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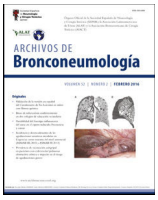

Editorial

FeNO for Asthma Diagnosis in Adults: More Lights Than Shadows

Utilidad del FeNO para el diagnóstico de asma en el adulto: más luces que sombras

Nitric oxide (NO) was measured for first time in healthy individuals in 1991, and its discovery provided relevant information about many biologic processes.[1] NO is a free radical that is synthesized from the amino acid L-arginine by the nitric oxide synthases through the L-arginine-nitric oxide pathway. The inducible NO synthase (iNOS) is induced by inflammatory mediators, macrophages and endotoxines, and it is upregulated in a large variety of inflammatory diseases. In this way, NO regulates the tone of the smooth muscle and blood vessels of the airways and it blockades diverse constituents of the inflammatory cascade.[2]

The measurement of the exhaled fraction of the NO (FeNO) has proved to be of great utility in clinical practice. In fact, it is widely accepted that increased FeNO levels are an acceptable surrogate of the T2 inflammatory pathway and also predict a good response to inhaled corticosteroids (ICS) in respiratory diseases.[3,4] In addition, FeNO can help in monitoring ICS dose titration, weaning and treatment adherence.[5] However, the utility of FeNO for the diagnosis of asthma sparks controversy among the scientific community in relation to the disparity of the results presented in the published series.

In the past 15 years many studies have analyzed the utility of FeNO for the diagnosis of asthma. Despite the large data available in the literature, different national and international asthma guidelines recommend opposite approaches regarding FeNO in the frame of asthma diagnosis. The Global Initiative for Asthma (GINA) specifically addresses this question and (in a perphaps too conservative statement) affirms that FeNO has not been established to be useful for ruling in or ruling out a diagnosis of asthma, since it is also elevated in non-asthma conditions (e.g. atopy & eosinophilic bronchitis among others) and it is not elevated in some asthma phenotypes (e.g. neutrophilic asthma).[3] In a less categoric but still harsh position, the National Institute for Health and Care Excellence (NICE) asthma guidelines recommends using FeNO in patients with symptoms suggestive of asthma in combination with other diagnostic tools such as peak flow variability, bronchodilator test or bronchial challenge test (BCT), to confirm the diagnosis of asthma.[6] In this way, according to NICE guidelines, an increased FeNO alone in a patient with symptoms suggestive of asthma would not be enough to establish asthma diagnosis. The Japanese asthma guidelines address this topic with a different positioning stating that "asthma like symptoms, reversible airway limitation and airway hyperresponsiveness are important for asthma diagnosis" and that "atopy and airway inflammation (FeNO) in combination with typical symptoms support the diagnosis of asthma[7]". In a similar and even more pragmatic diagnostic approach, the Spanish asthma guidelines (GEMA) supports establishing asthma diagnosis in subjects with asthma-like symptoms and increased FeNO values (higher than 50 ppb), when spirometry with bronchodilator test were normal and negative respectively, if an ulterior good response to asthma treatment is confirmed.[8]

The number of studies that have aimed to analyze the diagnostic utility of FeNO for asthma diagnosis in adults is large. In 2003, Dupont et al.[9] analyzed 240 nonsmoking, steroid naïve individuals with symptoms suggestive of obstructive airway disease. After FeNO measurement, asthma was ruled in based on airway reversibility or airway hyperresponsiveness in this sample of patients. The authors calculated a sensibility (Se) and a specificity (Sp) of 69.4% and 90% respectively at a cutoff value of 16 parts per billion (ppb) for the diagnosis of asthma, concluding that it could be used as additional diagnostic tool for the screening of asthma. In 2006, Heffler et al.[10] analyzed the utility of FeNO for the diagnosis of asthma in individuals with rhinitis and asthma symptoms. They concluded that a cutoff value of 36 ppb, which is considerably higher than the values presented by Dupont et al., had a Se of 78% and a Sp of 60%, again ratifying its possible utility for the screening of asthma. One year later in 2007, Fortuna et al.[11] performed a 50-patient prospective study with a similar design, encompassing steroid naïve subjects with asthma symptoms who underwent FeNO and BCT. Twenty-two patients presented positive BCT and were diagnosed of asthma, stablishing a Se of 77% and a Sp of 64% for a cutoff value of 20 ppb. In 2008 Kostikas et al.[12] reported a Se and a Sp of 52.4% and 85.2% respectively for a cutoff FeNO value > 19 ppb. Later on, a great amount of studies have also addressed this topic, recommending 40 ppb as the best cutoff value for ruling in asthma, with Se values that range from 70 to 80% and Sp values ranging between 80 and 90%.[13–16] In 2017 a systematic review reported that a cut off of 50 ppb might guarantee a sufficient positive predictive value for ruling in asthma and to determine ICS responsiveness at the same time.[17]

The diversity in terms of cutoffs, Se and Sp values are very likely related to the heterogenic inclusion criteria and several confounding factors. These incoherencies may raise doubts and have

impacted the diagnostic algorithms presented in some clinical practice guidelines (GINA, NICE), avoiding its implementation. In fact, patients with allergic rhinitis and atopic status have been reported to present higher FeNO values than control subjects and smoking has been linked to lower FeNO values comparing to non-smokers.[12] Although it is necessary to take into account these particularities, we do not think that they should prevent us from taking advantage of FeNO in the frame of asthma diagnosis, given the lack of a gold standard technique and that asthma diagnosis is often challenging in daily clinical practice. In fact, the spirometry and the bronchodilator test which are the cornerstone of asthma diagnosis, are usually within normal limits in mild asthmatics. Given the high percentage of mild asthmatics (around 70%) out of the total asthmatic population it is mandatory to implement further techniques beyond spirometry. In this context, it seems reasonable not to undermine an additional technique which is non-invasive and not time consuming. Despite the discrepancies in the available data, it seems that a FeNO above 40–50 ppb with an appropriate clinical context it is indeed, a useful diagnostic tool for the diagnosis of asthma, particularly in the allergic asthma phenotype.

Conflict of interests

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