



Editorial

Nitric Oxide (NO) in Managing Asthma[☆]

El óxido nítrico (NO) en el manejo del asma

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“If I am rich in anything, it is in perplexities, not in certainties”.

J.L. Borges

The intention of science (and medicine is a science) is to explain aspects of physical reality. However, and despite undeniable successes and advances, we know that surpassing one limit merely takes us to the next limit. We feel, like Achilles and his chase with the tortoise that although the goal seems closer and closer, it will always be unreachable. We have no other alternative than to become accustomed to living with a certain degree of uncertainty, taking risks and making decisions based on an unstable foundation, with the hopes that tomorrow we will make fewer mistakes than today.

If there is one disease among the respiratory pathologies that is elusive, changing and multi-form that disease is surely asthma. None of the tools available (questionnaires, function tests, histologic studies, etc.) provide us with complete knowledge of the clinical situation of asthma patients. That is not to say, though, that we should consider these tools useless. In clinical practice, there is no such a thing as a perfect test, and the measurement of the fraction of nitric oxide (NO) in exhaled air (FeNO) is no exception. Its utility, however, is endorsed by a growing flow of clinical studies, and in this brief space, I will try to argue how it can help us to diagnose asthma and to decide the best treatment for each patient.

In medicine, all tests should have a biological basis on which they are founded. NO is a reactive molecule synthesized by enzymes (synthase) that are expressed in structural cells of the airway and which are presented in two isoforms: constitutive and inducible. In asthmatics, the inducible isoform is overexpressed, which causes an increase in the production of NO, a gas that diffuses into the alveolar or bronchial lumen and can be detected in exhaled air. Its usefulness in asthma lies in the relationship between FeNO levels and the eosinophilic inflammation that is characteristic in this disease.^{1,2} A recent publication³ quantified the capacity of FeNO for predicting eosinophilia in sputum ($\geq 3\%$ of the cell total) using

an ROC curve and obtain a sensitivity of 65% and a specificity of 79% for values ≥ 41 ppb (area under the curve: 0.77). These values could be considered modest and, in fact, some renowned authors⁴ question if FeNO is a valid marker for eosinophilia. This disparity of opinions may perhaps be explained if we keep in mind that the relationship between both parameters can be affected by tobacco smoke, by steroid treatment or by the presence or absence of atopy. It has also been observed that FeNO may be more sensitive to the action of these factors than the underlying eosinophilic inflammation.³ In this manner, an asthmatic who smokes or who is using an inhaled corticosteroid could have normalized his/her FeNO values but, at the same time, continues to maintain a high percentage of eosinophils in sputum.

From this biological basis, practical applications should be drawn; thus, different studies have evaluated the use of measuring FeNO as a diagnostic test in asthma.^{5–11} The populations that are analyzed in these studies are heterogeneous (adults selected due to clinical suspicion for asthma, adults with chronic cough, non-selected adults with respiratory symptoms, etc.), the number of participants is variable and the results are very disparate: sensitivities are found to be between 72.2% and 88%, specificities fluctuate between 64% and 88% and areas under the ROC curve oscillate between 0.79 and 0.89. The use of different cut-points (from 7 ppb to 40 ppb) and different analyzers does no more than complicate the interpretation of these results. Despite this, our scientific society considers that a FeNO ≥ 30 ppb (measured by chemiluminescence; this value should be corrected according to the device used) is diagnostic in cases of clinical suspicion for asthma and a negative results in the bronchodilator test,¹² avoiding more difficult and less accessible tests such as the demonstration of bronchial hyperreactivity. In any case, in my opinion, the capacity of FeNO to predict response to steroid treatment is much more interesting, especially in those cases in which the control of the disease is difficult. This use is endorsed by the results of recent research.^{13–15} According to this research, in an asthmatic with a low score on the ACT or ACQ and high FeNO values, we should suspect therapeutic insufficiency (due to non-compliance or to a dosage of corticosteroids that is too low). Contrarily, if the result of the measurement were low, we would have to consider alternative diagnoses (COPD, bronchiectasis, etc.), the influence of comorbidities (smoking, obesity, depression, etc.), resistance to the action of the drug or non-eosinophilic phenotypes.

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Lastly, it has been examined whether associating the measurement of FeNO to other asthma management methods (based on clinical guidelines) can improve control. The results have been equivocal and often disappointing^{16–18} but, as has already been shown,¹⁹ the study design contains numerous defects: inadequate populations have been chosen, with a low probability of suffering a loss of control and exacerbations, and therefore, with hardly any prospect for improving evolution with more sophisticated methods; in addition, the context of a clinical assay, which favors therapeutic compliance, eliminates one of the possible advantages of measuring FeNO (to detect the lack of adherence); on the other hand, it is absurd to establish therapeutic strategies based on the same tools (for example questionnaires) that will later be used as variables for effectiveness (e.g. control defined by the results of those same questionnaires); finally, it is very much possible that predetermining a value for each individual and estimating the changes during the follow-up period (increase or decrease over baseline) are more effective than establishing a set value of FeNO for the entire sample.

In conclusion, I believe that the measurement of FeNO can be useful for diagnosing asthma in some cases, but its fundamental use will be in consonance with other tools to optimize patient treatment, especially in difficult-to-control cases, identifying those who are able to respond to steroids. Studies should be designed to determine its efficacy for predicting future risk. The ability to anticipate which asthmatics are at risk of suffering exacerbations would be of great clinical interest in order to adjust the therapeutic strategy to each particular case.

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