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Two variants of occupational asthma separable by exhaled breath nitric oxide level

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Summary

Exhaled nitric oxide (FE_{NO}) has been used as a marker of asthmatic inflammation in non-occupational asthma, but some asthmatics have a normal FE_{NO}. In this study we investigated whether, normal FE_{NO} variants have less reactivity in methacholine challenge and smaller peak expiratory flow (PEF) responses than high FE_{NO} variants in a group of occupational asthmatics. **Methods:** We measured FE_{NO} and PD₂₀ in methacholine challenge in 60 workers currently exposed to occupational agents, who were referred consecutively to a specialist occupational lung disease clinic and whose serial PEF records confirmed occupational asthma. Bronchial responsiveness (PD₂₀ in methacholine challenge) and the degree of PEF change to occupational exposures, (measured by calculating diurnal variation and the area between curves score of the serial PEF record in Oasys), were compared between those with normal and raised FE_{NO}. Potential confounding factors such as smoking, atopy and inhaled corticosteroid use were adjusted for.

Results: There was a significant correlation between FE_{NO} and bronchial hyper-responsiveness in methacholine challenge ($p = 0.011$), after controlling for confounders. Reactivity to methacholine was significantly lower in the normal FE_{NO} group compared to the raised FE_{NO} group ($p = 0.035$). The two FE_{NO} variants did not differ significantly according to the causal agent, the magnitude of the response in PEF to the asthmagen at work, or diurnal variation.

Conclusions: Occupational asthma patients present as two different variants based on FE_{NO}. The group with normal FE_{NO} have less reactivity in methacholine challenge, while the PEF changes in relation to work are similar.

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Introduction

Measurement of exhaled breath nitric oxide (FE_{NO}) has been promoted as a measure of airway inflammation in asthma.^{1–4} It has been shown to be correlated with sputum eosinophilia and non-specific reactivity in asthmatics^{2,4–12} but has the advantages of being less invasive for the patient and less labour intensive for the clinician. However, some symptomatic asthmatics have been reported to have normal levels of FE_{NO} ^{7,12–14} even when factors such as inhaled corticosteroid therapy and smoking have been accounted for. In the diagnosis of occupational asthma, one of the best first line investigations for occupational asthma is serial peak expiratory flow (PEF) monitoring and is recommended by several guidelines.^{15,16} It has been suggested previously that using changes in sputum eosinophil counts between periods of exposure and non-exposure increases the sensitivity and specificity of serial PEF measurement in the diagnosis of occupational asthma.¹⁷ Specific inhalation challenge tests to occupational agents have resulted in a mean increase of exhaled nitric oxide levels.^{18–21} However, some workers with positive challenges have not showed changes. We have previously found a strong positive correlation between exhaled nitric oxide level and sputum eosinophil count in workers with occupational asthma exposed to low molecular weight agents and a relationship between sputum eosinophilia and non-specific reactivity.⁷ The study suggested that workers can be separated into two variants, those with eosinophilic airways inflammation and those with non-eosinophilic inflammation and that they would also be separable by FE_{NO} due to the strong relationship between the two indices. The aim of this study was to see whether our retrospective analysis could be confirmed with a prospective group, and whether the magnitude of PEF response to occupational exposure is related to FE_{NO} .

Methods

Study population

Consecutive workers referred to the Occupational Lung Disease Clinic, Birmingham, UK between November 2001 and December 2004 were recruited who had performed an exhaled nitric oxide measurement (FE_{NO}), methacholine challenge test and serial PEF record while still exposed at work. Sixty subjects whose serial PEF measurements showed occupational asthma while exposed to the causative agent and who had a diagnosis of occupational asthma formed the study population. The study was approved by the East Birmingham Local Ethics Committee (reference 929).

Measurements

Workers were requested to record PEF every 2 h from waking to going to bed on work days and days away from work for a total of 4 weeks. The best of 3 PEF readings were recorded on each occasion, provided that the best 2 readings were within 20 L/min of each other. Records were plotted, linearised²² (if recorded on a non-linear PEF meter) and analysed by the Oasys computer program.²³

Those with a work effect index score ≥ 2.51 , (that was used as a cut-off point for definite occupational effect)²³ were included in this analysis.

Spirometry, FE_{NO} and non-specific bronchial reactivity in methacholine challenge were performed within 24 h of work exposure after withholding treatment with long acting β -agonists for 24 h (including combined steroid and long acting β -agonists inhalers), short-acting β -agonists for 6 h and tiotropium for 36 h as part of their routine clinic visit.

Spirometry was performed on either a wedge bellows Vitalograph spirometer or on the Jaeger pulmonary function system according to ERS/ATS standards.²⁴ Non-specific bronchial reactivity to methacholine was measured using the Yan technique.²⁵ FE_{NO} was measured during exhalation at 50 ml/s using the Niox from Aerocrine, which requires values from two readings to be within 10% as recommended by the ATS/ERS²⁶ and performed before spirometry. The Oasys program²³ was used to calculate diurnal variation on days at and away from work and the area between curves (ABC) score based on mean PEF on work days and days away from work plotted by waking time (Fig. 1).²⁷

Workers were split into normal and raised nitric oxide level groups based on an eosinophil cut off of 2.2% which was used in our previous study to separate eosinophilic and non-eosinophilic variants.⁷ A cut off of 14.7 ppb for smokers and 22.1 ppb for non-smokers (equivalent to $<$ or $\geq 2.2\%$ sputum eosinophilia) was selected from a regression analysis of all our previous combined measurements of sputum eosinophils and FE_{NO} . These values were then used to

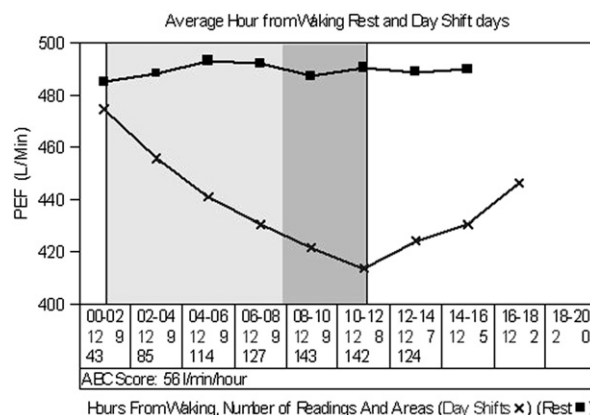


Figure 1 The ABC plot of a worker exposed to chrome from stainless steel welding. He has normal methacholine reactivity (>4800 mcg) and an FE_{NO} of 6.1 ppb. The plot has a 56 L/min/h difference between the mean curves of PEF on work and rest days. In the bottom panel, the first row of numbers is the time from waking in 2-hourly sections, e.g. 00–02; 02–04, etc. The second row shows the number of readings used for the mean PEF curves in each 2-hourly section (left side shows work readings and right side shows rest readings). The third row shows the area between the curves for each 2-hourly section which are then used to calculate the ABC score which is in L/min/h. A score of ≥ 15 L/min/h has a sensitivity of 69% and specificity of 100% for occupational asthma diagnosis.²⁷

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