



Differences in nitric oxide airway diffusion after maximum oxygen uptake test in asthmatic and nonasthmatic elite junior cross-country skiers

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ABSTRACT Asthma is common in cross-country skiers and is often treated with β_2 -agonists and inhaled corticosteroids (ICS). Exhaled nitric oxide (NO) is often used to guide ICS treatment in asthma. This study investigated the change in pulmonary NO dynamics before and after a maximum oxygen uptake ($V'_{O_{2max}}$) test.

An extended NO analysis was performed among Swedish elite junior cross-country skiers ($n=25$), with and without declared asthma, before and after a $V'_{O_{2max}}$ test using roller skis. Asthma was declared by six boys and two girls among whom five occasionally used ICSs.

There were no differences in baseline NO parameters between those with and without declared asthma. The median (interquartile range) diffusion capacity over airway wall (D_{awNO}) was 21 (17–25) $mL \cdot s^{-1}$, which is much increased for this age group. After the $V'_{O_{2max}}$ test, there were statistically significant differences from the baseline fraction of exhaled NO ($F_{ENO_{50}}$), NO flux from airways, D_{awNO} and alveolar NO values; but not in the NO content in airway wall (C_{awNO}) for all subjects together as one group. However, in the asthma group, differences were only seen in $F_{ENO_{50}}$ and C_{awNO} .

Interestingly, a majority of the subjects had an increase in the D_{awNO} . An increase in D_{awNO} has been found with allergic asthma together with elevated C_{awNO} . The skiers did not have elevated C_{awNO} , which indicates an absence of inflammation in the airway wall. Modelling of lung NO production clearly shows that the asthma among our skiers is distinct from the allergic asthma in nonathletes.



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NO pulmonary dynamics of junior cross-country skiers with asthma respond differently to the $V'_{O_{2max}}$ test than in those without asthma. Analysis of airway inflammation should be considered before inhaled corticosteroids are prescribed. <https://bit.ly/3eWB1JZ>

Cite this article as: Högman M, Wedholm L, Carlsson T, *et al.* Differences in nitric oxide airway diffusion after maximum oxygen uptake test in asthmatic and nonasthmatic elite junior cross-country skiers. *ERJ Open Res* 2021; 7: 00378-2020 [<https://doi.org/10.1183/23120541.00378-2020>].



Introduction

Respiratory symptoms are common in elite athletes. The prevalence of asthma/airway hyperreactivity is as high as 15% [1]. In cross-country skiers, the prevalence is even higher. In a Swedish study among skiers that used a postal questionnaire, 29% in the age group 15–19 years self-reported physician-diagnosed asthma [2]. In another Swedish postal questionnaire study among adolescent skiers that also included control subjects, the prevalence of physician-diagnosed asthma was 23% among skiers and 12% in the control group [3]. Beta₂-agonists and inhaled corticosteroids (ICS), which are asthma medications, are often used among skiers for the treatment of respiratory symptoms. According to a 2008 joint task force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology, a diagnosis of exercise-induced asthma is not the same as exercise-induced bronchoconstriction (EIB), and most of the elite athletes referred for respiratory problems do not suffer from asthma [4].

Elite cross-country skiers are exposed to cold dry air, and with a minute volume around 200 L during training or competition, their airways will be challenged to heat and to humidify the air. Stress on the airway also entails inflammatory cell attraction. However, these cells do not seem to be activated [5] so low values of exhaled nitric oxide (F_{ENO}) can therefore be expected. It has been shown that F_{ENO} was not elevated in a group of skiers when compared to a group of people with asthma even though significant bronchial responsiveness to inhaled methacholine was present [6].

F_{ENO} has been shown to decrease after a short exercise challenge [7], as well as after a marathon race [8]. A measurement of F_{ENO} at one flow will only reveal a sum of the changes in the pulmonary NO dynamics, whereas an extended NO analysis can localise specific NO parameter changes. When assessing pulmonary NO dynamics, the nonlinear method makes it possible to estimate the alveolar NO (C_{ANO}), the airway flux of NO (J_{awNO}), the content of NO in the airway wall (C_{awNO}) and the diffusing capacity of NO (D_{awNO}). Published C_{ANO} , C_{awNO} and D_{awNO} data on winter sports athletes have not been found. This study investigated the pulmonary NO dynamics and the change before and after a maximum oxygen uptake ($V'_{\text{O}_2\text{max}}$) test in elite junior cross-country skiers.

Material and methods

Study design and subjects

Swedish elite junior cross-country skiers (n=25) were recruited during their yearly check-up to determine their maximum oxygen uptake. Among these were 17 boys and 8 girls. Our sample was taken from the top performing cross-country skiers, which was 12% of the total 210 from this age group in Sweden. The Regional Review Board in Uppsala, Sweden (Dnr 2018/349) approved the study on 28 November 2018. All subjects gave written informed consent.

The subjects filled out a questionnaire regarding their health that contained questions about illnesses, medications, training, diet, hydration, current injuries as well as any heart, airway, dizziness, blood pressure, head trauma or allergy issues. Exhaled NO was analysed before and within 5–10 min after a $V'_{\text{O}_2\text{max}}$ test that used roller skis.

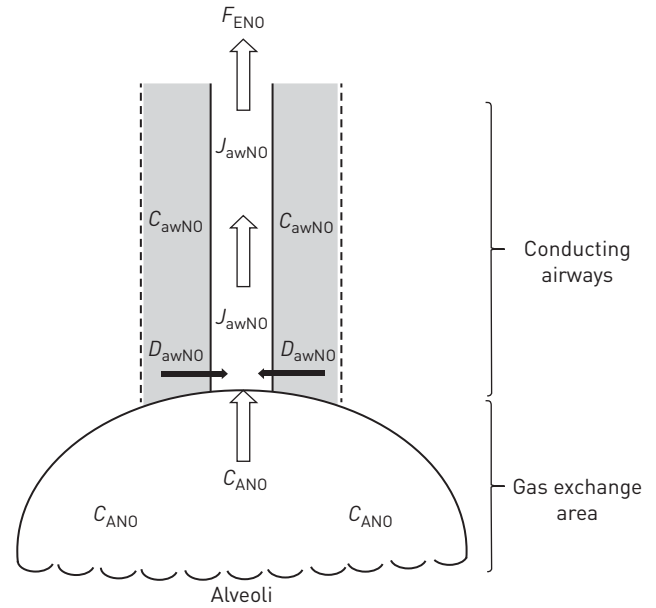
Testing procedures

An analyser (EcoMedics DLC 88; Eco Medics AG, Dürnten, Switzerland) was used to measure NO levels. Calibration and maintenance of the analyser was performed according to the manufacturer's instructions. The zero-point off-set was controlled before the measurements. The subjects' statures (Harpender Stadiometer, Holtain Ltd., Crymych, UK) and body masses (Midrics 2, Sartorius AG, Göttingen, Germany) were measured before a standardised warm-up that consisted of 10 min of roller-skiing on a treadmill. The roller-skiing tests to determine the subjects' $V'_{\text{O}_2\text{max}}$ were performed on a motor-driven treadmill (Saturn 450/300 rs; h/p/Cosmos Sports & Medical GmbH, Nussdorf-Traunstein, Germany). The subjects used the laboratory's roller skis (Pro-Ski C2; Sterners Specialfabrik AB, Dala-Järna, Sweden) and their own poles with plastic tips (black plastic tip; LEKI Lenhart GmbH, Kirchheim, Germany) provided by the laboratory. Throughout the $V'_{\text{O}_2\text{max}}$ test, variables of expired air were continuously analysed using a metabolic cart in the mixing-chamber mode (Jaeger Oxycon Pro, Erich Jaeger GmbH, Friedberg, Germany). Before each test, the expiratory flow meter and the O₂ and CO₂ analysers were calibrated according to the manufacturer's specifications. Capillary blood samples were collected from a fingertip at 2 and 5 min after the $V'_{\text{O}_2\text{max}}$ test. These samples were then analysed to determine blood lactate concentrations (Biosen 5140, EKF-diagnostic GmbH, Barleben, Germany). Within 10 min after the $V'_{\text{O}_2\text{max}}$ test, the exhaled NO levels were re-analysed.

NO analysis

In conformity with the 2005 American Thoracic Society and the ERS recommendations for NO measurements, exhaled NO was analysed at an exhalation flow rate of 50 mL·s⁻¹ ($F_{\text{ENO}50}$). In accordance

FIGURE 1 The two-compartment model consists of the conducting airways and the gas exchange area. In the conducting airways, all airways of the lungs are equally represented. The gas exchange area contains the alveolar or acinar compartment as well as the respiratory bronchiole. When the alveolar gas with its low content of nitric oxide (NO) (C_{ANO}) is expelled, the contribution of NO from the airways is driven by a concentration gradient of NO from the airway wall (C_{awNO}). The rate is governed by the diffusion capacity of the airway wall (D_{awNO}). The airway NO flux (J_{awNO}) is therefore dependent on both the C_{awNO} and the D_{awNO} . Exhaled NO (F_{ENO}) is dependent on all of the NO parameters.



with the ERS technical standards of modelling NO dynamics, two methods were used: the nonlinear method with exhalation flows of 20, 100 and 300 mL·s⁻¹, and the linear method with exhalation flows of 100, 200 and 300 mL·s⁻¹ [9]. Flow resistors were used with the subjects to facilitate a constant exhaled flow. A visual feedback system was used to guide the subjects so that they could achieve the targeted flow throughout the exhalation. The Högman–Meriläinen algorithm (HMA) nonlinear method and the Tsoukias and George linear method (TG) [9] were both used with the software in the NO analyser. For quality control, a calculated $F_{ENO_{50}}$ for the HMA and an r-value for the linearity of the TG method were derived for each subject on the two NO analysis occasions. The HMA method estimates the following NO parameters: C_{ANO} , C_{awNO} , D_{awNO} and J_{awNO} , whereas the TG method only estimates C_{ANO} and J_{awNO} . As they could find it difficult to breathe after the $V'_{O_{2,max}}$ test and perform an exhalation at the low flow of 20 L·s⁻¹, all of the subjects were to perform the HMA method and TG method on both test occasions. The two-compartment model of the lung NO dynamics is seen in figure 1.

Maximum oxygen uptake test

The incremental treadmill roller-skiing test to determine the $V'_{O_{2,max}}$ was begun using the diagonal-stride technique. During the initial 30 s of the test, the treadmill inclination was 2.4° and the treadmill speeds were 9.0 km·h⁻¹ for females and 10.9 km·h⁻¹ for males. Thereafter, the inclination was increased by 0.4° and the speed was increased by 0.1 km·h⁻¹ every 30 s until volitional fatigue. The $V'_{O_{2,max}}$ was defined as the highest mean oxygen uptake during a 60-s period when meeting the criterion of a plateau in oxygen uptake despite an increase in exercise intensity. Determination of the plateau was based on the recognition of data points that fell outside (and below) the extrapolated 95% confidence interval for the V'_{O_2} -work rate relationship [10]. In addition to the oxygen uptake plateau, a blood lactate concentration of ≥ 8 mmol·L⁻¹ was also required to confirm that the participant achieved $V'_{O_{2,max}}$.

Analysis

All statistical analyses were performed using SPSS, version 26 for Windows (SPSS Inc., Chicago, MI, USA). Data are expressed as median (interquartile range). The Mann–Whitney U-test was used to make comparisons between any two groups. For pairwise comparisons the Wilcoxon signed-rank test was applied. Correlations were tested with Spearman’s rank order correlation. A p-value of <0.05 was considered significant. Plots were made with SigmaPlot graphic software, version 14 for Windows (SYSTAT, Alfasoft AB, Göteborg, Sweden).

Results

Of the 25 elite junior cross-country skiers that participated, eight declared that they had asthma that was diagnosed by a physician. Of these, five occasionally used ICSs together with a β_2 -agonist (short or long acting), one only used a short-acting β_2 -agonist and two did not use any medication. Allergies (mite, furry animals, pollen or grass) were declared by seven subjects, four of whom had asthma that was treated with ICSs together with a β_2 -agonist (short or long acting) and one that was treated with a short-acting

TABLE 1 Characteristics expressed as median (upper and lower quartiles) for all the subjects together as a group and also divided into nonasthma and declared asthma groups

	All	Nonasthma	Asthma	p-value
Subjects n	25	17	8	
Age years	18 (17–20)	19 (17–20)	18 (17–19)	0.75
Body mass index kg·m⁻²	22 (21–24)	22 (22–23)	22 (21–26)	0.84
V_{O₂max} L·min⁻¹	4.25 (3.77–4.79)	4.25 (3.74–4.80)	4.20 (3.77–4.79)	0.93
V_{O₂max} mL·min⁻¹·kg⁻¹	60 (55–64)	60 (55–66)	61 (52–64)	0.80
Blood lactate mmol·L⁻¹	12.7 (11.7–14.6)	12.7 (11.7–14.1)	12.7 (11.1–16.2)	0.67
Time to exhaustion min	7.37 (6.24–8.21)	7.50 (6.51–8.52)	6.50 (6.11–7.73)	0.12

Data are presented as median (interquartile range), unless otherwise stated. The p-values given are from a comparison of nonasthma and declared asthma groups. V_{O₂max}: maximal oxygen uptake.

β₂-agonist. All of the remaining three who declared allergies took an antihistamine. There were no statistically significant baseline differences in the NO parameters when comparisons were made between the nonasthma and the asthma groups, the nonallergic and the allergic groups and nonallergic asthmatic and the allergic asthmatic groups. Therefore, the subjects were divided into nonasthma (n=17) and asthma (n=8) groups. Subject characteristics are presented in table 1. There were no differences in relation to age or body mass index between the nonasthma and asthma groups. For the V_{O₂max} test, all subjects used roller skis except for three male skiers who preferred to run. There was no statistically significant difference in their performance in regard to asthma. When those with asthma and allergy were treated as one group, their time to exhaustion was shorter than the nonasthma/nonallergy group: 6.72 (6.14–7.52) versus 7.96 (6.91–8.79) min, p=0.002.

All subjects were able to perform the HMA and TG methods on both test occasions. The quality control measurement results were well within the ERS standardisation recommendations [9]. For the HMA method, the calculated F_{ENO₅₀} in comparison to the measured F_{ENO₅₀} was -1 (-2, 0) ppb, and the r-value for the TG method was 0.99 (0.97–1). There was no difference in the estimation of C_{AWNO} between the methods: 1.9 (1.6–2.4) and 1.9 (1.3–2.3) ppb, respectively, p=0.71. The estimation of J_{awNO} using the HMA method was 0.63 (0.33–0.90) nL·s⁻¹, and with the TG method 0.67 (0.50–1.0) nL·s⁻¹, p=0.34. As all subjects were able to perform the low-flow exhalation, the results are from the data using the HMA method.

Before the V_{O₂max} test, the F_{ENO₅₀} and NO parameters were not significantly different in regard to sex, or treatment with ICS and/or β₂-agonists. Neither were there any differences in F_{ENO₅₀} (p=0.37), J_{awNO} (p=0.59), C_{awNO} (p=0.10), D_{awNO} (p=0.19) or C_{ANO} (p=0.71) between those with and those without declared asthma, as shown in table 2. There were no statistically significant differences between those with declared allergy and those without: F_{ENO₅₀} (14 (12–29) ppb and 17 (10–23) ppb, respectively) p=0.57, J_{awNO} (0.9 (0.6–1.7) nL·s⁻¹ and 0.8 (0.6–1.5) nL·s⁻¹) p=0.70, C_{awNO} (63 (38–113) ppb and 52 (32–72) ppb)

TABLE 2 F_{ENO₅₀} and NO parameters expressed as median (upper and lower quartiles), before and after V_{O₂max} test for all subjects together as a group and also divided into nonasthma and declared asthma groups

	All (n=25)			Nonasthma (n=17)			Asthma (n=8)		
	Before	After	p-value	Before	After	p-value	Before	After	p-value
F_{ENO₅₀} ppb	17 (11–24)	11 (7–17)	<0.001	17 (10–24)	11 (7–18)	<0.001	16 (13–28)	13 (8–16)	0.012
J_{awNO} nL·s⁻¹	0.91 (0.60–1.57)	0.63 (0.33–0.90)	<0.001	0.74 (0.55–1.57)	0.63 (0.26–0.88)	<0.001	0.93 (0.68–1.67)	0.69 (0.42–0.94)	0.093
C_{awNO} ppb	52 (36–81)	43 (31–73)	0.427	51 (24–64)	36 (31–96)	0.554	64 (45–131)	51 (33–59)	0.036
D_{awNO} mL·s⁻¹	20 (15–25)	16 (8–19)	0.032	21 (16–25)	11 (7–18)	0.004	16 (8–24)	19 (11–22)	0.401
C_{ANO} ppb	1.6 (1.1–1.9)	1.9 (1.6–2.4)	0.006	1.5 (1.0–1.9)	2.0 (1.6–2.8)	0.005	1.6 (1.4–2.0)	1.7 (1.4–2.0)	0.401

Data are presented as median (interquartile range), unless otherwise stated. F_{ENO₅₀}: baseline exhaled nitric oxide fraction; V_{O₂max}: maximal oxygen uptake; J_{awNO}: the airway flux of NO; C_{awNO}: content of NO in the airway wall; D_{awNO}: diffusing capacity of NO; C_{ANO}: alveolar NO.

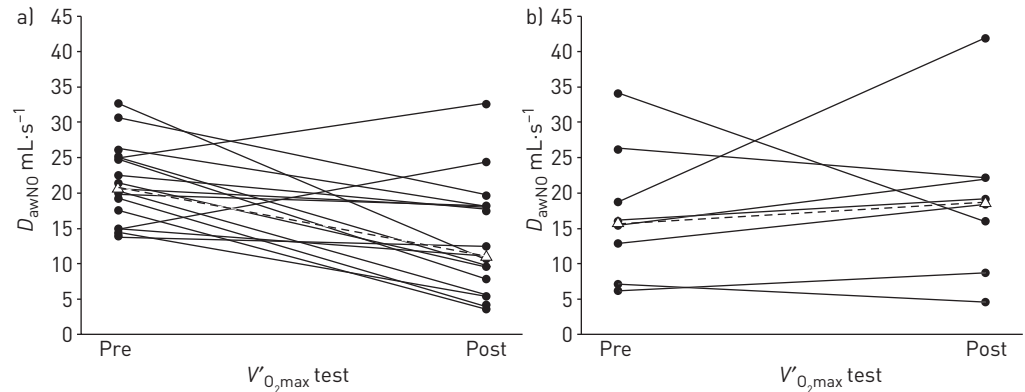


FIGURE 2 In the nonasthma group a) the NO diffusion capacity over the airway wall (D_{awNO}) is decreased ($p=0.004$) after the maximal oxygen uptake (V'_{O_2max}) test, whereas in the asthma group b) there was no statistical change in the median value ($p=0.40$).

$p=0.46$, D_{awNO} (19 (15–26) $mL\cdot s^{-1}$ and 20 (15–25) $mL\cdot s^{-1}$) $p=1.0$ and C_{ANO} (1.6 (1.4–1.7) ppb and 1.6 (1.0–2.0) ppb) $p=0.84$. Additionally, there were still no statistically significant differences when those with declared asthma and allergy were combined as one group and compared to those without asthma or allergy: $F_{ENO_{50}}$ (18 (13–29) ppb and 14 (9–22) ppb respectively) $p=0.17$, J_{awNO} (0.9 (0.7–1.7) $nL\cdot s^{-1}$ and 0.7 (0.5–1.3) $nL\cdot s^{-1}$) $p=0.32$, C_{awNO} (63 (44–113) ppb and 46 (25–62) ppb) $p=0.13$, D_{awNO} (19 (15–26) $mL\cdot s^{-1}$ and 20 (15–25) $mL\cdot s^{-1}$) $p=0.85$ and C_{ANO} (1.6 (1.4, 1.7) ppb and 1.5 (1.0, 2.0) ppb) $p=0.94$.

After the V'_{O_2max} test, there were statistically significant differences from the baseline values in $F_{ENO_{50}}$, J_{awNO} , D_{awNO} and C_{ANO} (all $p<0.05$), but not in C_{awNO} for all subjects when grouped together as one group. These statistically significant differences were the same in the nonasthma group, but in the asthma group the differences could only be seen in the $F_{ENO_{50}}$ and in C_{awNO} values as shown in table 2. The D_{awNO} decreased in the nonasthma group, but no change was found in the asthma group. The C_{awNO} decreased in the asthma group, but no change was found in the nonasthma group. This is illustrated with the data from the individual D_{awNO} values plotted in figure 2 and the C_{awNO} values plotted in figure 3.

$F_{ENO_{50}}$ is highly correlated with the NO flux (J_{awNO}) from the airways ($\rho=0.96$, $p\leq 0.001$). J_{awNO} is estimated from the C_{awNO} and D_{awNO} values using the nonlinear method with an adjustment for C_{ANO} [11]. The C_{awNO} has a correlation to the $F_{ENO_{50}}$ ($\rho=0.83$, $p\leq 0.001$), but not to the D_{awNO} ($\rho=-0.19$, $p=0.37$). In the nonasthma group the correlation between $F_{ENO_{50}}$ and the C_{awNO} remains ($\rho=0.96$, $p\leq 0.001$), but not in the asthma group ($\rho=0.50$, $p=0.21$). This is possibly due to too few individuals, because when the numbers are increased with the allergy subjects, the correlation is present ($\rho=0.70$, $p=0.007$).

Discussion

Elite junior cross-country skiers decreased their $F_{ENO_{50}}$ after a V'_{O_2max} test. When modelling NO production in the lung, a difference was seen between the subjects who declared asthma and in those who

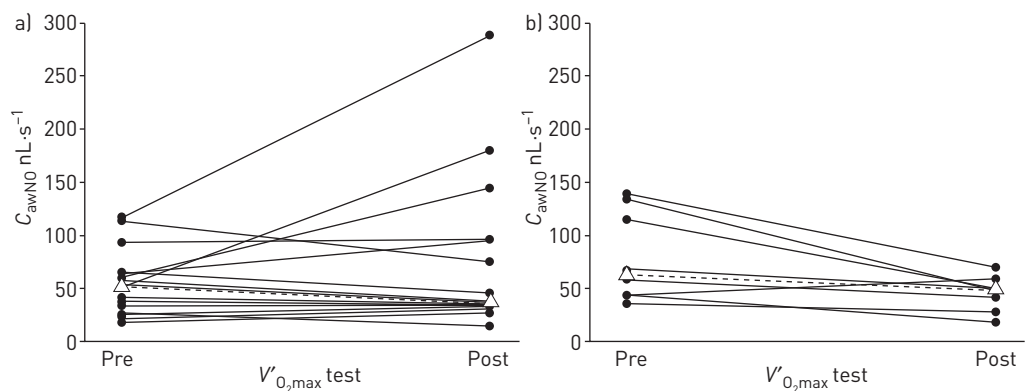


FIGURE 3 In the nonasthma group a) the NO content in the airway wall (C_{awNO}) did not change ($p=0.55$) after the maximal oxygen uptake (V'_{O_2max}) test, whereas in the asthma group b) there was a statistically significant decrease in the median value ($p=0.036$).

did not. The most prominent difference was in the change in the airway wall diffusion rate of NO; D_{awNO} . It decreased in those without asthma, whereas those with asthma and those with allergies had no change.

The $F_{ENO_{50}}$ values are in line with data from healthy subjects of the same age [12]. The same NO levels were also found by SUE-CHU *et al.* [6] in skiers and control subjects. They used a high flow of $250 \text{ mL}\cdot\text{s}^{-1}$, which resulted in a $F_{ENO_{250}}$ of 6 (4–10) ppb for their skiers. Using the NO parameters to retrieve the same flow, we found the $F_{ENO_{250}}$ to be 5 (4–7) ppb, which is quite similar. After the $V'_{O_{2max}}$ test, our skiers decreased their F_{ENO} levels by 35% and this is in line with the 34% decrease seen after a marathon race [8]. A short exercise challenge with a work intensity designed to increase the minute ventilation 40–50%, gave only a 10% decrease in F_{ENO} [7]. This is most likely due to the difference in the degree of insult to the airways, and this should be investigated.

The most interesting finding in this study is the different response to the exercise test found in the diffusion rate of NO over the airway wall. Only among those subjects who declared asthma and/or allergy demonstrated no change in the diffusing rate of NO. This exercise test forces the subjects to breathe heavily and the dry air causes a reduction in the extravascular water in the airways. The airway mucosa becomes hyperosmotic. The hyperosmolarity in the airway epithelial cells, which is due to cell shrinkage, releases mediators that may directly or indirectly increase the airway blood flow [5]. These mediators may also be responsible for the EIB. After cell shrinkage, there is a regulatory cell volume increase in healthy subjects and a transport of sufficient water to the mucosa to overcome the hyperosmolarity of the airway surface liquid. A result of this may also be airway wall oedema, which could be the cause of the decrease in D_{awNO} . In subjects with asthma, however, the rate of the transfer of water to the airway surface is slower due to airway inflammation [13]. This could possibly explain the lack of change in the D_{awNO} in our subjects with asthma and allergies. In addition, the majority of our subjects with asthma were treated with β_2 -agonists that relax the bronchial smooth muscles and prevent EIB. β_2 -agonists can also increase the rate of water transport to the airway surface by stimulating chloride ion secretion on the apical surface of the of epithelial cells [14]. Hence, the formation of oedema is prevented. The overuse of short-acting β_2 -agonists, which has recently been demonstrated among persons with asthma, is shown to be associated with an increased risk for exacerbations and asthma related mortality [15].

Persons with allergic asthma and rhinitis have an increased D_{awNO} and C_{awNO} [16]. In our skiers, we found a doubling of D_{awNO} . This is more than we had previously reported for people with allergic asthma [16, 17]. Additionally, the C_{awNO} was half as much as in a healthy population [18]. In EIB, there is an increase of inflammatory cells and remodelling of the airway [19]. The inflammatory cells do not seem to be activated in athletes [5], which is a probable reflection of the low NO content in the airway walls of our skiers. In atopic asthma, where there is an increased C_{awNO} , ICS prove very effective in treating the inflammation. Treatment guidelines for asthma recommend the combination of a β_2 -agonist together with ICS. The interpretation from the results obtained with our young skiers is that they do not have inflammation of the airway wall. Therefore, they will not benefit from treatment with an anti-inflammatory drug. A lack of response to ICS by skiers has been shown by SUE-CHU *et al.* [20]. ICS treatment does not affect the D_{awNO} [21], only the C_{awNO} . This explains why, for persons receiving ICS treatment for atopic asthma, the $F_{ENO_{50}}$ level barely reaches the reference values and thereby a risk for over treatment with ICS exists. $F_{ENO_{50}}$ is the product of D_{awNO} and C_{awNO} with adjustment for C_{ANO} [11]. A high $F_{ENO_{50}}$ can be due to an increase in either D_{awNO} or C_{awNO} . An individual's optimal $F_{ENO_{50}}$ can therefore be calculated when the level of D_{awNO} is taken into account [22]. In our skiers, the D_{awNO} was increased and the C_{awNO} was low. Hence, their $F_{ENO_{50}}$ levels were not different from those found among the healthy controls. This does not mean, however, that their airways are unaffected by their strenuous training and competitions in cold dry air.

There are limitations to our study that need addressing. We did not test the skiers for bronchial hyperreactivity and did not perform lung function tests. Since we did not have access to the subject's medical records, we could not examine them and we could not determine the asthma phenotype among those who declared having physician-diagnosed asthma. Also, we do not know how adherent the subjects with asthma were to their anti-inflammatory therapy. This additional information may have been useful when we were interpreting our NO results. The NO analysis could have been made with different time intervals, but the subjects needed to stabilise their breathing to be able to perform the different flows for the extended NO analysis. Additionally, the testing may have benefited from a third measurement, but the skiers' time was too limited.

In summary, we have shown that elite junior cross-country skiers included in the current study have an increase in the diffusion capacity of NO over the airway wall. Such an increase has been found in subjects with allergic asthma together with an elevated content of NO in the airway wall. The skiers did not have an elevated C_{awNO} , which indicates an absence of inflammation in the airway wall. Modelling of lung NO

production clearly shows that the asthma among our skiers is distinct from the allergic asthma in nonathletes and points to the need for an analysis of the airway inflammation in skiers before ICS are prescribed.

Acknowledgements: The authors wish to thank Robin Quell for proofreading and editing this manuscript.

Authors' contributions: M. Högman, L. Wedholm, T. Carlsson, M. Carlsson and M. Tonkonogi participated in the study design. M. Högman and L. Wedholm collected and, together with T. Carlsson, M. Carlsson and M. Tonkonogi, analysed the data. M. Högman prepared the initial draft. All authors have discussed and adjusted the draft, and have read and approved the final manuscript.

Conflict of interest: None declared.

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