# Fractional exhaled nitric oxide (FeNO) measurement in asthma and rhinitis

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*Artur Gevorgyan[1], Wytske J Fokkens[2]

[1] Clinical Fellow, Advanced Rhinology and Skull Base Surgery, Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, The Netherlands
[2] Professor and Head of Department of Otorhinolaryngology, Academic Medical Centre, Amsterdam, The Netherlands

*Correspondence: Dr Artur Gevorgyan, Department of Otorhinolaryngology, Academic Medical Centre, Meibergdreef 9, A2-234, 1105 AZ Amsterdam, The Netherlands
Tel: + 31 (0) 61 025 4047 Fax: +31 (0) 20 566 9662
E-mail: artur.gevorgyan@mail.utoronto.ca

The article by de Bot *et al*. in this issue of the *PCRJ* demonstrates that fractional exhaled nitric oxide (FeNO) does not correlate with symptoms or quality of life (QoL) in children with allergic rhinitis (AR) with and without asthma.[1] Patients were assessed for FeNO, nasal and asthma symptom scores, rhinitis-related QoL and house dust mite-specific immunoglobulin E level. Cross-sectional and longitudinal correlations were sought between these parameters at baseline and after two years. The authors found no or very weak correlations between FeNO levels and nasal symptoms, asthma symptoms or QoL in both groups in both years, and concluded that FeNO is unlikely to be a useful biomarker of the clinical severity of upper or lower airway disease in primary care. These findings are not surprising.

Nitric oxide (NO) is produced endogenously in cells by NO synthase.[2] Its production is increased in response to inflammatory cytokines, and FeNO is thought to be an indirect measurement of airway eosinophilic inflammation. Initial enthusiasm about FeNO as a marker of airway inflammatory disease[3,4] has now turned into a more balanced outlook, with it being seen as one of the many indirect outcome measures which still require much fine-tuning before they can find (if ever) broad clinical applicability in primary or secondary care.

The advantages of FeNO testing are non-invasiveness, speed, simplicity, ease of tolerance by children and adult patients with severe airway obstruction, and lack of known risks to the patient.[5,6] The disadvantages include the expense of purchasing and maintaining equipment, the variability of FeNO measurement between centres, and significant overlap of FeNO levels between populations with and without asthma, which thus far renders it as a research tool only.

The American Thoracic Society (ATS) has approved a set of clinical practice guidelines of FeNO interpretation for clinical applications.[5] There are recommendations concerning the use of FeNO in asthma, particularly for diagnosis and monitoring of eosinophilic airway inflammation and determining the likelihood of steroid responsiveness, whilst accounting for age and allergen exposure as factors. This contrasts with a limited role for the measurement of nasal NO levels, which, though altered in several diseases (e.g. cystic fibrosis, primary ciliary dyskinesia), cannot be recommended for routine clinical practice.[7,8]

A sample of recent literature supports the observations by de Bot *et al*. Ciprandi *et al*. evaluated children with AR or asthma and found a correlation between FeNO levels and change in forced expiratory volume in 1 second ($FEV_1$) after bronchodilator testing (bronchial reversibility).[9] The correlation was moderate for both asthma (r = 0.69) and rhinitis (r = 0.54). Levels of 34 parts per billion (ppb) of FeNO were predictive of bronchial reversibility. The same group also found a moderate negative correlation between FeNO levels and bronchial hyperreactivity in adult patients with persistent AR.[10] A similar negative correlation was found in children with AR with or without asthma. However, correlations between FeNO and rhinitis or bronchial symptoms were weak (r=0.18 and 0.38, respectively), agreeing with the present findings of de Bot *et al*.[1,10] Also, in children with asthma, FeNO monitoring could predict exacerbations – but at least 3-5 FeNO measurements in the three weeks preceding the exacerbation were needed.[11]

In a study of adult patients, Kalpaklioglu found no difference between the levels of orally exhaled FeNO in AR, non-allergic rhinitis (NAR) and control patients.[12] NAR with asthma was associated with higher FeNO levels than AR with asthma. Perennial sensitisations caused higher FeNO levels. In contrast, Takeno *et al*. demonstrated significantly higher oral FeNO levels in patients with AR and vasomotor rhinitis compared to controls.[13] Significantly higher levels were also recorded for nasal FeNO in AR patients, especially with asthma. However, in AR patients with and without asthma the correlations were weak between nasal symptom scores and oral (r = 0.303) or nasal (r = 0.356) FeNO levels. In a prospective cohort study of children with AR, NAR and without rhinitis, children with AR compared with controls had increased FeNO levels (15.9 ppb vs. 6.6 ppb), along with several other markers of inflammation.[14] These levels of FeNO, however, are not considered clinically significant; the current ATS guidelines suggest that only FeNO values >50 ppb (>35 ppb in children) indicate that eosinophilic inflammation and responsiveness to corticosteroids in asthma are likely, whereas values of 25-50 ppb (20-35 ppb in children) should be interpreted with caution.[5] Interestingly, FeNO levels in healthy controls tend to vary depending on patient age, lung function,[15] and gender.[16] Also, common variants in the NO synthesis pathway genes contribute to variation in FeNO levels in children.[2] Some of these genetic influences were stronger in children with asthma. Surprisingly, lower FeNO levels have been observed in smokers versus non-smokers.[17]

Like orally-measured FeNO, nasal FeNO has not been found to be predictive of severity of disease and patient symptoms. Bozek *et al*.

found no significant correlations between the levels of nasal FeNO and nasal symptom scores in young and elderly patients with seasonal allergic rhinitis.[18]

Several conclusions can be made from the above studies in light of the recent findings by de Bot *et al*. Firstly, despite reported positive associations between the diagnoses of AR and asthma with FeNO, the correlation between symptom scores and FeNO levels is weak or absent. Secondly, usage of nasal FeNO does not improve the correlation with patient-reported symptoms. Finally, despite several reported correlations with other measures of airway disease, the absolute levels of FeNO are highly varying in different studies, and in some these levels are significantly lower than the ATS-recommended cut-off levels indicating eosinophilic inflammation and responsiveness to corticosteroids.

Therefore, the study by de Bot *et al*. in this issue of the *PCRJ* is supported by the available literature. The consequence is that FeNO should be delegated as a research tool which does not predict the clinical severity of upper or lower airway disease in children in primary care.

**Conflicts of interest** The authors declare that they have no conflicts of interest in relation to this article.

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