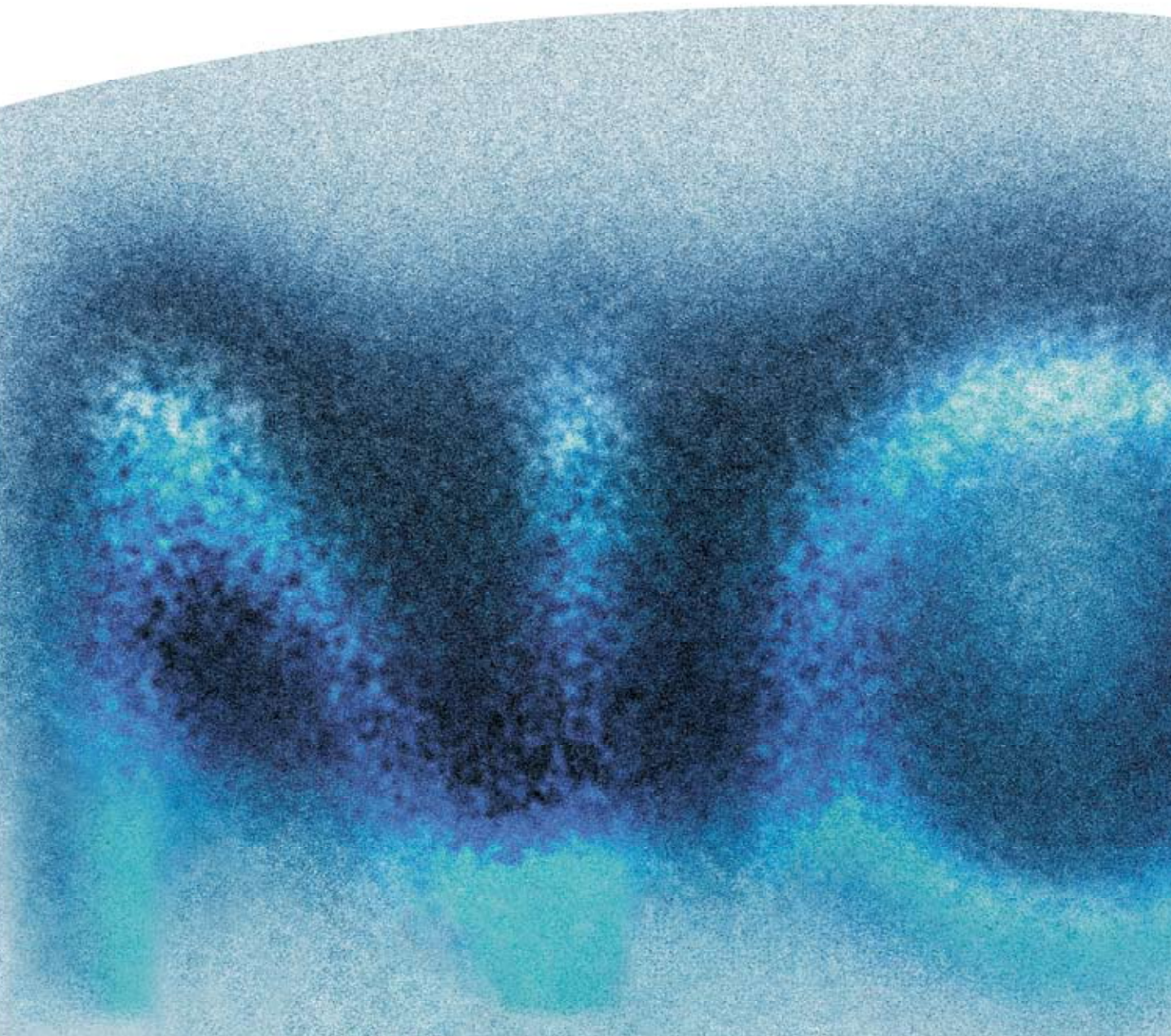


Scientific Publication Review **2008**

Produced by Aerocrine provider of NIOX® Flex and NIOX MINO®

Exhaled Nitric Oxide **A Non-invasive Marker for Inflammation**



This 2008 Scientific Publication Review provides a collection of key research papers from 2007 and early 2008 that discuss current understanding in the field of fractional exhaled nitric oxide (FE_{NO}) and its clinical utility, with a particular emphasis on asthma. It is intended to accompany the 2007 Scientific Backgrounder, which reviewed all relevant pre-2007 publications.

Key developments reported in this booklet include:

- asthma control
- reference values
- health economics.

Aerocrine

Aerocrine is a medical technology company focused on the improved management and care of patients with inflammatory airway diseases. As the pioneer and leader in the technology to monitor and manage airway inflammation, Aerocrine markets NIOX® Flex and NIOX MINO®. Both products enable fast and reliable management of airway inflammation and may therefore play a critical role in more effective diagnosis, treatment and follow-up of patients with inflammatory airway diseases such as asthma. Aerocrine is based in Sweden with subsidiaries in the US, Germany and the UK. Aerocrine shares were listed on the Stockholm Stock Exchange on 15 June 2007.

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Asthma control, longitudinal study

Michils A, Baldassarre S, Van Muylem A. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. Eur Resp J 2008; 31: 539–46.

Michils' prospective study investigated the predictive value of FE_{NO} in asthma control in regular clinical practice, as well as identifying FE_{NO} cut-off points and changes.

Three hundred and forty-one non-smoking patients with asthma, aged 41 ± 16 years (mean \pm standard deviation [SD]), completed an asthma control questionnaire and underwent FE_{NO} measurements. Of these, 142 were previously untreated for asthma and 199 were taking inhaled corticosteroids (ICS) with or without other asthma medications. Eighty-eight per cent of patients were allergic.

The results showed that a decrease in FE_{NO} levels of $<40\%$ precluded optimal asthma control, whereas an increase of $<30\%$ precluded deterioration (negative predictive values [NPVs] 79% and 82%, respectively). In patients taking low doses of ICS, a $>40\%$ decrease indicated optimal asthma control (positive predictive value [PPV] 83%) and in ICS-naïve patients, FE_{NO} levels >35 ppb predicted asthma control improvements in response to ICS (PPV = 68%). In comparison, forced expiratory volume in 1 sec (FEV_1) assessments were not useful in most cases.

In conclusion, this study showed that FE_{NO} is a reliable marker of asthma control over time, especially in patients taking low doses of ICS. Changes in FE_{NO} values, rather than absolute cut-offs, may be valuable to assessing long-term asthma control.

Health economic analysis

Berg J, Lindgren P. *Economic evaluation of FE_{NO} measurement in diagnosis and 1-year management of asthma in Germany*. *Respir Med* 2008; **102**: 219–31.

Berg and Lindgren reported the first economic evaluation of the use of FE_{NO} measurements in the diagnosis and management of asthma. Their study was designed to compare the cost-effectiveness of a FE_{NO}-driven asthma management strategy with standard diagnostics and treatment guidelines, from the perspective of a German payer.

The impact of the two strategies on resource use and health outcomes was evaluated over a 1-year period, with the different alternatives in asthma management and diagnosis and their consequences captured on two decision trees. NIOX MINO (Aerocrine AB, Sweden), a new hand-held, non-invasive FE_{NO} monitor, was used for measuring FE_{NO} levels with a reimbursement price of €4 per test.

Diagnosis of asthma using FE_{NO} measurements alone was €2 more expensive per patient than standard diagnostics (€8 vs. €6, respectively). However, FE_{NO} measurements provided more accurate results. Moreover, for longer term asthma management, cost savings of €0 per patient-year were reported for patients with mild-to-severe asthma following the FE_{NO}-driven strategy rather than standard guidelines – and this increased to €60 per patient-year with severe asthma. Health outcomes were similar with both approaches to asthma management.

In conclusion, FE_{NO} reduces overall costs and provides similar health benefits, when compared with standard asthma management.

Exercise-induced bronchoconstriction

Lex C, Dymek S, Heying R, Kovacevic A, Kramm CM, Schuster A. Value of surrogate tests to predict exercise-induced bronchoconstriction in atopic childhood asthma. *Pediatr Pulmonol* 2007; **42**: 225–30.

The diagnosis and control of exercise-induced bronchoconstriction (EIB) is helpful in patients with asthma as EIB is related to bronchial eosinophilic inflammation. However, the diagnostic methodology of exercise testing is complex and time-consuming. This study investigated the value of three non-invasive surrogate tests in predicting EIB in a group of 85 children (mean age 11 years [range: 5–16]) with atopic asthma.

At baseline, patients' lung function was assessed, FE_{NO} measurements were taken, and a questionnaire was completed to record respiratory symptoms during the preceding 2 weeks. Standardized exercise testing was also performed.

The NPV of elevated FE_{NO} levels predicting EIB was 100%, as EIB was not seen in any children with normal (≤ 25.0 ppb) FE_{NO} values. However, the PPV was only 28%. The questionnaire was almost as reliable at ruling out EIB (NPV 96% and PPV 26%), whereas baseline lung function tests were not predictive. Combining FE_{NO} levels and questionnaire results improved the PPV to 40%. Exercise challenge procedures are resource intensive; therefore, surrogate testing by FE_{NO} measurement and symptom questionnaires has significant time-saving potential.

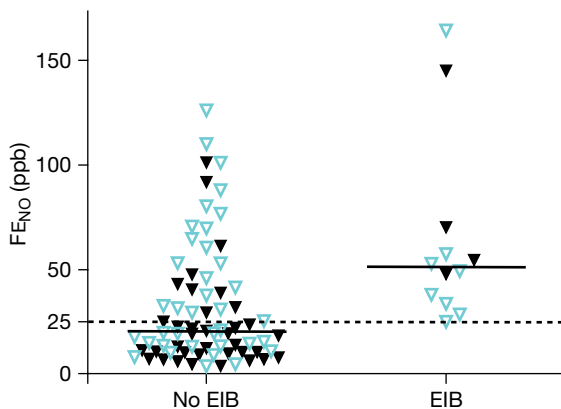


Figure 1. FE_{NO} in patients with atopic asthma, grouped according to whether they had EIB. Open symbols indicate patients without ICS.

In conclusion, FE_{NO} measurement and symptom questionnaires (preferably in combination) can be used to exclude EIB in childhood asthma, and thereby save considerable time compared with standard exercise testing.

Flow-independent parameters and disease severity

Brindicci C, Ito K, Barnes PJ, Kharitonov SA. Differential flow analysis of exhaled nitric oxide in patients with asthma of differing severity. *Chest* 2007; **131**: 1353–62.

Brindicci *et al.* partitioned bronchial and alveolar nitric oxide (NO) levels by using multiple exhalation flow rates (10, 50, 100, 200 and 260 mL/s). The study was performed in 56 patients with asthma at different severity levels (mild, $n = 10$; moderate stable, $n = 17$; moderate during exacerbation, $n = 11$; severe, $n = 18$) and in 18 healthy subjects. Seven of the severe asthma patients were receiving oral as well as inhaled corticosteroids.

The alveolar NO level was highest in patients with severe asthma receiving oral corticosteroids (3.0 ppb), significantly higher than in all other groups except patients with moderate asthma during exacerbations.

All NO measurements at all flow rates were highly reproducible and free from day-to-day or diurnal variations. This led to high reproducibility of the calculated bronchial and alveolar NO.

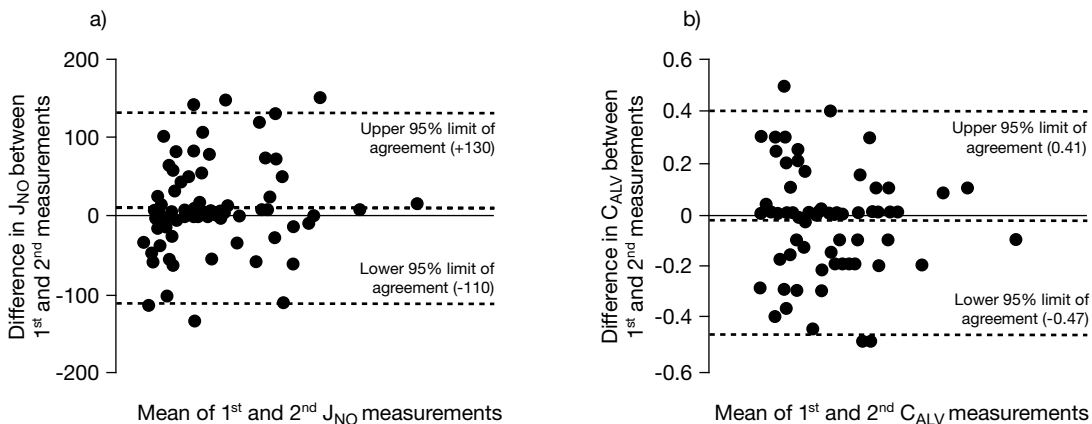


Figure 2. Bland-Altman analysis for the repeatability of a) bronchial NO (J_{NO}) and b) alveolar NO (C_{ALV}) in the studied groups.

The authors concluded that multiple flow analysis of FE_{NO} was easy to perform and non-invasive. It can distinguish airway and peripheral inflammation, and may have implications for the assessment and treatment of patients with asthma.

Inhaled corticosteroids and chronic cough

Hahn PY, Morgenthaler TI, Lim KG. Use of exhaled nitric oxide in predicting response to inhaled corticosteroids for chronic cough. *Mayo Clin Proc* 2007; **82**: 1350–5.

Hahn's retrospective observational study explored the relationship between FE_{NO} levels in patients with chronic cough and their response to treatment with ICS.

Sixty-four patients with chronic cough underwent FE_{NO} and methacholine challenge tests and were either prescribed ICS or had their current ICS dose altered. Elevated FE_{NO} levels (>35 ppb) were recorded in 41 patients, 36 (88%) of whom documented significant improvements in chronic coughing following therapy. Only 5 (12%) patients with elevated FE_{NO} levels did not respond, giving a likelihood ratio of a positive response of 4.9 (95% confidence interval [CI]: 2.2–10.9). The vast majority (91%) of patients with normal FE_{NO} levels did not respond to ICS therapy. A FE_{NO} threshold of 38 ppb was found to provide the best combination of sensitivity and specificity for predicting response and non-response to ICS. Responders and non-responders to ICS therapy had significantly different FE_{NO} levels (mean \pm SD: 51.25 \pm 20.1 and 26.0 \pm 16.5 ppb, respectively; $p < 0.001$). These results suggest a role for FE_{NO} testing in this patient population, which may preclude the need for more invasive tests.

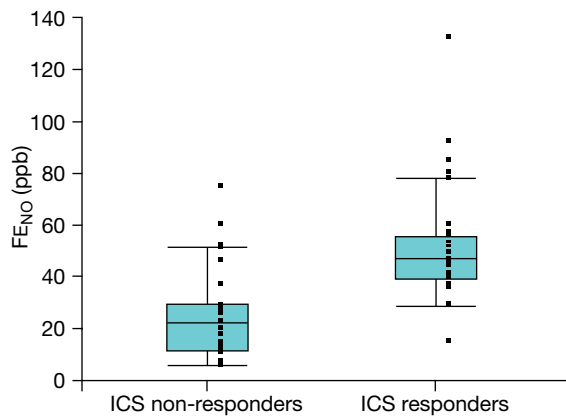


Figure 3. Mean FE_{NO} levels in ICS responders and non-responders. Error bars indicate SD.

The investigators concluded that chronic cough patients with FE_{NO} levels above 38 ppb are likely to respond positively to ICS therapy, but those with FE_{NO} levels in the normal range are unlikely to respond. This may impact the evaluation and treatment of such patients.

Dose titration

Shaw DE, Berry MA, Thomas M, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide to guide asthma management. A randomized controlled trial. *Am J Respir Crit Care Med* 2007; **176**: 231–7.

Current asthma guidelines recommend that lung function tests and symptom assessments guide anti-inflammatory treatment decisions. However, neither is closely associated with airway inflammation. FE_{NO} is a non-invasive surrogate marker of airway inflammation and evidence suggests that it can be used in asthma patients to reduce treatment and predict preventable exacerbations.

One hundred and eighteen patients with asthma were randomized to single-blind treatment with ICS, administered according to either British Thoracic Society guidelines ($n = 60$) or a FE_{NO} -driven treatment strategy ($n=58$). The latter involved titrating ICS doses according to FE_{NO} concentrations. Participants were assessed monthly for 4 months, then bi-monthly for a further 8 months. The FE_{NO} -based strategy produced a non-significant reduction in asthma exacerbations (estimated exacerbation frequency [mean \pm SD] 0.33 ± 0.69 vs. 0.42 ± 0.79 per patient per year in the FE_{NO} and control groups, respectively; $p = 0.43$). The final daily ICS dose was significantly lower in the FE_{NO} group (557 vs. 895 μ g; $p = 0.028$), although there was a non-significant 11% increase in overall ICS administration in the FE_{NO} group (95% CI: 17–42%; $p = 0.40$). This study was underpowered to demonstrate a treatment difference, and previous studies have all indicated reduced exacerbations with FE_{NO} -dependent dose titration.

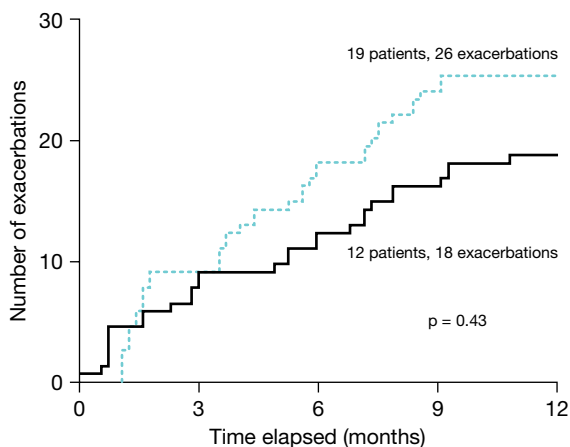


Figure 4. Cumulative asthma exacerbations in patients undergoing a FE_{NO} -driven treatment strategy (solid line) and the control group (dotted line).

In conclusion, this study showed a trend towards fewer exacerbations in the FE_{NO} group compared with the standard treatment group, and a significant reduction in final ICS dose.

FE_{NO} reference values

The following tables show selected normal values data from articles published in 2007–8. For full details, please refer to the original publications.

Table 1. Reference ranges derived from a multivariate model in normal subjects. Atopy was defined as positive skin prick test to at least one common allergen [Travers J *et al.* 2007].

Atopy status	Smoking status	Reference Range for FE _{NO} (ppb)	Atopy status	Smoking status	Reference Range for FE _{NO} (ppb)
Female			Male		
No atopy	Current smoker	5.9–30.5	No atopy	Current smoker	7.5–38.4
	Ex-smoker	6.4–32.2		Ex-smoker	8.1–40.8
	Non-smoker	7.5–37.4		Non-smoker	9.5–47.4
Atopy	Current smoker	6.9–36.4	Atopy	Current smoker	8.8–45.9
	Ex-smoker	7.6–38.5		Ex-smoker	9.6–48.6
	Non-smoker	8.8–44.6		Non-smoker	11.2–56.5

Table 2. 95% upper limits of FE_{NO} according to classes of height and age among 1131 healthy never-smoking subjects [Olin A-C *et al.* 2007].

Height	Age				
	25–34yr	35–44yr	45–54yr	55–64yr	65–75yr
≤ 160 cm	24.0	24.5	28.8	31.5	34.1
160–169 cm	27.4	29.7	32.8	35.9	38.9
170–179 cm	31.2	34.1	37.3	40.9	44.3
180–189 cm	35.5	38.9	42.5	46.5	50.4
> 190 cm	40.4	44.3	48.4	53.0	57.4

Table 3. Mean values and reference ranges for FE_{NO} (with 95% CIs), based on prediction equations for males and females aged 32 years. For comparison, the measured values obtained in the study group members are provided [Taylor DR *et al.* 2007].

Population		Males		Females	
		FE _{NO} (ppb)	95% CI	FE _{NO} (ppb)	95% CI
Non-smokers, non-atopic, non-asthmatic	Predicted	15.6	14.1, 17.2	11.3	10.3, 12.4
	Actual	14.7	13.4, 16.1	11.2	10.3, 12.2
Smokers (smoked on day of testing, non-atopic, non-asthmatic)	Predicted	7.0	5.6, 8.8	6.5	5.1, 8.2
	Actual	7.3	6.4, 8.3	6.5	5.8, 7.3

Table 4. The effects of age, height, gender and race on FE_{NO} concentrations in healthy schoolchildren aged 9–12 years [Kovesi T *et al.* 2007].

Variable	Percentile	n	Range or percentage	FE _{NO} (ppb): mean (SD)
Age		656		
	<25th		9.14–10.03	12.8 (12.2)
	25th–50th		10.03–10.87	14.2 (12.5)
	50th–75th		10.87–11.59	13.7 (11.1)
Height	>75th	656	11.59–12.73	15.6 (17.0)
	<25th		123–140	13.8 (12.3)
	25th–50th		141–145.5	11.6 (8.7)
	50th–75th		146–151	14.6 (15.0)
Gender	>75th	657	152–176	16.1 (15.9)
	Male		44.6	14.3 (13.1)
	Female		55.4	13.9 (13.6)
Race		651		
	Caucasian		85.9	12.7 (11.1)
	Asian-Canadian		10.8	22.8 (20.6)
	African-Canadian		3.3	17.4 (23.6)

Hand-held airway inflammation monitor – feasibility articles

Bodini A, Peroni D, Loiacono A, Costella S, Pigozzi R, Baraldi E, Boner AL, Piacentini GL. Exhaled nitric oxide daily evaluation is effective in monitoring exposure to relevant allergens in asthmatic children. *Chest* 2007; **132**: 1520–5.

Bodini investigated the feasibility of monitoring FE_{NO} using a new hand-held device (NIOX MINO, Aerocrine AB, Sweden) in allergic asthmatic children.

Twice-daily FE_{NO} measurements were taken for 3 months in 22 asthmatic children (aged 6–15 years) sensitized to house dust mite (HDM) residing in an asthma clinic in the Italian Alps. This high-altitude location created an HDM-free environment. Children relocated to their family homes with normal mite exposure for 19 days before returning for 6 days of follow-up.

Mean FE_{NO} levels significantly increased during natural mite exposure before decreasing on their return to the clinic (26.4 ppb [95% CI: 19.3–36.2] at baseline, 37.3 ppb [27.3–51.0] during natural mite exposure and 34.9 ppb [25.2–48.2] at follow-up). There were no differences in FE_{NO} levels between children on ICS treatment and those not receiving ICS, during any time period. Six children reported asthma symptoms during mite exposure, all accompanied by increased FE_{NO} levels ($p < 0.031$).

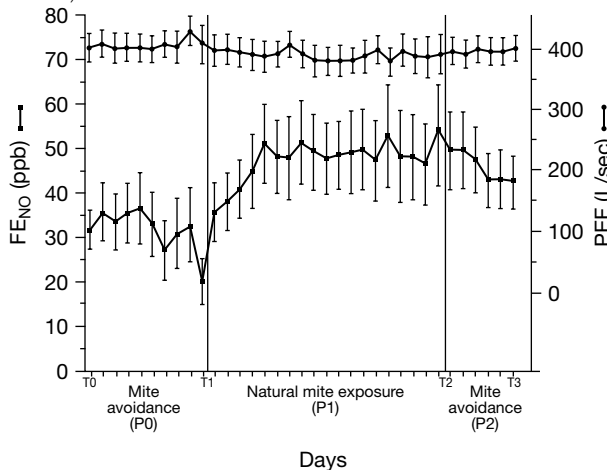


Figure 5. Peak expiratory flow (PEF) and FE_{NO} values (mean \pm standard error) throughout the study period.

These data provide further evidence of the potential role of frequent FE_{NO} monitoring to monitor airway inflammation in asthmatic children.

Hand-held airway inflammation monitor – feasibility articles (continued)

Kostikas K, Papaioannou AI, Tanou K, Koutsokera A, Papala M, Gourgoulialis KI. Portable exhaled nitric oxide as a screening tool for asthma in young adults during pollen season. *Chest* 2007, Nov 7 [Epub ahead of print].

Kostikas investigated the value of FE_{NO} readings in accurately screening for asthma. Students (n=149) who had at least one positive answer to a respiratory screening questionnaire provided FE_{NO} measurements using the new NIOX MINO device (Aerocrine AB, Sweden). They also underwent spirometry testing and were evaluated by a physician blinded to the FE_{NO} results. Seventy students with no respiratory symptoms served as controls.

Asthma was diagnosed in 63 subjects and allergic rhinitis in 57 subjects. Significantly higher median FE_{NO} levels were recorded in asthmatics than controls (20 ppb [interquartile range: 14, 31] vs. 11 ppb [7, 13], respectively, $p < 0.0001$), whereas there was no significant difference between asthmatic and allergic rhinitis patients (17 ppb [12, 23], $p = 0.28$). FE_{NO} values >19 ppb presented a specificity of 82.5% and sensitivity of 52.4% for the diagnosis of asthma (AUC = 0.723).

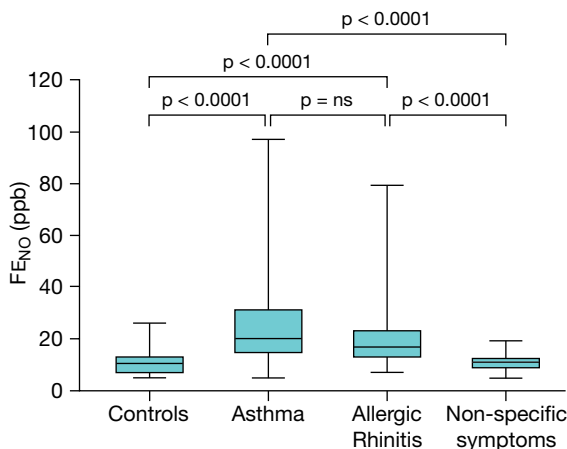


Figure 6. Levels of FE_{NO} in the study groups. Data are presented as box-plots showing the median values with interquartile ranges.

The investigators concluded that FE_{NO} monitoring is useful for asthma screening in young adults.

Hand-held airway inflammation monitor – correlation/ comparison articles

Menzies D, Nair A, Lipworth BJ. Portable exhaled nitric oxide measurement. Comparison with the “Gold Standard” technique. *Chest* 2007; **131**: 410–4.

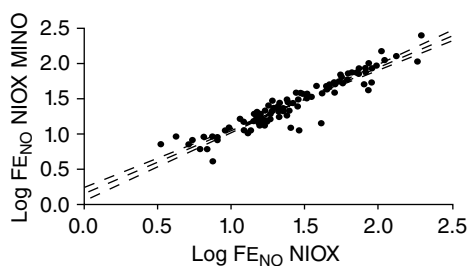


Figure 7. Linear regression with 95% CI for NIOX MINO versus NIOX values in asthma patients.

Menzies’ study compared the new NO device, NIOX MINO (Aerocrine AB, Sweden), with an established research-based analyzer (NIOX, Aerocrine AB) in 101 patients with asthma (mean age 48 years; 64 treated with inhaled corticosteroids) and 50 healthy volunteers (mean age 35 years).

In both patients and volunteers, there was a good correlation between the fractional exhaled NO measurements taken with each device ($r = 0.94$ and 0.96 , respectively). Both devices were able to discriminate between asthmatic and non-asthmatic subjects, using cut-offs of 13 and 12.5 ppb, respectively.

The investigators concluded that the new device may facilitate practical measurement of asthmatic airway inflammation in primary care.

Khalili B, Boggs PB, Bahna SL. Reliability of a new hand-held device for the measurement of exhaled nitric oxide. *Allergy* 2007; **62**: 1171–4.

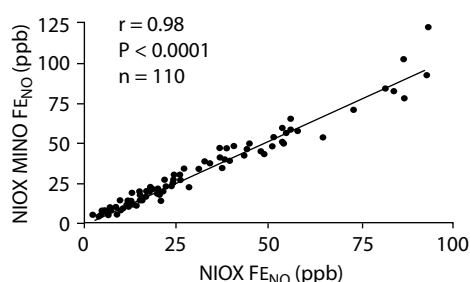


Figure 8. Correlation between FE_{NO} measurements taken by NIOX MINO (mean of three measurements) or NIOX (mean of two measurements).

The performance of the new hand-held FE_{NO} device (NIOX MINO, Aerocrine AB, Sweden) was compared with the current clinical standard (NIOX, Aerocrine AB) in this single-centre study of 110 patients aged between 6 and 68 years presenting to an asthma and allergy clinic. Sixty-nine percent of the patients were Caucasian, 30% were African-American, and 1% were Hispanic. FE_{NO} levels were measured in each patient using a NIOX machine and three separate NIOX MINO devices.

FE_{NO} levels recorded on the three NIOX MINO devices were not significantly different ($p = 0.59$). In addition, there was a strong consistent correlation between readings on the NIOX and NIOX MINO devices ($r = 0.98$, $p < 0.0001$).

The investigators concluded that NIOX MINO may be reliably used in clinical practice.

Review

Pijnenburg MWH, De Jongste JC. Exhaled nitric oxide in childhood asthma: a review. Clin Exp Allergy 2007; 38: 246–59.

This comprehensive review focuses on the clinical applications of FE_{NO} measurements in pediatric asthma and covers the following key points:

- FE_{NO} is increasingly being used in the management of pediatric asthma
- As an ‘inflammometer’, FE_{NO} provides valuable information on underlying airway inflammation
- FE_{NO} provides a practical tool to aid in the diagnosis of asthma
- FE_{NO} facilitates differentiation of those who will benefit from ICS therapy from those who will not, and enables more efficient and effective ICS administration
- FE_{NO} is helpful in predicting exacerbations
- FE_{NO} is successful in guiding steroid dose reduction or withdrawal
- In preschool children, FE_{NO} may help in the differential diagnosis of respiratory symptoms and may allow for better targeting and monitoring of anti-inflammatory treatment
- In primary ciliary dyskinesia, FE_{NO} is likely to become the screening tool of choice.

In summary, FE_{NO} as an indicator of anti-inflammatory status may help to rationalize and improve steroid therapy in children with asthma.

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NIOX[®], NIOX[®] Flex and NIOX MINO[®] are cleared for clinical use in the US according to FDA 510(k) process. US patent 5,447,165, US patent 5,922,610, US patent 6,038,913, US patent 6,063,027, US patent 6,099,480, US patent 6,149,606, US patent 6,183,416, US patent 6,511,425, US patent 6,626,844, US patent 6,723,056, US patent 6,733,463, US patent 6,761,185, US patent 7,014,692, US patent 7,270,638 and patents pending.

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Based on the company's intellectual property, Aerocrine develops and commercializes products for the monitoring of nitric oxide (NO) as a marker of inflammation, to improve the management and care of patients with inflammatory disease in the airways.

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