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SHORT COMMUNICATION

Comparison of exhaled nitric oxide measurements between NIOX MINO® electrochemical and Ecomedics chemiluminescence analyzer

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KEYWORDS
Airway inflammation;
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Summary
Background: Exhaled nitric oxide (eNO) is an established, noninvasive biomarker of active airway inflammation in (atopic) asthma. Treatment with anti-inflammatory therapy, such as inhaled corticosteroids, effectively decreases eNO levels. The NIOX MINO® (MINO) is a hand-held, relatively inexpensive, electrochemical device that has been shown to yield comparable eNO measurements to the NIOX stationary unit.
Aim: To compare measurements of MINO with another widely used and validated stationary chemiluminescence analyzer, the Ecomedics (ECO).
Methods: We performed subsequent eNO measurements on ECO and MINO in 50 subjects (19 healthy volunteers, 18 healthy smokers and 13 non-smoking, atopic asthmatics, not on controller therapy) on two visits 4–10 days apart. The mean of three acceptable measurements by ECO and the first acceptable measurement with the MINO were used for analysis.
Results: Both devices yielded reproducible eNO values for all subjects on both visits, with an overall CV of 22.7% (ECO) and 18.3% (MINO). A significant correlation was found between both devices ($r = 0.97$, $p < 0.0001$). Bland-Altman plots showed a high degree of agreement for the entire study population (mean difference MINO vs ECO = −10%; 95% limit of agreement were −36% and +28%) and in the three individual subgroups.
Conclusions: Exhaled NO values measured with the MINO are reproducible and in agreement with the ECO. Our results add further evidence to the reliability of the MINO and warrant its applicability in research and clinical practice.

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Introduction

Asthma is a chronic inflammatory disease presenting with variable symptoms and mostly reversible airway obstruction within the lower airways. According to international guidelines, modern asthma management is aimed at the suppression of airway inflammation by avoidance of allergens and anti-inflammatory, 'controller' therapy.[1] For optimal guidance of disease control, measuring biomarkers of airway inflammation has become increasingly important.[1] To this aim, several non- and semi-invasive sampling techniques have been developed and validated.[2]

Exhaled nitric oxide (NO) is an established biomarker of airway inflammation that may serve to monitor the response to (novel) controller therapy. In asthma, elevated levels of eNO have been shown to correlate with disease severity, showing increases prior and during an asthma exacerbation and decreases following anti-inflammatory treatment.[2] In addition, using eNO measurements to guide individual doses of inhaled corticosteroids resulted in reduced airway hyperresponsiveness along with an overall lower dose of inhaled corticosteroids without compromising asthma control.[3,4]

Stationary chemiluminescence NO analyzers are validated devices for online measurement of NO levels in exhaled air.[5] However, their usage is largely hampered by their bulkiness and high costs. More recently, MINO has been marketed for portable, online eNO measurements. This hand-held and relatively inexpensive device is simple to use and yields reproducible measurements, even when performed by children at home.[6] In addition, a recent economic evaluation revealed that the use of MINO in the treatment of asthma offers cost savings compared to asthma management based on standard guidelines, while both methods result in comparable health benefits.[7] These properties warrant its potential applicability in both primary health care setting and in clinical trials. However, its reliability needs to be fully assessed.

So far, MINO has been compared with the NIOX stationary unit but, to our knowledge, not with the other validated and widely used chemiluminescence analyzer, ECO.[8–10] In this study we compared eNO measurements by MINO with the previously validated ECO in healthy volunteers, healthy smokers and atopic asthmatics.

Methods

Subjects

The study population consisted of three subgroups: 19 healthy volunteers, 18 healthy smokers and 13 non-smoking, atopic asthmatics (Table 1).

The healthy volunteers were non-smokers for at least 12 months with less than 5 pack years (1 pack year = 20 cigarettes or equivalent smoked per day for 1 year). The healthy smokers were current smokers (last cigarette was smoked 1–2 h before the study procedures) with a smoking history of at least 10 pack years. The asthmatic-subgroup only used inhaled short-acting β2-agonists as needed and had no controller medication for at least 1 month prior to the study. All had intermittent to mild persistent asthma and clinical stability was assessed by stable lung function (FEV_1 within 10% on both study visits), absence of symptoms and stable, infrequent use of rescue medication in the last 3 months. Atopy was demonstrated by a positive skin prick test for at least 1 of 10 airborn allergens. None of the participants had a history of airway infection in the previous 4 weeks prior and during the study. All subjects gave written informed consent and the study was approved by the Ethics Committee of Leiden University Medical Centre.

Study design

Exhaled NO measurements were performed in all subjects on ECO and MINO on 2 study visits, 4–10 days apart. All the measurements were performed during the same time of the day (±2 h).

Exhaled NO measurements

All eNO measurements were performed according to current guidelines.[11] Briefly, subjects were sitting in upright position and wearing a nose clip during the eNO measurements with both devices. They inhaled NO-free air through the device and subsequently exhaled at 50 ml/s for approximately 10 s. The mean of the first three technically acceptable measurements within 10% performed with the ECO (Ecomedics CLD88sp; Ecomedics, Duernten, Switzerland) were implicated into analysis. For measurements by the MINO (Aerocrine AB, Solna, Sweden), the first technically acceptable measurement was used for analysis.[10]

Spirometry

Following eNO measurements, spirometry (forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and peak expiratory flow (PEF)) was performed according to standardized lung function techniques by a calibrated spirometer connected to a personal computer (Vmax Spectra Sensor Medics; Cardinal Health, Houten, The Netherlands).[12]

Analysis

As eNO values were not normally distributed, data were log transformed prior to analysis. Comparisons between healthy volunteers and the other subgroups were made using an unpaired *t*-test. The reproducibility of both devices was assessed by the within subject variation between visits and expressed as a coefficient of variation (CV = the standard deviation expressed as percentage of the mean). In order to compare both devices, data were plotted in a scattergraph and the Pearson correlation was calculated on log-transformed data. Bland-Altman plots were made with the difference (ECO − MINO) of measurements of both methods on the *y*-axis and the mean of the two methods on the *x*-axis, along with an estimation of the upper and lower limit of agreement, being 1.96 times the standard deviation (SD). The presented Bland-Altman plots incorporated all data and were constructed as if every

Table 1 Patients' characteristics at baseline

	Healthy volunteers	Healthy smokers	Atopic asthmatics	*p*-Value
Total number	19	18	13	
Female : Male	10:9	9:9	8:5	
Age (years)	41 (30–53)	40 (32–52)	29 (21–54)	
FEV_1 (% predicted)	104.4 (87.5–119.5)	103.6 (82.1–121.1)	91.8 (61.0–122.0)	
Exhaled NO Ecomedics (ppb)	18.0 (7.4–35.5)	11.1 (4.7–20.5)	60.8 (10.9–184.6)	<0.01[a]
Exhaled NO NIOX MINO (ppb)	20.3 (8.0–39.0)	12.2 (5–23)	63.8 (13–172)	<0.01[a]

All values are given as mean (range).
[a] Healthy volunteers compared to healthy smokers and compared to atopic asthmatics.

pair of measurements was independent. Analysis of the first and second visit independently yielded similar results.

All calculations were performed using SAS for windows V9.1.2 (SAS Institute, Inc., Cary, NC, USA).

Results

One subject from the healthy non-smokers' group produced eNO values <5 ppb on both occasions. Two subjects (one healthy volunteer and one atopic asthmatic) failed to perform acceptable eNO measurements on the ECO. These measures were excluded from analysis. All other subjects completed the study and performed technically acceptable manoeuvres on both study visits. Overall, healthy smokers had significantly lower and atopic asthmatics significantly higher eNO values compared to healthy volunteers (Table 1). Exhaled NO values by MINO were slightly, but not significantly, higher than the ECO values in all three subgroups (Table 1).

Both devices yielded reproducible eNO values for all subjects on both visits, with an overall CV of 22.7% (ECO) and 18.3% (MINO). The Pearson correlation analysis yielded an r of 0.975 ($p < 0.0001$) between eNO values measured by MINO and ECO (Fig. 1).

In addition, Bland-Altman plots demonstrate agreement between both devices in the entire study population and the three subgroups (Fig. 2) for both low and high values of eNO.

Discussion

In recent years, eNO has become widely accepted as a biomarker of airway inflammation in asthma. The availability of simple and reliable eNO measurements is of major importance in the diagnosis and monitoring of day-to-day asthma. Hence, we compared the hand-held MINO to the widely used stationary ECO analyzer in a study population consisting of three subgroups: healthy volunteers, healthy smokers and atopic asthmatics not on controller therapy. Apart from a good reproducibility of eNO values on both study visits, a significant correlation and a high degree of agreement was observed between eNO measurements yielded by both devices. Subgroup analysis revealed a superior agreement in the high eNO ranges (atopic asthmatics) compared to the low eNO ranges (healthy smokers). However, with respect to the latter the group sizes were too small to draw definitive conclusions. Our results are in agreement with previous data comparing the MINO to the stationary NIOX unit and extend the findings to another widely used and validated chemiluminescence analyzer, (Ecomedics).[8–10]

Exhaled NO values are not normally distributed and require log-transformation prior to analysis.[10] Therefore, in the current paper the upper and lower limits of agreement are presented in percentages difference which may not be suitable for clinical interpretation. However, if we use the mean value of eNO for the entire study population (26.4 ppb for the ECO) and back-translate to an arithmetic scale the upper and lower limit of agreement are +7.4 ppb and −9.5 ppb, respectively. In our study, both devices yielded comparable eNO measurements in individual subjects, while MINO systematically produced slightly higher values. Although similar with other studies comparing MINO with the NIOX stationary unit, this may impact clinical interpretation if patients are assessed on both devices alternately.[3,4,10,13] Hence, the cut-off eNO values should be adjusted for MINO. In a previously conducted study comparing chemiluminescence analyzers, the ECO produced overall lower eNO values than the other stationary analyzers.[14,15] In conclusion, it is clear that eNO analyzers yield comparable, but not interchangeable eNO values. This implicates that, ideally, in an individual

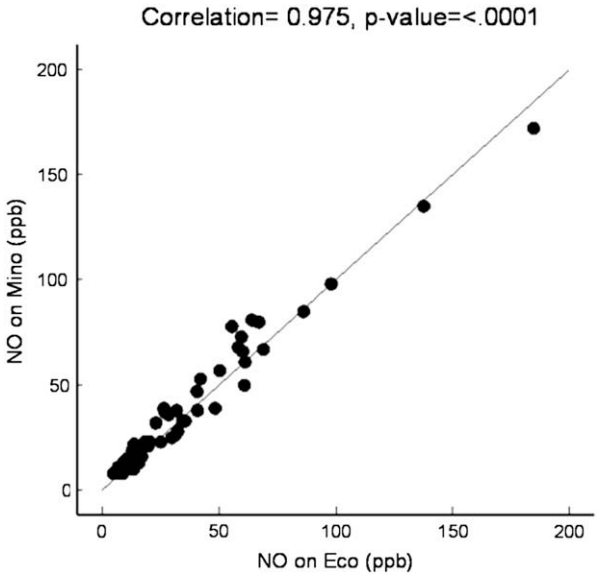

Figure 1 Pearson correlation between exhaled NO levels measured with the Ecomedics (*x*-axis) and the NIOX MINO (*y*-axis) analyzer.

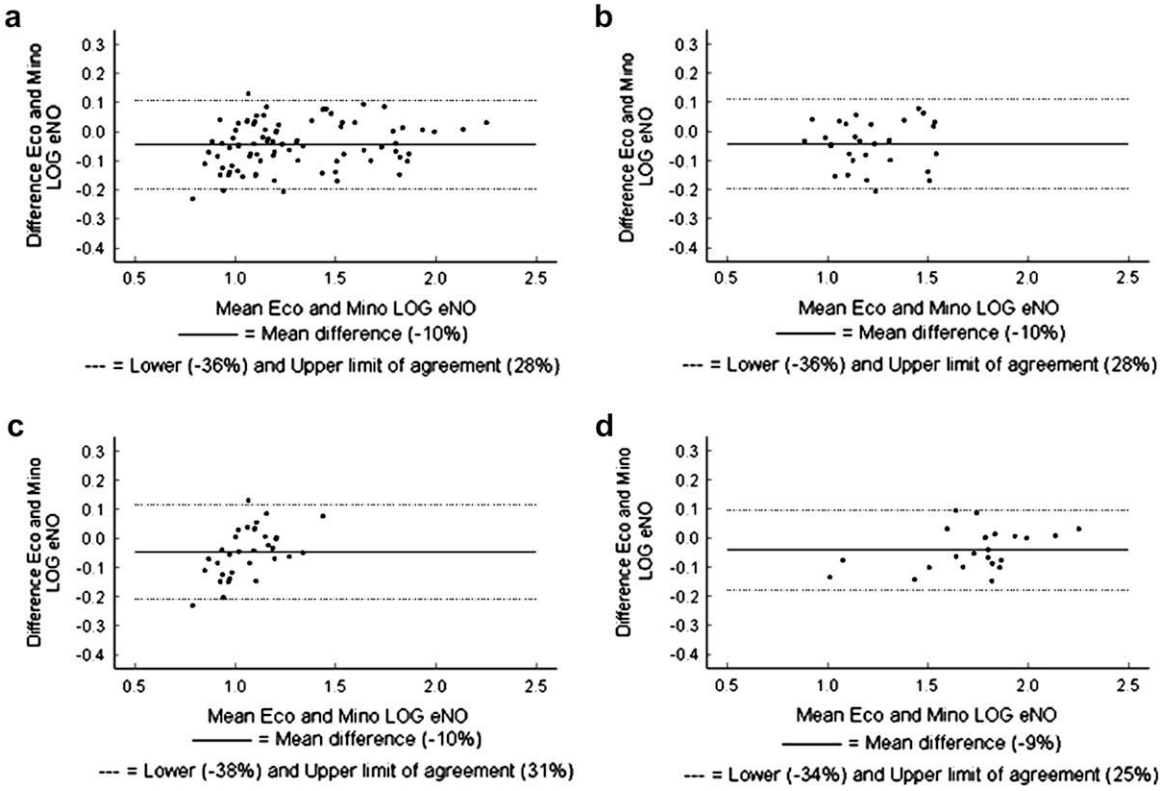

Figure 2 Bland-Altman plot of exhaled NO measurements using the Ecomedics vs NIOX MINO for the entire study population (a), healthy volunteers (b), healthy smokers (c) and atopic asthmatics (d).

patient, all eNO measurements should be performed on the same analyzer.

A potential issue may be the difference in lower detection limits between the ECO (0.1 ppb) and the MINO (5 ppb). Indeed, in this study one subject (smoker) had to be excluded from analysis because his eNO values on the ECO were under the detection limit of the MINO. From a clinical perspective, this may not have consequences since very low eNO values are not clinically relevant in asthma. However, should the device need to be employed in the lower detection range, this issue will have to be resolved. This may explain the larger variance between both devices in the smoker group, although the subject numbers were too small to show a significant difference in variances in the lower detection ranges between study groups. Other studies comparing the MINO device with chemiluminescence analyzers did not find any difference between the lower and higher eNO values.[8,10]

In conclusion, eNO values measured with MINO are reproducible and generally in agreement with the ECO. Its simplicity, relatively low costs and small size make the MINO device more suitable than the stationary chemiluminescence analyzers for primary healthcare and large clinical trials. Conversely, it cannot be used in research settings requiring more sophisticated measurements including nasal NO, very high or low eNO values or samplings at different flow rates. Our results add further evidence to the reliability of MINO and warrant its applicability in clinical practice and research.

Conflict of interest

The authors have no conflict of interest to declare.

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