Primary Care Respiratory Journal (2008); 17(2): 97-103

Primary Care RESPIRATORY JOURNAL
www.thepcrj.org

ORIGINAL RESEARCH

Supporting the diagnosis of non-specific respiratory symptoms in primary care: the role of exhaled nitric oxide measurement and spirometry

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Received 29th August 2007; revised version received 31st January 2008; accepted 16th February 2008

Abstract

Aims: To assess whether exhaled nitric oxide (FE_{NO}) measurements improve management and clinician confidence in patients presenting with non-specific respiratory symptoms.

Methods: This observational study was based in a large primary care practice (15,500 patients, 14 GPs). Patients had non-specific respiratory symptoms for at least six weeks. FE_{NO} and spirometry measurements were performed at initial assessment. An algorithm was employed to assist interpretation of FE_{NO} and spirometry results. GPs evaluated the diagnostic contribution of FE_{NO} and spirometry at 3-month follow-up.

Results: In 48/51 (94%) of cases FE_{NO} was considered significant in formulating a diagnosis. Spirometry was deemed helpful in 27/51 (54%).

Conclusion: FE_{NO} measurements improved diagnostic confidence when assessing non-specific respiratory symptoms. This may be because, in contrast to spirometry, both low and high FE_{NO} values have clinical significance.

Trial registration: Australian Clinical Trials Registry ACTRN012605000354684

RS Hewitt, *et al. Prim Care Resp J* 2008; **17**(2): 97-103.
doi:10.3132/pcrj.2008.00025

Keywords diagnosis, asthma, exhaled nitric oxide, decision support, spirometry, respiratory symptoms

Introduction

Chronic cough, wheeze, and breathlessness are commonly encountered symptoms in primary care. Often they point to a diagnosis of asthma,[1] but the symptoms are non-specific and there is an extensive differential diagnosis. Other conditions such as chronic obstructive pulmonary disease (COPD), gastro-oesophageal reflux disease (GORD), anxiety with hyperventilation, and mild bronchiectasis, may be wrongly identified as asthma and the patient managed inappropriately. In order to support a diagnosis, objective tests of airway physiology are often employed, such as spirometry, reversibility testing and peak expiratory flow (PEF) monitoring. However, obtaining serial PEFs is challenging and compliance is often poor.[2] Their usefulness is also limited by poor sensitivity and specificity.[3,4] Furthermore, they do not predict the likely response to inhaled corticosteroids (ICS) and such treatment is often initiated empirically. Prior prediction of steroid responsiveness would help to rationalise the management of chronic respiratory symptoms.

A common pathological feature of asthma is the presence of eosinophilic airway inflammation, although other histological subgroups are recognised.[5] Importantly,

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eosinophilic airway inflammation is steroid responsive.[6,7] Exhaled nitric oxide (FE_{NO}) correlates well with airway eosinophilia.[8,9] The clinical significance of an elevated FE_{NO} is not so much that it may help to distinguish asthma from non-asthma[4,10] but, more importantly, it may be used as a predictor of steroid responsiveness.[11,12] FE_{NO} measurements thus provide complementary information, not readily obtained from assessing symptoms and airway physiology.

The availability of diagnostic testing in primary care is limited. We undertook to make FE_{NO} measurements immediately available in a primary care setting. We hypothesised that, coupled with spirometry, this would improve diagnostic and therapeutic decision making as well as enhancing clinician confidence when assessing patients with non-specific respiratory symptoms.

Methods

Subjects

The study aims were explained to 14 general practitioners (GPs) in a large primary care practice (15,500 patients) in Dunedin, New Zealand at a practice management meeting. Thereafter, between July 2005 and June 2006, 55 patients, aged 12-80, with a history of cough, wheeze or shortness of breath for at least six weeks, were invited by their GP to participate. Patients were included if they had no previous respiratory diagnosis or if their previous diagnosis was uncertain, and were excluded if they had received oral or inhaled (including nasal) corticosteroids within the last six weeks. Smokers and recent ex-smokers (<6 months) were also excluded due to the confounding effect of smoking on FE_{NO} measurements.[13,14] The study received ethical approval from the Lower South Regional Ethics Committee, and each participant gave written informed consent.

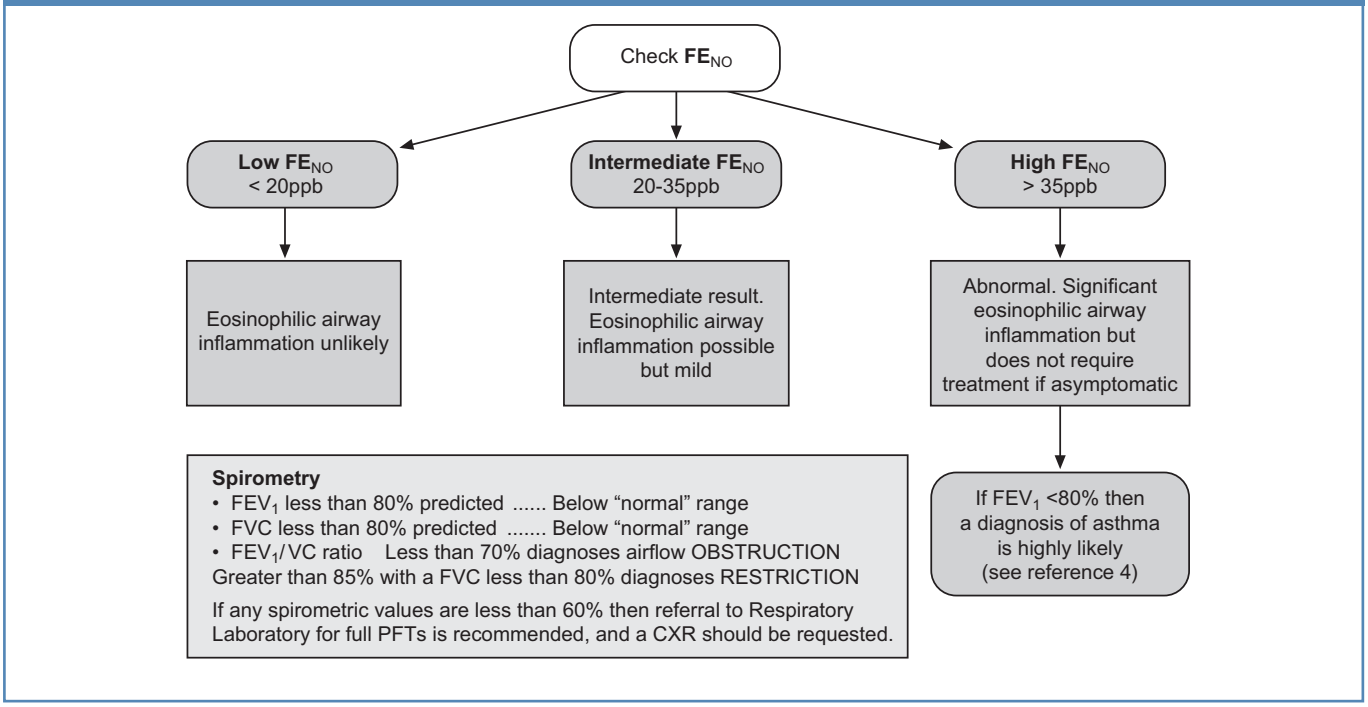
Study design

The study was observational. All patients were seen by their GP and then by the practice nurse. FE_{NO} measurement and spirometry were performed. Using these results, and with reference to an algorithm (Figure 1), the GP then made a provisional clinical diagnosis for each patient. The algorithm focused on whether or not the FE_{NO} result indicated a high, intermediate or low likelihood of eosinophilic airway inflammation and hence the potential for steroid responsiveness, rather than specific diagnostic labelling. The algorithm was based on published data defining the upper limit of normal for FE_{NO}.[15,16] The GP then recorded a response to each of the following questions:

- Was there a prior diagnosis and if so, has it been confirmed or refuted?
- Was the availability of FE_{NO} significantly helpful in making the provisional diagnosis?
- Was the availability of spirometry significantly helpful in making the provisional diagnosis?

Management was then instituted based on clinical judgement and the results of the FE_{NO} and spirometric tests as appropriate. Treatment decisions were not specifically prompted by the algorithm.

Figure 1. Algorithm given to GPs for interpretation of FE_{NO} and spirometry results at initial visit.



The final clinical diagnosis was made at 3 months in the light of the patient's clinical course, and was based on joint consultation between the GP and the research fellow (RSH), an advanced trainee in respiratory medicine. Further FE_{NO} and/or spirometric measurements were available at that time at the discretion of the clinician.

For the purposes of this study, and given the study aims, a working diagnosis of atopic asthma was defined as variable respiratory symptoms with a FE_{NO} level of >35ppb and/or a positive response to a trial of corticosteroid, where such therapy had been administered.

Study procedures

FE_{NO} was measured according to current guidelines[17] using a NIOX MINO electrochemical analyser[18] or a NIOX chemiluminescence analyser (both Aerocrine, Solna, Sweden). The mean of two values was used. To validate FE_{NO} results, the sensors from the NIOX MINO device were tested at the end of the life time of each sensor against a calibrated standard, and where appropriate, a correction factor was applied to take account of signal drift. Where any later correction in the FE_{NO} result affected the use of the diagnostic algorithm, that patient was excluded from analysis.

Spirometry was performed according to accepted standards[19] using either a Spida 5 spirometer (Micro Medical, Rochester, Kent, UK) or a Vitalograph (Vitalograph Ltd, Buckingham, UK). The response to bronchodilator was not measured given that the presence or absence of response to bronchodilator is very poorly correlated with either the underlying pathological phenotype or potential improvements with inhaled corticosteroid therapy.[20]

Results

Of the 55 patients recruited, four were excluded because retrospective correction of FE_{NO} results led to changes that affected the use of the diagnostic algorithm. Demographic details of the remaining 51 subjects are presented in Table 1. Detailed data for patients who were considered for inclusion but failed to satisfy inclusion criteria were not recorded.

Initial diagnosis

The diagnoses made at the first consultation were as follows: asthma (n=20, 39.2%); non-specific cough (n=10, 19.6%); exercise-induced wheeze (n=6, 11.8%); extended post-viral respiratory syndrome (n=5, 9.8%); anxiety with hyperventilation (n=4, 7.8%); GORD (n=3, 5.9%); COPD (n= 2, 3.9%); and ACE inhibitor-induced cough (n=1, 2.0%). Details regarding prior, initial and follow up diagnoses are given in Table 2. The diagnoses stratified by FE_{NO} categories are shown in Table 3.

Thirty-four of the 51 patients had no previous diagnosis for their respiratory symptoms. Of the 17 patients who had a prior diagnosis, the diagnosis was changed at the initial study visit in five. Three of these five had low FE_{NO} readings (<20 parts per billion (ppb)) and their diagnosis was changed from atopic asthma to either COPD (n=2, FE_{NO} 8ppb and 16.5ppb) or non-atopic exercise-induced wheeze (n=1, FE_{NO} 14.5ppb). The two other patients, previously labelled as having COPD and angina, had high FE_{NO} (50 and 106ppb respectively) and the diagnosis was changed to atopic asthma. In each case where the diagnosis was changed at the initial consultation, it was reconfirmed at 3-month follow-up. In the remaining 12 out of 17 patients, their prior diagnosis was confirmed as: atopic asthma (n=6, geometric mean FE_{NO} = 72.4ppb); GORD (n=3, geometric mean FE_{NO} = 11.1ppb); non-specific cough (n=2, geometric mean FE_{NO} = 13.2ppb); and exercise-induced wheeze (n=1, FE_{NO} = 14.0ppb).

Table 1. Demographic details of patients presenting with respiratory symptoms of > 6 weeks duration (n=51).

Age (years)	Mean 39.8 (range 12 – 76)	
Sex M / F	18 / 33	
Smoking history (n)	Ex-smoker 19 (37.3%)	Never smoked 32 (62.7%)
Prior history of ICS use	> 6 weeks previously 14 (27.5%)	Never 37 (72.5%)
Duration of presenting symptoms (weeks)	Median 16.0 (range 6 – 520)	
Symptoms (number of patients)		
Nocturnal wakening	29 (56.9%)	
Cough	44 (86.3%)	
Wheeze	32 (62.7%)	
Shortness of breath	44 (86.3%)	

Follow-up diagnosis

The working diagnosis was changed at 3-month follow-up in 10 out of the 51 cases (19.6%) – see Table 2. Three patients initially diagnosed with atopic asthma received ICS treatment but their symptoms resolved and did not recur after the trial of steroid was concluded. They had high FE_{NO} at their first visit but were subsequently shown to have low FE_{NO} at least six weeks after discontinuing ICS treatment. The remaining patient with atopic asthma (FE_{NO} 20ppb) was subsequently diagnosed as chronic cough of uncertain aetiology. Other changes in diagnosis included GORD to non-specific cough (n=1, FE_{NO} 8.1ppb), post-viral respiratory syndrome to COPD (n=1, FE_{NO} 18.5ppb), and five patients in whom the diagnosis of chronic cough of uncertain aetiology was changed to either COPD (n=1, FE_{NO} 28.0ppb), post-viral respiratory syndrome (n=2, FE_{NO} 13.0ppb and 12.4ppb), GORD (n=1, FE_{NO} 24.5ppb) or anxiety with hyperventilation (n=1, FE_{NO} 14.0ppb).

Table 2. Working diagnoses at presentation (initial diagnosis) and follow-up (3 months). The number of additions and subtractions is shown to indicate where the working diagnosis was changed at each time point on the basis of FE_{NO} or spirometry results. See text for further details

Diagnosis	Prior diagnosis n	Initial diagnosis n	Follow-up n
Atopic asthma	9	9 – 3 + 14 = 20	20 – 4 = 16
Non-specific cough	2	2 + 8 = 10	10 – 5 + 2 = 7
Exercise induced wheeze (non-atopic)	1	1 + 5 = 6	6
Post-viral respiratory syndrome	-	5	5 + 2 = 7
Anxiety with hyperventilation	-	4	4 + 1 = 5
Gastro-oesophageal reflux disease	3	3	3 – 1 + 1 = 3
COPD	1	1 – 1 + 2 = 2	2 + 1 = 3
ACE-inhibitor cough	0	1	1
Angina	1	1 – 1 = 0	-
No prior diagnosis	34	-	-
Resolved	-	-	3

Table 3. Mean values (standard deviation) for FE_{NO} (geometric mean), FEV_1 % predicted and FEV_1/FVC, stratified by FE_{NO} at initial diagnosis. [1]Other lower respiratory tract pathology includes exercise-induced wheeze, chronic cough of unknown aetiology, extended post-viral respiratory syndrome and pneumonia. [2] Non-respiratory pathology includes gastro-oesophageal reflux, anxiety with hyperventilation and ACE inhibitor-induced cough.

FE_{NO} grouping	N	FE_{NO} (ppb)	FEV_1 % predicted	FEV_1/FVC ratio
All patients	51	25.3 (2.4)	94.6 (23.4)	78.6 (10.9)
Low FE_{NO} (<20ppb)	22	11.9 (1.31)	92.7 (24.9)	79.0 (11.4)
Asthma	0	-	-	-
COPD	2	11.2 (1.7)	37.4 (21.9)	50.4 (14.8)
Other LRT pathology[1]	14	12.5 (1.3)	98.8 (18.8)	82.8 (7.5)
Non-respiratory pathology[2]	6	10.9 (1.4)	105.9 (15.2)	81.8 (4.5)
Intermediate FE_{NO} (20-35ppb)	12	23.9 (1.1)	95.6 (10.3)	81.6 (5.6)
Asthma	3	24.7 (1.3)	84.7 (12.9)	75.9 (3.6)
COPD	0	-	-	-
Other LRT pathology	8	23.4 (1.1)	101.2 (5.4)	84.0 (5.0)
Non-respiratory pathology	1	25.0 (n/a)	92.0 (n/a)	82.0 (n/a)
High FE_{NO} (>35ppb)	17	73.2 (1.7)	85.0 (27.5)	73.6 (12.1)
Asthma	17	73.2 (1.7)	85.0 (27.5)	73.6 (12.1)
COPD	0		-	-
Other LRT pathology	0		-	-
Non-respiratory pathology	0		-	-

Response to treatment in relation to FE_{NO}

Of the 22 patients with low FE_{NO}, the algorithm was overruled in three, and they were given ICS treatment. However, none of these three were deemed to have obtained a beneficial clinical response. Similarly three out of 12 patients with intermediate FE_{NO} (in the range 20-35ppb) were given ICS, two-thirds of whom were adjudged to have benefited. All of the 17 patients who had high FE_{NO} (>35ppb) readings were subsequently treated with ICS. Fourteen out of the 17 showed a satisfactory clinical response as judged by their GP at follow up. Three subjects who did not show any improvement with ICS had that treatment withdrawn; their symptoms subsequently resolved and they all had low FE_{NO} at follow-up.

Clinician appraisal of diagnostic tests

GPs adjudged that arriving at a working diagnosis was significantly helped by access to FE_{NO} in 48 out of 51 (94%) cases, and by spirometry in 27 out of 51 (53%) cases. In the three cases where FE_{NO} was not considered to be helpful, FE_{NO} was either low (14.0ppb) or intermediate (20.0 and 23.0ppb). These three patients had normal spirometry and were diagnosed as having non-atopic exercise-induced wheeze based on their history. For spirometry, in all 24 cases where it was deemed not to have been helpful, the results were normal. In the 27 cases where spirometry was considered helpful it was abnormal in only six cases, all of whom had an obstructive defect (FEV_1/FVC ratio < 0.7). Four of these six were diagnosed with atopic asthma (geometric mean FE_{NO} 130.3ppb (SD 34.0)) and the remaining two as COPD (geometric mean FE_{NO} 11.5ppb (SD 6.0)).

Discussion

The results of the present study confirm that FE_{NO} measurements obtained in a primary care setting offer helpful diagnostic information. Our aim was to demonstrate that immediate availability of FE_{NO}, coupled with spirometry, would improve diagnostic confidence and therapeutic decision making in managing patients with non-specific respiratory symptoms. In 94% of cases, the clinicians deemed this to be the case.

Initially, an empirical approach is often adopted in the management of airways-related symptoms. Later, objective tests may be sought to clarify or support the diagnosis, particularly if symptoms are persistent or troublesome. The latter are important given the non-specific nature of cough, wheeze and dyspnoea. Distinguishing asthma (or perhaps more appropriately "steroid-responsive airways disease") from other conditions such as post-viral bronchial hyper-responsiveness, COPD, GORD and anxiety-hyperventilation is important, given that both the anticipated natural history and therapeutic decisions in favour of using inhaled anti-inflammatory treatment will be influenced by such distinctions.

Unfortunately, conventional lung function tests provide only indirect evidence regarding either the aetiology of respiratory symptoms i.e. airflow obstruction, or the likelihood of steroid-responsiveness.[20] Although undoubtedly important, notably for identifying patients with COPD,[21] spirometry is not widely available. Quality assurance is also a major issue,[22] as is the case for serial PEF recordings.[2] Even when performed adequately, spirometry is poorly sensitive in diagnosing asthma, or in identifying the cause of non-specific cough.[23] Thus, in a study from the United States, although 66% of surveyed primary care practices owned a spirometer, only 50% of patients with suspected asthma had spirometry performed. The most commonly cited reason for not doing so was a perceived lack of impact that the results would have on clinical decision-making.[24] Overall, our results are consistent with that perception: spirometry was normal in the majority of patients (45/51, 88%), and was only considered helpful in aiding a diagnosis in 53% of cases.

In contrast, the perceived relevance and yield from FE_{NO} measurements in our study was much greater at 94%. There are several reasons for this. Firstly, FE_{NO} measurements are a surrogate marker for eosinophilic airway inflammation,[8,9,25] which in turn indicates the likelihood of steroid responsiveness.[6,7] Hence in patients with non-specific respiratory symptoms and high FE_{NO} levels, a positive response to ICS may be anticipated.[14] FE_{NO} results not only provide insight regarding the underlying airway pathology (the presence or absence of eosinophilic airway inflammation), but also guidance regarding specific treatment. This is not the case for spirometry. Whether or not to prescribe a trial of ICS is often decided empirically, and this aspect of management was simplified in our study using FE_{NO}. Follow-up evaluation confirmed that 14 of the 17 patients with a high FE_{NO} had a satisfactory clinical response when treated with ICS.

Secondly, both low and high FE_{NO} levels are meaningful in the interpretation of respiratory symptoms.[26] This is not the case for changes in lung function, where only low values are clinically instructive.

Despite the fact that access to FE_{NO} improved diagnostic confidence, the follow-up diagnosis at 3-month review was different in 10 out of 51 cases (20%). FE_{NO} was either intermediate (n=2) or low (n=5) and the diagnoses given at initial presentation and follow-up included GORD, non-specific cough, post-viral respiratory syndrome and anxiety hyperventilation. Neither FE_{NO} measurements nor spirometry categorically distinguish between these various conditions and so it is perhaps not surprising that after observing the natural history of the patients' symptoms for three months,

the initial diagnoses were altered. This does not negate the usefulness of FE_{NO} in these cases. Low values may identify the absence of potentially steroid responsive airway pathology.[14] It is also important to note that in three out of 10 patients, elevated FE_{NO} levels occurred only transiently, and their initial diagnosis of eosinophilic asthma was changed. This highlights a significant interpretive issue with regard to FE_{NO}. Transiently elevated levels may occur with limited exposure to allergen,[27] or with viral infection.[28] Although we sought to avoid this by enrolling patients whose symptoms were present for six weeks or longer, it remained an issue. It is also possible that such patients might have had symptomatically intermittent atopic asthma characterised by improved symptoms and normalised FE_{NO} levels, which might later recur. Our follow-up interval was not sufficiently long to confirm or deny this possibility. Alternatively these elevated FE_{NO} results may have been false positives. Discordance between high FE_{NO} levels and corresponding induced sputum eosinophil counts has been reported.[8]

Our study was not designed to repeat earlier more robust studies to investigate the utility of FE_{NO} measurements,[4,10,14] but to assess their usefulness in a busy general practice. Perhaps the study would have been strengthened if repeated measurements, application of the algorithm, and applying *a priori* treatment options had all been obligatory rather than optional. But this was not a controlled trial: it was set up to be a "real world" evaluation. Furthermore, smokers and recent ex-smokers were excluded from participation. Arguably, diagnostic testing is even just as important in this group. However, given that FE_{NO} measurements are significantly lower in smokers, and the interpretation of results is problematic, we opted not to include current or ex-smokers.[11,12]

Obtaining reliable FE_{NO} measurements is an easily learned skill for both patient and practitioner. The test is reproducible, acceptable and achievable in the vast majority of patients from the age of 6 upwards. The results are available almost immediately and therefore clinical decisions can be made promptly. The development of less expensive portable devices[18] is set to make FE_{NO} analysis much more accessible, including in primary care. We deliberately chose to trial the use of a portable device in a large primary care health centre, and we demonstrated that it is a feasible option in the context of running a busy practice. Although we did not undertake a cost-benefit analysis, economies of scale are likely to operate in this setting, given the very frequent need to diagnose and treat non-specific respiratory complaints. Potentially one of the other major economic benefits would be a reduction in the costs of unnecessary inhaled corticosteroid prescribing.

In conclusion, there is a need for diagnostic support in primary care regarding the likely cause of chronic respiratory symptoms. When provided, such support has the potential to improve not only the standards of patient care but also clinician satisfaction.[29] Conventional tests such as spirometry are limited in the information they can provide. FE_{NO} measurements are reliable and easily performed, and provide complementary data which inform the assessment and management of patients with an exceedingly common clinical presentation.

Acknowledgements

The authors wish to thank the general practitioners, nursing staff and patients of the Mornington Health Centre for their help with this study. The study was supported by the Strategic Research Initiative 2005, awarded by the Dean of the Dunedin School of Medicine of the University of Otago. Dr Hewitt was in receipt of an unrestricted educational grant from Aerocrine AB, Solna, Sweden, in order to conduct this study. Dr Hewitt also received the Tony Hocken Research Scholarship for 12 months – from the Department of Medicine, Dunedin School of Medicine – during the course of this study.

The nitric oxide analysers used in this study were donated to the Mornington Health Centre by Aerocrine, Solna, Sweden.

Conflict of interest declaration

Professor D Robin Taylor has received lecture fees from Aerocrine (Solna, Sweden). There are no competing interests for any other author.

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