

# Towards a practical clinical use of fractionated exhaled nitric oxide levels in chronic cough

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Fractionated exhaled nitric oxide (FeNO) is the amount of nitric oxide (NO) present in the airways detectable with chemiluminescent or electrochemical methods in the exhaled air. The exhaled NO measured is the sum of the constitutive gas produced by the neuronal and the endothelial isoforms of the NO synthases and the amount produced after activation of the inducible isoform of this enzyme (1). The inducible isoform produces a high quantity of NO, nM range, compared to the constitutive isoforms, which produce pM amount of the gas. The inducible isoform is mainly present in macrophages and epithelial cells in the airways and it accounts for most of the FeNO detected. One interesting characteristic of the inducible production of FeNO is that it is quite well down-modulated by corticosteroids compared to the NO produced by the constitutive isoforms (1).

From the early Nineties, when the first studies measuring FeNO in the airways of asthmatic patients were published (2,3), the amount of publications in this field increased over the years, reaching the top in 2013. Feasibility and noninvasiveness of FeNO determination for the evaluation of airway inflammation produced an increase in the number of publications with different methodologies raising the need of standardization. An ATS and ERS recommendation for standardized procedures for FeNO measurements was published in 2005 (4) and an ATS official clinical practice guideline on interpretation of FeNO levels and clinical application in 2011 (5).

The noninvasiveness of FeNO evaluation and the possibility to evaluate it with portable devices spread the diffusion of this determination from research to routine practice, opening its use sometimes even in the absence

of strict clinical evidence. In healthy subjects upper limits of FeNO ranges from 24.0 to 54.0 ppb, depending on age and height (6). Up to now, its main application is in the assessment of airway inflammation, since high FeNO levels are associated with eosinophilic inflammation in the airways (7). Smoking is an important interfering factor in the evaluation of FeNO, since smoking subjects have lower FeNO levels, limiting the clinical value of FeNO determination to non-smokers (8).

Many studies, including International guidelines (5,9), proposed the use of FeNO to support the diagnosis of asthma although, other more recent publications, concluded that FeNO sensitivity and specificity is insufficient to accurately diagnose asthma (10,11).

FeNO results in obese subjects are conflicting: in obese adult subjects wheezing was significantly associated with reduced FeNO, whereas a positive association between wheezing and FeNO among the nonobese subjects was found, suggesting possible differences in FeNO levels according to asthma phenotypes based on body weight (12). In children, a positive correlation between BMI and FeNO levels was reported only in nonasthmatic subjects, which suggests a link between obesity and increased airway inflammation independently from asthma development (13).

Among asthmatic patients FeNO evaluation seems more useful to define the Th2 phenotype, characterized by eosinophilic inflammation, high periostin levels and higher probability to respond to inhaled corticosteroid therapy (10).

Furthermore, FeNO was measured in many other respiratory conditions, particularly either when the inflammatory pattern may be useful to the diagnosis or to the follow up or when the response to corticosteroid

therapy should be assessed (14).

Chronic cough is an exclusion diagnosis made in patients with cough which persists at least for 8 weeks (15). The different causes responsible for this symptom have been considered in order to subgroup chronic cough in cough variant asthma, upper airway cough syndrome, eosinophilic bronchitis, gastroesophageal reflux-related cough and atopic cough (15). FeNO levels have been used to define asthma among subjects with chronic cough (16) but again the utility of this non-invasive methodology relies more in defining a subgroup of subjects among those with chronic cough than on the diagnosis of chronic cough itself.

Recently, Yi *et al.* reported the results of a study conducted on the utility of FeNO in diagnosing subjects with corticosteroid-responsive cough (CRC) (17). The authors evaluated 244 patients with chronic cough and 59 healthy subjects, more than half of the patients enrolled had CRC; in these subjects, FeNO is higher than in patients with corticosteroid non-responsive cough and significantly correlated with sputum eosinophils. Among chronic cough patients, FeNO level of 31.5 ppb has high specificity (91.4%) but low sensitivity (54.0%) in predicting those with CRC, with a positive predictive value of 89.3% and a negative predictive value of 60%. The combination of low FeNO levels, low sputum eosinophils (<2.5%) and absence of atopy has a sensitivity of 93.5% in predicting subjects with corticosteroid-resistance. These results, as those published in the asthma field (18), highlighted that the usefulness of airway inflammation evaluation through non-invasive markers, consists not in supporting the diagnosis but in discriminating a particular subset of subjects for whom a specific therapy is more useful. These results are particularly interesting in trying to use biological markers in an alternative way, which could favor its entrance in clinical practice. Most of the patients with chronic cough are prescribed inhaled corticosteroids without the evidence that this approach may be the right one for the patient. FeNO evaluation, with the proper cut-off levels, could be useful to direct therapy towards personalized treatment. In this view, step-down therapy in subjects with CRC could be monitored with FeNO levels and more successfully done, considered that step-down therapy is not always easily practiced and discontinuation of ICS/LABA causes worsening of the disease in patients with cough variant asthma (19).

Monitoring the step down therapy through the evaluation of airway inflammation is a strategy already proposed for asthmatic patients. Green *et al.* reported

that patients with moderate to severe asthma in whom the therapy was adapted according to sputum eosinophils count had less exacerbations than subjects managed with standard clinical guidelines (20). Unfortunately, sputum induction and differential cell count are available only in a limited number of specialized centers and results are not immediately provided, suggesting FeNO evaluation as an easier and more rapid methodology to assess eosinophilic inflammation.

In the last few years, many studies in asthmatic subjects, particularly clinical trials (21), considered the percentage or the number of blood eosinophils as surrogate marker of airway eosinophils. In the study by Yi *et al.* (17), such a biomarker was not considered, even if it would have been interesting to evaluate its sensitivity and specificity in predicting CRC compared to FeNO levels.

The study by Yi *et al.*, presented different cut-off levels of FeNO in patients with chronic cough, resulting in different sensitivity and specificity. FeNO higher than 22.5 ppb resulted in 74.6% sensitivity and 77.2% specificity to predict sputum eosinophils >2.5%, while with a cut-off value of 33.5 ppb the specificity was adjusted to 95%. In the meantime, a cut-off value of 31.5 ppb has the higher specificity in discriminating CRC (17). Considering such small differences in cut-offs, the inter-individual variability of FeNO evaluation, as measured in each specific setting, should always be checked.

Patients enrolled in Yi's study were non-smokers or ex-smokers with cessation of smoking for at least 6 months before the study. Considering the decreasing effect of the smoking habit on FeNO levels (11) the application in real life of these cut-offs values should be limited to non-smoking subjects.

Atopy is another variable considered by Yi *et al.* in their study in order to define a cut-off level for CRC. The authors found that low FeNO levels (<22.5 ppb), normal sputum eosinophils (<2.5%) and absence of atopy suggested a lower probability of CRC (19). Many studies reported the association between FeNO levels and atopy with increasing threshold for FeNO levels in atopic asthmatic subjects both in adults (22) and in children (23).

Yi *et al.*, did not report in their study whether a possible occupational cause for chronic cough had been considered (17). Despite published recommendations, both in cough guidelines/protocols and in clinical practice, it is quite frequent that an occupational trigger is not contemplated among the causes of chronic cough (24,25). The lack of recognition of an occupational cause of

chronic cough could have important consequences since it could delay preventive measures at work and could lead to a wrong therapy prescription. FeNO evaluations in subjects with work related cough could be useful for both the occupational diagnosis (26) and management of the disease in the workplace. More data are needed on the utility of FeNO evaluation as a marker of corticosteroid responsiveness also in occupational cough.

In conclusion, the study by Yi *et al.*, provides useful indication to the practical use of FeNO levels in subjects with chronic cough, particularly to predict subjects sensitive to corticosteroid therapy. This approach will favor personalized therapy and spare corticosteroid treatment in subjects not sensitive to it.

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### Footnote

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*Comment on:* Yi F, Chen R, Luo W, *et al.* Validity of Fractional Exhaled Nitric Oxide in Diagnosis of Corticosteroid-Responsive Cough. *Chest* 2016;149:1042-51.

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