Alveolar and exhaled NO in relation to asthma characteristics – effects of correction for axial diffusion

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Keywords
alveolar nitric oxide; asthma; axial diffusion; exhaled nitric oxide; peripheral inflammation.

Abstract

Background: Inflammation in the small airways might contribute to incomplete asthma disease control despite intensive treatment in some subgroups of patients. Exhaled NO (FeNO) is a marker of inflammation in asthma and the estimated NO contribution from small airways (CalvNO) is believed to reflect distal inflammation. Recent studies recommend adjustments of CalvNO for trumpet model and axial diffusion (TMAD-adj). This study aimed to investigate the clinical correlates of CalvNO, both TMAD-adjusted and unadjusted.

Methods: Asthma symptoms, asthma control, lung function, bronchial responsiveness, blood eosinophils, atopy and treatment level were assessed in 410 subjects, aged 10–35 years. Exhaled NO was measured at different flow-rates and CalvNO calculated, with TMAD-adjustment according to Condorelli.

Results: Trumpet model and axial diffusion-adjusted CalvNO was not related to daytime wheeze (P = 0.27), FEF50 (P = 0.23) or bronchial responsiveness (P = 0.52). On the other hand, unadjusted CalvNO was increased in subjects with daytime wheeze (P < 0.001), decreased FEF50 (P = 0.02) and with moderate-to-severe compared to normal bronchial responsiveness (P < 0.001). All these characteristics correlated with increased FeNO (all P < 0.05). Unadjusted CalvNO was positively related to bronchial NO flux (JawNO) (r = 0.22, P < 0.001) while TMAD-adjCalvNO was negatively related to JawNO (r = −0.38, P < 0.001).

Conclusions: Adjusted CalvNO was not associated with any asthma characteristics studied in this large asthma cohort. However, both FeNO and unadjusted CalvNO related to asthma symptoms, lung function and bronchial responsiveness. We suggest a potential overadjustment by current TMAD-corrections, validated in healthy or unobstructed asthmatics. Further studies assessing axial diffusion in asthmatics with different degrees of airway obstruction and the validity of proposed TMAD-corrections are warranted.

Chronic inflammation of the airways is the hallmark of asthma. However, diagnostic workup and tailoring of treatment strategy are traditionally based on symptoms and lung function tests (1). Despite intensified and sometimes costly treatment, a significant subgroup of patients with asthma do not achieve disease control (2). The development and standardization of methods to measure the fraction of exhaled nitric oxide (FeNO) has provided a reproducible and noninvasive means to obtain information about inflammatory activity, especially Th2-cytokine-driven, in the airways (3, 4). Inflammation in peripheral airways (internal diameter of <2 mm) has been highlighted as an important aspect of...
asthma (5–7). It has been speculated that one factor underlying failure to achieve asthma control could be peripheral inflammation that is not accessible to conventional therapies (5). With the availability of new extra-alarine drug formulations that can potentially reach farther into the airways, a clinically useful marker of inflammation in peripheral airways in asthma is needed to guide treatment decisions. The alveolar NO concentration (CalvNO) has been proposed as such a marker (8).

Alveolar NO has been validated as a marker of alveolar inflammation in allergic alveolitis, and previous studies have shown raised alveolar NO in uncontrolled asthma (9), symptomatic asthma (10), asthma with nocturnal symptoms (11), and severe asthma (12). Further, alveolar NO levels decrease after oral corticosteroid treatment (12). However, recent mathematical modeling of NO transport in the lungs has indicated that axial molecular diffusion brings NO from the higher concentration in the airway lumen into the alveolar compartment during exhalation (13); thus, measurements would overestimate alveolar NO concentrations, especially in situations with raised bronchial NO flux. With models that compensate for axial diffusion (14, 15), more recent studies have presented variable results on alveolar NO (16–18). Moreover, the relation between alveolar NO and asthma characteristics has been little studied.

The primary aim of this study was to investigate the clinical signal provided by CalvNO, by evaluating associations between CalvNO and various asthma characteristics such as symptoms, asthma control, lung function, bronchial hyperresponsiveness, atopy, blood eosinophils, and treatment level, with estimates of CalvNO calculated with and without correction for back diffusion. A secondary aim was to examine associations between standardized exhaled NO at 50 ml/s (FeNO50), bronchial NO flux (JawNO), and the above-named asthma characteristics.

Material and methods

Subjects

A total of 410 subjects, aged 10–35 years, with physician-diagnosed asthma and daily treatment with inhaled corticosteroids (ICS) and/or oral leukotriene receptor antagonist (LTRA) during at least three of the preceding 12 months were included in this study. Subjects were recruited from both primary and secondary care in Uppsala, Sweden, between March 2010 and March 2012. Exclusion criteria were other chronic respiratory diseases, active tuberculosis, and severe asthma (10), asthma with nocturnal symptoms (11), and severe asthma (12).

Clinical asthma characteristics

Subjects responded to questions regarding asthma symptoms during the last 12 months (19). The degree of asthma control was assessed by asthma control test (ACT) (20). The subjects’ use of ICS, LTRA, and any short courses of oral corticosteroids during the last three months was recorded in the interview. The prescribed daily dose of ICS was also collected from the subjects’ medical record.

Exhaled NO and extended NO analysis

Exhaled NO was measured according to the American Thoracic Society/European Respiratory Society recommendations using a chemiluminescence analyzer (NIOX Flex; Aerocrine AB, Solna, Sweden) (21) and always before spirometry. A more detailed description of the patients’ instructions and calibration is given in Patéis et al. (22). Measurements of exhaled NO were performed at four exhalation flow rates (50, 100, 200, and 300 ml/s) in random order, as previously described (23). Alveolar and central airway contributions to exhaled NO were calculated using the slope intercept model and the NO measurements at 100–300 ml/s (24). The Pearson correlation coefficient (r) between NO output and expiratory flow was calculated, and subjects were defined as model compliers if r ≥ 0.80, as previously described by Mahut et al. (16). A total of 29 noncompliers were excluded because CalvNO < 0 (n = 4), JawNO < 0 (n = 4), or r < 0.8 (n = 21). Estimated alveolar NO was adjusted for the trumpet shape of the airways and axial diffusion (TMAD) according to Condorelli (TMAD-adjusted CalvNO = CalvNO – JawNO/860) (15). The Condorelli method was chosen rather than the Kerckx method (14) because the Condorelli method gave fewer negative TMAD-adjusted CalvNO (20 vs 47). Negative TMAD-adjusted CalvNO values were assigned an arbitrary value of 0.01 to allow logarithmic transformation.

Lung function

Flow–volume curves were obtained according to American Thoracic Society recommendations (25) with a MasterScope spirometer (Erich Jaeger, Hoenzberg, Wurzburg, Germany). The lower limit of normal (LLN) for the ratio between forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) was calculated according to Hankinson (26). Subjects were subdivided according to normal or impaired lung function values (FEV1/ FVC < 0.80%, FVC < 0.80%, FEV1/FVC ≥ 0.80%, forced expired flow at 50% of vital capacity (FEF50) < 0.50%). For subjects <18 years of age, Zapletal reference values for lung function were used (27), and for subjects >18 years of age, Hedenström reference values were used (28, 29).

Bronchial responsiveness

Methacholine provocation was performed with aerosol provocation system (Viasys Healthcare GmbH, Hoechberg, Germany) according to a simplified protocol described in detail elsewhere (22). Bronchial responsiveness was defined according to Schulze et al. (30) as normal when methacholine cumulative dose causing a fall in FEV1 (PD20) >1.0 mg, borderline-to-mild 0.3–1.0 mg, and moderate-to-severe <0.3 mg.

Blood eosinophil count

Blood eosinophils (B-eos) were counted at the Department of Clinical Chemistry at Uppsala University using a routine method (Cell-Dyn 4000, Abbott, IL, USA). Subjects were
divided into three groups according to the level of B-eos: normal ($<0.3 \times 10^9/\text{l}$), intermediate ($0.3 - 0.5 \times 10^9/\text{l}$) and high ($>0.5 \times 10^9/\text{l}$).

**Atopy**

IgE against a mix of aeroallergens (grass, tree and weed pollen, animal, mite, and mould allergens) (Phadiatop; Immunodiagnostics Thermofisher Scientific, Uppsala, Sweden) (31) was measured in all subjects except three. Subjects were defined as atopic if they had IgE antibodies against Phadiatop $\geq 0.35 \text{kU/l}$.

**Statistics**

Statistical analyses were performed with STATA/IC 12.1 (StataCorp LP, College station, TX, USA) using log-transformed NO parameters. Unpaired $t$-test was used to compare NO parameters in dichotomized subject groups, linear regression models were applied for correlation between $J^{awNO}$ and $\text{CalvNO}$, and multiple linear regression models for differences in NO parameters for asthma characteristics adjusted for age, sex, height, and smoking. A $P$-value of $<0.05$ was considered significant.

**Ethics**

Uppsala Regional Ethical Review Board approved the study (approval number 2009/349), and all subjects and their legal guardians gave written informed consent.

**Results**

**Description of the subjects**

Most subjects were IgE-sensitized and their asthma well controlled. Demographic details and asthma characteristics are presented in Table 1. A total of 376 of 410 (91.7%) subjects were slope intercept model compliers. The noncompliers ($n = 29$) were younger and shorter and had a higher $\text{FEF50}$ than compliers ($P < 0.05$, Table 1). For all further analyses, results are based on model compliers only.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Data presented as mean (SD) unless otherwise indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All asthma subjects ($n = 410^\ast$)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.4 ± 7.1</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>209 (51.0)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.8 ± 12.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.7 ± 16.5</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>18 (4.4)</td>
</tr>
<tr>
<td>ACT</td>
<td>20.6 (±3.4)</td>
</tr>
<tr>
<td>ACT ≥ 20, n (%)</td>
<td>267 (70)</td>
</tr>
<tr>
<td>FEV1 (%pred)</td>
<td>92.0 ± 14.1</td>
</tr>
<tr>
<td>FVC (%pred)</td>
<td>99.6 ± 14.2</td>
</tr>
<tr>
<td>FEV1/FVC (%)</td>
<td>81.4 ± 8.4</td>
</tr>
<tr>
<td>FEF50 (%pred)</td>
<td>82.0 ± 26.2</td>
</tr>
<tr>
<td>PD20 methacholine (mg)†</td>
<td>0.69 (0.52–0.93)</td>
</tr>
<tr>
<td>Atopic, n (%)</td>
<td>322 (79.1)</td>
</tr>
<tr>
<td>B-eos ($\times 10^9/\text{l}$)†</td>
<td>0.18 (0.17–0.20)</td>
</tr>
<tr>
<td>ICS-use</td>
<td>81 (19.8)</td>
</tr>
<tr>
<td>ICS &lt;500, n (%)</td>
<td>244 (59.5)</td>
</tr>
<tr>
<td>ICS 500–800, n (%)</td>
<td>53 (12.9)</td>
</tr>
<tr>
<td>ICS &gt;800, n (%)</td>
<td>32 (7.8)</td>
</tr>
<tr>
<td>LTRA, n (%)</td>
<td>74 (18.0)</td>
</tr>
<tr>
<td>FeNO50 (ppb)†</td>
<td>15.8 (14.6–17.0)</td>
</tr>
<tr>
<td>$J^{awNO}$ (pl/s)†</td>
<td>644 (584–710)</td>
</tr>
<tr>
<td>$\text{CalvNO}$ (ppb)†</td>
<td>2.7 (2.6–2.9)</td>
</tr>
<tr>
<td>TMAD-adj.$\text{CalvNO}$ (ppb)†</td>
<td>1.3 (1.1–1.5)</td>
</tr>
</tbody>
</table>

ACT, asthma control test; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; NO, nitric oxide; TMAD, trumpet model and axial diffusion.

Forced vital capacity (FVC) and FEV1 presented as percentage predicted adjusted for age, sex, and height. Atopic = Phadiatop positive.

*Five individuals had a valid FeNO50 measurement, but failed a set of measurements between 100 and 300 ml/s.

†Data presented as geometric means (95% confidence interval).
Correlation between unadjusted and TMAD-adjusted CalvNO and J'awNO

Unadjusted CalvNO was positively associated with J'awNO ($r = 0.22$, $P < 0.001$). For TMAD-adjusted CalvNO, a negative correlation with J'awNO was found ($r = -0.38$, $P < 0.001$), see Fig. 1. These results remained unchanged when subjects were divided into two groups: <18 years of age ($r = 0.25$, $P < 0.001$ and $-0.41$, $P < 0.001$) or $\geq 18$ years of age ($r = 0.20$, $P < 0.001$ and $r = 0.34$, $P < 0.001$).

NO parameters and asthma symptoms in the year preceding the study

TMAD-adjusted CalvNO was similar for subjects who did and did not report any of the asthma symptoms studied. Unadjusted CalvNO and FeNO50 were higher in subjects with reported daytime wheeze in last 12 months ($n = 271$) compared with subjects without daytime wheeze ($n = 105$) ($P < 0.001$ for both) (Fig. 2), as was J'awNO ($P < 0.001$). In subjects reporting an asthma attack in last 12 months...
Table 2: Nitric oxide (NO) parameters in relation to reported asthma symptoms during the last 12 months

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reported symptoms during the last 12 months</th>
<th>n</th>
<th>No. (%)</th>
<th>P</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awakened by dyspnea</td>
<td>Yes</td>
<td>276</td>
<td>100</td>
<td>0.44</td>
<td>0.042</td>
</tr>
<tr>
<td>Daytime dyspnea at rest</td>
<td>Yes</td>
<td>276</td>
<td>100</td>
<td>0.44</td>
<td>0.042</td>
</tr>
<tr>
<td>Awakened by feeling of chest tightness</td>
<td>Yes</td>
<td>276</td>
<td>100</td>
<td>0.44</td>
<td>0.042</td>
</tr>
<tr>
<td>Exercise-induced dyspnea</td>
<td>Yes</td>
<td>276</td>
<td>100</td>
<td>0.44</td>
<td>0.042</td>
</tr>
</tbody>
</table>

Data presented as geometric means (95% confidence interval).

Bold values show P-values < 0.05.

TMAD-adjusted CalvNO and FeNO50 were similar in subjects with controlled (ACT ≥ 20) and noncontrolled asthma (ACT < 20) (P = 0.17). Unadjusted CalvNO was higher in subjects with noncontrolled asthma (n = 109) than in the controlled group (n = 267): 3.0 ppb (2.8–3.4 95% CI) vs 2.6 ppb (2.4–2.8 95% CI), P = 0.02. However, no difference in unadjusted CalvNO was found between very poorly controlled asthma (ACT < 15) (n = 20) vs poorly controlled asthma (ACT ≥ 15 and ACT < 20) (n = 89): 2.7 ppb (2.0–3.8 95% CI) vs 3.1 ppb (2.8–3.5 95% CI), P = 0.32. Likewise, unadjusted CalvNO did not differ (P = 0.84) between the group with totally controlled asthma (ACT = 25) (n = 37) and the rest of the well-controlled group (ACT ≥ 20 and <25) (n = 230). These results were consistent after adjustment for age, sex, height, and smoking.

NO parameters and lung function

TMAD-adjusted CalvNO was similar in subjects with normal and impaired lung function values (Table 3). Unadjusted CalvNO, FeNO50, and J'awNO were raised in the group with lower FEF50; also FeNO50 and J'awNO were higher in subjects with lower FEV1 (Table 3). A trend was found for raised FeNO50 with lower FEV1/FVC. No correlation with any NO parameter and FVC could be found (data not shown). These results were consistent after adjustment for age, sex, height, and smoking.

NO parameters and bronchial responsiveness

TMAD-adjusted CalvNO was similar for subjects with normal and moderate-to-severe bronchial responsiveness. Raised unadjusted CalvNO and FeNO50 were found in moderate-to-severe bronchial hyperresponsiveness compared with normal bronchial responsiveness (Fig. 3A), and the same was found for J'awNO (P < 0.001). These results were consistent after adjustment for age, sex, height, and smoking.

NO parameters and blood eosinophils

TMAD-adjusted CalvNO was similar in asthmatic individuals with high and low/normal level of B-eos. Higher unadjusted
CalvNO and FeNO50 were seen in subjects with raised level of B-eos compared with normal levels (Fig. 3B), and the same was found for JawnsNO (P < 0.001). These results were consistent after adjustment for age, sex, height, and smoking.

NO parameters and atopy

TMAD-adjusted CalvNO was similar in atopic and nonatopic asthmatics: 1.3 ppb (1.1–1.5) vs 1.5 ppb (1.2–2.0), P = 0.33. Unadjusted CalvNO was increased in those with atopy: 2.8 ppb (2.7–3.0) vs 2.3 ppb (2.0–2.7), P = 0.01. Also, FeNO50 was higher in atopic subjects, 17.9 ppb (16.4–19.5) vs 11.3 ppb (9.6–13.2), P < 0.001 as was JawnsNO, P < 0.001. These results were consistent after adjustment for age, sex, height, and smoking.

NO parameters and medical treatment regimen

TMAD-adjusted CalvNO was similar in the different treatment groups (Fig. 4). Unadjusted CalvNO and FeNO50 were decreased in asthma subjects on higher ICS dose (Fig. 4A), and the same was found for JawnsNO (data not shown). FeNO50 was decreased in subjects on LTRA treatment (Fig. 4B), and so was JawnsNO (P = 0.001). Reported treatment with a short course of oral steroids during the last 3 months did not correlate with any NO parameter (data not shown). These results were consistent after adjustment for age, sex, height, and smoking.

Discussion

The main findings in our study were that when estimates of alveolar NO were adjusted for axial diffusion as recommended, no associations with asthma symptoms, asthma control, lung function, bronchial responsiveness, atopy, blood eosinophils, or treatment level could be found. On the other hand, increased FeNO50 and unadjusted alveolar NO were significantly associated with reporting daytime wheeze last 12 months, FEF50, bronchial responsiveness, atopy, and blood eosinophilia. Interestingly, the adjusted alveolar NO levels showed a negative correlation with bronchial NO flux, which raises the question of overadjustment.

This is the largest study to date investigating the clinical signal of alveolar NO in asthma. Our subjects were recruited both from primary and secondary care in Uppsala county and thus should be representative of individuals with asthma aged 10–35 years in Sweden, covering different asthma severities and underlying inflammatory subtypes. Most of our subjects were compliant with the slope intercept model, based on the quality measure suggested by Mahut et al. (16), and thus, only a fraction were excluded. Smokers were not excluded, but were only a small proportion (5%) of our subjects, which might be explained by the relatively low prevalence of smoking in the general population in Sweden (32). Another strength of the study is that we included both children and young adults, and we could demonstrate a similar pattern of results in both populations as no interaction with age group was found regarding the main outcomes. A limitation of the
Figure 3  TMAD-adjusted Calv\textsubscript{NO}, unadjusted Calv\textsubscript{NO}, FeNO\textsubscript{50}, and (A) level of bronchial responsiveness and (B) level of B-eos. Data presented as geometric means (95% confidence interval).

Figure 4  TMAD-adjusted Calv\textsubscript{NO}, unadjusted Calv\textsubscript{NO}, FeNO\textsubscript{50}, and (A) inhaled corticosteroid (ICS) and (B) leukotriene receptor antagonist (LTRA) treatment. Data presented as geometric means (95% confidence interval).
study is the lack of physiological measurements of small airways function, for example, nitrogen washout tests or forced oscillation technique (33). As respiratory symptoms were assessed within the time frame of 12 months previous to the study, recall bias cannot be ruled out.

Our main finding was the lack of association between any of the above-mentioned asthma characteristics and TMAD-adjusted CalvNO. Thus, our results corroborate those presented by Mahut et al. (16) where 200 individuals with age range, lung function, and medication level comparable with our cohort were evaluated for correlation between TMAD-adjusted CalvNO and asthma control/severity. However, some smaller studies have presented association between TMAD-adjusted CalvNO and medical treatment (17), and also asthma control (34).

Biopsy-verified distal airways inflammation is correlated with uncontrolled, severe asthma (35), and unadjusted CalvNO has been reported to be increased in patients with uncontrolled, severe asthma (9, 12), making CalvNO an appealing noninvasive marker of small airways inflammation. However, recent studies have highlighted the difficulties of using this marker: for example, alveolar NO can paradoxically increase after antiinflammatory treatment in a subgroup of asthmatics (36). This probably reflects that in more constricted peripheral airways, back diffusion would increase once treatment has relieved the peripheral obstruction. Moreover, the need to correct for axial diffusion should be smaller in patients with a larger degree of peripheral obstruction. It might therefore be argued that the axial diffusion adjustment is not a ‘one size fits all’ adjustment. The present study reports a negative correlation between TMAD-adjusted CalvNO and J′awNO, in contrast to the only two studies known to us that reported correlations between TMAD-adjusted CalvNO and J′awNO (16, 37). This has not been studied or reported before, but might signal an adjustment of CalvNO in our material. The original study by Condorelli et al. (15) was performed in eight healthy subjects, and the correction parameters were based on data from these subjects. However, both the degree and location of airways constriction vary from one individual to another in asthma, and the degree of peripheral airways constriction would interfere with the axial diffusion correction. Therefore, it would be relevant to investigate whether these corrections are valid in asthmatic individuals with different degree of airway obstruction and whether corrections should take into account the degree and location of obstruction.

In our study, FeNO50, J′awNO, and unadjusted CalvNO were correlated with daytime wheeze. As the recall period for asthma symptoms was 12 months prior to the measurements of exhaled NO, it could be argued that this symptom report mainly reflects a wheezing phenotype, and consequently its relation to FeNO50 results in line with our report on the association between self-reported wheeze during the last 12 months and increased FeNO50 in a large population-based study (38). Exhaled NO was not correlated with asthma control defined by ACT score, which is in line with previous findings (16). Bronchial hyperresponsiveness was related to higher FeNO50 in our material, which is in line with previous studies (39). However, the relation with raised unadjusted CalvNO has not to our knowledge been previously reported. Impaired FEF25–75 related to increased FeNO50, J′awNO and unadjusted CalvNO, in line with previous findings (40). FeNO50 was also related to FEV1. Atopy was related not only to increased FeNO50 and J′awNO but also to unadjusted CalvNO, which contradicts a previous study from our group (41). This might be explained by the population-based setting of the previous study and the relatively small size of the effect: a large population of patients with asthma as in the present study is probably required to find significant differences. The relation between higher unadjusted CalvNO and history of asthma attack in the preceding year is a novel and interesting finding, suggesting that unadjusted CalvNO might identify asthmatics at risk of asthma attack. However, we are cautious due to the design of our study as this information was retrospective and the difference in CalvNO was small (<0.5 ppb) between subjects with and without an asthma attack previous year, casting doubt on the potential clinical applicability of this information.

In conclusion, no associations between TMAD-adjusted CalvNO and asthma characteristics were found in this large asthma cohort study. Standard measures of exhaled NO, FeNO at 50 ml/s, as well as unadjusted CalvNO correlated with reported daytime wheeze during last 12 months, lung function, bronchial responsiveness, atopy, blood eosinophilia, and treatment level, and the findings on the associations between unadjusted CalvNO and bronchial hyperresponsiveness and atopy are novel. As we raise the potential problem that the suggested adjustments may lead to overadjustment, we conclude that further studies assessing axial diffusion in subjects with asthma and the validity of proposed adjustment algorithms are warranted. With the increased awareness of asthma as a disease also in the small airways and availability of therapies better able to reach the small airways, more studies are needed to establish the role of adjusted – or unadjusted –alveolar NO in identifying this phenotype and following up on the effects of treatment.

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The work of the present study would not have been possible without the expert contribution of research nurses Pia Kalm Stephens and Katarina Nisser and laboratory engineers Helene Lettesjö and Britt-Inger Nyberg.

Author contributions

C. Heikenskjold-Rentzhog, L. Nordvall, C. Jansson, Magnus P. Borres, K. Alving, and A Malinovschi contributed to the study design. C. Heikenskjold-Rentzhog, L. Nordvall, C. Jansson, K. Alving, and A Malinovschi were involved in the data acquisition. C. Heikenskjold-Rentzhog and A. Malinovschi contributed to statistics. C. Heikenskjold-Rentzhog wrote the first draft of the manuscript. C. Heikenskjold-Rentzhog, L. Nordvall, C. Jansson, K. Alving, and A Malinovschi critically revised and approved the final version.
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Conflicts of interest

Kjell Alving is an employee of Aerocrine AB (producer of exhaled NO devices) and minority shareholder, but participated in the study with his role as adjunct professor at Uppsala University. Magnus Borres is an employee of Thermo Fisher Scientific, Immunodiagnostics, and participated in the study as adjunct professor at Uppsala University. None of the funding agencies or industry partners had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References


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