

Exhaled nitric oxide's ability to predict methacholine challenge A matter of definition



I read with interest the article “Evaluation of Exhaled Nitric Oxide's Ability to Predict Methacholine Challenge in Adults With Non-obstructive Spirometry” by Nickels and Lim, recently published on *Annals of Allergy, Asthma, and Immunology*.¹ Their study, which was retrospectively conducted and selected patients who performed fractional exhaled nitric oxide (FeNO) and methacholine bronchial challenge within 2 weeks of each other, found that FeNO had a nonbrilliant ability to predict the outcome of a methacholine challenge, despite patients with positive methacholine challenge result having significantly higher levels of FeNO.

This result is at least unexpected because most of the previous literature found opposite findings. In many reports, FeNO was able to rule out, with very high negative predictive values for cutoffs of 25 to 27 ppb, the diagnosis of asthma assessed by airway hyperresponsiveness^{2–5} or by bronchial reversibility test.^{5,6} In most of the above mentioned studies, airway hyperresponsiveness assessed by methacholine challenge was defined, as suggested also by the American Thoracic Society, as a decrease in forced expiratory volume in 1 second of at least 20% of basal values (PD₂₀FEV₁) at a methacholine dose less than 800 µg; from the methods of the study by Nickels and Lim, it seems that the definition was broader and also included patients with higher cutoff providing that a PD₂₀FEV₁ is reached before the end of the test. In this way, patients with borderline hyperresponsiveness or even with normal reactivity could have been defined as hyperreactive, therefore decreasing the sensitivity of FeNO as predictor of airway hyperresponsiveness.

Moreover, the authors did not mention the exclusion of active or ex-smokers from the study. For these patients, FeNO should be carefully interpreted because they generally have a reduced production of nitric oxide in the airways.⁷

Therefore, a matter of definition (regarding methacholine challenge positivity) could be the crucial point that makes FeNO able or not to predict airway hyperreactivity.

Currently, FeNO is particularly helpful in ruling out asthma, for example, in those patients with atypical presentation (ie, only cough)⁸ or concomitant frequent asthma comorbidities (ie, rhinitis²), in predicting inhaled corticosteroid response,⁹ or in

tapering inhaled corticosteroid treatment.¹⁰ Moreover, it is currently the only available reliable point-of-care biomarker for asthma.

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Exhaled nitric oxide or FEF_{25%–75%} Balancing diagnostic value with efficacy despite evidentiary uncertainty



We appreciate the comments^{1,2} on our recent publication investigating the value of exhaled nitric oxide (FeNO) in predicting the outcome of a methacholine challenge (MCH) in adults with respiratory symptoms presenting to a tertiary care center.³ Despite our hypothesis not being confirmed, the performance profile of FeNO (inexpensive, point of care, information predicting treatment response) makes this testing modality attractive compared with MCH testing (more expensive, logistically more cumbersome, helpful primarily when the result is negative).⁴ The commentary

suggests that forced expiration flow between 25% and 75% (FEF_{25%–75%}) is similarly an attractive clinical measurement, particularly because it is collected at the same time as routine spirometric results.

The utility of the FEF_{25%–75%} in predicting or characterizing pulmonary pathology in adult patients is unclear. Based on data from the Third National Health and Nutrition Examination Survey, when using a cut point lower than 80% of predicted for FEF_{25%–75%}, more than 20% subjects would be falsely classified as abnormal compared with using a lower limit of normal.⁵ As with FeNO, the optimal value to determine abnormal for FEF_{25%–75%} remains unknown.

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Similar to our findings of a minimal correlation between FeNO levels and MCH outcome, FeNO levels might not collate with FEF_{25%–75%}. Steerenberg et al⁶ reported on a sample of 450 children 7 to 12 years of age with and without atopy (as measured by skin testing) and found no relation between FeNO and FEF_{25%–75%} (reported as maximum midexpiratory flow). Similarly, the correlation between FeNO and maximum midexpiratory flow in adults with nonallergic rhinitis and allergic rhinitis was poor ($r = 0.114$ and 0.253 , respectively).⁷

We note the studies cited showing FeNO predicting bronchial hyperactivity were in patients with allergic sensitivity.^{8,9} By selecting patients with respiratory symptoms and allergic sensitivity, FeNO might predict bronchial hyperactivity, which our study did not. Also notable, the studies cited point to pediatric evidence and we respectfully assert that pediatric and adult patients presenting with chronic respiratory complaints differ in underlying pathophysiology.

Further study is needed to confirm our hypothesis, that FeNO is a clinically useful and economically favorable tool compared with the MCH in patients presenting with respiratory symptoms. Phenotyping and identification of appropriate populations is needed to understand the optimal utility of FeNO and FEF_{25%–75%}. Furthermore, appropriate cut points are needed for FeNO and FEF_{25%–75%} to appropriately identify normal versus abnormal results in a clinical context. Until such information becomes available, it is important, when faced with the uncertain utility of diagnostic or therapeutic modalities, to use a shared decision-making approach when developing a care plan.¹⁰

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