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Effects of pollen season on central and peripheral nitric oxide production in subjects with pollen asthma

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KEYWORDS

Pollen;
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Summary

Background: Pollen exposure of allergic subjects with asthma causes increased nitric oxide (NO) in exhaled air (FENO) suggestive of increased airway inflammation. It is, however, unclear to what extent NO production in peripheral airways and alveoli are involved.

Objectives: The aim of the present investigation was to analyze the relationship between central and peripheral components of FENO to clarify the distribution of pollen induced inflammation in asthma.

Subjects and methods: 13 pollen allergic non-smoking subjects with mild-intermittent asthma and 12 healthy non-smoking control subjects were examined with spirometry and FENO at flows between 50 and 270 mL/s during and out of pollen season.

Results: Spirometry was normal and unaffected by season in subjects with asthma as well as controls. Out of season subjects with asthma had significantly higher FENO, elevated airway production (J_{aw}NO) and preacinar/acinar production (CANO) than controls. Pollen exposure resulted in significantly increased FENO and J_{aw}NO but not CANO. FENO among controls were not affected by season. Individual results showed, however, that CANO increased substantially in a few subjects with asthma. The increased CANO in subjects with asthma may be explained by increased NO production in preacinar/acinar airways and back diffusion towards the alveoli.

Conclusions: The findings may indicate that subjects with allergic asthma have airway inflammation without alveolar involvement outside the pollen season and pollen exposure causes a further increase of airway inflammation and in a few subjects obstruction of intra acinar airways causing impeded back diffusion. Increased NO production in central airways, unassociated with airway obstruction could be an alternative explanation. These effects were not disclosed by spirometry.

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Introduction

During natural pollen exposure exhaled nitric oxide (FENO) is increased compared to out of season in subjects with pollen allergic asthma and allergic rhinitis [1–8]. FENO originates from central and peripheral airways and alveoli [9,10] but the origin of the increased FENO during pollen season is unclear.

By measuring FENO at various constant exhalation flows between 50 and 300 mL/s a central (JáwNO) and a peripheral (CANO) NO source can be estimated according to the so called “slope intercept method” [9–11]. FENO obtained at an exhalation flow of 50 mL/s (FENO_{0.05}) has been shown to be intimately related to JáwNO ($R^2 = 0.99$) among normal subjects and subjects with asthma with normal spirometry [12] indicating that JáwNO and FENO_{0.05} carry the same information. The so called “central” source is, however, a composite of NO produced by central conducting airways and preacinar/ acinar airways. About half of FENO_{0.05} originates from the preacinar region in normal subjects according to Kerckx et al. [13,14]. At this very peripheral zone NO transport by diffusion becomes important because of the large airway cross sectional area [15] and the concentration gradient with lower concentration towards the alveoli. During exhalation NO is transported by bulk flow towards the mouth whereas the NO transport by diffusion is in the opposite direction towards the alveolar end. At the onset of the acinus the airway cross sectional area is about 300 cm² [2] and increases drastically towards the periphery [15]. NO transport by bulk flow and by diffusion in the opposite direction becomes equal approximately at the level of the onset of the acinus i.e. about 0.6 cm from the alveolar end [16]. The importance of back diffusion of NO towards the alveolar end during exhalation is evidenced also by results from breathing a mixture of 80% helium and 20% oxygen when NO diffusion is increased 2.3 fold. Then FENO_{0.05} decreases by 45% [17] because more NO back diffuses towards the alveoli and escapes into the blood and is withheld from being exhaled. The increased NO diffusivity influences the preacinar/ acinar NO transport only and accordingly demonstrates that a substantial part of FENO originates in the pre-acinar/ acinar zone. Thus bulk flow and back diffusion splits the preacinar/ acinar NO production.

The peripheral NO source (CANO), is the steady state alveolar NO concentration that is a result of back diffusion from intra acinar airways, NO production by the preacinar/ acinar cells and diffusion into the blood [13,16–22]. There is a positive correlation between CANO and JáwNO or FENO_{0.05} [12,18] because acinar NO production contributes both to CANO and JáwNO. The determination coefficient $R^2 = 0.48$ [12] indicates that about half of the variation of CANO can be explained by variation of JáwNO or FENO_{0.05}. If e.g. acinar NO production increases both FENO_{0.05} (and JáwNO) and CANO increase. For any given acinar airway NO production FENO_{0.05} (and JáwNO) and CANO exploits the same NO source and the split is regulated by the balance between bulk flow in the mouth direction and back diffusion towards the alveolar end. The contribution of NO back diffusion to CANO may be estimated and subtracted from CANO in order to estimate the alveolar production, CANO_{corrected} [12,18].

Constriction and reduction of the crosssectional area of acinar airways may reduce back diffusion and result in

increased FENO [22,23]. Conversely dilatation e.g. by steroid treatment, may decrease FENO [24] due to increased back diffusion and disappearance into the blood. Thus FENO_{0.05} and JáwNO are dependent on preacinar/ acinar airway NO production and back diffusion besides the production in central conducting airways. Mere obstruction of central conducting airways results in decreased FENO as demonstrated by histamine provocation of normal subjects [22]. The mechanisms are yet controversial.

Increased CANO during pollen season compared to out of season was reported by Tufvesson et al. [25], whereas CANO was not significantly different between out of season and pollen season in a recent report by Lopez et al. in similar subjects with seasonal asthma and allergic rhinitis [26]. These two studies did, however, consider back diffusion differently. Therefore, the purpose of the present study has been to try to evaluate the effect of pollen season on acinar and alveolar involvement in pollen allergic subjects with asthma and in healthy subjects by considering the interdependence of FENO_{0.05} (or JáwNO) and CANO and the effect of back diffusion.

Methods

We recruited 13 pollen allergic non-smoking subjects with mild-intermittent asthma aged between 26 and 61 years. They were allergic to birch pollen as diagnosed by history and presence of specific IgE against birch-pollen (Pharmacia & Upjohn Diagnostics; Uppsala, Sweden) and were clinically stable. They had no or mild symptoms out of pollen season. Six of the subjects were taking inhaled glucocorticoids regularly, and four of them in combination with long acting β -2 stimulators, the others had only bronchodilators on demand, i.e. particularly during season. Long acting β -2 stimulators were withheld for two days before the clinical examination. 12 healthy non-smoking control subjects were recruited. They were between 34 and 67 years, had no history of lung disease and were on no medication. All subjects were without respiratory tract infections within 3 weeks prior to the clinical test.

All subjects were examined during pollen season 2011, i.e. between 2011-04-29 and 2011-06-02 and out of pollen season either during the autumn 2010 or 2011. Birch pollen levels during the pollen-season 2011 are illustrated in Fig. 1.

Spirometry was performed according to ERS/ATS criteria [27] and at each occasion before and after bronchodilatation (3×0.5 mg nebulized Bricanyl; AstraZeneca; Sweden). Predicted normal values were according to the ECCS/ERS equations [28].

FENO was measured by a NIOX system (NIOX; Aerocrine AB, Stockholm, Sweden) and was obtained before spirometry and in duplicate at three exhalation flow rates within $\pm 10\%$ of 50 mL/s (FENO_{0.05}), 100 mL/s (FENO_{0.1}) and 270 mL/s (FENO_{0.27}). Measurements followed the ATS-ERS guidelines and ensured a positive mouth pressure of at least 5 cm H₂O during exhalations. Plateau FENO values and the corresponding exhalation flow rates were registered. CANO and JáwNO were calculated according to Pietropaoli et al. [9] and included FENO_{0.05}. The effect of back

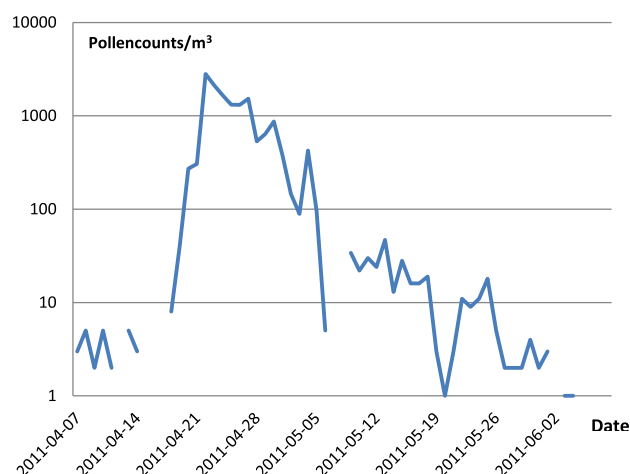


Figure 1 Pollen counts (count/m³) during the pollen season 2011 in Gothenburg.

diffusion was estimated according to Kerckx et al. and the "true" alveolar concentration (CANO_{corrected}) was calculated [12]. FENO_{0.1} and FENO_{0.27} were not obtained during season in one asthma subject.

The statistical analysis was performed using SAS (Statistical Analysis System, version 9.3; SAS Institute Inc.; NC, USA) and Excel. Nonparametric two sided tests were used: Wilcoxon exact test and Wilcoxon signed rank test of differences between paired observations. Differences of spirometric variables between seasons were tested by two sided paired *t*-test.

The local ethics committee had approved of the protocol and subjects signed an informed consent form.

Results

Individual results of subjects with asthma and mean data of controls are presented in Table 1. Specific IgE against birch

pollen varied considerably among the subjects with asthma. Pollen season did not induce significant changes neither in subjects with asthma nor in controls. Subjects with asthma had on average close to normal spirometry both out of season and during season and they were not significantly different from controls regarding the forced vital capacity (FVC) and the forced expired volume in 1 s (FEV₁). Effects of bronchodilatation (Δ FVC and Δ FEV₁) were rather small among both subjects with asthma and controls but the subjects with asthma showed a slight but significantly greater effect than controls during season.

FENO values are presented in Table 2. Subjects with asthma exhaled substantially higher NO concentrations during season compared to out of season whereas controls are unaffected by season. Furthermore, subjects with asthma exhaled higher NO concentrations compared to controls at all three exhalation flows both out of season and during season.

J_{aw}NO, the acinar/alveolar NO concentration (CANO) and CANO_{corrected} for back diffusion (CANO_{corrected}), are presented in Table 3. Pollen exposure resulted in substantially increased J_{aw}NO, unchanged CANO and reduced CANO_{corrected} among subjects with asthma but had no significant effects among controls. Furthermore, subjects with asthma had significantly higher J_{aw}NO compared to controls irrespective of season as expected from the FENO results. CANO was also higher among subjects with asthma compared to controls irrespective of season. CANO_{corrected} on the other hand was not significantly different between subjects with asthma and controls irrespective of season.

Fig. 2 illustrates the relationship between FENO_{0.05} and CANO out of season and during season. The relationship is particularly evident among subjects with asthma due to the higher variability of FENO in this group. The relationship is highly significant both out of season (adj $R^2 = 0.86$; $p < 0.0001$) and during season (adj $R^2 = 0.74$; $p < 0.0001$). The regression equations are

Table 1 Individual data of asthmatic patients and mean data of controls. Specific IgE against birch pollen and spirometry data. Δ FVC and Δ FEV₁ are the differences between post- and pre-bronchodilatation values expressed as a percentage of the pre bronchodilatation values.

Asthmatics idnr and controls average	Specific IgE, total counts	Out of season				Season			
		FVC (% pred)	Δ FVC (%)	FEV ₁ (% pred)	Δ FEV ₁ (%)	FVC (% pred)	Δ FVC (%)	FEV ₁ (% pred)	Δ FEV ₁ (%)
2	6.2	92	-1.5	91	-0.9	87	5.4	87	9.8
3	1.5	105	1.7	85	7.9	105	2.0	82	10.3
4	22	87	4.8	71	14.7	97	-4.9	81	2.2
5	2.3	107	-0.5	105	1.2	106	-0.5	104	0
7	0.8	101	15.4	92	17.4	108	10.5	94	17.8
10	16	87	-3.2	86	0.7	90	5.7	90	6.8
11	1.2	96	-1.4	98	-0.2	97	-1.0	100	1.6
12	0.04	124	3.8	121	7.9	122	0.2	121	3.5
13	17.7	108	0.5	86	1.5	108	-3.9	88	-1.1
14	>100	108	0.2	108	2.6	111	0.6	109	2.4
15	39.2	110	0.2	110	3.0	101	1.6	97	7.6
16	6.8	106	3.7	102	9.4	109	1.5	107	4.9
17	2.4	100	8.0	75	15.9	102	11.7	80	19.3
Controls	neg	109	-1.0	104	1.1	108	-1.3	103	1.5

Table 2 Exhaled NO concentrations measured at constant exhalation flows, 0.05, 0.1 and 0.27 L/s. Q1 and Q3 refer to the first and third quantiles and *p* values refer to differences between autumn and spring.

	Out of season			Season			<i>p</i>
	Median	Q1	Q3	Median	Q1	Q3	
<i>Subjects with asthma</i>							
FENO _{0.05} (nL/L)	20.3	17.0	31.5	54.1	23.3	84.9	<0.001
FENO _{0.1} (nL/L)	13.1	10.6	19.0	22.1	1.5	68.6	0.02
FENO _{0.27} (nL/L)	7.5	5.7	8.4	9.6	5.9	35.4	0.007
<i>Controls</i>							
FENO _{0.05} (nL/L)	13.4	11.1	17.7	15.6	10.3	20.0	0.62
FENO _{0.1} (nL/L)	8.9	6.2	10.4	9.2	6.3	12.5	0.85
FENO _{0.27} (nL/L)	5.1	4.1	5.8	4.2	3.5	5.9	0.52

$$\text{CANO (nL/L)} = 0.0787 \times \text{FENO}_{0.05} \text{ (nL/L)} + 1.70 \text{ out of season}$$

$$\text{CANO (nL/L)} = 0.0507 \times \text{FENO}_{0.05} \text{ (nL/L)} + 2.02 \text{ pollen season}$$

Individual changes of FENO_{0.05} ($\Delta\text{FENO}_{0.05}$) and CANO (ΔCANO) that develop between out of season and season, i.e. season – out of season, are demonstrated in Fig. 3. There are rather small differences between seasons among almost all controls (with one exception) and the majority of the subjects with asthma. Comparatively large effects of pollen season are observed in four subjects with asthma. The relationship between $\Delta\text{FENO}_{0.05}$ and ΔCANO is highly significant (adj $R^2 = 0.56$; $p < 0.0001$) and the regression equation is

$$\Delta\text{CANO (nL/L)} = 0.0556 \times \Delta\text{FENO}_{0.05} \text{ (nL/L)} - 0.49$$

Table 3 Estimated maximal flux of NO from airways (J_{aw}NO), alveolar NO concentration (CANO) and CANO_{corrected} for back diffusion (CANO_{corrected}). Q1 and Q3 refer to the first and third quantiles and *p* values refer to differences between autumn and spring.

	Out of pollen season			Pollen season			<i>p</i>
	Median	Q1	Q3	Median	Q1	Q3	
<i>Subjects with asthma</i>							
J _{aw} NO (nL/s)	0.84 ^S	0.66	1.49	1.84 ^S	0.94	5.69	0.001
CANO (nL/L)	3.51 ^S	2.87	4.33	4.67 ^S	2.67	8.07	0.68
CANO _{corrected} (nL/L)	1.61 ^{NS}	1.44	2.31	1.01 ^{NS}	0.33	2.00	0.012
<i>Controls</i>							
J _{aw} NO (nL/s)	0.53	0.43	0.75	0.72	0.40	0.87	0.27
CANO (nL/L)	2.60	2.08	3.25	2.09	1.55	3.36	0.38
CANO _{corrected} (nL/L)	1.61	1.15	2.30	1.14	0.77	2.11	0.27

p values are two sided Wilcoxon signed rank of differences between season and out of season.

^S and ^{NS} denotes a significantly/non-significantly higher value for subjects with asthma compared to controls (one sided Wilcoxon exact test).

Numeric results regarding the four subjects with asthma and the one control that developed comparatively large changes as an effect of pollen season are presented in Table 4. There are large inter individual differences: $\Delta\text{FENO}_{0.05}$ ranges from -0.6 – 7.2 nL/s and ΔCANO from -5.3 – 9.2 nL/L.

Discussion

The present study showed that birch pollen allergic subjects with asthma have on average significantly higher FENO_{0.05}, J_{aw}NO and CANO than controls and that during pollen season FENO_{0.05} and J_{aw}NO increase, CANO is not significantly affected and CANO_{corrected} decreases. Individual results show, however, that CANO increases substantially in a few subjects with asthma. FENO among controls are not affected by season.

The pollen-season 2011 was characterized by a high peak of birch pollen in the end of April, where the levels were 2800 counts/m³, and remained significantly elevated for more than two weeks. Exposure to pollen from trees, like birch, above 15 per m³ is likely to give rise to symptoms in many sensitized subjects and levels > 90 have been

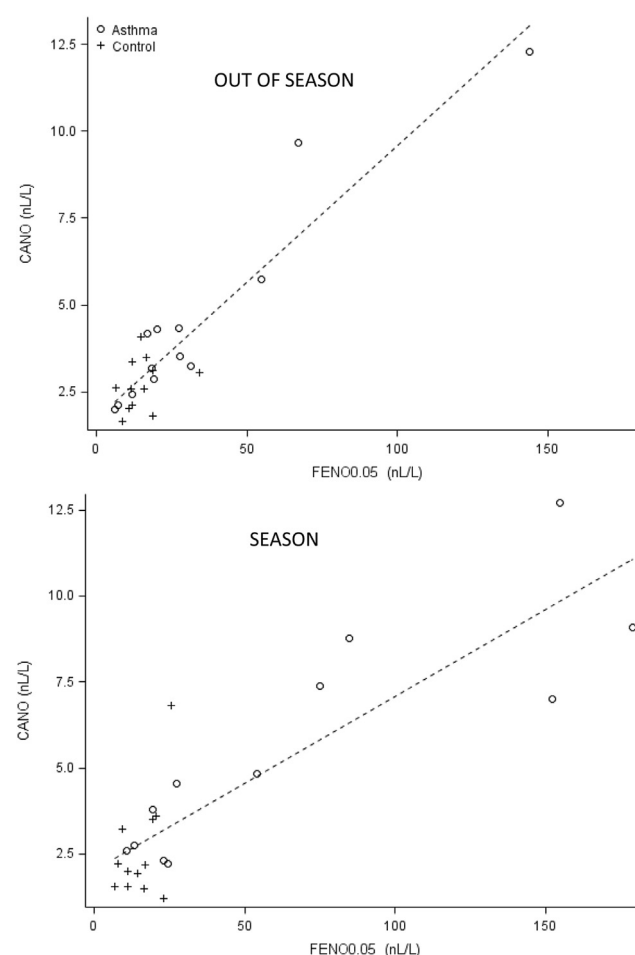


Figure 2 The relationship between airway NO production (FENO_{0.05}) and acinar/alveolar nitric oxide concentration (CANO) uncorrected for back-diffusion out of pollen season and during pollen season.

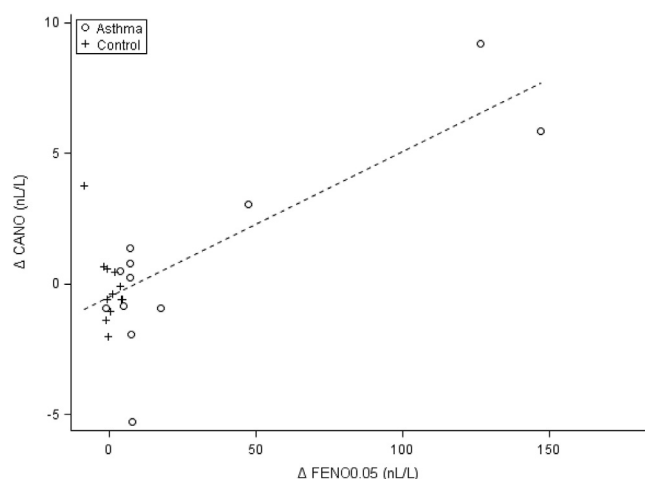


Figure 3 Individual changes of FENO0.05 (Δ FENO0.05) and CANO (Δ CANO) that developed between out of season and pollen season.

described to induce symptoms in most subjects [29], i.e. an effect is described at substantially lower levels than the exposure of the subjects in the present study. It is well known that respiratory symptoms from the lower airways often lag for two days or more after exposure, and that repeated pollen exposure, also at lower levels, increase the symptomatology due to priming of the mucosa [29]. The individual exposure levels are not known in the present study, and may vary considerably. Highly sensitized persons in particular may choose to stay indoors to reduce exposure. Nevertheless FENO increased during pollen-season in all sensitized subjects, indicating sufficient exposure to give rise to eosinophilic airway inflammation.

FENO_{0.05} was increased out of season and increased further during season among subjects with asthma whereas controls remained unaffected (Table 2). This is in line with the results of many previous publications [1,2,4,7,30] and indicates that pollen exposure build up eosinophilic airway inflammation in pollen allergic subjects with asthma but not in controls. This is in line also with results summarized by Tilles et al., showing increased bronchial reactivity during pollen season among allergic subjects with asthma [31]. The likely interpretation in view of the normal FEV₁, is that the increased NO does not originate from the most central airway generations. Obstruction of these central airways would have been associated with a decrease of FEV₁, whereas obstruction of more peripheral airway

generations may not [32]. An alternative explanation could be that the increased formation of NO in central airways does not necessarily cause airway obstruction. Anyhow, FENO measurements are evidently superior to spirometry regarding the detection of allergic airway inflammation.

The axial distribution of airway NO production in subjects with asthma during and out of pollen season is, however, not clearly delineated. JáwNO increased significantly whereas CANO remained unaffected by season among the subjects with asthma in the present study (Table 3). Tufvesson et al. found significantly increased CANO during season compared to out of season in rhinitic subjects with asthma [25]. JáwNO increased in both studies. Tufvesson et al. investigated 13 rhinitic subjects with asthma during season and out of season whereof 11 subjects showed an increased CANO and 2 subjects a decreased CANO during season whereas in the present study 7 subjects showed an increased CANO and 5 subjects a decreased CANO during season. Thus the difference in CANO results is moderate. The degree of airway obstruction was not reported in the study by Tufvesson et al. [25]. Spirometry was normal and did not change during season in the present study (Table 1). If the subjects of Tufvesson et al. became more obstructive during season this might explain the discrepancy regarding CANO. Tufvesson et al. used FENO obtained at 100 mL/s and 400 mL/s and the model of Tsoukias et al. for the calculation of CANO [10]. Applying that model and flows of 100 mL/s and 270 mL/s to the present material resulted in CANO = 3.31 nL/L and 3.16 nL/L in asthma subjects out of season and during season respectively. Thus the different methods do not explain the different results. Different characters of subjects with asthma appear to be the most likely reason for the moderate difference of CANO results between the present and that of Tufvesson et al. In the very recent report by Lopez et al. 20 subjects with allergic rhinitis, 11 subjects with asthma and allergic rhinitis and 11 controls were studied [26]. In the asthma group there were no significant effects of pollen season on either JáwNO or CANO whereas in subjects with allergic rhinitis JáwNO increased significantly during pollen season but CANO was not affected. Thus, in line with the present results CANO appears to be unaffected by pollen season. The unchanged JáwNO among subjects with asthma in the study by Lopez et al. is probably due to the substantially increased values out of season compared to controls: 2.27 pL/s compared to 0.60 pL/s. In the present study the corresponding results were 0.84 pL/s compared to 0.53 pL/s (Table 3). In

Table 4 Individual results of the four subjects with asthma and the one control that deviates from majority by showing large effects of pollen season.

Idnr	Asth/Contr	FENO _{0.05} (nL/s)			CANO (nL/L)			FEV%		Delta FEV ₁ (L)	
		Out of season	Season	Δ	Out of season	Season	Δ	Out of season	Season	Out of season	Season
10	Asth	28	75	48	4.3	7.4	3.1	86	88	0.0	0.2
14	Asth	32	179	147	3.3	9.1	5.8	83	82	0.1	0.1
15	Asth	28	155	127	3.5	12.7	9.2	82	78	0.2	0.3
17	Asth	144	152	8	12.3	7.0	-5.3	65	68	0.4	0.5
22	Contr	34	26	-9	3.1	6.8	3.7	80	82	0.0	0.0

summary we consider the present and the studies of Tufvesson et al. and Lopez et al. [25,26] to indicate that JáwNO increase during season whereas CANO may increase depending on the characteristics of the subjects with asthma.

How then to interpret the axial distribution of NO production in view of increased JáwNO, FENO_{0.05} and CANO in allergic subjects with asthma out of season and during season? In a recent letter to the editor, Verbanck et al. suggested that the relationship between JáwNO or FENO_{0.05} and CANO provides information about alveolar production and impeded back diffusion [33]. CANO as a function of FENO_{0.05} out of season (Fig. 1 upper panel) shows that on average CANO increase by $0.0787 \times \text{FENO}_{0.05}$. Kerckx et al. showed by consentient model experiments and measurements that CANO increases by $0.075 \times \text{FENO}_{0.05}$ [12]. Thus, the higher CANO among subjects with asthma compared to controls (Table 3) appears to be due entirely to increased NO production in the preacinar/acinar airways and does not imply increased alveolar production. CANO as a function of FENO_{0.05} during pollen season shows that on average CANO increased by $0.0507 \times \text{FENO}_{0.05}$ in the present study (Fig. 1 lower panel). The 95% confidence interval of the FENO_{0.05}/CANO slope is 0.049–0.150 [24]. Thus, the less steep slope between CANO and FENO_{0.05} during season may be due to impeded back diffusion caused by constriction of acinar airways and brought about by pollen exposure induced inflammation. This interpretation is, however, dependent on the assumption that the substantially increased FENO_{0.05} during season is due to elevated NO flux from preacinar/acinar airways. Had the substantially increased FENO_{0.05} during season been due primarily to elevated NO flux from the most central airways then CANO would not depend on FENO_{0.05}. The interpretation regarding impeded back diffusion and constriction of preacinar/acinar airways could therefore possibly be incorrect. Anyhow, involvement of the most distal and smallest airways in asthma has been demonstrated by multiple breath washout [34–36] supporting the interpretation that acinar airways are indeed affected in asthma causing ventilation heterogeneity. In addition, the present spirometric results are compatible with effects on peripheral airways of pollen exposure as there was no evidence of effects on central airways despite the substantially increased JáwNO.

When the estimated effect of back diffusion from acinar airways to alveoli had been subtracted from CANO the resulting CANO_{corrected} decreased significantly during pollen season in subjects with asthma. It is unlikely that NO produced by the alveolar cells would decrease during pollen season. It seems more likely that the back diffusion correction is inappropriate. Indeed Tufvesson et al. observed that when CANO was corrected for back diffusion several rhinitic subjects with high JáwNO got negative CANO_{corrected}, i.e. unrealistic values [25]. A possible explanation has been suggested by Verbanck et al. i.e. the calculated effect of back diffusion is erroneously overestimated because of constriction of intra acinar airways reducing the available total cross sectional area and thereby impeding back diffusion [22]. Accordingly one may conclude that pollen sensitized subjects with asthma may develop intra acinar airway obstruction during pollen season. Then JáwNO would be expected to increase as less NO

is lost to the blood and more NO is being exhaled. This is in line with the results of the present study and could contribute to the increased FENO_{0.05} and JáwNO in subjects with asthma during pollen season.

Individual changes during pollen season, i.e. $\Delta\text{FENO}_{0.05}$ or $\Delta\text{JáwNO}$ and ΔCANO show that despite of no significant effect of season on CANO in subjects with asthma in general there appears to be a relationship between $\Delta\text{FENO}_{0.05}$ and ΔCANO when the three subjects with asthma with substantial changes are considered (Fig. 3 and Table 4). Presumably the asthma group is composed of subjects with different characteristics. The average quotient $\Delta\text{CANO}/\Delta\text{FENO}_{0.05}$ of these three subjects with asthma is 0.059 i.e. close to the lower end of the 95% confidence interval [24] and consistent with the notion of impeded back diffusion and constriction of intra acinar airways. This interpretation is consistent also with the obtained negative $\Delta\text{CANO}_{\text{corrected}}$ and the unrealistic negative CANO_{corrected} during pollen season in two of the subjects with asthma. The majority of the subjects with asthma showed small increases of FENO_{0.05} but no systematic changes of CANO and therefore presumably unaffected NO production in the preacinar/acinar airways and no constriction of intra acinar airways.

The limitations of the present study are above all the limited number of subjects with asthma. FENO was measured at three flows only and e.g. five flows between 70 and 300 mL/s would have been preferable, ensuring valid regressions of the “slope intercept method”. It had of course been favorable to have measured nitrogen multiple breath washout also to get independent information on individual effects of pollen season on acinar involvement.

We conclude regarding allergic subjects with mild asthma 1) that out of pollen season many but not all suffer from airway inflammation including acinar/preacinar airways but normal alveolar production, 2) that exposure to birch pollen induces increased airway inflammation in almost all subjects with asthma sensitized to pollen, 3) that exposure to birch pollen may induce obstruction of intra acinar airways but unaffected alveolar production in a minority of subjects. Furthermore, FENO measurements are far superior to ordinary spirometry to detect changes in pollen allergic asthmatic subjects.

Conflict of interest

None declared.

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