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Fractional exhaled nitric oxide measurement: Comparison between the Sunvou-CA2122 analyzer and the NIOX VERO analyzer

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ABSTRACT

Background and objectives: Fractional exhaled nitric oxide (FeNO) has been developed as a useful marker for eosinophilic airway inflammation and is widely used in clinical practice due to its convenience and noninvasiveness. There are two NO analyzers commonly used in China: the Sunvou-CA2122 Analyzer (NOS) and the NIOX VERO Analyzer (NOV). However, the relationships between the two devices have not yet been reported. The aim of our study was to determine the correlation and differences in the FeNO levels measured by the two devices.

Methods: FeNO levels were measured by both NOS and NOV in 107 adult patients with asthma. The asthma control test (ACT) score and lung function were also evaluated. This study was registered in the Chinese Clinical Trial Registry (<http://www.chictr.org.cn>).

Results: NOS yielded generally higher FeNO values than NOV [median (range): 87.0 (16~276) vs 58.0 (9~228); $p < .001$], and the difference increased with increasing FeNO levels. There was a high degree of correlation between FeNO values obtained with both devices ($r_s = 0.878$, $p < .001$). However, the Bland-Altman plot showed a low degree of agreement, with a mean difference of -0.16 between $\log\text{FeNO}_{\text{NOS}}$ and $\log\text{FeNO}_{\text{NOV}}$ (95% CI: $-0.45 \sim 0.14$). The conversion equation was calculated as follows: $\log\text{FeNO}_{\text{NOS}} = 0.027 + 0.904 \times \log\text{FeNO}_{\text{NOV}}$.

Conclusion: This was the first report to compare FeNO levels measured by NOS and NOV, showing a strongly positive correlation and a low degree of consistency between the two devices. Further prospective studies are required to verify our conclusions and determine the validity of the equation.

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Asthma; exhaled nitric oxide; airway inflammation; Sunvou-CA2122 analyzer; NIOX VERO analyzer

Introduction

The measurement of fractional exhaled nitric oxide (FeNO) provides a novel method of noninvasively evaluating airway eosinophilic inflammation and has been recommended in international guidelines as an additional tool supporting the diagnosis and long-term management of bronchial asthma, such as the 2018 Global Initiative For Asthma (GINA) (1). FeNO has been demonstrated to play a vital role in monitoring patients' responses to corticosteroids (2), predicting asthma exacerbations (3–5), measuring adherence to therapy (6) and identifying poor corticosteroid adherence (7,8). As a biomarker with the advantages of easy operation, stable results and low cost, FeNO

has been increasingly widely recognized and applied in clinical practice.

Several different NO analyzers have been developed, of which the NIOX VERO analyzer (NOV, Aerocrine, Solna, Sweden) is commonly used worldwide. NOV utilizes electrochemical NO measurement technology; compared to chemiluminescent stationary NO analyzers, which have been thought to be the gold standard for testing FeNO, NOV is characterized by convenient use and long service life, which contributes to its widespread clinical application. A Nano Coulomb nitric oxide analyzer, Sunvou-CA2122 analyzer (NOS, Sunvou Medical Electronics Co. Ltd., Wuxi, Jiangsu, China) has been developed and used

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in some Chinese hospitals for several years, but no studies have been published evaluating the relationship between the FeNO levels measured by NOS and NOV. The aim of this study was, therefore, to compare the correlation and differences in FeNO values detected by the two analyzers and to determine whether they were comparable.

Methods

Subjects

This single-center and cross-sectional study was prospectively conducted with asthma patients who visited the outpatient clinic of West China Hospital of Sichuan University from June 2018 to January 2019. The inclusion criteria were as follows: (1) age ≥ 18 years and (2) a diagnosis of bronchial asthma based on the 2018 GINA guidelines (1). The relevant data for each patient were collected and recorded, including demographics and clinical history. FeNO was measured with both analyzers. Lung function and the Asthma Control Test (ACT) score were also evaluated. The present study was approved by the Ethics Committee of West China Hospital of Sichuan University and registered in the Chinese Clinical Trial Registry (ChiCTR1800020303) (<http://www.chictr.org.cn>).

On the basis of the FeNO values measured by NOV, patients were divided into 4 groups with the cutoff points of 25, 50, and 100 ppb: <25 ppb for group 1, $25 \sim 49$ ppb for group 2, $50 \sim 99$ ppb for group 3 and ≥ 100 ppb for group 4.

FeNO measurement

FeNO was measured according to the manufacturer's instructions and the guidelines of the American Thoracic Society/European Respiratory Society (ATS/ERS) (9) with both devices. The test order was assigned at random. A subgroup of patients was tested 3 times with NOS to investigate within analyzer variability, with an interval of at least 30 s between the tests. In previous studies, it was reported that spirometric maneuvers had an impact on FeNO values (10–13); thus, FeNO measurements were performed before spirometry in this study.

To ensure the accuracy of the FeNO measurements and eliminate external interference, patients abstained from alcohol, coffee, chocolate, nitrate-rich foods (such as sausage, animal innards, lettuce, and spinach), strenuous exercise, tobacco and bronchodilators for one hour preceding the test.

The main steps in taking the FeNO measurements were as follows. Remaining seated comfortably, the patients were asked to inhale deeply through the mouth to total lung capacity (TLC) and then to exhale through the mouthpiece guided by a visual animation at a constant flow rate of 50 ml/s. The required exhalation time was approximately 6–10 s. Both devices displayed the results automatically once acceptable values were obtained. The measurement ranges of the two devices were both set at $5 \sim 300$ ppb, and subjects with FeNO values below 5 ppb or above 300 ppb were excluded from our study. NOV utilizes an electrochemical sensor, while NOS is based on a Nano Coulomb current sensor. The sensors are replaced after a certain number of tests to avoid frequent calibration (for NOV or NOS, every 500 or 300 tests, respectively).

ACT assessment

Asthma control was assessed by the Chinese version of the ACT (14). Asthma symptoms, the utilization of rescue medications and the impact of asthma on daily activities during the preceding 4 weeks were subjectively evaluated in patients with a five-item questionnaire, with each item answered on a five-point scale. The sum of the scores of the five questions was the total ACT score (range: $5 \sim 25$), with a cutoff score of 20 or more identifying patients with well controlled asthma (15,16).

Lung function measurement

Lung function was measured by a portable spirometer (version: 5.32.0, JACGER, Germany) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) standards (17). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and the FEV_1/FVC ratio were recorded in this study. FVC and FEV_1 are expressed as percentages of the predicted values, and FEV_1/FVC is expressed as a percentage.

Statistical analysis

For continuous variables, the Kolmogorov–Smirnov test was used to test for the normality of the distribution. Normally distributed data were expressed as the mean $\pm$ standard deviation (SD) and analyzed by one-way ANOVA, while nonnormally distributed data were displayed as the median and interquartile range (IQR) and tested with nonparametric tests.

Categorical data were expressed as numbers and percentages. The relationship between FeNO levels obtained by NOS and NOV was analyzed by the Pearson correlation coefficient (in the present study, FeNO values were log-transformed to a normal distribution). The conversion equation was calculated by linear regression analysis. The Bland-Altman method was used to assess the agreement between the two devices. The repeatability of the measures was expressed as the intraclass correlation coefficient. Receiver operating characteristic (ROC) curves of FeNO values were used to discriminate patients with poorly controlled asthma from those with well controlled asthma. A two-sided $p < .05$ was defined as statistically significant.

The statistical analysis was performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). The Bland-Altman plot and ROC curves were generated and analyzed in MedCalc version 15.8 (MedCalc Software, Ostend, Belgium), and others were generated in GraphPad Prism 7 (Graphpad Software, San Diego, CA, USA).

Results

Among the 212 patients initially screened, a total of 105 patients were ruled out, of which 87 cases were excluded for failure of FeNO measurements by either NOS or NOV, 16 cases for a second visit (data obtained were not analyzed) and 2 cases for FeNO values above 300 ppb. Overall, 107 asthma patients [age range: 21~72 years, 68 females, 18 smokers, 80 with comorbid allergic rhinitis (AR)] successfully completed the study. The results of spirometry ranged from severe ventilation dysfunction to normal (FEV₁% range: 19.3~118.2%). The ACT assessment indicated overall well controlled asthma with a median score of 21.0 points. Patients receiving inhaled corticosteroid (ICS) or inhaled corticosteroid/long-acting beta2-agonist (ICS/LABA) treatment accounted for 76.6% (82), and 46 (43.0%) patients took leukotriene receptor antagonists (LTRA) (Table 1).

FeNO_{NOV} and FeNO_{NOS} were significantly different ($p < .001$, Figure 1), with median levels of 58.0 (range: 9~228) and 87.0 (range: 16~276), respectively (Table 1). FeNO_{NOS} values were generally higher than FeNO_{NOV} values, and their differences increased with increasing FeNO levels (Figure 2). Patients were divided into 4 groups, and the first, second, third and fourth groups had 15, 28, 37 and 27 patients, respectively, with median differences of 12.0, 16.5, 32.0, and 43.0 between FeNO_{NOS} and FeNO_{NOV} in each group,

Table 1. Basic clinical parameters of subjects.

Clinical parameter	Value
Total, number (n)	107
Age (year)	40.2 ± 11.7
Female, n (%)	68 (63.6)
Height (cm)	162.0 (157.0, 168.0)
Weight (kg)	58.8 ± 9.6
BMI (kg/m ²)	22.2 ± 2.8
Combined with AR, n (%)	80 (74.8)
Smokers, n (%)	18 (16.8)
FVC %	99.7 (88.7, 110.0)
FEV ₁ %	88.1 (73.2, 98.0)
FEV ₁ /FVC%	73.3 (66.4, 78.3)
ACT score	21.0 (19.0, 24.0)
FeNO _{NOV} ppb	58.0 (35.0, 100.0)
FeNO _{NOS} ppb	87.0 (49.0, 135.0)
Treatment, n (%)	
ICS or ICS/LABA	82 (76.6)
LTRA	46(43.0)

*Normally distributed data are expressed as the mean ± standard deviation, while nonnormally distributed data are expressed as the median (interquartile range); others are presented as the number (percentage). BMI: body mass index; AR: allergic rhinitis; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; FEV₁/FVC: forced expiratory volume in one second/forced vital capacity ratio; ppb, parts per billion; ICS: inhaled corticosteroids; ICS/LABA: inhaled corticosteroids/long-acting beta2-agonists; LTRA: leukotriene receptor antagonists.

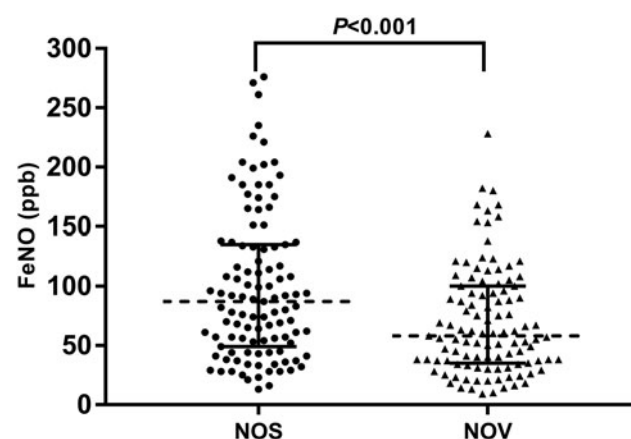


Figure 1. A scatter plot of FeNO values measured by both NOV and NOS. The points represent FeNO_{NOS} values, and triangles represent FeNO_{NOV} values. The solid lines represent the maximum and minimum values of interquartile ranges and the dotted line represents median values. The comparison was analyzed by related-samples non-parameters Wilcoxon rank-sum test, showing statistically significant difference ($p < .001$).

respectively. FeNO values obtained with the two devices differed significantly in the subgroups (all $p \leq .001$; Table 2). Moreover, FeNO_{NOS} values were significantly higher than FeNO_{NOV} values in patients whether treated with ICS or not (all $p < .001$) (Supplementary table). Patients treated with ICS showed significantly lower median FeNO values than those without ICS therapy (FeNO_{NOS} 73.5 vs 116.0, $p = .005$ and FeNO_{NOV} 58.5 vs 87.0, $p = .02$).

There was a strong positive correlation between FeNO values tested by both devices (Pearson

correlation coefficient: $r_s = 0.878$, $p < .001$; Figure 3). However, the Bland–Altman plot showed a low degree of agreement, with a mean difference of -0.16 (95% CI: $-0.45 \sim 0.14$) between $\log\text{FeNO}_{\text{NOS}}$ and $\log\text{FeNO}_{\text{NOV}}$ (Figure 4). A conversion equation was calculated by linear regression as follows: $\log\text{FeNO}_{\text{NOS}} = 0.027$ [standard error (SE), 0.093] + 0.904 (SE, 0.048) $\times \log\text{FeNO}_{\text{NOV}}$ ($R^2 = 0.770$, adjusted $R^2 = 0.768$, $p < .001$) (Figure 3).

FeNO was repeatedly measured by NOS three times in a subgroup of 20 patients (age range: 23–72 years; 10 females; FEV₁% range: 30.6–109.1%), with FeNO values of 100.8 ± 68.8 , 102.0 ± 65.0 , 98.5 ± 64.5 for the first, second and third measurements, respectively, showing no significant difference ($p = .693$, Figure 5). The three repeated FeNO values were significantly related, with an intraclass correlation coefficient of 0.988 (95% CI: 0.974–0.995, $p < .001$).

Seventy-two out of the 107 patients had well-controlled asthma (ACT ≥ 20) and significantly lower FeNO_{NOV} and FeNO_{NOS} values than those of patients with poorly-controlled asthma (ACT < 20), [FeNO_{NOV} 48.0 (31.5, 87.8) vs 82.0 (52.0, 121.0), $p < .05$, and FeNO_{NOS} 68.5 (43.3, 120.0) vs 108.0 (83.0, 165.0), $p < .05$, respectively]. The area under ROC curve (AUC) values generated using the NOV and NOS values to differentiate patients with poorly-controlled asthma from those with well-controlled

asthma were 0.679 (95% CI: 0.567–0.790; $p < .05$) and 0.662 (95% CI: 0.551–0.772; $p < .05$), respectively. Pairwise comparison of the ROC curves revealed a difference in the AUC of 0.0171 (95% CI: $-0.0349 \sim 0.0691$; $p = .520$) between the FeNO_{NOV} and FeNO_{NOS} values (Figure 6). The cutoff points for FeNO_{NOV} and FeNO_{NOS} were 50.0 (82.9% sensitivity and 52.8% specificity) and 82.0 (77.1% sensitivity and 61.1% specificity), respectively. There was a significant difference in FEV₁% [81.1 (59.0, 93.8) vs 90.3 (78.6, 99.3), $p = .025$] between patients with poorly-controlled asthma and those with well-controlled asthma.

Discussion

In this study, FeNO levels tested by NOS and NOV were found to be significantly different in a cohort of adults with asthma. There was a strong positive correlation but a low degree of agreement between FeNO values obtained with the two devices. Previous studies (18–23) showed that FeNO values were influenced by the devices used to obtain the measurement and varied in devices from different manufacturers, with different measuring technologies or both. In our study, a Nano Coulomb current sensor was utilized in NOS, while an electrochemical sensor was used in NOV.

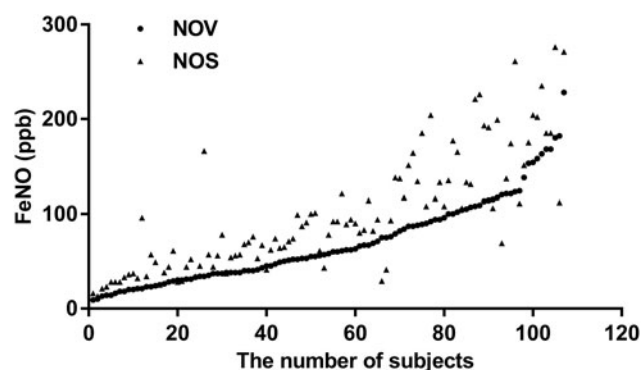


Figure 2. A point diagram of the pairwise distribution of FeNO values measured by NOV and NOS. The points represent FeNO_{NOV} values, and the triangles represent FeNO_{NOS} values. The diagram was generated according to the increasing FeNO_{NOV} values.

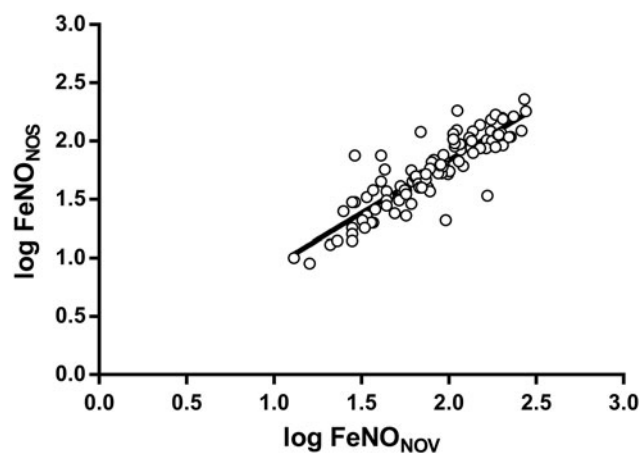


Figure 3. A scatter diagram of the correlation between $\log\text{FeNO}_{\text{NOS}}$ and $\log\text{FeNO}_{\text{NOV}}$ (FeNO values were log-transformed to a normal distribution). The solid line represents the linear regression equation, with a Pearson correlation coefficient (r_s) of 0.878 ($p < .001$).

Table 2. Comparison of FeNO_{NOS} and FeNO_{NOV} in subgroups.

Group	<i>n</i>	FeNO_{NOV} , ppb	FeNO_{NOS} , ppb	Difference in FeNO_{NOS} and FeNO_{NOV} , ppb	<i>p</i>
1($\text{FeNO} < 25$)	15	18.0 (14.0, 21.0)	32.0 (23.0, 37.0)	12.0 (9.0, 17.0)	$=.001$
2(FeNO :25–49)	28	37.0 (31.0, 40.0)	55.0 (41.8, 66.3)	16.5 (8.0, 26.3)	$<.001$
3(FeNO :50–99)	37	67.0 (56.5, 85.5)	94.0 (81.0, 119.0)	32.0(16.5,46.5)	$<.001$
4($\text{FeNO} \geq 100$)	27	121.0(108.0, 158.0)	177.0(133.0, 204.0)	43.0(16.0,77.0)	$<.001$

*FeNO values are presented as the medians (interquartile ranges). Comparisons between FeNO_{NOS} and FeNO_{NOV} in subgroups were tested by the related-samples nonparametric Wilcoxon rank-sum test.

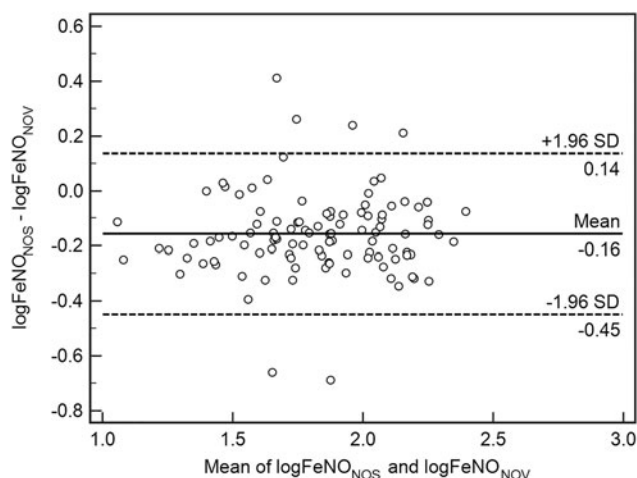


Figure 4. The Bland–Altman plot shows the relationship between $\log\text{FeNO}_{\text{NOS}}$ and $\log\text{FeNO}_{\text{NOV}}$. The mean values were plotted on the x-axis, and the difference values were plotted on the y-axis. The mean difference was -0.16 (95% CI: $-0.45 \sim 0.14$). The solid line represents the mean difference, and the dotted lines represent the maximum and minimum values for the 95% CI of the mean difference. *CI: confidence interval.

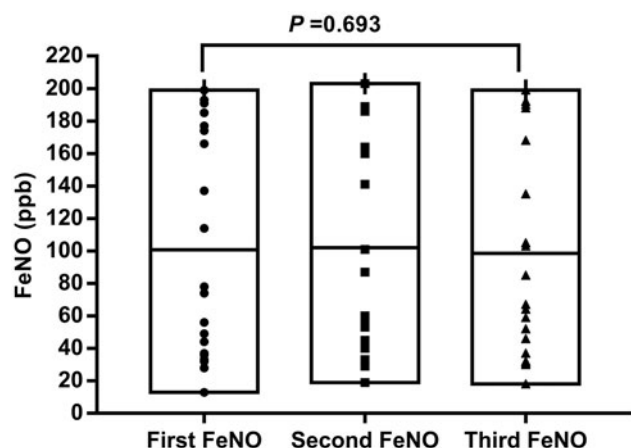


Figure 5. A bar graph of three repeatedly measured FeNO_{NOS} values. The points, squares and triangles represent the values obtained in the first, second and third FeNO_{NOS} measurements, respectively; the three solid lines in each bar from top to bottom represent the maximum, mean and minimum values, respectively. *The comparison of three FeNO_{NOS} values was analyzed by one-way repeated measurement ANOVA, showing no significant difference ($p = .693$).

We speculated that the different measuring technologies adopted by the two devices might be one of the reasons for our results. Routine calibrations are not required in NOS and NOV; instead, the sensors in the two devices should be replaced every 300 and 500 tests, respectively; thus, different calibrations were unlikely to be the reason for our findings. However, whether the discrepancy in the frequency of sensor replacement impacts FeNO measurements remains to

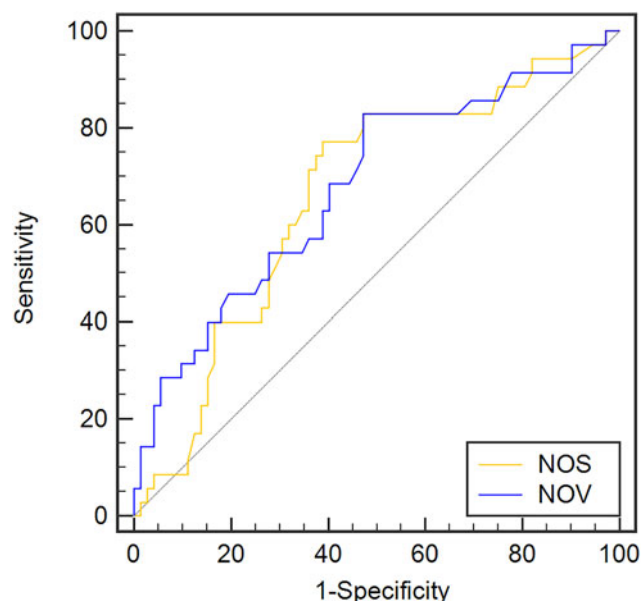


Figure 6. Receiver operating characteristic (ROC) curve analysis evaluated different cutoff points of FeNO values detected by NOV and NOS, with an ACT score ≤ 19 as the threshold value. The blue solid line represents the ROC curve of NOV, the yellow line represents NOS, and the black dotted line represents the diagonal line.

be determined. The test procedures of both devices were in accordance with the manufacturers' guidelines and the ATS/ERS standards (24); hence, errors in testing methods could also be excluded. In brief, as far as the current evidence was concerned, the differences observed might be attributed to the technologies used and frequency of sensor replacement, rather than calibration or testing method.

As recommended in the official ATS/ERS guidelines (24), adults with low FeNO (<25 ppb) are less likely to have eosinophilic inflammation, while those with high FeNO (>50 ppb) probably have eosinophilic inflammation and respond well to corticosteroids; those with moderate FeNO ($25 \sim 50$ ppb) need careful clinical evaluation. In our study, the analysis of low, moderate and high FeNO groups suggested clinically significant differences in FeNO values obtained by NOV and NOS (Table 2). At FeNO_{NOV} levels below 25 or 50, the FeNO_{NOS} levels were mostly higher than 25 or 50, respectively; if interpreted according to the ATS/ERS criteria (24), these values would lead to the overestimation of airway inflammation and thus the over-treatment of asthma. Therefore, in clinical practice, when interpreting FeNO levels obtained with different analyzers, the clinical context (such as symptoms, lung function, asthma control) should be taken into consideration, and a numerical conversion could be conducted based on the regression equation if necessary.

The differences between analyzers increased with increasing FeNO levels, and that trend corresponded to the degree of airway inflammation. Collin et al. (18) observed an inverse phenomenon where the differences between devices were more obvious at low FeNO levels, especially those below 10 ppb, but with no clinical significance. They speculated that the reason might be different NO detection technologies or inaccuracy of the devices at a very low measurement range. In our study, the FeNO values (NOS: 16~276 versus NOV: 9~228) obtained were within the measurement range (5~300). However, we could not rule out the possibility that the devices might not be accurate at a high measurement range because a second NOS or NOV was not available for comparison. Of course, the difference in the technologies used might be another reason.

There was no significant difference in the FeNO values repeatedly measured by NOS, suggesting that NOS had excellent repeatability and low within-analyzer variability. Therefore, a single operation was sufficient to obtain a reliable FeNO value if steps were carried out correctly.

We assessed the capability of FeNO values obtained by both devices to differentiate patients with poorly-controlled asthma from those with well-controlled asthma. According to the ROC curve analysis, patients with FeNO values above 50 ppb tested by NOV or above 82 ppb tested by NOS were more likely to have poor asthma control. NOV generated a higher AUC value than NOS, but the difference had no statistical significance. Meanwhile, NOV showed a higher sensitivity and a correspondingly lower specificity than NOS. Taken together, NOV is superior to NOS in terms of discriminating patients with poorly-controlled asthma from those with well-controlled asthma. Roberta et al. (21) assessed the discriminating capability of two other analyzers in another cohort of asthma patients, showing that NIOX (a chemiluminescent analyzer) was better than NObreath (an electrochemical analyzer), with cutoff points of 15 and 25 ppb, respectively. Our study identified higher cutoff points. We speculated that the discrepancy of enrolled subjects might be one of the reasons. The variations within patients were wider in our study, as a significant difference in lung function was observed between patients with well-controlled asthma and those with poorly-controlled asthma, but none of Roberta's study, which might explain why the two studies obtained far different cutoff points. In addition, due to a small number of patients (35, 32.7%) with poorly-controlled asthma enrolled in our study, there might be a

selection bias, which could affect the results. However, due to different analyzers used in the two studies, we could not make unambiguous interpretations.

Medications such as ICS, ICS/LABA, and LTRA were not controlled in our study, which were reported to inhibit expression of inducible NO synthase, thus decreasing the FeNO levels in subjects treated with corticosteroids (2,25,26) or LTRA (27,28). Our study yielded consistent results that patients treated with ICS or ICS/LABA showed lower FeNO levels than those without ICS therapy. Owing to a small number of patients (only 4 subjects) under single LTRA therapy, we couldn't analyze the effect of LTRA on FeNO levels. In short, steroids interference could not be ignored in FeNO measurements.

There are several limitations in our study. First, the patients included were from a single hospital, and a selection bias might exist. Second, single Asian race of the subjects and relative small sample size may limit the generalization of the findings to some extent. Third, the detection time of day in FeNO tests were not controlled in our study, which might have influenced the measured FeNO values, as a circadian rhythm effect on FeNO values was observed in the study by Mattes et al. (29). Fourth, our study was only conducted in a population of adults with asthma; thus, it is unclear whether the conclusions are applicable to another cohort. Further studies are needed to compare FeNO values in healthy subjects, asthmatic adolescents, or patients with other types of airway diseases. Our research team will continue to focus on the impact of the differences between FeNO devices on clinical work. Further studies are needed to overcome the limitations and confirm our conclusions.

In conclusion, the present study showed that FeNO values measured by NOV and NOS were strongly correlated but significantly different; the FeNO values obtained with NOS cannot be interpreted according to the ATS/ERS criteria, but need to be converted by a regression equation before being used for clinical purposes. Prospective and multicenter studies are required to further verify our conclusions, and validate the equation in other populations.

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Declaration of interest

The authors report no conflicts of interest.

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Authors' contribution

CTL, TXH, BCL conceived and designed the study. TXH, BCL, DY collected the data. TXH, BCL analyzed the data. TXH, BCL wrote the manuscript. CTL oversaw all aspects and reviewed the manuscript. All authors read and approved the final manuscript.

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Supplementary table: Comparison between FeNO_{NOS} and FeNO_{NOV} in patients treated with ICS or ICS/LABA and those without ICS therapy

ICS or ICS/LABA	n	FeNO _{NOV} , ppb	FeNO _{NOS} , ppb	Difference in FeNO _{NOS} and FeNO _{NOV} , ppb	P
No	21	87.0(57.5,115.0)	116.0(90.5,162.5)	27.0(19.0, 54.0)	<0.001
Yes	36	58.5(31.5, 89.8)	73.5(38.8, 119.3)	17.0(8.8, 33.5)	<0.001

*A total of 57 patients were analyzed in the table (50 cases were excluded for under treatment of systemic corticosteroids or LTRA or Omalizumab to avoid interference). Comparisons between FeNO_{NOS} and FeNO_{NOV} in subgroups were tested by the related-samples nonparametric Wilcoxon rank-sum test.