inflammatory response, accumulates in the lungs of mice infected with *S pneumoniae* correlating with the onset of neutrophil extravasation. We tested the hypothesis that gal-3 reduces the severity of pneumococcal pneumonia by augmenting neutrophil function using both in vivo and in vitro techniques. In vivo, gal-3 deficient (gal-3-/-) mice develop more severe pneumonia following *S pneumoniae* infection, as demonstrated by increased bacteraemia and lung damage compared with wild-type mice. In vitro we show that gal-3 directly acts as a neutrophil-activating agent and potentiates the effect of fMLP, exogenous gal-3 augments neutrophil phagocytosis of bacteria and delays neutrophil apoptosis, phagocytosis of apoptotic neutrophils by gal-3-/- macrophages is less efficient compared with wild type, gal-3 demonstrates bacteriostatic properties against *S pneumoniae*. Furthermore, add-back of recombinant gal-3 in vivo protects gal-3-/- mice from developing severe pneumonia. Together, these results demonstrate that gal-3 is a key molecule in the host defence against pneumococcal infection. Therapeutic strategies designed to augment gal-3 activity may both enhance inflammatory cell function (by directly affecting neutrophil responsiveness and prolonging neutrophil longevity) and have direct bacteriostatic activity, improving clinical outcomes after severe pneumococcal infection.

S120 THE *STREPTOCOCCUS PNEUMONIAE* CAPSULE IS ESSENTIAL FOR EVASION OF ALVEOLAR MACROPHAGE-MEDIATED PULMONARY IMMUNITY

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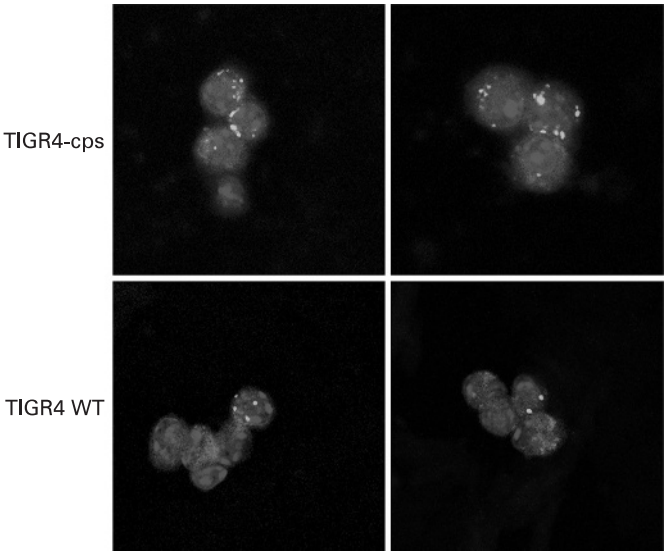
Introduction: Although the *Streptococcus pneumoniae* capsule is known to be an essential virulence factor, there are surprisingly few data on how the capsule prevents pneumonia. We have therefore investigated the effects of the *S pneumoniae* capsule on complement-dependent phagocytosis and on interactions with alveolar macrophages (AM) in a mouse model of pneumonia.
Methods: Using encapsulated and genetically engineered unencapsulated *S pneumoniae* strains from two serotypes (2 and 4) the following experiments were performed using flow cytometry and confocal microscopy: C3b/iC3b deposition on bacteria in human serum; phagocytosis by a macrophage cell line and neutrophils extracted from human volunteers (using cytochalasin D and trypan blue to differentiate between phagocytosis and adherence to cell surfaces); phagocytosis by mouse AM 6 h post-intranasal inoculation of bacteria into wild-type and complement-deficient mice. In addition the rate of clearance of bacteria from the lungs was assessed.
Results: C3b deposition was markedly increased on unencapsulated compared with encapsulated strains (eg, relative fluorescence index (RFI) of C3b deposition of 211 130 ± 19 227 vs 11 378 ± 1814, respectively, for the serotype 4 strain). Unencapsulated bacteria were more readily phagocytosed by neutrophils than encapsulated bacteria (proportion of neutrophils associated with bacteria 49 ± 1.56 vs 17 ± 0.6, respectively, for the ST4 strain) and these differences were mainly complement dependent. Furthermore, unencapsulated bacteria stimulated greater nuclear transfer of nuclear factor kappa B (NFκB) in macrophages than encapsulated bacteria (median of nuclear : cytoplasmic ratio for unencapsulated of 4.096 (interquartile range (IQR) 3.32–4.664) vs 2.943 (IQR 2.719–3.122) for encapsulated strain). Within 6 h of intranasal inoculation there was a marked increase in phagocytosis by AM of the unencapsulated (RFI of 2498 ± 615) compared with encapsulated (RFI 9349 ± 3404) (fig), and this was associated with rapid clearance of unencapsulated bacteria (>3 $\log_{10}$ fewer unencapsulated bacteria for the serotype 4 strains) from lavage fluid. Interestingly, repeated experiments with complement-deficient mice demonstrated that the effect of the capsule on interactions with AM was only partly complement dependent.
Conclusions: These data demonstrate that capsule is vital for *S pneumoniae* evasion of early pulmonary immune responses by inhibiting complement-dependent and independent interactions with AM.



Ex vivo alveolar macrophages from CD1 mice inoculated intra-nasally with FAM-SE labelled bacteria and harvested after 4 h (red = F4/80, blue = Dapi, green = FAM-SE)

Abstract S120 Figure

Clinical investigation of pulmonary vascular diseases

S121 COMPUTERISED TOMOGRAPHY PULMONARY ANGIOGRAPHY: SIGNIFICANT SECONDARY FINDINGS AND QUANTIFYING THE ADDED BURDEN TO RESOURCES

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Introduction and Objectives: Paralleling the increased use of computerised tomography pulmonary angiography (CTPA) in the investigation of pulmonary thromboembolsm (PTE) is anecdotal evidence that there has been an increased subsequent demand particularly on radiology resources as a result of incidental or co-lateral findings. Presently we set out to quantify and investigate the nature of these investigations with an evaluation of return on investment.
Methods: All 252 CTPA undertaken over a 12-month period to 31 December 2007 for primary exclusion of PTE were identified. The median age of patients was 69 years (range 18–98) with 148 (59%) women. Supporting data were gathered retrospectively from the hospital PACS radiology reporting system, from e-script electronic result reports and discharge summaries.
Results: Although 83/252 (33%) had confirmed PTE on CTPA, from the group as a whole (n = 252), additional diagnoses other than PTE were also reported in 136 (54%) patients and in whom for 91/252 (36%) this was a new and significant finding. Comparatively, more of these additional outcomes were reported in the group with no PTE (103/169 (61%) vs 33/83 (40%), p = 0.002). Analysed together, these additional findings included consolidation (10%), emphysema (9%), primary lung carcinoma

(4%), lung metastases (4%), mediastinal lymphadenopathy (4%), pleural thickening (4%), pleural effusions (4%) and lobar/segmental collapse (3%). Follow-up investigations, excluding plain chest radiology, were undertaken in 30/136 (22.1%) of those with reported abnormal CTPA, with further staging or high resolution computerised tomography (CT) (14%), fibreoptic bronchoscopy (9%), chest or abdominal ultrasound (3%) and cardiac echo (2%). Collectively, initial CTPA and subsequent investigations identified eight new diagnoses of primary lung carcinoma, nine of lung metastases, 10 of mediastinal lymphadenopathy and nine pleural effusions.

Conclusions: CTPA reports generate concerns about new diagnoses in a significant proportion of patients and the anecdotal evidence regarding added workload seems to be well founded with, in particular, the number of malignancies detected inadvertently. With the increased use of CT services further resources will also have to be matched to maintain and drive standards. The disparity in reporting findings between scans in which PTE is found and not, is not explained here but may be a bias in reporting and requires further evaluation.

S122 IDENTIFYING LOW-RISK PATIENTS WITH PULMONARY EMBOLISM SUITABLE FOR OUTPATIENT TREATMENT: A VERITY REGISTRY PILOT STUDY

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Background: The British Thoracic Society guidelines for the management of suspected acute pulmonary embolism (PE) recommend that the ''current organisation for outpatient management of DVT should be extended to include stable patients with PE''. Five years later, outpatient treatment is not widely accepted, largely because no explicit clinical criteria exist to identify low-risk patients accurately. However, recent studies suggest that the pulmonary embolism severity index (PESI) accurately identifies low-risk patients.

Methods: Four hospitals enrolling patients in VERITY (a UK multicentre observational registry aiming to assess and improve venous thromboembolic event outpatient treatment practice) volunteered to participate in this pilot study to assess the potential accuracy of the PESI to predict 3-month mortality. Centres provided completed case report forms after retrospective review of patients' notes on a total of 176 consecutive PE patients who had been in their care. The diagnosis had been confirmed by objective diagnostic testing. These patients do not represent an outpatient population, although some of these cases were treated as outpatients. Using baseline data, we calculated the PESI risk class for each patient (class I–V) and assigned patients as low risk (risk classes I and II) or high risk (risk classes III–V). We calculated the sensitivity and specificity of the PESI; the accuracy of the index to classify patients was tested by receiver operating characteristic (ROC) curve analysis, plotted as 1 specificity versus sensitivity for 3-month all-cause mortality and the area under the curve (AUC) was estimated using the Wilcoxon non-parametric approach.

Results: Overall mortality at 3 months was 4.5% (8/176), and ranged from 0% to 10.8% (7/65) across the four centres. There were no deaths in the low-risk group (0/111); overall mortality was 12.3% (8/65) for high-risk patients. The sensitivity of the PESI was 1 (0.63 to 1 (97.5% one-sided CI)); the specificity was 0.64 (95% CI 0.56 to 0.71). The AUC of the ROC curve was high (0.90; 95% CI 0.83 to 0.96).

Conclusions: This pilot study suggests that the PESI accurately identifies PE patients at low risk of death. Prospective assessment will be undertaken by the VERITY registry at centres moving to an outpatient (or short hospital stay) model for PE treatment.

S123 THE EFFECT OF THE ENDOTHELIN-1 DUAL RECEPTOR ANTAGONIST, BOSENTAN, ON PLATELET FUNCTION

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Background: The pathogenetic role of platelet activation in pulmonary arterial hypertension (PAH) is not clear. Platelets are activated in PAH and may influence endothelial cell dysfunction. Advanced therapies for PAH, such as prostacyclin, inhibit platelet function. However, the effect of endothelin 1 (ET-1) and endothelin receptor antagonists on platelet function remains unclear.

Aim: To assess the effect of the dual endothelin receptor antagonist, bosentan, on platelet function in normal volunteers (and patients with PAH).

Methods: In vitro platelet aggregation was performed on 10 normal volunteers. Lumi-aggregation was used with collagen (2 μg/ml) as the agonist, before and after bosentan (1 μmol final concentration) spiking. In vivo platelet aggregation with collagen (2 μg/ml) has been tested, to date, on seven PAH patients. Venesection prior to commencing bosentan, 4 h after administration and one month after chronic dosing was performed.

Results: Impedance aggregation in the healthy volunteers was 17.38 ± 5.3 ohms at baseline, and was significantly lower at 3.75 ± 4.4 ohms following bosentan spiking ($p \leqslant 0.001$). In the seven PAH patients studied (idiopathic PAH, n = 1; Eisenmenger complex, n = 2; chronic thromboembolic disease, n = 4), impedance aggregation with collagen fell non-significantly from baseline at 12.86 ± 10.51 ohms, to 2.8 ± 6.26 ohms at 4 h (n = 5; $p = 0.06$). At day one, impedance aggregation was significantly lower than baseline (mean 3.43 ± 5.74; n = 7; $p = 0.02$), but at one month, this difference was non-significant (7.40 ± 10.85; n = 5; $p = 0.06$).

Conclusion: These findings support the concept that bosentan has an antiplatelet aggregatory effect in vitro and in vivo. Larger in vivo studies are necessary to confirm this finding and to study longer-term in vivo antiplatelet effects.

S124 STROKE VOLUME RESPONSE TO UPRIGHT EXERCISE IN PULMONARY HYPERTENSION

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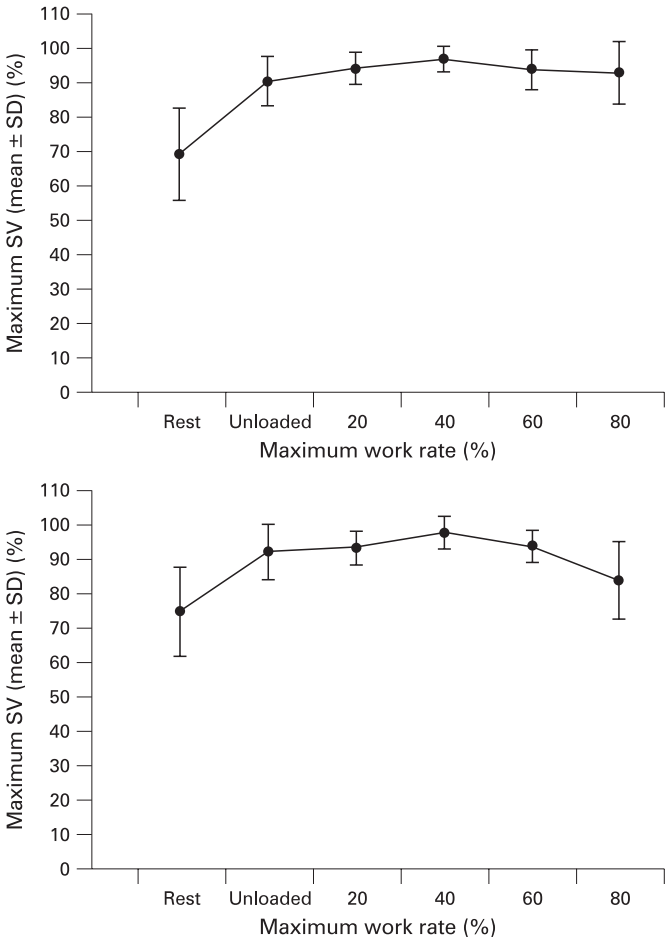
Background: In healthy subjects cardiac output and heart rate (HR) increases linearly with exercise intensity, whereas stroke volume (SV) plateaus at approximately 40% of maximal exercise tolerance. This is due to progressive restriction in ventricular diastolic filling at high exercise levels. The aim of this study was to determine the relationship between stroke volume and work rate in patients with pulmonary hypertension (PH).

Methods: 10 healthy subjects and eight patients with PH underwent an incremental cycle ergometer cardiopulmonary exercise test to determine the maximum work rate (WR_{max}) they could achieve. They then underwent a stepwise cardiopulmonary exercise test in which they cycled for 3 minutes unloaded and at 20%, 40%, 60% and 80% WR_{max}. SV was derived from HR and pulmonary blood flow using the inert gas rebreathing technique (Innocor) at each step during exercise.

Results: Patients with PH had lower SV at rest and during exercise than healthy subjects (mean SV index at rest 27.5 ± 6.5 (SD) vs 40.9 ± 9.1 ml m^{-2}, $p = 0.001$; at 40% WR_{max} 36.5 ± 9.7 vs 57.3 ± 8.8 ml m^{-2}, $p = 0.001$). In both healthy and PH subjects, SV represented as a percentage of the subject's maximum peaked at 40% WR_{max} (97 ± 3.5% healthy vs 98 ± 4.8% PH). At 80% WR_{max}, SV maintained peak levels in healthy subjects but fell in PH patients (93.2 ± 9.0% healthy vs 84.1 ± 11.2% PH).



Abstract S124 Figure

Conclusions: SV peaked at 40% WR_{max} in both healthy subjects and PH patients. This is of interest as it demonstrates that it would be possible to use SV during submaximal exercise as a marker of right heart function in PH patients. In addition, SV declined at exercise intensities greater than 40% WR_{max} in PH patients but not in healthy subjects. This probably reflects greater dependence on diastolic filling to augment cardiac output response to exercise in PH patients.

S125 INCREMENTAL SHUTTLE AND 6-MINUTE WALK TESTS: CORRELATIONS WITH PULMONARY HAEMODYNAMICS AND CARDIOPULMONARY EXERCISE TESTING IN PULMONARY HYPERTENSION

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Introduction: The 6-minute walk test (6MWT) is widely used in patients with pulmonary hypertension (PH). Its role in the clinical and research setting has, however, been questioned. The incremental shuttle walking test (ISWT) is an externally paced field test that has been used in other cardiopulmonary diseases. We hypothesised that the ISWT could provide an alternative exercise field test in PH.

Methods: Pulmonary haemodynamics, walk test and cardiopulmonary exercise testing (CPET) results were compared for 20 patients with PH (10 idiopathic pulmonary arterial hypertension (PAH), five chronic thromboembolic pulmonary hypertension, four systemic sclerosis PAH and one portopulmonary PAH). All exercise testing was performed within 3 days of right heart catheterisation. Each test was performed twice, with the greater of the two distances for each test being used in the analysis. To reduce the impact of coexisting respiratory disease on exercise capacity, patients were excluded if their FEV_1 or FVC was less than 60% of predicted values.

Results: Both walk tests correlated with CPET parameters measured at anaerobic threshold (oxygen consumption vs ISWT $r = 0.792$; vs 6MWT $r = 0.584$; work rate vs ISWT $r = 0.879$; vs 6MWT $r = 0.684$; ventilatory efficiency vs ISWT $r = -0.668$; vs 6MWT $r = -0.645$; ventilatory equivalent for CO_2 vs ISWT $r = -0.675$; vs 6MWT $r = -0.653$). Peak oxygen consumption, however, only correlated significantly with ISWT ($r = 0.55$). More modest correlations between mean pulmonary artery pressure (mPAP), cardiac index (CI) and pulmonary vascular resistance (PVR) and ISWT were observed (ISWT vs mPAP, $r = -0.495$; vs CI, $r = 0.447$; v PVR, $r = -0.538$). 6MWT had similar correlations with mPAP ($r = -0.448$) and PVR ($r = -0.538$); however, it did not correlate significantly with CI ($r = -0.355$, $p = 0.124$).

Conclusions: The ISWT correlated at least as strongly as the 6MWT with pulmonary haemodynamics and CPET parameters. Although several variables (eg, oxygen consumption, work rate and CI) did appear to correlate more strongly with ISWT than with the 6MWT, due to small patient numbers no confident conclusions regarding superiority could be made. The findings do, however, support further investigation of the use of the ISWT in the initial and subsequent assessment of patients with PH.

S126 TROPONIN AND D-DIMER LEVELS CORRELATE WITH SEVERITY IN PATIENTS PRESENTING WITH ACUTE PULMONARY EMBOLISM

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Introduction: D-dimer, cardiac troponins and C-reactive protein (CRP) are routinely measured in patients presenting with suspected pulmonary embolism (PE). The aim of this study was to assess whether admission levels of these biomarkers are associated with severity of PE.

Methods: A retrospective analysis of 337 acute admissions with confirmed PE on computerised tomography pulmonary angiogram (CTPA). Exclusion criteria were: recurrent thromboembolic disease, thrombophilia or prior anticoagulation; recent surgery; concomitant inflammatory disease and previous evidence of right ventricular/biventricular failure. Admission levels of D-dimer, CRP and troponin I were recorded. The presence of right ventricular strain on CTPA was judged independently by two experienced radiologists. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the area under the receiver operator characteristic curve (AUC) were used to assess the performance of predictive biomarkers. The Kruskal–Wallis test was used for comparison of tests. The outcomes of interest were 30-day mortality and development of right ventricular strain determined by CTPA.

Results: 337 patients were included in the study. Overall 30-day mortality was 8.1% and 29% of patients had evidence of right ventricular strain on CTPA. 73.1% of patients had a D-dimer greater than 1000 ng/ml, 20.3% of patients had a troponin greater than 0.02 μg/l and 36.8% of patients had a CRP greater than 100 mg/l. The predictive value of D-dimer, troponin and CRP for these cut-offs is shown in the table.

Discussion: Admission D-dimer and troponin levels are predictive of severity in patients presenting with PE. D-dimer less than 1000 ng/ml has a high negative predictive value for PE with accompanying right ventricular strain and 30-day mortality and thus may be useful to identify low-risk patients. A raised troponin

Abstract S126 Table Biomarkers and prediction of right ventricular strain and 30-day mortality

	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	AUC	p Value
Prediction of right ventricular strain on CTPA						
D-dimer ⩾1000 ng/ml	32.8	97.0	95.1	44.9	0.74 (0.70 to 0.78)	<0.001
Troponin ⩾0.02	74.2	70.3	51.1	86.7	0.69 (0.65 to 0.73)	<0.001
CRP >100 mg/l	10.5	91.8	25.0	79.8	0.55 (0.50 to 0.60)	0.3
Prediction of 30-day mortality						
D-dimer ⩾1000 ng/ml	10.4	95.7	86.7	28.2	0.70 (0.62 to 0.78)	0.01
Troponin ⩾0.02	15.2	97.0	58.3	80.7	0.70 (0.62 to 0.78)	0.02
CRP >100 mg/l	15.0	89.3	31.0	76.6	0.54 (0.48 to 0.59)	0.5

AUC, area under the receiver operator characteristic curve; CRP, C-reactive protein; CTPA, computerised tomography pulmonary angiogram; NPV, negative predictive value; PPV, positive predictive value.

may be more useful to identify high-risk patients. CRP has no value in prediction of severity for patients with PE. Further prospective studies are required to establish if troponin or D-dimer can be used to guide risk stratification of patients presenting with PE, either alone, or in combination with clinical prediction scores.

S127 COMPARISON OF THE BRITISH THORACIC SOCIETY RECOMMENDED, WELLS' AND MODIFIED GENEVA SCORES FOR ASSESSING CLINICAL PROBABILITY OF PULMONARY THROMBOEMBOLISM

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Introduction: Suspected pulmonary thromboembolism (PTE) is a common admission to acute medical units (AMU) and that often causes diagnostic uncertainty. The British Thoracic Society (BTS) PTE guidelines recommend a clinical probability score, which includes a subjective element, in the assessment of suspected PTE. However, two predictive rules more commonly recognised are the Wells' rule, including a subjective element, and the modified Geneva score, which is entirely standardised. Wells' and Geneva scoring have previously been found to be comparable. The BTS score offers the advantage of simplicity. We assessed the predictive accuracy and the concordance of the three prediction rules: Wells', modified Geneva and BTS recommended.
Methods: We prospectively studied consecutive admissions with suspected PTE, over 12 weeks, to a city teaching hospital without D-dimer availability. Clinical probability was assessed prospectively with the three prediction rules.
Results: Eighty patients were included; 60% women. The median age was 53 years (interquartile range 41–69). The overall prevalence of PTE was 10%. The BTS score produced the highest sensitivity (75%; 95% CI 35% to 97%) and negative predictive value (97%; 95% CI 89% to 99%) for PTE with a high probability score. The sensitivity of a high Wells' (25%) and Geneva (12.5%) score was markedly lower, but failed to reach significance. Receiver operating characteristic curve showed a greater area under the curve (AUC) with the BTS score than Geneva or Wells' (AUC being 0.84, 0.74 and 0.69, respectively). Concordance between Wells' and Geneva scoring was moderate (weighted kappa coefficient 0.52). However, poorer concordance was evident between BTS and Geneva or Wells' (kappa 0.23–0.25). All extreme disagreements in individual patient scores occurred between the BTS and either Wells' or Geneva.
Conclusion: This study suggests that the BTS recommended probability score for suspected PTE may have superior performance compared with the two more complex, yet widely recognised, predictive rules. Confirmation in a larger prospective cohort is recommended. D-dimers were not available within our unit, as is the situation in a number of UK hospitals; however, future comparison should also assess the probability scores in combination with D-dimers.

Cellular mechanisms in chronic lung disease

S128 ALVEOLAR SEPTAE IN SEVERE END-STAGE EMPHYSEMA SHOW MORPHOLOGICAL EVIDENCE OF DYSREGULATED MESENCHYMAL CELL PROLIFERATION AND LOSS OF MICROVASCULARITY

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Emphysema is defined as permanent enlargement of alveolar air spaces with loss of alveolar wall connectivity. This definition does not reflect the true complexity of histological phenotypes seen. In particular, septal thickening and matrix deposition have been recognised in alveolar septae. Changes in microvascular density also occur in alveolar septae and we therefore hypothesised that alteration in the phenotype of septal remodelling may be related to the loss of alveolar microvascularity.
Methods: Lung tissue resections were obtained from patients undergoing lung transplantation for emphysema (n = 9) and compared with archival "normal" tissue obtained from lung cancer resections. All material was examined using haematoxylin and eosin stained sections to establish variations in lesion phenotypes. Mesenchymal cell distribution, matrix deposition and microvascularity were assessed by α-SMA, collagen I and CD31 immunohistochemistry, respectively. All emphysema lung material presented with wide heterogeneity in lesion phenotypes and so all of the section was examined.
Results: All emphysema sections presented with classic (distended, thin, disconnected) alveolar septae with focal areas of mesenchymal cell and matrix deposition. Thickened septae were also a very common feature in the emphysema group and more marked than in control samples. Two phenotypes were seen: acellular thickening, occupying the whole of the septal unit and a "reticular" pattern of mesenchymal cells and matrix occupying the external facets of the septal wall. Within these thickened zones there was loss of the normal anatomy of the microvasculature, with CD31 immunoreactivity seen as granular deposits within the expanded collagen zones or focal regions abutting the septal margins.
Conclusions: We suggest that the focal areas of mesenchymal cell and collagen deposition associated with thin septae may reflect a dysfunctional attempt at repair, possibly reflecting shear-stress responses consequent upon changes in lung biomechanics. By contrast, the thickened septae showed an amplified mesenchymal and collagen response. This may reflect a continuum with the focal reactions, a development that may be amplified by the loss of microvascularity. These observations suggest that the loss of microvascularity may be associated with a change in the repair phenotype and may thus provide insights into the detailed microanatomy of emphysema progression.