Comparison Study of a NEW portable FeNO breath device: the second generation NObreath®

Don Perera
BSc(Hons) MSc
Regulatory Affairs
Clinical Researcher |
Bedfont Scientific Ltd.

Contents

Abstract:

Background: Measurement of fractional nitric oxide (NO) concentration in exhaled breath (FeNO) is a quantitative, non-invasive, simple, and safe method of measuring airway inflammation that provides a complementary tool to other ways of assessing airways disease, including asthma. A method comparison study was conducted with the NObreath V2, the recognised gold standard method of chemiluminescence (LR2000, Logan Research) and three other commercially available devices.

Purpose: To establish if FeNO readings provided by the NObreath V2 correlate with the recognised gold standard method of chemiluminescence.

Methods: Method comparison study: FeNO was measured in 23 subjects, linear relationship was estimated with Pearson's coefficient (r), absolute agreement by intra-class correlation coefficient (ICC) and bias with limits of agreement (95% of paired differences). FeNO measurements were made using (1) NObreath V2 (Bedfont), (2) NObreath V1 (Bedfont), (3) LR2000 (Logan Research) , (4) NIOX VERO (Circassia) (5) Vivatmo Pro (Bosch).

Results: The data was pooled together (n=79) and the mean readings were compared using regression analysis, which resulted in: 95% Lower CI 0.96994 and Upper CI of 1.04901102 and a slope of y=1.0095x -2138, R^2=1. The mean CV of FENO readings by NObreath V2 are 7.97% and the mean CV of FENO readings for the LR2000 are 7.79%. This shows superior agreement between the two devices. Whereas the mean reading for the NIOX VERO are 80.0% and the mean FeNO reading for LR2000 are 96.01%.

Conclusions: The closest relationship between the recognised gold standard method of chemiluminescence was displayed by the NObreath V2 device; however all devices (apart from Bosch which could not be tested) also displayed good agreement and interchangability with the gold standard. This indicates that the NObreath V2 device is suitable for use in clinical practice.

Keywords: nitric oxide, asthma, inflammation, airway disease, exhaled breath.

Introduction:

To determine the level of airway inflammation, various markers such as bronchial hypersensitivity tests, induced sputum analysis, and fractioned exhaled nitric oxide (FeNO) have been used. Some studies have suggested that monitoring and management will benefit the patient more greatly and aid in control of their asthma [1].

FeNO measurement and breath analysis stands out as the easiest and most non-invasive alternative among this group of markers.

Asthma is characterised by airway inflammation and presence of airway inflammatory mediators, and diagnosis and management is based on clinical history, physical exam and spirometry testing. However, clinical history provided by the child and/or parent can be unreliable and spirometry may not aid in diagnosis or management or reflect airway inflammation. Fractional exhaled nitric oxide (FeNO) has been shown to correlate with levels of eosinophils in the sputum and has been studied as a biomarker tool to help guide clinicians in the management of asthma in children [4].

Nitric oxide (NO) is a signalling molecule produced by respiratory epithelial cells, is found in exhaled breath and functions as a vasodilator and bronchodilator in the lungs. NO is synthesized from l-arginine by inducible NO synthase enzymes in response to inflammatory cytokines and is present in the exhaled breath of humans. FeNO has been found to be elevated in children with asthma and is felt to reflect eosinophilic airway inflammation resulting from the type 2 T-helper cell pathway. Given that NO is found in exhaled human breath, it was felt that measurement of FeNO could be a non-invasive quantitative measure of airway inflammation, and that FeNO levels could provide clinicians with objective data in the treatment of children with asthma [5].

The potential for FeNO to provide objective data is especially important considering that spirometry and specifically FEV_1 has been shown to be mostly normal in children with asthma of all severities, and in children with symptoms of uncontrolled asthma. Reduced lung function in school-aged children may be present even in the absence of respiratory symptoms, making the interpretation of spirometry results challenging [5].

Chemiluminescence analysers were first used in the 1990s to detect NO in exhaled breath, and they were cleared for clinical use by the US FDA in 2003. FeNO testing is relatively easy to achieve in school-aged children, even in as young as 4 years of age, and is therefore practical for clinicians to use to gain objective data about their patients. Levels of FeNO are increased in children with asthma compared to children without asthma. In 2011, the American Thoracic Society (ATS) published Clinical Practice Guidelines on the subject of FeNO and recommended that FeNO be used in the diagnosis of eosinophilic airway inflammation [5, 7].

A paper recently published by Antoni Molinio, compared the NIOX VERO to the Vivatmo-PRO and HypAIR-FeNO, the results show that the NIOX VERO tends to read higher than the other devices, although the devices weren't compared to the gold standard, which is chemliuensence [6].

The aim of this study was to conduct a method comparison between the NIOX VERO and NObreath V2. To evaluate the agreement of FeNO measured with both these devices at 4 sites [1, 2].

As the NObreath V2 is a new device there is no data comparing this device to other FeNO portable devices, although the sensor in the NObreath V2 is the same its predecessor (NObreath V1)[7].

Subjects and Methods:

Patients with and without asthma were tested according to the international guidelines were eligible to take part in the study.

FeNO Measurement: FeNO was measured according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using a hand-held device NObreath (FeNO NObreath) and a stationary NIOX (FeNO NIOX)[6]. The order of the measurements was random. For both types of measurements, patients were seated in the upright position without a nose clip. In a subgroup of patients, the within-subject reproducibility of FeNO NObreath and FeNO NIOX was assessed by repeating of up to 3 measurements.

In detail, FeNO results using the NObreath was obtained by asking subjects to exhale, guided by an auditory cue, through the mouthpiece, keeping the incentive i.e. Car or fish or flow meter, at a constant flow rate of 50 ml/s. The required exhalation time is approximately 15s. To ensure a breath sample was taken at the correct flow rate, the monitor was held upright at all times during the test.

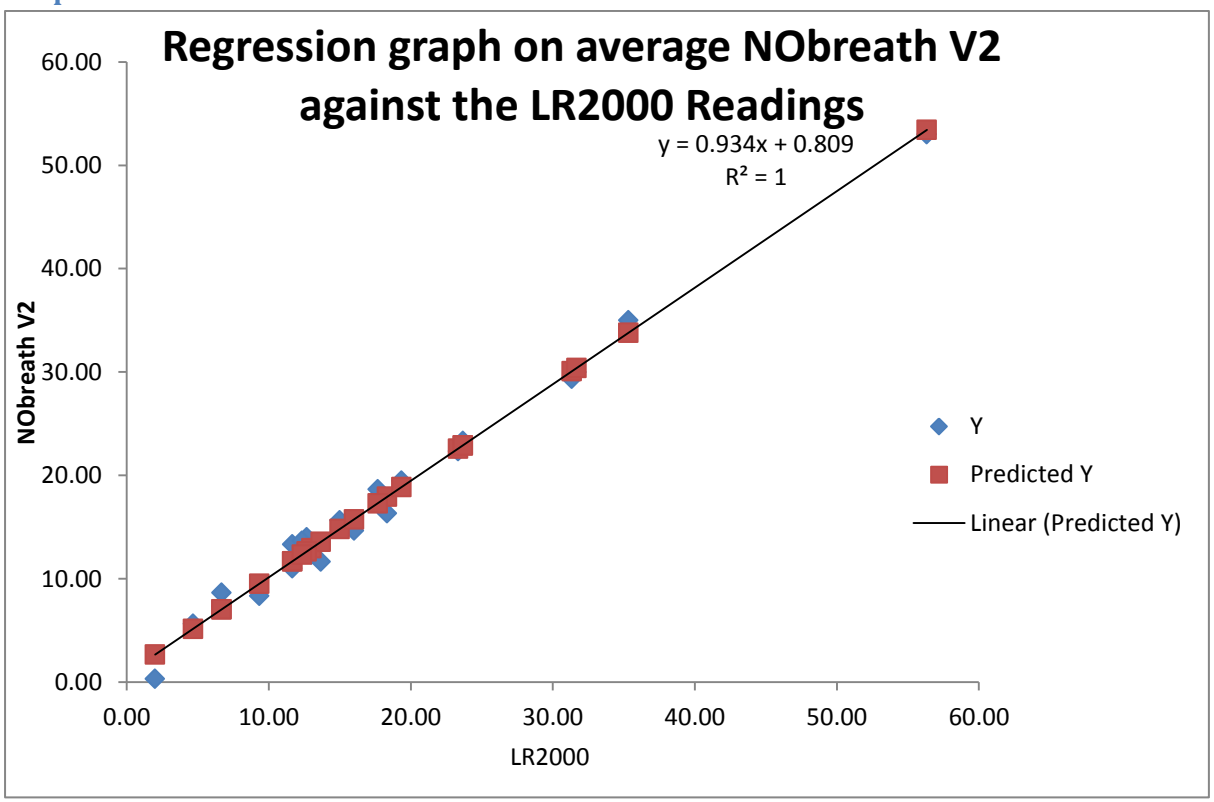
FeNO NIOX was performed by asking the subjects to inhale nitric oxide-free air deeply to total lung capacity through a filter connected to the device and then to exhale for 10 s at a constant pressure guided by a visual cue to stabilise flow rate, to maintain a fixed flow rate of 50 ml/s (following ATS guidelines). Measurements were repeated after a brief rest period until two acceptable values (±5 ppb for measurements <50 ppb and ±10% for measurements≥50 ppb) were performed (maximum three attempts). The mean of two adequate values for each subject was recorded for analysis. For NIOX, the system calibration was performed every 14 days. After FeNO NObreath® and FeNO NIOX patients completed a usability study on the NObreath.

Statistical analysis was conducted with the data; numerical variables were expressed as mean ± SD, unless otherwise specified. Paired t and unpaired t-test were used for comparisons, when appropriate. The relationship between measures was estimated by Pearson's correlation coefficient (r) and linear regression analysis. The agreement between measures was assessed by the method of differences against the means according Spearman correlation coefficient (rs) was used to identify any potential tendency for the separation of agreement at higher or lower values.

Results:

Statistical Analysis:

Graph 1



Graph 2

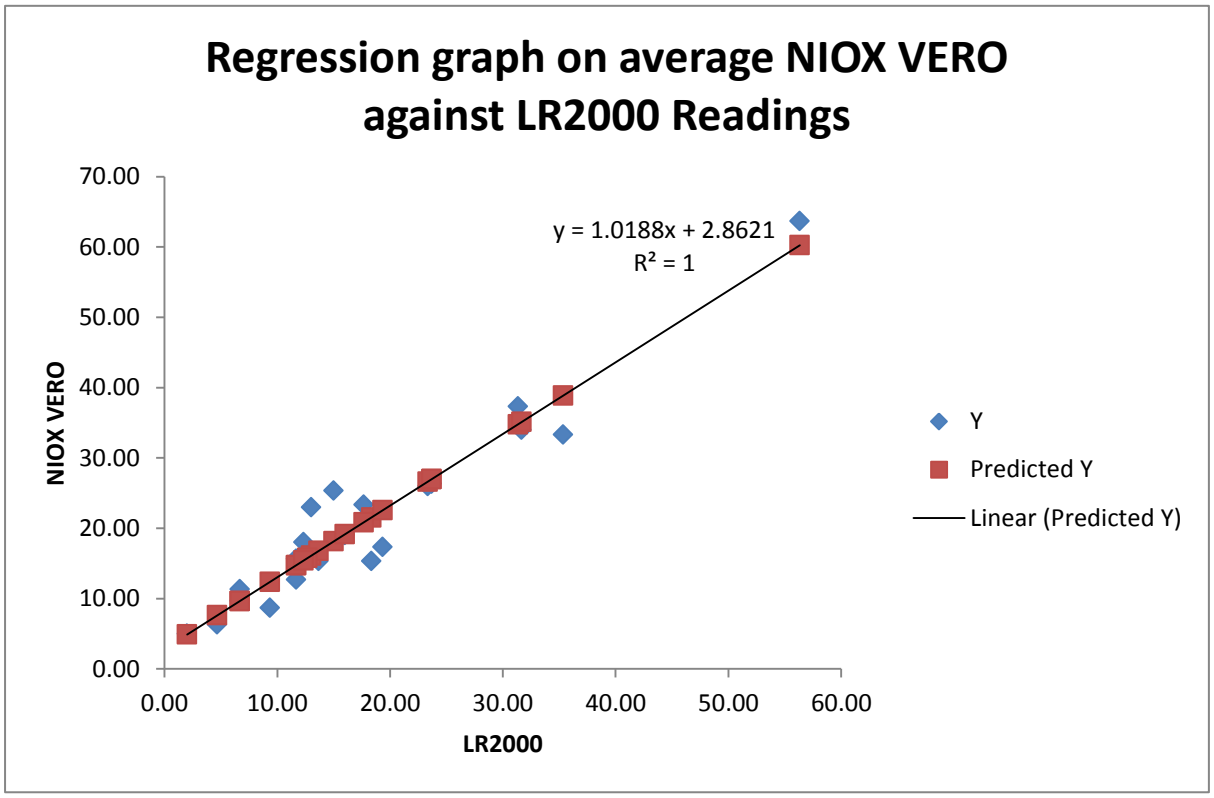


Table 1: Results from each device used in study:

Subjects	NObreath			AVERAGE	Niox Vero			AVERAGE	Chemi			AVERAGE
1	8	7	7	7.33	10	9	10	37.33	7	6	7	6.67
2	30	29	29	29.33	38	38	36	33.33	30	32	32	31.33
3	34	35	36	35.00	34	32	34	23.00	33	36	37	35.33
4	12	11	14	12.33	24	26	19	25.33	14	13	12	13.00
5	15	17	15	15.67	23	27	26	11.33	15	14	16	15.00
6	7	7	12	8.67	12	11	11	15.33	5	6	9	6.67
7	11	12	12	11.67	15	16	15	26.00	14	14	13	13.67
8	23	22	22	22.33	27	26	25	16.67	22	23	25	23.33
9	14	14	14	14.00	16	17	17	15.33	10	14	14	12.67
10	19	14	16	16.33	12	16	18	15.67	18	18	19	18.33
11	10	12	11	11.00	16	15	16	26.33	10	11	14	11.67
12	22	23	24	23.00	27	26	26	26.33	22	25	24	23.67
13	23	23	24	23.33	27	26	26	63.67	22	25	24	23.67
14	52	55	52	53.00	57	68	66	8.67	54	58	57	56.33
15	8	7	10	8.33	9	9	8	23.33	10	8	10	9.33
16	17	20	19	18.67	25	20	25	17.33	18	18	17	17.67
17	21	19	18	19.33	17	17	18	34.00	19	19	20	19.33
18	32	29	29	30.00	32	36	34	5.00	33	31	31	31.67
19	1	0	0	0.33	5	5	5	6.33	2	2	2	2.00
20	7	5	5	5.67	6	7	6	12.67	4	5	5	4.67
21	12	14	14	13.33	16	16	6	18.00	13	10	12	11.67
22	11	14	16	13.67	16		20	19.00	10	13	14	12.33
23	15	15	14	14.67	19	20	18	19.00	14	16	18	16.00

Discussion:

The second generation NObreath is new, portable, easy-to-use device with an electrochemical sensor similar to that of NIOX MINO.

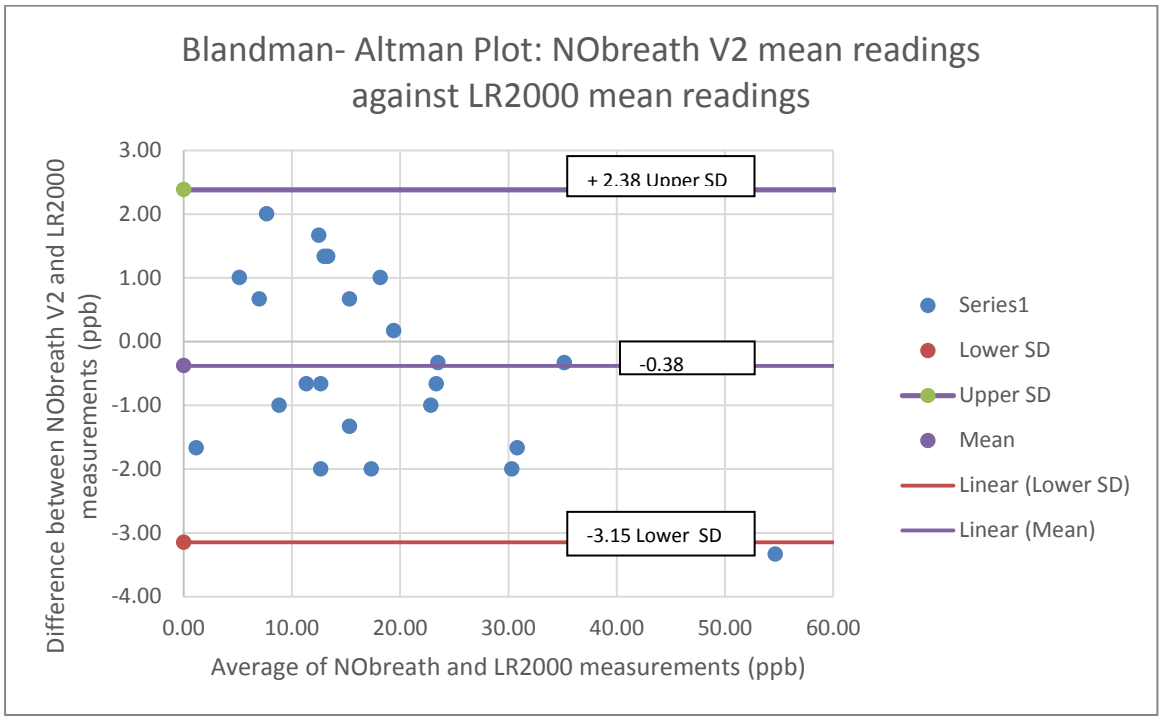
In this study LR2000 and NObreath yielded similar FENO readings at each time-point. There was a close correlation between FENO values obtained by the devices in both parts of our study.

Repeated measurements were analysed by the CV and the Bland–Altman method to determine the limits of agreement. Using NObreath we found that the mean CV tended to be lower and the limits of agreement were somewhat larger compared to NIOX MINO indicating that the reproducibility of FENO measurements with NObreath is slightly better. By employing triplicate measurements at each assessment point in the first series, the mean CV of FENO readings by NObreath are 7.97% and the mean CV of FENO readings for the LR2000 are 7.79%. This shows superior agreement between the two devices. Whereas the mean reading for the NIOX VERO are 80.0% and the mean FeNO reading for LR2000 are 96.01% (Compared to the NObreath V2, the agreement is not as consistent).

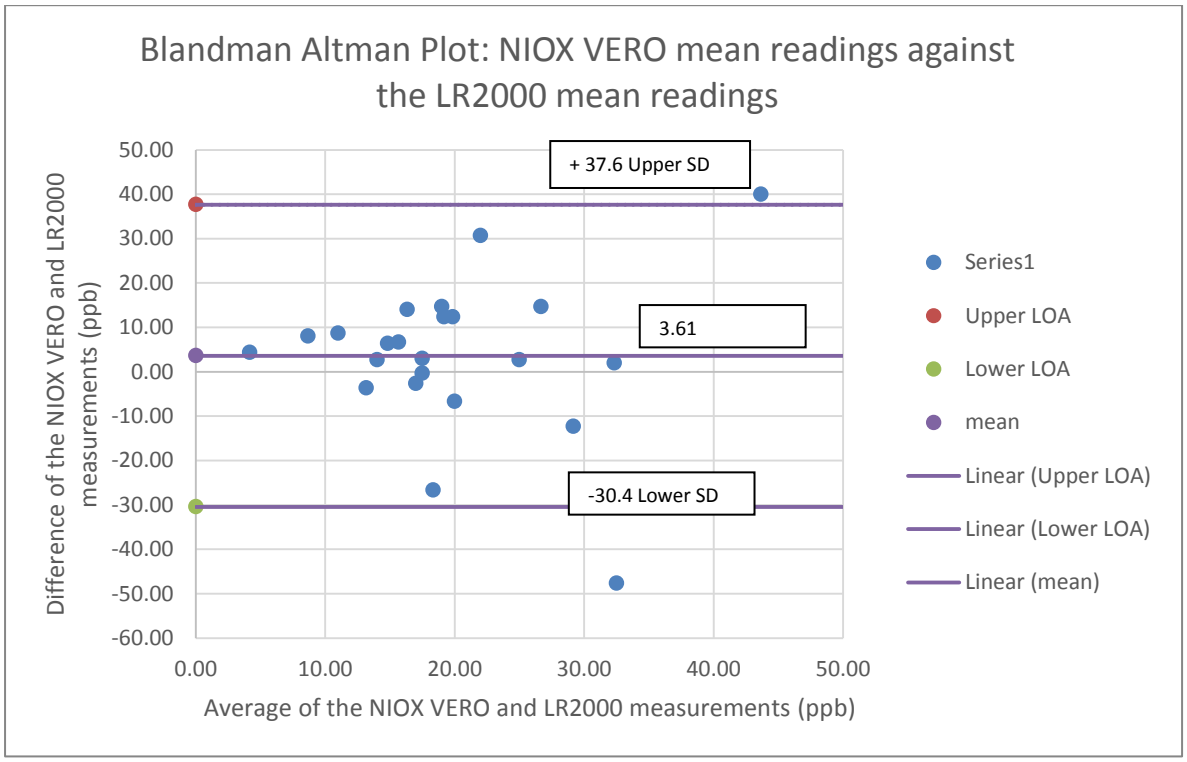
Each point represents the absolute difference between the first and second FeNO measurements for each participant versus the mean of these two measurements (n = 23). Reference lines correspond to the mean difference in two FeNO measurements taken in one individual and the 95% Confidence Interval [8]. The results from this graph show that both devices have good correlation between each other, especially at lower levels of ppb.

The Bland Altman Plot: Agreement between (a) NObreath and LR2000 and (b) NObreath and NIOX MINO as reflected by the Blandman - Altman plot comparing the inter-device mean to the inter-device difference (measurements at three time-points are presented in each graph).

Graph 3



Graph 4



In conclusion, the NObreath V2 shows good agreement against the NIOX VERO, the mean CV of FENO readings by NObreath V2 are 7.97% and the mean CV of FENO readings for the LR2000 are 7.79%. This shows superior agreement between the two devices. Whereas the mean reading for the NIOX VERO are 80.0% and the mean FeNO reading for LR2000 are 96.01%. The values generated were statistically significant ($P<0.05$) and within the stated accuracy of both devices the closest relationship between the recognised gold standard method of chemiluminescence was displayed by the NObreath V2 device; however all devices (apart from Bosch which could not be tested) also displayed good agreement and interchangability with the gold standard. This indicates that the NObreath V2 device is suitable for use in clinical practice.

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