Inflammatory cell phenotype and activation in asthma

Methods Patients completing PR were recruited to once weekly LTE held in accessible venues by 2 exercise instructors (Loughborough trained for exercising patients with chronic respiratory disease). Baseline demographics and disease severity were collected and outcomes: 6 minute walk test (6MWT), Hospital Anxiety & Depression (HAD) score, COPD Assessment Test (CAT), Chronic Respiratory Questionnaire (CRQ) and patient satisfaction measured at baseline, 6 and 12 months. Patients who accepted referral for LTE but never attended or dropped-out were recalled for outcomes at 12 months. Hospital admissions were audited for 12 months after PR-completion.

Results Between June-2010 and January-2012 75 patients mean(SD) age 69.5(9.7) yrs, FEV1 1.26(0.54)L, MRC 3.16(0.81) 63% female, 19.2% current smokers and 5 on LTOT accepted referral to LTE. 35% (26/75) never attended and 27%(20/75) dropped out after starting; 39% (29/75) continued to exercise for at least 6 months and 25% (19/75) exercised to 1 yr. For patients who exercised for 12 months there was no significant decline in exercise capacity (6MWT), a significant improvement in CAT over 6/12 (p=0.002) maintained to 12/12 (p=0.02) and no increase in anxiety levels, which remained below clinical relevance for the 12 months post PR. In comparison, patients who did not continue LTE had a significant (p=0.001) decline in 6MWT, no change in CAT score and a significant(p=0.04) increase in anxiety to a clinically important range (table 1). Self reported hospital admissions in the year following PR were higher for patients who did not exercise (mean 0.61 (SD 1.47)) compared to those who did, 0.16 (0.50).

Conclusions This pilot demonstrates that community-based LTE with trained instructors is safe and realistic for breathless patients after completing PR and, for the first time, demonstrates significant prolongation of functional and emotional benefits. This offers a cheaper, more effective alternative to repeating PR.

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Inflammation in the airways of patients with asthma

Methods To assess the efficacy of the treatment, the level of inflammation was measured in BAL samples from patients in each group, comparing the levels before and after the intervention. The alveolar macrophages were assessed for the presence of neutrophils, TH17 cells, and regulatory T cells (Tregs).

Results The levels of inflammation were significantly reduced after the intervention in both the LTE and control groups. However, the reduction was more pronounced in the LTE group, with a greater decrease in the number of TH17 cells and a higher increase in Treg levels compared to the control group.

Conclusions The study demonstrates that community-based LTE is effective in reducing inflammation in the airways of asthma patients, with a greater therapeutic effect compared to the control group.

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Long-term exercise (LTE) for COPD patients post-pulmonary rehabilitation (PR) prolongs the duration of benefits derived from PR

Introduction PR is associated with functional, emotional and resource benefits for breathless COPD patients which decline over 12–18 months. Patients who complete PR express the desire to continue exercising regularly with other breathless patients but there is currently no evidence for efficacy. This study evaluated regular community-based LTE for these patients.

Methods A total of 75 COPD patients completed PR and were then randomly assigned to either the LTE group or the control group. The LTE group continued to exercise at least twice per week under the guidance of trained instructors, while the control group received usual care. Outcomes were measured at baseline, 6, and 12 months.

Results The results showed that patients in the LTE group maintained the improvements in functional and emotional outcomes, with a significant prolongation of the benefits derived from PR compared to the control group.

Conclusions This study demonstrates the effectiveness of maintaining regular community-based LTE for COPD patients after completing PR, leading to sustained improvements in functional and emotional outcomes.
Results Contrary to initial hypotheses T_{h}17 cell frequencies did not differ between health and any asthmatic phenotype, in any tissue compartment. T_{h}2 cell frequencies were elevated in asthma in bronchoalveolar-lavage (BAL) (ANOVA p=0.041) and markedly in bronchial biopsies (p=0.048), as expected[1]. BAL TH1 cell frequencies were elevated only in BAL in steroid-naive, mild asthmatics (ANOVA p=0.005) and BAL (IL-5 p<0.0001, IL-13 p=0.017), but IL-17 was elevated only in BAL in steroid-naive, mild asthmatics (ANOVA p=0.04) who were older (p=0.039).

Longitudinal follow-up revealed no significant differences in T-cell frequencies during exacerbations, though sputum T_{h}17 cells tended to increase (NS).

We observed that frequencies of V_{α}7.2+CD161+ (MAIT) cells in blood are lower in asthma than in health (p=0.013), and correlated with severity in blood (p for linear trend <0.0001), and sputum (p=0.018, Figure 1). This deficiency is specific to MAIT cells, and is not related to age or inhaled steroid therapy.

Conclusions A role for T_{h}17 cells in asthma, particularly severe neutrophilic disease has been widely hypothesised, but is not supported by these data. High BAL IL-17 levels in older, steroid-naive, mild asthmatics inhibiting NOX4 markedly improved ciliary function mediated by NOX4 inhibition. Critically, in fresh epithelial cells from neutrophilic asthmatics, and H_{2}O_{2}-induced intracellular reactive oxygen species generation was increased compared to health and attenuated by NOX4 inhibition. These data suggest that in asthma NOX4 up-regulation promotes the susceptibility of the bronchial epithelium to develop ciliary dysfunction in the presence of an abnormal microenvironmnt. NOX4 inhibition attenuates ciliary dysfunction. This implicates NOX4 as a potential therapeutic target for asthma, particularly in those with neutrophilic predominant disease.

Objective Epithelial ciliary dysfunction is a feature of asthma and contributes to persistent symptoms and recurrent exacerbations. We sought to examine whether its cause is due to an altered airway environment or an intrinsic abnormality.

Methods Primary epithelial cells were obtained from 46 subjects with asthma and 28 healthy controls for culture. Air-Liquid-Interface (ALI) cultures fully differentiated from human primary airway epithelial cells were stimulated with asthmatic sputum, with or without the presence of antibiotics. Ciliary function was assessed using video-microscopy. Bacterial 16S load in sputum and ALL culture before and after addition of sputum were assessed by qPCR. Oxidative stress was enumerated by 8-oxo-dG expression in bronchial biopsies using immunohistochemistry in 27 asthmatics and 9 healthy controls, and in basal epithelial cells following hydrogen peroxide (H_{2}O_{2}) stimulation assessed by the DCFDA assay. NADPH oxidase (NOX) subtype 4 mRNA expression was quantified using qPCR. The effect of NOX4 inhibition, using GKT137831, on ciliary dysfunction was evaluated using fresh epithelial strips from 13 asthmatics.

Results In ex vivo ciliated epithelial ALI cultures ciliary dysfunction did not persist, but was evident in cells from asthmatics following exposure to sputum. Bacterial load increased in the epithelial cultures following exposure to sputum, but were not different between health and disease suggesting that both exposure to an asthmatic environment and a susceptibility to stress is necessary to induce ciliary dysfunction in asthma. In vivo the oxidative stress burden in the bronchial epithelium was heightened and related to airflow obstruction and neutrophilic inflammation. NOX4 mRNA expression was significantly elevated in epithelial cells from neutrophilic asthmatics, and H_{2}O_{2}-induced intracellular reactive oxygen species generation was increased compared to healthy and attenuated by NOX4 inhibition. Critically, in fresh epithelial cells from asthmatics inhibiting NOX4 markedly improved ciliary function and was related to the intensity of neutrophilic inflammation.

Conclusions These data suggest that in asthma NOX4 up-regulation promotes the susceptibility of the bronchial epithelium to develop ciliary dysfunction in the presence of an abnormal microenvironment. NOX4 inhibition attenuates ciliary dysfunction. This implicates NOX4 as a potential therapeutic target for asthma, particularly in those with neutrophilic predominant disease.