS ADMITTED TO INTENSIVE CARE

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Introduction: The decision to admit adult patients with cystic fibrosis (CF) to the intensive care unit (ICU) is controversial because of a perceived poor outcome and the likely need for prolonged multiorgan support. Although scoring systems (APACHE II, SAPS II, MODS and SOFA) are available to help predict morbidity and mortality following ICU admission for the general population, their relevance to CF patients is unknown. To look at this further, we looked at the performance of these scoring systems in patients attending our large adult CF unit.

Patients and Methods: All 10 CF patients (mean age 21 years (range 17–27), seven respiratory failures, two upper gut haemorrhages, one following thoracotomy, four male) admitted to ICU over 5 years (2002–7) formed the study population. Data on chronic disease history and acute physiological parameters were collected and scores were calculated from the ICU admission dataset.

Results: Mean ventilated days was 5 (0–12), mean ICU stay was 5.6 days (1–14) and ICU mortality was 60%. Only two patients were alive at one year. Low body weight was associated with mortality ($p = 0.02$), but the presenting complaint, spirometry, recent hospital admission, presence of diabetes, transplant listing or admission blood gases did not predict outcome. In terms of scoring systems, only SAPS II was significantly associated with mortality both on ICU ($p = 0.029$) and at one year ($p = 0.04$). Both MODS and SOFA showed a trend towards predicting outcome, but APACHE II was poor at predicting both ICU and one-year mortality in our patients.

Conclusion: CF patients admitted to ICU have a poor outcome, both immediately and within one year. With the exception of SAPS II, organ dysfunction scores used for the general population are not useful in predicting outcome in these patients. The association of low body weight with mortality again highlights the careful attention that needs to be paid to the nutritional status of CF patients.

Chronic obstructive pulmonary disease: measuring disease progression

S86 BRONCHODILATOR REVERSIBILITY AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE: RELATIONSHIP TO LUNG FUNCTION, COMPUTED TOMOGRAPHY SCANS AND PROGRESSION

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Introduction and Objectives: Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation with a post-bronchodilator FEV_1 : FVC less than 0.7.[1] Reversibility (post-bronchodilator increase in FEV_1 of 12% and 200 ml)[1] is still used to exclude a diagnosis of COPD;[2] however, recent baseline data from the UPLIFT trial have shown that the majority of patients with COPD fulfil these criteria.[3] An increase of 400 ml is considered clinically significant,[1] is highly suggestive of asthma and should be treated as such.[4] The current study explores the relationship between spirometric bronchodilator response and other lung function tests and computed tomography (CT) scans in patients with a diagnosis of COPD including a 4-year follow-up.

Methods: The study population consists of well-characterised patients with post-bronchodilator FEV_1 : FVC less than 0.7 and clinical features of COPD. Full lung function tests and CT analysis (presence of visible emphysema and densitometry) were performed at baseline and at 4 years. The results of these were compared for three groups based on FEV_1 increase post-bronchodilator: A <200 ml or <12%; B >12% and >200 ml but <400 ml; C >400 ml.

Results: There was no significant difference in smoking status, gender or age between the three groups. However, group C had a significantly greater baseline FEV_1 (% predicted) and absolute decline in FEV_1 but a lesser decline in lower zone voxel index and KCO (% predicted). In addition, group C had a greater decline in FEV_1 (% predicted), although this just fell short of the criteria for significance relative to group B ($p = 0.058$). The results are summarised in the table.

Conclusions: The majority of patients in this study exhibited a bronchodilator response supporting the findings of the UPLIFT trial.[3] The data suggest that significant bronchodilator reversibility does not reflect other differences in COPD phenotype; however, it does indicate a subgroup with a more rapid increase in airflow

Abstract S86 Table

Variable	Bronchodilator response group A	B	C
No of patients at baseline	33	38	22
FEV_1 % predicted	59.09 (4.03)	58.38 (3.03)	74.65 (4.29)*†
FEV_1 : FVC	0.47 (0.02)	0.45 (0.02)	0.51 (0.02)
KCO % predicted	90.24 (5.19)	90.42 (5.21)	94.86 (6.79)
Visible emphysema (at baseline)	44.6%	65.1%	50%
UZVI	26.91 (3.08)	28.32 (2.83)	28.00 (2.94)
LZVI	25.51 (3.02)	27.83 (2.24)	28.96 (3.00)
Change in FEV_1 (ml/year)	−29.88 (16.28)	−25.26 (9.42)	−67.35 (19.18)†
Change in FEV_1 (% predicted/year)	−0.705 (0.808)	−0.604 (0.396)	−1.989 (0.928)
Change in FEV_1 : FVC (%/year)	−4.01 (4.99)	−2.32 (2.27)	−5.10 (3.05)
Change in KCO (% predicted/year)	−2.75 (0.83)†	−0.77 (0.59)*	−0.02 (0.61)*
Change in UZVI (%/year)	+1.23 (0.74)	+0.37 (0.47)	−0.28 (0.59)
Change in LZVI (%/year)	+1.16 (0.47)	+0.52 (0.43)	−0.62 (0.89)*

Post-bronchodilator lung function values and voxel indices are from baseline and expressed as mean (standard error). *Significant difference ($p<0.05$) from group A; †Significant difference ($p<0.05$) from group B; LZVI, lower zone voxel index (−910 Hounsfield units); UZVI, upper zone voxel index (−910 Hounsfield units).

limitation (FEV_1) but less rapid deterioration of lung parenchyma (KCO and densitometry).

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2007. http://www.goldcopd.org/ (accessed Oct 2008).
2. **Currie,** *et al*. *BMJ* 2006;**332**:1261–3.
3. **Tashkin,** *et al*. *ERJ* 2008;**31**:742–50.
4. *Thorax* 2008;**63**:iv1–121.

S87 ULTRASOUND VERSUS DUAL ENERGY *X* RAY ABSORPTIOMETRY TO MEASURE THIGH MUSCLE MASS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background: Dual energy *x* ray absorptiometry (DEXA) is an established method to measure thigh muscle mass in chronic obstructive pulmonary disease (COPD). However, it is expensive, not readily accessible and involves exposure to ionising radiation. An alternative technique using ultrasonography can be used as a non-ionising, bedside method to measure quadriceps size, although its use in COPD has been limited. We used ultrasound to measure two indices of quadriceps size—muscle thickness (Qt), and cross-sectional area of the rectus femoris (Qcsa), in a group of COPD subjects. The relationships between these indices to total (T_{lean}) and thigh lean mass (Q_{lean}) measured by DEXA and to quadriceps strength were also determined.
Methods: 18 COPD patients (mean (SD) age 67.06 years (8.24), body mass index (BMI) 28.21 (5.86), FEV_1 48.83% (19.25) predicted, 11 men) underwent scans of the dominant thigh using a portable ultrasound machine (Hitachi EUB-425). With subjects in the supine position, the scanning site was identified as the mid-point between the tip of the greater trochanter and the lateral knee joint line. From frozen, real-time cross-sectional images, the outline of the rectus femoris was traced to calculate Qcsa, and Qt was measured as the distance from the superficial fat–muscle interface to the underlying femur. Scans were repeated by the same operator after a minimum of 2 days. T_{lean} and Q_{lean} were determined by DEXA, and isometric quadriceps strength was measured on an isokinetic dynamometer (Cybex II Norm) during a maximal static contraction with the knee at 70°.
Results: Mean (SD) values were as follows: Qcsa 4.72 cm^2 (1.02), Qt 22.86 mm (7.10), quadriceps isometric strength 128.72 Newton-metres (56.69), T_{lean} 48.38 Kg (11.69), Q_{lean} 4.20 Kg (1.24). Qcsa and Qt were significantly correlated to both T_{lean} and Q_{lean}, whereas quadriceps strength was only correlated to Qcsa (table). Intraclass correlation coefficients for the repeat measures of Qcsa and Qt were highly significant, indicating good reproducibility for this method ($r = 0.94$; $p<0.001$ for Qcsa and $r = 0.98$; $p<0.001$ for Qt).
Conclusions: Our data suggest that a simple bedside method using portable ultrasound can be employed to measure quadriceps size in COPD. The technique has good reproducibility and correlates well with DEXA.

Abstract S87 Table Correlations for ultrasound measurements to DEXA and quadriceps strength

	Q_{lean} (DEXA)	T_{lean} (DEXA)	Quadriceps isometric strength
Qcsa (n = 18)	0.79***	0.77***	0.50*
Qt (n = 18)	0.63**	0.64**	0.20 NS

***p<0.001; **p<0.01; *p<0.05; NS, not significant. DEXA, dual energy *x* ray absorptiometry; Qcsa, cross-sectional area of the rectus femoris; Q_{lean}, thigh lean mass; Qt, muscle thickness; T_{lean}, total lean mass.

S88 TIMED UP AND GO: AN ASSESSMENT TOOL FOR MOBILITY IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE?

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Background: The Timed up and Go (TUG) test assesses functional mobility based on the time to stand from armchair, walk 3 m, turn around, walk back and sit down.[1] The potential for its use in chronic obstructive pulmonary disease (COPD) is unclear. We determined the relationship of TUG with the incremental shuttle walking test (ISWT) and other accepted measures in COPD.
Methods: We studied 30 clinically stable male patients with COPD and 15 age-matched controls. Spirometry, oximetry, TUG, ISWT, DXA scan for bone mineral density (BMD) and body composition (Hologic, Discovery) together with circulating albumin and IL-6 were determined. Patients completed quality of life scores (SGRQ).
Results: Demographics of patients and controls are shown in the table. In patients, TUG was inversely related to ISWT ($r = -0.68$, $p<0.001$) and the following clinical parameters: FEV_1 % predicted ($r = -0.496$), oxygen saturation ($r = -0.590$) and directly to SGRQ total ($r = 0.524$) ($p<0.05$). ISWT was also related to these variables (all $p<0.05$). However, TUG was also inversely related to fat-free mass index (FFMI; $r = -0.400$), BMD of hip ($r = -0.542$) and albumin ($r = -0.509$) and directly related to log IL-6 ($r = 0.413$; $p<0.05$), whereas ISWT was unrelated to these variables ($p>0.05$).

Abstract S88 Table Demographics of patients and controls

	Patients	Controls
Age (years)	66.0 (8.5)	63.5 (5.7)
FEV_1 % predicted	63.7(17.9)	92.9 (10.6)**
FFMI (kg/m^2)	18.3 (2.4)	20.4 (1.7)*
ISWT (m)	424 (171)	563 (221)*
TUG (s)	9.7 (1.7)	8.5 (1.7)*
TUG >10 s	8/30 (27%)	3/15 (20%)
BMD Hip (g/cm^2)	0.93 (0.14)	1.05 (0.17)*
BMD lumbar spine (g/cm^2)	1.03 (0.20)	1.13 (0.22)

*p<0.05; **p<0.001. BMD, bone mineral density; FFMI, fat-free mass index; ISWT, incremental shuttle walking test; TUG, Timed up and Go.

Conclusions: The TUG test and ISWT were strongly related in male patients with COPD. Both tests had similar relationships with indicators of the severity of lung disease and health status. However, the TUG test was related additionally to indicators of musculoskeletal comorbidities and systemic inflammation. The TUG test is simpler to perform than the ISWT and may have a role in detecting reduced mobility in COPD patients that could be applied in primary care.

1. **Podsiadlo**. *D J Am Geriatr Soc* 1991.

S89 EFFECT OF AIRWAYS INFLAMMATION AND PREDNISOLONE TREATMENT ON BRONCHOALVEOLAR LAVAGE GLUCOSE CONCENTRATIONS IN ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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Background: The luminal epithelium of the respiratory tract is lined by a thin layer of liquid (epithelial lining fluid, ELF). In healthy humans ELF glucose concentrations are approximately 12.5 times lower than plasma (Baker *et al*, *J Appl Physiol* 2007;**102**:1969–75). ELF glucose concentrations are elevated 4–8-fold in patients with cystic fibrosis, but it is not known whether this is due to a

disease-specific defect of glucose transport or the general effect of lung inflammation. This study aimed to determine the effects of lung inflammation due to asthma and chronic obstructive pulmonary disease (COPD) on ELF glucose concentrations before and after prednisolone treatment.

Methods: 12 healthy volunteers (FEV_1 109 + 12% predicted), 21 COPD (FEV_1 54 + 16% predicted) and 21 moderate–severe asthma (FEV_1 59 + 14% predicted) patients underwent bronchoscopy and bronchoalveolar lavage (BAL). Venous blood and BAL fluid were analysed for glucose, urea and albumin. 13 COPD and 12 asthma patients underwent repeat bronchoscopy after 2 weeks prednisolone 40 mg/1.72 m^2 surface area.

Results: BAL glucose concentrations were significantly greater in COPD (0.12 mmol; 0.07–0.16; median (interquartile range)) and asthma (0.11 mmol; 0.06–0.13) than in healthy volunteers (0.03; 0.01–0.05; $p<0.001$, Kruskal–Wallis). Neither BAL urea ($p = 0.329$) nor BAL albumin ($p = 0.853$) differed between groups. BAL : blood glucose ratios were COPD (0.018; 0.011–0.046), asthma (0.017; 0.010–0.025), healthy volunteers (0.006; 0.003–0.010; $p = 0.001$). Neither BAL : blood urea ($p = 0.527$) nor BAL : blood albumin ($p = 0.524$) ratios differed between groups. There was no change in spirometry, systemic (C-reactive protein) or lung (BAL cell count) inflammation, BAL glucose concentrations or BAL : blood glucose ratios after prednisolone treatment.

Discussion: Low ELF concentrations are maintained by the epithelial barrier, which restricts glucose movement from blood to ELF, and by epithelial glucose transporters, which remove glucose from ELF (Kalsi *et al*. *Pflugers Arch* 2008;**456**:991–1003). Elevated BAL glucose concentrations in COPD and asthma are unlikely to be accounted for by impaired epithelial barrier function as BAL urea and albumin concentrations are not elevated. Airway inflammation in asthma and COPD may therefore impair epithelial glucose transport processes. In these patients prednisolone did not significantly reduce inflammation or improve lung function, which may have accounted for its lack of effect on ELF glucose concentrations.

S90 AIR POLLUTION AND DECLINE OF LUNG FUNCTION IN ALPHA-1-ANTITRYPSIN DEFICIENCY

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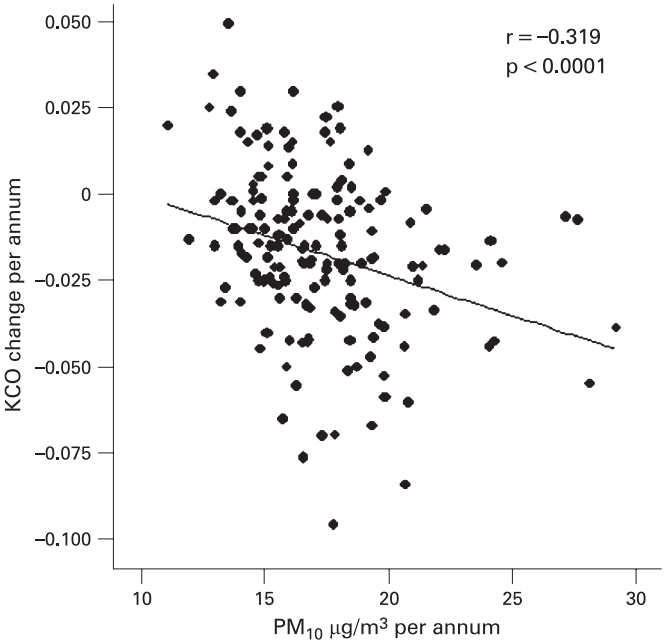
Introduction: Several outdoor air pollutants have been associated with respiratory morbidity and mortality, but specific effects can be difficult to ascertain without detailed clinical phenotyping and controlling for covariates. Patients with alpha-1-antitrypsin deficiency (AATD) exhibit faster decline of lung function than subjects with usual chronic obstructive pulmonary disease (COPD), thus represent a group in whom studies of factors influencing decline may be more sensitive.

Methods: All subjects of the PiZZ genotype from the UK AATD registry with at least four annual assessments of lung function were studied. Decline of FEV_1 and KCO for each of the resultant 220 patients was calculated using linear regression. Pollution exposure (particles, ozone, sulphur dioxide, nitrogen dioxide) from the period of decline was extracted from GIS maps, matching the measurement to the patients' home address. Clinical predictors of decline were sought using univariate models, and those significant added to multivariate models that included pollutant data. Single pollutant models were used due to multicollinearity.

Results: In the univariate models of FEV_1 decline, male gender, higher exacerbation frequency and baseline KCO were associated with more rapid decline ($p = 0.034$, 0.025 and 0.001, respectively). In similar models for KCO decline only exacerbation frequency predicted rapid decline ($p = 0.016$) although male subjects tended to decline faster ($p = 0.064$). Past cigarette smoke exposure and current smoking status were non-significant in both models. In the multivariate models no pollutants independently predicted FEV_1 decline, although baseline KCO remained predictive ($p<0.001$). Similar models for KCO decline did show an association between higher PM_{10} exposure and rapid decline ($p<0.001$), such that PM_{10} explained 9% of KCO variability (fig).



Abstract S90 Figure PM_{10} correlates with decline of KCO in AATD.

Conclusions: Exposure to ambient particulate matter predicts KCO decline in AATD, unlike smoke exposure and other covariates. FEV_1 decline is predicted by exacerbation frequency, similar to usual COPD, but also by baseline KCO, emphasising the importance of this measure in the assessment of disease.

S91 EFFECTS OF AZD9056, A P2X7 ANTAGONIST, IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Background: AZD9056 is a potent selective antagonist at the purinergic $P2X_7$ receptor, which is involved in processing and release of the pro-inflammatory cytokines IL-1b and IL-18 (Ferrari *et al*. *J Immunol* 2006;**176**:3877–83). We have shown that sputum IL-1b concentrations are increased in chronic obstructive pulmonalry disease (COPD) and may play a key pro-inflammatory role (Newbold *et al*, *Proc Am Thorac Soc* 2005;**2**:A395).

Methods: We conducted a double-blind, randomised, parallel-group, multicentre study comparing the effects of 4 weeks' treatment with oral AZD9056 400 mg daily and placebo in patients with mild/moderate COPD (GOLD stages 2–3) who produced sputum on most days. Efficacy measures included lung function (FEV_1, FVC, VC, IC, PEF), exercise tolerance (6-minute walk), symptoms (Bronkotest diary card, and BDI/TDI for dyspnoea), quality of life (SGRQ), inflammatory markers in the blood (differential leucocyte count, IL-6, IL-8, TNFα and CRP), and also in the sputum (differential leucocyte count, IL-1b, IL-8, IL-18) in a subgroup of patients. Plasma and sputum concentrations of AZD9056 were measured.

Results: 134 patients were randomly assigned to treatment, of whom 120 completed the study (60 patients were included in the sputum subgroup of whom 57 completed). Statistical analysis was

carried out on an intent-to-treat basis. AZD9056 was well tolerated, with similar numbers of adverse events (none serious) occurring in each treatment group; consistent with other studies, gastrointestinal side effects were more common in the AZD9056 group. AZD9056 was measurable in the sputum. However, no statistically or clinically significant effects of AZD9056 were seen on any of the clinical outcome measures, nor on cellular or soluble inflammatory markers in blood or sputum (including sputum IL-1b concentrations).

Discussion: The lack of clinical benefit seen in this study was disappointing, particularly since a 4-week phase 2a study of AZD9056 in patients with rheumatoid arthritis (RA), another disorder associated with elevated IL-1b concentrations, showed significant positive clinical effects (McInnes *et al*. *Arthritis Rheum* 2007;**56**:s793). It may be that in COPD, in contrast to RA, other pathways of IL-1b production are more important than $P2X_7$ receptor activation.

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Bio-markers in pulmonary vascular diseases

S92 PULMONARY ENDOTHELIAL CELL SECRETION OF FACTOR VIII

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Introduction: Activated factor (F)VIII is responsible for sustained intravascular generation of thrombin via its role as a cofactor for FIXa in the coagulation cascade. Elevated plasma levels of FVIII are a strong predictor of recurrent venous thromboses/pulmonary emboli and are associated with thromboembolic pulmonary hypertension. The sources of plasma FVIII have remained elusive. Having demonstrated that FVIII levels are elevated in hereditary haemorrhagic telangiactasia associated with pulmonary arteriovenous malformations (Shovlin *et al*. *Thromb Haemost* 2007), we tested the hypothesis that human pulmonary artery endothelial cells (HPAEC) secrete FVIII and compared expression patterns with three other primary endothelial cell types under basal and stimulated conditions.

Methods: Primary human endothelial cells (Promocell) were cultured in individual wells of BD Falcon Culture Slides, fixed and permeablised with methanol. Wells were treated with one of four hybridoma-derived murine anti-human FVIII:Ag monoclonal antibodies and rabbit-raised anti-von Willebrand Factor (vWF), anti-calnexin or anti-COPII. Primary antibodies were detected with Alexa-Fluor labelled anti-rabbit or anti-mouse IgG. Stained cells covered with Vectashield were imaged on an LSM 510 Zeiss inverted fluorescence confocal microscope using sequential acquisition and LSM Image Browser software. Prior to immunohistochemistry of lung tissue blocks, antigen retrieval methods were optimised using paraffin-embedded formalin-fixed blocks derived from cultured HPAEC. FVIII secretion into conditioned media was quantified by ELISA (Immunobind, Axis-Shield) using manufacturer's protocols.

Results: All four anti-FVIII antibodies to both heavy and light FVIII chains demonstrated significant reactivity in HPAEC. In contrast to reported retention of endogenous FVIII in hepatocyte endoplasmic reticulum (ER) (Becker *et al*. *Thromb Haemost* 2004), in HPAEC there was limited colocalisation with calnexin. Colocalisation was observed with COPII demonstrating ER–Golgi traffic and in some cells, with vWF-containing Weibel Palade bodies. FVIII expression differed markedly between different endothelial cell types. Following 48 h of culture, secretion of FVIII into conditioned media was demonstrable. Immunohistochemistry confirmed FVIII staining of CD31-positive pulmonary endothelial cells in surgically resected lung tissue.

Conclusion: Pulmonary endothelial cells secretion of factor VIII may be relevant to intravascular prothrombotic states.

S93 INVESTIGATION OF THE PROTEASE/ANTIPROTEASE BALANCE IN THE BRONCHOALVEOLAR LAVAGE FLUID OF PATIENTS WITH WEGENER'S GRANULOMATOSIS

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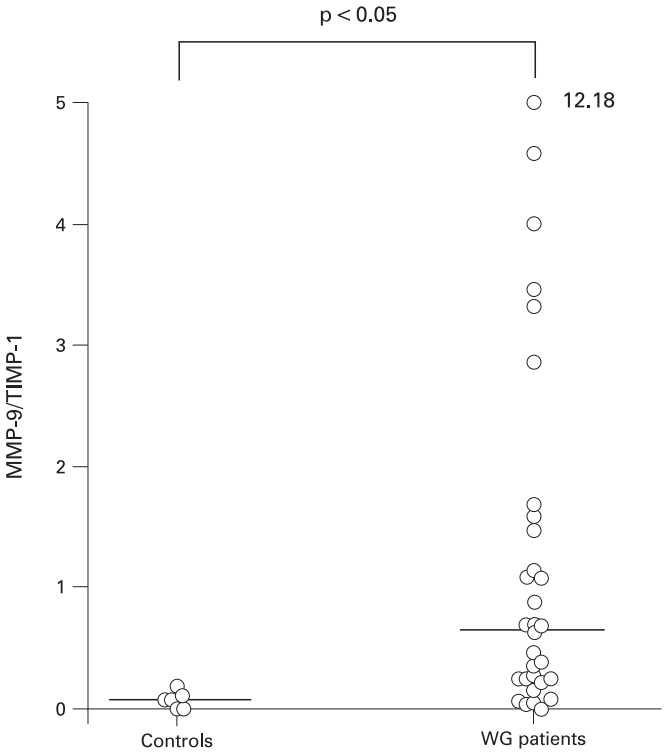
Wegener's granulomatosis (WG) is a multisystem necrotising vasculitis of small arteries and veins that is characterised by granuloma formation. Recent studies have suggested that significant numbers of WG patients have abnormal lung function particularly of the small airways. This is thought to be due to the abnormal airway remodelling seen in this condition. Remodelling of the airways may be related to an imbalance in the protease/anti-protease ratio such as is thought to be present in chronic obstructive pulmonary disease (COPD). The aim of this study was to determine whether there is an imbalance in the MMP-9/TIMP-1 axis in these patients.

Method: Bronchoalveolar lavage fluid (BALF) samples from 31 WG patients were analysed and compared with six healthy controls. MMP-9 and TIMP-1 concentrations were determined by ELISA and the molecular profile of MMP-9 was analysed by zymography.

Results: MMP-9 was significantly higher in patients with WG than in controls, with median values of 6.31 vs 0.38 ng/ml ($p<0.05$). The ratio of MMP-9/TIMP-1 was also elevated in WG patients (median 0.65 vs 0.08, $p<0.05$), respectively. Interestingly, a large variation was seen throughout the WG samples that remained even once MMP-9 was corrected for total protein. Patients in all disease stages (acute, relapse and remission) had elevated MMP-9/TIMP-1 ratios when compared with controls with median values of 0.27, 0.88 and 0.69, respectively. MMP-9 levels positively correlated with neutrophil count in the BALF (Rho 0.493 and $p<0.05$). WG patients with bronchiectasis on HRCT had significantly higher levels of MMP-9 than those without (median 251 vs 4.37 ng/ml, $p<0.05$). Zymography showed that both active and pro-MMP-9 are elevated in WG patients (see fig).



Abstract S93 Figure MMP-9/TIMP-1 ratio. Shows the MMP-9/TIMP-1 ratio in the samples. Samples have been split into controls and WG patients. Individual patients are shown as an open circle and the solid bar represents the median. A value of $p<0.05$ was accepted as statistical significance.