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Portable Exhaled Nitric Oxide Measurement*

Comparison With the “Gold Standard” Technique

Daniel Menzies, MBChB; Arun Nair, MBBS; and Brian J. Lipworth, MD

Background: The measurement of fractional exhaled nitric oxide (FENO) can assist in the diagnosis of asthma and may also act as a useful surrogate inflammatory marker on which to base treatment decisions in asthma management algorithms. Until recently, this technique was confined to research facilities and secondary care institutions. A portable nitric oxide analyzer (MINO; Aerocrine AB; Smidesvägen, Sweden) has been developed, but few data exist comparing this device with established, larger laboratory-based analyzers (NIOX; Aerocrine AB).

Methods: A total of 101 asthmatic patients (64 treated with regular inhaled corticosteroids) and 50 healthy volunteers had simultaneous FENO measurements undertaken using NIOX and MINO devices.

Results: In both asthmatic patients and healthy volunteers, there was a good correlation between the measurements obtained using each device ($r = 0.94$ and 0.96 , respectively). Altman-Bland plots confirmed this agreement. Receiver operating characteristic curves discriminating asthmatic patients from healthy volunteers obtained using the NIOX and MINO showed a sensitivity of 83.2% and a specificity of 72% using cutoff values of 13 and 12.5 parts per billion, respectively.

Conclusion: FENO values obtained using a portable analyzer correlate well with those obtained using an established laboratory analyzer and can be used to discriminate asthmatic from nonasthmatic patients. This may facilitate the measurement of asthmatic airway inflammation in primary care. (CHEST 2007; 131:410–414)

Key words: asthma; exhaled nitric oxide

Abbreviations: AUC = area under the curve; CI = confidence interval; FENO = fractional exhaled nitric oxide; ICS = inhaled corticosteroid; ppb = parts per billion; ROC = receiver operating characteristic

The measurement of fractional exhaled nitric oxide (FENO) in asthmatic patients is increasingly recognized as a potential tool to aid diagnosis and management. Elevated levels of FENO in asthmatic patients have been shown to correlate with disease

severity and, importantly, also with subsequent deterioration in asthma control.^{1,2} Two prospective randomized controlled trials^{3,4} in children and adults have demonstrated the utility of incorporating this measure of airway inflammation into treatment algorithms. Using FENO to dictate a patient's daily dose of an inhaled corticosteroid (ICS) led to reductions in airway hyperresponsiveness and in the total dose of an ICS required to maintain control when compared with a traditional spirometry and symptom-based approaches. In addition, in steroid-naïve patients in whom diagnosis is uncertain, the measurement of FENO has a positive predictive value comparable with that of methacholine challenge.⁵ The use of this tool has until now been confined to secondary care because of the relative expense and physical size of the equipment required

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to undertake the measurement. In contrast, FENO measurement may arguably be of the most value in primary care where the majority of asthmatic patients are routinely cared for. A new hand-held portable nitric oxide sampling device (MINO; Aerocrine AB; Smidesvågen, Sweden) has been developed that may be ideally suited for use in a primary care environment, although few data exist on whether measurements obtained using this instrument are comparable with those obtained with conventional chemiluminescence analyzers. We have prospectively evaluated the MINO device with an established laboratory chemiluminescence analyzer (NIOX; Aerocrine AB; Smidesvågen, Sweden) in both asthmatic patients and healthy volunteers to determine whether the results are comparable.

MATERIALS AND METHODS

A total of 101 patients known to have persistent mild-to-moderate asthma (64 of whom were receiving ICSs) from our clinical trials database and 50 healthy volunteers were invited to participate (Table 1). The Tayside Committee for Research Ethics was consulted, and a favorable opinion was granted.

Exhaled Nitric Oxide Measurements

All participants underwent the measurement of FENO using the NIOX analyzer at a mouth flow rate of 50 mL/s and a pressure of 10 cm H₂O. Three technically adequate measurements were performed with a sustained plateau of at least 8 s, and the arithmetic mean derived was in line with the current European Respiratory Society/American Thoracic Society recommendations.⁶ A single measurement was then undertaken immediately afterward using the portable MINO device with identical mouth flow rate and pressure settings. The sensor on the device was changed periodically, in line with the manufacturer's guidance.

Spirometry

Spirometry was undertaken after the measurement of FENO (SuperSpiro spirometer; MicoMedical Ltd; Rochester, UK) in accordance with American Thoracic Society guidelines.⁷

Statistical Analysis

Nitric oxide data were log-transformed to normalize the distribution prior to analysis. Comparisons between the asthmatic and nonasthmatic populations were made using unpaired *t* tests; the Pearson correlation and Altman-Bland plots were used to compare the devices, and the Spearman correlation was employed to identify any potential tendency for the separation of agreement at higher or lower values. Receiver operating characteristic (ROC) curves were constructed using the raw data (*ie*, before transformation) to determine the area under the curve (AUC), and the sensitivity and the specificity for discriminating between asthmatic patients and healthy volunteers for each device.⁸ Thereafter, the AUC from each device was compared in a pairwise fashion to determine whether any differences existed in the discriminative power between the NIOX and the MINO. Given the nature of the trial, it was not possible to blind the study, although the data were gathered by a researcher who was blinded to the analysis. The analysis was carried out in an unblinded fashion.

RESULTS

All of the recruited patients were able to provide technically acceptable maneuvers using each device. The arithmetic mean (SD) for the measurements obtained using the NIOX and the MINO in healthy volunteers was 22.6 (SD, 20.0) and 24.7 (SD, 22.3), respectively; in asthmatic patients these values were 36.7 parts per billion (ppb) [SD, 37.8 ppb] and 37.8 ppb (SD, 36.5 ppb), respectively. A statistically significant linear relationship was found between the results obtained using the NIOX laboratory-based system and those obtained using the portable MINO in asthmatic patients ($r = 0.94$; $p < 0.001$) [Fig 1] and healthy volunteers ($r = 0.96$; $p < 0.001$) [Fig 2]. The significant correlation was maintained for asthmatic patients receiving steroids ($r = 0.88$; $p < 0.001$) and for those who were steroid-naïve ($r = 0.98$; $p < 0.001$). In addition, the Altman-Bland plots suggested a high degree of agreement between the devices (Fig 3, 4), and Spearman correlation values confirmed the lack of bias at either end of the

Table 1—Baseline Characteristics

Characteristics	Asthmatic Patients	Healthy Volunteers	Difference*	p Value
Gender				
Male	47	18		
Female	54	32		
Mean age, † yr	48.5 (1.29)	35.6 (1.70)		
FEV ₁ , † % predicted	84.3 (1.84)	98.7 (1.61)	14.4 (9.5–19.2)	0.001
FENO, ‡ ppb				
NIOX	26.9 (24.8–29.6)	17.7 (16.1–19.4)	1.52§ (1.18–1.96)	0.001
MINO	26.6 (24.5–28.9)	19.3 (17.6–21.1)	1.38§ (1.08–1.77)	0.011
ICS daily dose	400 (200–775)			

*Values in parentheses are 95% CI.

†Values are given as the mean (SEM).

‡Values are given as the geometric mean (SE of geometric mean).

§Values are given as the geometric mean fold difference.

||Values are given as the median (interquartile range).

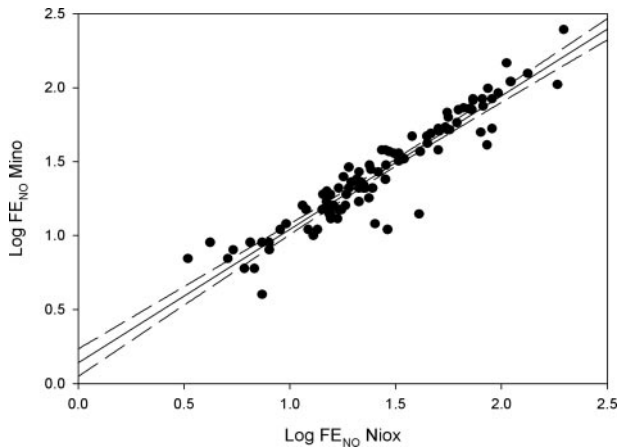


FIGURE 1. Linear regression with 95% CI of MINO vs NIOX values in asthmatic subjects.

range of values (asthmatic patients, $p = 0.458$; healthy volunteers, $p = 0.444$). Asthmatic patients had higher levels of FENO and lower FEV₁ values than healthy volunteers (Table 1), although the magnitude of the difference was greater using the NIOX (1.52-fold difference) than using the MINO (1.38-fold difference). The ROC AUC values generated using the NIOX and MINO devices differentiating asthmatic patients from healthy volunteers was 0.654 (95% confidence interval [CI], 0.565 to 0.744; $p = 0.002$) and 0.619 (95% CI, 0.527 to 0.711; $p = 0.018$), respectively. The ROC curve analysis indicated a sensitivity of 83.2% and a specificity of 27% for identifying asthmatic patients from healthy volunteers using a cutoff of 13 ppb for the NIOX device and 12.5 ppb for the MINO device. Pairwise comparisons of the ROC curves revealed a difference in the AUC of 0.036 (95% CI, -0.002 to 0.073;

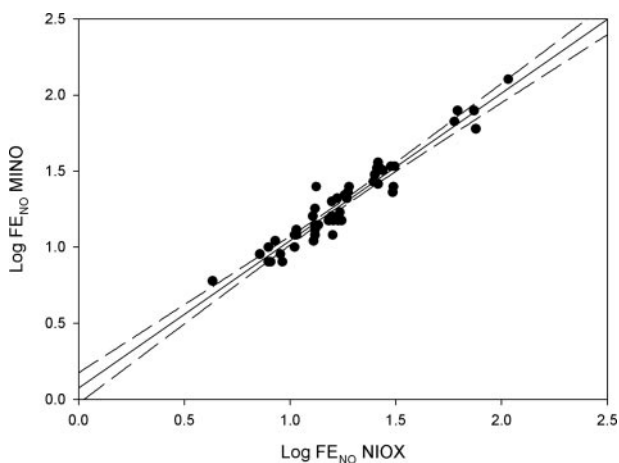


FIGURE 2. Linear regression with 95% CI of MINO vs NIOX values in healthy volunteers.

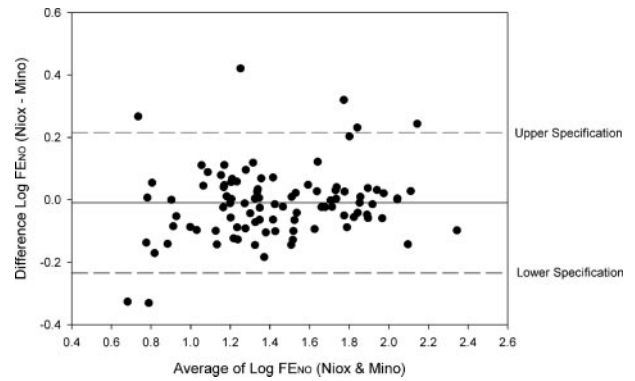


FIGURE 3. Altman-Bland plot of MINO vs NIOX in asthmatic subjects.

$p = 0.061$) between the MINO and NIOX for discriminating asthmatic patients from healthy volunteers.

DISCUSSION

The current study demonstrates that FENO values deriving using the MINO device are directly comparable with those using the NIOX device. We have evaluated the MINO device against the current “gold standard” arithmetic mean value of three measurements on a validated instrument. However, it is important to note that as this is a relatively new device there is currently no accepted technique by which to obtain measurements, and it is conceivable that the accuracy of the MINO device may be improved further by increasing the number of exhaled breath samples. When analyzing these data, it is important to appreciate that FENO measurements in both healthy volunteers and asthmatic patients are

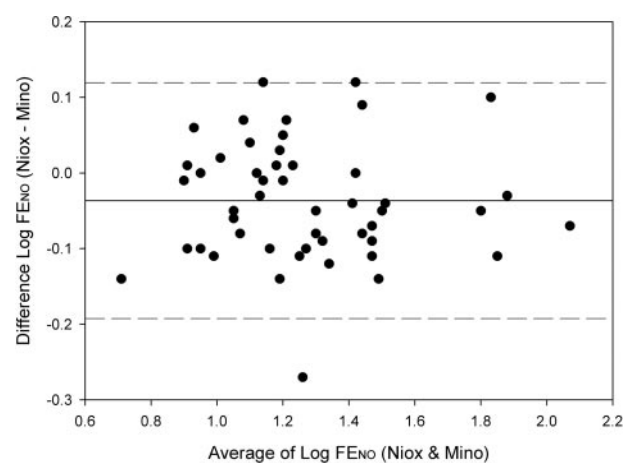


FIGURE 4. Altman-Bland plot of MINO vs NIOX in healthy volunteers.

right-skewed and require appropriate transformation prior to statistical analysis. In this regard, it would be inappropriate to carry out correlations on non-Gaussian data obtained from these devices, although this presents some difficulties for interpreting measurements obtained in a clinical setting. Reassuringly, the upper and lower specifications on the Altman-Bland plots equate to ± 2 ppb on the arithmetic scale. Given that the difference between values for differentiating asthmatic and nonasthmatic patients and for predicting asthma relapse is on the order of 10 to 15 ppb at a conventional flow rate of 50 mL/s, this degree of accuracy would appear to be acceptable.^{5,9} Figures 1 and 2 both show that the regression line does not dissect the origin of the axis, indicating a consistently higher value from the MINO device compared with the NIOX device. Subsequent analysis revealed that this amounts to approximately 1 ppb in both asthmatic and nonasthmatic volunteers, which would not be clinically significant.

Previous authors¹⁰ have reported that spirometry maneuvers in asthmatic patients lead to a drop in FENO values. It is possible that by undertaking measurements using the NIOX then using the MINO may have led to a slight underestimation of the value obtained using the second device, although, as noted, we found a consistently higher value with the MINO device. We have not obtained data on the accuracy of the MINO device over time, and it is conceivable that as the sensor nears the end of its shelf-life its accuracy tails off. This potential problem is confounded by the fact that the MINO device cannot be calibrated, unlike its laboratory-based counterpart. In addition, there are no data on the within-patient repeatability of this test over time. Of note, our data are in agreement with those from a smaller trial,¹¹ which also demonstrated good correlation between the devices and a similar consistent bias toward slightly higher readings from the MINO device compared with the NIOX device, on the order of 1 to 2 ppb. In addition, this previous study¹¹ also showed that the repeatability of measurements obtained using both devices was similar, with median values of 1.1 and 1.2 ppb, respectively, for the NIOX and MINO devices. The data from the ROC curves showed that undertaking FENO measurements with both devices is a reliable method of differentiating asthmatic patients from healthy volunteers, as has been previously reported.⁵ The majority of the patients in our study were receiving regular therapy with ICSs, and therefore were likely to have suppressed airway inflammation, or were patients who had mild asthma and did not require regular therapy with ICSs. This may explain the reduced discriminating power of the test in our cohort compared with the previously published data,

in which an entirely steroid-naïve population with high levels of airway inflammation was tested. In addition, while there was no difference in the AUC ($p = 0.061$) between the two devices in our cohort, the relatively small sample size means the possibility of β -error cannot be completely discounted.

Basing asthma management strategies on surrogates of airway inflammation instead of relying on spirometric indexes and symptoms is increasingly recognized as a method that may allow more targeted use of ICS therapy, leading to a reduction in the exacerbation rate and less airway remodeling.^{3,4,12–14} However, many of the methods thus far employed to undertake the quantification of inflammatory activity (*eg*, airway hyperresponsiveness and induced sputum eosinophil count) are cumbersome, expensive, unpleasant for the patient, and impractical for primary care. In contrast measuring FENO is quick and noninterventional with a high degree of patient acceptability, but has thus far been confined to research institutions and secondary care facilities. However, determining the clinically relevant level of FENO remains an unanswered question, with different prospective trials adopting different limits.^{3,4} The cost of a single measurement using the MINO device is approximately \$10 (in US dollars). The advent of a portable device may allow the extension of inflammation-based asthma management algorithms into primary care, but it is important to know whether this instrument accurately reflects disease activity and correlates with measurements obtained using established laboratory equipment that has been used in the trials to date. While our study demonstrates the latter, further prospective trials are required in order to determine whether this is a practical tool for primary care and, more importantly, whether incorporating measures such as FENO into everyday practice will lead to real improvements in patient care.

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