Acute effect of environmental tobacco smoke on exhaled nitric oxide, in healthy passive smokers

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PURPOSE: Environmental tobacco smoke (ETS), is a mixture of gases and particles, including sidestream smoke from the burning cigarette and exhaled (mainstream) smoke. In order to assess the effect of acute exposure to ETS on the respiratory system, we utilized Fractional Exhaled Nitric Oxide (FeNO), a significant airway inflammation marker.

METHOD: Ten healthy non-smoker volunteers underwent FeNO measurement, using a chemiluminescence analyzer (Ecomedics CLD 88sp). Measurements were performed before and after the exposure to ETS. All volunteers abstained from exposure to smoking environment, at least 8 hours prior to measurement. They also avoided physical exercise and consumption of coffee, beverages or food, for at least two hours before measurement.

A smoker offered to consume a number of cigarettes (no more than 5), inside a 7 cubic meter room, where a TSI Sidepak AM510 particle monitor was measuring constantly particulate matter with an aerodynamic diameter of ≤2.5 microns. Particle concentration reached the level of at least 5mg/m3. After performing a baseline FeNO measurement, the non-smoker volunteer entered the room and remained there for 20 (twenty) minutes. A second measurement of FeNO was performed at the end of this period. FeNO values were compared before and after exposure to ETS with the aid of the nonparametric sign test for paired values (p=0.05)

RESULTS: FeNO mean values ± standard deviation (in ppb) before (15.57 ± 4.87) and after (10.79 ± 5.19) differed significantly (p=0.008).

CONCLUSIONS: The acute exposure to environmental tobacco smoke leads to a decrease in FeNO, demonstrating the influence of acute exposure to ETS on the respiratory system.
Exhaled nitric oxide measured at different flow rates to detect early bronchiolitis obliterans syndrome after lung transplantation

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Background
In a preliminary study, we have shown that extended FeNo (exhaled nitric oxide) measurements with different flow rates are feasible after lung transplantation (LTx) (ERJ 2008, 26: Suppl 49).

Aim
To prospectively investigate FeNO measured with different exhalation flows in patients under maintenance immunosuppression (at least one year after LTx) without bronchiolitis obliterans syndrome (BOS) and with early BOS (BOS 0-p = FEV₁ between 80% and 90% baseline or FEV₁>90% baseline and FEF₂₅₋₇₅ lower than 75% baseline).

Methods
FeNo was measured with Eco Medics™ (CLD 88 sp) with three different flows of 50 (FeNO₅₀), 100 (FeNO₁₀₀) and 200ml/sec (FeNO₂₀₀). According to Tsoukias and George, and Hoegman et al., bronchial NO-flux (JNO,Br) and alveolar NO-concentration (CAₐ) were calculated.

Results
Between 5/09 and 9/09 57 LTx patients were evaluated (24 stable patients without BOS and 20 with BOS 0-p). Mean age was 46±15 years and mean time after LTx 5.4±3.5 years. We found no significant differences between FeNO₅₀, FeNO₁₀₀ and FeNO₂₀₀ in the two groups (15±7ppb, 8±4ppb and 5±2ppb in stable patients and 13±6ppb, 8±6ppb and 5±2ppb in early BOS). CAₐ and JNO,Br was similar in the two groups (2.3±1.6ppb and 2.1±1.3ppb; 0.610±0.336nl/sec and 0.543±0.268nl/sec). In contrast, the ratio of FeNO₅₀ and FeNO₂₀₀ was significantly lower in early BOS compared to patients without BOS (2.5±0.6 and 3.1±0.9, p=0.01).

Conclusions
1) FeNO₅₀ does not differentiate between patients without BOS and patients with early BOS. 2) No difference between CAₐ and JNO,Br in both groups was found. 3) The ratio of FeNO₅₀ and FeNO₂₀₀ seems to be a strong marker for early BOS.
Exhaled NO is independently related to the degree of allergic sensitisation and bronchial responsiveness in atopic subjects

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Bakground: Atopic subjects have increased exhaled NO levels and increased bronchial responsiveness. It is suggested that IgE sensitisation, characterized by subclinical eosinophilic inflammation, is the common denominator behind these two findings.

Aim: To study in a multicenter, population-based study which are the determinants of FENO, with special regard to the degree of IgE sensitisation and bronchial responsiveness.

Method: Exhaled NO and bronchial responsiveness (BR) to methacholine (ECRHS slope) were performed in 444 adults from the random samples of Uppsala, Gothenburg (both Sweden) and Turin (Italy) centres of ERCHS II study. Degree of IgE sensitisation was defined as the sum of specific IgE titers against cat, timothy, mite and mould.

Results: Atopic subjects (n=131) had 29% higher FENO levels and a ECRHS slope that was 0.5 units lower (which denotes an increased BR) than non-atopic subjects. Exhaled NO correlated to BR only in atopic subjects (r=0.36, p<0.0001) and the FENO variance that could be explained by a multiple linear regression model (R²) increased from 0.12 to 0.24 with the addition of gender, height, age, FEV1(%pred), smoking habits. The addition of the degree of IgE sensitisation further increased R² to 0.28 and an independent relation of FENO to the degree of IgE sensitisation (p=0.01) as well as to BR (p=0.001) was found.

Conclusion: Our results suggest that the relation between exhaled NO and BR in atopic subjects is more complex than believed. The independent effects of degree of IgE sensitisation and bronchial responsiveness on exhaled NO suggest that exhaled NO is more than only a marker of allergic inflammation in atopic subjects.
The need for a personal target value for NO in allergic asthma

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Studies have been designed to use exhaled NO to target the treatment. Recently a Cochrane review has concluded that defining the dose of inhaled corticosteroids based on exhaled NO cannot be routinely advocated1. It has been shown that non-atopic asthma could not be distinguished from healthy controls regarding NO parameters provided by the extended NO analysis, i.e. airway wall NO (CawNO), alveolar gas phase NO (CANO) and diffusion rate of NO (DawNO). In atopy, both rhinitis and asthma, the DawNO is typically increased.

The non-linear NO model2 was used to give theoretical FNO values from different stage of atopic airway disease. Different values of CNO, CawNO and DawNO was fed into a computer program based on the non-linear model. If an atopic asthmatic has normal CawNO and CANO, but a DawNO of 24 mL/s, this will result in a FNO,0.05 of 41 ppb, a value that any pulmonologist will recommend a higher dose of ICS – without success! To clearly illustrate the effect of CawNO, CANO and DawNO on FNO some examples are given in the Table. An extended NO analysis will set the target value of FNO,0.05 and this value can then be monitored.

In conclusion, it is essential that every patient receive his/her target value of FNO,0.05. In our opinion, this is the reason why there are few successful studies trying to target the NO value with ICS.

<table>
<thead>
<tr>
<th>Theoretical example</th>
<th>CNO ppb</th>
<th>CawNO ppb</th>
<th>DawNO mL/s</th>
<th>FNO,0.05 ppb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subject</td>
<td>1</td>
<td>106</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Atopic rhinitis</td>
<td>1</td>
<td>106</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Atopic asthma</td>
<td>1</td>
<td>130</td>
<td>16</td>
<td>36</td>
</tr>
<tr>
<td>Symptomatic atopic asthma</td>
<td>2</td>
<td>200</td>
<td>16</td>
<td>56</td>
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<tr>
<td>Nocturnal atopic asthma</td>
<td>5</td>
<td>250</td>
<td>24</td>
<td>99</td>
</tr>
<tr>
<td>Optimal treated atopic asthma</td>
<td>1</td>
<td>106</td>
<td>24</td>
<td>41</td>
</tr>
</tbody>
</table>

Application of two-compartment models of nitric oxide exchange in the evaluation of patients with asbestos occupational exposure

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Objectives: To analyze several two-compartment models of the exhaled NO in patients with asbestos exposure. To associate these measurements with the lung function.

Methods: We included 77 patients with asbestos exposure and 21 healthy controls without exposition. A chemiluminescence analyzer (Analyzer CLD 88 Series, EcoMedics, Switzerland) was used to measure the fractional exhaled nitric oxide (FENO) and its elimination rate (VNO) using four expiratory flow rates (30, 50, 150, 200 ml/s). The Tsoukias, Pietrapaoli and Silkoff lineal techniques, the mixed Silkoff technique and the Hogman and George non-lineal techniques were employed to calculate the NO alveolar concentration (CANO), the NO airway concentration (CawNO), the NO maximum flux in the airway (J'awNO) and the NO diffusing capacity (DawNO).

Results: Exposure subjects group was homogeneous comparing with control group. There were significant differences in the CANO, the CawNO and in the DawNO between patients with exposition to asbestos and control subjects. Patients with respiratory symptoms had significant differences in the CANO, J'awNO, CawNO and DawNO comparing with asymptomatic patients. Subjects with exposition to asbestos and with obstructive ventilatory pattern had lesser CANO than cases without ventilatory alteration. In patients with exposition to asbestos, the FEV1 was associated with FENO, CANO and DawNO, while the PEF was associated with J'awNO and CawNO.

Conclusions: Asbestos exposure produces alterations in the alveolar and in the airway nitric oxide compartments. This alteration is greater in patients with respiratory symptoms or airflow obstruction.
Evaluation of bronchial and alveolar outputs of nitric oxide in children with allergy and asthma using the multiple exhalation flow technique

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Aim: To validate the multiple exhalation flow technique for the measurement of the fractional concentration of nitric oxide in exhaled air (FENO) in children with allergy and asthma.

Methods: FENO was measured using a single exhalation technique at five expiratory flow rates from 50 to 250 ml/s into the chemiluminiscence analyzer CLD88sp (Ecomedics, Duernten, Switzerland). Children and adolescents (21 girls, 27 boys) aged 5.2 to 18.4 yr with ICS-treated mild to moderate severe asthma were recruited. Alveolar concentration of NO (Calv,NO) and bronchial flow of NO (J´awNO) were estimated using a combination of linear and nonlinear regression analyses of the FENO-flow rate relationship assuming the two-compartment model of NO exchange.

Results: In the group of 41 patients who successfully performed the test, the geometric mean (range) Calv,NO and J´awNO values were 3.0 (0,6 - 15) ppb and 1,2 (0,2-8,9) nl/s, respectively. J´awNO (r²=0.91, p<0.001) was strongly correlated with FENO,50 and Calv,NO showed modest correlation with FENO,250 (r²=0.74, p<0.001). The failure rate to adequately perform the technique was 15 %. Estimates of Calv,NO and J´awNO were precise in 60% of patients while the results of remaining 25% of subjects had poor quality (negative non-physiological values of Calv,NO or big uncertainty of estimates).

Conclusions: The failure to precisely estimate of Calv,NO and J´awNO could be caused by an over-simplified model of NO exchange, a non-ideal range of expiratory flows or by other reasons. The multiple exhalation flow technique requires further improvements. Supported by a grant from the Ministry of Health IGA NS/9692 – 2.
Reduced bronchial nitric oxide flux but unchanged alveolar nitric oxide concentration after exposure to hyperbaric hyperoxia

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Introduction
Alveolar nitric oxide concentration (C.NO) and bronchial NO flux (JawNO) contribute to the concentration of NO in exhaled gas (FENO). FENO is reduced with 30-40% after exposure to hyperbaric hyperoxia. The reduction in FENO persists for more than 4hrs but is normalised within 24hrs (1). The purpose of this study was to examine the alveolar and bronchial contributions to the reduction in FENO after exposure to hyperbaric hyperoxia.

Methods
Ten healthy non-smoking subjects (4 men) with normal lung function undergoing hyperbaric oxygen treatment (HBO2) were included. They were exposed to HBO2 daily for four weeks for 90min (PO2 = 240 kPa). Their mean age was 52 years (range 41-63). FENO was measured at flow rates of 30, 50, 100 and 250 ml/s before and after one single HBO2 exposure with an on-line chemiluminiscence analyser (Eco Medics AG, Duernten, Switzerland). The Högman and Meriläinen algorithm was used to estimate C.NO and JawNO.

Results
After one single HBO2 exposure FENO at 50 ml/s was reduced by 32 ± 14 % (p = 0.001) and FENO at the other flow rates were significantly reduced as well. JawNO was significantly reduced from 1086 ± 643 to 748 ± 521 pl/s (p = 0.008). There were no changes in C.NO, FVC or FEV1.

Discussion
The reduction in FENO after hyperbaric hyperoxia appears to be predominantly an airway effect. Reductions in maximal expiratory flow rates take place before reductions in vital capacity and diffusion capacity with the development of oxygen toxicity. No changes in C.NO were seen in this small preliminary study.

References
Long-term, seasonal and diurnal variation of fractional exhaled nitric oxide

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Introduction
There is a lack of data about seasonal and diurnal variation of fraction of exhaled nitric oxide (FENO) in healthy subjects.

Aim
To analyze diurnal, long-term and seasonal variation of FENO in adults.

Methods
Diurnal variation: 21 healthy, non-smoking subjects participated in the study. FENO was measured at three time points during one day, 8:00-9:00 AM, 11:00-12:00 AM, 3:30-4:30 PM at two consecutive days.

Long-term variation: 9 non-smoking females participated in the study, two had mild asthma. FENO was measured at 1042 occasions over a period of 7 years. FENO was measured with three different exhalation flows: 50, 100 and 270mL/s, with NIOX™.

Result
FENO varies substantially, both diurnal and seasonal, see table 1.

<table>
<thead>
<tr>
<th>Table 1. Diurnal and seasonal variation of FENO (ppb)</th>
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<tbody>
<tr>
<td>8:00-9:00 AM</td>
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<tr>
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<tr>
<td>FENO50</td>
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<td>FENO100</td>
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<td>FENO270</td>
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* p<0.05 ; 8.30 PM v.s.2.30 PM

The diurnal variation was statistically significant but very low, lower in the morning than in the afternoon. We found significant seasonal variations for all flow-rates; however FENO50 peaked in June and FENO270 in September. The highest seasonal variation was between March and June, when FENO50 increased 2.9 ppb.

Coefficient of variation over seven years was 34% for FENO50.

Conclusion
There is a significant but very low diurnal and seasonal variation of FENO, that not seem of clinical importance, when measuring FENO.
The aim of this study was to assess the usefulness of nitric oxide measurement at multiple exhalation flows in former asbestos-exposed subjects.

**Patients and methods:** Lung function testing, blood gas analyses and FeNO measurements (with five constant flow rates varying from 20 to 300 ml/s) were performed in 42 former asbestos workers. 83% (35/42) of these subjects completed all five exhalations successfully. By using a two-compartment model $C_{aw}$ (bronchial NO concentration), $C_{alv}$ (alveolar NO concentration) and $D_{aw}$ (diffusing capacity) were estimated by nonlinear regression.

**Results:** There is no significant difference in FeNO between asbestos workers (n=35) and healthy unexposed controls (n=38) (17.6 ± 1.9 vs. 13.7 ± 0.9 ppb).

The two differential NO parameters, $C_{aw}$ and $D_{aw}$, were significant elevated in asbestos workers, however (1.3 ± 0.2 vs. 0.5 ± 0.1 ppb, p<0.001; 19.1 ± 2.0 vs. 13.1 ± 1.2 pl/s, p<0.05, respectively). $C_{aw}$ showed a trend to reduced values (57.2 ± 6.3 vs. 69.7 ± 5.0 ppb, p=0.1).

**Conclusions:** Our findings of increases in alveolar NO concentration ($C_{alv}$) and diffusing capacity of NO ($D_{aw}$) in asbestos workers are new. An explanation may be parenchymal inflammatory processes, but also ventilatory inhomogeneities in these subjects who mostly showed decreased forced expiratory flow rates. Further studies are necessary to elucidate the pathophysiologic background in more detail.
Role of bronchial and alveolar exhaled nitric oxide in patients with ulcerative colitis (UC)

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Ulcerative colitis is a chronic inflammatory bowel disease characterized by an important local tissue inflammation and associated to a variety of systemic manifestations, with an active involvement also of the airways. Exhaled Nitric Oxide (FENO) analysis is a non invasive marker that directly reflect airway inflammation. The aim of our study was to compare bronchial and alveolar FENO values of UC patients with different clinical disease activity. We enrolled 12 patients UC in clinical activity (mean age 39.5±16.2 years) without pulmonary diseases and a healthy control group of 9 subjects (mean age 28.8±3.4 years) non smokers, without atopy. The diagnosis of UC was based on clinical, radiographic, endoscopic and pathologic features, and disease activity was calculated with the colitis activity index (CAI) defining 3 classes of growing clinical gravity (A, B, C). They were clinically evaluated with optimisation of the therapy if necessary and FENO values were collected at different flows, also reactive C protein (RCP) values were collected. Bronchial and alveolar FENO and CRP values were found significantly increased proportionally to the disease activity (mean bronchial FENO class B: 10,2 ± 9,8 ppb vs class C: 20,1 ± 14,1 ppb; mean alveolar FENO class B: 4,4 ± 7,1 ppb vs class C: 7,1 ± 5,4 ppb). Moreover FENO values were found increased in UC patients when compared with healthy controls (mean patients bronchial FENO: 17,0 ± 14,9 ppb vs controls: 9,7 ± 5,4 - mean alveolar patients FENO: 6,3 ± 1,5 ppb vs controls: 1,9 ± 1,1 p<0.05). The results of this study suggest the presence of a subclinical airway inflammation directly correlated with the inflammatory bowel disease activity.
Clinical evaluation of exhaled nitric oxide measurement in monitoring childhood asthma

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Background: Fractional exhaled nitric oxide (FeNO) is a well-known indicator of airway inflammation in asthma and can be measured using noninvasive techniques.
Objective: The aim of this study was to investigate the potential yield of incorporating FeNO measurements in the monitoring of childhood asthma.
Methods: 99 children aged 5 to 14 years with a documented history of mild to severe persistent allergic asthma were included in a multicentre, randomized, parallel group effectiveness study. One strategy involved the determination of asthma control and treatment based on symptoms and spirometry according to GINA guidelines as in standard care. In the second strategy supplementary FeNO measurements were performed to guide the decision-making concerning asthma treatment. Health outcomes were evaluated over a one-year timeframe.
Results: Determining asthma treatment with FeNO resulted in less asthma exacerbations and unscheduled asthma related contacts. 24% of the children in the FeNO strategy group experienced one or more exacerbations per year and 12% underwent one or more unscheduled contacts per year, compared with respectively 48% and 35% of the children in the standard care strategy group (p<0.05). Regarding number of emergency room visits or days spent in hospital or days on which school was missed or a caregiver had to take time off from work no differences were observed. Asthma control, evaluated by a doctor every 3 months was similar for the two strategy groups.
Conclusion: The implementation of FeNO measurement in clinical practice features a promising tool in the monitoring of childhood asthma, reducing the number of asthma exacerbations and unscheduled asthma related contacts.
Model of nitric oxide production considering the gradient bronchial wall concentration from respiratory bronchioles to trachea

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Objective. The two-compartment model of nitric oxide production in the lung (2 CM) assumes a constant NO concentration in airway wall (Caw) along the whole bronchial tree. However, directly measured NO concentrations in different sections of the bronchial trees indicate a gradient of Caw from respiratory bronchioles towards trachea (DuBois et al., 1999; Silkoff PE et al., 1998; Tornberg et al., 2002, 2003).

Methods. By means of the morphological and histological assessment data of bronchial wall thickness and NO production in various layers, we estimated an 15-20 fold increase of the Caw concentration from the 16th generation of bronchi to the trachea. Using Weibel's morphometrical lung model, we developed a computation simulation model to assess the influence of the gradient of the bronchial wall concentration on exhaled NO.

Results. We subdivided the bronchial tree into eight sections according to morphology and bronchial thickness. Our model with the 20 fold gradient (Caw of 25 ppb in the 16th generation of bronchi to 500 ppb in the trachea) estimated FeNO at different flows that perfectly conformed to classic 2 CM (Table). It provides a proportion of 30% FeNO (instead of 5% in the 2 CM) arisen in large airways and trachea (generation 0-6).

<table>
<thead>
<tr>
<th>Estimated FeNO (ppb)</th>
<th>Flow (mL/S)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Classic 2 CM (Caw=70 ppb)</td>
<td>27.8</td>
</tr>
<tr>
<td>Model with Caw gradient</td>
<td>29.4</td>
</tr>
</tbody>
</table>

Conclusions. Our model with gradient of bronchial wall concentration describes FeNO at different flows just as well as the 2 CM, but it is more relevant to experimental data of NO production in upper and lower airways.
Exhaled NO, small airway obstruction and airway hyper-responsiveness in pediatric asthma

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Background: Asthma is a chronic inflammatory disorder known to involve the peripheral airways of the lungs. Current guidelines state that diagnosis and treatment should be based on symptoms and spirometry (FEV₁) but there is often little or no correlation between symptoms or FEV₁ and airway inflammation.

Aims: To characterize large and small airway contribution to exhaled nitric oxide (NO), a marker of airway inflammation, in pediatric asthma and to assess the relationship between exhaled NO, airway hyper-responsiveness and small airway function, using the multiple inert breath gas washout (MBW).

Methods: Exhaled NO at 50 mL/s (FENO₅₀), bronchial NO flux and alveolar NO, obtained from exhaled NO at several different exhalation flows and small airway function using MBW were investigated in 43 asthmatic children (aged 4-19 years) and 35 healthy controls. Airway hyper-responsiveness was assessed using isocapnic dry air hyperventilation challenge.

Results: FENO₅₀ and bronchial NO flux were elevated in the asthmatic children compared to the healthy controls. There was no difference in alveolar NO. The lung clearance index (LCI) was significantly increased in children with asthma. FENO₅₀ correlated with Scond, an index of ventilation inhomogeneity in the small conductive airways (r=0.44, p=0.003) and with airway hyper-responsiveness (r=0.65, p=0.0001).

Conclusion: This study for the first time shows a significant association between FENO₅₀, small airway dysfunction and airway hyper-responsiveness in allergic asthma in children and it confirms the involvement of the small conductive airways in asthma.