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Keywords:	asthma, exhaled nitric oxide, children, airway inflammation

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CAN WE USE PORTABLE NITRIC OXIDE ANALYZER IN YOUNG CHILDREN?

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Keywords: asthma, exhaled nitric oxide, children, airway inflammation

Grant sponsor

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CAN WE USE PORTABLE NITRIC OXIDE ANALYZER IN YOUNG CHILDREN?**SUMMARY**

Objective: Management of asthma could be improved by measuring exhaled nitric oxide (FENO). Portable hand-held FENO analyzer (NIOX MINO) is practical and small and could be used also in the primary care office. It has demonstrated good repeatability and correlation with stationary device (NIOX) in adults and school aged children, but so far there have been no reports on young children. The aim of this study was to compare conventional chemiluminescence device (NIOX) with a hand-held electrochemical device (NIOX MINO) in young children. Design: Paired measurements of FENO were performed with the stationary chemiluminescence-based analyzer (NIOX) and with portable electrochemical device (NIOX MINO) in children with asthmatic symptoms and age-matched controls. Results: Fifty-five children with mean (range) age of 5.7 (3.9-8.5) years were evaluated with both devices. Measurements were successful with both devices in 40 out of 57 children. NIOX MINO was more difficult to use than NIOX in this age group, success rates being 73% and 93%, respectively ($p=0.004$). The reproducibility was similar and there was a close correlation between FENO measured by the two devices ($r=0.97$, $p< 0.001$). However, Bland-Altman plot demonstrated limits of agreement that were relatively wide compared to low levels of FENO in the sample. Both devices were sensitive enough to distinguish higher FENO levels in children with asthmatic symptoms, compared to healthy controls. Conclusions: We conclude that NIOX MINO can be used as a screening tool for the assessment of airway inflammation in children from the age of 4 years, but its applicability is limited by lower measurement success rate and relatively poor accuracy and detection limit at low levels of FENO.

INTRODUCTION

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4 The need of noninvasive biomarkers to reflect eosinophilic inflammation in asthmatic airways
5 is widely recognized, as this is the primary target of anti-inflammatory therapy. Exhaled nitric
6 oxide (FENO) has been proposed as a method for monitoring bronchial eosinophilic inflamma-
7 tion in asthmatic patients.[1] FENO is an indirect measure of eosinophilic inflammation and
8 several studies have found correlation between elevated levels of FENO and steroid respon-
9 siveness in asthma and disease control but also conflicting results exist.[2] International guide-
10 lines for FENO measurements in children strive for measurements to be comparable between
11 laboratories.[3,4]

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Currently available chemiluminescence analyzers for measurement of FENO are compara-
tively expensive and bulky and their use needs special technical expertise. For these reasons
their usage is mostly restricted to specialist clinics. Recently, a portable, hand-held, small
FENO analyzer (NIOX MINO) which measures FENO via an electrochemical sensor has be-
come available. MINO has demonstrated good repeatability and correlation with the stationary
device (NIOX) in adults and school aged children.[5,6,7] Recently this device was also cleared
by U.S. Food and Drug Administration for the measurement of airway inflammation. However,
this clearance was restricted to measurement mode suitable for adults and older children. So
far, there is limited amount of data on the performance of NIOX MINO in younger children,
which may have special demands as regards the accuracy of the device and cooperation dur-
ing measurement.

Therefore, the aims of this study were to compare feasibility, repeatability and accuracy of
FENO measurements with stationary vs. portable analyzer in young children.

SUBJECTS

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4 During a period from October 2004 to February 2005, 55 children were evaluated at Division
5 of Allergy, Helsinki University Central Hospital. 28 children were referred to hospital due to
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7 asthmatic symptoms.[8] Two children in this group had regular inhaled corticosteroid medica-
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9 tion for asthma, and all the other were free from antiasthmatic medication at the time of test-
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11 ing. Other half of the study group were healthy age matched young children (n=27) from a co-
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13 hort of children taking part in a prospective outcome study of adenoidectomy, without any res-
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15 piratory signs or symptoms. These children had recurrent or persistent otitis media at the age
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17 of 12-48 months and were then randomised to undergo insertion of tympanostomy tubes with
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19 or without adenoidectomy. At the time of the present study 3 years after randomisation, all the
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21 participating control children were clinically healthy, without any respiratory signs or symp-
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23 toms. [9] The demographics of the patients and controls are shown in Table 1. The mean age
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25 of all children was 5.7 years (range 3.9-8.5 years).
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METHODS

FENO measurements

Paired measurements of FENO were performed with the stationary chemiluminescence-based analyzer NIOX (Aerocrine AB, Sweden) and with portable electrochemical NIOX MINO (Aerocrine AB, Sweden) according to the ATS recommendations.[3] NIOX measurements were preceded by the measurements with NIOX MINO, with a 10-15 min interval. The chemiluminescence analyzer was calibrated according to the manufacturer's specifications. Children were seated, without a nose clip, and were asked to fill their lungs completely with NO-free air, and thereafter to exhale with a mean and instantaneous flow of 50 ± 5 ml/s for at least 6 seconds. Both devices automatically rejected exhalations not fulfilling the guidelines. Consecutive, acceptable paired measurements of FENO with both devices were recorded, and the repeatability and mean results were calculated. When using the stationary device, the children were able to follow the balloon animation on the computer screen to aid with the exhalation technique. For the measurements with NIOX MINO, the children followed the pitch of the flow marker sound. Both devices incorporate a dynamic flow control to keep a constant rate during exhalation. The duration of exhalation was set to 6 second in both devices as recommended for young children.[3] According to the manufacturer's specifications the lowest detection limit with NIOX MINO is 5 ppb and the analytical accuracy is ± 5 ppb or max 15 % of the measured value.[10] With NIOX the corresponding specifications are the following: lowest detection limit 2 ppb and accuracy ± 2.5 ppb of measured value < 50 ppb and $\pm 5\%$ of the measured value > 50 ppb. [11] The study was approved by institutional pediatrics ethics committee of Helsinki University Central Hospital, and informed consent was obtained from the parent of each child participating in the study.

Statistical analysis

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2 Repeatability was estimated using the mean difference between paired measurements and
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4 the coefficient of repeatability (CoR). In order to analyze agreement between the two devices,
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6 a Bland Altman plot including 95% confidence intervals for limits of agreement was con-
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8 structed.[12] Paired student t test was used to compare mean FENO between devices and
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10 unpaired Student t test to compare results between asthmatics and controls. Pearson correla-
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12 tion test was used for correlation analyses. As FENO values were not normally distributed,
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14 data were log transformed prior to analyses.
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RESULTS

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4 Measurement was successful for both devices in 40 children with mean (range) age of 6.1
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6 (4.1-8.5) years. The overall success rate with NIOX was higher (93%, 51/55) than with NIOX
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8 MINO (73%, 40/55, $p=0.004$). The mean age of children who did not succeed with MINO (15
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10 children) was 4.8 years (range 3.9-5.5 years; $p < 0.001$ compared to children with successful
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12 measurements). Four children were not able to perform either of the devices, and the mean
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14 age of them was 4.4 years (range 4.2-4.7 years). Eleven children that were successful with
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16 NIOX but could not perform MINO were on average 4.9 years old (range 3.9-5.5 years). The
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18 success rates by age are shown in Figure 1.
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23 The mean FENO was slightly higher with NIOX than with NIOX MINO, geometric means being
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25 9.9 ppb and 7.8 ppb respectively ($p=0.002$). The mean difference of paired measurements
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27 with NIOX was 1.4 ppb (range 0.1-7.2) and with NIOX MINO 1.0 (range 0-3) ($p=0.13$), corre-
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29 sponding to CoR of 1.66 ppb for NIOX MINO and 2.67 ppb for NIOX. We found a significant
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31 correlation between FENO measured by the two devices ($r=0.972$; $p<0.001$; Figure 2.). Bland-
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33 Altman (Figure 3) plot demonstrated a mean difference between devices of 1.1 ppb with limits
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35 of agreement between -4.4 and 6.7 ppb.
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39 FENO values were significantly higher in children with asthmatic symptoms than in healthy
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41 controls. The mean FENO value with NIOX MINO in children with respiratory symptoms was
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43 14.3 ppb and in controls 6.4 ppb ($p=0.028$) and with NIOX 15.0 ppb and 8.6 ppb ($p=0.071$),
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45 respectively.
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DISCUSSION

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4 In recent years, FENO has become widely accepted as an indirect marker of eosinophilic in-
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In recent years, FENO has become widely accepted as an indirect marker of eosinophilic inflammation in asthmatic airways, and cheaper, easy-handling devices are needed for wider clinical use of the technique. This study showed that, in terms of repeatability and correlation, the hand-held FENO-analyzer provides reliable measurements of FENO also in young children, compared to those of a calibrated stationary device. The devices were equally sensitive to distinguish higher FENO levels in children with asthmatic symptoms, compared to asymptomatic controls. So far for the portable device, only the 10 second mode suitable for adults and older children has been accepted for clinical use to measure exhaled FENO. Our results suggest that clinically reliable results may be obtained also by using the 6 second mode suitable for younger children. This finding is in agreement with a recent study by Ito et al who showed a good agreement between 10 and 6 second modes in FENO measurements. They also found 6 second mode to be more feasible when measuring FENO in younger children under 8 years. [13]

Our study population is younger than in earlier published studies. Schiller et al compared conventional chemiluminescence FENO analyser with a hand-held device and offline FENO measurements in children aged 6-16 years (mean 11.8 years).[5] In this population all of the children were able to perform acceptable results in all three methods. Somewhat younger children were studied by McGill et al (median age 9 years), and they found 71% success rate with MINO among their study population.[7] Our finding is consistent with this finding (73% success rate), although children were younger (median age 5.6 years).

Values measured by NIOX MINO were slightly lower than by the reference device NIOX. Previous studies have found contradictory results. Vahlkvist et al found values being higher from NIOX MINO than those from NIOX in a study of asthmatic children during birch pollen exposure but, but generally, there was a good agreement between the devices.[14] Alving et al observed a positive difference for NIOX MINO when compared with NIOX.[15] The portable

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NIOX MINO devices have been precalibrated by the manufacturer, and their clinical accuracy should be within 5 ppb. The current observed mean difference of 1.1 ppb between NIOX and NIOX MINO is within these specifications.

The Bland-Altman plot showed limits of agreement that were relatively wide compared to low levels of FENO in most of the children in the sample (-55 to 84% of the median FENO). These observed limits could be acceptable for adults with higher FENO levels as well as for the children with abnormal FENO, but the FENO values in healthy preschool population are often at or below 5 ppb which is the detection limit in NIOX MINO device. Low values of FENO may be characteristic also during the follow-up of young asthmatic children under inhaled corticosteroid treatment. In this study population eleven children (28%) had FENO below 5 ppb, including those with asthmatic symptoms. Although the clinical implication of this limitation cannot be evaluated in the current study, it suggests that accurate measurements of FENO may be difficult to obtain in all preschool children with NIOX MINO. At higher FENO levels, the agreement between the devices was acceptable. Mc Gill et al found in school aged children, that the agreement was less at FENO levels above 50 ppb.[7] Our study sample did not include subjects with as high FENO levels, but as FENO tends to be lower in young children and to our experience seldom exceeds 50 ppb in preschool children, we believe that the results represent well those of a typical preschool population.

NIOX MINO was more difficult to use in this age group of young children, success rate being significantly lower with NIOX MINO than with NIOX. The lack of visual motivation in NIOX MINO may explain the difference observed in the success rate between the devices. The screen of NIOX MINO is not easily utilized for the patient, and in contrast to the stationary device, the patient should follow the pitch of the flow marker sound, which may be less efficient than visual motivation in young children. New models of portable NO analyzers incorporating the option for visual feedback during measurement may improve the feasibility of the device in young children. Even shorter exhalation time of 4 seconds might also help the performance of method in young children as ATS recommendations suggests.[3] In our study design children

1 performed measurements with NIOX first and NIOX MINO after a break in the same day. It
2 could be speculated that the success rate with NIOX MINO could have been even lower and
3 the difference between devices greater without this prior training session with NIOX. While
4 controlled breathing techniques are often challenging for young children, off-line techniques
5 such as uncontrolled single exhalation in to a reservoir and tidal breathing in to a collection
6 bag, or online measurement of FENO during spontaneous breathing, afford an alternative to
7 measure FENO in preschool children, but are less well standardized as the online single-
8 breath technique. [3]

9 We conclude that the applicability of the portable NIOX MINO is limited in young children, due
10 to lower measurement success rate and wide limits of agreement relative to low FENO levels.
11 The latter may result from the poorer detection limit of the portable device, and lower FENO
12 levels typical for young children. However, as the FENO measurements correlate with those of
13 a stationary FENO analyzer and are equally reproducible, the NIOX MINO can be used as a
14 screening tool for the assessment of airway inflammation in children from the age of 4 years.
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CONFLICT OF INTEREST

No financial or any other potential conflicts of interest exist.

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FIGURE LEGENDS

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4 Figure 1. Success rate by different age groups (%) in the sample of the healthy (n=27) and
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Figure 1. Success rate by different age groups (%) in the sample of the healthy (n=27) and asthmatic (n=28) young children, by using portable NIOX MINO (MINO) and stationary device (NIOX).

Figure 2. The relationship of FENO measured with the conventional analyzer NIOX and NIOX MINO, and the line of identity.

Figure 3. Bland-Altman plot of the difference between NIOX and NIOX MINO against the mean FENO measured with both devices including the line of mean difference ± 2 SD.

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INTRODUCTION

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4 The need of noninvasive biomarkers to reflect eosinophilic inflammation in asthmatic airways
5 is widely recognized, as this is the primary target of anti-inflammatory therapy. Exhaled nitric
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25 of all children was 5.7 years (range 3.9-8.5 years).
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METHODS

FENO measurements

Paired measurements of FENO were performed with the stationary chemiluminescence-based analyzer NIOX (Aerocrine AB, Sweden) and with portable electrochemical NIOX MINO (Aerocrine AB, Sweden) according to the ATS recommendations.[3] NIOX measurements were preceded by the measurements with NIOX MINO, with a 10-15 min interval. The chemiluminescence analyzer was calibrated according to the manufacturer's specifications. Children were seated, without a nose clip, and were asked to fill their lungs completely with NO-free air, and thereafter to exhale with a mean and instantaneous flow of 50 ± 5 ml/s for at least 6 seconds. Both devices automatically rejected exhalations not fulfilling the guidelines. Consecutive, acceptable paired measurements of FENO with both devices were recorded, and the repeatability and mean results were calculated. When using the stationary device, the children were able to follow the balloon animation on the computer screen to aid with the exhalation technique. For the measurements with NIOX MINO, the children followed the pitch of the flow marker sound (Figure 1). Both devices incorporate a dynamic flow control to keep a constant rate during exhalation. The duration of exhalation was set to 6 second in both devices as recommended for young children.[3] According to the manufacturer's specifications the lowest detection limit with NIOX MINO is 5 ppb and the analytical accuracy is ± 5 ppb or max 15 % of the measured value.[10] With NIOX the corresponding specifications are the following: lowest detection limit 2 ppb and accuracy ± 2.5 ppb of measured value < 50 ppb and $\pm 5\%$ of the measured value > 50 ppb. [11] The study was approved by institutional pediatrics ethics committee of Helsinki University Central Hospital, and informed consent was obtained from the parent of each child participating in the study study children.

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2 Statistical analysis
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4 Repeatability was estimated using the mean difference between paired measurements and
5 the coefficient of repeatability (CoR). In order to analyze agreement between the two devices,
6 a Bland Altman plot including 95% confidence intervals for limits of agreement was con-
7 structed.[12] Paired student t test was used to compare mean FENO between devices and
8 unpaired Student t test to compare results between asthmatics and controls. Pearson correla-
9 tion test was used for correlation analyses. As FENO values were not normally distributed,
10 data were log transformed prior to analyses.
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RESULTS

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4 Measurement was successful for both devices in 40 children with (mean (range) age of 6.1
5 years, range (4.1-8.5) years and median 5.9 years). The mean age of all 55 children was 5.7
6 years (range 3.9-8.5 years, median 5.6 years). The overall success rate with NIOX was
7 higher (93%, 51/55) than with NIOX MINO (73%, 40/55, $p=0.004$). The mean age of children
8 who did not succeed with MINO (15 children) was 4.8 years (range 3.9-5.5 years; $p < 0.001$
9 compared to children with successful measurements). Four children were not able to perform
10 either of the devices, and the mean age of them was 4.4 years (range 4.2-4.7 years). Eleven
11 children that were successful with NIOX but could not perform MINO were on in average 4.9
12 years old (range 3.9-5.5 years). The success rates by age are shown in Figure 1.

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The mean FENO was slightly higher with NIOX (12.9 ppb) than with NIOX MINO, (11.8 ppb
 $p=0.01$) geometric means being 9.9 ppb and 7.8 ppb respectively ($p=0.002$). The reproducibil-
ity was good in both devices. The mean difference of paired measurements with NIOX was 1.4
ppb (range 0.1-7.2) and with NIOX MINO 1.0 (range 0-3) ($p=0.13$), corresponding to CoR of
1.66 ppb for NIOX MINO and 2.67 ppb for NIOX. We found a strong significant correlation be-
tween FENO measured by the two devices ($r=0.972$; $p<0.001$; Figure 2.). Bland-Altman (Fig-
ure 3) plot demonstrated also a good agreement (Figure 3.), the a mean difference between
devices being of 1.1 ppb with limits of agreement between -4.4 and 6.7 ppb.

FENO values were significantly higher in children with asthmatic symptoms than in healthy
controls. The mean FENO value with NIOX MINO in children with respiratory symptoms was
14.3 ppb and in controls 6.4 ppb ($p=0.028$) and with NIOX 15.0 ppb and 8.6 ppb ($p=0.071$),
respectively.

DISCUSSION

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4 In recent years, FENO has become widely accepted as an indirect marker of eosinophilic in-
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In recent years, FENO has become widely accepted as an indirect marker of eosinophilic inflammation in asthmatic airways, and cheaper, easy-handling devices are needed for wider clinical use of the technique. This study showed that, in terms of repeatability and **correlation agreement**, the hand-held FENO-analyzer provides reliable measurements of FENO also in young children, compared to those of a calibrated stationary device. The devices were also equally sensitive to distinguish higher FENO levels in children with asthmatic symptoms, compared to asymptomatic controls. So far for the portable device, only the 10 second mode suitable for adults and older children has been accepted for clinical use to measure exhaled FENO. Our results suggest that clinically reliable results may be obtained also by using the 6 second mode suitable for younger children. **This finding is in agreement with a recent study by Ito et al who showed a good agreement between 10 and 6 second modes in FENO measurements. They also found 6 second mode to be more feasible when measuring FENO in younger children under 8 years. [13]**

Our study population is younger than in earlier published studies. Schiller et al compared conventional chemiluminescence FENO analyser with a hand-held device and offline FENO measurements in children aged 6-16 years (mean 11.8 years).[5] In this population all of the children were able to perform acceptable results in all three methods. Somewhat younger children were studied by McGill et al (median age 9 years), and they found 71% success rate with MINO among their study population.[7] Our finding is consistent with this finding (73% success rate), although children were younger (median age 5.6 years).

Values measured by NIOX MINO were slightly lower than by the reference device NIOX. Previous studies have found contradictory results. Vahlkvist et al found values being higher from NIOX MINO than those from NIOX in a study of asthmatic children during birch pollen exposure but, **generally, there was a** good agreement between the devices.[14] Alving et al observed a positive difference for NIOX MINO when compared with NIOX.[15] The portable

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NIOX MINO devices have been precalibrated by the manufacturer, and their clinical accuracy precision should be within 5 \pm ppb. The current observed mean difference of 1.1 ppb between NIOX and NIOX MINO is within these specifications.

The Bland-Altman plot showed limits of agreement that were relatively wide compared to low levels of FENO in most of the children in the sample (-55 to 84% of the median FENO). These observed limits could be acceptable for adults with higher FENO levels as well as for the children with abnormal FENO, but the FENO values in healthy preschool population are often at or below 5 ppb which is the detection limit in NIOX MINO device. Low values of FENO may be characteristic also during the follow-up of young asthmatic children under inhaled corticosteroid treatment. In this study population eleven children (28%) has FENO below 5 ppb, including those with asthmatic symptoms. Although the clinical implication of this limitation cannot be evaluated in the current study, it suggests that accurate measurements of the FENO may be difficult to obtain in all preschool children with NIOX MINO. At higher FENO levels, the agreement between the devices was acceptable. McGill et al found in school aged children, that the agreement was less at FENO levels above 50 ppb.[7] Our study sample did not include subjects with as high FENO levels, but as FENO tends to be lower in young children and to our experience seldom exceeds 50 ppb in preschool children, we believe that the results represent well those of a typical preschool population.

However NIOX MINO was more difficult to use in this age group of young children, success rate being significantly lower with NIOX MINO than with NIOX. The lack of visual motivation in NIOX MINO may explain the difference observed in the success rate between the devices.

The screen of NIOX MINO is not easily utilized for the patient, and in contrast to the stationary device, the patient should follow the pitch of the flow marker sound, which may be less efficient than visual motivation in young children. New models of portable NO analyzers incorporating the option for visual feedback during measurement, may improve the feasibility of the device in young children. Even shorter exhalation time of 4 seconds might also help the performance of method in young children as ATS recommendations suggests.[3] In our study de-

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sign children performed measurements with NIOX first and NIOX MINO after a break in the same day. It could be speculated that the success rate with NIOX MINO could have been even lower and the difference between devices greater without this prior training session with NIOX. While controlled breathing techniques are often challenging for young children, off-line techniques such as uncontrolled single exhalation in to a reservoir and tidal breathing in to a collection bag, or online measurement of FENO during spontaneous breathing, afford an alternative to measure FENO in preschool children, but are less well standardized as the online single-breath technique.[3]

We conclude that the applicability of the portable NIOX MINO is limited in young children, due to lower measurement success rate and wide limits of agreement relative to low FENO levels. The latter may result from the poorer detection limit of the portable device, and lower FENO levels typical for young children. However, as the FENO measurements correlate with those of a stationary FENO analyzer and are equally reproducible, the NIOX MINO can be used as a screening tool for the assessment of airway inflammation in children from the age of 4 years.

~~We conclude that the portable NIOX MINO could be used in measuring exhaled FENO also in young children from the age of 4 years. However, the performance of the measurement with the hand held device was more difficult in young children than the measurement with the older stationary device.~~

CONFLICT OF INTEREST

No financial or any other potential conflicts of interest exist.

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13 **FIGURE LEGENDS**
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17 Figure 1. Success rate by different age groups (%) in the sample of the healthy (n=27) and
18 asthmatic (n=28) young children, by using portable NIOX MINO (MINO) and stationary device
19 (NIOX).
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27 Figure 2. The relationship of FENO measured with the conventional analyzer NIOX and NIOX
28 MINO, and the line of identity.
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34 Figure 3. Bland-Altman plot of the difference between NIOX and NIOX MINO against the
35 mean FENO measured with both devices including the line of mean difference \pm 2 SD.
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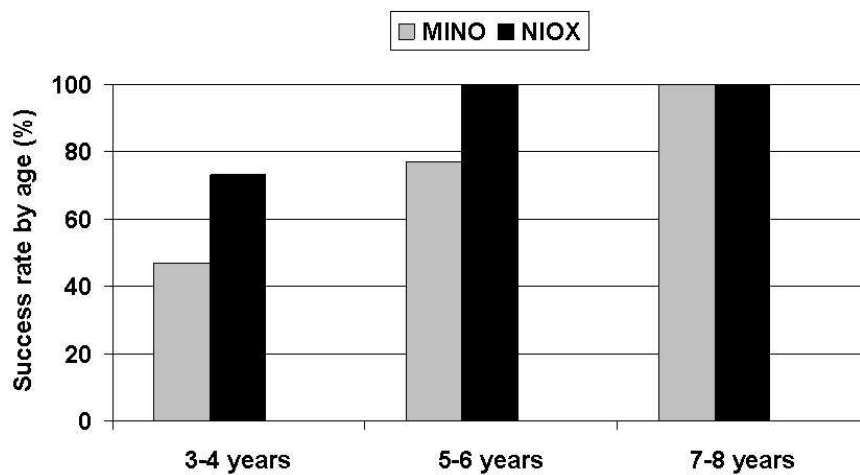
Table 1. Demographic data of the children

	Children with respiratory symptoms	Controls	All
N	28	27	55
Age (years) #	6.2 (4.2-8.4)	5.2 (3.9-8.5)	5.7 (3.9-8.5)
Male, n (%)	12 (43)	19 (70)	31 (56)
Height (cm) #	118.5 (101.9-134.0)	112.2 (98.6-128.8)	115.4 (98.6-134.0)
Atopy (%)*	21 (75)	9 (33)	30 (55)

Mean (range); * Skin prick test positivity or atopic dermatitis

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Figure1. Success rate by age (%)



254x190mm (96 x 96 DPI)

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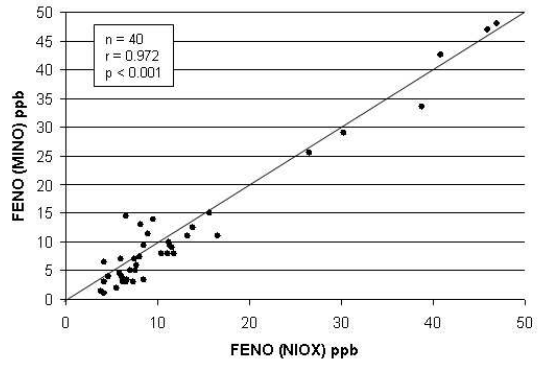


Figure 2. The relationship of FENO measured with the conventional analyzer NIOX and NIOX MINO, and the line of identity.

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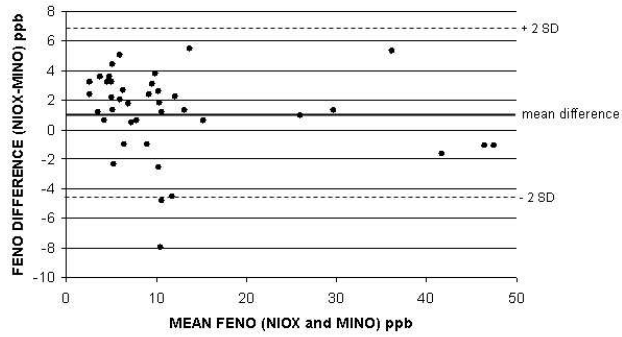


Figure 3. Bland-Altman plot of the difference between NIOX and NIOX MINO against the mean FENO measured with both devices including the line of mean difference \pm 2 SD.

254x190mm (96 x 96 DPI)

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