
Evaluation of exhaled nitric oxide measurements in the emergency department for patients with acute asthma

Alan P. Baptist, MD*; Radha Sengupta, MS*; Sukanya Pranathiageswaran, MBBS*; Yun Wang, MS†; and Joel Ager, PhD†

Background: Fraction of exhaled nitric oxide (FE_{NO}) measurements performed on patients with acute asthma in the emergency department (ED) have previously shown poor reproducibility.

Objectives: To evaluate the reproducibility of FE_{NO} measurements in the ED using a new monitoring device, to evaluate any factors that may correlate with FE_{NO} measurements, and to investigate if FE_{NO} levels predict the need for admission to the hospital.

Methods: Thirty-five adult patients with asthma seen in the ED performed FE_{NO} , forced expiratory volume in 1 second, and peak expiratory flow rate maneuvers in triplicate. Reproducibility was evaluated using the intraclass correlation coefficient and the coefficient of variation. Associations between FE_{NO} , demographic, and traditional asthma measurements were investigated. The FE_{NO} levels between patients admitted for further care and those discharged home were compared.

Results: The FE_{NO} measurements showed acceptable intraclass correlation coefficient and coefficient of variation values (0.98 and 9.42%, respectively) for reproducibility. These values were superior to the values obtained for forced expiratory volume in 1 second and peak expiratory flow rate. No correlation was found between FE_{NO} and traditional asthma factors, although length of the asthma attack trended toward statistical significance ($P = .08$). The FE_{NO} levels did not differ between those admitted and those discharged home ($P = .53$).

Conclusions: Fraction of exhaled nitric oxide measurements can be obtained in the ED setting with good reproducibility. These measurements may provide useful information not obtainable by other means. Further research is needed to determine how best to incorporate FE_{NO} values into the ED setting.

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INTRODUCTION

Asthma is one of the most common chronic diseases in the United States, affecting approximately 22 million people.^{1,2} Asthma exacerbations are a frequent cause for patients to seek care at an emergency department (ED), accounting for approximately 1.8 million ED visits per year or 2% of the total ED visits.³ The annual costs of ED visits for asthma have been estimated to be approximately \$1 billion.⁴ There is concern that all of these numbers may be increasing.

Emergency department monitoring of asthmatic patients is essential for accurate therapeutic decisions and for determining which patients require hospitalization. This monitoring has traditionally focused on subjective symptoms,^{5,6} physical examination findings,^{7,8} forced expiratory volume in 1 second (FEV_1),⁹ peak expiratory flow rate (PEFR),^{6,10} and pulse

oximetry.¹¹ However, even the use of a combination of these measurements has not been effective in predicting which patients may have a relapse (often defined as the need to return to the ED, hospital, or urgent care after discharge). This may be because of the fact that none of the previously described markers effectively measures the hallmark feature of asthma—airway inflammation.¹²

During the past 10 years, fraction of exhaled nitric oxide (FE_{NO}) has evolved as an accurate biomarker of airway inflammation.¹³ The FE_{NO} can be measured noninvasively.¹⁴ Unfortunately, use of the traditional nonportable FE_{NO} device was shown to have poor reproducibility in the ED, limiting the usefulness of such technology.¹⁵ A new portable FE_{NO} monitoring device has recently been developed. This device (NIOX MINO) has shown excellent reproducibility in a small validation study¹⁶ but has not been analyzed in the ED.

The objectives of this study were to evaluate the reproducibility of the NIOX MINO in the ED, to evaluate any traditional factors that may correlate with FE_{NO} measurements, and to investigate the extent to which FE_{NO} levels can predict the need for admission to the hospital.

METHODS

Study Setting and Population

This was a single-center, prospective, clinical trial at 1 large teaching hospital in Detroit, Michigan (Detroit Receiving

Affiliations: * Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Wayne State University School of Medicine, Detroit, Michigan; † Department of Family Medicine and Public Health Sciences, Wayne State University School of Medicine, Detroit, Michigan. Dr Baptist is now with the Division of Allergy and Clinical Immunology, University of Michigan, Ann Arbor, Michigan.

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Hospital), between October 1, 2006, and March 15, 2007. Detroit Receiving Hospital treats an average of 1,130 adult asthmatic patients each year in the ED. The study was approved by the institutional review board, and patients were enrolled after written informed consent was obtained.

Subjects who presented to the ED for an acute asthma exacerbation were invited to participate. Subjects were eligible to participate if they had a prior physician diagnosis of asthma and were between the ages of 18 and 65 years. All subjects were recruited from the ED. Subjects were excluded if they had a chronic cardiopulmonary disease other than asthma (including chronic obstructive pulmonary disease), had a greater than 10-pack-year smoking history, had used systemic corticosteroids or leukotriene receptor antagonists in the previous week, were receiving long-term immunosuppressive therapy, were pregnant, or could not provide informed consent. Subjects who were unable to provide 1 acceptable FE_{NO} reading were excluded from further participation in the study.

Study Protocol

Patients who met the inclusion and exclusion criteria were approached immediately on presentation to the ED at the first opportunity that did not interfere with patient care. Subjects were asked to provide demographic information, including age, race, sex, time the current asthma attack had started, and asthma severity based on National Institutes of Health (NIH) guidelines.¹² The FE_{NO} readings were evaluated in triplicate, and immediately after these measurements spirometry was performed. Peak expiratory flow rates were also evaluated, as were respiratory symptom scores (measured by the modified Borg index⁵).

All subjects were treated in a standard fashion according to NIH guidelines for care in the ED and hospital. This included oral systemic steroids, along with ipratropium bromide (Atrovent; Boehringer-Ingelheim Pharmaceuticals, Ridgefield, Connecticut) and albuterol by metered-dose inhaler or nebulizer. Necessity of hospital admission was determined by the ED physician of record, who had been trained and instructed to use the National Asthma Education and Prevention Program guidelines in making this decision.¹²

Measurement of FE_{NO}

Subjects were asked to perform 3 FE_{NO} measurements using the NIOX MINO airway inflammation monitor (Aerocrine AB, Solna, Sweden). The NIOX MINO is a portable, handheld, FE_{NO} measurement device. It uses a built-in flow control that requires subjects to exhale at a constant pressure between 10 and 20 cm H_2O and adjusts flow to the American Thoracic Society (ATS) recommended flow rate of a mean (SD) of 50 (5) mL/s.¹⁴ A visual and audio biofeedback system on the device assists subjects in maintaining constant pressure. The NIOX MINO has an NO scrubber inside the machine that effectively removes ambient nitric oxide contamination. It has a device lifespan of 1,500 measurements, and each precalibrated sensor has a lifespan of 300 measurements, after which it must be replaced. By using electrochemistry rather

than a chemiluminescence assay, the device does not require recalibration before each use. The NIOX MINO has previously shown excellent correlation with traditional nitric oxide analyzers¹⁷ and meets all essential aspects of the ATS recommendations for nitric oxide analysis.¹⁴ The device was set on the 6-second mode rather than the 10-second "standard" mode, because it was not believed that most subjects experiencing an acute asthma exacerbation would be able to exhale at a steady rate for 10 seconds.

Measurement of FEV_1 and PEF

Subjects were asked to perform FEV_1 using a portable spirometer (Puritan-Bennett Renaissance II; Puritan-Bennett, Wilmington, Massachusetts) in accordance with ATS standards.¹⁸ Subjects performed 3 FEV_1 maneuvers, because they were experiencing an acute asthma exacerbation and, therefore, ATS recommendations of up to 8 spirometric measurements were not followed. The FEV_1 percentage predicted was calculated using Morris standards. Peak expiratory flow rate readings were also obtained using the same portable spirometer.

Statistical Analysis

Statistical analysis was performed in 3 stages. In the first stage, the reproducibility of FE_{NO} , FEV_1 , and PEF measurements was determined using the intraclass correlation coefficient (ICC) and the coefficient of variation (CV). For the CV approach, a value was calculated for each subject based on 3 measurements for each of the 3 methods. Because the CV distributions were skewed, median and interquartile range values were calculated. Comparisons between CV values were made using the Friedman test.

In the second stage, correlation of FE_{NO} measurements with other factors was done by a correlation matrix. Variables that were 2 interval, natural dichotomous with interval, 2 dichotomous, or ordinal were analyzed using Pearson product moment correlation, point biserial, ϕ , or the Kendall τ , respectively.

In the third stage, predictors of hospitalization were first evaluated using bivariate analysis, and all significant factors were then analyzed with logistic regression using a forward selection likelihood ratio model.

RESULTS

Fifty-one patients with asthma presenting to the ED who met the inclusion and exclusion criteria were approached for participation in the trial. Of these patients, 13 (25%) refused to participate. Of the 38 who agreed to participate, 3 (8%) were unable to perform 1 acceptable FE_{NO} measurement and were excluded from further analysis. The demographic information for the remaining 35 subjects is provided in Table 1.

Table 2 provides the values of the measured variables. The FE_{NO} was elevated to 48.60 ppb, indicative of airway inflammation. There was no difference in FE_{NO} measurements between those receiving controller medications (inhaled corticosteroids or inhaled corticosteroid and long-acting β -agonist combination) and those with no controller medications (52.0 vs 46.0 ppb; $P = .70$). Both FEV_1 and PEF measurements

Table 1. Characteristics of the 35 Patients^a

Characteristic	Value
Age, mean (SD), y	37.6 (12.8)
Female sex	18 (51)
Asthma related	
NIH severity	
Mild intermittent	5 (14)
Mild persistent	3 (9)
Moderate persistent	11 (31)
Severe persistent	16 (46)
Home asthma medication	
Albuterol	34 (97)
ICS	7 (20)
ICS-LABA combination	10 (29)
Anticholinergic agent	3 (9)
Previous ICU visit or intubations	9 (26)
Previous ED visit in the past year ^b	
0	4 (12)
1–3	11 (33)
4–7	12 (36)
>8	6 (18)
Previous hospitalization in the past year ^b	
0	21 (64)
1–2	5 (15)
3–5	7 (21)
Time from asthma symptom onset to ED presentation, h ^c	
≤6	10 (29)
7–24	10 (29)
25–72	6 (18)
≥73	8 (24)

Abbreviations: ED, emergency department; ICS, inhaled corticosteroid; ICU, intensive care unit; LABA, long-acting β -agonist; NIH, National Institutes of Health.

^a Values are given as number (percentage) of patients unless otherwise indicated. The race of all patients was black.

^b Percentages are based on a total of 33 patients.

^c Percentages are based on a total of 34 patients.

Table 2. Measured Variables for the 35 Patients^a

Variable	Value
FE _{NO} , ppb	48.60 (45.16)
FEV ₁ , L/min	2.24 (1.27)
FEV ₁ % of predicted	67.48 (32.85)
PEFR, L/min	5.52 (3.21)
PEFR % of predicted	79.55 (43.39)
Borg scale score	5.84 (2.47)

Abbreviations: FE_{NO}, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate; ppb, parts per billion.

^a Data are given as mean (SD).

indicated airflow obstruction. Finally, the modified Borg index, which measures respiratory symptoms on a scale from 0 to 10 (higher values indicate more severe symptoms), showed an elevated value of 5.84.

Table 3. Coefficient of Variation Values for the 35 Patients^a

Method	Median	Interquartile range	75th Percentile	25th Percentile
FE _{NO}	9.42	10.50	14.41	3.91
FEV ₁	8.90	20.06	24.80	4.74
PEFR	11.10	21.54	29.31	7.77

Abbreviations: FE_{NO}, fraction of exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; PEFR, peak expiratory flow rate.

^a Data are given as percentages.

Reproducibility of FE_{NO}

The ICC is a range from 0 to 1, where higher values represent a greater degree of reproducibility. The FE_{NO} measurements had a high ICC of 0.98 (95% confidence interval, 0.97–0.99). The FEV₁ had a moderate ICC of 0.75 (95% confidence interval, 0.62–0.86). Finally, PEFR had a lower ICC of 0.64 (95% confidence interval, 0.46–0.78).

When analyzing the CV, lower values represent a higher degree of reproducibility. Table 3 provides the results of the CV analysis. Using the median values (because of skewness of data), no significant differences were found between CV measurements for FE_{NO}, FEV₁, and PEFR ($P = .22$). However, the interquartile range was much more narrow for FE_{NO} than for FEV₁ or PEFR.

The CV scatterplots for FE_{NO}, FEV₁, and PEFR are shown in Figure 1. Throughout the range of measured values, the CV for FE_{NO} remained low. The FEV₁ and PEFR have higher CV values throughout, indicating lesser reproducibility.

Correlation of FE_{NO} With Other Factors

There were no significant correlations (P value range, .17–.99) between FE_{NO} and other factors, including FEV₁, FEV₁ percentage predicted, PEFR, PEFR percentage predicted, age, sex, history of intensive care unit visits or intubations, modified Borg scale score, NIH asthma severity, and number of previous hospitalization in the past year. However, the time from when asthma symptoms had started to the time when the patient presented to the ED showed a trend toward statistical significance ($P = .08$).

Predictors of Hospitalization

Of the 35 subjects who presented to the ED, 10 were admitted to the hospital for further management of their asthma and 25 were discharged home. There was no significant difference in FE_{NO} levels between those who were admitted and those who were discharged home (57.5 vs 46.2 ppb; $P = .53$). An analysis of factors associated with admission from the ED found that hospitalizations in the past year were positively correlated ($P = .03$) and that low FEV₁ trended toward statistical significance ($P = .09$).

DISCUSSION

We found that FE_{NO} values can be obtained with acceptable reproducibility for asthmatic patients in the ED, FE_{NO} measurements give additional information not readily obtained by

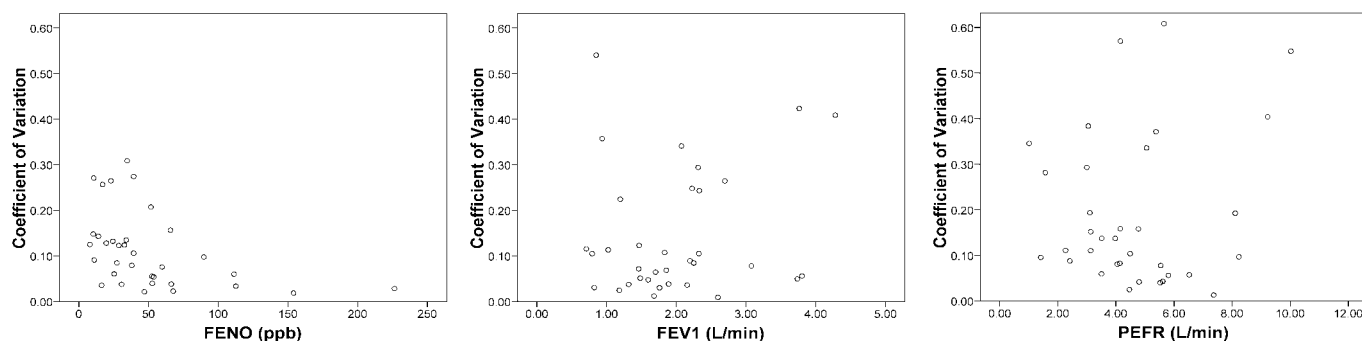


Figure 1. Scatterplots showing the coefficient of variation (CV) for individual subjects for fraction of exhaled nitric oxide (FE_{NO}) (A), forced expiratory volume in 1 second (FEV₁) (B), and peak expiratory flow rate (PEFR) (C) measurements. Lower CV values indicate greater reproducibility.

other sources, and FE_{NO} measurements do not seem to correlate with the need for admission from the ED.

An earlier ED study of FE_{NO} in patients with acute asthma, performed using a traditional stand-alone chemiluminescence gas analyzer, was discontinued early because of poor reproducibility.¹⁵ The NIOX MINO uses an electrochemical sensor and is a handheld device, which makes it ideal for use in the ED setting. The NIOX MINO has previously shown outstanding agreement with the traditional FE_{NO} analyzers.¹⁷

In the present study, the NIOX MINO showed excellent reproducibility, as measured by the ICC, with a value of 0.98 (95% confidence interval, 0.97–0.99). This is similar to a validation study of the NIOX MINO in the outpatient setting, in which the ICC was 0.99.¹⁶ The ICC value is also comparable to FE_{NO} measurements obtained by chemiluminescence gas analyzers in stable asthmatic patients.^{19,20} In our study, the NIOX MINO showed a greater degree of reproducibility than FEV₁ and PEFR measurements, as determined by the ICC.

Using a different measure of reproducibility (the CV), the NIOX MINO again showed clinically acceptable measurements. The median CV obtained was similar to the values for FEV₁ and PEFR and had a value of approximately 10%. Other researchers^{21,22} have suggested that a diagnostic test should have a CV acceptance limit of less than 15%. When comparing the interquartile range for each of the 3 methods, FE_{NO} values were lower, indicating less dispersion among subjects. Consistent with the results of the ICC analysis, the reproducibility of FE_{NO} measurements seems superior to that of FEV₁ and PEFR measurements.

We also attempted to determine if initial FE_{NO} measurements were correlated with other demographic or measured characteristics. Some studies have suggested that FEV₁ measurements may be correlated with FE_{NO}, whereas others have not found this association.^{23–26} In our study, spirometric measurements, asthma severity, asthma history, and demographic factors were not correlated with FE_{NO}. This indicates that FE_{NO} readings are potentially providing additional information in the ED setting that cannot be obtained by other measures.

Although no factor was statistically correlated with FE_{NO} measurements at the $P < .05$ level, 1 factor did trend toward

statistical significance ($P = .08$). This factor was the length of time that the asthma attack had been present before the patient presented to the ED. This finding makes sense intuitively, because FE_{NO} is purported to measure the amount of airway inflammation. Asthma attacks present for a longer time tend to respond more slowly to treatment and may require higher doses of medications, because of increased airway inflammation.²⁷ The FE_{NO} measurements might, therefore, be useful to guide therapeutic decisions in the ED, but more research is needed.

We also tried to determine if FE_{NO} could predict which patients would require hospitalization and which would be discharged home. No correlation was found between the need for admission and FE_{NO} level. Therefore, FE_{NO} measurements may need to be combined with other values, such as spirometric readings or symptom scores, to be useful as a tool to guide admission decisions in the ED. This has been done successfully in the outpatient setting by others to predict future exacerbations.²⁸ In our study, the number of previous hospitalizations and FEV₁ values were correlated with admission for asthma. However, these results may have been biased by the fact that asthma guidelines recommend using these factors (along with others) in determining the need for admission.¹²

Although the NIOX MINO did not predict which patients would require admission, it may be a useful tool to predict relapse after discharge from the ED. The relapse rates for asthma are unacceptably high,²⁹ and future studies are needed to determine if measures of airway inflammation can play a role to decrease such rates.

There are several limitations to our study. This was a single-center inner-city hospital and, therefore, the results may not be applicable to other settings. The diagnosis of asthma was not independently verified (ie, methacholine challenge), and atopic status determination by skin testing was not performed. However, these tests are not routinely done for patients presenting to EDs and would, therefore, be artificial in our study. A number of patients with acute asthma refused to participate, and their inclusion may have altered the results. We elected to exclude subjects who had used systemic corticosteroids or leukotriene receptor antagonists

within the week before the ED visit because of their known effects on FE_{NO}. Based on the pharmacokinetic properties of these medications,^{30,31} we assumed a 1-week washout period was adequate, but this theory has not been formally evaluated. Finally, we did not observe subjects after discharge to evaluate for relapse events.

In conclusion, we have shown that the NIOX MINO can provide reproducible FE_{NO} measurements in the ED setting. These readings represent the degree of airway inflammation and are not correlated with traditional asthma measurements. Finally, when used alone, FE_{NO} measurements are not able to predict the need for hospitalization. Further research is needed to determine how best to use FE_{NO} values in the ED setting.

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Requests for reprints should be addressed to:
 Alan P. Baptist, MD
 Division of Allergy and Clinical Immunology
 University of Michigan
 24 Frank Lloyd Wright Dr
 PO Box 442, Suite H-2100
 Ann Arbor, MI 48106
 E-mail: abaptist@med.umich.edu