234. Phrenotyping asthma: a clue for treatments?

1871 Late-breaking abstract: Genome-wide association of GLCCI1 with asthma steroid treatment response

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Introductions: Blood eosinophils >1000/mm3 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 hyper eosinophilia.

Methods: Retrospective study of 79 adult asthma patients with blood eosinophils count >1000/mm3, compared with a control group of 30 asthma patients without blood hyper eosinophilia (<1000/mm3), defined as Nonhyper eosinophilic 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.

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 polypsis. 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-naive adults with allergic and non-allergic asthma.

Methods: The study comprised 191 Japanese adults (67 men and 124 women, median (range) 51 (20-88) years) with asthma who were untreated with glucocorticosteroids and during attack-free periods. We used the levels of fractional 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 38 non-allergic patients (33.9±5.64 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.

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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 and March 2010 was performed. The magnitude of improvement in asthma related quality of life, exacerbation frequency, emergency healthcare utilisation 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 being analysed and will be presented at the congress including the outcomes for quality of life, healthcare utilisation and changes to treatment regimes.

Baseline data from systematic assessment of asthma

<table>
<thead>
<tr>
<th>Gender</th>
<th>Confirmation ≥ 1</th>
<th>Lost to Discharged Died of diagnosis co-morbidity follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male 25 (37%)/Female 43 (63%)</td>
<td>59 (87%)</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>

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

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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 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).

Secondary outcome measures supported these findings showing reduced dyspnea and cough as well as overall better health condition amongst the cineole treatment group.

Conclusion: Concomitant therapy with cineole 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.
Assessment of relative regional lung compliance in patients with COPD
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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).

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).

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

Reference:

Novel ventilation-perfusion ratio measurements in COPD using MRI
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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.

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.
VENTILATION-PERFUSION MISMATCH IN COPD WITH OR WITHOUT EMPHYSEMA: COMPARISON OF STRUCTURAL CT AND FUNCTIONAL OE-MRI

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Single-slice coronal 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 (LLA%) in matched single-slice CT images: LLA% ≤1% - non-emphysematous COPD (n=8), >1% - emphysematous COPD (n=16).

V/Q maps in COPD were 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.

Results:

Fig 1: 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%, LLA%=74.5%). Fig 3a and 3b: the V/Q map and matched CT slice of a male COPD patient with emphysema (57yrs, FEV1%=26%, LLA%=41.7%). 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.

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, 1,075 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±0.6 g/L, and was higher in women (17.6±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/Lyr and was higher in women, with additional (0.30±0.07 g/Lyr), current smokers with additional (0.53±0.08 g/Lyr) and for subjects with AFO with additional (0.34±0.07 g/Lyr).

Conclusion: Active smoking, female sex and the presence of airflow obstruction are associated with accelerated decline in lung density.

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 (FEV1, FEV1/FVC, RV/TLC and Kco).

Results: Quantitative CT measurements were strongly related to airflow limitation, with the best univariate R-square value was 0.72 (p<0.001) for percentage of voxels <{-850 Hounsfield units (EXP-850)} and FEV1/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 (FEV1, FEV1/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.

COMPUTER MODELLING AND VISUALISATION OF THE MICROSCOPIC DISTRIBUTIONS OF HYPERPOLARIZED 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 3He and 129Xe gas diffusion and 129Xe exchange between gas and tissue.

Results:

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Oriental Presentation
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.