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

Marios Kougias,[1,2] Irene Avlonitou,[1,2] Vassiliki Evangelopoulou,[1] Miltos Vassiliou,[2] Panagiotis Behrakis.[1,2]. [1] "Smoking and Lung Cancer Research Center, Donation of George D. Behrakis", "Hellenic Cancer Society", Athens, Attiki, Greece [2] "Experimental Physiology Laboratory", "Medical School, University of Athens", Athens, Attiki, Greece

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 non parametric 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

Markus Hofer,[1] Christian Benden,[1] Thomas Rechsteiner,[1] Annette Boehler.[1]. [1]Lung Transplant Programm, Division of Pulmonary Medicine, Univiersity Hospital, Zuerich, Switzerland

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 = FEV_1 between 80% and 90% baseline or FEV_1>90% baseline and FEF_{25-75} lower than 75% baseline).

Methods

FeNo was measured with Eco Medics™ (CLD 88 sp) with three different flows of 50 ($FeNO_{50}$), 100 ($FeNO_{100}$) and 200ml/sec ($FeNO_{200}$). According to Tsoukias and George, and Hoegman et al., bronchial NO-flux ($J_{NO,Br}$) and alveolar NO-concentration (C_{Alv}) 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 $FeNO_{50}$, $FeNO_{100}$ and $FeNO_{200}$ 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). C_{Alv} and $J_{NO,Br}$ 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 $FeNO_{50}$ and $FeNO_{200}$ 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) $FeNO_{50}$ does not differentiate between patients without BOS and patients with early BOS. 2) No difference between C_{Alv} and $J_{NO,Br}$ in both groups was found. 3) The ratio of $FeNO_{50}$ and $FeNO_{200}$ seems to be a strong marker for early BOS.

Exhaled NO is independently related to the degree of allergic sensitisation and bronchial resposiveness in atopic subjects

Andrei Malinovschi,[1] Giovanni Rolla,[2] Dan Norbäck,[3] Marieann Högman,[4] Kjell Torén,[5] Anna-Carin Olin,[5] Christer Janson.[4]. [1]Dept. of Medical Sciences: Clinical Physiology, Uppsala University, Uppsala, Sweden [2]Dept. of Allergy and Clinical Immunology, Hospital Mauriziano, Turin, Italy [3]Dept. of Medical Sciences: Occupational and Environmental Medicine, Uppsala University, Uppsala, Sweden [4]Dept. of Medical Sciences: Respiratory Medicine and Allergology, Uppsala University, Uppsala, Sweden [5]Dept. of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Göteborg, Sweden

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 FE_{NO}, 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 FE_{NO} 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 FE_{NO} variance that could be explained by a multiple linear regression model (R^2) increased from 0.12 to 0.24 with the addition of gender, height, age, FEV_1(%pred), smoking habits. The addition of the degree of IgE sensitisation further increased R^2 to 0.28 and an independent relation of FE_{NO} 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

Marieann Högman,[1,2] Pekka Meriläinen.. [1]Centre for Research and Development, Uppsala University/County Council of Gävleborg, Gävle, Sweden [2]Medical Sciences, Uppsala University, Uppsala, Sweden

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 advocated[1]. 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 ($C_{aw}NO$), alveolar gas phase NO (C_ANO) and diffusion rate of NO ($D_{aw}NO$). In atopy, both rhinitis and asthma, the $D_{aw}NO$ is typically increased.
The non-linear NO model[2] was used to give theoretical F_ENO values from different stage of atopic airway disease. Different values of C_ANO, $C_{aw}NO$ and $D_{aw}NO$ was fed into a computer program based on the non-linear model.
If an atopic asthmatic has normal $C_{aw}NO$ and C_ANO, but a $D_{aw}NO$ of 24 mL/s, this will result in a $F_ENO_{0.05}$ of 41 ppb, a value that any pulmonologist will recommend a higher dose of ICS – without success! To clearly illustrate the effect of C_ANO, $C_{aw}NO$ and $D_{aw}NO$ on F_ENO some examples are given in the Table. An extended NO analysis will set the target value of $F_ENO_{0.05}$ and this value can then be monitored.
In conclusion, it is essential that every patient receive his/her target value of $F_ENO_{0.05}$. In our opinion, this is the reason why there are few successful studies trying to target the NO value with ICS.

Theoretical example	C_ANO ppb	$C_{aw}NO$ ppb	$D_{aw}NO$ mL/s	$F_ENO_{0.05}$ ppb
Healthy subject	1	106	8	16
Atopic rhinitis	1	106	12	23
Atopic asthma	1	130	16	36
Symptomatic atopic asthma	2	200	16	56
Nocturnal atopic asthma	5	250	24	99
Optimal treated atopic asthma	1	106	24	41

[1]Petsky et al. Cochrane Database of Systemic Reviews 2009 [2]Hogman et al. J Breath Res 2007

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

Carlos Javier Carpio Segura,[1] Manuel González Viñolis,[1] David Romero Ribate,[1] Santiago Zudaire-Tejeiro,[1] Darwin Féliz Rodríguez,[1] Isabel Fernández Navarro,[1] Ana Santiago Recuerda,[1] María Antonia Gómez Mendieta,[1] Francisco García-Río,[1] Rodolfo Álvarez-Sala Walther.[1]. [1]Respiratory Medicine, Hospital Universitario La Paz, Madrid, Spain

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 FEV_1 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

Jirina Chládková,[1] Jaroslav Chládek,[2] Zuzana Havlínová.[2]. [1]Department of Pediatrics, Faculty of Medicine and Hospital, Hradec Králové, Czech Republic [2]Department of Pharmacology, Charles University, Faculty of Medicine in Hradec Králové, Hradec Králové, Czech Republic

Aim: To validate the multiple exhalation flow technique for the measurement of the fractional concentration of nitric oxide in exhaled air (FE_{NO}) in children with allergy and asthma.
Methods: $FE_{NO}$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 ($C_{alv,NO}$) and bronchial flow of NO (J'_{awNO}) were estimated using a combination of linear and nonlinear regression analyses of the FE_{NO}-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) $C_{alv,NO}$ and J'_{awNO} values were 3.0 (0,6 – 15) ppb and 1,2 (0,2-8,9) nl/s, respectively. $J'a_{wNO}$ (r^2=0.91, p<0.001) was strongly correlated with $FE_{NO,50}$ and $C_{alv,NO}$ showed modest correlation with $FE_{NO,250}$ (r^2=0.74, p<0.001). The failure rate to adequately perform the technique was 15 %. Estimates of $C_{alv,NO}$ 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 $C_{alv,NO}$ or big uncertainty of estimates).
Conclusions: The failure to precisely estimate of $C_{alv,NO}$ 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

Cecilie Caspersen, Einar Thorsen.. Institute of Medicine, University of Bergen, Bergen, Norway Department of Hyperbaric Medicine, Haukeland University Hospital, Bergen, Norway

Introduction

Alveolar nitric oxide concentration (C_ANO) and bronchial NO flux (JawNO) contribute to the concentration of NO in exhaled gas (FE_{NO}). FE_{NO} is reduced with 30-40% after exposure to hyperbaric hyperoxia. The reduction in FE_{NO} 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 FE_{NO} after exposure to hyperbaric hyperoxia.

Methods

Ten healthy non-smoking subjects (4 men) with normal lung function undergoing hyperbaric oxygen treatment (HBO_2) were included. They were exposed to HBO_2 daily for four weeks for 90min (PO_2 = 240 kPa). Their mean age was 52 years (range 41-63). FE_{NO} was measured at flow rates of 30, 50, 100 and 250 ml/s before and after one single HBO_2 exposure with an on-line chemiluminiscence analyser (Eco Medics AG, Duernten, Switzerland). The Högman and Meriläinen algorithm was used to estimate C_ANO and JawNO.

Results

After one single HBO_2 exposure FE_{NO} at 50 ml/s was reduced by 32 ± 14 % (p = 0.001) and FE_{NO} 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_ANO, FVC or FEV_1.

Discussion

The reduction in FE_{NO} 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_ANO were seen in this small preliminary study.

References

1. Taraldsøy, T. et al. Undersea Hyperbaric Medicine; 2007; 34:321-27.

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

Marianne Andersson,[1] Kristina Wass,[1] Johan Nilsson,[2] Bertil Forsberg,[2] Anna-Carin Olin.[1]. [1]Occupational and Environmental Medicine, Sahlgrenska University Hospital, Sahlgrenska Academy at Göteborg University, Sweden [2]Occupational and Environmental Medicine, Umeå University, Department of Public Health and Clinical Medicin, Umeå, Sweden

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 consecutative 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 1. Diurnal and seasonal variation of FENO (ppb)

	8:00-9:00 AM	11:00-12:00 AM	3:30-4:30 PM	*Spring*	*Summer*	*Autumn*	*Winter*
FENO50	21.5	22.0	20.6*	*16.4*	*18.3*	*17.4*	*16.6*
FENO100	11.5	11.5	10.8*	*9.3*	*10.7*	*10.7*	*9.9*
FENO270	*5.2*	*5.1*	*5.0**	*4.8*	*5.4*	*5.4*	*4.8*

* $p<0.05$; 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 $FENO_{50}$ peaked in June and $FENO_{270}$ in September. The highest seasonal variation was between March and June, when $FENO_{50}$ increased 2.9 ppb.
Coefficient of variation over seven years was 34% for $FENO_{50}$.
Conclusion
There is a significant but very low diurnal and seasonal variation of FENO, that not seem of clinical importance, when measuring FENO.

FeNO parameters in asbestos workers

Alexandra M. Preisser,[1] Liubov Barbinova,[1] Eva Sabine Goldenstein,[2] Xaver Baur.[1].
[1]Department of Clinical Occupational Medicine, Institute for Occupational and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2]Occupational Medicine, Vattenfall Europe Business Services GmbH, Hamburg, Germany

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_{awNO} (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_{alv} 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)

Beatrice Ragnoli,[1] Mario Malerba,[1] Alessandro Radaeli,[1] Laura Buffoli,[1] Francesco Lanzarotto,[1] Chiara Ricci,[1] Alberto Lanzini.[1]. [1]Internal Medicine, Università di Brescia, Italy

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

Eva Peirsman,[1] Thierry Carvelli,[2] Pierre Hage,[3] Laurence Hanssens,[3] Luc Pattyn,[4] Marc Raes,[5] Kate Sauer,[6] Françoise Vermeulen,[7] Kristine Desager.[1]. [1]Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Antwerp, Belgium [2]Pediatrics, Centre Hospitalier Peltzer – La Tourelle, Verviers, Belgium [3]Pediatrics, Universitair Kinderziekenhuis Koningin Fabiola – Hôpital Universitaire Des Enfants Reine Fabiola, Brussels, Belgium [4]Pediatrics, Algemeen Ziekenhuis Turnhout, Campus Sint-Jozef, Turnhout, Belgium [5]Pediatrics, Jessa Ziekenhuis, Hasselt, Belgium [6]Pediatrics, Algemeen Ziekenhuis Sint-Jan, Bruges, Belgium [7]Pediatrics, Hôpital Erasme, Brussels, Belgium

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

Liubov Barbinova,[1] Xaver Baur.[1]. [1]Department of Clinical Occupational Medicine, Institute for Occupational and Maritime Medicine, University Hamburg, Hamburg, Germany

Objective. The two-compartment model of nitric oxide production in the lung (2 CM) assumes a constant NO concentration in airway wall (C_{aw}) along the whole bronchial tree. However, directly measured NO concentrations in different sections of the bronchial trees indicate a gradient of C_{aw} 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 C_{aw} 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 (C_{aw} 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).

Estimated FeNO (ppb)					
	Flow (mL/S)				
	20	50	100	200	300
Classic 2 CM (Caw=70 ppb)	27.8	13.1	7.1	3.9	2.8
Model with Caw gradient	29.4	13.0	6.9	3.7	2.7

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

Christina Keen,[1] Anna-Carin Olin,[2] Göran Wennergren,[1] Per Gustafsson.[1,3]. [1]Dept of Pediatrics, University of Gothenburg, Gothenburg, Sweden [2]Dept of Occupational and Environmental Medicine, University of Gothenburg, Gothenburg, Sweden [3]Dept of Pediatrics, Central Hospital, Skövde, Sweden

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 (FEV_1) but there is often little or no correlation between symptoms or FEV_1 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 ($FENO_{50}$), 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 isocapnoic dry air hyperventilation challenge.
Results: $FENO_{50}$ 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. $FENO_{50}$ correlated with S_{cond}, 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 $FENO_{50}$, small airway dysfunction and airway hyper-responsiveness in allergic asthma in children and it confirms the involvement of the small conductive airways in asthma.