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EXHALED NITRIC OXIDE MONITORING IN COPD USING A PORTABLE ANALYZER

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ABSTRACT

BACKGROUND

Exhaled nitric oxide (FeNO) is a non-invasive marker of airway inflammation in asthma. A very recent statement has suggested FeNO as potential outcome in chronic obstructive pulmonary disease (COPD). Recently, a new hand-held FeNO analyzer (NIOX MINO) has been developed.

PATIENTS AND METHODS

We have evaluated the NIOX MINO in COPD patients and monitored FeNO levels during 1-year assessment in the outpatient setting. Short-term variability in FeNO was compared using a NIOX MINO and a stationary chemiluminescence analyser (NOA, Sensormedics) in healthy volunteers and COPD patients on two consecutive months. Long-term FeNO variability was assessed on a cohort of 70 COPD outpatients measuring FeNO for one year. The intra-individual FeNO coefficient of variation (eNOCov) was taken as index FeNO long-term variability.

RESULTS

In COPD there were no significant differences between NIOX MINO and NOA FeNO values recorded at baseline and one month later. 95% limits of agreement between NIOX MINO and NOA were -2.7 and 1.9 ppb with significant reliability ($r=0.96$, $p<0.0001$). Mean FeNO at baseline was 15.0 ± 9.5 ppb. Over the one year period the overall mean FeNO was 15.5 ± 10.1 ppb. The long term eNOCov was 33.9 ± 16.4 % (range 8.1-83.1 %), and it was significantly associated with exacerbation rate ($r=0.57$, $p<0.0001$).

CONCLUSION

FeNO electrochemical handheld analyser is feasible in COPD showing good agreement with stationary chemiluminescence analyser. COPD patients exhibit a wide range of FeNO levels and a

high variability of FeNO over time, which was positively associated with the number of exacerbations.

Keywords: exhaled nitric oxide, airway inflammation, chronic obstructive pulmonary disease, hand-held analyzer, exacerbation.

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1. INTRODUCTION

Exhaled NO (FeNO) has been proposed as an useful non-invasive marker of lower airways inflammation in asthma [1] and specific guidelines have been developed for standardized measurements [2]. The most common way of measuring exhaled NO is by chemiluminescence [3]. Recently, a novel handheld NO analyser based on electrochemical sensor has been developed and it has been tested in healthy subjects and patients with asthma showing an high reproducibility and a good correlation with other methods [4-10].

Differently from asthma, studies of exhaled NO in patients with COPD are somewhat conflicting [11, 12]. Interestingly, FeNO levels have been reported to increase significantly in a group of COPD patients during cold weather and at the onset of exacerbation [13], suggesting that the monitoring of FeNO variation in COPD might have clinical implications [14]. Furthermore, a very recent statement has suggested FeNO as potential outcome in COPD [15].

While in healthy people short and long term FeNO variations have been evaluated [16, 17], the feasibility of FeNO monitoring in COPD is still unknown.

In this study we aimed at validating the feasibility of a hand-held FeNO analyzer in COPD patients and at examining the short and long-term variability of exhaled NO in COPD outpatients.

2. MATERIALS AND METHODS

2.1 Patients

The study was conducted between November 2005 and November 2006 on a cohort of COPD patients visiting our Department as outpatients. They have received COPD diagnosis in the past according to Global Obstructive Lung Disease (GOLD) guidelines [18]. Patients with a history of atopy or bronchial asthma, severe co-morbidities (heart and/or liver and/or kidney diseases, recent (< 2 weeks) upper airway infection or ongoing acute exacerbations at first visit were excluded.

All patients gave the informed consent and the study protocol was approved by the Ethics Committee of the Monaldi Hospital.

2.2 FeNO measurement validation

We compared the electrochemical FeNO device (NIOX MINO, Aerocrine, Sweden) to the chemiluminescence analyser (NOA, Sensormedics, Italy). Twenty subjects, including 10 COPD patients and 10 age-matched healthy controls were examined (HC). All COPD patients did not show clinical or spirometric features of present or past (at least 4 weeks before) pulmonary exacerbation event. **HC subjects were all not smokers, with not history of atopy or bronchial asthma or recent upper airway infection.**

All participants were invited to perform the FeNO measurement with both analysers, exhaling for 10 seconds with a constant expiration flow (50 ml/sec) against a mean of 15 cmH₂O mouth pressure. Standard FeNO was measured before any forced expiratory maneuvers, according to current guidelines [2]. Maneuvers not resulting in a FeNO plateau or those with irregular pressure tracings were excluded. **The recorded ambient NO concentration was always less than 5 ppb.**

The FeNO measurements with the handheld analyser were obtained following the manufacturer's instructions. Subjects performed a 10-second slow steady exhalation, which was assisted by visual and audio biofeedback systems located on the device.

Using both the stationary and the electrochemical analysers all participants repeated the manoeuvre until two acceptable tests were performed.

The mean of the measurements in each device, or the first approved measurement in the NIOX MINO was used for agreement studies [4]. Moreover, to assess comparatively short term variability of FeNO measurement with two devices in COPD patients and in controls, the FeNO measurements with NIOX MINO and with NOA analyzers were obtained on two different occasions (at the first visit and after one month). On both occasions NIOX MINO measurements were acquired using six and ten seconds schedules of expiratory time.

2.3 Long term FeNO variability

FeNO levels, spirometry, pulsoxyemoglobin saturation and clinical status including previous exacerbation were assessed over 1 year in 70 COPD patients (table 1).

Clinical evaluation was based on a score of breathlessness, sputum, cough and night awakenings (BSCN) rated on a scale from 0 to 4 [19] being calculated as the mean value of the last three days. We also collected relevant clinical data including drug utilization. The numbers of exacerbation during the previous month before the visit were also collected. Accordingly, event-based exacerbation was defined, using data recorded monthly, as the use of oral corticosteroids and/or antibiotics and/or hospitalization for a worsening in the patient's respiratory symptoms at the discretion of their usual physician. Furthermore, recent exacerbation was defined if the event-exacerbation occurred within the week before or the week after the visit.

The FeNO monthly intra-subject variability, as individual coefficient of variability (CoV) percent, was retrospectively assessed by calculating the CoV (mean/SD) x (100).

At each visit spirometry (MasterScreen PFT, Jaeger, Sensormedics, Italy) and oxyhemoglobin saturation (Nonin, Palmsat 2500) were measured.

2.4 Statistic

Data are presented as arithmetic mean $\pm$ standard deviation (SD). For comparison between analysers, Bland-Altman and scatter plots were constructed.

Student's paired t-test was used to compare the mean number of measurements in the two devices.

Long term FeNO data and CoV are presented as mean with 95 % CI. **Comparison between groups was evaluated using parametric tests (paired and unpaired t-test and Pearson correlation test)**

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4. RESULTS

4.1 Validation of the handheld NO analyzer

Eighty FeNO measurements were taken with both analysers in 10 HC and in 10 COPD patients.

The FeNO range was 5 - 25 ppb with the NIOX MINO device and 4.7 - 20.9 ppb with the NOA device. The mean values for the NIOX MINO and NOA were 14.8 ± 5.7 ppb and 14.2 ± 5.9 ppb (total readings = 80) respectively with a significant reliability ($r=0.96$, $p<0.0001$) when comparing the individual mean values in two devices (Figure 1a).

The Bland-Altman plot showed good agreement between NIOX MINO and NOA when comparing the mean of two exhaled NO measurements (mean value = - 0.4 ppb, 95 % limits of agreement - 2.7 and 1.9 ppb, (figure 1b). Paired samples t-test confirmed the high reliability of two devices ($p=0.002$) with a mean difference of 0.6 ppb with a significant correlation ($r= 0.97$, $p<0.0001$). The **mean** of the intra-subjects FeNO difference was **0.21** (range - 4.1 to + 2.1) suggesting that NIOX MINO FeNO measurements were generally slightly higher than NOA FeNO readings. A good degree of agreement (95 % degree limits -2.8 and 3.3 ppb) was showed when comparing the mean of two approved exhaled NO measurements in the NOA and the first approved measurement in the NIOX MINO in the clinical setting.

There were no significant differences in COPD patients between NIOX MINO and NOA FeNO values recorded at baseline (15.3 ± 6.4 ppb and 15.0 ± 6.3 ppb respectively, $p=0.9$) and one month later (16.9 ± 5.9 ppb and 15.9 ± 6.9 ppb respectively, $p=0.7$).

A good correlation degree was showed between FeNO NIOX MINO 10 seconds and 6 expiratory time schedules when considering among overall group (14.8 ± 5.7 ppb and 14.4 ± 5.9 ppb respectively, $p<0.0001$, $r = 0.92$) and both groups separately (13.5 ± 5.0 ppb and 13.2 ± 5.9 ppb in HC, $p<0.0001$ $r=0.91$, and 16.0 ± 6.1 ppb and 15.5 ± 6.4 ppb in COPD, $p<0.0001$ $r=0.92$).

However, the intra-individual CoV between the two monthly sessions was $6.5\pm5.1\%$ in HC and $26.3\pm30.2\%$ in COPD patients ($p=0.0082$).

4.2 Long term FeNO variability in COPD

Eleven patients (10M/1F) did not attend at least three visits (4 patients) or did not manage to perform a correct expiratory manoeuvre (2 patients with no adherence with device, 5 patients with FEV₁= 0.6 L and they were not included in the data analysis).

The clinical characteristics of remaining COPD patients included in the data analysis are reported in the table 1.

Baseline (first visit) mean FeNO in COPD was 15.0 ± 9.5 ppb, and it was not significantly different from HC (13.5 ± 5.0 ppb, $p=0.60$). The subgroup of COPD current smokers ($n=12$), showed significantly lower FeNO than COPD ex smoker (12.6 ± 7.3 ppb vs 18.1 ± 11.0 ppb, $p<0.0001$).

The FeNO validation COPD group did not significantly differ in terms of smoking habit, **drug usage** and FeNO levels **in comparison to** the long-term cohort.

Over the one year period of the study mean FeNO measured **from a total of 426 visits** was 15.5 ± 10.1 ppb.

In COPD patients mean CoV FeNO was 34.4 ± 17.9 % (95 % CI 22.3-39.5) and it was significantly higher than in HC (6.2 ± 5.1 %, 95 % CI 3.8-8.6) ($p<0.0001$).

Both FeNO concentration and FeNO CoV were unrelated to BSCN, oxygen saturation and FEV₁.

There was a significant correlation between individual exacerbation rates and FeNO CoV ($r=0.57$, $p<0.0001$) (figure 2). Moreover, the COPD patients with eNO CoV $\geq 40\%$ reported a two-fold increase in exacerbation rate as compared to the COPD with eNO CoV less than 40% (table 2), with the highest FeNO values close to the exacerbation (figure 3).

There was not significant difference between smoking habit between the two groups ($p=0.61$, data shown in table 2).

There were not significant differences between two COPD groups in inhaled corticosteroids and long acting beta2 agonist consumption.

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5. DISCUSSION

In order to validate the reproducibility and the reliability of the electrochemical handheld device in COPD patients, we have evaluated the NIOX MINO measurements against the gold standard chemiluminescence method, finding a good agreement between the two methods.

Previous studies have shown NIOX MINO reproducibility and accuracy in healthy people at different ages and in asthma [4, 5, 7-9], but no data on COPD patients are available.

In our study the upper and lower specifications on the Altman-Bland plots comparing data from the two analyzers equate to almost ± 2 ppb on the arithmetic scale. Given that the differences between values for HC and COPD patients were not statistically significant at the conventional flow rate of 50 mL/s, this degree of accuracy appeared to be acceptable. Moreover, the median of the intra-subjects FeNO difference suggested that FeNO measurements by NIOX MINO were generally slightly higher than NOA FeNO readings, similar to data obtained from previous studies [4, 8].

The use of handheld analyzer at standard 50ml/sec flow rate allowed for easy monitoring of wide ranges of FeNO in outpatients COPD, which could be of interest when comparing the measurements in healthy people and patients with asthma.

The comparison between analyzers gave similar results after one month and when the handheld analyzer was used employing different expiratory flow times from six to ten seconds. We used these different expiratory times for two reasons: as the handheld analyzer does not allow the visual inspection of expiratory curve, abnormalities in the plateau phase leading to an increase in FeNO should be unmasked decreasing expiratory time. Furthermore, six second expiratory time might be a valid option for COPD patients with very low FEV₁. For these reasons our data indicate that COPD patients (with FEV₁ greater than 0.85 L/sec) could handle the device using a 6 seconds time expiratory schedule as patients with almost normal lung function use the 10 seconds schedule.

Accordingly, previous studies concerning the comparability of different types of chemiluminescence NO analyzers have shown that significant differences could exist but they were mainly related to differences in gas calibration/procedure. Our data suggest that FeNO method of

analysis does not significantly influence the results of measurements. The intra-individual reliability of NIOX MINO measurements obtained after one month when comparing the measurements performed both with stationary and handheld analyzer in healthy controls and in COPD showed a good agreement. During the validation study in COPD group there were four patients who presented a high FeNO levels variability between two months, with no apparent differences in clinical or spirometric data with other COPD subjects. On these bases we have designed a long-term study to evaluate the variability of FeNO in COPD patient, monitoring the impact of multiple factors on the disease natural history.

Differences in FeNO between COPD and healthy controls have been reported with conflicting results postulating a role for airway inflammation, as NO levels are usually reported only slightly increased, except during exacerbation.

Our data indicate that COPD patients have a greater intra-individual FeNO variation over time during relatively stable clinical conditions despite mean FeNO values comparable to those obtained from healthy subjects. The variation in FeNO was greater in COPD patients compared to controls during the long-term follow-up over one year. Moreover, this intra-individual FeNO variability was positively associated with the number of exacerbations during the study period.

Levels of FeNO in COPD patients, at date, are not univocally determined and their relationship with disease exacerbation is not fully clarified.

Several studies have documented that FeNO levels during acute exacerbations were significantly higher than during a stable phase of COPD as Browmik *et al.* in a large cohort study have demonstrate to obtain paired stable and exacerbation FeNO measurements from 38 patients [13]. Accordingly, Ekroos and coworkers have evaluated a change in FeNO by 30-35% or more within a 1-3 weeks interval as being abnormal and proposed this value as cut-off for a significant fluctuation in relation to FeNO in healthy subjects [16]. In our study the cut-off in exhaled nitric oxide variation **> 40% was chosen as the upper limit of 95 % of CI of the mean of the overall COPD group (39.5%). In this way, a cut-off in FeNO variation > 40-50% when using a handheld**

analyser seems **to be** reasonable as an index of previous mild to moderate exacerbation. Actually, this FeNO CoV was not influenced by the baseline FeNO, number of visits, GOLD stage, while a significant correlation with the rate of exacerbations was found. It could be reasonable that all the variability in FeNO may reflect disease exacerbation. However, we cannot exclude other possible causes of larger FeNO variation in stable COPD such as airway persistent inflammation outside of the clinical overt exacerbation. Indeed cell sputum composition, abnormal mechanics, oxidative stress and alveolar inflammation are all factors potentially involved in changes over the time of airway NO output in apparently stable COPD [20]. **Accordingly, in another study on FeNO long term variability in lung transplant recipients Antus *et al.* [21] have reported that FeNO variation greater than 30% was a specific marker of acute infection during a two years period of follow-up. On the other hand, our data on long term eNO variability in COPD differ from what reported in asthma, where inhaled corticosteroid treatment was the main factor responsible for decrease of exhaled NO long term variation [22].**

Noteworthy the differences in FeNO variation were not influenced by smoking habit. This may depend on the limited number of smokers included in the study; however, according to previous reports [23, 24] in our study COPD current smokers had significant lower FeNO levels measured by hand-held analyzer than COPD ex smokers.

A limit of our study was that we did not analyze cause-effect relationship between FeNO variation and rate of exacerbation in COPD as the aim of our study was to examine the long term FeNO variability in stable COPD. Therefore we have not data to investigate whether the temporal relationship between exacerbation and FeNO elevations could reflect an early rise in FeNO prior to disease exacerbation.

In conclusion in COPD exhaled NO measurement with an electrochemical handheld analyser shows good agreement with the standard stationary chemiluminescence analyser. In outpatients COPD FeNO shows a greater variation than reported in healthy people, with a significant association to the rate of exacerbation. Although the underlying mechanisms of these FeNO fluctuations in apparently

stable COPD patients requires further studies, FeNO measurement with a handheld analyzer is feasible for FeNO monitoring in COPD.

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Table 1. Overall COPD patients characteristics at baseline. Data are represented as mean $\pm$ SD

Male/Female	52/7
Age (years)	66.3 $\pm$ 8.6
Current Smokers number (pk/year)	12 (51.4 $\pm$ 19.3)
FEV ₁ (L)	1.4 $\pm$ 0.5
GOLD stage (score)	2.6 $\pm$ 0.9
BMI (kg /m ²)	27.1 $\pm$ 5.5
FeNO (ppb)	15.0 $\pm$ 9.6
Visit rate (number)	7.2
BSCN (score)	5.5 $\pm$ 1.7
SaO ₂ (%)	92.1 $\pm$ 3.8

Table 2. Anthropometrics, pulmonary function parameters (FEV₁, GOLD stage), exhaled nitric oxide levels (FeNO) at the first visit and analysis results of monthly intra-subject variability, as individual variability coefficient (CoV) percent, of clinical and functional parameters in a cohort of 59 COPD outpatients during one year of study.

	eNO CoV ≥ 40 % (n = 17)	eNO CoV < 40 % (n = 42)	p
Male/Female	15/2	37/5	
Age (year)	64.5 $\pm$ 6.7	67.0 $\pm$ 9.2	0.30
Current Smokers number (pk/year)	4 (47.5 $\pm$ 20.6)	8 (53.3 $\pm$ 16.8)	0.61
FEV ₁ (L)	1.3 $\pm$ 0.5	1.4 $\pm$ 0.5	0.64
GOLD stage (score)	2.8 $\pm$ 0.8	2.5 $\pm$ 0.9	0.17
BMI (kg/m ²)	29.4 $\pm$ 7.3	26.2 $\pm$ 4.4	0.11
FeNO (ppb)	20.1 $\pm$ 16.0	13.9 $\pm$ 7.1	0.28
Visit rate (number)	7.7 $\pm$ 3.3	7.0 $\pm$ 3.1	0.71
Exacerbation rate	2.1 $\pm$ 1.7	0.9 $\pm$ 1.3	0.002

FIGURE LEGENDS

Figure 1.

a) Device agreement. Scatter plots of the mean of two valid FeNO measurements using the NOA vs the mean of two valid FeNO measurements using the NIOX MINO (n = 80). The reliability coefficient was high ($r = 0.96$, $p < 0.0001$). b) Device agreement. Bland-Altman plots of the mean of two valid FeNO measurements using the NOA vs the mean of two valid FeNO measurements using the NIOX MINO (n = 40).

Figure 2.

Correlation between long term intra-individual exhaled NO coefficient of variation (FeNO CoV) and exacerbation rate in 59 COPD outpatients.

Figure 3.

Individual exhaled nitric oxide value (FeNO) in the seventeen COPD patients with high exhaled NO coefficient of variation over one year period.

The unfilled circles represent the timepoint close to the exacerbation. Clinical exacerbation was based on an increase in breathlessness, sputum, cough and night awakenings as specified in the text.