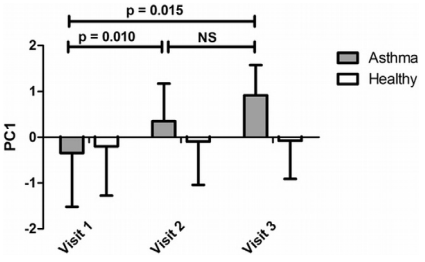
Methods: Patients with mild intermittent asthma (no ICS; age 22±3; M/F 4/5) and healthy controls (22±3; 1/13) underwent intranasal RV16 inoculation. Efficacy of inoculation was assessed by antibodies and PCR. Exhaled breath was collected using a standardized method 1 day before (visit 1), and 4 days (visit 2) and 2 months (visit 3) after exposure. Exhaled VOCs were measured by eNose (Cyranose 320) resulting in breathprints. Changes in breathprints were analyzed by principal component and mixed model analysis.
Results: 9/14 Asthmatics/healthy controls were included. Breathprint principal components (PC) changed significantly in asthmatics between visits 1 and 2 (p=0.010), and between visits 1 and 3 (p=0.015), but there was no change between visits 2 and 3. Breathprints of healthy controls did not change between any visit.



Conclusion: Rhinovirus infection changes exhaled VOC-patterns in asthmatics but not in healthy controls. This suggests that the change in exhaled VOC-pattern during and after RV infection in asthma may be used to monitor and predict exacerbations.

215. Clinical application of exhaled biomarkers

1692
Exhaled molecular patterns change after experimental rhinovirus 16 infection in asthma
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Rationale: The majority of asthma exacerbations is caused by rhinovirus (RV) infection. Metabolomic assessment of exhaled Volatile Organic Compounds (VOCs) using an electronic nose (eNose) offers the opportunity to simplify and improve monitoring of asthmatics with exacerbations.
Hypothesis: We hypothesized that exhaled VOC-patterns change after experimental rhinovirus infection.

1693
Increased exhaled breath condensate cysteinyl leukotriene concentration in exercise-induced bronchoconstriction
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Background: Several studies support the role of cysteinyl leukotrienes (Cys-LTs) in exercise-induced bronchoconstriction (EIB), however the concentration of these mediators during the development of EIB has not been investigated yet.
Aim: To study the effect of exercise on airway concentration of Cy-LTs in asthmatic patients by measuring Cy-LT in exhaled breath condensate (EBC).
Methods: Seventeen asthmatic patients with previous history of EIB and six healthy subjects participated in the study. Lung function was measured and EBC was collected at rest (baseline), immediately and ten minutes after exercise challenge on treadmill. Exhaled NO (FENO) was also determined at baseline. To compare the exercise-induced changes in FEV1 and Cys-LT between groups, repeated-measures ANOVA was used. Pearson correlation was applied to assess the relationship between variables. Cys-LT levels are expressed as median (range).
Results: Baseline Cys-LT level was higher in asthmatic than in healthy subjects (168 pg/ml (112-223) vs. 77 pg/ml (36-119), p=0.03). Exhaled breath condensate Cys-LT concentration increased in all asthmatic patients post-exercise (n=17, p=0.03), with the increase significantly greater in patients developing exercise-induced bronchospasm (n=7, p=0.03), while no change was observed in healthy controls (p=0.59). There was a strong correlation between baseline FENO and the maximal increase in Cys-LT concentration in the asthmatic group (p=0.01, r=-0.57). A significant relationship was observed between the increase in EBC Cys-LT and the exercise-induced fall in FEV1.
Conclusion: Our study supports the concept that the release of Cys-LTs is involved in the development of EIB.

1694
Exhaled nitric oxide may predict future benefit in patients with poorly controlled asthma
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Dynamic changes in exhaled nitric oxide fraction (FeNO) are highly predictive for asthma control, whereas its absolute values are often in discrepancy with patients' clinical status.
Aim: To evaluate the potential of baseline FeNO to identify in regular clinical practice the individuals with suboptimal controlled asthma who have the potential to achieve control according to a guideline-based approach.
Methods: 165 patients seen for two consecutive visits with uncontrolled asthma (defined as a score of $\leq$ 19 in the Asthma Control Test) at the first visit were included in the study. The exclusion criteria were limited to smokers and overlaping COPD since the study was purported to reflect the real-life practice.
Results: In ROC curve analysis, a greater absolute value of FeNO at the first visit

was associated with the acquirement of asthma control in the second one (AUC – area under the curve was 0.7816, p<0.0001). Its predictive performance with respect to the future control of the disease did not significantly differ between patients with and without allergic rhinitis (AUC was 0.7661 *vs.* 0.7918; p = 0.35), even if the mean value of FeNO was greater in the former group (33.72±1.98 *vs.* 29.27±1.96, p=0.006). In uncontrolled asthma, values of FeNO > 35 ppb in patients with, and > 30 ppb in patients without allergic rhinitis, predicted future benefits (the positive predictive value was 85.42% and 91.97%, respectively).
Conclusion: Our results suggest that the fractional concentration of exhaled nitric oxide might be an important predictive tool in assessing asthma control and future benefit over time even in patients with underlying atopy, as expressed by the presence of allergic rhinitis.

1695
Exhaled nitric oxide is better related to bronchial responsiveness and eosinophil activation in children than adults with asthma
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Background: The fraction of exhaled nitric oxide (FeNO), a marker of steroid-sensitive airways inflammation, is moderately related to bronchial responsiveness (BR) in asthma. Serum eosinophil cationic protein (sECP), a systemic eosinophil activation marker, is weakly-moderately related to exhaled NO. However, no studies have concomitantly compared these relationships in children and adults with asthma.
Aim: To analyse in an ongoing asthma study the relation between exhaled NO and BR as well as sECP with respect to age of subjects.
Methods: FeNO, lung function, methacholine provocation ($PC_{20}FEV_1$), sECP measurements and allergy testing were performed in 208 patients with asthma (94 children aged 10-17 years and 114 adults aged 18-34 years) within the frame of an industry-academy collaboration on minimally-invasive diagnostics (MIDAS).
Results: No differences between children and adults were found with regard to allergic sensitisation (80% vs 84% atopic), lung function (FEV_1(%pred)) (90% (81, 99%) vs 93% (86, 103%)) and asthma control (ACT score 21 (19, 23) vs 21 (19, 23) (all p-values>0.05). The correlation coefficients between FeNO and $PC_{20}FEV_1$ were rho=-0.46, p<0.001 in children and rho=-0.21, p=0.08 in adults. Similarly, FeNO was stronger related to sECP in children (rho=0.49, p<0.001) than adults (rho=0.25, p=0.006).
Conclusion: The relation between exhaled NO and bronchial responsiveness appears to be weaker in adults and this might be explained by other factors than ongoing allergic inflammation causing bronchial hyperresponsiveness, for example airway remodeling. The weaker relation between exhaled NO and sECP in adults warrants further research.

1696
Non-invasive biomarkers applied in a case-control study
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Background: Exhaled breath contains various potential noninvasive biomarkers for airway disease.
Aim: This study aims to evaluate the performance of known exhaled markers and to search for potential new markers in exhaled breath.
Methods: Asthmatic (N=72) and healthy (N=67) children (6-12 years) donated exhaled breath condensate (EBC; RTube) and exhaled gasses (Tedlar bag). Fractional exhaled nitric oxide (FeNO) was measured (NIOX MINO). EBC pH was measured directly after sampling without deaeration, EBC 8- isoprostane was measured by ELISA (Cayman). Patterns of exhaled proteins and gasses were analysed by LC/MS or GC/MS to obtain a fingerprint of molecules which are indicative for the airway status.
Results: Increased FeNO values were observed in the asthma group compared to the healthy controls (Mann-Whitney U test; p=0.057), and in the allergic asthmatic patients compared to the non-allergic asthmatic patients (p=0.01). EBC pH was significantly lower in the asthma group compared to healthy controls (p=0.047). EBC 8-isoprostane was comparable between children with asthma and healthy controls, but was significantly increased in allergic asthma patients compared to non-allergic patients (p=0.032). Various proteins that might be relevant in respiratory health outcomes were for the first time identified in EBC, amongst which annexin A1 and A2, calgranulin A and B, catalase, galectin-7, and prolactin-induced protein. Prediction models of selected proteolytic peptides or gasses were build (Support Vector Machine analysis) based on the health outcome asthma.
Conclusion: Exhaled molecules are influenced by asthma or allergy status. This study identified new exhaled molecules that might be relevant for respiratory health.

1697
Pattern of exhaled volatile organic compounds is altered in children with obstructive sleep apnea
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Background: Obstructive sleep apnea syndrome (OSAS) is a common disorder in children. Systemic and local airway inflammation is involved in disease pathogenesis. Non-invasive tools for inflammometry are needed in pediatrics. The analysis of exhaled volatile organic compounds (VOCs) by sensor arrays such as electronic noses offers a novel method to assess inflammation-related metabolic changes and oxidative stress.
Objective: To study if exhaled VOC pattern in children with OSAS can be discriminated with an electronic nose.
Methods: Eight children with mild-moderate OSAS (age 8±2 yrs) and ten healthy control subjects (10±3 yrs) were recruited. Subjects did not present any acute or chronic airway disease. After a single deep inspiratory capacity, VOC pattern of exhaled breath (collected from the lower airways without the dead space) was recorded with Cyranose 320 (Smiths Detection) and analyzed off-line using principal component analysis, Mahalanobis regression and receiving operator curve (ROC) analysis (SPSS 16.0).
Results: All subjects provided technically adequate breath samples. Exhaled VOC pattern of OSAS patients could be discriminated from that of control subjects using the Mahalanobis method (Wilks' lambda=0.02; 73% classification accuracy) and also with ROC analysis (sensitivity: 88%, specificity: 70%, positive predictive value: 70%, negative predictive value: 88%).
Conclusions: In this first preliminary study, we show that exhaled VOC sampling is feasible in children, and VOC pattern analysis can discriminate patients with OSAS from healthy controls. Exhaled VOC analysis might serve as a new tool for airway inflammometry in children.
This study was supported by OTKA 68808.

1698
Increased exhaled nitric oxide predicts new-onset rhinitis in asymptomatic children
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Background: The fraction of nitric oxide in exhaled air (FeNO) is increased in rhinitis and asthma. Recent studies have reported that high FeNO levels in asymptomatic subjects can predict later onset of asthma. No studies have analysed if increased FeNO in asymptomatic subjects can predict later onset of rhinitis.
Aim: To investigate in a cohort of schoolchildren if increased FeNO levels at the age of 13-14 years predict new-onset of rhinitis within a 4-years period.
Methods: A total of 959 randomly selected schoolchildren, aged 13-14 years, answered questions on respiratory and allergy symptoms, family history of asthma. Lung function and FeNO were also measured at baseline. A follow-up with the same questions was performed four years later. After exclusion of subjects with asthma or rhinitis symptoms at baseline, 555 participants were eligible for the present study.
Results: Subjects with new-onset rhinitis (n=92) had a trend of higher FeNO than subjects who did not develop rhinitis (p=0.06). Increased FeNO predicted new-onset rhinitis in a multiple logistic regression model (p=0.009) and the risk of new-onset rhinitis was 2.4-fold (1.2, 4.4) elevated if FeNO > 90th percentile of all included subjects (n=555). A similar risk increase for new-onset rhinitis, 2.4 (1.2, 4.9) was found in subjects with no allergy symptoms and 2.3 (1.04, 5.1) after further excluding subjects with a family history of asthma.
Conclusion: Increased FeNO levels predicted new-onset rhinitis in this population-based study of schoolchildren. The predictive value in subjects without allergic symptoms or family history of asthma suggests that these children with increased FeNO should be tested for allergy and followed-up.

1699
Differentiation of chronic obstructive pulmonary disease (COPD) including lung cancer from healthy control group by breath analysis using ion mobility spectrometry
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Introduction: Non-invasive methods with potential for diagnosis of lung diseases gain increasing interest. Ion mobility Spectrometry detects volatile analytes within human breath directly. Therefore its usefulness in discriminating COPD patients and healthy persons is tested.
Methods: Exhaled breath of 132 persons (97 COPD patients [35 without lung cancer, 62 with lung cancer] and 35 healthy volunteers) was investigated using an Ion Mobility Spectrometer (IMS) coupled to a Multi-Capillary Column (MCC)

without any pre-separation or pre-enrichment. One hundred four different peaks were considered within the IMS-Chromatograms of the 10 mL breath samples of both groups. A principal component analysis (PCA) of these 104 peaks was applied to find disriminant analytes.

Results: A single analyte could be identified, that allowed a separation of the healthy persons and the COPD patients (with and without lung cancer). The sensitivity obtained was 60%, the specificity 91%, the positive predictive value 95%. The peak was characterrized as cyclohexanone (CAS 108-94-1).

Discussion: Breath gas analysis using ion mobility spectrometry offers a chance of separating healthy persons and COPD patients. In this study a single analyte (cyclohexanon) at a defined concentration had a high positive predictive value. However, subsequent studies in a greater population are necessary to validate the usefulness of the cyclohexanon peak. Further research is necessary to find peaks with a higher sensitivity.