234. Phenotyping asthma: a clue for treatments?

1871

Late-breaking abstract: Genome-wide association of *GLCCI1* with asthma steroid treatment response

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Background: Asthma treatment response is characterized by wide inter-individual variability and a significant number of non-responders.
Aims: We hypothesized that a genome-wide association study would yield novel determinants of inhaled glucocorticosteroid (ICS) response in asthma.
Methods: We analyzed change in FEV_1 following ICS usage in a small number of statistically powerful variants selected via a family-based screening algorithm on 534,290 single nucleotide polymorphisms genotyped in the Childhood Asthma Management Program. Finding a significant, replicated association, we characterized its functional effects.
Results: We identified a significant pharmacogenetic association at rs37972, which was replicated in four independent populations totaling 935 individuals (p=0.0007). This variant maps to the glucocorticoid induced transcript 1 *(GLCCI1)* gene and is in complete linkage disequilibrium (i.e., perfectly correlated) with rs37973; both are associated with decrements in *GLCCI1* expression. In isolated cell systems the rs37973 variant is associated with significantly decreased luciferase reporter activity; in pooled data from treatment trials patients with the variant allele have reduced FEV_1 responses to ICS (pooled p=0.0007). Overall, subjects homozygous for the mutant rs37973 allele had only 1/3 the FEV_1 increase on inhaled corticosteroids vs. those homozygous wild type (3.2±1.6% vs. 9.4±1.1%), accompanied by a significantly higher risk of a poor (i.e. lowest quartile) response (OR 2.36, 95% CI: 1.24-4.51), with genotype accounting for ~6.6% of response variability.
Conclusion: A functional *GLCCI1* variant is associated with substantial decrements in inhaled glucocorticosteroid response in asthma.

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Frequent exacerbators – A distinct phenotype of severe asthma

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In order to analyse exacerbations, 93 patients with severe asthma (SA) and 76 with mild-to-moderate asthma (MA) were screened and followed up for 1 year in the BIOAIR European multicentre study. Severe asthma has been defined by use of high doses of inhaled corticosteroids (≥1600 μg of budesonide or equivalent) and despite this treatment at least 1 exacerbation in the year preceding the start of the study. Risk factors for frequent exacerbations (FE) (defined as either ≥2 or ≥3 events/year) were evaluated.
In total, 122 exacerbations were recorded, including 104 events in 52 SA patients (55.9% of SA cohort) and 18 events in 16 MA (22.2% of MA cohort). The average rate of exacerbations was 1.1 events per patient per year in SA and 0.2 events in MA. Significant decrease in PEF values, FEV_1, increase in rescue medication use, day and night symptoms during exacerbations were recorded ($p<0.05$). All FE were found only in SA, not MA group. Juniper ACQ score, sputum eosinophils≥2%, smoking history, quality of life, and $FEV_1 \leq 70\%$ were associated with the development of exacerbations in FE defined as ≥2 events/year (odds ratios OR: 5.06, 4.38, 3.48, 2.48, 2.34, respectively, $p<0.05$). BMI>25, quality of life, smoking and Juniper ACQ score were risk factors for exacerbations in FE defined as ≥3 events/year (odds ratios OR: 8.07, 6.7, 4.25, 4.14, respectively, $p<0.05$).
Frequent exacerbators represent a distinct phenotype of severe asthma group. Identification of factors associated with a higher risk of exacerbations enables us to improve the standards of every day care in this subgroup of patients.
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1873

Is hypereosinophilic asthma a specific phenotype of asthma?

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Introduction: Blood eosinophilia $>1000/mm^3$ in patients with asthma should evoke particular forms of the disease, especially Churg-Strauss Syndrome (CSS) and allergic bronchopulmonary aspergillosis (ABPA). Little is known about patients who do not fulfill criteria for these diseases, usually referred as Hypereosinophilic Asthma (HA).
Aim of the study: To describe clinical and functional characteristics of patients with HA and to assess the prevalence of CSS and ABPA in asthma patients with blood hypereosinophilia.
Methods: Retrospective study of 79 adult asthma patients with blood eosinophils count $>1000/mm^3$, compared with a control group of 30 asthma patients without blood hypereosinophilia ($<1000/mm^3$), defined as Non hyperEosinophilic Asthma (NEA)
Results: 90% of patients and 100% of controls had severe asthma, according to GINA. Main characteristics of the 4 groups are available on table 1.

	HA, n=47 (59%)	CSS, n=18 (23%)	ABPA, n=14 (18%)	NEA, n=30	p
Age(mean±SD)	55±3	51±2	64±3	55±7	<0.01
Sex (% of female)	57.4%	55.6%	71.4%	72.4%	<0.01
Total blood IgE (UI/l)	528±143	770±199	1940±650	483±218	<0.01
Blood eosinophils count (/mm^3)	2295±337	7180±1780	2570±272	258±147	<0.01
Nasal polyposis (% patients)	36%	50%	21%	18%	<0.01
Atopy (% of patients)	42%	33%	75%	65%	<0.01
Daily oral steroids use (% patients)	28%	100%	50%	30%	<0.01

HA, Hypereosinophilic Asthma; CSS, Churg-Strauss Syndrome; NEA, Non Eosinophilic Asthma.

Conclusion: When compared with the NEA group, HA seems to represent a subgroup of patients, mostly male, characterized by non atopic disease and high prevalence of nasal polyposis. CSS and HA share many similarities, suggesting an overlap between the diseases in some cases.

1874

Exhaled nitric oxide levels differ between allergic and non-allergic asthma in men, but not in women

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Introduction: Several studies have shown potential gender specific differences in the pathophysiology and clinical presentation of asthma, whose mechanisms are not fully understood.

Aims and objectives: We examined the effect of gender on differences in eosinophilic airway inflammation between steroid-naïve adults with allergic and non-allergic asthma.
Methods: The subjects comprised 191 Japanese adults [67 men and 124 women, median (range) age 51 (20-88) years] with asthma who were untreated with glucocorticosteroids and during attack-free periods. We used the levels of fractional exhaled nitric oxide (FeNO) as a marker of eosinophilic airway inflammation. The FeNO concentration was measured using the recommended online method. We compared the levels of FeNO between patients with allergic and non-allergic asthma, separately for men and women.
Results: In 67 men, 49 allergic patients had significantly higher FeNO levels compared with 18 non-allergic patients (53.9±54.6 versus 28.3±18.8 ppb, respectively; *P*=0.005); in 124 women, there was no significant difference in FeNO levels between 76 allergic and 48 non-allergic patients (38.0±37.0 versus 33.5±26.3 ppb, respectively; *P*=0.4).
Conclusions: Our results suggest that the importance of eosinophils in airway inflammation differs between allergic and non-allergic asthma in men, but not in women. Other inflammatory cells than eosinophils alone may play a major role in the pathogenesis in men with non-allergic asthma.

1875
Does systematic assessment improve healthcare outcomes and healthcare utilisation in patients with severe asthma?
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Introduction: The management of severe asthma remains a significant problem in terms of patient symptoms, quality of life, effects of high dose oral corticosteroid therapy and emergency healthcare utilisation.The key to the effective management of severe asthma lies with making the correct clinical diagnosis. A systematic approach to aid effective diagnosis, identify co-morbidities and evaluate adherence was first introduced in 1993 and is now widely used. Little published data currently exists on the longer term benefits of utilising a systematic approach.
Methods: A retrospective audit of 68 patients that underwent a systematic assessment protocol at the Royal Brompton Hospital between April 2009 & March 2010 was performed. The magnitude of improvement in asthma related quality of life, exacerbation frequency, emergency healthcare utilization and oral corticosteroid requirements was assessed.
Results: The table below represents a selection of demographic data, confirmation of diagnosis, mortality rate, discharge and lost to follow up rates. Further data is currently being analysed and will be presented at the congress including the outcomes for quality of life, healthcare utilization and changes to treatment regimes.

Baseline data from systematic assessment of asthma

Gender	Confirmation of diagnosis	≥1 co-morbidity	Lost to follow up	Discharged	Died
Male 25 (37%)/Female 43 (63%)	59 (87%)	34 (58%)	5 (7%)	5 (7%)	1 (1.5%)

Conclusion: Systematic assessment of patients with difficult asthma identifies an alternative diagnosis in 13% of patients and one or more co-morbidity in 58% of patients referred to the difficult asthma service at the Royal Brompton Hospital.

1876
Improvement of asthma control by a concomitant therapy with cineole
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With its proven mucolytic and anti-inflammatory effects it is hypothesized that cineole, the main constituent of eucalyptus oil, improves asthma control. In a double blind, placebo controlled multi-centre-study 247 patients with symptomatic asthma were randomly administered 3x200 mg of cineole (n: 126;mean age, 52.3 years) or a placebo (n:121;mean age,53.5 years), per day as a concomitant therapy over 6 months.
The combined primary outcome measures, which were implemented as a multiple criteria testing process were: improvement of FEV1, asthma symptoms and quality of life (AQLQ). Secondary outcome measures included changes in hypersecretion, various respiratory symptoms, and the use of ICS.
Results: 1.Patients treated with cineole showed significantly more improvements to the multiple testing criteria (i.e. improvement of FEV1,p=0.0398; mean improvement of AQLQ, p=0.0475; symptom score of nocturnal asthma, p=0.0325) as compared to placebo group, (p= 0,0027, Wei Lachin test).
2. Secondary outcome measures supported these findings showing reduced dyspnea and cough as well as overall better health condition amongst the cineole treatment group.
3. Adverse events were comparable in both groups.
Conclusion: Concomitant therapy using cineol can lead to improvement in asthma symptoms, lung function and quality of life. This study underlines the fact that cineole actively controls airway inflammation in patients with asthma, and that it is more that simply a mucolytic drug.

1877
Pragmatic controlled trial of azithromycin for asthma in adults
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Background: Macrolides are a novel treatment for asthma.
Aims: To investigate macrolide effects after treatment.
Methods: Randomized (RAND), placebo-controlled, double-blind parallel group, practice-based trial of azithromycin (AZ), 600 mgm for 3 days, then weekly for 11 weeks or placebo (PLA) with follow up 1 year from randomization. Eligible subjects who declined randomization received open-label (OL) azithromycin.
Results: Compared to RAND, OL subjects had more adult-onset asthma, chronic sinusitis, severe persistent asthma and hospitalizations for asthma. Compared to PLA, OL subjects had significant improvements in asthma symptoms and quality of life (QOL) at 1 year (9 months post-treatment). AZ subjects did not have comparable benefits (Table).

Outcomes at 1 year compared to pretreatment

Mean paired difference (SD)	PLA, n=20	AZ, n=29	OL, n=13	P-value, OL v PLA
Overall asthma symptoms	–0.10 (1.07)	–0.07 (0.88)	–1.07 (0.95)	0.011
Control	–0.45 (1.00)	–0.34 (0.88)	–1.08 (1.20)	0.132
QOL	0.40 (1.33)	0.50 (1.10)	1.70 (1.42)	0.015

The proportions of subjects achieving a QOL score change ≥1 unit at 9 months (6 months after finishing treatment) were 22% for PLA, 27% for AZ and 80% for OL (P<.001 compared to PLA). At 1 year the comparable figures were 21%, 36% and 54% (P=.072).
Conclusions: OL subjects had severe asthma and persisting benefits, number needed to treat (NNT) = 2 to 4. AZ subjects had milder asthma and did not show benefits, although this study was not powered to detect the NNT = 7 suggested by some results. Azithromycin should be considered as adjunctive therapy for severe asthma unresponsive to guideline treatments. Larger studies are warranted to confirm results in severe asthma and to explore potential benefits in milder asthma.

1878
Persistent asthma and long-term work disability
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Backround: Mortality in asthma is very low but the disease has effects on quality of life and work ability. Here, the probability of long-term work disability associated with asthma alone or asthma together with chronic comorbidity(ies) was studied.
Methods: A total of 2 332 asthmatic employees in public sector in Finland were analysed for long-term (≥90 days) work disability. Employees without asthma were used as control subjects (N=66 354) and were adjusted for age, gender, socioeconomic status, type of employment contract and type of organization. Diagnosis of asthma was based on reimbursement for asthma medication granted by the Social Insurance Institution and data on all sickness absences were obtained from national registers. Six main disease categories were used in this study as comorbidity for asthma: depression, ischemic heart disease, diabetes, rheumatic disease, malignancy and hypertension. Diagnoses for comorbidities were based on the reimbursement for disease medication by the Social Insurance Institution.
Results: Asthma increased the risk of all-cause work disability with HR 1.8 (95% CI 1.6-2.1) compared to controls (no asthma). Asthma and one other chronic co-morbidity increased the risk for work disability with HR 2.2 (95% CI 1.8-2.8). Asthma together with two or more other chronic conditions increased the risk with HR 4.5 (95% CI 3.0-6.8). Depression together with asthma increased the risk of long-term work disability by threefold compared to those without asthma.
Conclusions: Asthma alone or together with another chronic comorbidity increased the risk of long-term work disability and the risk was especially high for those with asthma and depression.

235. Imaging in COPD

1879

Assessment of relative regional lung compliance in patients with COPD

Alexandra Morgan[1,2], Geoff Parker[1,2], Penny Hubbard[1,2], David Singh[2,3], Jørgen Vestbo[2,3], Simon Young[4], Eva Bondesson[5], Lars Wigström[5], Lars Olsson[6], Marietta Scott[7], Josephine Naish[1,2]. *[1]Imaging Sciences, School of Cancer and Enabling Sciences, University of Manchester, Manchester, United Kingdom; [2]Biomedical Imaging Institute, University of Manchester, Manchester, United Kingdom; [3]Airway Pharmacology Group, School of Translational Medicine, University Hospital of South Manchester, Manchester, United Kingdom; [4]AstraZeneca, R&D, Charnwood, United Kingdom; [5]AstraZeneca, R&D, Lund, Sweden; [6]AstraZeneca, R&D, Mölndal, Sweden; [7]AstraZeneca, R&D, Alderley Park, Macclesfield, United Kingdom*

Pathologically altered lung mechanical properties are difficult to assess regionally. A method has been developed utilising structural proton MRI in conjunction with post-processing and image registration techniques to provide measures of relative regional lung compliance [1].

This method was applied in 23 COPD patients and 11 healthy controls. Each subject had two supine scans, 1 week apart. Compliance maps were found to be reproducible, with increased spatial heterogeneity seen in patients compared to controls (Figure 1).

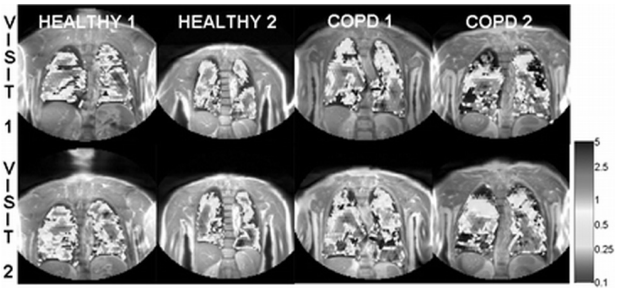


Figure 1. Relative regional compliance maps for healthy controls and COPD patients (mapped on log scale).

The gradient of relative compliance from lung apex to diaphragm was calculated. An increased compliance gradient was seen in moderate COPD ($p<0.05$), with a more significant increase in severe COPD ($p<0.001$) (Figure 2).

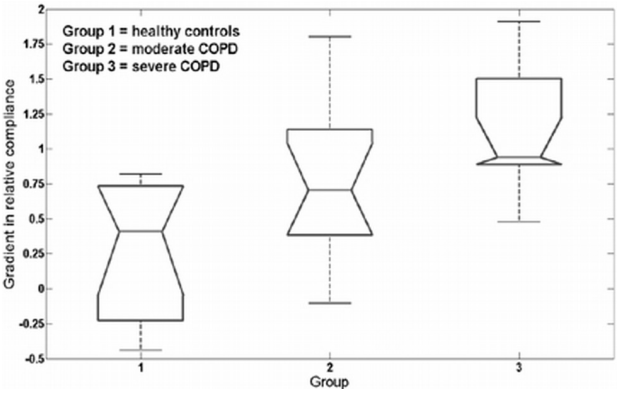


Figure 2. Box plot of relative compliance gradients (found using regional relative compliance and position as fraction of lung length).

The method shows significant differences between COPD patients and healthy controls with areas of altered relative regional compliance indicating likely regions of disease.

Reference:

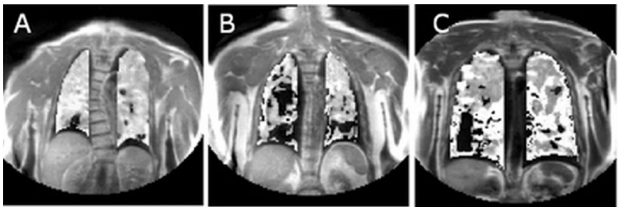
[1] Morgan, A.R. et al. Proc ISMRM 2010; p.2520.

1880

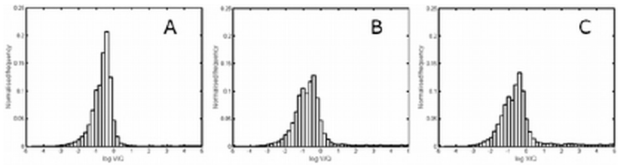
Novel ventilation-perfusion ratio measurements in COPD using MRI

Penny L. Hubbard[1,2], Geoff J.M. Parker[1,2], Dave Singh[3], Jørgen Vestbo[2,3], Eva Bondesson[4], Lars E. Olsson[4], Lars Wigström[4], Simon S. Young[5], Josephine H. Naish[1,2]. *[1]Imaging Sciences, School of Cancer and Enabling Sciences, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom; [2]The Biomedical Imaging Institute, University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom;[3]Airway Pharmacology Group, School of Translational Medicine, University Hospital of South Manchester, Manchester, United Kingdom; [4]AstraZeneca, R&D, Mölndal, Sweden; [5]AstraZeneca, R&D, Alderley Park, Macclesfield, United Kingdom*

We present a novel analysis of oxygen-enhanced (OE)MRI data in COPD that allows quantitative ventilation-perfusion ratio (V/Q) maps to be determined. Representative V/Q maps of: *A* healthy; *B* moderate & *C* severe COPD subjects reveal homogeneous maps for *A* and considerable heterogeneity in *B/C*.



Group-average histograms (labelled as above) show a narrow peak in *A*; the peak broadens and a lower V/Q peak becomes evident in *B/C*. A high V/Q tail is also seen in *C*.



OEMRI parameters, enhancing fraction (EF) and interquartile range (IQR) V/Q, show significant differences between *A* & *B/C*. Each group had 12 subjects, data averaged over 2 scans. Using a single slice, minimum group sizes to detect a 50% difference of the healthy group window are 27 (EF) & 14 (IQR V/Q). Power calculations are specific to this implementation of the methods, we envisage improvements with further development.

Group mean and SD for OEMRI parameters

	Healthy	Moderate	Severe
EF	0.87±0.06	0.70±0.09*	0.68±0.11*
IQR-V/Q	0.55±0.13	0.80±0.16*	0.81±0.12*

*Significantly different to healthy ($p<0.05$).

The results show strong similarities to published literature using more invasive techniques and enable powering of future intervention studies.

1881

Repeatability of MR imaging in chronic obstructive pulmonary disease (COPD)

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Purpose: COPD is a broad disease entity defined by PFT, however providing only a global measure of the disease. With the increasing number of therapeutic options, particularly when it is advanced, there is a high demand for a non-invasive imaging test to identify different phenotypes providing regional information on structural and functional changes in order to target therapies accordingly. Recent developments have opened the way for introduction of proton MRI of the lung into the clinical arena. This technique allows for radiation free assessment of the above mentioned issues. So far, no data regarding the repeatability of this technique is available.

Materials/Methods: A comprehensive MR protocol (1.5T) was developed to investigate different aspects of the disease. The protocol consisted of morphological, pulmonary perfusion, cardiac function and respiratory dynamics sequences. Overall, 9 patients (COPD stages III&IV) were investigated twice in a 24h interval.

Results: The mean examination time was 64min and all patients tolerated the examination well. Visual evaluation of morphological and perfusion sequences demonstrated a good repeatability of the visualization of the parenchymal loss and perfusion defects. Quantitative evaluation of flow measurements revealed considerable variations (interexamination difference for the PA flow: 7-64ml). Evaluation of the respiratory dynamics showed a broad variation allowing for no meaningful interpretation.

Conclusions: Overall, the proposed imaging protocol is feasible and applicable even in significantly ill COPD patients. The protocol is easy to use and shows a high repeatability in the key aspects for assessment of morphological and functional disease components.

1882

Ventilation-perfusion mismatch in COPD with or without emphysema: Comparison of structural CT and functional OE-MRI

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Single-slice conoral oxygen-enhanced MRI (OE-MRI) images were acquired in 24 patients with chronic obstructive pulmonary disease (COPD) and 12 healthy subjects, from which color-coded V/Q maps were extracted by pixelwise model fitting. COPD were structurally classified by percentage of low attenuation areas under -950 HU (LAA%) in matched single-slice CT images: LAA%≤1%–non-emphysema (n=8), >1%–emphysema (n=16).

V/Q maps in COPD were much more heterogeneous than those in healthy subjects, while they showed similar or mildly lower heterogeneity in non-emphysematous COPD than in emphysematous COPD, which demonstrates that comparative V/Q mismatch exists in COPD even if there is no emphysema. To explore potentially different structure-function relationship in two COPD types, correlation between CT and OE-MRI parameters was measured. Median V/Q did not correlate with LLA% in COPD. However, inter-quartile range of V/Q, representing the extent of heterogeneity, was fairly correlated with LLA% in emphysematous COPD (r=0.449, p=0.017), indicating V/Q mismatch in COPD gets worse as emphysema increases. However, the correlation was not found in non-emphysematous COPD.

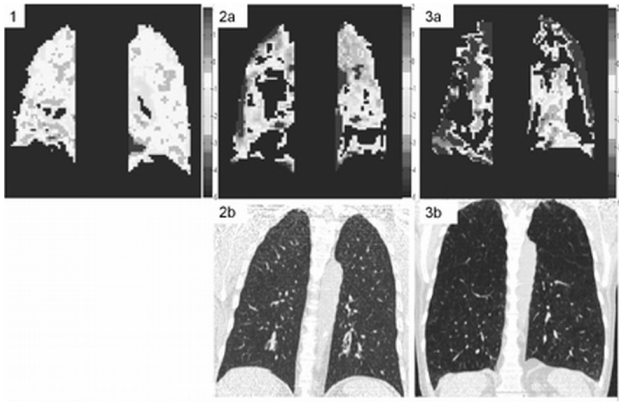

Fig1: V/Q map of a male healthy subject (69 yrs, FEV1%=117%,). Fig 2a and 2b: the V/Q map and matched CT image of a male COPD patient without emphysema (64yrs, FEV1%=65%, LAA%=0.74%). Fig 3a and 3b: the V/Q map and matched CT slice of a male COPD patient with emphysema (63yrs, FEV1%=26%, LAA%=41.78%). CT was not performed in healthy subjects.

This study elucidates that distinction between emphysematous COPD and non-emphysematous COPD does not affect the presence of V/Q imbalance substantially but that the relationship between V/Q and CT measures does vary between these two types.

1883

Decline in lung density is accelerated in active smokers

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Background: Emphysema is associated with rapid decline in lung density; however, this decline may be influenced by other factors including smoking habits.
Objective: To compare the annual decline in lung density between current and ex-smokers with or without airflow obstruction (AFO).
Material and methods: As part of the Danish Lung Cancer Screening Trial, 2,052 current or ex-smokers aged 50-70 years were screened annually for 5 years (2005-2009) with low dose CT. At annual screening rounds, smoking habits were recorded; carbon monoxide level in exhaled breath was measured; and spirometry was performed. CT lung density was measured as the volume-adjusted 15th percentile density (PD15). The influence of sex, age, smoking and AFO on PD15 was analysed in a mixed effects model with random intercept and random slope of time effect. Former smoking men with less than 30 pack-years and with no AFO at entry were chosen as reference group.
Results: Data were analysed for all subjects throughout the study although censored after they changed their smoking habit. At study entry, 1075 subjects did not have AFO and 843 subjects had AFO based on GOLD spirometry criteria. For the reference group, PD15 was (mean±SE) 72.4±0.8 g/L, and was higher in women (17.0±0.6 g/L); and in active smokers (10.5±0.7 g/L); and lower in subjects with AFO (–3.4±0.6 g/L). Annual decline in PD15 for the reference group was –0.38±0.08 g/L/yr and was higher in women, with additional (0.30±0.07 g/L/yr), current smokers with additional (0.53±0.08 g/L/yr) and for subjects with AFO with additional (0.34±0.07 g/L/yr).
Conclusion: Active smoking, female sex and the presence of airflow obstruction are associated with accelerated decline in lung density.

1884

The relationship between airflow limitation and quantitative computed tomographic assessment of air trapping and emphysema

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Background: Small airways disease and emphysema are the main components of airflow limitation in COPD. The independent contribution of quantitative CT measurements of these components to airflow limitation in COPD is yet unknown.
Purpose: To determine to what extent the combination of quantitative CT measurements of air trapping and emphysema can explain the variance in lung function in a population that covers the total spectrum of airflow limitation.
Methods: We studied 248 subjects (50 without airflow limitation; 50 GOLD 1; 50 GOLD 2; 50 GOLD 3; 48 GOLD 4) with paired inspiratory and expiratory CT scans and pulmonary function tests. We calculated CT emphysema (2 methods) and CT air trapping (4 methods), and used univariate and multivariate linear regression analysis to relate the quantitative CT measurements to lung function parameters (FEV_1, FEV_1/FVC, RV/TLC and Kco).
Results: Quantitative CT measurements were strongly related to airflow limitation; the best univariate R-square value was 0.72 ($p<0.001$) for percentage of voxels <-850 Hounsfield units (EXP_{-850}) and FEV_1/FVC. In multivariate analysis (corrected for sex, age and height) the combination of CT emphysema and CT air trapping explained 68% to 83% ($p<0.001$) of the variance in lung function parameters of airflow limitation (FEV_1 and FEV_1/FVC).
Conclusion: Quantitative CT air trapping and CT emphysema measurements are strongly associated with lung function impairment, and when combined they explain a large part of the variance in airflow limitation. Our results may prove useful in automated detection and phenotyping of COPD cases.

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Computer modelling and visualisation of the microscopic distributions of hyperpolarised gas diffusivity in models of acinar airways

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Diffusion MRI using hyperpolarized gases is sensitive to lung microstructure. Computer simulations used to investigate the relationship between diffusivity (ADC) and airway dimensions are generally limited by non-realistic geometric assumptions (e.g. infinite cylindrical airways). In this work, we use histology sections to generate realistic models of acinar airways that are used in finite element computer simulations of ^{3}He and ^{129}Xe gas diffusion and ^{129}Xe exchange between gas and tissue.
Results:

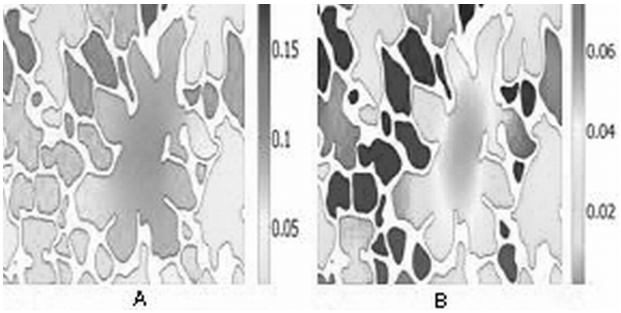

Figure 1. The different diffusivities of ^{3}He (A) and ^{129}Xe (B) result in different ADC (in cm^2/s) distributions.

For ^{3}He, the distribution over the largest airway is nearly uniform due to motional averaging. For ^{129}Xe, its reduced diffusivity limits the mixing between intra and extra-alveolar gas resulting in a non-uniform distribution, which can be described with a two-compartment analytical model.
These results suggest that ^{129}Xe MRI may be more sensitive to alveolar structure than ^{3}He, while being less sensitive to branching and localized diffusion effects.

Conclusion: Computer simulation and visualization of maps of microscopic diffusivity distributions in realistic acinar geometries have helped provide a better understanding of the length scales and diffusion regimes relevant to hyperpolarized gas lung MRI and may help simplify the development of ^{129}Xe-based MR lung morphometry techniques.