

Comparative Repeatability of Two Handheld Fractional Exhaled Nitric Oxide Monitors

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Summary. Background: The use of portable fractional exhaled nitric oxide (FENO) devices is increasingly common in the diagnosis and management of allergic airways inflammation. Methods: We tested two handheld FENO devices, to determine (a) if there was adequate intradevice repeatability to allow the use of single breath testing, and (b) if the devices could be used interchangeably. In a mixed pediatric population, including normal, asthmatic, and children with peanut allergies, 858 paired values were collected from the NIOX-MINO[®] and/or the NObreath[®] devices. Results: The NIOX-MINO[®] showed excellent repeatability (mean difference of 0.1 with 95% limits of agreement between -7.93 to 7.72 ppb), while the NObreath[®] showed good repeatability (mean difference of -1.61 with 95% limits of agreement between -14.1 and 10.8 ppb). Intradevice repeatability was good but not adequate and the NIOX-MINO[®] systematically produced higher results than the NObreath[®] [mean difference of 7.8 ppb with 95% limits of agreement from -11.55 to 27.52 ppb (-33% to 290%)]. Conclusions: Our results support the manufacturer's advice that single breath testing is appropriate for the NIOX-MINO[®]. NObreath[®] results indicate that the mean of more than one breath should be utilized. The devices cannot be used interchangeably. **Pediatr Pulmonol.**

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INTRODUCTION

Fractional exhaled nitric oxide (FENO) levels can easily be measured in both children and adults and FENO relates moderately well with the presence of airways allergic or eosinophilic inflammation.^{1,2} An increased FENO is associated with an increased risk for the development of new onset wheezing.³ In asthmatics, the use of inhaled corticosteroids (ICS) is associated with a reduction in FENO values^{4,5} and the finding of an elevated FENO value suggests on-going eosinophilic airways inflammation which may relate to either poor adherence to ICS or the need to increase therapy. However, despite much research it is still unclear how much benefit measuring FENO in routine clinical practice has when added to the clinical history and lung function measurement.⁶

While FENO measurements using chemiluminescence (the current gold standard method) are easy to perform and give useable on-line results this requires expensive equipment that is not easily portable and therefore has largely been used in the research setting.⁷ Recently handheld devices which incorporate electrochemical sensors have become available for FENO

measurement and these will likely result in more widespread clinical use.

FENO measurements from the NIOX-MINO[®] (Aerocrine AB, Solna, Sweden) handheld device closely

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agreed with simultaneous measurements using the chemiluminescence method from the same and a different manufacturer.^{8–13} The NIOX-MINO[®] was useable in many children but unfortunately, its operation requires the use of a mirror to allow children to have sight of the visual incentive which is on the opposite side of the device to the mouth piece. In addition, the sensor is time-limited and the number of times measurements are repeated adds to the cost. The operational characteristics of the NIOX-MINO[®] require that the child exhales at a constant flow rate for more than 6 sec before a measurement can be recorded. The manufacturer suggest only one test value is required while the ATS/ERS recommendation is that the average of 2 or more repeated values is recorded.¹⁴ In our experience, **The NObreath[®] (Bedfont Scientific Ltd, Kent, UK) was easier to demonstrate and to use; a detachable mouth-piece allows for coaching on technique. Also, repeated measures on the same child do not add to the cost.** However, it has the disadvantage of giving a result even with poor technique, for example, with a variable flow rate. This may reduce repeatability especially in children. In a small study, with a relatively narrow range of FENO measurements (<40 ppb) the NObreath[®] has been reported to be in good agreement with the NIOX-MINO[®] but the NObreath[®] reported the FENO on average to be 4.3 parts per billion (ppb) higher than the NIOX-MINO[®] with wide 95% limits of agreement (–7.38 to 16.1 ppb) relative to the narrow range 3–36 ppb.¹⁵

As both devices become more widely used, it is important to have more information on the immediate repeatability of measurement by addressing the questions; (1) do two repeated measurements of FENO need to be made and (2) how interchangeable will FENO measurements be between devices if different clinics are using different devices?

Here, we report the repeatability of paired measurements of FENO for both NIOX-MINO[®] and NObreath[®] recorded in three separate pediatric research studies and compare agreement between FENO measurements using the NIOX-MINO[®] and NObreath[®] devices in children.

MATERIALS AND METHODS

Subjects

The first set of data included 510 children (aged 5–9 years) who had had paired FENO measurements using

ABBREVIATIONS:

FENO	Fractional exhaled nitric oxide
ICS	Inhaled corticosteroids
ATS/ERS	American Thoracic Society/European Respiratory Society
SD	Standard deviation

the NIOX-MINO[®]; this was extracted from a current longitudinal cohort study of the offspring of mothers recruited in the antenatal period. The children are currently being studied for cardio-respiratory risk factors and should be representative of those in the community. The second dataset included 89 children with peanut allergy (aged 4–15 years) who also had repeated measures of FENO using the NIOX-MINO[®]. The average FENO values for this study had previously been reported.¹⁶ The third dataset of 259 asthmatic children (aged 4–14 years) attending the tertiary referral asthma clinic at the Royal Belfast Hospital Sick Children, was extracted from an ongoing study comparing exhaled breath temperature with FENO and current asthma control. In addition, since both NIOX-MINO[®] and NObreath[®] devices were available for use at this clinic, we obtained approval to assess the interchangeability between the FENO measurements by both devices at the same visit as part of a service development. One hundred nine children had measurements recorded using both the NIOX-MINO[®] and the NObreath[®]. Written informed parental consent and child assent was obtained and each project had approval from the Office of Research Ethics Committee (Northern Ireland). All values obtained were based on technically acceptable use of each device which in the case of the NObreath[®] was a value judgment based on a linear visual scale and for the NIOX-MINO[®] was determined by the device itself.

Study Design

Both the NIOX-MINO[®] and NObreath[®] operate at an exhalation flow rate of 50 ml/sec, in accordance with ATS/ERS guidelines.¹⁴ The NObreath[®] was calibrated according to manufacture guidelines prior to use; the NIOX-MINO[®] is pre-calibrated. FENO measurements were recorded before spirometry as the latter has been shown to reduce FENO levels when performed prior to FENO measurement.¹⁴ The order in which FENO devices were tested was not randomized as the FENO maneuver has not been shown to affect FENO results.¹⁴

METHODS

Participants were educated briefly on technique and then a practice blow was performed. This was followed by two test blows: the patient was then allowed to “rest” between blows, while the machines reset. In accordance with international guidelines,¹⁴ there was a minimum of 30 sec between blows on the same device and this was considerably exceeded when moving between devices. Where patients were unable to perform the practice or actual blows after a few attempts, this

was recorded and these results were excluded from the study.

Analysis

The NIOX-MINO[®] reported low values as <5 ppb which were coded as values of 4 ppb for analysis. The lower range reported by the NObreath[®] was 0 ppb, however for the comparison between devices, NObreath[®] recordings below 5 were also coded as 4 ppb.

Data was analyzed for agreement, using the method of Bland and Altman and Lin's concordance correlation coefficient¹⁷ using the Stata version 11 command "concord." The concordance correlation coefficient combines measures of both precision and accuracy to determine how far the observed data deviate from the line of perfect concordance (i.e., the line at 45° on a square scatterplot). Lin's coefficient increases in value as a function of the nearness of the data's reduced major axis to the line of perfect concordance (the accuracy of the data) and of the tightness of the data about its reduced major axis (the precision of the data).

RESULTS

NIOX-MINO[®]

Five hundred ninety-nine paired FENO values were available using the NIOX-MINO[®] with a range of 4–173 ppb (median 11 ppb). The average difference between the 2 repeated measurements was 0.1 (SD 4) with 95% limits of agreement between –7.93 to 7.72 ppb (Fig. 1). Lin's concordance correlation (ρ) was 0.98 with the reduced major axis slope of 0.996 and intercept of –0.03. Similarly excellent and close agreement was observed when only children with an FENO value <50 ppb were analyzed (ρ 0.97, slope 0.994, intercept –0.01 and with a mean difference of –0.085 and 95% limits of agreement –4.54 to 4.37, N = 555).

NObreath[®]

Two hundred fifty-nine paired values were collected using the NObreath[®] device. The range was 0–256 ppb (median 6 ppb). We observed good agreement between the two measurements. The average difference between the 2 measures was –1.61 with 95% limits of agreement between –14.1 and 10.8 ppb (Fig. 2). Lin's concordance correlation (ρ) was 0.983 with the reduced major axis slope of 0.97 and intercept of –1.1. Similarly good agreement was observed when only children with an FENO value <50 ppb were analyzed (ρ 0.91, slope 0.995, intercept –1.06 and with a mean difference of –1.10 and 95% limits of agreement –9.8 to 7.6).

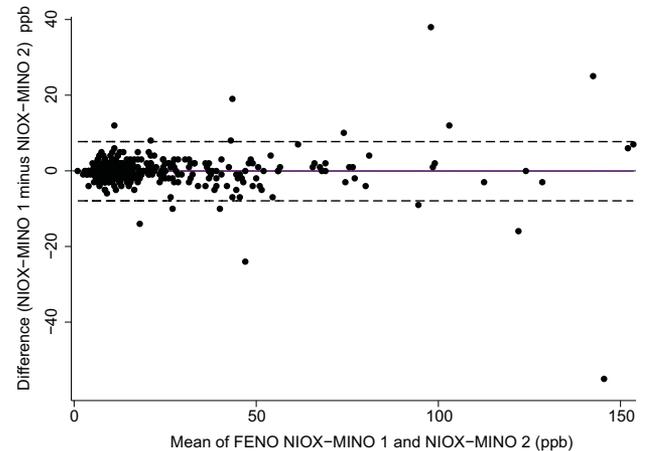


Fig. 1. Bland–Altman plot of repeated fractional exhaled nitric oxide (FENO) measurements taken using the NIOX-MINO[®] device. Solid and dashed lines represent mean and mean \pm 2 standard deviation (SD), respectively.

NIOX-MINO[®] Versus NObreath[®]

Of the 109 children that were tested on both devices, 7 (6.4%) were unable to perform FENO testing on one of the devices. All seven were unable to use the NIOX-MINO[®]. We found the average of the paired NIOX-MINO[®] results was systematically higher than the average of the paired NObreath[®] results, in the 109 children who had both measurements. The mean difference (NIOX-MINO[®] minus NObreath[®]) FENO was 7.8 ppb ($P < 0.001$) with 95% limits of agreement from –11.55 to 27.52 ppb (–33% to 290%) (Fig. 3). Lin's concordance correlation (ρ) was 0.65 with the reduced major axis slope of 1.32 and intercept of 5.03.

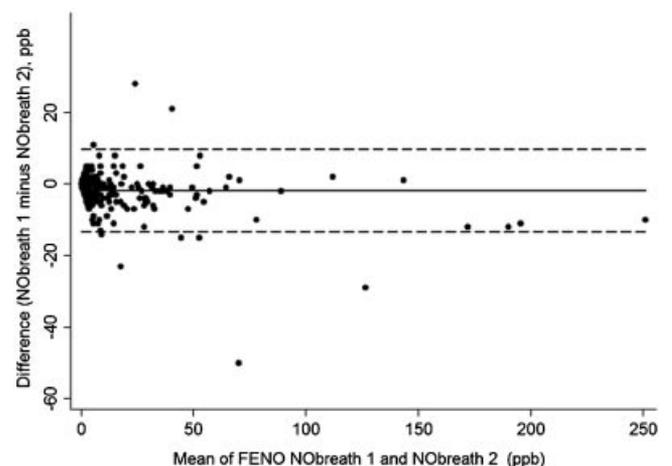


Fig. 2. Bland–Altman plot of repeated fractional exhaled nitric oxide (FENO) measurements taken using the NObreath[®] device. Solid and dashed lines represent mean and mean \pm 2 standard deviation (SD), respectively.

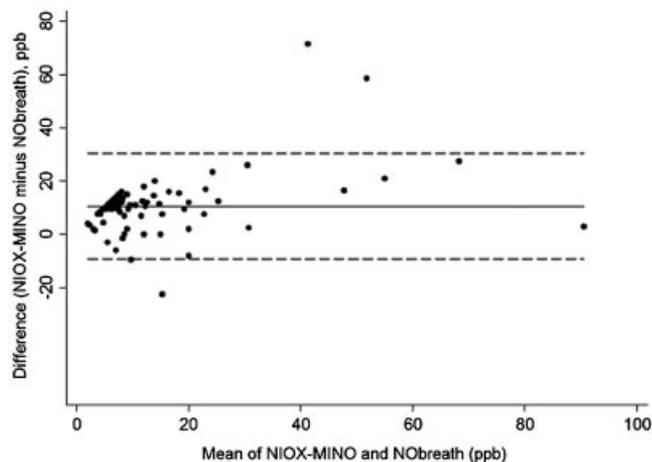


Fig. 3. Bland–Altman plot of mean fractional exhaled nitric oxide (FENO) measurements taken using the NIOX-MINO[®] device compared with mean FENO measurement taken using the NObreath[®]. Solid and dashed lines represent mean and mean \pm 2 standard deviation (SD), respectively.

DISCUSSION

We found that the repeatability of the paired FENO values for the NIOX-MINO[®] in children was excellent with a mean difference of -0.1 with 95% limits of agreement of -7.9 to 7.7 . Even tighter limits of agreement occurred when looking at children with an FENO <50 ppb (95% limits of agreement -4.5 to 4.3). **Achieving two acceptable blows as per international guidelines¹⁴ with the NIOX-MINO[®] is both time-consuming and is associated with additional cost.** Our results concur with the manufacturer's recommendation that a single blow is sufficient and using one blow will reduce costs.

We found good agreement for repeated values of FENO using the NObreath[®], however, the 95% limits of agreement were wider at -12.8 and 9.9 ppb and -10 to 8.1 (children with FENO <50 ppb) compared to the NIOX-MINO[®]. A value judgment is required as to whether the limits of agreement are clinically acceptable to allow the use of only one value when using the NObreath[®] device. We consider that this variability in the two repeated measurements is too great to allow only one value to be recorded confidently for the NObreath[®] and therefore recommend a minimum of three blows when using this device.

In contrast to the NIOX-MINO[®] (which is designed such that no recording is made for a poor technique maneuver), the NObreath[®] will report FENO values from technically poor maneuvers. This is particularly relevant when studying children. With the NObreath[®], we aimed to only include FENO values, as judged by the operator, from children who were able to maintain

the flow rate (50 ml/sec) for greater than the first 50% of the testing time (16 sec). International guidelines state that exhalation should be at least 4 sec in the under 12 and 6 sec in the over 12 sec,¹⁴ and by including the children who required a single additional inhalation that took place after 50% of the testing time had passed, we are confident that this criteria has been met. However, we are uncertain of the effect of short pauses in flow rate which younger children tend to make despite coaching. We believe the solution to this problem would be for the manufacturers of the NObreath[®] to include a check system so that results will be reported only when an adequate maneuver has been performed.

The NIOX-MINO[®], the first commercially available handheld device¹⁸ has been extensively compared with gold-standard chemiluminescent devices^{8–11,13,19–25} and found to have clinically acceptable levels of agreement.^{8–13} Because the NObreath[®] device is relatively new, there are only a few studies involving its use.

Antus et al.¹⁵ described good agreement with the Logan LR2500 (Logan Research Ltd, Rochester, UK) gold-standard machine with tight limits of agreement (-4.6 to 5.0 ppb) in a small group of healthy adult volunteers with a limited range of FENO values (3–49 ppb). In the same study, the NObreath[®] produced values 4.3 ppb higher than the NIOX-MINO[®], with wide 95% limits of agreement (-7.38 to 16.1 ppb) relative to the small range of FENO values (3–36 ppb).¹⁵ Pisi et al.²⁶ showed the NObreath[®] to be consistently lower than the chemiluminescent NIOX[®].

In our study, we found good agreement between FENO measured by NIOX-MINO[®] and NObreath[®], but this was not adequate to allow the devices to be used interchangeably. **We found that NIOX-MINO[®] systematically produced a higher value than the NObreath[®] (mean difference 10.5 ppb, SD 10.2, $P < 0.001$).**

This finding is in keeping with the majority of reports where others have found that the NIOX-MINO[®] gives higher FENO values when compared to various gold standard machines,^{8–12,19–21,23,24} while NObreath[®] results are similar to those obtained from gold standard chemiluminescence systems.^{15,19,26}

A few of these studies have attempted to provide correction equations.^{9,19} At present, we do not think that correction regression equations relating average expected responses between both devices will be useful because of the variability in NObreath[®] measurements. Instead, like Boot et al., we recommend that for each patient, where possible, the same device should be used at each clinical encounter.

In conclusion, children using the NIOX-MINO[®], repeated FENO measurements taken within the same occasion show excellent repeatability. The NObreath[®] shows good but not adequate repeatability. From this,

we conclude that a single breath is sufficient for the NIOX-MINO[®] but not for the NObreath[®]. The NIOX-MINO[®] and NObreath[®] cannot be used interchangeably; agreement between the two devices is good, but not adequate and NIOX-MINO[®] FENO values are systematically higher than those from the NObreath[®].

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